IARC MONOGRAPHS

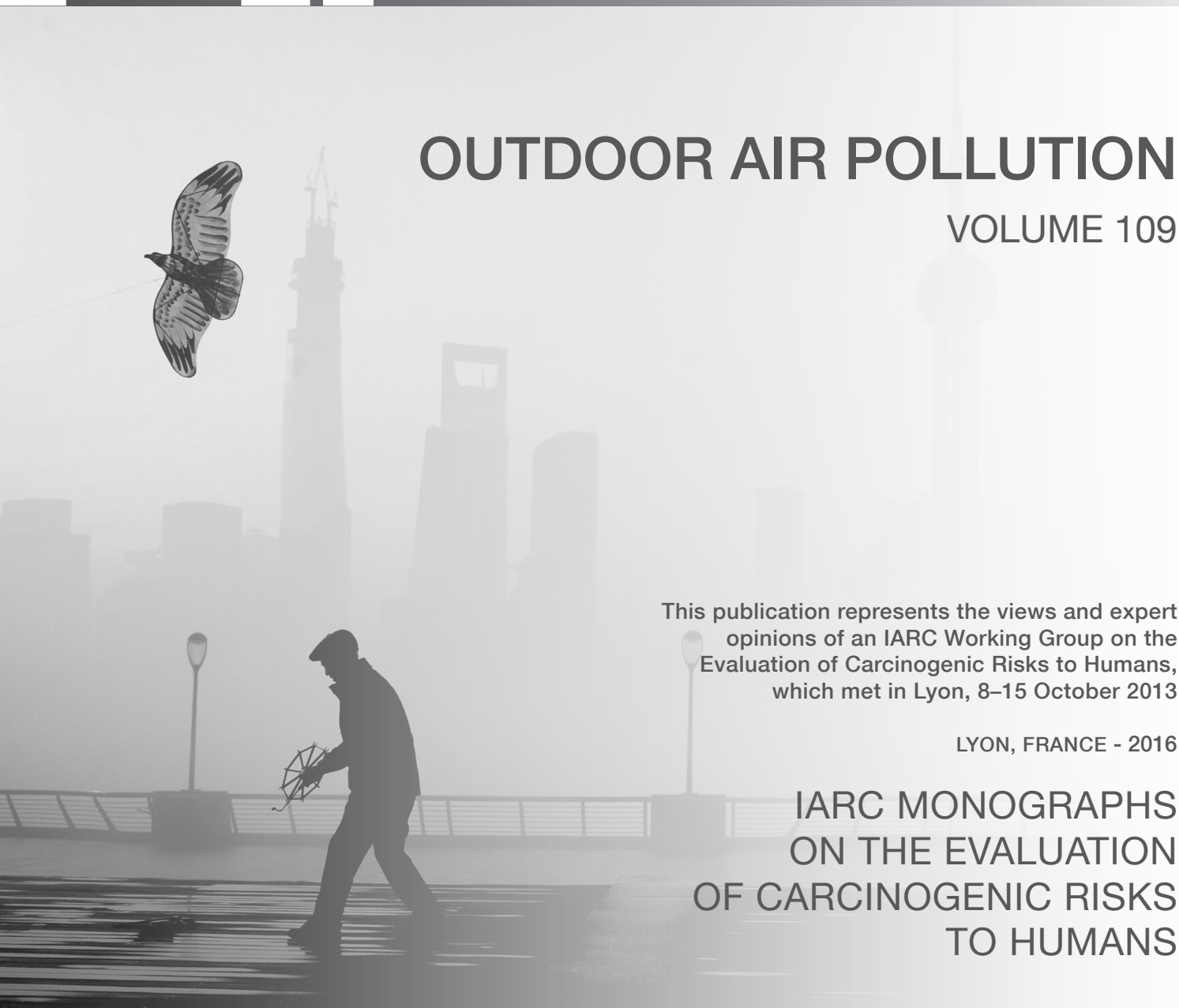
OUTDOOR AIR POLLUTION

VOLUME 109

IARC MONOGRAPHS
ON THE EVALUATION
OF CARCINOGENIC RISKS
TO HUMANS

International Agency for Research on Cancer
World Health Organization

IARC MONOGRAPHS



OUTDOOR AIR POLLUTION

VOLUME 109

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 8–15 October 2013

LYON, FRANCE - 2016

IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer

World Health Organization

IARC MONOGRAPHS

In 1969, the International Agency for Research on Cancer (IARC) initiated a programme on the evaluation of the carcinogenic risk of chemicals to humans involving the production of critically evaluated monographs on individual chemicals. The programme was subsequently expanded to include evaluations of carcinogenic risks associated with exposures to complex mixtures, lifestyle factors and biological and physical agents, as well as those in specific occupations. The objective of the programme is to elaborate and publish in the form of monographs critical reviews of data on carcinogenicity for agents to which humans are known to be exposed and on specific exposure situations; to evaluate these data in terms of human risk with the help of international working groups of experts in carcinogenesis and related fields; and to indicate where additional research efforts are needed. The lists of IARC evaluations are regularly updated and are available on the Internet at http://monographs.iarc.fr/.

This programme has been supported since 1982 by Cooperative Agreement U01 CA33193 with the United States National Cancer Institute, Department of Health and Human Services. Additional support has been provided since 1986 by the European Commission Directorate-General for Employment, Social Affairs, and Inclusion, initially by the Unit of Health, Safety and Hygiene at Work, and since 2014 by the European Union Programme for Employment and Social Innovation "EaSI" (2014–2020) (for further information please consult: http://ec.europa.eu/social/easi). Support has also been provided since 1992 by the United States National Institute of Environmental Health Sciences, Department of Health and Human Services. The contents of this volume are solely the responsibility of the Working Group and do not necessarily represent the official views of the United States National Cancer Institute, the United States National Institute of Environmental Health Sciences, the United States Department of Health and Human Services, or the European Commission.

Published by the International Agency for Research on Cancer,
150 cours Albert Thomas, 69372 Lyon Cedex 08, France

On-line publication, 17 December 2015

Distributed by WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland
(tel.: +41 22 791 3264; fax: +41 22 791 4857; email: bookorders@who.int).

Corrigenda to the IARC Monographs are published online at http://monographs.iarc.fr/ENG/Publications/corrigenda.php
To report an error, please contact: editimo@iarc.fr

Co-funded by the European Union

IARC Library Cataloguing in Publication Data

Outdoor air pollution/ IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2013.

(IARC monographs on the evaluation of carcinogenic risks to humans ; volume 109)

1. Carcinogens, Environmental 2. Air Pollution - adverse effects 3. Environmental Exposure - adverse effects 4. Risk Factors 5. Neoplasms - etiology
I. International Agency for Research on Cancer
II. Series

ISBN 978-92-832-0175-5 (NLM Classification: W1)
ISSN 1017-1606

CONTENTS

NOTE TO THE READER

The term 'carcinogenic risk' in the *IARC Monographs* series is taken to mean that an agent is capable of causing cancer. The *Monographs* evaluate cancer hazards, despite the historical presence of the word 'risks' in the title.

Inclusion of an agent in the *Monographs* does not imply that it is a carcinogen, only that the published data have been examined. Equally, the fact that an agent has not yet been evaluated in a *Monograph* does not mean that it is not carcinogenic. Similarly, identification of cancer sites with *sufficient evidence* or *limited evidence* in humans should not be viewed as precluding the possibility that an agent may cause cancer at other sites.

The evaluations of carcinogenic risk are made by international working groups of independent scientists and are qualitative in nature. No recommendation is given for regulation or legislation.

Anyone who is aware of published data that may alter the evaluation of the carcinogenic risk of an agent to humans is encouraged to make this information available to the Section of IARC Monographs, International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 08, France, in order that the agent may be considered for re-evaluation by a future Working Group.

Although every effort is made to prepare the *Monographs* as accurately as possible, mistakes may occur. Readers are requested to communicate any errors to the Section of IARC Monographs, so that corrections can be reported in future volumes.

LIST OF PARTICIPANTS

Members[1]

Kalpana Balakrishnan (unable to attend)

Department of Environmental Health Engineering
WHO Collaborating Centre for Occupational Health
Sri Ramachandra University
Porur, Chennai
India

Michael Brauer (Subgroup Chair, Exposure Data)

School of Population and Public Health
University of British Columbia
Vancouver, BC
Canada

Guosheng Chen

Hazard Methodology Division
Existing Substances Risk Assessment Bureau
Safe Environments Directorate
Healthy Environments and Consumer Safety Branch
Health Canada
Ottawa, ON
Canada

Judith Chow

Division of Atmospheric Sciences
Desert Research Institute
Reno, NV
USA

[1] Working Group Members and Invited Specialists serve in their individual capacities as scientists and not as representatives of their government or any organization with which they are affiliated. Affiliations are provided for identification purposes only. Invited Specialists do not serve as Meeting Chair or Subgroup Chair, draft text that pertains to the description or interpretation of cancer data, or participate in the evaluations.
Each participant was asked to disclose pertinent research, employment, and financial interests. Current financial interests and research and employment interests during the past 4 years or anticipated in the future are identified here. Minor pertinent interests are not listed and include stock valued at no more than US$ 1000 overall, grants that provide no more than 5% of the research budget of the expert's organization and that do not support the expert's research or position, and consulting or speaking on matters not before a court or government agency that does not exceed 2% of total professional time or compensation. All grants that support the expert's research or position and all consulting or speaking on behalf of an interested party on matters before a court or government agency are listed as significant pertinent interests.

David M. DeMarini (unable to attend)

Integrated Systems Toxicology Division
US Environmental Protection Agency
Research Triangle Park, NC
USA

Francesco Forastiere [2]

Department of Epidemiology
Regional Health Service of the Lazio Region
Rome
Italy

Uwe Heinrich (Subgroup Chair, Cancer in Experimental Animals)

Fraunhofer Institute of Toxicology and Experimental Medicine
Hanover
Germany

Rogene Henderson

Lovelace Respiratory Research Institute
Albuquerque, NM
USA

Wei Huang

Department of Occupational and Environmental Health
School of Public Health
Peking University Health Science Center
Beijing
China

Lisbeth E. Knudsen

Department of Public Health
University of Copenhagen
Copenhagen
Denmark

Francine Laden

Departments of Environmental Health and Epidemiology
Harvard T.H. Chan School of Public Health
Boston, MA
USA

Daniel L. Morgan (unable to attend)

Respiratory Toxicology Group
National Toxicology Program
National Institute of Environmental Health Sciences
Research Triangle Park, NC
USA

Peter Møller

Department of Public Health
Section of Environmental Health
University of Copenhagen
Copenhagen
Denmark

David H. Phillips

Analytical and Environmental Sciences Division
School of Biomedical Sciences
King's College London
London
United Kingdom

[2] Francesco Forastiere has been serving during 2012 as an expert to the Court of Taranto, Italy on a case of industrial pollution. He worked for the judge and not for any of the parties. The compensation only covered his expenses.

Ole Raaschou-Nielsen [3]

Department of Nutrition, Genes and the Environment
Danish Cancer Society Research Center
Copenhagen
Denmark

Paulo Hilario Nascimento Saldiva

Department of Pathology
School of Medicine
University of São Paulo
São Paulo, SP
Brazil

Jonathan M. Samet (Overall Chair)

Institute for Global Health
University of Southern California
Los Angeles, CA
USA

James J. Schauer

Environmental Chemistry and Technology Program
Civil and Environmental Engineering
University of Wisconsin-Madison
Madison, WI
USA

Paolo Vineis (Subgroup Chair, Cancer in Humans)

Department of Environmental Epidemiology
Imperial College London
London
United Kingdom

Paul A. White (Subgroup Chair, Mechanisms)

Environmental Health, Science and Research Bureau
Healthy Environments and Consumer Safety Branch
Health Canada
Ottawa, ON
Canada

Takashi Yorifuji

Department of Human Ecology
Okayama University
Okayama
Japan

Invited specialists

Aaron J. Cohen [4]

Health Effects Institute
Boston, MA
USA

Gerard Hoek [5]

Department of Environmental Epidemiology
Institute for Risk Assessment Sciences
Utrecht University
Utrecht
The Netherlands

[3] Ole Raaschou-Nielsen holds stock of in total less than US$ 10 000 in a company active in the sector of insulation.
[4] Aaron J. Cohen is the principal scientist of the Health Effects Institute (HEI), which conducts research worldwide on the health effects of air pollution. The Institute's core funding comes in equal parts from the United States Environmental Protection Agency and the makers of motor vehicles for sale in the USA.
[5] Gerard Hoek has received significant research funding (until 2011) from CONCAWE, the oil companies' European association for environment, health and safety in refining and distribution.

Armistead (Ted) Russell [6]

School of Civil & Environmental Engineering
Georgia Institute of Technology
Atlanta, GA
USA

Representatives

Emmanuelle Durand

French Agency for Food, Environment and Occupational Health and Safety
ANSES
Maisons-Alfort
France

Matteo Redaelli

French Agency for Food, Environment and Occupational Health and Safety
ANSES
Maisons-Alfort
France

Andre Zuber

European Commission
Brussels
Belgium

Observers

G. Bruce Copley [7]

ExxonMobil Biomedical Sciences, Inc.
Annandale, NJ
USA
Observer for CONCAWE, Belgium

Paolo Crosignani [8]

National Cancer Institute
Milan
Italy
Observer for the International Society of Doctors for the Environment (ISDE), Italy

Béatrice Fervers

Department of Cancer and the Environment
Cancer et Environnement
Centre Léon Bérard
Lyon
France

Gaëlle Guillosou [9]

Evaluation des risques sanitaires et environnementaux
EDF
Levallois-Perret
France
Observer for Eurelectric, Belgium

[6] Armistead Russell is also Associate Editor of *Environmental Science & Technology*, a journal that is governed by the American Chemical Society. He received significant funding for research at the Georgia Institute of Technology from Phillips 66, a company with business in oil refineries, and from Southern Company, an energy company serving the Southeast of the USA. He also received research support from and consulted for the Electric Power Research Institute, Inc.

[7] G. Bruce Copley is employed as a consultant/technical advisor by ExxonMobil Corporation and also holds shares of ExxonMobil stock. His participation is sponsored by CONCAWE, Belgium.

[8] Paolo Crosignani's participation is sponsored by the International Society of Doctors for the Environment (ISDE), Italy.

[9] Gaëlle Guillosou is employed by the EDF Group, a worldwide energy company. Her participation is sponsored by Eurelectric, Belgium.

David Morgott [10]

Philadelphia, PA
USA
Observer for CONCAWE, Belgium

Rashid Shaikh [11] *(unable to attend)*

Health Effects Institute
Boston, MA
USA

John Andrew Tomenson [12]

Causation Ltd
Macclesfield
United Kingdom
Observer for CONCAWE, Belgium

IARC/WHO Secretariat

Robert Baan, Visiting Scientist, Section of *IARC Monographs*
Lamia Benbrahim-Tallaa, Section of *IARC Monographs*
Véronique Bouvard, Section of *IARC Monographs*
Anya Burton, Section of Environment and Radiation
Graham Byrnes, Section of Genetics
Rafael Carel, Visiting Scientist, Section of *IARC Monographs*
Rachel Denholm, Section of Environment and Radiation
Caroline Dickens, Section of Environment and Radiation
Carlos Dora, WHO, Switzerland
Fatiha El Ghissassi, Section of *IARC Monographs*
Carolina Espina Garcia, Section of Environment and Radiation
Davide Degli Esposti, Section of Mechanisms of Carcinogenesis
Nicolas Gaudin, Communications Group
Yann Grosse, Section of *IARC Monographs*
Neela Guha, Section of *IARC Monographs*
Ghassan Hamra, Section of Environment and Radiation
Marie-Eve Héroux, WHO European Centre for Environment and Health, Germany
Béatrice Lauby-Secretan, Section of *IARC Monographs*
Dana Loomis, Section of *IARC Monographs* (Responsible Officer)
Heidi Mattock, Section of *IARC Monographs* (Editor)
Fiona McKenzie, Section of Nutrition and Metabolism
Christopher J. Portier, Visiting Scientist, Section of *IARC Monographs*
Isabelle Romieu, Section of Nutrition and Metabolism
Kurt Straif, Section of *IARC Monographs* (Section Head)
Véronique Terrasse, Communications Group

[10] David Morgott is owner and sole proprietor of Pennsport Consulting, LLC, Philadelphia, PA. His participation is sponsored by CONCAWE, Belgium.
[11] Rashid Shaikh is the Director of Science of the Health Effects Institute (HEI), which conducts research worldwide on the health effects of air pollution. The Institute's core funding comes in equal part from the United States Environmental Protection Agency and the makers of motor vehicles for sale in the USA.
[12] John Andrew Tomenson is director of Causation Ltd, UK, and has consulted for the Lower Olefins Sector Group of Cefic, The European Chemical Industry Council, and the Lower Olefins Aromatics REACH Consortium. His participation is sponsored by CONCAWE, Belgium.

Administrative Assistance

Sandrine Egraz
Brigitte Kajo
Michel Javin
Annick Leroux
Helene Lorenzen-Augros

Production Team

Elisabeth Elbers
Solène Quennehen
Dorothy Russell

Post-Meeting Assistance

Wiebke Mohr
Karen Müller (Scientific Editor for Volume 109)

PREAMBLE

The Preamble to the IARC Monographs describes the objective and scope of the programme, the scientific principles and procedures used in developing a Monograph, the types of evidence considered and the scientific criteria that guide the evaluations. The Preamble should be consulted when reading a Monograph or list of evaluations.

A. GENERAL PRINCIPLES AND PROCEDURES

1. Background

Soon after IARC was established in 1965, it received frequent requests for advice on the carcinogenic risk of chemicals, including requests for lists of known and suspected human carcinogens. It was clear that it would not be a simple task to summarize adequately the complexity of the information that was available, and IARC began to consider means of obtaining international expert opinion on this topic. In 1970, the IARC Advisory Committee on Environmental Carcinogenesis recommended '... that a compendium on carcinogenic chemicals be prepared by experts. The biological activity and evaluation of practical importance to public health should be referenced and documented.' The IARC Governing Council adopted a resolution concerning the role of IARC in providing government authorities with expert, independent, scientific opinion on environmental carcinogenesis. As one means to that end, the Governing Council recommended that IARC should prepare monographs on the evaluation of carcinogenic risk of chemicals to man, which became the initial title of the series.

In the succeeding years, the scope of the programme broadened as *Monographs* were developed for groups of related chemicals, complex mixtures, occupational exposures, physical and biological agents and lifestyle factors. In 1988, the phrase 'of chemicals' was dropped from the title, which assumed its present form, *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*.

Through the *Monographs* programme, IARC seeks to identify the causes of human cancer. This is the first step in cancer prevention, which is needed as much today as when IARC was established. The global burden of cancer is high and continues to increase: the annual number of new cases was estimated at 10.1 million in 2000 and is expected to reach 15 million by 2020 (Stewart & Kleihues, 2003). With current trends in demographics and exposure, the cancer burden has been shifting from high-resource countries to low- and medium-resource countries. As a result of *Monographs* evaluations, national health agencies have been able, on scientific grounds, to take measures to reduce human exposure to carcinogens in the workplace and in the environment.

The criteria established in 1971 to evaluate carcinogenic risks to humans were adopted by the Working Groups whose deliberations resulted in the first 16 volumes of the *Monographs* series. Those criteria were subsequently updated by further ad hoc Advisory Groups (IARC, 1977, 1978, 1979, 1982, 1983, 1987, 1988, 1991; Vainio et al., 1992; IARC, 2005, 2006).

The Preamble is primarily a statement of scientific principles, rather than a specification of working procedures. The procedures through which a Working Group implements these principles are not specified in detail. They usually involve operations that have been established as being effective during previous *Monograph* meetings but remain, predominantly, the prerogative of each individual Working Group.

2. Objective and scope

The objective of the programme is to prepare, with the help of international Working Groups of experts, and to publish in the form of *Monographs*, critical reviews and evaluations of evidence on the carcinogenicity of a wide range of human exposures. The *Monographs* represent the first step in carcinogen risk assessment, which involves examination of all relevant information to assess the strength of the available evidence that an agent could alter the age-specific incidence of cancer in humans. The *Monographs* may also indicate where additional research efforts are needed, specifically when data immediately relevant to an evaluation are not available.

In this Preamble, the term 'agent' refers to any entity or circumstance that is subject to evaluation in a *Monograph*. As the scope of the programme has broadened, categories of agents now include specific chemicals, groups of related chemicals, complex mixtures, occupational or environmental exposures, cultural or behavioural practices, biological organisms and physical agents. This list of categories may expand as causation of, and susceptibility to, malignant disease become more fully understood.

A cancer 'hazard' is an agent that is capable of causing cancer under some circumstances, while a cancer 'risk' is an estimate of the carcinogenic effects expected from exposure to a cancer hazard. The *Monographs* are an exercise in evaluating cancer hazards, despite the historical presence of the word 'risks' in the title. The distinction between hazard and risk is important, and the *Monographs* identify cancer hazards even when risks are very low at current exposure levels, because new uses or unforeseen exposures could engender risks that are significantly higher.

In the *Monographs*, an agent is termed 'carcinogenic' if it is capable of increasing the incidence of malignant neoplasms, reducing their latency, or increasing their severity or multiplicity. The induction of benign neoplasms may in some circumstances (see Part B, Section 3a) contribute to the judgement that the agent is carcinogenic. The terms 'neoplasm' and 'tumour' are used interchangeably.

The Preamble continues the previous usage of the phrase 'strength of evidence' as a matter of historical continuity, although it should be understood that *Monographs* evaluations consider studies that support a finding of a cancer hazard as well as studies that do not.

Some epidemiological and experimental studies indicate that different agents may act at different stages in the carcinogenic process, and several different mechanisms may be involved. The aim of the *Monographs* has been, from their inception, to evaluate evidence of carcinogenicity at any stage in the carcinogenesis process, independently of the underlying mechanisms. Information on mechanisms may, however, be used in making the overall evaluation (IARC, 1991; Vainio et al., 1992; IARC, 2005, 2006; see also Part B, Sections 4 and 6). As mechanisms of carcinogenesis are elucidated, IARC convenes international scientific conferences to determine whether a broad-based consensus has emerged

on how specific mechanistic data can be used in an evaluation of human carcinogenicity. The results of such conferences are reported in IARC Scientific Publications, which, as long as they still reflect the current state of scientific knowledge, may guide subsequent Working Groups.

Although the *Monographs* have emphasized hazard identification, important issues may also involve dose–response assessment. In many cases, the same epidemiological and experimental studies used to evaluate a cancer hazard can also be used to estimate a dose–response relationship. A *Monograph* may undertake to estimate dose–response relationships within the range of the available epidemiological data, or it may compare the dose–response information from experimental and epidemiological studies. In some cases, a subsequent publication may be prepared by a separate Working Group with expertise in quantitative dose–response assessment.

The *Monographs* are used by national and international authorities to make risk assessments, formulate decisions concerning preventive measures, provide effective cancer control programmes and decide among alternative options for public health decisions. The evaluations of IARC Working Groups are scientific, qualitative judgements on the evidence for or against carcinogenicity provided by the available data. These evaluations represent only one part of the body of information on which public health decisions may be based. Public health options vary from one situation to another and from country to country and relate to many factors, including different socioeconomic and national priorities. Therefore, no recommendation is given with regard to regulation or legislation, which are the responsibility of individual governments or other international organizations.

3. Selection of agents for review

Agents are selected for review on the basis of two main criteria: (a) there is evidence of human exposure and (b) there is some evidence or suspicion of carcinogenicity. Mixed exposures may occur in occupational and environmental settings and as a result of individual and cultural habits (such as tobacco smoking and dietary practices). Chemical analogues and compounds with biological or physical characteristics similar to those of suspected carcinogens may also be considered, even in the absence of data on a possible carcinogenic effect in humans or experimental animals.

The scientific literature is surveyed for published data relevant to an assessment of carcinogenicity. Ad hoc Advisory Groups convened by IARC in 1984, 1989, 1991, 1993, 1998 and 2003 made recommendations as to which agents should be evaluated in the *Monographs* series. Recent recommendations are available on the *Monographs* programme web site (http://monographs.iarc.fr). IARC may schedule other agents for review as it becomes aware of new scientific information or as national health agencies identify an urgent public health need related to cancer.

As significant new data become available on an agent for which a *Monograph* exists, a re-evaluation may be made at a subsequent meeting, and a new *Monograph* published. In some cases it may be appropriate to review only the data published since a prior evaluation. This can be useful for updating a database, reviewing new data to resolve a previously open question or identifying new tumour sites associated with a carcinogenic agent. Major changes in an evaluation (e.g. a new classification in Group 1 or a determination that a mechanism does not operate in humans, see Part B, Section 6) are more appropriately addressed by a full review.

4. Data for the *Monographs*

Each *Monograph* reviews all pertinent epidemiological studies and cancer bioassays in experimental animals. Those judged inadequate or irrelevant to the evaluation may be cited but not summarized. If a group of similar studies is not reviewed, the reasons are indicated.

Mechanistic and other relevant data are also reviewed. A *Monograph* does not necessarily cite all the mechanistic literature concerning the agent being evaluated (see Part B, Section 4). Only those data considered by the Working Group to be relevant to making the evaluation are included.

With regard to epidemiological studies, cancer bioassays, and mechanistic and other relevant data, only reports that have been published or accepted for publication in the openly available scientific literature are reviewed. The same publication requirement applies to studies originating from IARC, including meta-analyses or pooled analyses commissioned by IARC in advance of a meeting (see Part B, Section 2c). Data from government agency reports that are publicly available are also considered. Exceptionally, doctoral theses and other material that are in their final form and publicly available may be reviewed.

Exposure data and other information on an agent under consideration are also reviewed. In the sections on chemical and physical properties, on analysis, on production and use and on occurrence, published and unpublished sources of information may be considered.

Inclusion of a study does not imply acceptance of the adequacy of the study design or of the analysis and interpretation of the results, and limitations are clearly outlined in square brackets at the end of each study description (see Part B). The reasons for not giving further consideration to an individual study also are indicated in the square brackets.

5. Meeting participants

Five categories of participant can be present at *Monograph* meetings.

(a) The Working Group

The Working Group is responsible for the critical reviews and evaluations that are developed during the meeting. The tasks of Working Group Members are: (i) to ascertain that all appropriate data have been collected; (ii) to select the data relevant for the evaluation on the basis of scientific merit; (iii) to prepare accurate summaries of the data to enable the reader to follow the reasoning of the Working Group; (iv) to evaluate the results of epidemiological and experimental studies on cancer; (v) to evaluate data relevant to the understanding of mechanisms of carcinogenesis; and (vi) to make an overall evaluation of the carcinogenicity of the exposure to humans. Working Group Members generally have published significant research related to the carcinogenicity of the agents being reviewed, and IARC uses literature searches to identify most experts. Working Group Members are selected on the basis of (a) knowledge and experience and (b) absence of real or apparent conflicts of interests. Consideration is also given to demographic diversity and balance of scientific findings and views.

(b) Invited Specialists

Invited Specialists are experts who also have critical knowledge and experience but have a real or apparent conflict of interests. These experts are invited when necessary to assist in the Working Group by contributing their unique knowledge and experience during subgroup and plenary discussions. They may also contribute text on non-influential issues in the section on exposure, such as a general description of data on production and use (see Part B, Section 1). Invited Specialists do not serve as meeting chair

or subgroup chair, draft text that pertains to the description or interpretation of cancer data, or participate in the evaluations.

(c) Representatives of national and international health agencies

Representatives of national and international health agencies often attend meetings because their agencies sponsor the programme or are interested in the subject of a meeting. Representatives do not serve as meeting chair or subgroup chair, draft any part of a *Monograph*, or participate in the evaluations.

(d) Observers with relevant scientific credentials

Observers with relevant scientific credentials may be admitted to a meeting by IARC in limited numbers. Attention will be given to achieving a balance of Observers from constituencies with differing perspectives. They are invited to observe the meeting and should not attempt to influence it. Observers do not serve as meeting chair or subgroup chair, draft any part of a *Monograph*, or participate in the evaluations. At the meeting, the meeting chair and subgroup chairs may grant Observers an opportunity to speak, generally after they have observed a discussion. Observers agree to respect the Guidelines for Observers at *IARC Monographs* meetings (available at http://monographs.iarc.fr).

(e) The IARC Secretariat

The IARC Secretariat consists of scientists who are designated by IARC and who have relevant expertise. They serve as rapporteurs and participate in all discussions. When requested by the meeting chair or subgroup chair, they may also draft text or prepare tables and analyses.

Before an invitation is extended, each potential participant, including the IARC Secretariat, completes the WHO Declaration of Interests to report financial interests, employment and consulting, and individual and institutional research support related to the subject of the meeting. IARC assesses these interests to determine whether there is a conflict that warrants some limitation on participation. The declarations are updated and reviewed again at the opening of the meeting. Interests related to the subject of the meeting are disclosed to the meeting participants and in the published volume (Cogliano et al., 2004).

The names and principal affiliations of participants are available on the *Monographs* programme web site (http://monographs.iarc.fr) approximately two months before each meeting. It is not acceptable for Observers or third parties to contact other participants before a meeting or to lobby them at any time. Meeting participants are asked to report all such contacts to IARC (Cogliano et al., 2005).

All participants are listed, with their principal affiliations, at the beginning of each volume. Each participant who is a Member of a Working Group serves as an individual scientist and not as a representative of any organization, government or industry.

6. Working procedures

A separate Working Group is responsible for developing each volume of *Monographs*. A volume contains one or more *Monographs*, which can cover either a single agent or several related agents. Approximately one year in advance of the meeting of a Working Group, the agents to be reviewed are announced on the *Monographs* programme web site (http://monographs.iarc.fr) and participants are selected by IARC staff in consultation with other experts. Subsequently, relevant biological and epidemiological data are collected by IARC from recognized sources of information on carcinogenesis, including data storage and retrieval systems such as PubMed. Meeting participants who are asked to prepare

preliminary working papers for specific sections are expected to supplement the IARC literature searches with their own searches.

Industrial associations, labour unions and other knowledgeable organizations may be asked to provide input to the sections on production and use, although this involvement is not required as a general rule. Information on production and trade is obtained from governmental, trade and market research publications and, in some cases, by direct contact with industries. Separate production data on some agents may not be available for a variety of reasons (e.g. not collected or made public in all producing countries, production is small). Information on uses may be obtained from published sources but is often complemented by direct contact with manufacturers. Efforts are made to supplement this information with data from other national and international sources.

Six months before the meeting, the material obtained is sent to meeting participants to prepare preliminary working papers. The working papers are compiled by IARC staff and sent, before the meeting, to Working Group Members and Invited Specialists for review.

The Working Group meets at IARC for seven to eight days to discuss and finalize the texts and to formulate the evaluations. The objectives of the meeting are peer review and consensus. During the first few days, four subgroups (covering exposure data, cancer in humans, cancer in experimental animals, and mechanistic and other relevant data) review the working papers, develop a joint subgroup draft and write summaries. Care is taken to ensure that each study summary is written or reviewed by someone not associated with the study being considered. During the last few days, the Working Group meets in plenary session to review the subgroup drafts and develop the evaluations. As a result, the entire volume is the joint product of the Working Group, and there are no individually authored sections.

IARC Working Groups strive to achieve a consensus evaluation. Consensus reflects broad agreement among Working Group Members, but not necessarily unanimity. The chair may elect to poll Working Group Members to determine the diversity of scientific opinion on issues where consensus is not readily apparent.

After the meeting, the master copy is verified by consulting the original literature, edited and prepared for publication. The aim is to publish the volume within six months of the Working Group meeting. A summary of the outcome is available on the *Monographs* programme web site soon after the meeting.

B. SCIENTIFIC REVIEW AND EVALUATION

The available studies are summarized by the Working Group, with particular regard to the qualitative aspects discussed below. In general, numerical findings are indicated as they appear in the original report; units are converted when necessary for easier comparison. The Working Group may conduct additional analyses of the published data and use them in their assessment of the evidence; the results of such supplementary analyses are given in square brackets. When an important aspect of a study that directly impinges on its interpretation should be brought to the attention of the reader, a Working Group comment is given in square brackets.

The scope of the *IARC Monographs* programme has expanded beyond chemicals to include complex mixtures, occupational exposures, physical and biological agents, lifestyle factors and other potentially carcinogenic exposures. Over time, the structure of a *Monograph* has evolved to include the following sections:

Exposure data

Studies of cancer in humans

Studies of cancer in experimental animals

Mechanistic and other relevant data

Summary

Evaluation and rationale

In addition, a section of General Remarks at the front of the volume discusses the reasons the agents were scheduled for evaluation and some key issues the Working Group encountered during the meeting.

This part of the Preamble discusses the types of evidence considered and summarized in each section of a *Monograph*, followed by the scientific criteria that guide the evaluations.

1. Exposure data

Each *Monograph* includes general information on the agent: this information may vary substantially between agents and must be adapted accordingly. Also included is information on production and use (when appropriate), methods of analysis and detection, occurrence, and sources and routes of human occupational and environmental exposures. Depending on the agent, regulations and guidelines for use may be presented.

(a) General information on the agent

For chemical agents, sections on chemical and physical data are included: the Chemical Abstracts Service Registry Number, the latest primary name and the IUPAC systematic name are recorded; other synonyms are given, but the list is not necessarily comprehensive. Information on chemical and physical properties that are relevant to identification, occurrence and biological activity is included. A description of technical products of chemicals includes trade names, relevant specifications and available information on composition and impurities. Some of the trade names given may be those of mixtures in which the agent being evaluated is only one of the ingredients.

For biological agents, taxonomy, structure and biology are described, and the degree of variability is indicated. Mode of replication, life cycle, target cells, persistence, latency, host response and clinical disease other than cancer are also presented.

For physical agents that are forms of radiation, energy and range of the radiation are included. For foreign bodies, fibres and respirable particles, size range and relative dimensions are indicated.

For agents such as mixtures, drugs or lifestyle factors, a description of the agent, including its composition, is given.

Whenever appropriate, other information, such as historical perspectives or the description of an industry or habit, may be included.

(b) Analysis and detection

An overview of methods of analysis and detection of the agent is presented, including their sensitivity, specificity and reproducibility. Methods widely used for regulatory purposes are emphasized. Methods for monitoring human exposure are also given. No critical evaluation or recommendation of any method is meant or implied.

(c) Production and use

The dates of first synthesis and of first commercial production of a chemical, mixture or other agent are provided when available; for agents that do not occur naturally, this information may allow a reasonable estimate to be made of the date before which no human exposure to the agent could have occurred. The dates of first reported occurrence of an exposure are also provided when available. In addition, methods of synthesis used in past and present commercial production and different methods of production,

which may give rise to different impurities, are described.

The countries where companies report production of the agent, and the number of companies in each country, are identified. Available data on production, international trade and uses are obtained for representative regions. It should not, however, be inferred that those areas or nations are necessarily the sole or major sources or users of the agent. Some identified uses may not be current or major applications, and the coverage is not necessarily comprehensive. In the case of drugs, mention of their therapeutic uses does not necessarily represent current practice nor does it imply judgement as to their therapeutic efficacy.

(d) Occurrence and exposure

Information on the occurrence of an agent in the environment is obtained from data derived from the monitoring and surveillance of levels in occupational environments, air, water, soil, plants, foods and animal and human tissues. When available, data on the generation, persistence and bioaccumulation of the agent are also included. Such data may be available from national databases.

Data that indicate the extent of past and present human exposure, the sources of exposure, the people most likely to be exposed and the factors that contribute to the exposure are reported. Information is presented on the range of human exposure, including occupational and environmental exposures. This includes relevant findings from both developed and developing countries. Some of these data are not distributed widely and may be available from government reports and other sources. In the case of mixtures, industries, occupations or processes, information is given about all agents known to be present. For processes, industries and occupations, a historical description is also given, noting variations in chemical composition, physical properties and levels of occupational exposure with date and place. For biological agents, the epidemiology of infection is described.

(e) Regulations and guidelines

Statements concerning regulations and guidelines (e.g. occupational exposure limits, maximal levels permitted in foods and water, pesticide registrations) are included, but they may not reflect the most recent situation, since such limits are continuously reviewed and modified. The absence of information on regulatory status for a country should not be taken to imply that that country does not have regulations with regard to the exposure. For biological agents, legislation and control, including vaccination and therapy, are described.

2. Studies of cancer in humans

This section includes all pertinent epidemiological studies (see Part A, Section 4). Studies of biomarkers are included when they are relevant to an evaluation of carcinogenicity to humans.

(a) Types of study considered

Several types of epidemiological study contribute to the assessment of carcinogenicity in humans — cohort studies, case–control studies, correlation (or ecological) studies and intervention studies. Rarely, results from randomized trials may be available. Case reports and case series of cancer in humans may also be reviewed.

Cohort and case–control studies relate individual exposures under study to the occurrence of cancer in individuals and provide an estimate of effect (such as relative risk) as the main measure of association. Intervention studies may provide strong evidence for making causal inferences, as exemplified by cessation of smoking and the subsequent decrease in risk for lung cancer.

In correlation studies, the units of investigation are usually whole populations (e.g. in

particular geographical areas or at particular times), and cancer frequency is related to a summary measure of the exposure of the population to the agent under study. In correlation studies, individual exposure is not documented, which renders this kind of study more prone to confounding. In some circumstances, however, correlation studies may be more informative than analytical study designs (see, for example, the *Monograph* on arsenic in drinking-water; IARC, 2004).

In some instances, case reports and case series have provided important information about the carcinogenicity of an agent. These types of study generally arise from a suspicion, based on clinical experience, that the concurrence of two events — that is, a particular exposure and occurrence of a cancer — has happened rather more frequently than would be expected by chance. Case reports and case series usually lack complete ascertainment of cases in any population, definition or enumeration of the population at risk and estimation of the expected number of cases in the absence of exposure.

The uncertainties that surround the interpretation of case reports, case series and correlation studies make them inadequate, except in rare instances, to form the sole basis for inferring a causal relationship. When taken together with case–control and cohort studies, however, these types of study may add materially to the judgement that a causal relationship exists.

Epidemiological studies of benign neoplasms, presumed preneoplastic lesions and other end-points thought to be relevant to cancer are also reviewed. They may, in some instances, strengthen inferences drawn from studies of cancer itself.

(b) Quality of studies considered

It is necessary to take into account the possible roles of bias, confounding and chance in the interpretation of epidemiological studies. Bias is the effect of factors in study design or execution that lead erroneously to a stronger or weaker association than in fact exists between an agent and disease. Confounding is a form of bias that occurs when the relationship with disease is made to appear stronger or weaker than it truly is as a result of an association between the apparent causal factor and another factor that is associated with either an increase or decrease in the incidence of the disease. The role of chance is related to biological variability and the influence of sample size on the precision of estimates of effect.

In evaluating the extent to which these factors have been minimized in an individual study, consideration is given to several aspects of design and analysis as described in the report of the study. For example, when suspicion of carcinogenicity arises largely from a single small study, careful consideration is given when interpreting subsequent studies that included these data in an enlarged population. Most of these considerations apply equally to case–control, cohort and correlation studies. Lack of clarity of any of these aspects in the reporting of a study can decrease its credibility and the weight given to it in the final evaluation of the exposure.

First, the study population, disease (or diseases) and exposure should have been well defined by the authors. Cases of disease in the study population should have been identified in a way that was independent of the exposure of interest, and exposure should have been assessed in a way that was not related to disease status.

Second, the authors should have taken into account — in the study design and analysis — other variables that can influence the risk of disease and may have been related to the exposure of interest. Potential confounding by such variables should have been dealt with either in the design of the study, such as by matching, or in the analysis, by statistical adjustment. In cohort studies, comparisons with local rates of disease may or may not be more appropriate than

those with national rates. Internal comparisons of frequency of disease among individuals at different levels of exposure are also desirable in cohort studies, since they minimize the potential for confounding related to the difference in risk factors between an external reference group and the study population.

Third, the authors should have reported the basic data on which the conclusions are founded, even if sophisticated statistical analyses were employed. At the very least, they should have given the numbers of exposed and unexposed cases and controls in a case–control study and the numbers of cases observed and expected in a cohort study. Further tabulations by time since exposure began and other temporal factors are also important. In a cohort study, data on all cancer sites and all causes of death should have been given, to reveal the possibility of reporting bias. In a case–control study, the effects of investigated factors other than the exposure of interest should have been reported.

Finally, the statistical methods used to obtain estimates of relative risk, absolute rates of cancer, confidence intervals and significance tests, and to adjust for confounding should have been clearly stated by the authors. These methods have been reviewed for case–control studies (Breslow & Day, 1980) and for cohort studies (Breslow & Day, 1987).

(c) Meta-analyses and pooled analyses

Independent epidemiological studies of the same agent may lead to results that are difficult to interpret. Combined analyses of data from multiple studies are a means of resolving this ambiguity, and well conducted analyses can be considered. There are two types of combined analysis. The first involves combining summary statistics such as relative risks from individual studies (meta-analysis) and the second involves a pooled analysis of the raw data from the individual studies (pooled analysis) (Greenland, 1998).

The advantages of combined analyses are increased precision due to increased sample size and the opportunity to explore potential confounders, interactions and modifying effects that may explain heterogeneity among studies in more detail. A disadvantage of combined analyses is the possible lack of compatibility of data from various studies due to differences in subject recruitment, procedures of data collection, methods of measurement and effects of unmeasured co-variates that may differ among studies. Despite these limitations, well conducted combined analyses may provide a firmer basis than individual studies for drawing conclusions about the potential carcinogenicity of agents.

IARC may commission a meta-analysis or pooled analysis that is pertinent to a particular *Monograph* (see Part A, Section 4). Additionally, as a means of gaining insight from the results of multiple individual studies, ad hoc calculations that combine data from different studies may be conducted by the Working Group during the course of a *Monograph* meeting. The results of such original calculations, which would be specified in the text by presentation in square brackets, might involve updates of previously conducted analyses that incorporate the results of more recent studies or de-novo analyses. Irrespective of the source of data for the meta-analyses and pooled analyses, it is important that the same criteria for data quality be applied as those that would be applied to individual studies and to ensure also that sources of heterogeneity between studies be taken into account.

(d) Temporal effects

Detailed analyses of both relative and absolute risks in relation to temporal variables, such as age at first exposure, time since first exposure, duration of exposure, cumulative exposure, peak exposure (when appropriate) and

time since cessation of exposure, are reviewed and summarized when available. Analyses of temporal relationships may be useful in making causal inferences. In addition, such analyses may suggest whether a carcinogen acts early or late in the process of carcinogenesis, although, at best, they allow only indirect inferences about mechanisms of carcinogenesis.

(e) Use of biomarkers in epidemiological studies

Biomarkers indicate molecular, cellular or other biological changes and are increasingly used in epidemiological studies for various purposes (IARC, 1991; Vainio et al., 1992; Toniolo et al., 1997; Vineis et al., 1999; Buffler et al., 2004). These may include evidence of exposure, of early effects, of cellular, tissue or organism responses, of individual susceptibility or host responses, and inference of a mechanism (see Part B, Section 4b). This is a rapidly evolving field that encompasses developments in genomics, epigenomics and other emerging technologies.

Molecular epidemiological data that identify associations between genetic polymorphisms and interindividual differences in susceptibility to the agent(s) being evaluated may contribute to the identification of carcinogenic hazards to humans. If the polymorphism has been demonstrated experimentally to modify the functional activity of the gene product in a manner that is consistent with increased susceptibility, these data may be useful in making causal inferences. Similarly, molecular epidemiological studies that measure cell functions, enzymes or metabolites that are thought to be the basis of susceptibility may provide evidence that reinforces biological plausibility. It should be noted, however, that when data on genetic susceptibility originate from multiple comparisons that arise from subgroup analyses, this can generate false-positive results and inconsistencies across studies, and such data therefore require careful evaluation. If the known phenotype of a genetic polymorphism can explain the carcinogenic mechanism of the agent being evaluated, data on this phenotype may be useful in making causal inferences.

(f) Criteria for causality

After the quality of individual epidemiological studies of cancer has been summarized and assessed, a judgement is made concerning the strength of evidence that the agent in question is carcinogenic to humans. In making its judgement, the Working Group considers several criteria for causality (Hill, 1965). A strong association (e.g. a large relative risk) is more likely to indicate causality than a weak association, although it is recognized that estimates of effect of small magnitude do not imply lack of causality and may be important if the disease or exposure is common. Associations that are replicated in several studies of the same design or that use different epidemiological approaches or under different circumstances of exposure are more likely to represent a causal relationship than isolated observations from single studies. If there are inconsistent results among investigations, possible reasons are sought (such as differences in exposure), and results of studies that are judged to be of high quality are given more weight than those of studies that are judged to be methodologically less sound.

If the risk increases with the exposure, this is considered to be a strong indication of causality, although the absence of a graded response is not necessarily evidence against a causal relationship. The demonstration of a decline in risk after cessation of or reduction in exposure in individuals or in whole populations also supports a causal interpretation of the findings.

Several scenarios may increase confidence in a causal relationship. On the one hand, an agent may be specific in causing tumours at one site or of one morphological type. On the other, carcinogenicity may be evident through the causation of

multiple tumour types. Temporality, precision of estimates of effect, biological plausibility and coherence of the overall database are considered. Data on biomarkers may be employed in an assessment of the biological plausibility of epidemiological observations.

Although rarely available, results from randomized trials that show different rates of cancer among exposed and unexposed individuals provide particularly strong evidence for causality.

When several epidemiological studies show little or no indication of an association between an exposure and cancer, a judgement may be made that, in the aggregate, they show evidence of lack of carcinogenicity. Such a judgement requires first that the studies meet, to a sufficient degree, the standards of design and analysis described above. Specifically, the possibility that bias, confounding or misclassification of exposure or outcome could explain the observed results should be considered and excluded with reasonable certainty. In addition, all studies that are judged to be methodologically sound should (a) be consistent with an estimate of effect of unity for any observed level of exposure, (b) when considered together, provide a pooled estimate of relative risk that is at or near to unity, and (c) have a narrow confidence interval, due to sufficient population size. Moreover, no individual study nor the pooled results of all the studies should show any consistent tendency that the relative risk of cancer increases with increasing level of exposure. It is important to note that evidence of lack of carcinogenicity obtained from several epidemiological studies can apply only to the type(s) of cancer studied, to the dose levels reported, and to the intervals between first exposure and disease onset observed in these studies. Experience with human cancer indicates that the period from first exposure to the development of clinical cancer is sometimes longer than 20 years; latent periods substantially shorter than 30 years cannot provide evidence for lack of carcinogenicity.

3. Studies of cancer in experimental animals

All known human carcinogens that have been studied adequately for carcinogenicity in experimental animals have produced positive results in one or more animal species (Wilbourn et al., 1986; Tomatis et al., 1989). For several agents (e.g. aflatoxins, diethylstilbestrol, solar radiation, vinyl chloride), carcinogenicity in experimental animals was established or highly suspected before epidemiological studies confirmed their carcinogenicity in humans (Vainio et al., 1995). Although this association cannot establish that all agents that cause cancer in experimental animals also cause cancer in humans, it is biologically plausible that agents for which there is *sufficient evidence of carcinogenicity* in experimental animals (see Part B, Section 6b) also present a carcinogenic hazard to humans. Accordingly, in the absence of additional scientific information, these agents are considered to pose a carcinogenic hazard to humans. Examples of additional scientific information are data that demonstrate that a given agent causes cancer in animals through a species-specific mechanism that does not operate in humans or data that demonstrate that the mechanism in experimental animals also operates in humans (see Part B, Section 6).

Consideration is given to all available long-term studies of cancer in experimental animals with the agent under review (see Part A, Section 4). In all experimental settings, the nature and extent of impurities or contaminants present in the agent being evaluated are given when available. Animal species, strain (including genetic background where applicable), sex, numbers per group, age at start of treatment, route of exposure, dose levels, duration of exposure, survival and information on tumours (incidence, latency, severity or multiplicity of neoplasms or preneoplastic lesions) are reported. Those studies in experimental animals that are judged to be irrelevant to the evaluation or judged to be inadequate

(e.g. too short a duration, too few animals, poor survival; see below) may be omitted. Guidelines for conducting long-term carcinogenicity experiments have been published (e.g. OECD, 2002).

Other studies considered may include: experiments in which the agent was administered in the presence of factors that modify carcinogenic effects (e.g. initiation–promotion studies, co-carcinogenicity studies and studies in genetically modified animals); studies in which the end-point was not cancer but a defined precancerous lesion; experiments on the carcinogenicity of known metabolites and derivatives; and studies of cancer in non-laboratory animals (e.g. livestock and companion animals) exposed to the agent.

For studies of mixtures, consideration is given to the possibility that changes in the physicochemical properties of the individual substances may occur during collection, storage, extraction, concentration and delivery. Another consideration is that chemical and toxicological interactions of components in a mixture may alter dose–response relationships. The relevance to human exposure of the test mixture administered in the animal experiment is also assessed. This may involve consideration of the following aspects of the mixture tested: (i) physical and chemical characteristics, (ii) identified constituents that may indicate the presence of a class of substances and (iii) the results of genetic toxicity and related tests.

The relevance of results obtained with an agent that is analogous (e.g. similar in structure or of a similar virus genus) to that being evaluated is also considered. Such results may provide biological and mechanistic information that is relevant to the understanding of the process of carcinogenesis in humans and may strengthen the biological plausibility that the agent being evaluated is carcinogenic to humans (see Part B, Section 2f).

(a) Qualitative aspects

An assessment of carcinogenicity involves several considerations of qualitative importance, including (i) the experimental conditions under which the test was performed, including route, schedule and duration of exposure, species, strain (including genetic background where applicable), sex, age and duration of follow-up; (ii) the consistency of the results, for example, across species and target organ(s); (iii) the spectrum of neoplastic response, from preneoplastic lesions and benign tumours to malignant neoplasms; and (iv) the possible role of modifying factors.

Considerations of importance in the interpretation and evaluation of a particular study include: (i) how clearly the agent was defined and, in the case of mixtures, how adequately the sample characterization was reported; (ii) whether the dose was monitored adequately, particularly in inhalation experiments; (iii) whether the doses, duration of treatment and route of exposure were appropriate; (iv) whether the survival of treated animals was similar to that of controls; (v) whether there were adequate numbers of animals per group; (vi) whether both male and female animals were used; (vii) whether animals were allocated randomly to groups; (viii) whether the duration of observation was adequate; and (ix) whether the data were reported and analysed adequately.

When benign tumours (a) occur together with and originate from the same cell type as malignant tumours in an organ or tissue in a particular study and (b) appear to represent a stage in the progression to malignancy, they are usually combined in the assessment of tumour incidence (Huff et al., 1989). The occurrence of lesions presumed to be preneoplastic may in certain instances aid in assessing the biological plausibility of any neoplastic response observed. If an agent induces only benign neoplasms that appear to be end-points that do not readily undergo transition to malignancy, the agent

should nevertheless be suspected of being carcinogenic and requires further investigation.

(b) Quantitative aspects

The probability that tumours will occur may depend on the species, sex, strain, genetic background and age of the animal, and on the dose, route, timing and duration of the exposure. Evidence of an increased incidence of neoplasms with increasing levels of exposure strengthens the inference of a causal association between the exposure and the development of neoplasms.

The form of the dose–response relationship can vary widely, depending on the particular agent under study and the target organ. Mechanisms such as induction of DNA damage or inhibition of repair, altered cell division and cell death rates and changes in intercellular communication are important determinants of dose–response relationships for some carcinogens. Since many chemicals require metabolic activation before being converted to their reactive intermediates, both metabolic and toxicokinetic aspects are important in determining the dose–response pattern. Saturation of steps such as absorption, activation, inactivation and elimination may produce nonlinearity in the dose–response relationship (Hoel et al., 1983; Gart et al., 1986), as could saturation of processes such as DNA repair. The dose–response relationship can also be affected by differences in survival among the treatment groups.

(c) Statistical analyses

Factors considered include the adequacy of the information given for each treatment group: (i) number of animals studied and number examined histologically, (ii) number of animals with a given tumour type and (iii) length of survival. The statistical methods used should be clearly stated and should be the generally accepted techniques refined for this purpose (Peto et al., 1980; Gart et al., 1986; Portier & Bailer, 1989; Bieler & Williams, 1993). The choice of the most appropriate statistical method requires consideration of whether or not there are differences in survival among the treatment groups; for example, reduced survival because of non-tumour-related mortality can preclude the occurrence of tumours later in life. When detailed information on survival is not available, comparisons of the proportions of tumour-bearing animals among the effective number of animals (alive at the time the first tumour was discovered) can be useful when significant differences in survival occur before tumours appear. The lethality of the tumour also requires consideration: for rapidly fatal tumours, the time of death provides an indication of the time of tumour onset and can be assessed using life-table methods; non-fatal or incidental tumours that do not affect survival can be assessed using methods such as the Mantel-Haenzel test for changes in tumour prevalence. Because tumour lethality is often difficult to determine, methods such as the Poly-K test that do not require such information can also be used. When results are available on the number and size of tumours seen in experimental animals (e.g. papillomas on mouse skin, liver tumours observed through nuclear magnetic resonance tomography), other more complicated statistical procedures may be needed (Sherman et al., 1994; Dunson et al., 2003).

Formal statistical methods have been developed to incorporate historical control data into the analysis of data from a given experiment. These methods assign an appropriate weight to historical and concurrent controls on the basis of the extent of between-study and within-study variability: less weight is given to historical controls when they show a high degree of variability, and greater weight when they show little variability. It is generally not appropriate to discount a tumour response that is significantly increased compared with concurrent controls by arguing that it falls within the range of historical controls, particularly

when historical controls show high between-study variability and are, thus, of little relevance to the current experiment. In analysing results for uncommon tumours, however, the analysis may be improved by considering historical control data, particularly when between-study variability is low. Historical controls should be selected to resemble the concurrent controls as closely as possible with respect to species, gender and strain, as well as other factors such as basal diet and general laboratory environment, which may affect tumour-response rates in control animals (Haseman et al., 1984; Fung et al., 1996; Greim et al., 2003).

Although meta-analyses and combined analyses are conducted less frequently for animal experiments than for epidemiological studies due to differences in animal strains, they can be useful aids in interpreting animal data when the experimental protocols are sufficiently similar.

4. Mechanistic and other relevant data

Mechanistic and other relevant data may provide evidence of carcinogenicity and also help in assessing the relevance and importance of findings of cancer in animals and in humans. The nature of the mechanistic and other relevant data depends on the biological activity of the agent being considered. The Working Group considers representative studies to give a concise description of the relevant data and issues that they consider to be important; thus, not every available study is cited. Relevant topics may include toxicokinetics, mechanisms of carcinogenesis, susceptible individuals, populations and life-stages, other relevant data and other adverse effects. When data on biomarkers are informative about the mechanisms of carcinogenesis, they are included in this section.

These topics are not mutually exclusive; thus, the same studies may be discussed in more than one subsection. For example, a mutation in a gene that codes for an enzyme that metabolizes the agent under study could be discussed in the subsections on toxicokinetics, mechanisms and individual susceptibility if it also exists as an inherited polymorphism.

(a) Toxicokinetic data

Toxicokinetics refers to the absorption, distribution, metabolism and elimination of agents in humans, experimental animals and, where relevant, cellular systems. Examples of kinetic factors that may affect dose–response relationships include uptake, deposition, biopersistence and half-life in tissues, protein binding, metabolic activation and detoxification. Studies that indicate the metabolic fate of the agent in humans and in experimental animals are summarized briefly, and comparisons of data from humans and animals are made when possible. Comparative information on the relationship between exposure and the dose that reaches the target site may be important for the extrapolation of hazards between species and in clarifying the role of in-vitro findings.

(b) Data on mechanisms of carcinogenesis

To provide focus, the Working Group attempts to identify the possible mechanisms by which the agent may increase the risk of cancer. For each possible mechanism, a representative selection of key data from humans and experimental systems is summarized. Attention is given to gaps in the data and to data that suggests that more than one mechanism may be operating. The relevance of the mechanism to humans is discussed, in particular, when mechanistic data are derived from experimental model systems. Changes in the affected organs, tissues or cells can be divided into three non-exclusive levels as described below.

(i) Changes in physiology

Physiological changes refer to exposure-related modifications to the physiology and/or response of cells, tissues and organs. Examples of potentially adverse physiological changes include mitogenesis, compensatory cell division, escape from apoptosis and/or senescence, presence of inflammation, hyperplasia, metaplasia and/or preneoplasia, angiogenesis, alterations in cellular adhesion, changes in steroidal hormones and changes in immune surveillance.

(ii) Functional changes at the cellular level

Functional changes refer to exposure-related alterations in the signalling pathways used by cells to manage critical processes that are related to increased risk for cancer. Examples of functional changes include modified activities of enzymes involved in the metabolism of xenobiotics, alterations in the expression of key genes that regulate DNA repair, alterations in cyclin-dependent kinases that govern cell cycle progression, changes in the patterns of post-translational modifications of proteins, changes in regulatory factors that alter apoptotic rates, changes in the secretion of factors related to the stimulation of DNA replication and transcription and changes in gap–junction-mediated intercellular communication.

(iii) Changes at the molecular level

Molecular changes refer to exposure-related changes in key cellular structures at the molecular level, including, in particular, genotoxicity. Examples of molecular changes include formation of DNA adducts and DNA strand breaks, mutations in genes, chromosomal aberrations, aneuploidy and changes in DNA methylation patterns. Greater emphasis is given to irreversible effects.

The use of mechanistic data in the identification of a carcinogenic hazard is specific to the mechanism being addressed and is not readily described for every possible level and mechanism discussed above.

Genotoxicity data are discussed here to illustrate the key issues involved in the evaluation of mechanistic data.

Tests for genetic and related effects are described in view of the relevance of gene mutation and chromosomal aberration/aneuploidy to carcinogenesis (Vainio et al., 1992; McGregor et al., 1999). The adequacy of the reporting of sample characterization is considered and, when necessary, commented upon; with regard to complex mixtures, such comments are similar to those described for animal carcinogenicity tests. The available data are interpreted critically according to the end-points detected, which may include DNA damage, gene mutation, sister chromatid exchange, micronucleus formation, chromosomal aberrations and aneuploidy. The concentrations employed are given, and mention is made of whether the use of an exogenous metabolic system in vitro affected the test result. These data are listed in tabular form by phylogenetic classification.

Positive results in tests using prokaryotes, lower eukaryotes, insects, plants and cultured mammalian cells suggest that genetic and related effects could occur in mammals. Results from such tests may also give information on the types of genetic effect produced and on the involvement of metabolic activation. Some end-points described are clearly genetic in nature (e.g. gene mutations), while others are associated with genetic effects (e.g. unscheduled DNA synthesis). In-vitro tests for tumour promotion, cell transformation and gap–junction intercellular communication may be sensitive to changes that are not necessarily the result of genetic alterations but that may have specific relevance to the process of carcinogenesis. Critical appraisals of these tests have been published (Montesano et al., 1986; McGregor et al., 1999).

Genetic or other activity manifest in humans and experimental mammals is regarded to be of

greater relevance than that in other organisms. The demonstration that an agent can induce gene and chromosomal mutations in mammals in vivo indicates that it may have carcinogenic activity. Negative results in tests for mutagenicity in selected tissues from animals treated in vivo provide less weight, partly because they do not exclude the possibility of an effect in tissues other than those examined. Moreover, negative results in short-term tests with genetic end-points cannot be considered to provide evidence that rules out the carcinogenicity of agents that act through other mechanisms (e.g. receptor-mediated effects, cellular toxicity with regenerative cell division, peroxisome proliferation) (Vainio et al., 1992). Factors that may give misleading results in short-term tests have been discussed in detail elsewhere (Montesano et al., 1986; McGregor et al., 1999).

When there is evidence that an agent acts by a specific mechanism that does not involve genotoxicity (e.g. hormonal dysregulation, immune suppression, and formation of calculi and other deposits that cause chronic irritation), that evidence is presented and reviewed critically in the context of rigorous criteria for the operation of that mechanism in carcinogenesis (e.g. Capen et al., 1999).

For biological agents such as viruses, bacteria and parasites, other data relevant to carcinogenicity may include descriptions of the pathology of infection, integration and expression of viruses, and genetic alterations seen in human tumours. Other observations that might comprise cellular and tissue responses to infection, immune response and the presence of tumour markers are also considered.

For physical agents that are forms of radiation, other data relevant to carcinogenicity may include descriptions of damaging effects at the physiological, cellular and molecular level, as for chemical agents, and descriptions of how these effects occur. 'Physical agents' may also be considered to comprise foreign bodies, such as surgical implants of various kinds, and poorly soluble fibres, dusts and particles of various sizes, the pathogenic effects of which are a result of their physical presence in tissues or body cavities. Other relevant data for such materials may include characterization of cellular, tissue and physiological reactions to these materials and descriptions of pathological conditions other than neoplasia with which they may be associated.

(c) Other data relevant to mechanisms

A description is provided of any structure–activity relationships that may be relevant to an evaluation of the carcinogenicity of an agent, the toxicological implications of the physical and chemical properties, and any other data relevant to the evaluation that are not included elsewhere.

High-output data, such as those derived from gene expression microarrays, and high-throughput data, such as those that result from testing hundreds of agents for a single end-point, pose a unique problem for the use of mechanistic data in the evaluation of a carcinogenic hazard. In the case of high-output data, there is the possibility to overinterpret changes in individual end-points (e.g. changes in expression in one gene) without considering the consistency of that finding in the broader context of the other end-points (e.g. other genes with linked transcriptional control). High-output data can be used in assessing mechanisms, but all end-points measured in a single experiment need to be considered in the proper context. For high-throughput data, where the number of observations far exceeds the number of end-points measured, their utility for identifying common mechanisms across multiple agents is enhanced. These data can be used to identify mechanisms that not only seem plausible, but also have a consistent pattern of carcinogenic response across entire classes of related compounds.

(d) Susceptibility data

Individuals, populations and life-stages may have greater or lesser susceptibility to an agent, based on toxicokinetics, mechanisms of carcinogenesis and other factors. Examples of host and genetic factors that affect individual susceptibility include sex, genetic polymorphisms of genes involved in the metabolism of the agent under evaluation, differences in metabolic capacity due to life-stage or the presence of disease, differences in DNA repair capacity, competition for or alteration of metabolic capacity by medications or other chemical exposures, pre-existing hormonal imbalance that is exacerbated by a chemical exposure, a suppressed immune system, periods of higher-than-usual tissue growth or regeneration and genetic polymorphisms that lead to differences in behaviour (e.g. addiction). Such data can substantially increase the strength of the evidence from epidemiological data and enhance the linkage of in-vivo and in-vitro laboratory studies to humans.

(e) Data on other adverse effects

Data on acute, subchronic and chronic adverse effects relevant to the cancer evaluation are summarized. Adverse effects that confirm distribution and biological effects at the sites of tumour development, or alterations in physiology that could lead to tumour development, are emphasized. Effects on reproduction, embryonic and fetal survival and development are summarized briefly. The adequacy of epidemiological studies of reproductive outcome and genetic and related effects in humans is judged by the same criteria as those applied to epidemiological studies of cancer, but fewer details are given.

5. Summary

This section is a summary of data presented in the preceding sections. Summaries can be found on the *Monographs* programme web site (http://monographs.iarc.fr).

(a) Exposure data

Data are summarized, as appropriate, on the basis of elements such as production, use, occurrence and exposure levels in the workplace and environment and measurements in human tissues and body fluids. Quantitative data and time trends are given to compare exposures in different occupations and environmental settings. Exposure to biological agents is described in terms of transmission, prevalence and persistence of infection.

(b) Cancer in humans

Results of epidemiological studies pertinent to an assessment of human carcinogenicity are summarized. When relevant, case reports and correlation studies are also summarized. The target organ(s) or tissue(s) in which an increase in cancer was observed is identified. Dose–response and other quantitative data may be summarized when available.

(c) Cancer in experimental animals

Data relevant to an evaluation of carcinogenicity in animals are summarized. For each animal species, study design and route of administration, it is stated whether an increased incidence, reduced latency, or increased severity or multiplicity of neoplasms or preneoplastic lesions were observed, and the tumour sites are indicated. If the agent produced tumours after prenatal exposure or in single-dose experiments, this is also mentioned. Negative findings, inverse relationships, dose–response and other quantitative data are also summarized.

(d) Mechanistic and other relevant data

Data relevant to the toxicokinetics (absorption, distribution, metabolism, elimination) and the possible mechanism(s) of carcinogenesis (e.g. genetic toxicity, epigenetic effects) are summarized. In addition, information on susceptible individuals, populations and life-stages is summarized. This section also reports on other toxic effects, including reproductive and developmental effects, as well as additional relevant data that are considered to be important.

6. Evaluation and rationale

Evaluations of the strength of the evidence for carcinogenicity arising from human and experimental animal data are made, using standard terms. The strength of the mechanistic evidence is also characterized.

It is recognized that the criteria for these evaluations, described below, cannot encompass all of the factors that may be relevant to an evaluation of carcinogenicity. In considering all of the relevant scientific data, the Working Group may assign the agent to a higher or lower category than a strict interpretation of these criteria would indicate.

These categories refer only to the strength of the evidence that an exposure is carcinogenic and not to the extent of its carcinogenic activity (potency). A classification may change as new information becomes available.

An evaluation of the degree of evidence is limited to the materials tested, as defined physically, chemically or biologically. When the agents evaluated are considered by the Working Group to be sufficiently closely related, they may be grouped together for the purpose of a single evaluation of the degree of evidence.

(a) Carcinogenicity in humans

The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories:

***Sufficient evidence of carcinogenicity*:**

The Working Group considers that a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence. A statement that there is *sufficient evidence* is followed by a separate sentence that identifies the target organ(s) or tissue(s) where an increased risk of cancer was observed in humans. Identification of a specific target organ or tissue does not preclude the possibility that the agent may cause cancer at other sites.

***Limited evidence of carcinogenicity*:**

A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

***Inadequate evidence of carcinogenicity*:**

The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available.

***Evidence suggesting lack of carcinogenicity*:**

There are several adequate studies covering the full range of levels of exposure that humans are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent and any studied cancer at any observed level of exposure. The results from these studies alone or combined should have narrow confidence intervals with an upper limit close to the null value (e.g. a relative

risk of 1.0). Bias and confounding should be ruled out with reasonable confidence, and the studies should have an adequate length of follow-up. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the cancer sites, conditions and levels of exposure, and length of observation covered by the available studies. In addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

In some instances, the above categories may be used to classify the degree of evidence related to carcinogenicity in specific organs or tissues.

When the available epidemiological studies pertain to a mixture, process, occupation or industry, the Working Group seeks to identify the specific agent considered most likely to be responsible for any excess risk. The evaluation is focused as narrowly as the available data on exposure and other aspects permit.

(b) Carcinogenicity in experimental animals

Carcinogenicity in experimental animals can be evaluated using conventional bioassays, bioassays that employ genetically modified animals, and other in-vivo bioassays that focus on one or more of the critical stages of carcinogenesis. In the absence of data from conventional long-term bioassays or from assays with neoplasia as the end-point, consistently positive results in several models that address several stages in the multistage process of carcinogenesis should be considered in evaluating the degree of evidence of carcinogenicity in experimental animals.

The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories:

***Sufficient evidence of carcinogenicity*:**

The Working Group considers that a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well conducted study, ideally conducted under Good Laboratory Practices, can also provide *sufficient evidence*.

A single study in one species and sex might be considered to provide *sufficient evidence of carcinogenicity* when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites.

***Limited evidence of carcinogenicity*:**

The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs.

***Inadequate evidence of carcinogenicity*:**

The studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations, or no data on cancer in experimental animals are available.

***Evidence suggesting lack of carcinogenicity*:**

Adequate studies involving at least two species are available which show that, within the limits of the tests used, the agent is not carcinogenic. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the species, tumour sites, age at exposure, and conditions and levels of exposure studied.

(c) Mechanistic and other relevant data

Mechanistic and other evidence judged to be relevant to an evaluation of carcinogenicity and of sufficient importance to affect the overall evaluation is highlighted. This may include data on preneoplastic lesions, tumour pathology, genetic and related effects, structure–activity relationships, metabolism and toxicokinetics, physicochemical parameters and analogous biological agents.

The strength of the evidence that any carcinogenic effect observed is due to a particular mechanism is evaluated, using terms such as 'weak', 'moderate' or 'strong'. The Working Group then assesses whether that particular mechanism is likely to be operative in humans. The strongest indications that a particular mechanism operates in humans derive from data on humans or biological specimens obtained from exposed humans. The data may be considered to be especially relevant if they show that the agent in question has caused changes in exposed humans that are on the causal pathway to carcinogenesis. Such data may, however, never become available, because it is at least conceivable that certain compounds may be kept from human use solely on the basis of evidence of their toxicity and/or carcinogenicity in experimental systems.

The conclusion that a mechanism operates in experimental animals is strengthened by findings of consistent results in different experimental systems, by the demonstration of biological plausibility and by coherence of the overall database. Strong support can be obtained from studies that challenge the hypothesized mechanism experimentally, by demonstrating that the suppression of key mechanistic processes leads to the suppression of tumour development. The Working Group considers whether multiple mechanisms might contribute to tumour development, whether different mechanisms might operate in different dose ranges, whether separate mechanisms might operate in humans and experimental animals and whether a unique mechanism might operate in a susceptible group. The possible contribution of alternative mechanisms must be considered before concluding that tumours observed in experimental animals are not relevant to humans. An uneven level of experimental support for different mechanisms may reflect that disproportionate resources have been focused on investigating a favoured mechanism.

For complex exposures, including occupational and industrial exposures, the chemical composition and the potential contribution of carcinogens known to be present are considered by the Working Group in its overall evaluation of human carcinogenicity. The Working Group also determines the extent to which the materials tested in experimental systems are related to those to which humans are exposed.

(d) Overall evaluation

Finally, the body of evidence is considered as a whole, to reach an overall evaluation of the carcinogenicity of the agent to humans.

An evaluation may be made for a group of agents that have been evaluated by the Working Group. In addition, when supporting data indicate that other related agents, for which there is no direct evidence of their capacity to induce cancer in humans or in animals, may also be carcinogenic, a statement describing the rationale for this conclusion is added to the evaluation narrative; an additional evaluation may be made for this broader group of agents if the strength of the evidence warrants it.

The agent is described according to the wording of one of the following categories, and the designated group is given. The categorization of an agent is a matter of scientific judgement that reflects the strength of the evidence derived from studies in humans and in experimental animals and from mechanistic and other relevant data.

Group 1: The agent is carcinogenic to humans.

This category is used when there is *sufficient evidence of carcinogenicity* in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than *sufficient* but there is *sufficient evidence of carcinogenicity* in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity.

Group 2.

This category includes agents for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost *sufficient*, as well as those for which, at the other extreme, there are no human data but for which there is evidence of carcinogenicity in experimental animals. Agents are assigned to either Group 2A (*probably carcinogenic to humans*) or Group 2B (*possibly carcinogenic to humans*) on the basis of epidemiological and experimental evidence of carcinogenicity and mechanistic and other relevant data. The terms *probably carcinogenic* and *possibly carcinogenic* have no quantitative significance and are used simply as descriptors of different levels of evidence of human carcinogenicity, with *probably carcinogenic* signifying a higher level of evidence than *possibly carcinogenic*.

Group 2A: The agent is probably carcinogenic to humans.

This category is used when there is *limited evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals. In some cases, an agent may be classified in this category when there is *inadequate evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent may be classified in this category solely on the basis of *limited evidence of carcinogenicity* in humans. An agent may be assigned to this category if it clearly belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A.

Group 2B: The agent is possibly carcinogenic to humans.

This category is used for agents for which there is *limited evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals. It may also be used when there is *inadequate evidence of carcinogenicity* in humans but there is *sufficient evidence of carcinogenicity* in experimental animals. In some instances, an agent for which there is *inadequate evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals together with supporting evidence from mechanistic and other relevant data may be placed in this group. An agent may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data.

Group 3: The agent is not classifiable as to its carcinogenicity to humans.

This category is used most commonly for agents for which the evidence of carcinogenicity is *inadequate* in humans and *inadequate* or *limited* in experimental animals.

Exceptionally, agents for which the evidence of carcinogenicity is *inadequate* in humans but *sufficient* in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.

Agents that do not fall into any other group are also placed in this category.

An evaluation in Group 3 is not a determination of non-carcinogenicity or overall safety. It often means that further research is needed,

especially when exposures are widespread or the cancer data are consistent with differing interpretations.

Group 4: The agent is probably not carcinogenic to humans.

This category is used for agents for which there is *evidence suggesting lack of carcinogenicity* in humans and in experimental animals. In some instances, agents for which there is *inadequate evidence of carcinogenicity* in humans but *evidence suggesting lack of carcinogenicity* in experimental animals, consistently and strongly supported by a broad range of mechanistic and other relevant data, may be classified in this group.

(e) Rationale

The reasoning that the Working Group used to reach its evaluation is presented and discussed. This section integrates the major findings from studies of cancer in humans, studies of cancer in experimental animals, and mechanistic and other relevant data. It includes concise statements of the principal line(s) of argument that emerged, the conclusions of the Working Group on the strength of the evidence for each group of studies, citations to indicate which studies were pivotal to these conclusions, and an explanation of the reasoning of the Working Group in weighing data and making evaluations. When there are significant differences of scientific interpretation among Working Group Members, a brief summary of the alternative interpretations is provided, together with their scientific rationale and an indication of the relative degree of support for each alternative.

References

Bieler GS, Williams RL (1993). Ratio estimates, the delta method, and quantal response tests for increased carcinogenicity. *Biometrics*, 49:793–801. doi:10.2307/2532200 PMID:8241374

Breslow NE, Day NE (1980). Statistical methods in cancer research. Volume I - The analysis of case-control studies. *IARC Sci Publ*, 32:5–338. PMID:7216345

Breslow NE, Day NE (1987). Statistical methods in cancer research. Volume II–The design and analysis of cohort studies. *IARC Sci Publ*, 82:1–406. PMID:3329634

Buffler P, Rice J, Baan R et al. (2004). Workshop on mechanisms of carcinogenesis: contributions of molecular epidemiology. Lyon, 14–17 November 2001. Workshop report. *IARC Sci Publ*, 157:1–27. PMID:15055286

Capen CC, Dybing E, Rice JM, Wilbourn JD (1999). Species differences in thyroid, kidney and urinary bladder carcinogenesis. Proceedings of a consensus conference. Lyon, France, 3–7 November 1997. *IARC Sci Publ*, 147:1–225. PMID:10627184

Cogliano V, Baan R, Straif K et al. (2005). Transparency in IARC Monographs. *Lancet Oncol*, 6:747. doi:10.1016/S1470-2045(05)70380-6

Cogliano VJ, Baan RA, Straif K et al. (2004). The science and practice of carcinogen identification and evaluation. *Environ Health Perspect*, 112:1269–1274. doi:10.1289/ehp.6950 PMID:15345338

Dunson DB, Chen Z, Harry J (2003). A Bayesian approach for joint modeling of cluster size and subunit-specific outcomes. *Biometrics*, 59:521–530. doi:10.1111/1541-0420.00062 PMID:14601753

Fung KY, Krewski D, Smythe RT (1996). A comparison of tests for trend with historical controls in carcinogen bioassay. *Can J Stat*, 24:431–454. doi:10.2307/3315326

Gart JJ, Krewski D, Lee PN et al. (1986). Statistical methods in cancer research. Volume III–The design and analysis of long-term animal experiments. *IARC Sci Publ*, 79:1–219. PMID:3301661

Greenland S (1998). Meta-analysis. In: Rothman KJ, Greenland S, editors. Modern epidemiology. Philadelphia: Lippincott Williams & Wilkins, pp. 643–673.

Greim H, Gelbke H-P, Reuter U et al. (2003). Evaluation of historical control data in carcinogenicity studies. *Hum Exp Toxicol*, 22:541–549. doi:10.1191/0960327103ht394oa PMID:14655720

Haseman JK, Huff J, Boorman GA (1984). Use of historical control data in carcinogenicity studies in rodents. *Toxicol Pathol*, 12:126–135. doi:10.1177/019262338401200203 PMID:11478313

Hill AB (1965). The environment and disease: Association or causation? *Proc R Soc Med*, 58:295–300. PMID:14283879

Hoel DG, Kaplan NL, Anderson MW (1983). Implication of nonlinear kinetics on risk estimation in carcinogenesis. *Science*, 219:1032–1037. doi:10.1126/science.6823565 PMID:6823565

Huff JE, Eustis SL, Haseman JK (1989). Occurrence and relevance of chemically induced benign neoplasms in long-term carcinogenicity studies. *Cancer Metastasis Rev*, 8:1–22. doi:10.1007/BF00047055 PMID:2667783

IARC (1977). IARC Monographs Programme on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Preamble (IARC Intern Tech Rep No. 77/002).

IARC (1978). Chemicals with sufficient evidence of carcinogenicity in experimental animals – IARC Monographs Volumes 1–17 (IARC Intern Tech Rep No. 78/003).

IARC (1979). Criteria to select chemicals for IARC Monographs (IARC Intern Tech Rep No. 79/003).

IARC (1982). Chemicals, industrial processes and industries associated with cancer in humans (IARC Monographs, volumes 1 to 29). *IARC Monogr Eval Carcinog Risk Chem Hum Suppl*, 4:1–292.

IARC (1983). Approaches to classifying chemical carcinogens according to mechanism of action (IARC Intern Tech Rep No. 83/001).

IARC (1987). Overall evaluations of carcinogenicity: an updating of IARC Monographs volumes 1 to 42. *IARC Monogr Eval Carcinog Risks Hum Suppl*, 7:1–440. PMID:3482203

IARC (1988). Report of an IARC Working Group to Review the Approaches and Processes Used to Evaluate the Carcinogenicity of Mixtures and Groups of Chemicals (IARC Intern Tech Rep No. 88/002).

IARC (1991). A consensus report of an IARC Monographs Working Group on the Use of Mechanisms of Carcinogenesis in Risk Identification (IARC Intern Tech Rep No. 91/002).

IARC (2004). Some drinking-water disinfectants and contaminants, including arsenic. *IARC Monogr Eval Carcinog Risks Hum*, 84:1–477. PMID:15645577

IARC (2005). Report of the Advisory Group to Recommend Updates to the Preamble to the IARC Monographs (IARC Intern Rep No. 05/001).

IARC (2006). Report of the Advisory Group to Review the Amended Preamble to the IARC Monographs (IARC Intern Rep No. 06/001).

McGregor DB, Rice JM, Venitt S (1999). The use of short-and medium-term tests for carcinogens and data on genetic effects in carcinogenic hazard evaluation. Consensus report. *IARC Sci Publ*, 146:1–18. PMID:10353381

Montesano R, Bartsch H, Vainio H et al., editors(1986). Long-term and short-term assays for carcinogenesis—a critical appraisal. *IARC Sci Publ*, 83:1–564. PMID:3623675

OECD (2002). Guidance notes for analysis and evaluation of chronic toxicity and carcinogenicity studies (Series on Testing and Assessment No. 35), Paris: OECD.

Peto R, Pike MC, Day NE et al. (1980). Guidelines for simple, sensitive significance tests for carcinogenic effects in long-term animal experiments. *IARC Monogr Eval Carcinog Risk Chem Hum Suppl*, 2:Suppl: 311–426. PMID:6935185

Portier CJ, Bailer AJ (1989). Testing for increased carcinogenicity using a survival-adjusted quantal response test. *Fundam Appl Toxicol*, 12:731–737. doi:10.1016/0272-0590(89)90004-3 PMID:2744275

Sherman CD, Portier CJ, Kopp-Schneider A (1994). Multistage models of carcinogenesis: an approximation for the size and number distribution of late-stage clones. *Risk Anal*, 14:1039–1048. doi:10.1111/j.1539-6924.1994.tb00074.x PMID:7846311

Stewart BW, Kleihues P, editors (2003). World cancer report, Lyon: IARC.

Tomatis L, Aitio A, Wilbourn J, Shuker L (1989). Human carcinogens so far identified. *Jpn J Cancer Res*, 80:795–807. doi:10.1111/j.1349-7006.1989.tb01717.x PMID:2513295

Toniolo P, Boffetta P, Shuker DEG et al. (1997). Proceedings of the workshop on application of biomarkers to cancer epidemiology. Lyon, France, 20–23 February 1996. *IARC Sci Publ*, 142:1–318. PMID:9410826

Vainio H, Magee P, McGregor D, McMichael A (1992). Mechanisms of carcinogenesis in risk identification. IARC Working Group Meeting. Lyon, 11–18 June 1991. *IARC Sci Publ*, 116:1–608. PMID:1428077

Vainio H, Wilbourn JD, Sasco AJ et al. (1995). [Identification of human carcinogenic risks in IARC monographs] *Bull Cancer*, 82:339–348. PMID:7626841

Vineis P, Malats N, Lang M et al., editors (1999). Metabolic polymorphisms and susceptibility to cancer. *IARC Sci Publ*, 148:1–510. PMID:10493243

Wilbourn J, Haroun L, Heseltine E et al. (1986). Response of experimental animals to human carcinogens: an analysis based upon the IARC Monographs programme. *Carcinogenesis*, 7:1853–1863. doi:10.1093/carcin/7.11.1853 PMID:3769134

GENERAL REMARKS

This one-hundred-and-ninth Volume of the *IARC Monographs* presents evaluations of the carcinogenic hazards to humans arising from exposure to outdoor air pollution and particulate matter (PM) contained in polluted outdoor air. A summary of the findings has been published in *The Lancet Oncology* (Loomis et al., 2013).

Outdoor air pollution has myriad sources, both natural and anthropogenic. It is a mixture of mixtures, and the mix of contaminants in outdoor air varies widely in space and time, reflecting variation in its sources, weather, atmospheric transformations, and other factors. In any particular place, the pollution in outdoor air comes not only from local sources but also from sources that affect air quality regionally and even globally.

The complex mixture of air pollution has not previously been evaluated, as such, in the *IARC Monographs*. However, this Volume is the culmination of a series that has examined individual pollutants that are found in outdoor air. The heterogeneity of air pollution was an acknowledged challenge in planning this series of *Monographs*. Consequently, the International Agency for Research on Cancer (IARC) convened a special Advisory Group in 2004 to provide guidance on how to address air pollution and cancer. This Advisory Group recommended a sequence of reviews that would begin with specific combustion products and sources and culminate with a *Monograph* on outdoor air pollution (Straif et al., 2013). With respect to the final *Monograph*, the Advisory Group noted that because outdoor air pollution cannot be readily defined, the final *Monograph* "should focus on those pollutants generated by human activities, particularly those entailing combustion and industrial processes" and should consider air pollution in rural as well as urban environments. Evaluations of a number of important air pollutants have been published in *IARC Monographs* Volumes 92, 93, 95, 100C, 100E, 103, and 105. The current Volume completes that planned sequence.

The nature of the evidence available to the Working Group differed across the sections of the *Monograph*. Exposure data were available on outdoor air pollution and in relation to mixtures associated with particular sources. Epidemiological studies that addressed the outdoor air pollution mixture and commonly measured indicators of exposure to it, notably including PM, were reviewed. Some studies of cancer in laboratory animals also assessed real-world outdoor air pollution mixtures, but most examined PM collected from outdoor air or organic matter extracted from outdoor air particles. Mechanistic studies also assessed effects related to a wide spectrum of exposure indicators, ranging from studies in exposed humans to experimental studies focusing on particular components of the mixture, such as PM, or samples derived from PM.

There is a substantial body of scientific literature on various sources of air pollution and on environmental concentrations of particular pollutants. The Working Group sought

representative data on air pollution worldwide, but as such data are often presented in government reports and online databases, this evidence could not be systematically reviewed. A systematic review of relevant epidemiological studies was conducted, and the evidence from animal carcinogenicity studies was systematically updated. Some of the same evidence was also considered in previous *IARC Monographs*. The Working Group cites the findings of these *Monographs* and of particular studies where they are informative with regard to the outdoor air pollution mixture.

The accumulated scientific evidence is notably consistent across studies of cancer in humans, cancer in animals, and mechanisms of carcinogenesis. The Working Group found that there is *sufficient evidence* in humans and in experimental animals for the carcinogenicity of outdoor air pollution in general and of PM in outdoor air pollution more specifically. These findings are supported by *strong mechanistic evidence* in exposed humans, including studies showing increased frequencies of micronuclei and chromosomal aberrations in individuals occupationally or residentially exposed to polluted air, as well as by studies showing genetic and related effects in animals and diverse experimental systems. A wide range of other effects related to carcinogenesis, including oxidative stress, inflammation, and epigenetic alterations, have also been observed in exposed humans and animals and in diverse experimental systems.

Given the variability of outdoor air pollution in space and time, the extent to which any classification of the cancer risk from outdoor air pollution can be generalized needs consideration. The Working Group acknowledged that the mix of pollution sources ranges widely and the exposures of any given population may be dominated by particular sources. Nonetheless, the exposure data document the presence of key mixture components, specifically particles, across diverse locations, and mechanisms of carcinogenicity apply across components and locations. Consequently, the Working Group concluded that its classification for outdoor air pollution has general applicability.

The Working Group also noted that much of the world's population is exposed to air pollution at levels substantially above those at which associations with lung cancer have been demonstrated. Thus, the findings of the epidemiological studies of outdoor air pollution and cancer need to be generalized both to levels comparable to those at which the studies were carried out and to levels well above those spanned in currently available epidemiological studies.

The classification of outdoor air pollution and PM as *carcinogenic to humans (Group 1)* raises questions regarding the extent of the cancer burden attributable to these exposures. Using PM with particles of aerodynamic diameter less than 2.5 μm ($PM_{2.5}$) as an indicator of population exposure to outdoor air pollution, the Global Burden of Disease Project has made estimates of the global burden of lung cancer associated with outdoor air pollution. According to these estimates, 223 000 deaths per year worldwide (about 15% of all deaths from lung cancer) are attributable to outdoor air pollution (Lim et al., 2012; Straif et al., 2013).

References

Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H et al. (2012). A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*, 380(9859):2224–60. doi:10.1016/S0140-6736(12)61766-8 PMID:23245609

Loomis D, Grosse Y, Lauby-Secretan B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L et al.; IARC Monograph Working Group (2013). The carcinogenicity of outdoor air pollution. *Lancet Oncol*, 14(13):1262–3. doi:10.1016/S1470-2045(13)70487-X PMID:25035875

Straif K, Cohen A, Samet J, editors (2013). Air pollution and cancer (IARC Scientific Publication No. 161). Lyon, France: International Agency for Research on Cancer. Available from: http://www.iarc.fr/en/publications/books/sp161/.

1. EXPOSURE DATA

1.1 Definition of outdoor air pollution

Air pollution is the presence in the air of one or more substances at a concentration or for a duration above their natural levels, with the potential to produce an adverse effect (derived from Seinfeld & Pandis, 2006). This definition implicitly acknowledges that some substances that are considered to be air pollutants are present naturally. Although some air pollutants are solely anthropogenic, or nearly so (e.g. chlorofluorocarbons and, for most purposes, some products of fossil fuel combustion), many, including ozone, particulate matter (PM), sulfur dioxide (SO_2), carbon monoxide (CO), and polycyclic aromatic hydrocarbons (PAHs), may also result from natural processes (Table 1.1). Anthropogenic activities have led to increases in many air pollutants to levels that have adverse impacts on human and environmental health. What is key in terms of assessing the potential health effects of air pollution are the levels of the thousands of substances present, recognizing that their composition varies from location to location, so the term "air pollution" can refer to very different exposure mixtures.

1.1.1 Characteristics of exposure to outdoor air pollution

(a) Overview

Exposure to outdoor air pollutants occurs virtually continuously, across microenvironments, including indoors. The composition of the mixture and the absolute levels of the air pollutants change, and many different air pollutants are present. The understanding of these exposures is complicated by the fact that the composition is seldom, if ever, well characterized in any environment, much less in all of the locations an individual may traverse. Although most of the more-abundant pollutants are known and can be measured, many trace species have not been identified, much less quantified routinely. Most trace pollutants typically are not measured; instead, they are characterized as being part of a class of pollutants that are more readily measured together (e.g. many organic compounds are aggregated in measurements), or they may be linked to other indicators.

In light of the complexities discussed in this *Monograph*, there is no standardized way to characterize exposure to outdoor air pollution. This text focuses on outdoor air pollutants, classes of pollutants, pollutant mixtures (characterized by source and/or components), and pollutant indicators that are of specific interest as potentially leading to human cancer due to direct contact with humans through their presence in outdoor air. This includes exposures to outdoor

Table 1.1 Major air pollutants and pollutant classes of interest, their physical state, and their sources

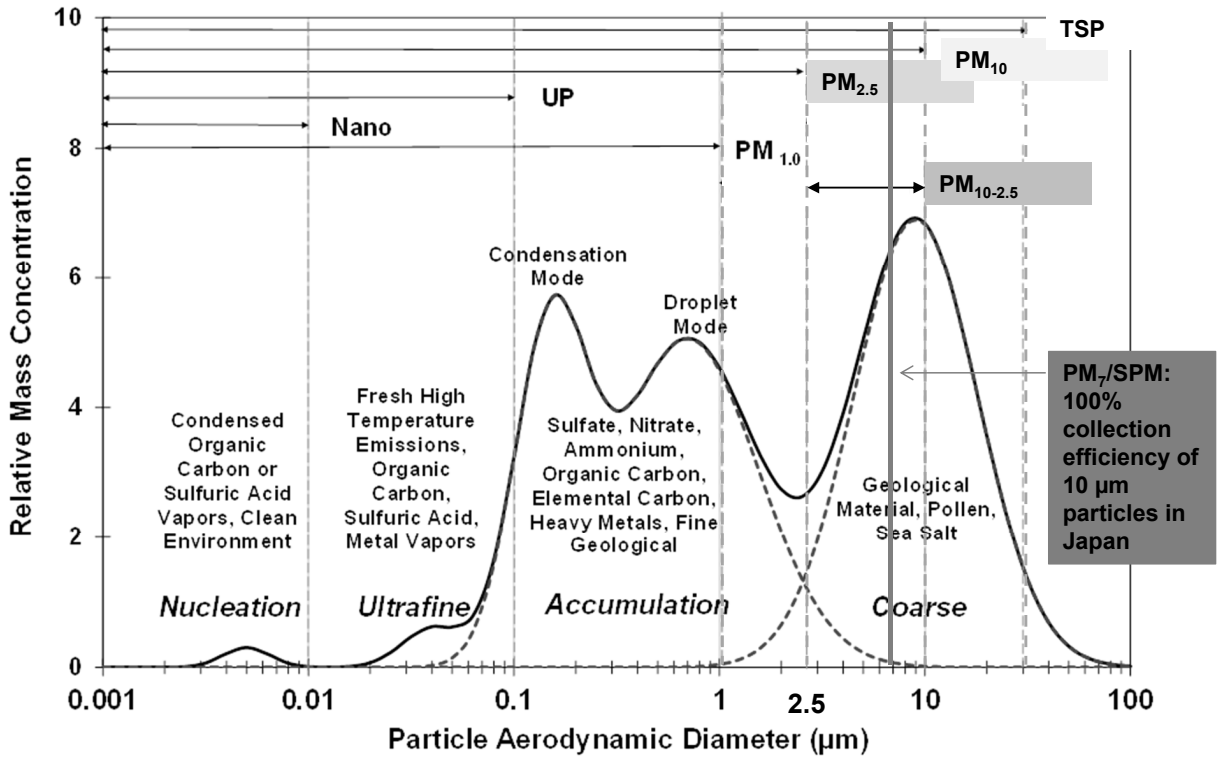
Pollutant/pollutant class	Examples	Physical state	Major sources
Photochemical oxidants	Ozone	Gas	Generated from NO_x, VOCs, and CO, as well as natural processes (e.g. stratosphere)
Sulfur dioxide (SO_2)	SO_2	Gas	Fossil fuel combustion, natural emissions
Carbon monoxide (CO)	CO	Gas	Fossil fuel combustion, particularly spark-ignition engines; oxidation of biogenic VOC emissions
Nitrogen oxides (NO_x)	NO_2	Gas	Combustion processes
Hazardous air pollutants (HAPs)	Benzene, 1,3-butadiene, formaldehyde, acids	Gas	Incomplete combustion, chemical processing, solvent use
Mercury (Hg)	Hg^0, methyl mercury	Gas and particulate	Coal combustion, ore refining, natural
Lead (Pb)	Pb	Particulate	Leaded fuel combustion, lead processing
PM, including $PM_{2.5}$, PM_{10}, inhalable PM, TSP	Inorganic ions (e.g. sulfate); metal oxides; carbonaceous material, including organic carbon (OC) and elemental carbon (EC)	Particulate (condensed phase)	Dust storms, fossil fuel combustion, biomass fuel combustion, biogenic emissions, fertilizer use, gas-to-particle conversion
Organic carbon (OC)	Hopanes, steranes, polycyclic aromatic hydrocarbons, levoglucosan (hundreds of species present, not all identified or quantified)	Particulate	Fossil and biomass fuel combustion, vegetative detritus, oxidation of gaseous organic compounds

CO, carbon monoxide; EC, elemental carbon; Hg^0, elemental mercury; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; OC, organic carbon; PM, particulate matter; PM_{10}, particulate matter with particles of aerodynamic diameter < 10 μm; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 μm; SO_2, sulfur dioxide; TSP, total suspended particles; VOCs, volatile organic compounds.
Prepared by the Working Group.

pollutants and their reaction products outdoors and indoors. Exposures to pollutants generated indoors and contained indoors (e.g. from cooking and heating) and to smoking are not considered, but pollutants generated indoors that migrate outdoors are considered. An increased focus is on those specific species, classes of pollutants, indicators, and mixtures that are most relevant to cancer in humans.

There are multiple ways to parse exposure to outdoor air pollution. First, the phase can be considered. Air pollutants are typically classified as being gaseous or PM, which contains suspensions of very small particles (with diameters of a few micrometres or less, down to nanometre scales) that are liquid and/or solid matter. Complicating this classification is the fact that some pollutants move between phases (e.g. semi-volatile organic compounds [SVOCs]). A second consideration is whether the pollutant is emitted directly, and thus is primary (e.g. dust), or is formed in the atmosphere, and thus is secondary (e.g. ozone). Some pollutants are both primary and secondary (e.g. formaldehyde). Primary and secondary pollutants are described in more detail in Section 1.2. A third approach would be to consider where the exposure takes place (e.g. outdoors, in a car, or indoors) and whether the pollutant mixture has been significantly altered by that microenvironment. A fourth consideration is the source of the pollutant mixture (e.g. fuel combustion, chemical manufacture) or whether the mixture is dominated by secondary compounds.

Fig. 1.1 Major features of atmospheric particle mass distribution



PM_{10}, particulate matter with particles of aerodynamic diameter < 10 μm; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 μm; SPM, suspended particulate matter; TSP, total suspended particles; UP, ultrafine particles.
Adapted from Watson (2002). Visibility: science and regulation. *J Air Waste Manag Assoc*, 52(6):628–713, by permission of the Air & Waste Management Association. (http://www.awma.org).

(b) Air pollutants

Air pollutants and pollutant classes of interest, their physical state, and their major sources are summarized in Table 1.1.

Gaseous compounds of interest include, but are not limited to: ozone; nitrogen oxides (NO_x), which comprise nitrogen oxide (NO) and nitrogen dioxide (NO_2) (in the atmosphere, NO is oxidized to NO_2, often rapidly in the presence of ozone); SO_2; and a myriad of volatile organic gases (often referred to as organic gases or volatile organic compounds [VOCs]). VOCs include aldehydes (e.g. formaldehyde), ketones, aromatics (e.g. benzene), alkanes, and other classes. PM is even more complex (and less well understood). PM is characterized by both its size and its chemical composition (see Fig. 1.1). Particle sizes range across about 5 orders of magnitude, from the nanometre scale (e.g. as clusters of molecules) up to grains of dust on the order of tens of micrometres. Although the distribution of particle sizes can be measured, most measurements capture the mass in specific size ranges; for example, $PM_{2.5}$ is PM with particles of aerodynamic diameter less than 2.5 μm. Other common size classes are PM_{10} (PM < 10 μm), total suspended particles (TSP), and ultrafine PM (PM < 0.1 μm). Coarse PM is taken as the fraction with diameters from 2.5 μm to 10 μm. These size classes are relevant

to PM dynamics in the atmosphere and uptake in the human body, and reflect size ranges used in health studies.

Broad classes of chemical compounds can be considered in PM: inorganic ionic compounds (e.g. sulfate), metal oxides (e.g. silicon oxide), and carbonaceous PM, which can in turn be classified as organic carbon (OC) and elemental carbon (EC).

EC is not truly pure carbon and is defined by the measurement approach; in some cases, the term black carbon (BC) is used, again being defined by the measurement approach.

OC comprises hundreds of compounds, and although the common inorganic compounds are reasonably well known and measured, only a fraction of the organic compounds in PM have been specifically identified (Schauer et al., 1996). Significant headway has recently been made to better understand the general structure of the unidentified compounds (Gentner et al., 2012; Liu et al., 2012).

In addition, some inorganic compounds (e.g. ammonium and nitrate) and a myriad of organic compounds (e.g. SVOCs and intermediate-volatility organic compounds) can move between the condensed (particle) phase and the gas phase.

Atmospheric chemistry and transport, and infiltration indoors, alter the exposure mixtures. Ozone, a major component of photochemical smog, is formed in the atmosphere due to reactions of NO_x with VOCs and CO. Sulfate PM is derived primarily from the oxidation of SO_2 (a gas), followed by gas-to-particle conversion. Although formaldehyde is emitted from some building materials and chemical facilities, more is formed in the atmosphere from the oxidation of other organic compounds, and is also destroyed by further reactions. A potentially important, but less well understood, set of chemistry involves larger organic molecules. Oxidation of gaseous organic molecules can lower their vapour pressure, leading to condensation, and they thus become part of the OC mixture in PM. There can be multiple generations of reactions, and some reactions can also take place in or on the particles themselves.

(c) Role of sources in the composition of outdoor air pollutants

Here, an overview is provided of the information described in detail for each pollutant in Section 1.2, focusing on sources.

Fossil fuel combustion leads to elevated levels of NO_x, VOCs, and carbonaceous PM. Reactions involving these compounds can further contribute to elevated levels of other compounds, such as ozone. Furthermore, any impurities in the fuel, for example sulfur and metals such as mercury, are also emitted, sometimes as a gas (e.g. SO_2) or as PM (e.g. fly ash, including metals such as selenium, vanadium, and nickel) or as both (e.g. mercury). The combustion process is complex, leading to a mixture of organic gases and PM that is just as complex, comprising species that were originally present in the fuel (e.g. benzene) and products of incomplete combustion. Some products of incomplete combustion include partially oxidized organic components (e.g. aldehydes), pyrolysis products (e.g. 1,3-butadiene and carbonaceous aerosol), and more oxidized products such as CO and carbon dioxide (CO_2) and PAHs. Some of these organic species of concern, including dioxins, quinones, and PAHs, are known or suspected carcinogens (see Table 1.2). The relative abundance of the constituents depends on the fuel type and combustion conditions. Historically, spark-ignition engines typically produced relatively less PM and NO_x than diesel, but more CO and VOCs. The carbonaceous PM from combustion is particularly complex (for detailed information, see HEI, 2013 and IARC, 2013a). Not all automobile emissions are from the exhaust pipe; brake and tyre wear can lead to copper and asbestos emissions, as well as resuspended dust. Biomass fuel combustion leads to emissions that can be similar to those from fossil fuel combustion, at least at the

macroscopic level. Typically biomass combustion in open burning and in stoves takes place at lower temperatures, leading to lower NO_x emissions but higher CO emissions. Organic gases are emitted, as is carbonaceous PM, along with impurities in the fuel (e.g. potassium). The major differences are at the molecular level. Chemical plants and other industries have been responsible for elevated levels of additional pollutants, including heavy metals and organic air toxics, and the compounds involved are process-specific. The air toxics may be due to leakage in the plant or from incomplete combustion of flaring used to control emissions.

Natural processes also play a role. Wildland fires, natural and human-related, lead to emissions of CO, NO, and organic gases (including air toxics) and PM. Lightning forms NO_x and ozone. Sea spray generates PM. Volcanoes emit sulfur oxides (SO_x), mercury, and other metals. Wind raises dust. Plants emit organic gases, some of which are highly reactive. Microbial activity leads to emissions of NO_x and ammonia, as well as bioaerosols. Biogenically emitted VOCs and NO_x react to form ozone and organic PM. In many cases, natural and anthropogenic sources, such as natural VOCs and emissions of NO_x and SO_x from fossil fuel combustion, interact to produce higher pollutant levels than would be present with either type alone. Together, these sources and the related atmospheric processing lead to air pollutant mixtures of tremendous complexity and variation, although at any one time most of the pollutants are present, just at varying levels.

Carbonaceous PM is a major component of outdoor PM in general, and it will take on a larger role as the levels of other components of PM are reduced. Characterizing the components of primary and secondary carbonaceous PM is difficult, and even specialized studies have typically identified and quantified a relatively small fraction of the potentially thousands of components (Schauer et al., 1996). Therefore, carbonaceous PM is often classified more simply as EC and OC. To the extent that they have been characterized, carbonaceous PM emissions typically resemble the components in the fuel they are derived from (and, in the case of internal combustion engines, the lubricating oil), along with pyrolysis products. OC from internal combustion engines includes PAHs, hopanes, steranes, and partially oxidized products of the underlying fuels and lubricant (Zheng et al., 2002; Gentner et al., 2012; Isaacman et al., 2012; Liu et al., 2012; Zhao et al., 2013). OC from biomass combustion contains large amounts of levoglucosan, a pyrolysis product of cellulose combustion. Atmospheric processing increases the complexity of the OC mixture. Secondary organic compounds are formed in part from the oxidation of gaseous organic compounds, which then have a lowered vapour pressure, leading to condensation. Organic compounds that were originally emitted as PM can volatilize, react, and then recondense. As discussed below, recent advances in analytical methods are leading to a more detailed understanding of both emitted and outdoor OC at the molecular level (Gentner et al., 2012; Isaacman et al., 2012).

(d) Role of spatial scales of pollutants

Concentrations of outdoor air pollutants vary across microenvironments, depending on source characteristics. A typical urban area is affected by the surrounding regional background pollutants, which have evolved from a variety of processes (e.g. chemistry, dispersion, and deposition, along with emissions from natural processes). Pollutant concentrations in a city increase due to the variety of urban emissions characteristic of populated areas, leading to elevated levels of primary and processed pollutants on spatial scales similar to the size of the city (1 km to tens of kilometres). On top of the urban mixture, locally elevated levels of freshly emitted pollutants occur over smaller scales (0 m to hundreds of metres). Specific locations that experience high levels of air pollution include sites near and on roadways (including in

vehicles), in fire plumes, and near chemical facilities. Karner et al. (2010) assessed near-roadway pollutant gradients and found that CO concentrations dropped by 90% to near background levels in about 170 m, and that concentrations of most other roadway-emitted species dropped to near background levels by 570 m. There are also locally large exposure gradients around factories and industrial complexes, although such gradients can be quite complex, depending on source characteristics. In contrast, plumes from power plants and fires, although they are diluted, can still be identified for tens to thousands of kilometres (Ryerson et al., 1998; Forster et al., 2001). Secondary pollutants (e.g. ozone, sulfate, and part of the OC) are found regionally with relatively smaller gradients. Dust has impacts at multiple scales; locally generated dust can have large impacts locally, and dust storms can lead to intercontinental transport.

For pollutants generated outdoors, concentrations may be lower when the pollutants are transported indoors. However, since people tend to spend most of their time indoors, most of the exposure to those pollutants occurs indoors. Also, indoor environments can lead to unique exposures as pollutants generated outdoors come into a very different environment, allowing new chemical pathways to occur. Studies have quantified exposures to specific chemicals or classes of chemicals across environments.

1.1.2 Pollutant concentrations

A better perspective on the potential impacts of air pollutants and air pollution is gained by considering typical levels of the major pollutants; more detailed descriptions of concentrations across regions are given in Section 1.4.

For primary pollutants, urban concentrations can be many hundreds of times background levels; ozone levels do not vary as dramatically. Approximate concentration ranges are given because pollutant concentrations vary by orders of magnitude between urban areas and within an urban area, depending on the location or day (or time of day). Although many measurements target a specific agent, the concentrations can be an indicator of a mixture and the presence of other compounds.

Ozone is produced naturally, and pre-industrial levels are estimated to have been approximately 30 μg/m^3. Background levels are now about twice that, due to worldwide anthropogenic emissions of NO_x and VOCs, along with natural emissions. Because ozone is produced photochemically, levels are typically highest during sunny periods with reduced atmospheric dispersion. In urban areas with photochemical pollution, ozone levels have reached much higher levels (likely > 1000 μg/m^3 in Los Angeles in the 1970s), but current levels in urban areas are much lower (e.g. summertime peaks of < ~400 μg/m^3). Ozone reacts with NO, so in areas where NO_x emissions are high and/or photochemical activity is low, ozone levels are depressed and can be well below background levels. When elevated levels of ozone are found in urban areas, levels of other photochemical oxidants are likely to be elevated as well, including aldehydes, organic acids, organonitrates, inorganic acids, hydrogen peroxide, and photochemically produced PM (typically in the fine fraction) (Finlayson-Pitts & Pitts, 2000a, 2000b, and references therein).

PM levels vary dramatically and depend on which size fraction is being considered (Seinfeld & Pandis, 2006, and references therein). PM_{10} levels are higher than $PM_{2.5}$ levels because that size range (PM_{10}) includes the particles between 2.5 μm and 10 μm in diameter, in addition to particles with diameters smaller than 2.5 μm. The ratio between the two is location- and time-dependent. For 21 regions analysed worldwide in 2005, Brauer et al. (2012) estimated the ratio of annual average levels ($PM_{2.5}/PM_{10}$) to range from 0.13 to 0.94. Areas with high levels of dust or sea salt will have a considerably higher fraction of coarse PM, but if the PM is derived from

combustion emissions or atmospheric reactions, the $PM_{2.5}$ can be a large proportion of the PM_{10}. In pristine areas or after rainstorms, $PM_{2.5}$ levels can be below 1 μg/m³. In more typical urban atmospheres, annual average levels of $PM_{2.5}$ are on the order of 4 μg/m³ to tens of micrograms per cubic metre (Brauer et al., 2012; Cooper et al., 2012). Background levels of SO_2 are very low, less than 1 μg/m³, except near natural sources (Finlayson-Pitts & Pitts, 2000b). In urban areas or near point sources, however, SO_2 levels can exceed tens of micrograms per cubic metre.

OC is present in urban atmospheres due to direct emissions and photochemical production. Levels are typically on the order of 1–10 μg/m³ but can be higher during stagnation events. Levels of the individual organic compounds that comprise OC are much lower, reflecting the hundreds of substances likely to be present. EC levels are typically less than OC levels, by about a factor of 2 or more, depending on the source distributions and photochemical activity. OC and EC levels are often highly correlated, because they share some of the same sources, and can also be correlated with levels of CO and NO_x (e.g. HEI, 2013).

Background CO levels are on the order of 50 μg/m³, varying both spatially and temporally (Seinfeld & Pandis, 2006). In urban areas with high levels of spark-ignition engine emissions, levels are about 10 times background levels and can be as high as 1000 or more times background levels during adverse meteorological conditions near sources. Concentrations tend to peak in cooler periods, when dispersion is reduced and cold-start emissions from vehicles are increased. CO levels in urban areas in developed countries have dropped dramatically due to automotive emission controls.

Average lead concentrations have decreased dramatically in countries where regulations have reduced the lead content in on-road motor vehicle gasoline. In the USA, lead concentrations in cities dropped from more than 5 μg/m³ in the early 1980s to about 0.1 μg/m³ after the use of leaded fuel was discontinued (EPA, 2010). Elevated lead concentrations are still found where leaded fuel is used and around lead processing facilities.

NO_x are emitted naturally by combustion and from microbial activity, leading to levels of 0.02–10 μg/m³. Urban concentrations can reach more than 1000 μg/m³, although they are typically more on the order of 10–100 μg/m³ (Seinfeld & Pandis, 2006).

A large number of other potentially hazardous air pollutants (HAPs; sometimes referred to as air toxics) are found in the atmosphere. Different organizations maintain different lists of air toxics. In many cases these pollutants are generally associated with specific source types and are found at elevated levels in limited geographical areas around point sources; exceptions include pollutants such as 1,3-butadiene from engines, PAHs from fossil and biomass fuel combustion, and mercury, which is long-lived and is deposited and re-emitted (UNEP, 2008). Special studies have produced information on potential levels of exposures. Levels of many of the compounds can be found in Seinfeld & Pandis (2006) and references therein, and are discussed below.

1.1.3 Pollutants classified by IARC

Outdoor air contains many substances that have been evaluated by IARC in the past (Table 1.2). The concentrations of these agents in the atmosphere are often very low, much lower than the levels that are found in environments where past epidemiological studies linking the substance to cancer may have occurred. Recently, IARC classified diesel engine exhaust in Group 1 and gasoline engine exhaust in Group 2B (IARC, 2013a). These are both significant components of urban air pollution mixtures, and include PM and other compounds.

Table 1.2 Agents in outdoor air that are established or probable IARC carcinogens[a]

Agent	CAS no.	Evaluation	Volume (reference)
Metals and fibres			
Arsenic and inorganic arsenic compounds	7440-38-2	1	100C (IARC, 2012a)
Asbestos		1	100C (IARC, 2012a)
Beryllium and beryllium compounds	7440-41-7	1	100C (IARC, 2012a)
Cadmium and cadmium compounds	7440-43-9	1	100C (IARC, 2012a)
Chromium (VI)	18540-29-9	1	100C (IARC, 2012a)
Lead compounds, inorganic/organic		2A/3	87 (IARC, 2006)
Nickel, metallic/compounds		2B/1	100C (IARC, 2012a)
Silica dust		1	100C (IARC, 2012a)
Organic chemicals			
1,3-Butadiene	106-99-0	1	100F (IARC, 2012b)
Benzene	71-43-2	1	100F (IARC, 2012b)
Ethylene oxide	75-21-8	1	100F (IARC, 2012b)
Formaldehyde	50-00-0	1	100F (IARC, 2012b)
Halogenated chemicals			
Ethylene dibromide	106-93-4	2A	71 (IARC, 1999)
2,3,7,8-Tetrachlorodibenzo-*para*-dioxin	1746-01-6	1	100F (IARC, 2012b)
Tetrachloroethylene	127-18-4	2A	106 (IARC, 2014a)
Trichloroethylene	79-01-6	1	106 (IARC, 2014a)
1,2,3-Trichloropropane	96-18-4	2A	63 (IARC, 1995)
Vinyl bromide	593-60-2	2A	97 (IARC, 2008)
Vinyl chloride	75-01-4	1	100F (IARC, 2012b)
Vinyl fluoride	75-02-5	2A	97 (IARC, 2008)
Polycyclic aromatic hydrocarbons			
Benzo[*a*]pyrene	50-32-8	1	100F (IARC, 2012b)
Cyclopenta[*cd*]pyrene	27208-37-3	2A	92 (IARC, 2010a)
Dibenz[*a,h*]anthracene	53-70-3	2A	92 (IARC, 2010a)
6-Nitrochrysene	7496-02-8	2A	105 (IARC, 2013a)
-Nitropyrene	5522-43-0	2A	105 (IARC, 2013a)
2-Nitrotoluene	88-72-2	2A	101 (IARC, 2013b)
Mixtures			
Biomass fuel (primarily wood), indoor emissions from household combustion of		2A	95 (IARC, 2010b)
Coal, indoor emissions from household combustion of		1	100E (IARC, 2012c)
Coal tar pitch	65996-93-2	1	100F (IARC, 2012b)
Coke production		1	100F (IARC, 2012b)
Creosotes	8001-58-9	2A	92 (IARC, 2010a)
Diesel engine exhaust		1	105 (IARC, 2013a)
Frying, emissions from high-temperature		2A	95 (IARC, 2010b)
Mineral oils, untreated or mildly treated		1	100F (IARC, 2012b)
Polychlorinated biphenyls	1336-36-3	1	107 (IARC, 2014b)
Polybrominated biphenyls	59536-65-1	2A	107 (IARC, 2014b)
Tobacco smoke, second-hand		1	100E (IARC, 2012c)
Wood dust		1	100C (IARC, 2012a)

[a] Established or probably carcinogens include Group 1 and Group 2A. The Working Group noted that many agents in Group 2B are also detected in outdoor air, such as gasoline engine exhaust, several individual polycyclic aromatic hydrocarbons, and acetaldehyde.
Prepared by the Working Group.

1.2 Sources of air pollutants

1.2.1 Introduction

Although there are hundreds of sources of outdoor air pollution, the source categories that are the largest contributors to most air pollutants in many locations are: vehicle emissions; stationary power generation; other industrial and agricultural emissions; residential heating and cooking; re-emission from terrestrial and aquatic surfaces; the manufacturing, distribution, and use of chemicals; and natural processes (Unger et al., 2010). Given the large differences in the number and density of these sources as well as in their design, fuel source, and effectiveness of emission control technology, the relative contribution of these sources to air pollution concentrations and exposures varies considerably across locations.

Daily, weekly, and seasonal changes in source activity, as well as meteorological factors, can also lead to very large changes in the temporal trends in atmospheric pollutant concentrations and the relative contributions from different sources.

Sources of air pollutants can be divided into several types. These can be helpful in understanding the spatial and temporal distribution of source emissions, which has a large impact on exposures to emissions from different sources. Sources are commonly classified into three broad groups: primary, secondary, and re-emission sources. A primary source results from the direct emissions from an air pollution source. In contrast, a secondary source results from the formation of a pollutant in the atmosphere from the chemical reaction of precursors emitted from air pollution sources. Finally, a re-emission source results from primary or secondary pollutants depositing on the Earth's terrestrial or aquatic surfaces, followed by re-emission to the atmosphere.

Not all pollutants fall exclusively into one group, but in many locations, the classification of a pollutant into these categories can provide insight into exposure gradients. Secondary and re-emission sources tend to have smaller temporal and spatial concentration gradients than primary sources, due to the physical processes controlling their emissions. Primary sources can be further subdivided into point sources, mobile sources, and area sources. Point sources' emissions are from emissions stacks and tend to lead to very large spatial and temporal gradients in concentration. Mobile sources are associated with transportation and tend to have large spatial gradients close to roadways but tend to be more homogeneous away from roadways in urban areas. Area sources are sources with relatively dispersed emissions over large areas and lead to relatively constant source contributions over space but can have very large temporal changes in emissions. In addition, fugitive sources, including VOCs and dust, result from the leakage of gases from storage and handling facilities and the resuspension of dust, respectively. The nature of these source categories leads to source contributions and exposures that can be parameterized with physical and statistical models to represent pollutant concentrations, given knowledge of emission factors.

Estimates of the source contribution to pollutant concentrations in the atmosphere and to exposures can be obtained with transport models, receptor models, or hybrid models that integrate aspects of transport models and receptor models. Transport models use emissions inventories along with mathematical representations of wind speed and direction to estimate pollutant concentrations over time and space. Receptor models use measurements of pollutants at a given location or from personal exposure measurements to elucidate the sources of the pollutants (EPA, 2014; European Commission, 2014). Reasonable confidence in source apportionment models usually requires agreement between transport and receptor models, but this is not always achieved if the applied models are not adequately developed.

In locations or scenarios where transport and receptor models have not been developed, the use of emissions inventories and source-specific intake fractions can provide reasonable estimates of exposures and the sources of the exposures.

Table 1.3 provides a global anthropogenic emissions inventory of key global pollutants by sector in 2000. On a global average, the power and industry sectors were the two major anthropogenic sources of SO_2 emission. These two sectors together with biomass burning and on-road transportation also contributed greatly to NO_x emission. Biomass burning, household biofuel, on-road transportation, and industry were the most important sources of carbonaceous emissions, including CO, BC, OC, and VOCs (Unger et al., 2010). It is important to note that the relative source contribution and absolute source contribution to these pollutants vary considerably across different regions of the world, across urban areas, and across seasons.

1.2.2 Photochemical oxidants

Photochemical oxidants are secondary pollutants that are formed during photochemical reactions in the atmosphere. These oxidants have short lifetimes but are continuously formed and destroyed through chemical reactions, leading to pseudo-steady-state concentrations that are important for chemical processing and can be inhaled. These oxidants include ozone, hydrogen peroxide, acids, peroxyacetyl nitrate, and reactive radicals. The reactive radicals, which include hydroxyl radical, oxygen radical, hydrogen radical, and several other radicals, have very short lifetimes and are not commonly measured (Finlayson-Pitts & Pitts, 2000a). A large number of VOCs, SVOCs, and non-volatile organic compounds are also produced in photochemical smog, and some are oxidants (see Section 1.2.10). Ozone is often used as an indicator for these oxidant compounds.

Photochemical oxidants are formed in the presence of sunlight from the chemical reactions of VOCs and NO_x. A more detailed discussion of the sources of NO_x and VOCs is presented in Sections 1.2.6 and 1.2.10, respectively.

Given the nonlinear response of ozone production from the reaction of VOCs and NO_x, the relative source contributions to ozone cannot be directly scaled from the relative source contributions to VOCs and NO_x. Chemical transport models are needed to apportion the incremental ozone to sources (Cohan et al., 2005).

1.2.3 Particulate matter

The size of atmospheric particles can be related to their sources, due to the physical processes that form atmospheric particles and the atmospheric processes that control the fate and evolution of particle size distributions in the atmosphere.

Coarse PM (particles with aerodynamic diameters between 2.5 μm and 10 μm) is generated largely by physical processes, including resuspension of soil and road dust, sea spray, agricultural tilling, vehicular abrasion (i.e. tyre and brake wear), and fugitive dust emission from industrial sources.

Accumulation mode particles (particles with diameters between 0.2 μm and 2.5 μm) comprise predominantly the condensation of secondary inorganic and organic compounds and coagulated nuclei mode particles (particles with diameters < 0.2 μm). These particles comprise predominantly secondary sulfate and bisulfate ion, secondary nitrate ion, secondary ammonium ion, and carbonaceous PM from primary and secondary sources, but also include some crustal materials due to the fact that accumulation mode particles include supermicrometre particles.

Nuclei mode particles originate predominantly from combustion sources and atmospheric nucleation. They have relatively short

Table 1.3 Global anthropogenic emissions inventory of air pollutants by sector in 2000

Sector	NO_x[b]	CO[a]	NMVOCs[a]	SO_2[a]	BC[c]	OC[c]	CH_4[a]	NH_3[b]	N_2O[a]	CO_2[a]
Industry	6.0	51	33.6	63.2	769	2559	2.7	0.2	0.7	8414
Power	7.8	12	33.3	57.7	22	18	93.9	0.1	0.1	9127
Household fossil fuel	0.9	27	1.2	8.1	453	486	1.7	2.2	0.02	3390
Household biofuel	2.2	237	27.3	3.1	1471	7823	13.8	0	0.2	495
On-road transportation	8.7	186	33.8	3.7	1235	1630	0.9	0	0.1	4276
Off-road (land) transportation	1.8	13	4.6	2.0	588	292	0.008	0	0.003	390
Shipping	2.9	0.1	0.02	7.3	97	136	0.028	0	0.003	428
Aviation	0.7	0	0	0.2	11	0	0.006	0	0.020	654
Agricultural waste burning	0.2	16	2.0	0.2	371	2266	0.8	1.4	0.020	0
Waste/landfill	0.04	4	2.7	0.05	0	0	58.2	2.7	0.3	0
Biomass burning	10.2	507	31.3	2.7	3500	37 200	21.2	1.8	0.9	2740
Animals	0	0	0	0	0	0	88.5	21.1	3.2	0
Agriculture	0	0	0	0	0	0	39.4	12.6	6.6	0

BC, black carbon; CH_4, methane; CO, carbon monoxide; CO_2, carbon dioxide; N_2O, nitrous oxide; NH_3, ammonia; NMVOCs, non-methane volatile organic compounds; NO_x, nitrogen oxides; OC, organic carbon; SO_2, sulfur dioxide.

[a] Expressed in teragram (Tg) full molecular mass/year

[b] Expressed in teragram (Tg) nitrogen/year

[c] Expressed in gigagram (Gg) full molecular mass/year

Adapted from Unger et al. (2010). Attribution of climate forcing to economic sectors. *Proc Natl Acad Sci U S A*, 107(8):3382–7. doi: 10.1073/pnas.0906548107 PMID:20133724, with permission from PNAS.

atmospheric lifetimes before they either grow to become accumulation particles or coagulate to form accumulation particles. Nuclei mode particles tend to be enriched in carbonaceous aerosols and metals from the combustion of heavy oil and fuel as well as emissions from the high-temperature processing of metals.

Coarse PM comprises predominantly inorganic crustal materials, abrasion particles from mobile sources and industrial sources, and sea spray.

It should be noted that $PM_{2.5}$ includes nuclei mode particles and accumulation mode particles and PM_{10} includes nuclei mode particles, accumulation mode particles, and coarse particles (Watson, 2002).

Source apportionment efforts for PM have typically been directed at source apportionment of particle mass; however, there are some studies that have been used to apportion the sources of components of PM (Querol et al., 2007; Heo et al., 2013).

Zhang et al. (2007) analysed the bulk composition of fine PM at more than 30 sites in the Northern Hemisphere, including urban, rural, and remote locations. They found that organic compounds accounted for 18–70% of the PM mass, sulfate ion accounted for 10–67%, nitrate ion accounted for a few percent to 28%, and ammonium ion accounted for 7–19% of the PM mass. EC and crustal materials are also important contributors to fine PM in the context of human exposure and health. Crustal material typically contributes 5–20% to $PM_{2.5}$ in most locations in Europe and the USA (Chow & Watson 2002; Belis et al., 2013), and EC usually contributes about 5–10% of the fine PM mass. Although $PM_{2.5}$ levels in China are much higher than those in cities in North America and Europe, the relative composition in megacities in China is similar (Chan & Yao, 2008; Cao et al., 2012). In addition, sea spray and road salt (used in cold climates to melt snow and ice on roadways) can account for up to 5–10% of fine PM mass (Chow & Watson 2002; Belis et al., 2013).

Sulfate ion in fine and ultrafine PM is predominantly from the oxidation of SO_2, which is largely from the combustion without emission controls of sulfur-containing fossil fuels. More information on the sources of SO_2 is provided in Section 1.2.4.

The contribution of nitrate ion and ammonium ion to fine PM is influenced by the fact that the two major forms of nitrate ion – nitric acid and ammonium nitrate – are semivolatile compounds, which can exist in both the gas phase and the particle phase. Atmospheric chemistry, temperature, and humidity control the rate of NO_x conversion to nitric acid. Further details are given in Section 1.2.6

The sources of carbonaceous fine PM have been a large area of research over the past decade, and the tools to understand the contribution of primary sources of carbonaceous PM and the split between primary and secondary organic aerosols are quite advanced and show reasonably good agreement (Docherty et al., 2008; Snyder et al., 2009a; Zhang et al., 2009a; Heo et al., 2013). In contrast, it is still difficult to quantify the specific sources of secondary organic aerosols at this time. The primary sources of fine particle organic aerosols are dominated by combustion sources, including gasoline-powered engines, diesel-powered engines, coal and residual oil combustion, biomass burning, and food cooking operations (Schauer et al., 1996; Bond et al., 2004). As previously noted, the distribution of sources and their fuels, operations, and degree of emission controls can have a very large impact on their relative contributions to primary organic aerosols, which can be dominated by mobile sources in cities such as Los Angeles (USA), Tel Aviv (Israel), Amman (Jordan), and Mexico City (Mexico) (Stone et al., 2008; von Schneidemesser et al., 2010; Heo et al., 2013), by biomass burning in locations such as Kathmandu (Nepal) and rural North Carolina (USA) (Sheesley et al., 2007; Stone et al., 2010), or by multiple combustion sources in locations such as Beijing (China) (Zheng et al., 2005).

EC emissions are mainly in the submicrometre range, and the contribution of EC to atmospheric PM is largely in the $PM_{2.5}$ fraction. EC is mainly from pyrolysis during combustion from sources including coal combustion, fuel oil combustion, diesel engines, poorly operating gasoline engines, and biomass burning. As PM controls are being placed on most stationary power generation sources, as well as diesel engines, in Europe, the USA, and Canada, the concentrations of EC in these locations continue to decrease. In regions of the world where diesel engine emissions are not being controlled and there are large primary emissions from residual fuel and solid fuel combustion, these sources dominate contributions to EC.

Source contributions to PM_{10} can be represented as the sum of source contributions to fine PM plus source contributions to coarse PM. In the Los Angeles Basin (USA), coarse PM was found to have average contributions of about 50% from crustal material, 20% from secondary inorganic ions, 20% from OC, and 10% from sea spray (Cheung et al., 2011). Similar results were observed in the United Kingdom (Yin & Harrison, 2008). In locations affected by dust storms, the dust contributions to coarse PM and fine PM can be significantly larger in terms of concentrations and relative contribution.

Emissions inventory data can provide an assessment of sources of primary emissions of PM on a global or local scale (Bond et al., 2004; Corbett et al., 2007).

1.2.4 Sulfur dioxide

Natural sources of SO_2 include the atmospheric oxidation of sulfur compounds emitted from microbial activity in the ocean and from the anaerobic degradation of organic material in terrestrial environments. In some locations, such

as Mexico City and parts of Japan, SO_2 emissions from volcanoes also affect urban areas and SO_2 exposures (de Foy et al., 2009; Kitayama et al., 2010).

However, in most locations in the world that are influenced by anthropogenic emissions, SO_2 emissions from natural sources are usually much lower than anthropogenic emissions. SO_2 in urban and industrialized areas is largely from the combustion without emission controls of sulfur-containing fuels and from uncontrolled metal processing facilities that roast sulfide ores to make metal oxides. Emissions inventories can provide a good understanding of the sources of SO_2, given the ability to accurately estimate sulfur contents of fuels (Bhanarkar et al., 2005; Smith et al., 2011; Ozkurt et al., 2013). Many countries have adopted regulations and technologies to reduce sulfur levels in gasoline and diesel fuels; however, there are still a large number of countries around the world that do not have good controls for SO_2 emissions and have not reduced sulfur levels in mobile-source fuels. Historically, there have been petroleum refining and coal liquefaction facilities that have removed sulfur during fuel processing and emitted it as SO_2 directly to the atmosphere. It is unclear whether such facilities are still operating, but they may be important sources in some local areas where adequate emission controls do not exist.

In addition, in some regions where coal is burned for residential heating and cooking, very high exposure to SO_2 can occur.

1.2.5 Carbon monoxide

The formation of CO is largely due to poor mixing of combustion air and combustion fuel, resulting in incomplete combustion. The dominant sources of outdoor concentrations of CO in urban areas are on-road transportation (gasoline- or diesel-powered engines) (IARC, 2013a), off-road engines, and biomass burning activity.

The use of catalytic convertors to convert emissions of CO to CO_2 for on-road gasoline-powered engines decreases CO emissions.

In rural areas and locations where biomass fuels are commonly used for residential cooking and heating, outdoor concentrations of CO are typically dominated by these biomass burning activities. Likewise, forest fires and controlled burns of vegetation can also be very large sources of CO.

Several global assessments of CO can be used to understand the regional distribution of CO sources using emissions inventory and chemical transport models (Holloway et al., 2000). On an urban scale, inverse models can be used to understand the local contributions of sources to CO (Bergamaschi et al., 2000).

1.2.6 Nitrogen oxides

Globally, the sources of NO_x are dominated by fossil fuel combustion, microbial activity in soils, and biomass burning, with smaller contributions from lightning and stratospheric oxidation of nitrous oxide (N_2O).

In urban areas, fossil fuel combustion is often the dominant source and includes stationary power generation, diesel-powered engines, and gasoline-powered engines. There has been some concern that diesel aftertreatment technologies aimed at reducing PM emissions will shift the distribution of NO_x emissions towards NO_2, which will lead to higher NO_2 exposures near roadways (Grice et al., 2009).

In rural areas where residential combustion of solid fuels is common, the residential combustion of solid fuels and microbial activity in soils are typically the dominant sources of NO_x.

Ammonia is a primary pollutant and on national scales is emitted largely as a result of agricultural practices, including direct emissions from livestock waste, emissions from spreading of manure, and emissions from the use of synthetic fertilizers (Battye et al., 2003). In

urban areas, ammonia emissions are dominated by mobile-source emissions (Battye et al., 2003), which result from three-way catalytic converters over-reducing NO_x to ammonia (Fraser & Cass, 1998).

As part of the photochemical cycle, NO reacts with ozone to form NO_2, and NO_2 undergoes photolysis in the presence of sunlight to form NO. This photochemical cycle is a key component of ozone formation and the production of photochemical oxidants.

Chemical transport models that use emissions inventories have been very successful at modelling both near-roadway (Karner et al., 2010) and continental-scale NO_x concentrations (Stedman et al., 1997; Martin et al., 2003). Such models are an effective means of quantifying the sources of NO_x on different time scales for current and future scenarios.

1.2.7 Lead and other toxic metals

Non-volatile metals are components of atmospheric PM and can greatly influence its biological activity. Industrial sources can be very large sources of metals that can be found in atmospheric PM even though the metals are not major contributors to particle mass (Schauer et al., 2006; Snyder et al., 2009b). In the absence of industrial sources, roadway emissions and stationary power generation are typically the largest source of many toxic metals in the urban atmosphere. The braking systems of motor vehicles and underground public transportation emit metals that are potentially of concern for human exposure, including iron, copper, chromium, strontium, manganese, and antimony (Schauer et al., 2006; Kam et al., 2013). Stationary power generation that does not have suitable particle controls can have substantial impacts on metal concentrations and exposures. In locations where residual oils are used for heating and emission controls do not exist, very high concentration of nickel and vanadium can be found in atmospheric PM (Peltier et al., 2009). Likewise, coal fly ash can contain relatively high levels of arsenic, copper, chromium, zinc, antimony, selenium, and cadmium (Ratafia-Brown, 1994), and if the fly ash is not controlled with aftertreatment technologies, then emissions will contribute to an increased presence of toxic metals in the PM downwind of the facility. In developing countries, the uncontrolled emissions from brick kilns, waste incineration, and cement plants are important sources of metals to communities close to these facilities (Christian et al., 2010; Tian et al., 2012). There are very few comprehensive studies of the emissions inventory of fine particulate metals; Reff et al. (2009) provided an assessment of the spatially resolved emissions inventory for 10 metals classified as air toxics by the United States Environmental Protection Agency (US EPA) from 84 source categories.

1.2.8 Volatile metals, including mercury

Atmospheric mercury concentrations are largely dominated by gaseous elemental mercury (GEM), reactive gaseous mercury (RGM), and particulate mercury (Hg-P). RGM and Hg-P are formed in the atmosphere from the oxidation of GEM. Global anthropogenic emissions of mercury have been assessed by Pacyna et al. (2010). Globally, in 2005, burning of fossil fuel (mostly coal) was the largest single source of GEM emissions, accounting for about 45% of the anthropogenic emissions; artisanal/small-scale gold mining was responsible for about 18%, and industrial gold production accounted for 5–6%. Other mining and metal production activities and cement production were each responsible for about 10% of global anthropogenic releases to the atmosphere. The proportion of emissions from waste incineration and product-use sources is more difficult to estimate (Pacyna et al., 2010).

GEM is a global pollutant that has an atmospheric lifetime in the range of months to years. In most urban and rural outdoor locations, GEM

levels are typically in the range of 2–10 ng/m^3, and the concentrations of RGM and Hg-P are typically in the range of tens to hundreds of picto-grams per cubic metre. Local sources of GEM, including anthropogenic sources and re-emissions from terrestrial and aquatic surfaces, can increase local concentrations to 5–10 ng/m^3, or hundreds of nanograms per cubic metre near large mercury sources (Manolopoulos et al., 2007).

In addition to mercury, other volatile metals have been measured in the atmosphere, including alkyl-lead compounds (Wang et al., 1997), arsines and methyl arsines (Mestrot et al., 2009), and selenium compounds (Zhang et al., 2002).

1.2.9 Polycyclic aromatic hydrocarbons

Poor combustion conditions can lead to high emissions of PAHs and are often associated with liquid and solid fuel combustion. Benzo[*a*]pyrene (B[*a*]P) is a specific PAH formed mainly from the burning of organic material, such as wood, and from car exhaust fumes, especially from diesel vehicles. B[*a*]P pollution is predominantly a problem in countries where domestic coal and wood burning is common (EEA, 2013).

In 2007, it was estimated that the global total atmospheric emission of 16 PAHs came from residential/commercial biomass burning (60.5%), open-field biomass burning (agricultural waste burning, deforestation, and wildfire) (13.6%), and petroleum consumption by on-road motor vehicles (12.8%) (Shen et al., 2013).

1.2.10 Other organic compounds, including VOCs, SVOCs, and particulate organic matter

Thousands of organic compounds can be found in the atmosphere. They are components of fossil fuel, partially combusted components of fossil fuel, and pyrolysis products of fossil fuel; industrial chemical, food cooking, and biomass burning emissions; biogenic compounds emitted from plants; and organic compounds formed in the atmosphere (EEA, 2013; Oderbolz et al., 2013). These compounds include VOCs, non-volatile organic compounds that are present in atmospheric PM, and SVOCs that are present in both the gas phase and the particle phase. Many known or suspected carcinogens (Table 1.2) come from combustion sources; they include benzene, 1,3-butadiene, formaldehyde, acetaldehyde, acrolein, and naphthalene (EPA, 2006). Industrial facilities and consumer products are also important sources of aromatic VOCs, oxygenated VOCs, and halogenated VOCs. These chemicals include benzene, toluene, xylenes, ethylbenzene, methyl ethyl ketone, acetophenone, and trichloroethylene. In addition, some VOCs of potential concern are also formed in the atmosphere from photochemical reactions; these include formaldehyde, acetaldehyde, and nitrobenzene. There is also a group of persistent organic pollutants (POPs), which include many SVOCs such as polychlorinated biphenyls, polybrominated biphenyls, furans, and dioxins, and several pesticides and insecticides that can be directly emitted from air pollution sources or re-emitted from previous contamination through volatilization or resuspension of soil material (EPA, 2006; EEA, 2013).

The three major sources of VOCs in Asia are stationary combustion, solvent and paint use, and transportation; the proportion of each of these sources varies between 25% and 50%, depending on the region (Kurokawa et al., 2013). In Europe, solvent and product use was reported to contribute to about half of the total VOC emissions; the contributions of three other major sources of VOCs – commercial, institutional, and household energy use; road transportation; and energy production – were 10–20% each (EEA, 2013). In the USA, the relative source contribution reported in 2008 by the US EPA was 50% for transportation and 20% each for solvent use and industrial processes (EPA, 2013d).

In recent years, significant progress in the development of emissions inventories has been made, including the current and future emissions of dioxins (Quass et al., 2004). To assess the sources of organic compounds that both are formed in the atmosphere and react in the atmosphere, such as formaldehyde, chemical transport models are needed (Zheng et al., 2005). Several integrated assessments of emissions inventories of toxic organic compounds have been conducted and are used to provide an integrated risk from these sources by source and receptor (George et al., 2011; Luo & Hendryx, 2011).

1.2.11 Mineral dust and fibres

Resuspended dust from roadways, agricultural lands, industrial sources, construction sites, and deserts is a major source of PM in many regions of the world. Roadway dust also contains metals associated with motor vehicles (Schauer et al., 2006). Agricultural soils often contain metals that accumulate from fertilizer and animal waste, and the content of dusts from industrial sources and construction sites will depend on the specific process activities occurring at those facilities.

Although fibres, such as asbestos, are not commonly measured in the outdoor atmosphere, they can be part of the atmospheric pollution mixture. The use of asbestos has been restricted or banned in many countries. However, outdoor air pollution with asbestos may still arise in some areas from releases from asbestos-containing building materials, asbestos brakes used on vehicles, and asbestos mining activity (IARC, 2012a).

1.2.12 Bioaerosols

Bioaerosols are part of the atmospheric PM. The term "bioaerosol" refers to airborne biological particles, such as bacterial cells, fungal spores, viruses, and pollens, and their products, such as endotoxins (Stetzenbach et al., 2004). A wide range of these biological materials have been measured in the outdoor atmosphere, including moulds, spores, endotoxins, viruses, bacteria, proteins, and DNA (Yeo & Kim, 2002). Knowledge about the dynamics and sources of airborne microbial populations is still scanty. Bioaerosols are believed to be ubiquitous, and studies demonstrate the long-range transport of microorganisms and biological particles in the atmosphere (Gandolfi et al., 2013). Bioaerosols may derive from many sources, for example plants, suspension of soils containing biological materials, cooking, and burning of biological materials.

1.3 Outdoor air pollution measurement methods

Measurements of gaseous and particle air pollutants have been used for exposure assessment and epidemiological studies. Methods include passive sampling (e.g. diffusion-based methods on an absorbent) and active sampling with pumps. Most methods for regulated gas pollutants (e.g. CO, NO_2, ozone, and SO_2) use in situ continuous monitors for hourly averaged concentrations. Airborne particles are sampled mostly using integrated sampling systems over a 24-hour period with defined inlets, sampler surfaces, filter substrates/holders, pumps, and flow controllers. Filter substrates are used to measure mass concentration by gravimetry. These substrates can be further analysed for their major components to explain the measured mass. Continuous monitoring for mass by β attenuation monitoring, an inertial balance, or particle light scattering (as a surrogate for PM mass) have been used at many central monitoring sites since the early 1980s. Continuous PM component measurements for precursor gases, elements, ions, and carbon along with particle number, size, and single particle measurement have been available since the late 1990s.

1.3.1 Overview

Table 1.4 (available online at: http://monographs.iarc.fr/ENG/Monographs/vol109/Table1.4-online.pdf) summarizes different measurement methods by pollutant, including relevant references that provide greater detail on measurement principles, practicality, measurement standards, detection limits, accuracy, precision, interferences, and intercomparability for different environments and costs. Table 1.4 (available online) also identifies opportunities for quantifying a wide range of pollutants beyond those that are currently regulated by ambient air quality standards (AAQS) (Chow & Watson, 2011; Billionnet et al., 2012; Pachon et al., 2012). The major categories in Table 1.4 (available online) are individual gases, multiple gases, PM for mass and chemical components, particle number and size, and mercury.

In Table 1.4, (available online) references associated with topic headings are more general reviews for that category, and more detailed treatments are associated with each method. The cited references are intended to inform about past measurement methods – for example, the British Smoke measurement of filter darkening dates from the 1920s (Hill, 1936; Brimblecombe, 1987) and has been used in retrospective exposure studies – as well as newly emerging technologies. A few critical reviews and textbooks provide broad descriptions of gas and particle measurements (Chow, 1995; Landsberger & Creatchman, 1999; Finlayson-Pitts & Pitts, 2000a; McMurry, 2000; Cohen & McCammon, 2001; Wilson et al., 2002; Clemitshaw, 2004; Fehsenfeld et al., 2004; Heard, 2006; Chow et al., 2008; Wexler & Johnston, 2008; Kulkarni et al., 2011; Chow & Watson, 2012), and detailed procedures for certain methods have been published by ASTM (2013), the US EPA (2013a, 2013b), ISO (2013), and the European Union (EU) (CEN, 2013).

1.3.2 Types of air quality monitors

Pollutants for which air quality standards have been established in many countries (called "criteria pollutants" under the statute defined by the US EPA, i.e. CO, NO_2, SO_2, ozone, $PM_{2.5}$ mass, PM_{10} mass, TSP, and lead) are monitored in populated areas to determine compliance with the AAQS, and these data can often be downloaded for specific study areas and time periods (e.g. EPA, 2013c). Gases are recorded continuously as hourly averages, and PM mass concentrations may be hourly or 24-hour averages.

Sampling sites are selected to represent neighbourhood (~1–5 km) to regional (100–1000 km) scales (EPA, 1997, 1998; Chow et al., 2002), although some are also located in near-road environments (~30–50 m) dominated by vehicle exhaust or in industrial fenceline environments. Monitoring methods and procedures are specified for compliance purposes, and the data are used to determine exceedances of the AAQS. Compliance data can be used as a first estimate of human exposure, but these can be supplemented with additional measurements in microscale (1–10 m) environments to obtain more representative exposure estimates.

Passive sampling is the most cost-effective approach for estimating spatial gradients around compliance monitors, surveying additional pollutants, identifying hotspots, and estimating individual exposure. However, passive samplers need to be co-located with calibrated gas and particle sampling systems at the central monitoring site to establish equivalence and comparability. Substrate passive samplers are simple, inexpensive, and unobtrusive and require no power (Kot-Wasik et al., 2007; Zabiegała et al., 2010).

Passive samplers can detect long-term averages to very low levels, depending on the environment. Diffusion tube and badge-type passive samplers are in most common use, and the references in Table 1.4 (available online) identify

impregnants suitable for several gaseous pollutants and specific VOCs. A passive PM sampler coupled with microscopic analysis is also listed.

In active sampling, an air mover (e.g. pump or blower) draws air through a substrate or absorbing solution, pumps it into a container, or directs it into an in situ sensor. Accurate and precise flow rates and sample durations must be quantified (Watson et al., 2013).

The largest variety of compounds is obtained from laboratory analysis of the substrates or container contents, but this is at the expense of averaging times and labour to change samples. Some of this is compensated for with in situ continuous instruments, which collect and analyse the sample in the field, but this comes at an even higher cost.

The trend is towards microsensors that use battery-powered miniature pumps and can be placed in microenvironments or carried by an exposure subject (Marć et al., 2012; Moon et al., 2012; Steinle et al., 2013). Miniature samplers are in common use for PM and certain gases, and the detection limits of optical light scattering/absorption systems and electrochemical gas sensors have been improving.

Particle scattering by nephelometer with a $PM_{2.5}$ inlet and a smart heater to remove moisture under high relative humidity (e.g. > 65%) is often used as a surrogate for $PM_{2.5}$ mass (Chow et al., 2006; Watson et al., 2008).

Remote sensing measures the scattering and absorption of infrared, visible, and ultraviolet radiation at different wavelengths along a sight path. Path lengths may range from a few metres, used for in-plume monitoring, to thousands of kilometres for geostationary satellites (Hidy et al., 2009; Hoff & Christopher, 2009). Satellite remote sensing estimates for PM, NO_2, SO_2, and some other pollutants often correspond to urban and industrial areas, but spatial resolution is limited to about 10 km.

1.4 Environmental occurrence and human exposure

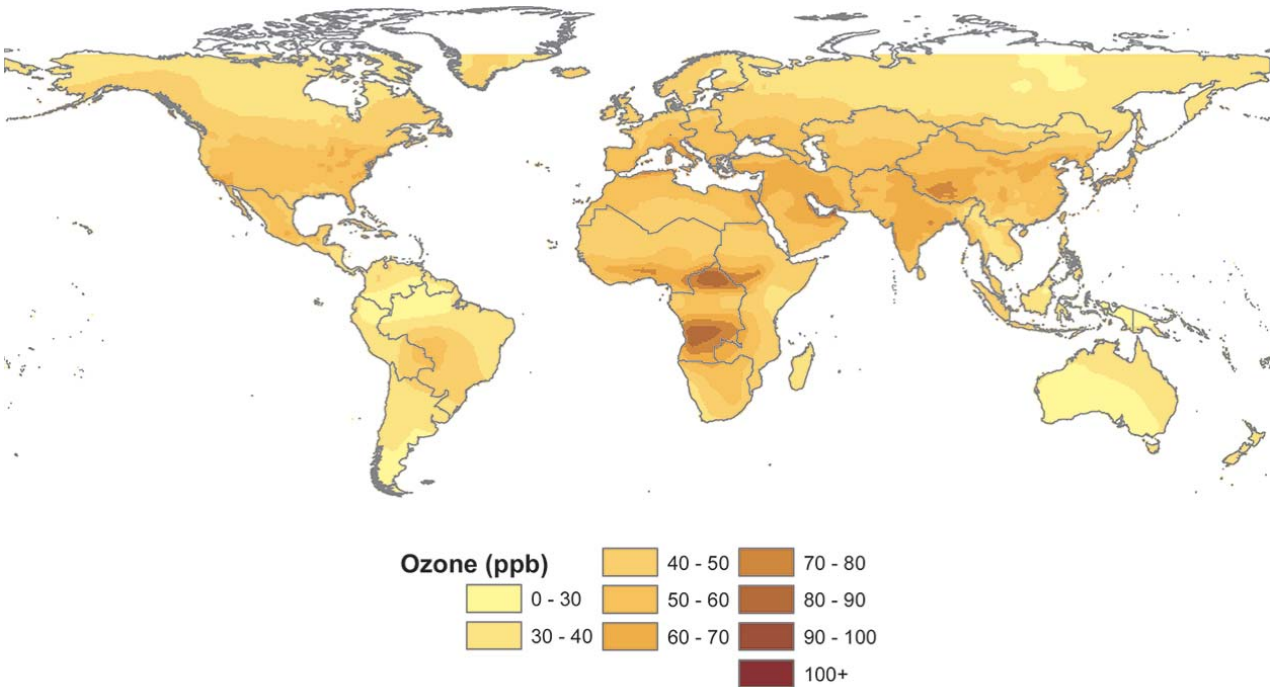
This section describes concentrations of air pollutants measured throughout the world. Because measurement approaches and methodologies differ by location, direct comparisons between countries of levels measured by ground-based monitoring should be made with caution. Furthermore, there are major differences in the overall availability of routine measurement data between countries. Although they are not available for all constituents of interest, satellite-based approaches provide estimates in a consistent manner for the entire globe and are therefore useful to identify spatial patterns (Lee et al., 2009; Brauer et al., 2012; Lamsal et al., 2013).

For ozone, a global chemical transport model simulation of seasonal maximum concentrations is available. The estimated levels of ozone are highest in North America, Latin America, Europe, and South and East Asia, as well as parts of Africa. For these regions, seasonal (3-month) hourly maximum ozone concentrations in 2005 were estimated to be greater than 40 ppb [80 μg/m^3], with concentrations in some areas in parts of Asia and Africa greater than 80 ppb [160 μg/m^3] (Fig. 1.2). As expected, given that ozone is a secondary pollutant, the spatial variability of the ozone concentration is less pronounced than that of $PM_{2.5}$, and levels are not as systematically higher in the rapidly developing countries of Asia (Brauer et al., 2012).

For $PM_{2.5}$, the concentration in 2005 was estimated to be high (> 50 μg/m^3) in South and East Asia. Similarly high concentration estimates due to airborne mineral dust, rather than combustion emissions, were reported in North Africa, central Asia, and Saudi Arabia (Brauer et al., 2012; Fig. 1.3).

Global variation in NO_2 generally follows the spatial variation in combustion sources such as motor vehicle exhaust. Broad regional patterns of higher NO_2 concentrations correspond to

Fig. 1.2 Estimated seasonal (3-month) hourly maximum ozone concentrations (ppb) from a global chemical transport model (TM5) for 2005



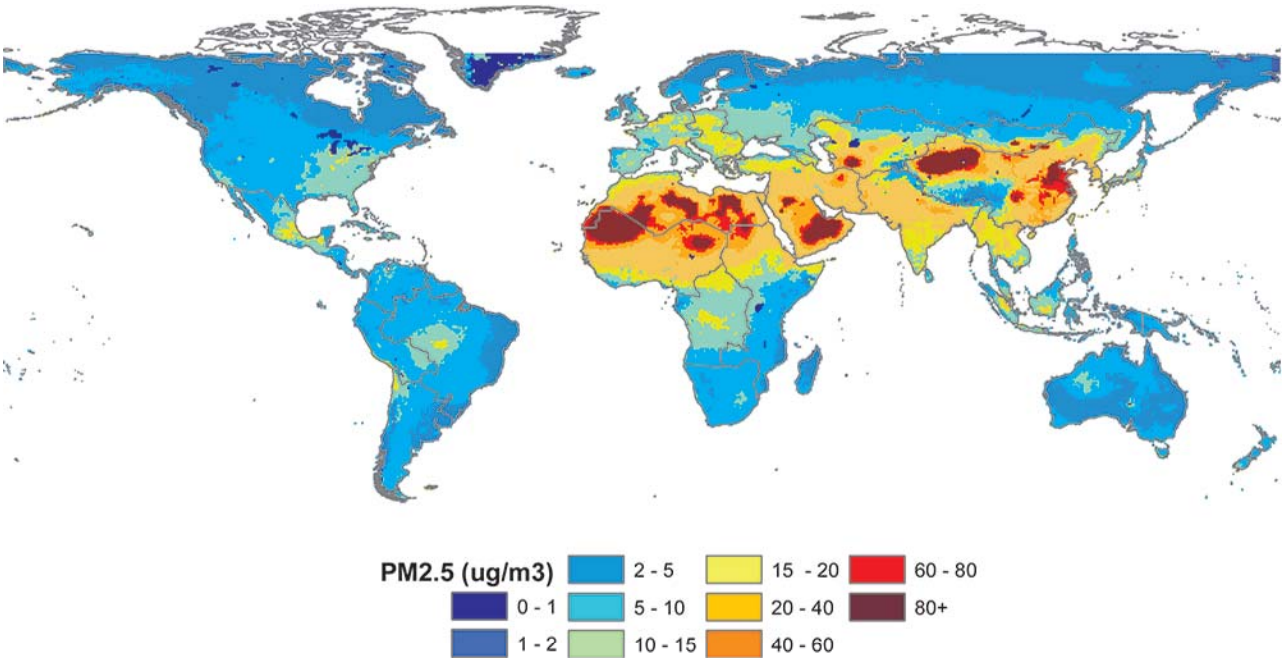
Ozone concentrations in μg/m³ = 2 × ozone concentrations in ppb.
Reprinted from Brauer et al. (2012). Exposure assessment for estimation of the global burden of disease attributable to outdoor air pollution. *Environ Sci Technol*, 46:652–660, with permission from the American Chemical Society. Copyright 2012, American Chemical Society.

population density, although absolute levels vary considerably according to economic development and air quality management programmes. In urban areas, lower concentrations are observed in cities in India (0.2–12 ppb [0.38–22.9 μg/m³]), substantially higher concentrations in cities in China (0.3–8 ppb [0.57–15.3 μg/m³]), and levels varying across this range for cities in the USA and Europe, reflecting differences in per capita fuel consumption. Globally, NO_2 concentrations increase in proportion to population raised to an exponent that varies by region (Lamsal et al., 2013).

Elevated SO_2 levels are observed over urban and industrial areas, especially in eastern China. Specific plumes related to volcanic activity are also evident in the satellite-based estimates. For example, the SO_2 plume from the Nyamuragira eruption in the Democratic Republic of the Congo can extend to South Asia (Lee et al., 2009).

High levels of formaldehyde are found in tropical regions in Africa and South America, where biogenic and biomass burning sources are important. High levels are also found in South-East Asia, resulting from biomass burning and anthropogenic sources. Seasonal variations in formaldehyde levels reflect increased biogenic and biomass burning emissions during summer in deciduous forests (mid-latitudes) and during the dry season in tropical forests (Amazon and Africa) (De Smedt et al., 2012).

Fig. 1.3 Estimated 2005 annual average $PM_{2.5}$ concentrations (μg/m³)



The $PM_{2.5}$ estimates are generated from the grid cell average of satellite-based estimates and chemical transport model (TM5) simulations that are calibrated with a prediction model incorporating surface measurements.
$PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 μm.
Reprinted from Brauer et al. (2012). Exposure assessment for estimation of the global burden of disease attributable to outdoor air pollution. *Environ Sci Technol*, 46:652–660, with permission from the American Chemical Society. Copyright 2012, American Chemical Society.

1.4.1 Outdoor pollutant concentrations

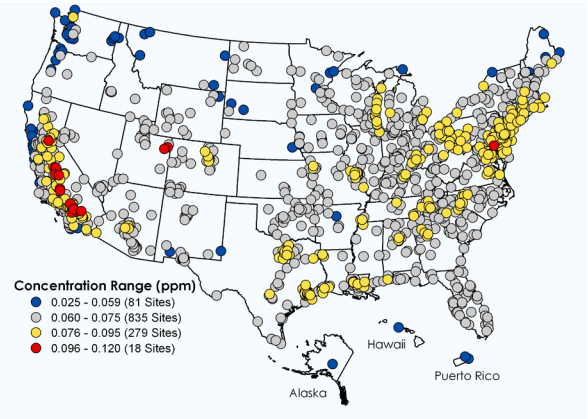
(a) North America (USA, Canada, and Mexico)

Measurements of air pollutant concentrations in North America at the country level are summarized in detail in this section. Differences in network composition, sampling and analysis methods, and available summary information hamper direct comparisons between countries. However, several global databases are available for a limited number of pollutants, which allow direct comparisons. The Global Burden of Disease Study 2010 provided estimates of $PM_{2.5}$ and ozone globally at about 10 × 10 km resolution, combining estimates from a chemical transport model, an approach using satellite retrievals of aerosol optical depth and a chemical transport model, and available measurements (Brauer et al., 2012). For 2005, the population-weighted annual mean $PM_{2.5}$ concentration in North America was estimated as 13 μg/m³, and the population-weighted seasonal 3-month hourly maximum ozone concentration was 57 ppb. Fig 1.2 and Fig. 1.3 present the estimated concentrations.

(i) USA

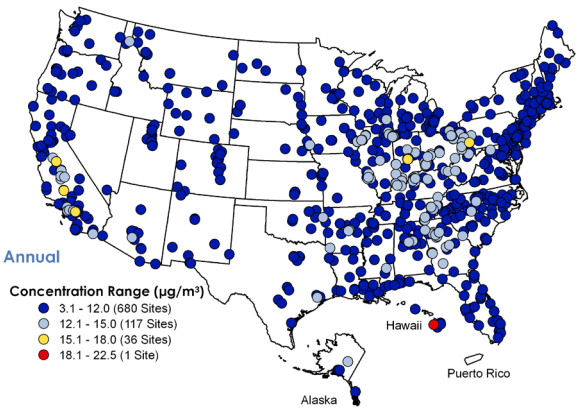
The US EPA collates a comprehensive database of outdoor air pollutant measurements conducted at about 3000 locations by state and local air quality monitoring agencies following Federal Reference Methods for the criteria air pollutants (ozone, NO_x/NO_2, SO_2, $PM_{2.5}$/PM_{10}, CO, and lead). This network (EPA, 2011a) was initiated in 1978, although monitoring approaches and specific pollutants that have been included have changed over time. At a subset of about 250 of these sites, several air toxics such as VOCs, metals in PM_{10}, and mercury are monitored (EPA, 2012a). This network is complemented by about

Fig. 1.4 Annual fourth-highest daily maximum 8-hour ozone concentrations in 2010 in the USA (applicable NAAQS is 0.075 ppm)



NAAQS, National Ambient Air Quality Standards.
Reprinted from EPA (2012c). Air quality monitoring information. Available from: http://www.epa.gov/airtrends/factbook.html.

Fig. 1.5 Annual average (98th percentile of 24-hour concentrations) $PM_{2.5}$ concentrations in 2010 in the USA

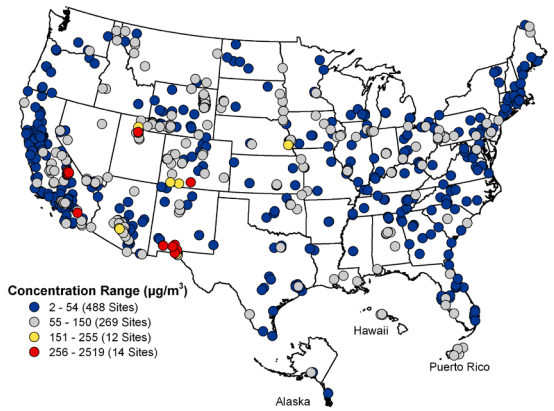


$PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 µm.
Reprinted from EPA (2012c). Air quality monitoring information. Available from: http://www.epa.gov/airtrends/factbook.html.

180 chemical speciation network monitoring sites (EPA, 2013e), where specific components of $PM_{2.5}$ are measured. Several smaller routine monitoring networks are also operated with specific objectives, for example the IMPROVE network to assess the impacts of air pollution on visibility in protected environments (IMPROVE, 2012). In addition, the National Air Toxics Trends Station (NATTS) Network (EPA, 2012b) provides long-term monitoring data for air toxics at 27 sites (20 urban, 7 rural) across the country.

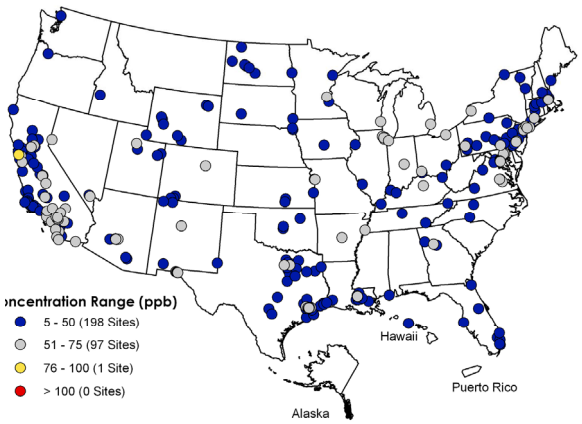
Regular status and trends reports provide information on concentrations of criteria and toxic air pollutants (EPA, 2012c). Summary information for 2010 is presented in Fig. 1.4, Fig. 1.5, Fig. 1.6, Fig. 1.7, and Fig. 1.8 and shows substantial variability in outdoor pollutant concentrations across the USA. The highest concentrations of ozone were observed in California as well as the Ohio River valley, the New England states, Texas, and several south-eastern states. Ozone levels are more heterogeneous over space, with most sites reporting levels below the National Ambient Air Quality Standards (NAAQS) of 75 ppb (annual fourth-highest daily maximum 8-hour concentration) (Fig. 1.4). Concentrations (annual average) of $PM_{2.5}$ were highest in California, Indiana, Pennsylvania, and Hawaii. Current levels of $PM_{2.5}$ (annual average) are below 15 µg/m³ at all but 6 (of > 700) reporting monitoring sites (Fig. 1.5). During winter periods, high concentrations of $PM_{2.5}$ were measured in regions where wood burning is prevalent, such as the Pacific Northwest and Alaska (EPA, 2012c). High PM_{10} concentrations were observed in California as well as Utah, Colorado, and New Mexico, especially in arid regions or industrial areas with multiple coarse particle sources (Fig. 1.6). NO_2 concentrations generally correspond to population density, with the highest concentrations observed in California, the Midwest, and the East Coast (Fig. 1.7). Annual average NO_2 levels have a range of 1–28 ppb, with a mean across 142 Metropolitan Statistical Areas of 10 ppb, well below the NAAQS of 53 ppb. To further describe spatial patterns at high resolution (30 m), Novotny et al. (2011) used a combination of satellite-based estimates and land-use

Fig. 1.6 Annual average (2nd highest maximum of 24-hour concentrations) PM_{10} concentrations in 2010 in the USA



PM_{10}, particulate matter with particles of aerodynamic diameter < 10 µm.
Reprinted from EPA (2012c). Air quality monitoring information. Available from: http://www.epa.gov/airtrends/factbook.html.

Fig. 1.7 NO_2 (98th percentile of 1-hour daily maximum) concentrations in 2010 in the USA



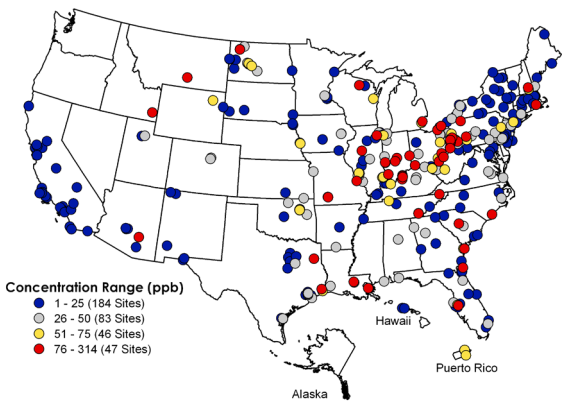
NO_2, nitrogen dioxide.
Reprinted from EPA (2012c). Air quality monitoring information. Available from: http://www.epa.gov/airtrends/factbook.html.

characteristics to model NO_2 across the USA. Using this approach, a population-weighted mean annual average concentration of 10.7 ppb was estimated. SO_2 concentrations are highest in the Upper Midwest and portions of the Northeast, where coal-fired power generation and industrial sources are common (Fig. 1.8). The 1-hour maximum SO_2 levels ranged from 0.1 ppb to 10.5 ppb, with a mean across 178 Metropolitan Statistical Areas of 2.4 ppb, well below the annual mean NAAQS of 30 ppb. Lead concentrations are much higher near stationary sources such as metals processing, battery manufacturing, and mining (~8 times the concentrations at sites not located near stationary sources) (Fig. 1.9). Levels of airborne lead (maximum 3-month average) are mostly below 0.07 µg/m³ (about half the level of the current NAAQS of 0.15 µg/m³), but levels as high as 1.4 µg/m³ have been measured at a subset of sites (EPA, 2012c).

For all of the criteria pollutants, concentrations have decreased over the past 10 years, after even larger decreases in earlier periods. $PM_{2.5}$ and PM_{10} concentrations show steady reductions that coincide with emissions reduction programmes (EPA, 2012c). Nationally, between 2001 and 2010, 24-hour $PM_{2.5}$ and PM_{10} concentrations declined by 28% and 29%, respectively.

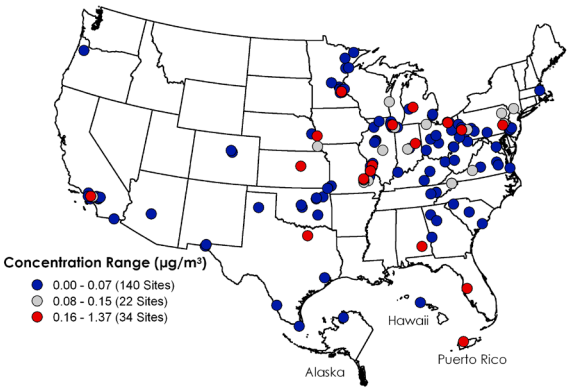
The US EPA operates several networks (the Urban Air Toxics Monitoring Program [UATMP], the National Air Toxics Trends Station [NATTS] Network, and the Community-Scale Air Toxics Ambient Monitoring [CSATAM] Program) that collect information on outdoor concentrations of HAPs. The 2010 report includes data from samples collected at 52 monitoring sites that collected 24-hour air samples, typically on a 1-in-6 day or 1-in-12 day schedule. Of these, 24 sites sampled for 61 VOCs, 30 sites sampled for 14 carbonyl compounds, 26 sites sampled for 22 PAHs, 14 sites sampled for 11 metals, and 23 sites sampled for hexavalent chromium (EPA, 2012d). The report provides detailed summary (and individual site) statistics on all of the measured pollutants, and a risk-based screening approach is applied to identify pollutants of highest priority based

Fig. 1.8 SO_2 (99th percentile of daily 1-hour maximum) concentrations in 2010 in the USA



SO_2, sulfur dioxide.
Reprinted from EPA (2012c). Air quality monitoring information. Available from: http://www.epa.gov/airtrends/factbook.html.

Fig. 1.9 Lead (maximum 3-month average) concentrations in 2010 in the USA



Reprinted from EPA (2012c). Air quality monitoring information. Available from: http://www.epa.gov/airtrends/factbook.html.

on the proportion of measurements exceeding risk-based screening levels. These "pollutants of interest" and 2010 summary concentrations are presented in Table 1.5. Information on trends is provided for individual sites, most of which indicate small decreases over the past about 8 years of monitoring, but data are not systematically analysed for temporal trends at the national level (EPA, 2012d).

The US EPA also produces the National-Scale Air Toxics Assessment (NATA) as a screening risk assessment tool that is used to identify pollutants and locations of specific concern in relation to potential cancer risk from air pollution and to assess trends. The most recent NATA, for 2005, was published in 2011 (EPA, 2012e) and includes information on 177 HAPs identified in the Clean Air Act as well as diesel PM.

In addition to government reporting, several research projects have reported outdoor concentrations of HAPs at the national scale. The Health Effects Institute (HEI) summarized outdoor concentrations of seven priority mobile-source air toxics (acetaldehyde, acrolein, benzene, 1,3-butadiene, formaldehyde, naphthalene, and polycyclic organic matter) because it was determined that mobile sources were a sizeable source of human exposure and existing data suggested potential for adverse health effects at outdoor concentrations. The report provides summaries of outdoor concentrations for each of these pollutants, except naphthalene (for which outdoor concentrations are reported as being < 1 µg/m³) (HEI, 2007).

(ii) Canada

In Canada, the National Air Pollution Surveillance (NAPS) network was initiated in 1969 and currently includes about 300 sites in more than 200 communities located in every province and territory of the country. Monitoring is focused on SO_2, NO_2, ozone, CO, PM_{10}, and $PM_{2.5}$, and a suite of 50 elements (including metals such as arsenic, lead, and mercury), 14 inorganic and organic anions, and 11 inorganic cations are measured in PM samples. Additional measurements of trace contaminants, including VOCs, PAHs, polychlorinated biphenyls (PCBs), and dioxins, are made at a subset of about 40 locations. Results are summarized in a series

Table 1.5 Summary concentrations of air toxics "pollutants of interest" in the USA for 2010

Compound	Mean	SD	Median	25th percentile	75th percentile
PAHs[a]					
Acenaphthene	3.98	7.69	2.04	0.983	4.30
Benzo[*a*]pyrene	0.131	1.32	0.02	0	0.1
Fluorene	4.82	8.09	2.91	1.75	5.39
Naphthalene	95.3	117	66.4	36.6	117
Metals[b]					
Arsenic (PM_{10})	0.558	0.535	0.415	0.240	0.700
Beryllium (PM_{10})	0.003	0.005	0.002	0.0003	0.004
Cadmium (PM_{10})	0.164	0.238	0.084	0.050	0.176
Lead (PM_{10})	3.67	4.95	2.32	1.45	3.74
Manganese (PM_{10})	6.82	11.6	4.03	2.15	7.97
Nickel (PM_{10})	1.06	0.915	0.845	0.594	1.22
Hexavalent chromium	0.037	0.129	0.018	0	0.032
Carbonyls[c]					
Acetaldehyde	1.06	0.718	0.893	0.597	1.29
Formaldehyde	2.01	1.80	1.66	1.09	2.47
VOCs[d]					
Acrylonitrile	0.017	0.084	0	0	0
Benzene	0.311	0.223	0.245	0.173	0.373
1,3-Butadiene	0.038	0.044	0.026	0.012	0.048
Carbon tetrachloride	0.567	1.38	0.037	0.013	0.272
Chloroform	0.038	0.119	0.020	0.014	0.031
p-Dichlorobenzene	0.019	0.105	0.007	0	0.019
1,2-Dichloroethane	0.003	0.008	0	0	0
Ethylbenzene	0.082	0.216	0.053	0.03	0.1
Tetrachloroethylene	0.025	0.029	0.016	0.008	0.03
Trichloroethylene	0.011	0.073	0	0	0
Vinyl chloride	0.0004	0.002	0	0	0

PAHs, polycyclic aromatic hydrocarbons; PM_{10}, particulate matter with particles of aerodynamic diameter < 10 μm; SD, standard deviation; VOCs, volatile organic compounds.

[a] PAHs: unit is ng/m^3.

[b] Metals: unit is ng/m^3.

[c] Carbonyls: unit is ppbv.

[d] VOCs: unit is ppbv.

Data extracted from the 2010 National Monitoring Programs Annual Report (EPA, 2012d) of the US EPA monitoring networks, which collect information on outdoor concentrations of hazardous air pollutants (Urban Air Toxics Monitoring Program [UATMP], National Air Toxics Trends Station [NATTS] Network, and Community-Scale Air Toxics Ambient Monitoring [CSATAM] Program).

of annual and summary reports (Environment Canada, 2010). Concentrations of major air pollutants have declined dramatically over the past about 40 years of measurement, as seen in Fig. 1.10, Fig. 1.11, Fig. 1.12, and Fig. 1.13.

In addition, the Canadian Air and Precipitation Monitoring Network operates 29 locations where $PM_{2.5}$ speciation is measured. Hystad et al. (2011) used a combination of satellite-based estimates and land-use characteristics to model the concentrations of $PM_{2.5}$ and NO_2 across Canada. National models for benzene, ethylbenzene, and 1,3-butadiene were also developed based on land use and source proximity characteristics (Hystad et al., 2011).

Setton et al. (2013) used data from the NAPS network (for 2006) and measurements reported in the literature or government reports since 2000 along with deterministic concentration gradients based on proximity to major roads and industrial sources to estimate exposure to several IARC Group 1 carcinogens in outdoor air in Canada. Table 1.6 presents estimated exposures to selected IARC Group 1, Group 2A, and Group 2B carcinogens in outdoor air in Canada for 2010, based on data from the CAREX database (CAREX Canada, 2013).

(iii) Mexico

The National Information System for Air Quality (SINAICA) operates about 50 sites in Mexico where ozone, NO_x, CO, SO_2, PM_{10}, TSP, and VOCs are measured (SINAICA, 2011). An additional network of about 60 sites is operated in Mexico City for the same general suite of pollutants (Secretaría del Medio Ambiente, 2013). Data from the air quality monitoring networks are centralized by the National Institute of Ecology, with detailed reports provided for specific airsheds. Parrish et al. (2011) provided summaries of trends of annual average concentrations in Mexico City over a 20-year period in which air quality has improved substantially (Fig. 1.14).

Annual average particulate PAH concentrations (in PM_{10}) collected at a site in Mexico City over a period of several years are summarized in Table 1.7. For several of the PAHs, concentrations increased during this 4-year period, even as PM_{10} concentrations decreased (Amador-Muňoz *et al.*, 2013).

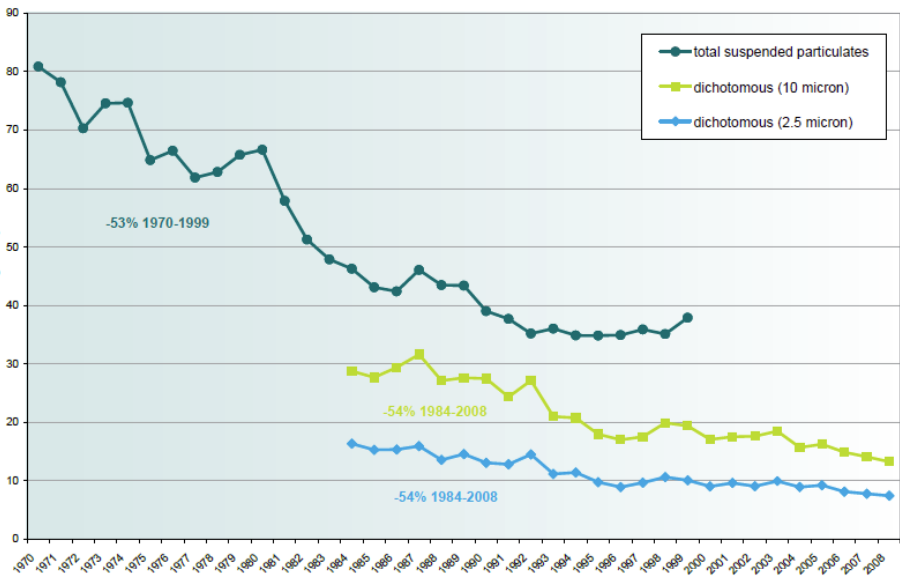
Mexico, Canada, and the USA operate a collaborative network for measurement of dioxins and furans, including nine stations in Mexico (five rural, two semi-urban, and two urban sites) (Cardenas et al., 2011). The mean concentrations for the background (rural) and semi-urban sites were 1.59 fg/m^3 and 18.6 fg/m^3, respectively, which are of the same order of magnitude as those reported by the outdoor monitoring networks in the USA and Canada. However, the mean concentration for the urban sites was 282 fg/m^3, which is significantly higher than concentrations measured at similar sites in the USA and Canada.

(b) Europe

In this section, information on outdoor concentration levels, spatial variation, and time trends in major outdoor air pollutants in Europe is summarized. Data are available from routine monitoring networks and several large research projects. This text focuses on concentration data from 38 countries that are members or cooperating members of the European Environment Agency (EEA), so that the spatial pattern across Europe is broadly represented.

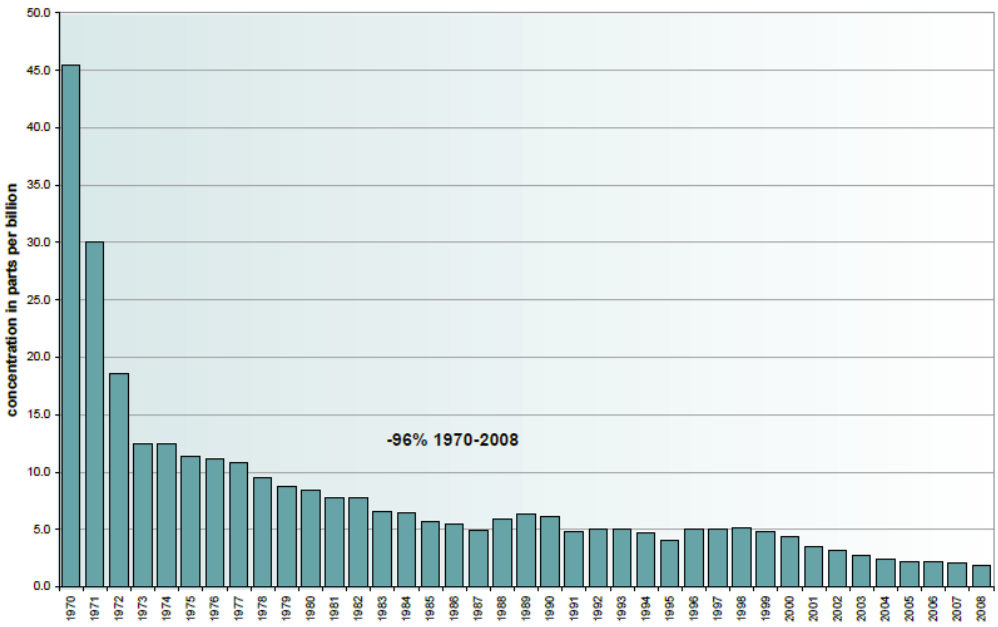
Routine monitoring networks are national in Europe; there is no comprehensive European network. EU Member States have to report their data to the EU, resulting in the European air quality database AirBase, maintained by the EEA, in which concentrations and metadata (site description, monitoring methods) are available (EEA, 2014). European reference methods have been defined for regulated pollutants. The EEA regularly reports assessment of air quality across Europe (e.g. EEA, 2012).

Fig. 1.10 Trends (1970–2008) in annual mean particle (TSP, PM_{10}, $PM_{2.5}$) concentrations measured at National Air Pollution Surveillance (NAPS) sites in Canada



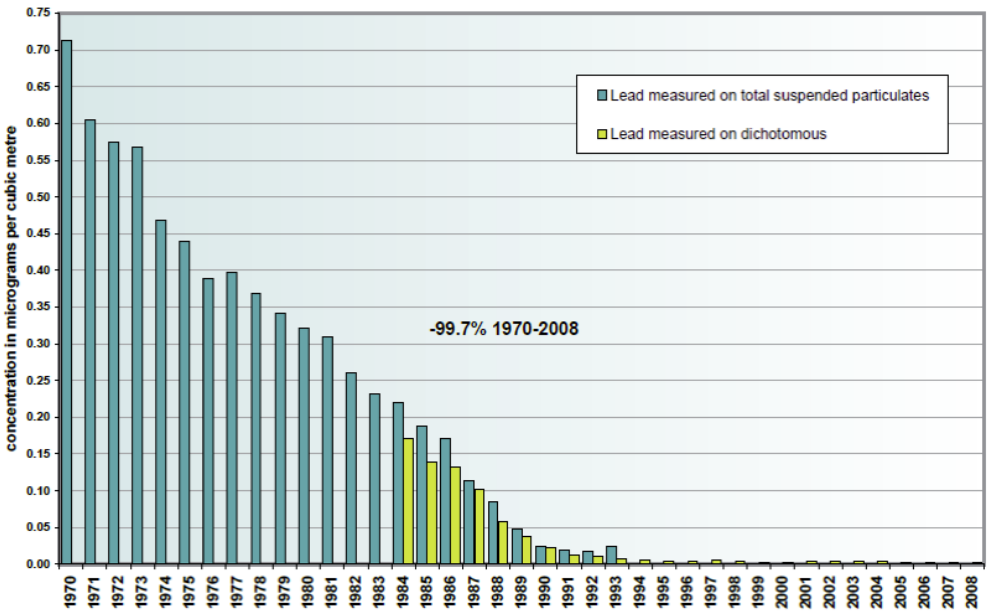
PM_{10}, particulate matter with particles of aerodynamic diameter < 10 μm; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 μm; SO_2, sulfur dioxide; TSP, total suspended particles.
Reprinted from Environment Canada (2010). National air pollution surveillance. Available from: http://www.ec.gc.ca/rnspa-naps/default.asp?lang=En&n=77FECF05-1#reports.

Fig. 1.11 Trends (1970–2008) in annual mean SO_2 concentrations at National Air Pollution Surveillance (NAPS) sites in Canada



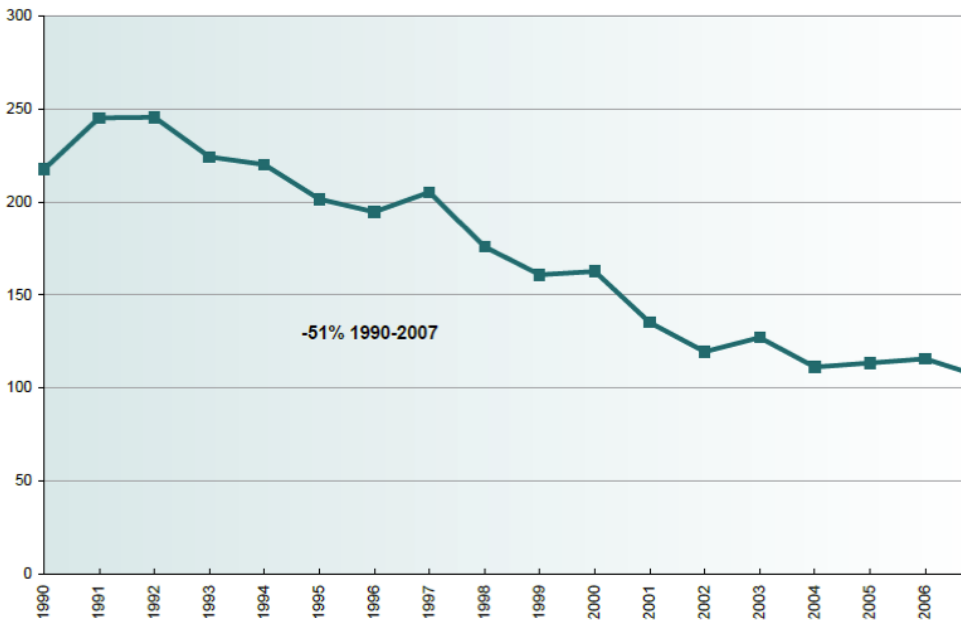
SO_2, sulfur dioxide.
Reprinted from Environment Canada (2010). National air pollution surveillance. Available from: http://www.ec.gc.ca/rnspa-naps/default.asp?lang=En&n=77FECF05-1#reports.

Fig. 1.12 Trends (1970–2008) in annual mean particulate lead concentrations at National Air Pollution Surveillance (NAPS) sites in Canada



Reprinted from Environment Canada (2010). National air pollution surveillance. Available from: http://www.ec.gc.ca/rnspa-naps/default.asp?lang=En&n=77FECF05-1#reports.

Fig. 1.13 Trends (1990–2007) in annual mean total volatile organic compounds (VOCs) at National Air Pollution Surveillance (NAPS) sites in Canada



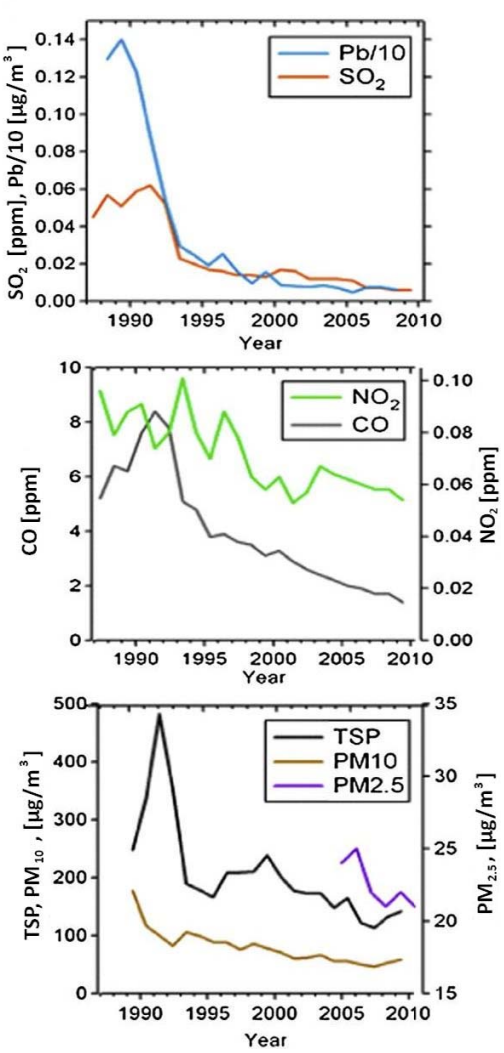
Reprinted from Environment Canada (2010). National air pollution surveillance. Available from: http://www.ec.gc.ca/rnspa-naps/default.asp?lang=En&n=77FECF05-1#reports.

Table 1.6 Estimated exposures (in 2010) to selected IARC Group 1, Group 2A, and Group 2B carcinogens in outdoor air in Canada

Compound	Mean concentration (μg/m³)
Group 1	
1,3-Butadiene	0.073
Benzene	0.84
Formaldehyde	1.4
Benzo[*a*]pyrene	1.1×10^{-4}
2,3,7,8-Tetrachlorodibenzo-*para*-dioxin	10^{-9}
Polychlorinated biphenyls (PCBs)	2.5×10^{-9}
Diesel engine exhaust	0.8
Arsenic	4.3×10^{-4}
Cadmium	1.1×10^{-4}
Hexavalent chromium	2×10^{-5}
Nickel compounds	5×10^{-4}
Group 2A	
Dichloromethane	0.68
Tetrachloroethylene	0.2
Lead compounds	0.0012
Group 2B	
Acetaldehyde	0.81
Chloroform	0.15
Ethylbenzene	0.55
Benzo[*b*]fluoranthene	4×10^{-4}
Benzo[*k*]fluoranthene	1.1×10^{-4}
Benz[*a*]anthracene	1.8×10^{-4}
Chrysene	2×10^{-4}
Indeno[1,2,3-*cd*]pyrene	1×10^{-4}

Prepared by the Working Group with data from CAREX Canada (2013).

Fig. 1.14 Trends in outdoor concentrations of lead, SO_2, NO_2, CO, and particles (TSP, PM_{10}, $PM_{2.5}$) in Mexico City



Plots show the average of the fifth-highest annual maximum from all stations with valid data for a given year.
CO, carbon monoxide; NO_2, nitrogen dioxide; Pb, lead; PM_{10}, particulate matter with particles of aerodynamic diameter < 10 μm; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 μm; SO_2, sulfur dioxide; TSP, total suspended particles.
Reprinted from Parrish et al. (2011). Air quality progress in North American megacities: a review. *Atmos Environ*, 45(39):7015–25, with permission from Elsevier.

The European Monitoring and Evaluation Programme (EMEP) is a European network of regional background stations that was designed in the 1970s in response to the observation of transboundary air pollution (Tørseth et al., 2012). The network includes measurements of SO_2, NO_2, sulfate/nitrate in aerosols, and more recently PM, ozone, and POPs.

Maps prepared by the EEA of the annual average concentrations across Europe of PM_{10}, $PM_{2.5}$, NO_2, SO_2, and ozone are presented in Fig. 1.15, Fig. 1.16, Fig. 1.19, Fig. 1.21, Fig. 1.22; other maps, for heavy metals in PM, CO, benzene, and PAH concentrations, can be found in the EEA report (EEA, 2012). These components were selected based on availability of at least reasonably comparable data across Europe.

Table 1.7 Annual medians of mass polycyclic aromatic hydrocarbons (PAHs) concentrations in PM_{10} (10th–99th percentile) (pg/m³) from the sampling days of 1999–2002 at a site in south-west Mexico City

PAH	1999 (*n* = 58)	2000 (*n* = 69)	2001 (*n* = 88)	2002 (*n* = 73)
Phenanthrene	116 (39–250)	122 (63–270)	141 (87–240)	135 (78–239)
Anthracene	21 (10–38)	17 (7–44)	25 (16–40)	21 (13–35)
Fluoranthene	230 (93–514)	204 (95–529)	260 (145–511)	253 (126–460)
Pyrene	334 (120–747)	290 (135–704)	387 (225–718)	322 (163–593)
Retene	134 (26–538)	5 (4–164)[d]	83 (51–258)	97 (49–261)
Benzo[*a*]anthracene	143 (46–361)	155 (61–403)	165 (87–334)	175 (82–380)
Chrysene[a]	212 (66–518)	200 (94–492)	187 (112–435)	234 (111–485)
Benzo[*b*]fluoranthene	588 (194–1179)	417[e] (147–963)	368[e] (199–814)	505 (314–1030)
Benzo[*k*]fluoranthene[b]	454 (159–896)	474 (240–1025)	382 (236–857)	440 (178–930)
Benzo[*e*]pyrene	506 (176–1052)	474 (235–950)	461 (290–924)	601 (356–1009)
Benzo[*a*]pyrene	240 (63–649)	313 (129–787)	274 (154–725)	357 (187–730)
Perylene	33 (0–92)[f]	53[e] (21–108)[f]	48[e] (25–108)[f]	74 (19–142)[g]
Indeno[1,2,3-*cd*]pyrene	734 (230–1587)	700 (306–1353)	623 (381–1388)	896 (506–1544)
Dibenzo[*a,h*]anthracene	45 (14–91)	43 (16–89)	43 (18–97)	46 (27–95)
Benzo[*ghi*]perylene	1342 (427–2793)	1289 (631–2644)	1342 (746–2891)	1856 (1058–2994)
Coronene	892 (267–1850)	755 (340–1624)	855 (49–2024)	1077 (564–2257)
Light PAH[c]	926 (293–2145)	686 (302–1595)	877 (531–1702)	836 (468–1636)
Heavy PAH[c]	5301 (1578–11 174)	4953 (2393–10 186)	4636 (2829–10 148)	6206 (3588–11 399)

PM_{10}, particulate matter with particles of aerodynamic diameter < 10 µm.

[a] Probably chrysene co-eluting with triphenylene

[b] Probably benzo[*k*]fluoranthene co-eluting with benzo[*j*]fluoranthene

[c] The values were calculated taking into account the corresponding PAH sum in each sampling day by year.

[d] Some values of retene were lower than the quantification limit.

[e] Contiguous medians were not statistically different.

[f] All daily values of perylene were lower than the quantification limit.

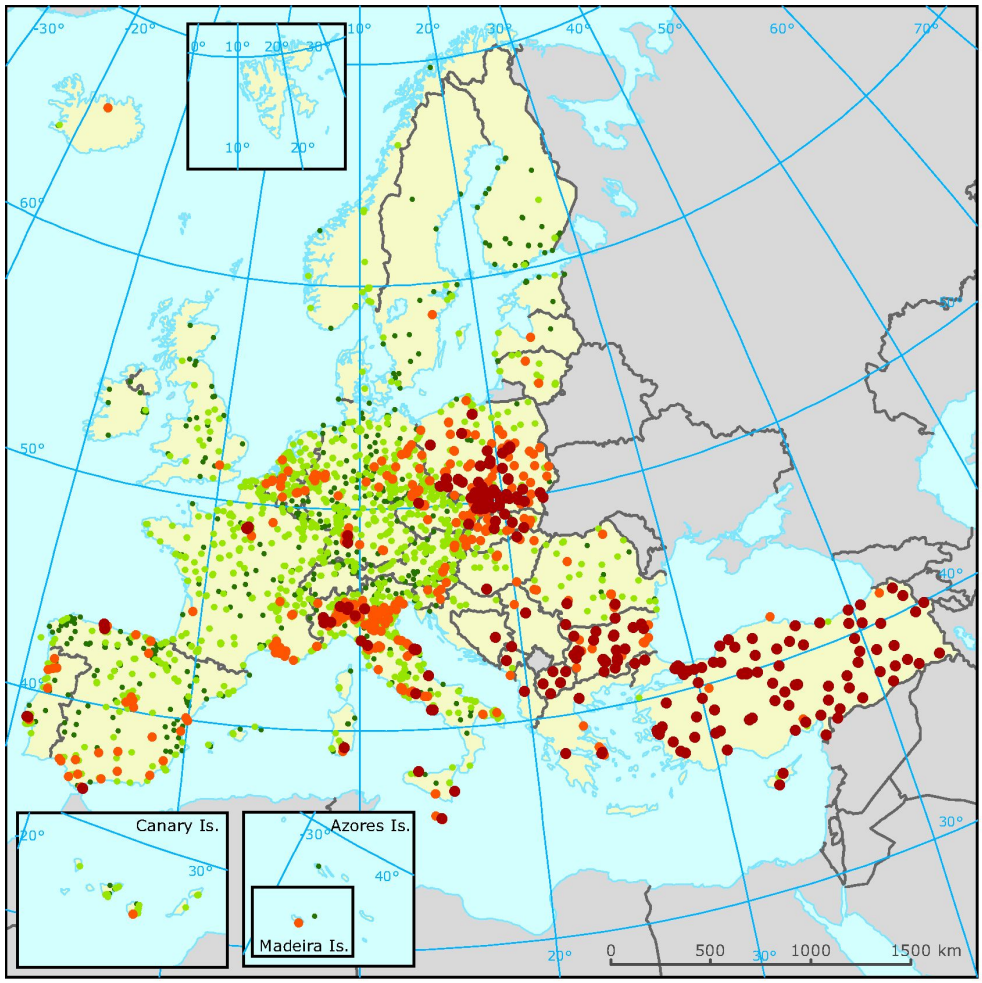
[g] Some daily values of perylene were lower than the quantification limit.

Adapted from Amador-Muñoz et al. (2013). Opposing seasonal trends for polycyclic aromatic hydrocarbons and PM_{10}: health risk and sources in southwest Mexico City. *Atmos Res*, 122:199–212. doi:10.1016/j.atmosres.2012.10.003, © with permission from Elsevier.

(i) PM_{10} and $PM_{2.5}$

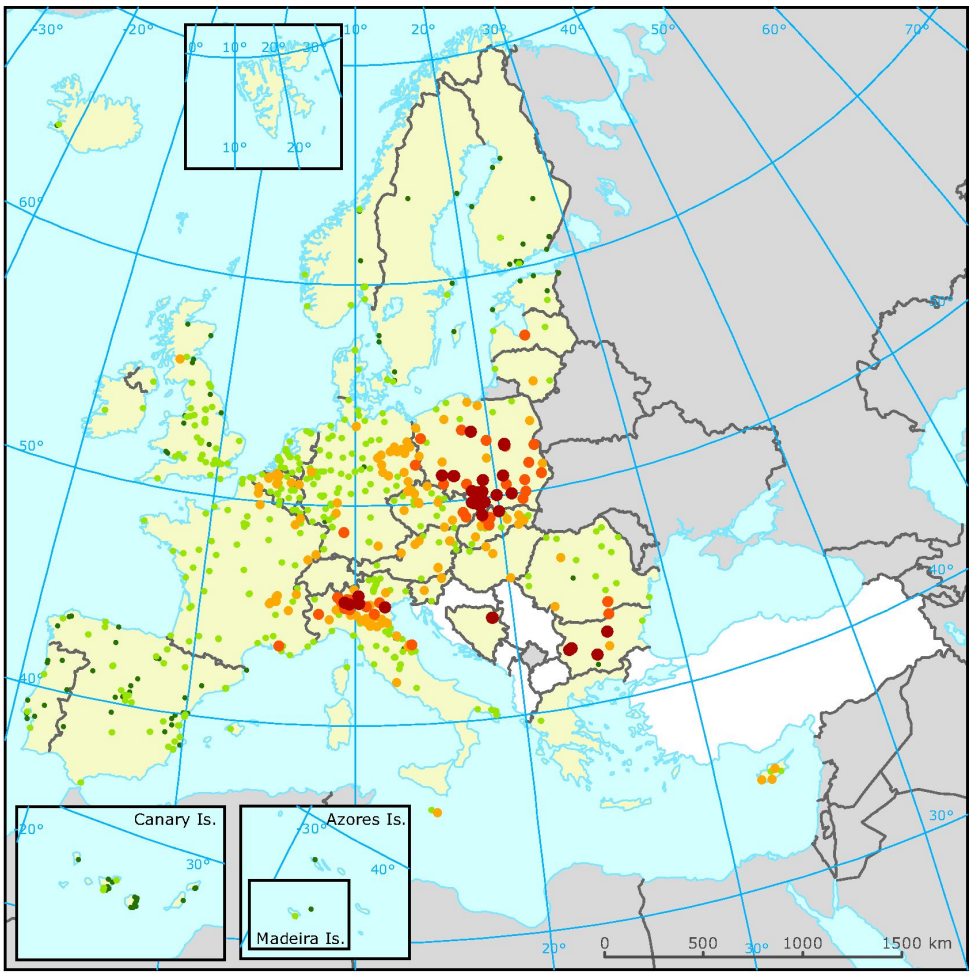
The PM_{10} and $PM_{2.5}$ maps (Fig. 1.15 and Fig. 1.16) show that concentrations are lower in northern Europe than in southern and eastern Europe. The PM_{10} map is based on a substantially larger number of sites than the $PM_{2.5}$ map, because $PM_{2.5}$ monitoring has not been fully developed within Europe because of later adoption of the air quality guideline for $PM_{2.5}$. Several research projects have broadly confirmed the general patterns across Europe (Hazenkamp-von Arx et al., 2004; Putaud et al., 2004, 2010; Van Dingenen et al., 2004; Eeftens et al., 2012). In the ESCAPE study (Eeftens et al., 2012), based on standardized gravimetric measurements using the Harvard impactor in 20 study areas, average $PM_{2.5}$ concentrations below 10 µg/m³ were found in northern Europe (Fig. 1.17). In southern European cities, for example Athens (Greece) and Turin (Italy), annual average $PM_{2.5}$ concentrations above 20 µg/m³ were measured. Relatively high concentrations were also found in the two central European cities Györ (Hungary) and Kaunas (Lithuania). Fig 1.17 further illustrates significant intra-urban spatial variation, particularly for coarse particles (calculated as PM_{10} – $PM_{2.5}$) and $PM_{2.5}$ absorbance. A regression analysis of $PM_{2.5}$ on PM_{10} concentrations for

Fig. 1.15 Annual mean concentrations of PM_{10} in 2010 in Europe



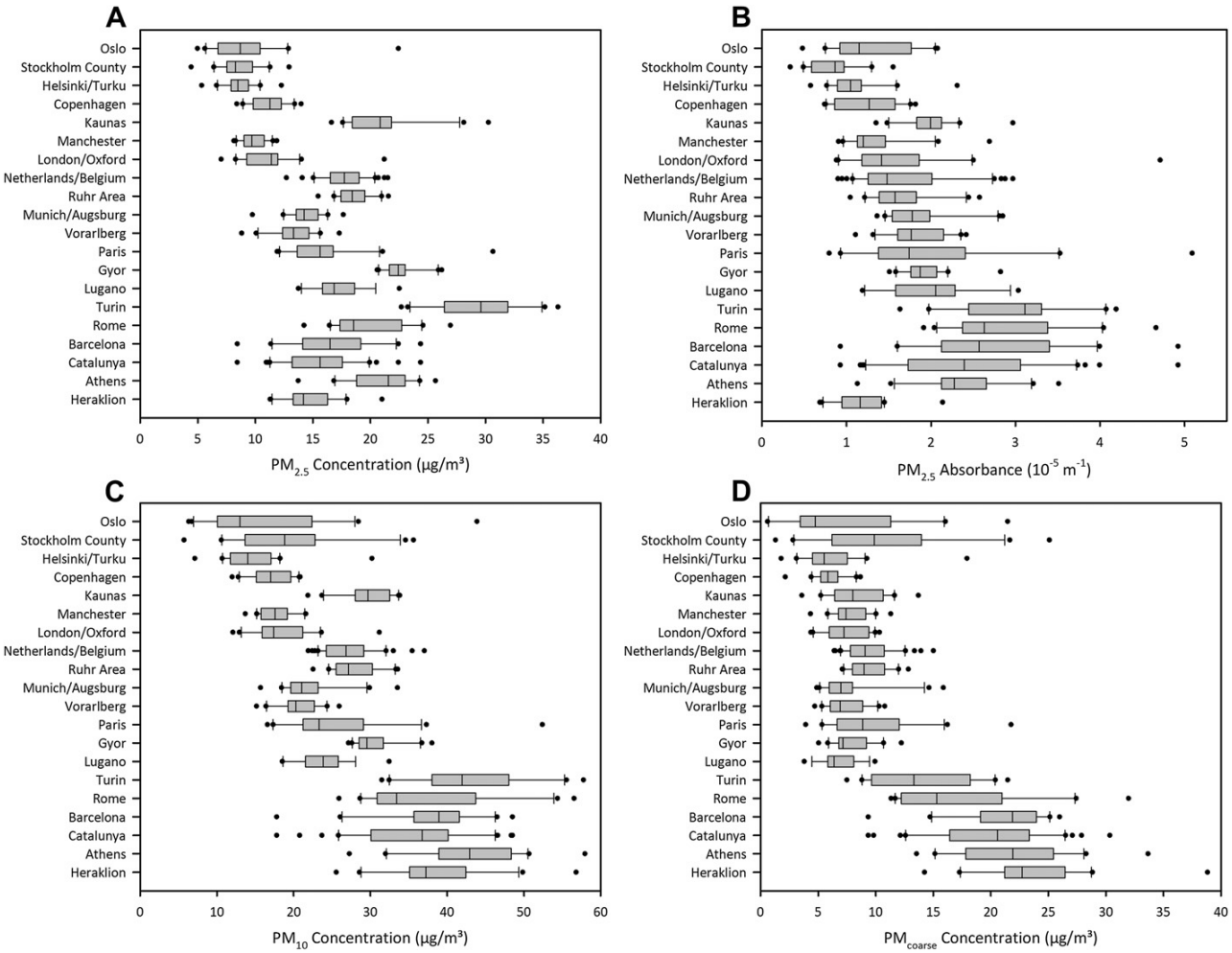
PM_{10}, particulate matter with particles of aerodynamic diameter < 10 µm.
The red dots indicate stations reporting exceedances of the 2005 annual limit value (40 µg/m³), as set out in the Air Quality Directive (EU, 2008).
The orange dots indicate stations reporting exceedances of a statistically derived level (31 µg/m³) corresponding to the 24-hour limit value, as set out in the Air Quality Directive (EU, 2008).
The light green dots indicate stations reporting exceedances of the WHO air quality guideline for PM_{10} of < 20 µg/m³ but not in exceedance of the limit values as set out in the Air Quality Directive (EU, 2008).
The dark green dots indicate stations reporting concentrations below the WHO air quality guideline for PM_{10} and implicitly below the limit values as set out in the Air Quality Directive (EU, 2008).
Reprinted from EEA (2012). Air quality in Europe – 2012 report. European Environment Agency Report 4/2012.

Fig. 1.16 Annual mean concentrations of $PM_{2.5}$ in 2010 in Europe



$PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 µm.
The red dots indicate stations reporting exceedances of the 2010 annual target value (25 µg/m³) plus at least 5 µg/m³.
The dark orange dots indicate stations reporting exceedances of the 2010 annual target value (25 µg/m³), as set out in the Air Quality Directive (EU, 2008).
The light orange dots indicate stations reporting exceedances of the 2020 indicative annual limit value (20 µg/m³), as set out in the Air Quality Directive (EU, 2008).
The light green dots indicate stations reporting exceedances of the WHO air quality guideline for $PM_{2.5}$ of < 10 µg/m³ but not in exceedance of the target or limit values for $PM_{2.5}$ as set out in the Air Quality Directive (EU, 2008).
The dark green dots indicate stations reporting concentrations below the WHO air quality guideline for $PM_{2.5}$ and implicitly below the target and limit values for $PM_{2.5}$ as set out in the Air Quality Directive (EU, 2008).
Reprinted from EEA (2012). Air quality in Europe – 2012 report. European Environment Agency Report 4/2012.

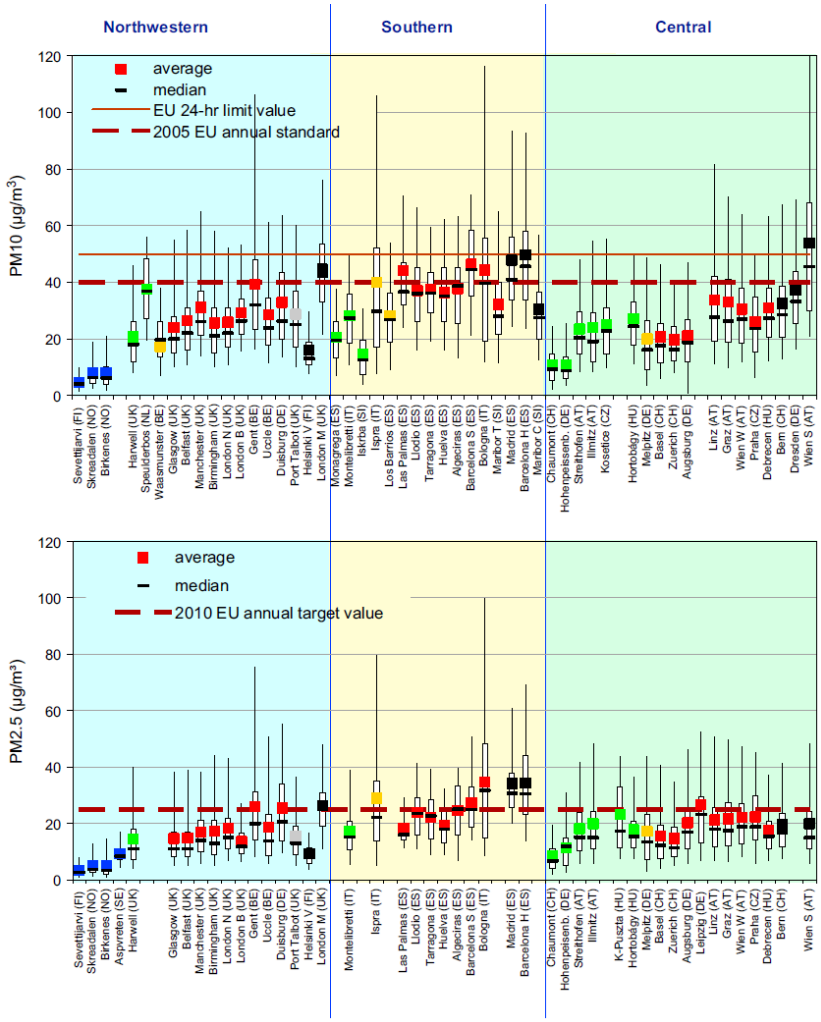
Fig. 1.17 Spatial variation of 2009–2010 annual average particulate matter (PM) concentrations across Europe



PM_{10}, particulate matter with particles of aerodynamic diameter < 10 µm; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 µm; PM_{coarse} calculated as $PM_{10} - PM_{2.5}$.
Median, 25th percentile, and 75th percentile are shown in the boxes; whiskers indicate the 10th and 90th percentiles, and individual outliers are shown as points.
Reprinted from Eeftens et al. (2012). Spatial variation of $PM_{2.5}$, PM_{10}, $PM_{2.5}$ absorbance, and PM_{coarse} concentrations between and within 20 European study areas and the relationship with NO_2 – results of the ESCAPE project. *Atmos Environ*, 62:303–317; with permission from Elsevier.

60 sites across Europe found site-specific slopes varying between 0.44 and 0.90 (Putaud et al., 2010). Fig 1.18 illustrates the spatial variation of $PM_{2.5}$ and PM_{10} concentrations across European cities. A large range of PM_{10} concentrations (5–54 µg/m³ annual average) is observed across the network. Urban background PM_{10} annual mean and median values are significantly larger in southern Europe (median, 36 µg/m³) than in north-western Europe (median, 24 µg/m³) and central Europe (median, 26 µg/m³). The range of $PM_{2.5}$ concentrations observed across the network (3–35 µg/m³ annual average) is similar to that of PM_{10}. In north-western and southern Europe, an increasing gradient in $PM_{2.5}$ is generally observed from rural to urban sites. In central Europe, $PM_{2.5}$ can be as large at rural sites as at urban sites (Putaud et al., 2010). The chemical composition of PM differs widely across Europe, with generally more carbonaceous matter in

Fig. 1.18 Spatial variation of 1996–2007 annual average particulate matter (PM) concentrations across Europe

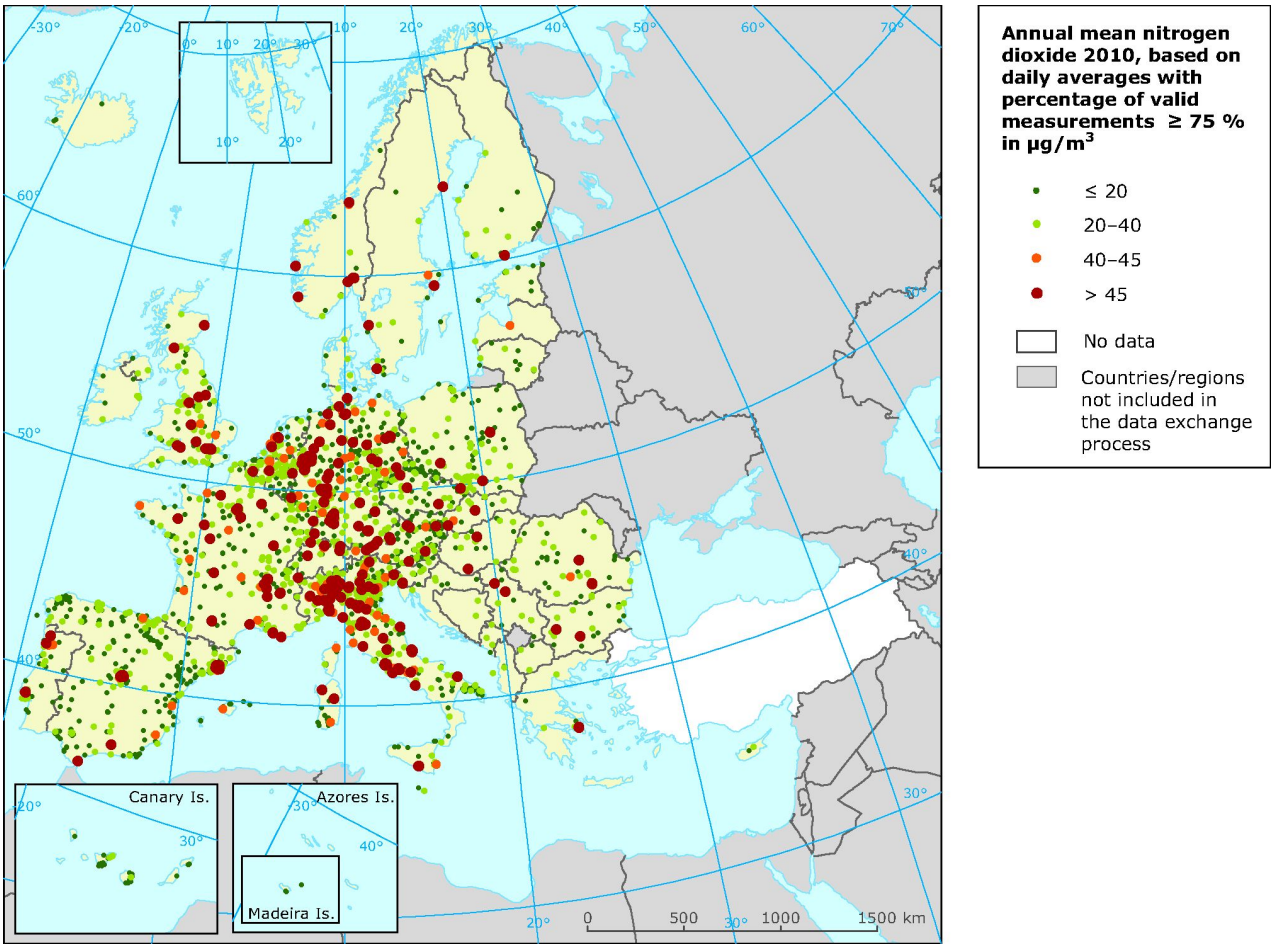


PM_{10}, particulate matter with particles of aerodynamic diameter < 10 µm; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 µm.
Median, 25th percentile, and 75th percentile are shown in the boxes; whiskers indicate the 10th and 90th percentiles, and individual outliers are shown as points.
Reprinted from Putaud et al. (2010). A European aerosol phenomenology – 3: physical and chemical characteristics of particulate matter from 60 rural, urban, and kerbside sites across Europe. *Atmos Environ*, 44(10):1308–1320; with permission from Elsevier.

central Europe, more nitrate in north-western Europe, and more mineral dust in southern Europe (Putaud et al., 2010; Tørseth et al., 2012). Table 1.8 presents the average contributions of major components to PM concentrations. The elemental composition of eight elements representing major sources across Europe has recently been published based on the ESCAPE study (de Hoogh et al., 2013). Significant variability of concentrations both within and between study areas across Europe was found.

There is a lack of comprehensive monitoring for the heavy metals lead, arsenic, cadmium, and nickel across Europe. In general, low concentration levels are measured (often below the lower assessment threshold), with the exception of sites located next to specific industries (EEA, 2012).

Fig. 1.19 Annual mean concentration of NO_2 in 2010 in Europe



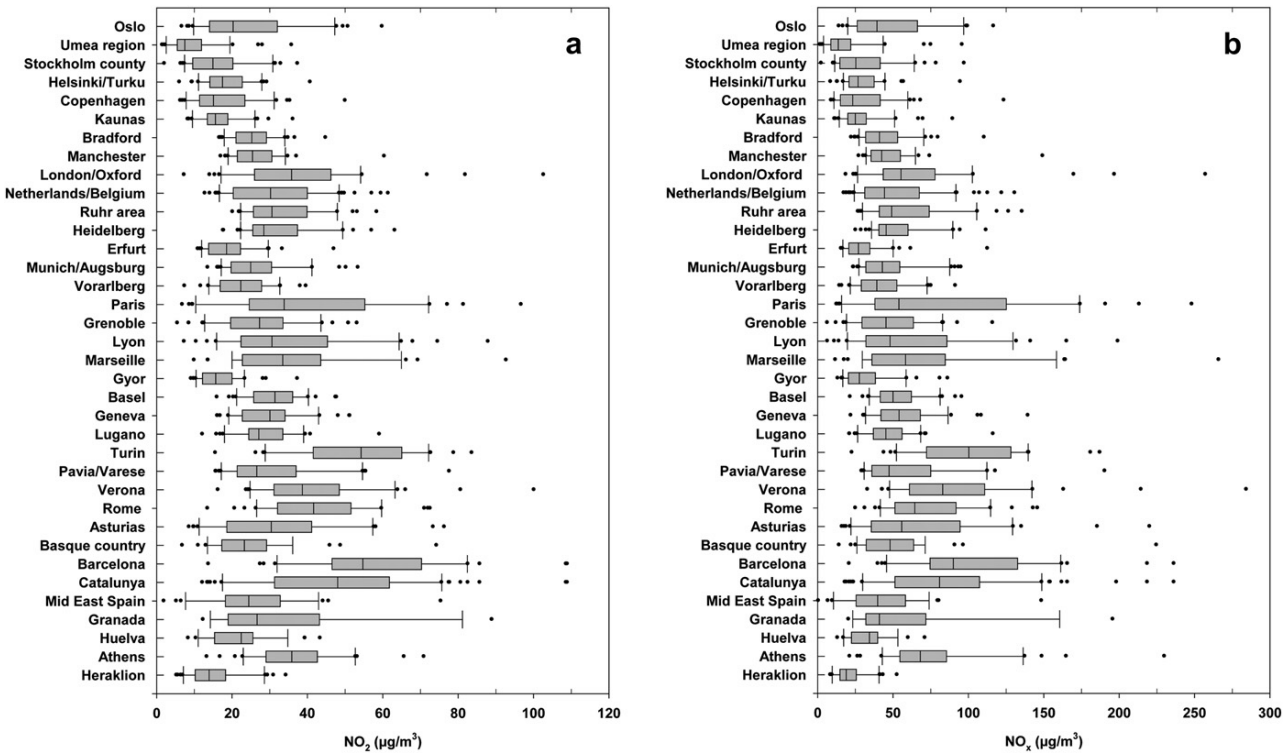
NO_2, nitrogen dioxide.
Orange and red dots correspond to exceedances of the annual limit value (40 µg/m³).
Red dots correspond to exceedances of the annual limit value plus 5 µg/m³.
Reprinted from EEA (2012). Air quality in Europe – 2012 report. European Environment Agency Report 4/2012.

There are no routine measurements of ultrafine particles available across Europe, as in other parts of the world. In individual cities, including Amsterdam (the Netherlands), Athens (Greece), Birmingham (United Kingdom), and Helsinki (Finland), total particle number counts are available. Research projects have included snapshots of spatial patterns across Europe (e.g. Puustinen et al., 2007). Urban background levels were about 10 000–20 000 particles/cm³ in four large cities, with substantially higher concentrations measured near major roads (Puustinen et al., 2007).

(ii) NO_2

The most striking feature of the NO_2 map is the higher concentrations in major cities (Fig. 1.19). European research studies have also shown a general north-to-south increasing gradient in NO_2 concentrations (Hazenkamp-von Arx et al., 2004; Cyrys et al., 2012). Fig 1.20 further illustrates significant intra-urban spatial variation, which exceeded between-area variability. In

Fig. 1.20 Spatial variation of 2008–2011 annual average nitrogen dioxide (NO_2) and nitrogen oxides (NO_x) concentrations across Europe



a Distribution of annual average concentration of NO_2 for each study area separately. **b** Distribution of annual average concentration of NO_x for each study area separately.
Median, 25th percentile, and 75th percentile are shown in the boxes; whiskers indicate the 10th and 90th percentiles, and individual outliers are shown as points.
In each study area, 40–80 sites were measured. Sites ordered from north to south.
Reprinted from Cyrys et al. (2012). Variation of NO_2 and NO_x concentrations between and within 36 European study areas: results from the ESCAPE study. *Atmos Environ*, 62:374–90; with permission from Elsevier.

virtually all study areas, there was at least one site in which the current EU annual average standard of 40 µg/m³ was exceeded.

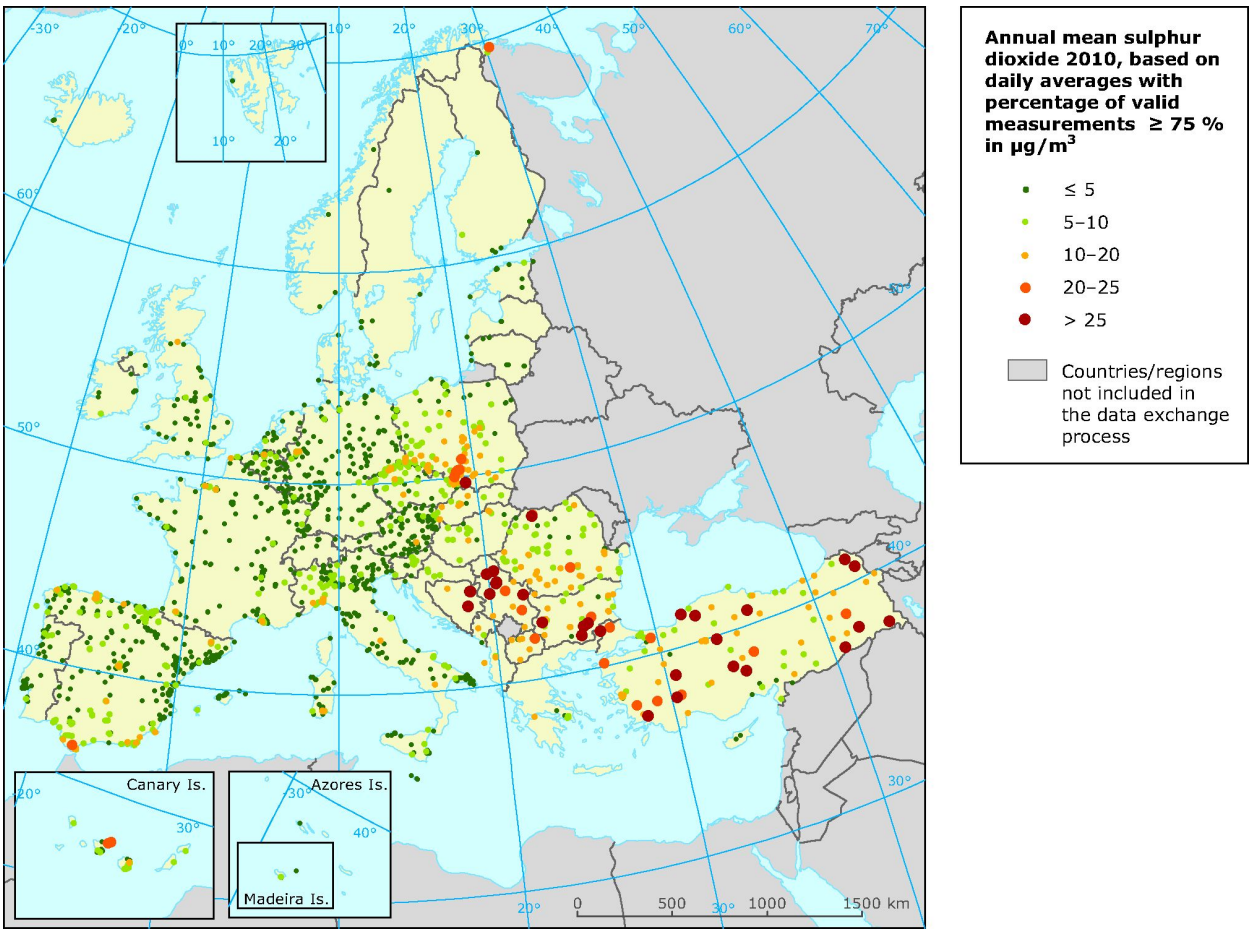
(iii) SO_2

Current average SO_2 concentrations in Europe are low, typically well below 10 µg/m³ in large parts of Europe (Fig. 1.21). The highest concentrations occur in eastern Europe, related to industrial activities and the remaining coal burning (EEA, 2012). Currently, emissions are predominantly from power generation (Tørseth et al., 2012). International shipping emissions have become a significant source because shipping emissions have been much less affected by policies than industrial emissions have (Tørseth et al., 2012).

(iv) CO

CO concentrations are typically low, due to the significant reduction in traffic emissions by catalytic converters. Still, the highest concentrations occur in urban areas, especially at traffic sites and occasionally at industrial locations (EEA, 2012). There is not a clear pattern across Europe.

Fig. 1.21 Annual mean SO_2 concentrations in Europe in 2010



The dark orange and red dots correspond to exceedances of the limit value (20 µg/m³) for the protection of vegetation.
Reprinted from EEA (2012). Air quality in Europe – 2012 report. European Environment Agency Report 4/2012.

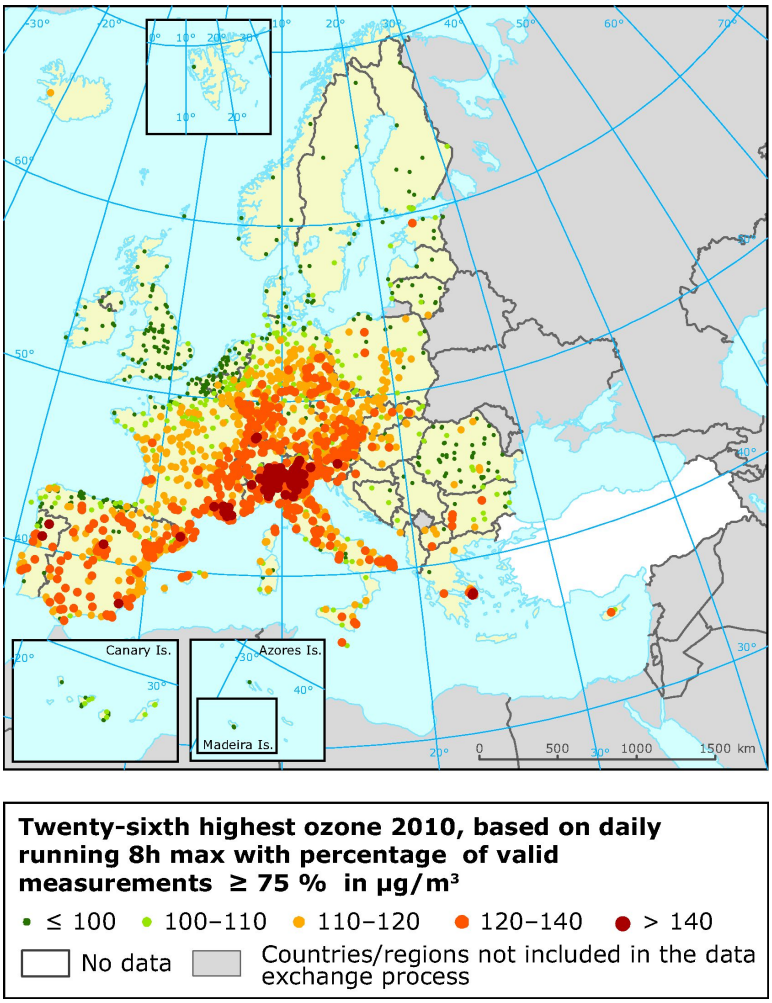
(v) Ozone

Fig. 1.22 shows the map of maximum 8-hour average ozone concentrations. The 26th highest value is shown because of the formulation of the EU standard (120 µg/m³ as an 8-hour maximum not to be exceeded on > 25 days). The highest concentrations occur in southern Europe and in Austria and Switzerland, related especially to higher temperatures and altitude (EEA, 2012). Ozone concentrations are generally higher at rural stations than at urban background stations. Concentrations at traffic sites are even lower, related to scavenging of ozone by NO (EEA, 2012).

(vi) Benzene

Current average benzene concentrations in Europe are low, typically below 5 µg/m³ in large parts of Europe. The highest concentrations occur at traffic sites and at industrial locations (EEA, 2012).

Fig. 1.22 Twenty-sixth highest daily maximum 8-hour average ozone concentration recorded in 2010 in Europe



The map shows the proximity of recorded ozone concentrations to the target value. At sites marked with dark orange and red dots, the 26th highest daily ozone concentrations exceeded the 120 µg/m³ threshold and the number of allowed exceedances by the target value.
Reprinted from EEA (2012). Air quality in Europe – 2012 report. European Environment Agency Report 4/2012.

(vii) Benzo[a]pyrene

Current average B[*a*]P concentrations in Europe are low, typically below 1 ng/m³ in large parts of Europe. There is no clear north-to-south gradient. The highest concentrations occur in areas with domestic coal or wood burning and industrial areas, particularly in eastern Europe (EEA, 2012).

(viii) Pollution trends

Fig. 1.23, Fig. 1.24, Fig. 1.25, and Fig. 1.26 show the trends in annual average concentrations of PM and major gaseous components based on the European AirBase database (EEA, 2012).

Annual average concentrations of PM_{10} and $PM_{2.5}$ have not decreased much since 2000 despite assumed decreases in emissions of precursors (Fig. 1.23). Between 1990 and 2004, a clear decrease (~44%) in total PM emissions

Table 1.8 Major constituent contributions to PM_{10}, $PM_{2.5}$, and PM_{coarse} in Europe

Region	Constituent	PM_{10}			$PM_{2.5}$			PM_{coarse}		
		Rural	Urban	Kerbside	Rural	Urban	Kerbside	Rural	Urban	Kerbside
North-western Europe	Mineral dust	4%	12%			5%	1%		26%	
	Sea salt	12%	10%	7%		4%	1%		15%	
	SO_4	13%	14%	8%		21%	18%		6%	
	NO_3	16%	14%	12%		16%			20%	
	OM	15%	18%	16%		25%			14%	
	EC	4%	5%	9%		7%			1%	
	TC	14%	18%	20%		25%			12%	
Southern Europe	Mineral dust	15%	21%	28%		11%	14%		42%	69%
	Sea salt	3%	12%	5%		6%	2%		22%	11%
	SO_4	16%	12%	12%		15%	15%		4%	5%
	NO_3	14%	9%	8%		7%	7%		11%	9%
	OM		26%			23%			13%	
	EC		6%			8%			2%	
	TC	13%	21%	28%		30%	38%		11%	
Central Europe	Mineral dust	9%	12%	15%	3%	5%	6%	22%	25%	29%
	Sea salt	2%	2%	2%	1%	1%	1%	2%	3%	5%
	SO_4	19%	15%	9%	17%	19%	12%	5%	4%	4%
	NO_3	13%	12%	8%	6%	13%	10%	10%	7%	6%
	OM	23%	21%	21%	15%	22%	26%	5%	15%	13%
	EC	6%	10%	17%	5%	14%	21%	3%	3%	10%
	TC	32%	32%	38%	19%	31%	35%	6%	14%	19%

EC, elemental carbon; OM, organic matter; PM, particulate matter; PM_{10}, particulate matter with particles of aerodynamic diameter < 10 μm; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 μm; PM_{coarse}, particulate matter with particles of aerodynamic diameter between 2.5 μm and 10 μm; TC, total carbon.

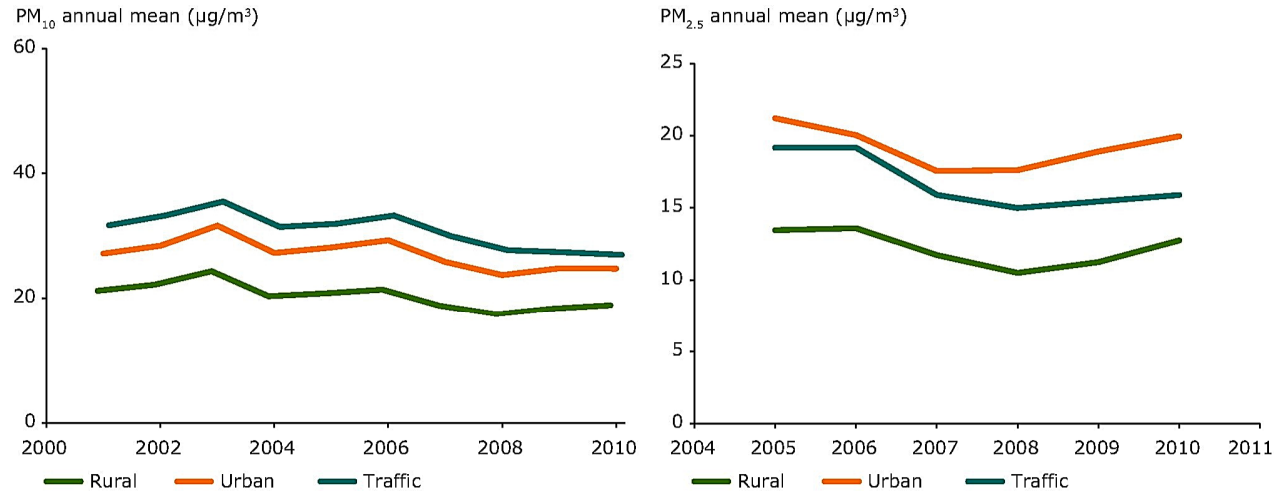
Adapted from Putaud et al. (2010). A European aerosol phenomenology – 3: physical and chemical characteristics of particulate matter from 60 rural, urban, and kerbside sites across Europe. *Atmos Environ*, 44(10):1308–20; with permission from Elsevier.

occurred (EEA, 2007; Harrison et al., 2008). At the EMEP regional background sites, concentrations of PM_{10} and $PM_{2.5}$ decreased by 18% and 27%, respectively, between 2000 and 2009 (Tørseth et al., 2012). Longer-term trends are difficult to quantify from monitoring networks because PM_{10} and especially $PM_{2.5}$ were often not measured until the 1990s. High annual average concentrations of PM_{10} and $PM_{2.5}$ were measured in research projects in central and eastern Europe in the 1990s (Hoek et al., 1997; Houthuijs et al., 2001). A series of studies in eastern Germany reported a significant decline in particle mass concentration, accompanied by an increase in concentrations of ultrafine particles (Kreyling et al., 2003).

Longer trends are available for sulfate, although sampling artefacts complicate the assessment (Tørseth et al., 2012). Consistent with the large reduction in SO_2 emissions, sulfate concentrations decreased by 70% between 1980 and 2009, mostly between 1990 and 2009 (56% reduction). Nitrate concentrations decreased by much less than sulfates (8% between 1990 and 2009), reflecting the smaller reduction in precursor emissions and a shift in the equilibrium with ammonia and nitric acid towards particulate nitrate (Tørseth et al., 2012).

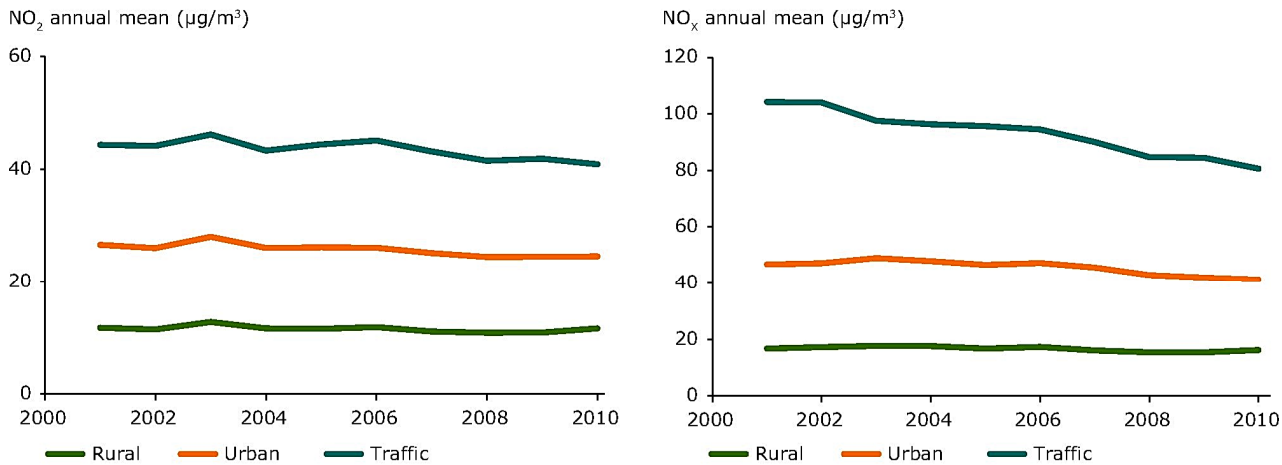
Annual average concentrations of NO_2 have remained fairly stable since 2000, whereas NO_x concentrations did decrease substantially at traffic sites (Fig. 1.24). At the EMEP regional

Fig. 1.23 Trends in annual average concentrations of PM_{10} (2001–2010) and $PM_{2.5}$ (2005–2010) by station type across Europe



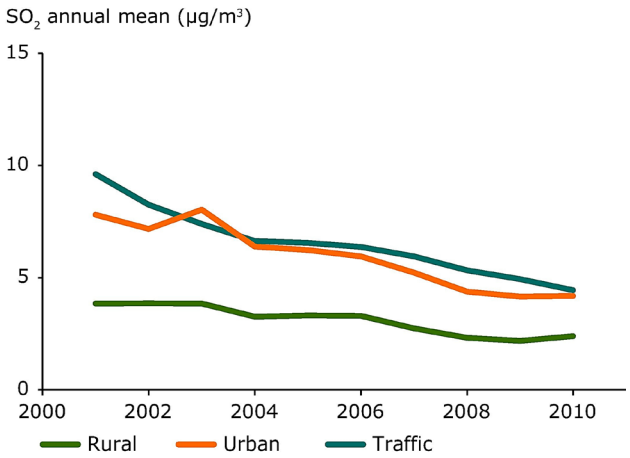
PM_{10}, particulate matter with particles of aerodynamic diameter < 10 µm; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 µm.
All stations in European Union Member States with at least 75% data coverage for at least 8 years (PM_{10}) or 6 years ($PM_{2.5}$) were included in the analysis. Concentrations by station type are given in µg/m³.
Reprinted from EEA (2012). Air quality in Europe – 2012 report. European Environment Agency Report 4/2012.

Fig. 1.24 Trends in NO_2 and NO_x annual mean concentrations (2001–2010) by station type across Europe



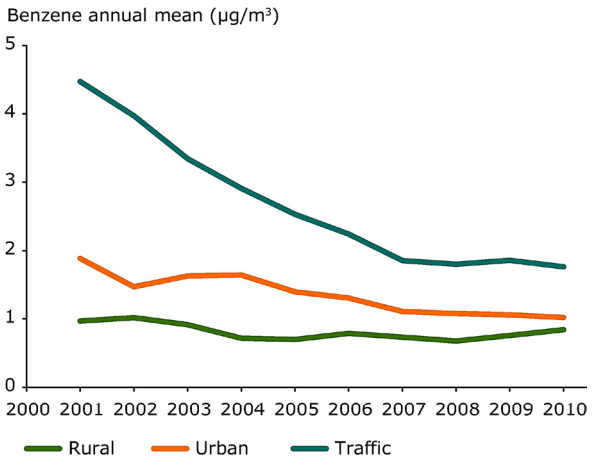
NO_2, nitrogen dioxide; NO_x, nitrogen oxides.
Reprinted from EEA (2012). Air quality in Europe – 2012 report. European Environment Agency Report 4/2012.

Fig. 1.25 Trend in annual average SO_2 concentrations (2001–2010) by station type across Europe



SO_2, sulfur dioxide.
All stations in European Union Member States with at least 75% data coverage for at least 8 years were included in the analysis.
Reprinted from EEA (2012). Air quality in Europe – 2012 report. European Environment Agency Report 4/2012.

Fig. 1.26 Trend in annual average mean benzene concentrations (2001–2010) by station type across Europe



All stations in European Union Member States with at least 75% data coverage for at least 8 years were included in the analysis.
Reprinted from EEA (2012). Air quality in Europe – 2012 report. European Environment Agency Report 4/2012.

background sites, NO_2 concentrations decreased by 23% between 1990 and 2009 (Tørseth et al., 2012). The decrease in NO_x concentrations is explained by lower emissions from motorized traffic, since NO_x emissions in Europe had increased, especially until about 1990, because of emissions from road transportation (Vestreng et al., 2009). The reduced fuel consumption and early technological changes in western Europe between 1980 and 1990 were not sufficiently effective to reduce emissions (Vestreng et al., 2009). After 1990, emissions decreased because of new technologies in western Europe and the economic recession in eastern Europe, while increasing car ownership in eastern Europe resulted in increased road traffic emissions from that region (Vestreng et al., 2009).

The limited decrease in NO_2 concentrations is due to an increase in primary NO_2 in road traffic emissions. Primary NO_2 emissions have gained importance compared with the ozone/NO_x equilibrium (Keuken et al., 2009; Mavroidis & Chaloulakou, 2011). The increase in primary NO_2 emissions has been attributed to increased use of diesel-powered vehicles, which emit a higher fraction of NO_2 compared with gasoline-powered vehicles (Grice et al., 2009; Anttila et al., 2011; Carslaw et al., 2011). In addition, the aftertreatment devices (such as oxidation catalysts) implemented for reducing PM emissions by diesel vehicles contribute to the increasing fraction of primary NO_2 in NO_x (Mavroidis & Chaloulakou, 2011; Williams & Carslaw, 2011). For diesel-fuelled vehicles equipped with catalytic diesel particulate filters, primary NO_2 fractions of about 40–50% are reported (Carslaw et al., 2007). A consequence of this trend is that the value of NO_2 as a marker of the mixture of traffic-related pollutants may have changed.

Concentrations of SO_2 have continued to decrease significantly in Europe at traffic sites, urban background sites, and regional background sites (Fig. 1.25). On average, concentrations were halved between 2000 and 2010

(EEA, 2012). Compared with the early 1990s, concentrations have decreased several-fold, due to significant reductions in the use of coal for power generation and other sources such as domestic heating, lower sulfur content in fuel, and substantial technological developments such as desulfurization at power plants (Tørseth et al., 2012). At the EMEP regional background sites, SO_2 concentrations decreased by 92% between 1980 and 2009, mostly between 1990 and 2009 (75% reduction) (Tørseth et al., 2012). Modest reductions in emissions between 1980 and 1989 occurred largely in western Europe, whereas large reductions between 1990 and 1999 occurred mainly in central and eastern Europe (Vestreng et al., 2007). Important factors were the drop in industrial activity in eastern Europe after the political changes in 1989 and a switch from solid fuel to oil and natural gas containing lower amounts of sulfur (Vestreng et al., 2007).

Concentrations of benzene have decreased substantially in the past decade, especially at traffic sites (Fig. 1.26). The main explanation for this trend is the lower benzene content of gasoline.

There are insufficient data from networks to specify a Europe-wide trend for B[*a*]P concentrations (EEA, 2012), although there are studies from selected locations. A study in Munich showed a decrease in concentrations by an order of magnitude between 1981 and 2001, with most of the change occurring before 1993 (Schauer et al., 2003). Large decreases in PAH concentrations have also been reported for the United Kingdom (Brown et al., 2013). Comparison of data from different sites in London showed a decrease in B[*a*]P concentrations from 10–100 ng/m^3 in the 1950s to less than 0.1 ng/m^3 currently. Median B[*a*]P concentrations of all sites in the current PAH network have decreased from about 1.4 ng/m^3 to 0.2 ng/m^3 (Brown et al., 2013). The decline in the past two decades was attributed to dramatically reduced emissions from industrial metal processing and a ban on burning agricultural stubble (Brown et al., 2013).

Overall, air quality has generally improved in Europe, and the mixture has clearly changed in composition.

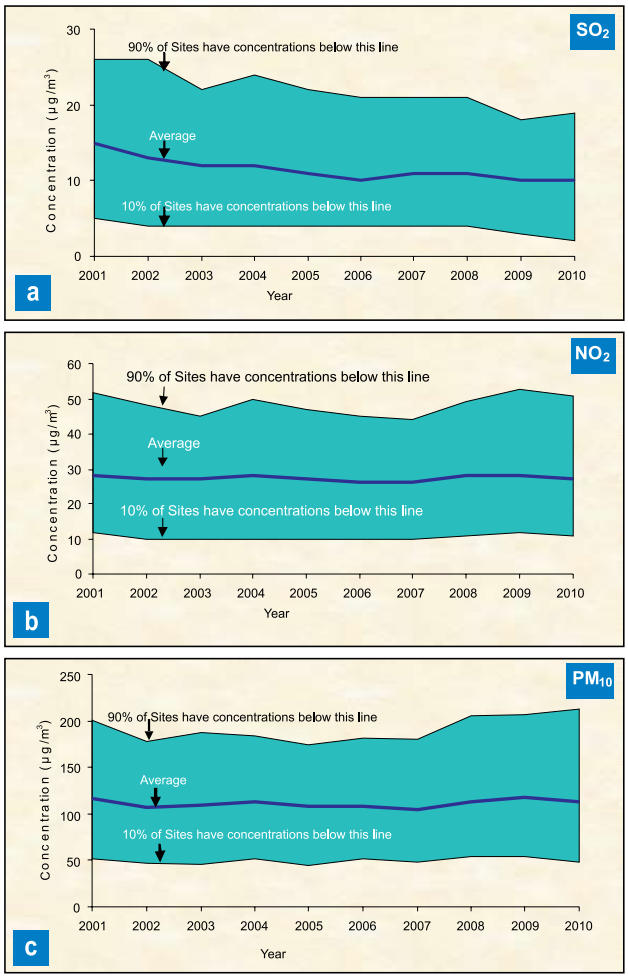
(c) Asia

(i) India

Outdoor air quality information in India is collected primarily by the National Air Quality Monitoring Programme (NAMP). Administered by the Central Pollution Control Board (CPCB), Ministry of Environment and Forests, Government of India, the NAMP network was initiated in 1984 with seven stations in the cities of Agra and Anpara (situated close to the National Capital Region). This network has steadily grown to include nearly 503 outdoor air quality monitoring stations across 209 cities in 26 states and 5 union territories in 2011. Criteria air pollutants listed under the earlier 1994 NAAQS and monitored under the NAMP include $PM_{10,}$ SO_2, and NO_2. Integrated 8-hour and 24-hour measurements are performed twice a week, resulting in about 104 observations from each station annually. In addition, CO, NH_3, lead, and ozone are monitored at selected locations. The NAAQS were recently revised (CPCB, 2009b). $PM_{2.5}$ and air toxics such B[*a*]P, arsenic, and nickel are now included in the revised NAAQS and are slowly being added to the routine monitoring performed under the NAMP. The CPCB collates the data received by the entire network in the central Environmental Data Bank. After completion of quality assurance/quality control, these data are made available in the public domain. This section summarizes pollutant-specific information available from the CPCB, with additional details from relevant published studies where available.

Analyses of CPCB data from 402 stations on criteria air pollutants for the 10-year period 2000–2010 indicate a decline in the national

Fig. 1.27 National mean concentrations derived from data across National Air Quality Monitoring Programme (NAMP) stations together with the 10th and 90th percentile for SO_2 (a), NO_2 (b), and PM_{10} (c) in India



NO_2, nitrogen dioxide; PM_{10}, particulate matter with particles of aerodynamic diameter < 10 µm; SO_2, sulfur dioxide.
Reprinted from CPCB (2012).

annual average SO_2 concentration; NO_2 levels remained largely unchanged, and PM_{10} levels showed a modest increase (Fig. 1.27). Although monitoring locations do not cover all cities across India, they do provide coverage across all states, indicating the extent of exposures that urban populations are likely to experience (CPCB, 2012).

The CPCB classifies the air quality at NAMP locations into four broad categories – low (acceptable), moderate, high, and critical levels of pollution – based on the exceedance factor (the ratio of annual mean concentration of a pollutant to that of the respective standard), as shown in Table 1.9.

By these criteria, the levels of SO_2 at most locations have not only declined but are mostly low across the locations monitored, whereas NO_2 and PM_{10} levels have remained moderately to critically high across many locations over the

Table 1.9 India Central Pollution Control Board (CPCB) criteria for classification of pollution levels

Pollution level	Annual mean concentration range (μg/m³)		
	SO_2	NO_2	PM_{10}
Low (L)	0–25	0–20	0–30
Moderate (M)	26–50	21–40	31–60
High (H)	51–75	41–60	61–90
Critical (C)	> 75	> 60	> 90

NO_2, nitrogen dioxide; PM_{10}, particulate matter with particles of aerodynamic diameter < 10 μm; SO_2, sulfur dioxide.
Adapted from CPCB (2012).

years (Fig. 1.28). Maximum levels in the most polluted states/cities often exceed the NAAQS by 2–5-fold, as may be seen in Table 1.10.

Limited information is currently available on chemical speciation of PM fractions or the differential distribution of PM and gaseous pollutants in relation to land use. In a recent national source apportionment study performed across six cities (CPCB, 2011), levels of PM_{10} and $PM_{2.5}$ in the outdoor air were consistently in excess of the NAAQS across background, kerbside, industrial, commercial, and residential sites, and winter and post-monsoon season levels were much higher than summer levels (CPCB, 2011). NO_2 levels were of concern at several locations, whereas SO_2, ozone, and CO levels were generally within the prescribed standards. Results from analyses of PM components indicate that EC and OC accounted for 20–45% of PM_{10} and 25–75% of $PM_{2.5}$ in cities. SO_4^{2-} and NO_3^- accounted for 10–30% of PM_{10} in cities. Vehicle exhaust, secondary particulates, construction activities, oil burning (e.g. diesel or heavy oil), biomass burning, coal combustion, kerosene combustion, and industrial emissions have been identified to be the dominant sources for criteria air pollutants in these cities (CPCB, 2011).

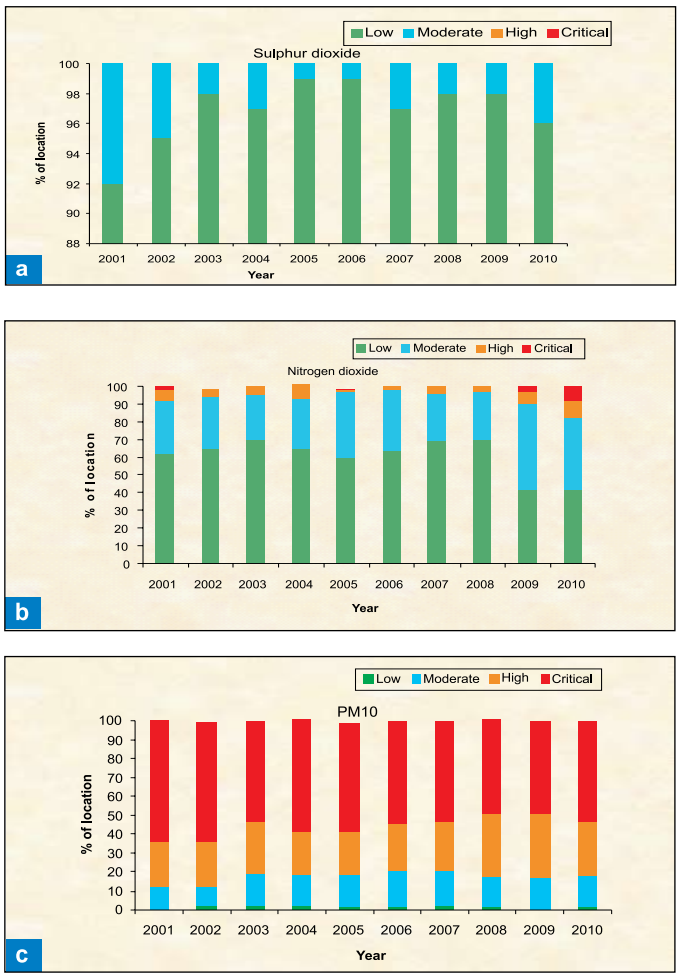
In addition, several industrial hotspots have been identified by the CPCB using the new risk assessment criteria of the Comprehensive Environmental Pollution Index (CEPI) (CPCB, 2009a). The CEPI weights the toxicity of the agents, the volume of emissions, the scale of the population exposed, and the exposure pathways involved. Of special relevance to carcinogenicity is the fact that unlike criteria air pollutant data provided by the NAMP, the CEPI includes weighted contributions from a range of compounds including probable carcinogens (US EPA Class 2 and 3 or substances with some systemic toxicity, such as VOCs, PAHs, and PCBs) as well as known carcinogens or chemicals with significant systemic or organ system toxicity (such as vinyl chloride, benzene, lead, radionuclides, hexavalent chromium, cadmium, and organophosphates) (CPCB, 2009a).

Data from the NAMP network of the CPCB provide the most comprehensive description of the status of air quality across Indian cities as far as criteria air pollutants are concerned. Air toxics are seldom monitored routinely, and hence information on air toxics is mostly contained in individual studies conducted by academic and/or research organizations.

(ii) China

As a result of the unprecedented rapid development in industrialization and urbanization in the past decades, many Chinese cities have air pollution levels well above health-based standards (HEI, 2010b; Gao et al., 2011), and air pollution associated with health impacts has become a growing concern (Zhang et al., 2010a). In this section, information on outdoor concentration

Fig. 1.28 Trends in pollution levels for 2000–2010 in India in relation to Central Pollution Control Board (CPCB) criteria given in Table 1.9



Reprinted from CPCB (2012).

levels, spatial variation, and time trends in major outdoor air pollutants is summarized. Data are extracted primarily from publications on air pollution and epidemiological research conducted in China, as well as from government routine monitoring networks.

In the last century, air pollution from coal combustion was the dominant type of air pollution in most cities in China, and the air pollution was severe. Various pollution control measures and devices have been gradually put in place for the industrial and residential sectors.

Coal will remain the major energy source in China for the near future. However, in recent years, outdoor air pollution in most Chinese cities has become a mixture of emissions from coal combustion, vehicles, and biomass burning, as well as from sandstorms in the north-western region (HEI, 2010b). The annual average levels of PM_{10}, SO_2, and NO_2 in 31 provincial capital cities in China are summarized in Fig. 1.29. The concentrations of PM_{10}, SO_2, and NO_2 in most large urban areas in China have generally stabilized or are decreasing (albeit with some

Table 1.10 Profile of the 10 most polluted Indian cities in 2010[a]

State	City	Minimum (µg/m³)	Maximum (µg/m³)	Annual average (µg/m³)	Standard deviation (µg/m³)	Air quality[b]
PM_{10} concentrations						
Madhya Pradesh	Gwalior	598	114	308*	107	C
Jharkhand	West Singhbhum	59	926	302*	229	C
Uttar Pradesh	Ghaziabad	162	510	290*	89	C
Chhattisgarh	Raipur	207	370	289*	39	C
Delhi	Delhi	46	748	261*	130	C
Haryana	Yamuna Nagar	64	523	261*	116	C
Jharkhand	Jharia	131	370	237*	40	C
Punjab	Khanna	152	283	231*	23	C
Punjab	Gobindgarh	125	534	224*	66	C
Punjab	Amritsar	181	258	219*	20	C
NO_2 concentrations						
West Bengal	Howrah	37	147	75*	25	C
West Bengal	Barrackpore	39	140	74*	24	C
Maharashtra	Badlapur	9	175	73*	37	C
Maharashtra	Ulhasnagar	8	162	68*	33	C
West Bengal	Durgapur	42	91	66*	11	C
West Bengal	Asansol	46	88	66*	10	C
West Bengal	Sankrail	28	120	65*	22	C
West Bengal	Raniganj	45	85	63*	10	C
West Bengal	Kolkata	23	142	62*	27	C
West Bengal	South Suburban	25	113	56*	23	C
SO_2 concentrations						
Jharkhand	Jamshedpur	27	42	35.4	1	M
Jharkhand	Saraikela Kharsawan	28	41	35	3	M
Maharashtra	Badlapur	5	86	32.3	15	M
Goa	Mormugao	7	253	31.8	35	M
Maharashtra	Ulhasnagar	5	109	31.2	17	M
Uttar Pradesh	Ghaziabad	21	37	30.3	3	M
Uttar Pradesh	Khurja	21	40	29.2	4	M
Maharashtra	Pune	10	96	28.7	15	M
Maharashtra	Chandrapur	12	35	21.3	4	L
Jharkhand	West Singhbhum	15	36	21	3	L

NAAQS, National Ambient Air Quality Standards; NO_2, nitrogen dioxide; PM_{10}, particulate matter with particles of aerodynamic diameter < 10 µm; SO_2, sulfur dioxide.

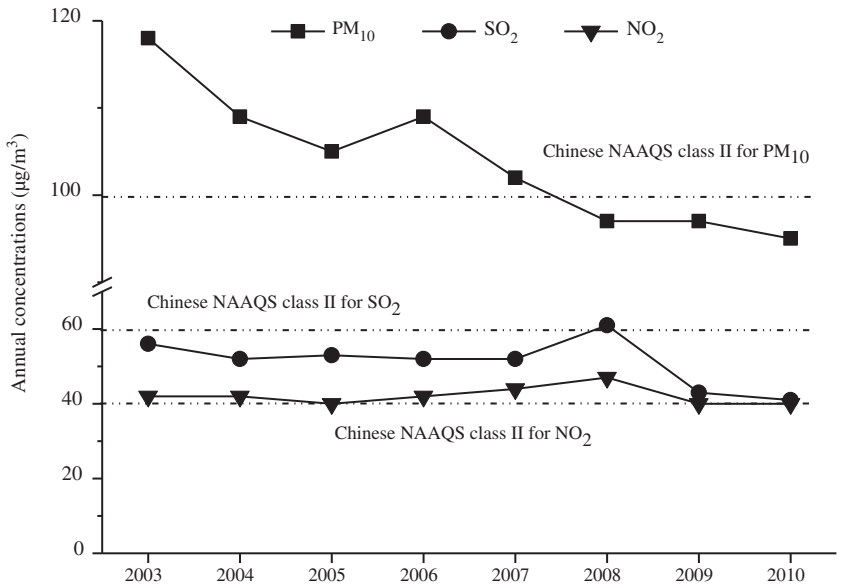
[a] Asterisks indicate cities where annual mean concentration exceeded the NAAQS of 60 µg/m³ (PM_{10}) or 40 µg/m³ (NO_2) or 50 µg/m³ (SO_2) for residential, industrial, and other areas.

[b] Classification based on criteria in Table 1.9: L, low; M, moderate; H, high; C, critical.

Compiled from CPCB (2012).

notable exceptions). However, along with the reductions in concentrations of PM_{10}, SO_2, and NO_2 in China, the pollution episodes of $PM_{2.5}$ and ozone in some city cluster areas suggest the degradation of regional air quality. As total air pollution sources and overall emissions increase in China, yet become more dispersed, regional and transboundary air quality issues are likely to become increasingly important. The mean concentrations of PM_{10}, $PM_{2.5}$, SO_2, NO_2, and

Fig. 1.29 Annual average levels of PM_{10}, SO_2, and NO_2 in 31 provincial capital cities in China, 2003–2010



NO_2, nitrogen dioxide; PM_{10}, particulate matter with particles of aerodynamic diameter < 10 μm; SO_2, sulfur dioxide.
The dotted-dashed line indicates the annual level of the Chinese National Ambient Air Quality Standards (NAAQS) class II.
Reprinted from Shang et al. (2013). Systematic review of Chinese studies of short-term exposure to air pollution and daily mortality. *Environ Int*, 54:100–11. doi:10.1016/j.envint.2013.01.010 PMID:23434817, © with permission from Elsevier.

ozone reported in time-series studies conducted in China from 1990 to 2012 are presented in Table 1.11.

PM_{10}

As a result of energy restructuring, the annual average levels of PM_{10} in 31 provincial capital cities in China decreased by about 25% from 2003 to 2010 (Fig. 1.29); however, the levels are still high compared with elsewhere in the world. In 2010, the annual concentrations of PM_{10} were 121 μg/m³ in Beijing, 79 μg/m³ in Shanghai, 69 μg/m³ in Guangzhou, and 126 μg/m³ in Xi'an (National Bureau of Statistics of China, 2011). The spatial variations of PM_{10} in major Chinese cities suggest more serious particulate pollution in northern regions in China, due to the longer heating season in winter as well as the local topography and the impact of sandstorms. The nationwide distribution of air pollution levels is likely to be related to the spatial distribution of emission sources across the country (National Bureau of Statistics of China, 2012).

SO_2

Trends in air quality in 31 provincial capital cities in China from 2003 to 2010 suggest a significant decrease of about 30% in annual average SO_2 concentrations in urban areas, with the exception of an average increase in SO_2 concentration during 2008 (Fig. 1.29). The reductions in SO_2 have resulted from the use of low-sulfur fuels and the relocation of major coal-fired power plants and industrial facilities from urban areas to outside cities. In more recent years, annual levels of SO_2 were below 60 μg/m³ in most cities, and PM_{10} concentration levels continued to decrease (National Bureau of Statistics of China, 2012).

Table 1.11 Mean concentrations of PM_{10}, $PM_{2.5}$, SO_2, NO_2, and O_3 reported in time-series studies conducted in China (1990–2012)

City, year(s)	Pollutant[a]					Reference
	PM_{10}	$PM_{2.5}$	SO_2	NO_2	O_3	
Beijing, 2003	141 (79)	—	60 (56)	—	—	Pan et al. (2008)
Beijing, 2004–2008	146 (92)	—	49 (49)	64 (26)	—	Zhang et al. (2010b)
Beijing, 2007–2008	172 (93)	82 (52)	—	—	—	Chen et al. (2011a)[b]
Shanghai, 2000–2001	91 (52)	—	43 (20)	33 (14)	—	Kan & Chen, (2003)
Shanghai, 2001–2004	102 (2)	—	45 (1)	67 (1)	63 (1)	Kan et al. (2008)
Shanghai, 2001–2004	102 (65)	—	45 (24)	67 (25)	63 (37)	Zhang et al. (2006b)
Shanghai, 2002–2003	112 (76)	69 (48)	38 (21)	59 (23)	—	Dai et al. (2004)[b]
Shanghai, 2004–2005	108 (2)	56 (1)	58 (1)	62 (1)	77 (3)	Huang et al. (2009)[b]
Shanghai, 2004–2005	108(2)	57 (1)	—	—	65 (3)	Kan et al. (2007)[b]
Shanghai, 2004–2008	105 (54)	55 (30)	—	—	—	Chen et al. (2011a)[b]
Shanghai, 2006–2008	86 (53)	—	53 (30)	56 (21)	—	Chen et al. (2011b)[b]
Guangzhou, 2004–2008	81 (45)	—	54 (36)	67 (30)	—	Huang et al. (2012b)
Guangzhou, 2006–2009	60 (24)	—	43 (21)	48 (26)	—	Yu et al. (2012)
Guangzhou, 2007–2008	—	70 (35)	50 (32)	66 (31)	—	Yang et al. (2012a)[b]
Tianjin, 2005–2007	105 (57)	—	68 (54)	47 (18)	—	Zhang et al. (2010c)
Hong Kong Special Administrative Region, 1995–1998	52 (25)	—	17 (12)	56 (20)	34 (23)	Wong et al. (2002)
Hong Kong Special Administrative Region, 1996–2002	52 (25)	—	18 (12)	59 (20)	37 (23)	Wong et al. (2008a)
Wuhan, 2000–2004	142 (64)	—	44 (25)	52 (19)	78 (41)	Qian et al. (2007)
Wuhan, 2001–2004	142	—	39	52	86	Wong et al. (2008b)
Pearl River Delta, 2006–2008	78	—	62	53	80	Tao et al. (2011)[b]
Xi'an, 2004–2008	131 (55)	—	48 (29)	39 (15)	—	Hou et al. (2011)
Xi'an, 2004–2008	—	177 (104)	—	—	—	Huang et al. (2012a)[b]
Anshan, 2004–2006	111 (60)	—	59 (74)	26 (16)	—	Chen et al. (2010)
Chongqing, 1995	—	147	213	—	—	Venners et al. (2003)[b]
Suzhou, 2006–2008	—	—	—	—	58 (40)	Yang et al. (2012b)
Hangzhou, 2002–2004	113	—	46	53	—	Ren et al. (2007)
Shenyang, 2006–2008	141 (66)	94 (52)	—	—	—	Chen et al. (2011a)[b]
Taiyuan, 2004–2008	132 (65)	—	77 (8)	23 (9)	—	Chen et al. (2011b)

NO_2, nitrogen dioxide; O_3, ozone; PM_{10}, particulate matter with particles of aerodynamic diameter < 10 μm; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 μm; SO_2, sulfur dioxide.

[a] Mean concentrations are given in μg/m³; when available, standard deviations are given in parentheses.

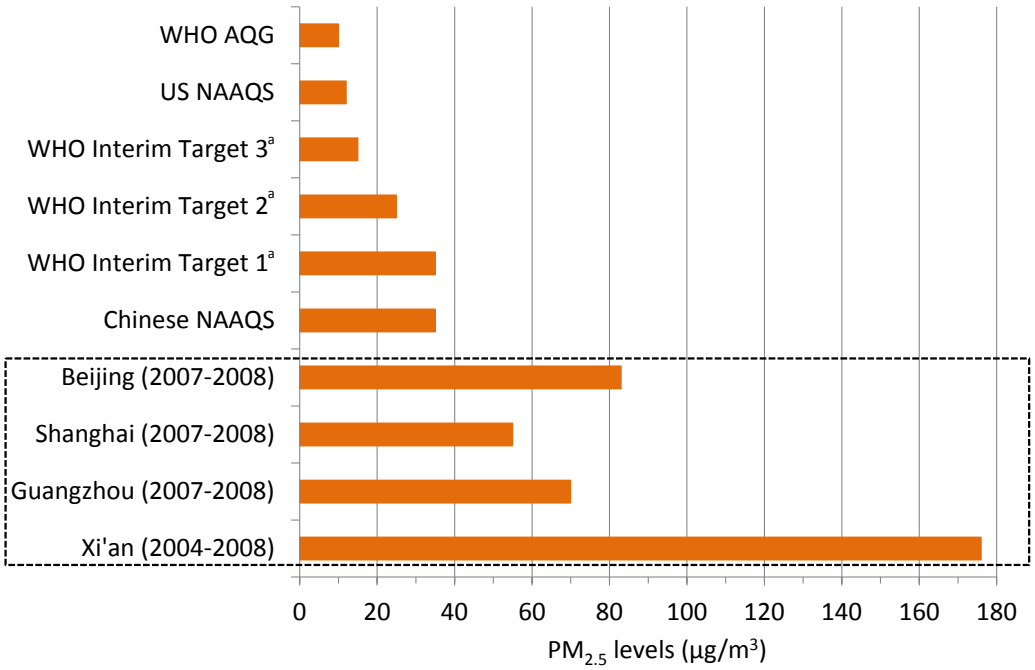
[b] Air pollution data collected not by state routine monitoring reporting system but by environmental science investigators.

Prepared by the Working Group.

NO_2

Due to tightened motor vehicle emission standards in place from the early 2000s, annual average NO_2 levels remained stable at 40 μg/m³, with some variations (Fig. 1.29). However, with the increasing numbers of motor vehicles in most Chinese cities, NO_2 levels in the more developed cities tend to be higher, at more than 45 μg/m³ (National Bureau of Statistics of China, 2012; Table 1.11).

Fig. 1.30 Comparisons of reported annual $PM_{2.5}$ levels (μg/m³) in Beijing, Shanghai, Guangzhou, and Xi'an with the Chinese national standards and international air quality standards



AQG, air quality guidelines; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter <2.5 μm; NAAQS, National Ambient Air Quality Standards.

[a] In addition to guideline values, WHO has proposed interim targets for each air pollutant in 2005. "These interim targets are proposed as incremental steps in a progressive reduction of air pollution, and are intended for use in areas where pollution is high. … Progress towards the guideline values should, however, be the ultimate objective of air quality management and health risk reduction in all areas" (WHO, 2006).

Prepared by the Working Group based on data from China Statistical Yearbook 2008–2009.

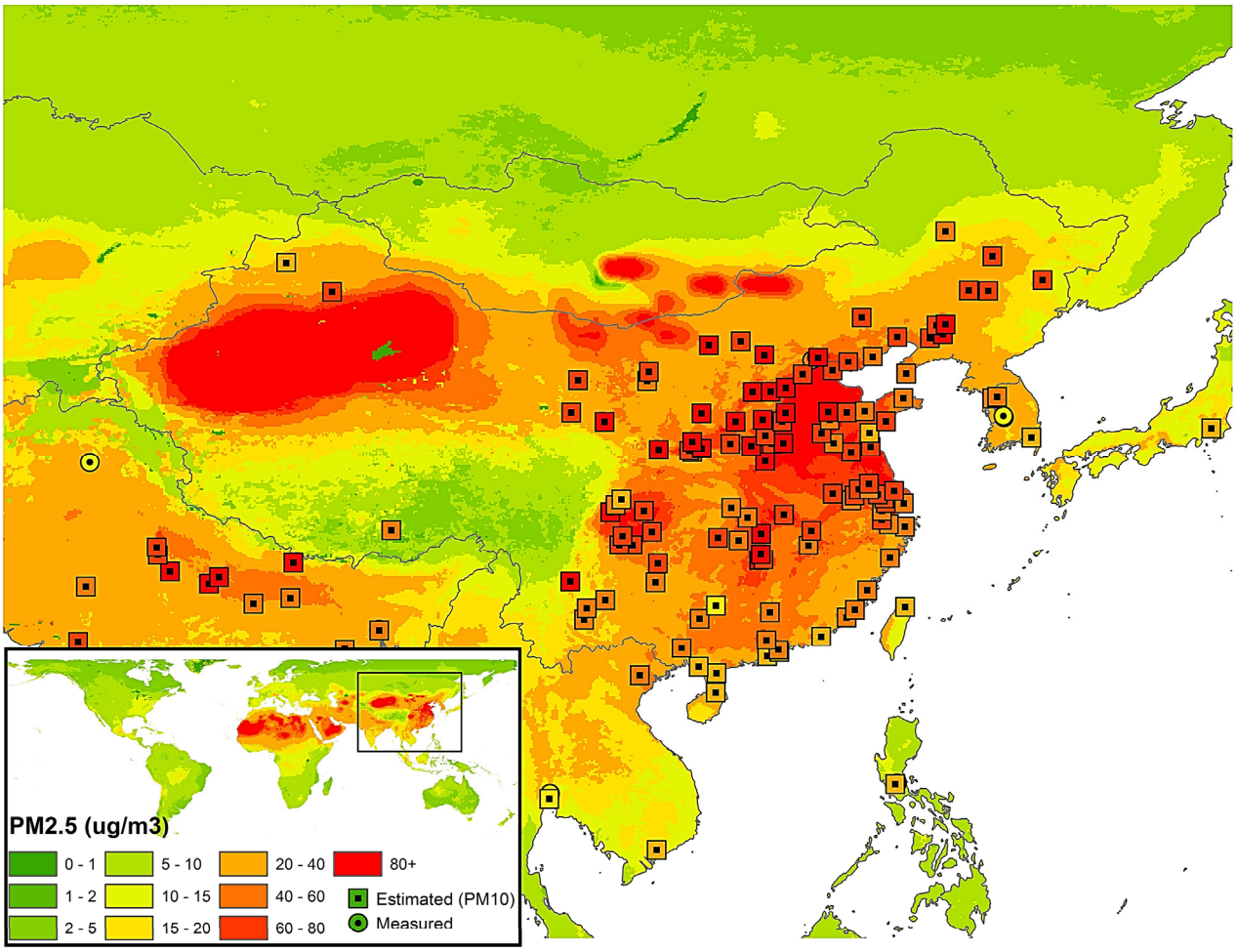
$PM_{2.5}$ and ozone

At present, very limited data are available on the annual levels of $PM_{2.5}$ and ozone, which were newly included in the revised Chinese AAQS released in March 2012 (MEPPRC, 2012).

To assess exposure, time-series studies have been conducted (Shang et al., 2013). The reported average concentrations of $PM_{2.5}$ and 8-hour ozone in these studies were in the ranges of 55–177 μg/m³ and 34–86 μg/m³, respectively (Table 1.11). In these studies, the reported $PM_{2.5}$ levels in Beijing, Shanghai, Guangzhou, and Xi'an were all well above the Chinese national standards and international air quality standards (Fig. 1.30). Brauer et al. (2012) estimated that the population-weighted annual average levels of $PM_{2.5}$ in East Asia had increased from 43 μg/m³ to 55 μg/m³ between 1990 and 2005, whereas they reported the highest measurement of annual average $PM_{2.5}$ concentration (in 2005) of 58 μg/m³ in Beijing and the highest derived $PM_{2.5}$ concentration (calculated from PM_{10} measurements) of 121 μg/m³ in Datong, a coal-mining centre in Shanxi Province (Brauer et al., 2012). In northern China, estimated $PM_{2.5}$ levels in 2010 were above 80 μg/m³ (Fig. 1.31).

Geological materials, organic materials, EC, and secondary aerosols (such as SO_4^{2-}, NO_3^-, and NH_4^+) are the primary components of $PM_{2.5}$ in China; however, due to source variations, the concentrations of primary $PM_{2.5}$ components vary significantly across locations and seasons (Niu et al., 2006; Cao et al., 2012). On average, SO_4^{2-}, NO_3^-, NH_4^+, organic materials, and EC

Fig. 1.31 Estimated levels of $PM_{2.5}$ (μg/m³) in 2010 in China



$PM_{2.5}$, particulate matter with particles of aerodynamic diameter <2.5 μm.
Compiled by the Working Group with data from Brauer et al. (2012).

account for more than 70% of the $PM_{2.5}$ mass in summer, whereas the percentage is even higher in winter (Cao et al., 2012).

Lead levels are still high in Chinese cities, reaching an average of 1.68 μg/m³ in Xi'an during winter. High correlations of lead with arsenic and SO_4^{2-} concentrations indicate that much of the lead derives from coal combustion rather than from leaded fuels, which were phased out by 2000 in China. Although limited fugitive dust markers were available, scaling of iron by its ratios in source profiles showed that in most of the cities, 20% of $PM_{2.5}$ derives from fugitive dust (Cao et al., 2012).

Photochemical smog, in the presence of solar radiation, is commonplace in city cluster areas of China with greatly increased numbers of vehicles (e.g. the Beijing–Tianjin–Hebei area and the Pearl River Delta region). Studies in these areas reported high concentrations of PM induced by photochemical smog. For example, in Shenzhen in 2004, the 24-hour average $PM_{2.5}$ and PM_{10} concentrations in summer were 35 μg/m³ and 57 μg/m³, respectively, and in winter were 99 μg/m³ and 137 μg/m³, respectively (Niu et al., 2006). In

Guangzhou, the summer 24-hour average $PM_{2.5}$ concentration was 97.5 μg/m³ (Wang et al., 2006).

Polycyclic aromatic hydrocarbons

Daily and hourly average or snapshot concentrations of outdoor PAHs in urban and industrial areas in China are high compared with elsewhere in the world (usually 10–20 ng/m³). Mean concentrations of 16 outdoor PAHs of up to 1400 μg/m³ were observed in Taiyuan, a coal-polluted city in central China, in December 2006 (Fu et al., 2010). Concentrations of PAHs in the gas phase were also reported at high levels, in particular in megacities and large cities (e.g. Beijing, Shanghai, and Hangzhou) (Liu et al., 2001, 2007; Wang et al., 2002; Zhang et al., 2009b; Zhu et al., 2009; Wei et al., 2011).

Volatile organic compounds

High daily and hourly average or snapshot concentrations of outdoor benzene, toluene, and xylene have been reported in Chinese megacities (e.g. Beijing, Shanghai, and Guangzhou) compared with the levels observed in the USA (Zou et al., 2003; Zhang et al., 2006a; Wei et al., 2007; Lu et al., 2008; Wang et al., 2010; Zhou et al., 2011).

(iii) Japan

As one of the most developed countries in Asia, Japan experienced serious pollution from industrial and automobile emissions in the 1950s and 1960s, and the main energy source shifted from coal to oil, making SO_2 a major air pollutant (Committee on Japan's Experience in the Battle Against Air Pollution, 1997). Air pollution levels declined after the introduction of pollution control measures in the 1970s. As an example, the nationwide annual average concentrations of SO_2 decreased to 0.015 ppm [42.3 μg/m³] in the 1970s and further to 0.006 ppm [16.9 μg/m³] in 1990 (Ministry of the Environment of Japan, 2011).

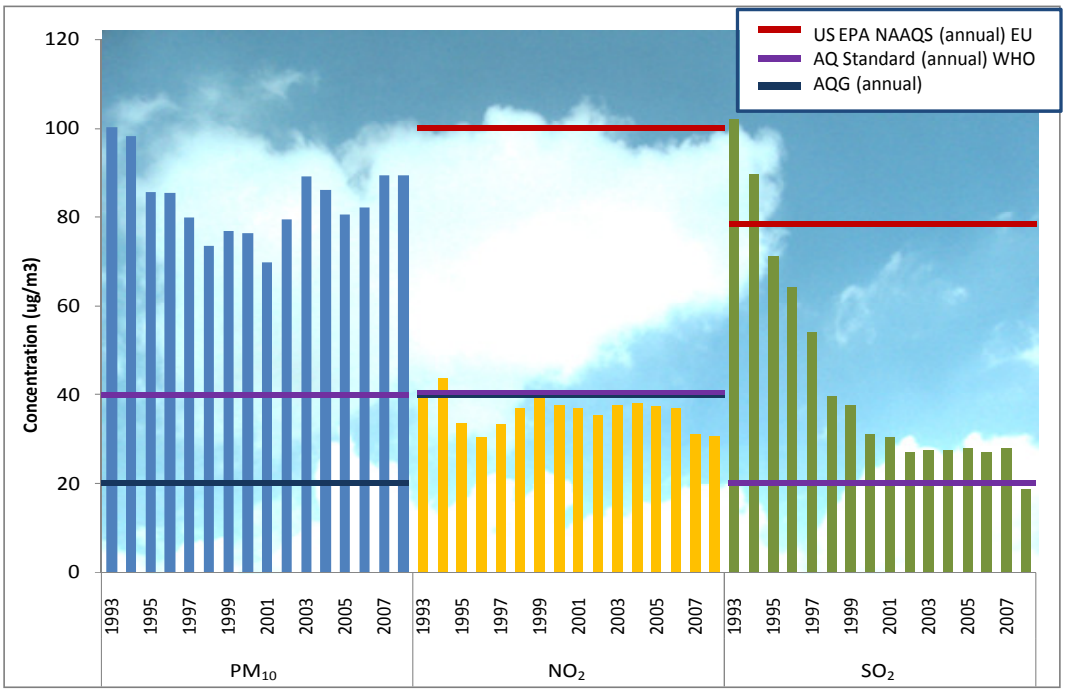
In contrast to the rapid decline in the concentrations of SO_2, pollution from mobile sources increased during the 1970s. The annual concentrations of NO_2 in 1970 were 0.035 ppm [70.9 μg/m³] at general sites and 0.042 ppm [85.1 μg/m³] at roadside sites; those of suspended PM (PM < 7 μm in diameter [SPM]) in 1975 were 50 μg/m³ at general sites and 84 μg/m³ at roadside sites (Ministry of the Environment of Japan, 2011). After the tightened mobile-source emission control regulations and measures were put in place, the concentrations of NO_2 and SPM declined gradually.

In 2011, the annual concentrations of major air pollutants in Japan were as follows: SO_2, 0.002 ppm [5.64 μg/m³] at general sites and 0.003 ppm [8.46 μg/m³] at roadside sites; NO_2, 0.011 ppm [22.3 μg/m³] at general sites and 0.021 ppm [42.5 μg/m³] at roadside sites; SPM, 20 μg/m³ at general sites and 22 μg/m³ at roadside sites; $PM_{2.5}$, 15.4 μg/m³ at general sites and 16.1 μg/m³ at roadside sites; and CO, 0.3 ppm [370 μg/m³] at general sites and 0.5 ppm [617 μg/m³] at roadside sites (Ministry of the Environment of Japan, 2011). In recent years, in addition to making the necessary efforts towards reducing the concentrations of these pollutants, Japan has also faced problems such as relatively high and stable concentrations of ozone in metropolitan areas (e.g. annual concentration of 0.028 ppm [59.2 μg/m³] in Tokyo in 2011) (Bureau of Environment of Tokyo, 2013).

(iv) Other Asian countries

Since the 1990s, most Asian countries have established national routine air quality monitoring networks for the criteria pollutants PM_{10}, SO_2, and NO_2, whereas the air quality data on $PM_{2.5}$ and ozone have been very limited. In the cities with routine air quality monitoring systems, some improvements in air quality have been achieved in the past decades; however, the levels of PM_{10} and SO_2 still exceed the World Health Organization (WHO) air quality guidelines (AQG) (Fig. 1.32; Clean Air Asia, 2010). PM_{10} has been a major pollutant in Asian cities, with

Fig. 1.32 Average of annual average outdoor air quality in selected Asian cities (1993–2008)



NAAQS, National Ambient Air Quality Standards; NO_2, nitrogen dioxide; PM_{10}, particulate matter with particles of aerodynamic diameter < 10 µm; SO_2, sulfur dioxide.
Air quality data are compiled by CAI-Asia Center from official sources (publications, personal communications) for 243 Asian cities, as of April 2010.
The US EPA NAAQS does not have a standard for PM_{10}, whereas the EU and WHO apply the same standards for NO_2 and SO_2.
Reprinted from Clean Air Asia (2010).

annual average PM_{10} concentrations well above the WHO AQG. Since 1995, most Asian cities have reported reduced NO_2 levels, with annual average concentrations below the WHO AQG. For SO_2, the annual average levels have decreased remarkably from the 1990s to the 2000s in most Asian cities, due to energy restructuring in the area.

PM_{10}

As of 2008, PM_{10} was still a major pollutant in Asia; annual average PM_{10} concentrations ranged from 11 µg/m³ to 375 µg/m³ in the 230 Asian cities with the highest levels observed in East and South-East Asia (Fig. 1.33; Clean Air Asia, 2010).

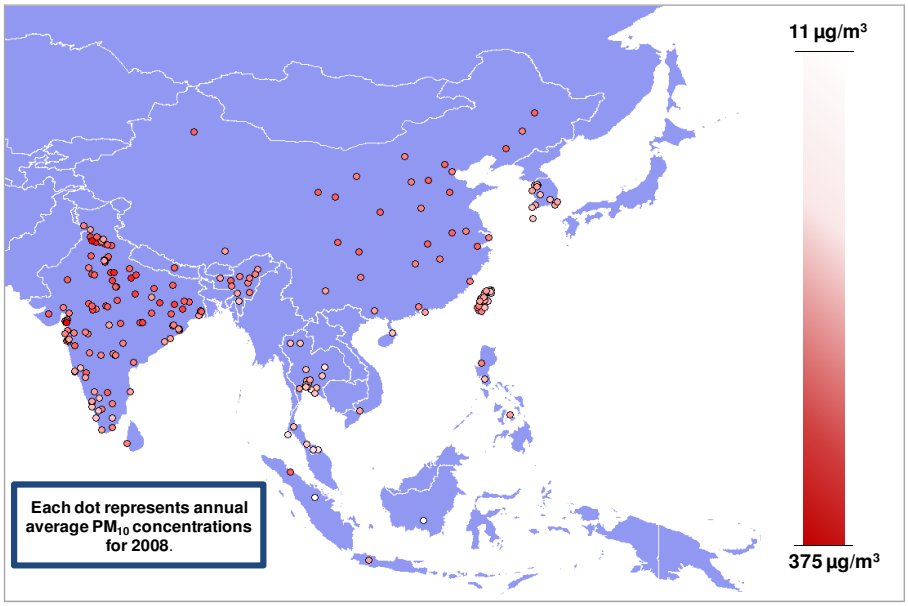
SO_2

In 2008, the monitoring data for 213 Asian cities showed that SO_2 levels were still high in some cities in East Asia, particularly those near industries. Annual average SO_2 concentrations ranged from 1.3 µg/m³ to 105 µg/m³. The mean of annual average SO_2 concentrations for 213 Asian cities was 18.7 µg/m³ in 2008. See Fig. 1.34 (Clean Air Asia, 2010).

NO_2

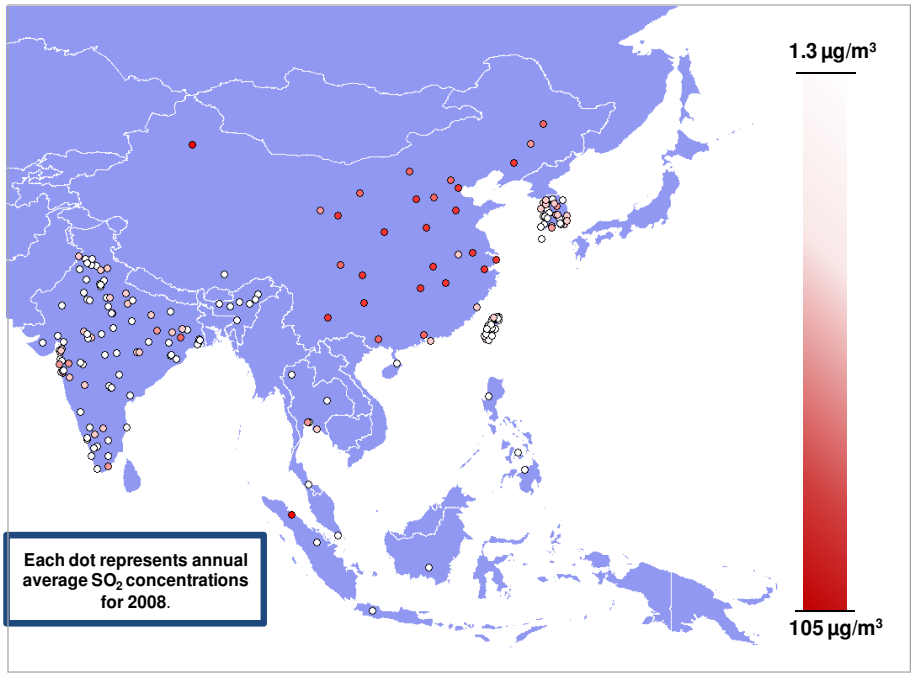
In 2008, annual average NO_2 concentrations ranged from 1.9 µg/m³ to 77 µg/m³ in 234 Asian cities; the mean of annual average NO_2 concentrations was 30.7 µg/m³. About 73% of the 234 cities had annual average NO_2 concentrations below the WHO AQG of 40 µg/m³. See Fig. 1.35 (Clean Air Asia, 2010).

Fig. 1.33 Annual PM_{10} concentrations (μg/m³) in 230 Asian cities



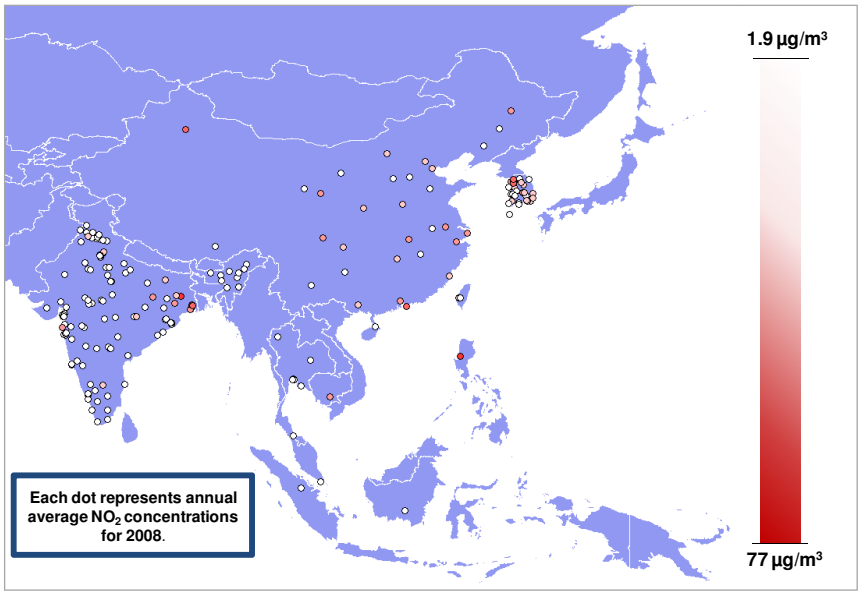
PM_{10}, particulate matter with particles of aerodynamic diameter < 10 μm.
Reprinted from Clean Air Asia (2010).

Fig. 1.34 Annual SO_2 concentrations (μg/m³) in 213 Asian cities



SO_2, sulfur dioxide.
Reprinted from Clean Air Asia (2010).

Fig. 1.35 Annual NO_2 concentrations (µg/m³) in 234 Asian cities



NO_2, nitrogen dioxide.
Reprinted from Clean Air Asia (2010).

$PM_{2.5}$

$PM_{2.5}$ levels have increased in medium to large Asian cities. Only a few Asian countries have set $PM_{2.5}$ air quality standards, and of those countries, none have standards equivalent to the WHO AQG, but generally the standards are close to the WHO interim target. The population-weighted annual average concentrations of $PM_{2.5}$ were estimated to range between 16 µg/m³ and 55 µg/m³, with the highest levels observed in East Asia, followed by South Asia, in 2005 (Brauer et al., 2012).

A multicity study examined the seasonal variations of $PM_{2.5}$ mass concentrations and species in mixed urban areas (2001–2004) in six Asian cities: Bandung (Indonesia), Bangkok (Thailand), Beijing (China), Chennai (India), Manila (Philippines), and Hanoi (Viet Nam) (Table 1.12). These cities differed in geographical location, topography, energy use, industry, mix of vehicles, and density. The climate of the region is dominated by monsoons, with two distinct seasons, dry and wet, although each dry and wet season may cover different months of the year in different countries. In these cities, the major components of $PM_{2.5}$ and PM_{10} were found to be organic matter (calculated in this study as 1.7 times the OC content); crustal material, including aluminium, calcium, silicon, titanium, iron, potassium, and their oxides; the secondary aerosols NO_3^- and SO_4^{2-}; and EC/BC. The "trace metals" group included all the remaining elements except crustal elements, sodium, and sulfur. OC was not analysed in most sites, except for the Bangkok Metropolitan Region and Beijing; hence, comparison of OC levels was not possible. In all these cities, the levels of PM_{10} and $PM_{2.5}$ were found to be high, especially during the dry season, frequently exceeding the US EPA standard for PM_{10} and $PM_{2.5}$, especially at the traffic sites (Kim Oanh et al., 2006).

PAHs in particles are also important in Asia. Shen et al. (2013) estimated that Asian countries contributed 53.5% of the global total PAH emissions, with the highest emissions from China (106 Gg) and India (67 Gg) in 2007.

Table 1.12 City-wise average mass and major components of $PM_{2.5}$ (μg/m³) during the dry and wet seasons in six cities in Asia (2001–2004)

Cities, country	Number of samples	Mass[a]	Crustal	Organic matter	Soot	Sea salt	NH_4^+	NO_3^-	SO_4^{2-}	Trace elements	Percentage of mass explained
Dry season $PM_{2.5}$											
Bangkok[b], Thailand	181	50	1.1	21.4	8.2	1.7	1.6	1.2	5.6	0.4	80
Beijing, China	142	168	9.9	64.3	18.7	1.6	12.5	14.2	20.8	1.5	40
Chennai, India	83	46									
Bandung, Indonesia	106	53	2.8	–	9.8	0.7	3.4	5.5	8.2	0.8	59
Manila, Philippines	407	44	1.4	–	21.6	0.9	–	–	(1.5)[c]	0.7	56
Hanoi[c], Viet Nam	75	124	7.5	–	–	1.1	–	–	(6.0)[c]	7.1	18
Wet season $PM_{2.5}$											
Bangkok[b], Thailand	106	18	0.9	–	5.3	1.5	0.5	0.4	2.4	0.3	71
Beijing, China	115	104	4.5	19.2	5.3	0.5	10.4	12.0	17.9	1.0	57
Chennai, India	10	42									
Bandung, Indonesia	38	38	3.1	–	7.5	0.8	3.9	3.5	6.3	1.5	71
Manila, Philippines	376	43	1.4	–	22.7	0.9	–	–	(0.8)	1.6	63
Hanoi[c], Viet Nam	21	33	4.0	–	4.3	–	–	–	–	3.8	47

[a] Average of all sites in the city.
[b] Bangkok metropolitan area.
[c] Hanoi metropolitan region.
Adapted from Kim Oanh et al. (2006).

(d) Other regions

(i) Africa

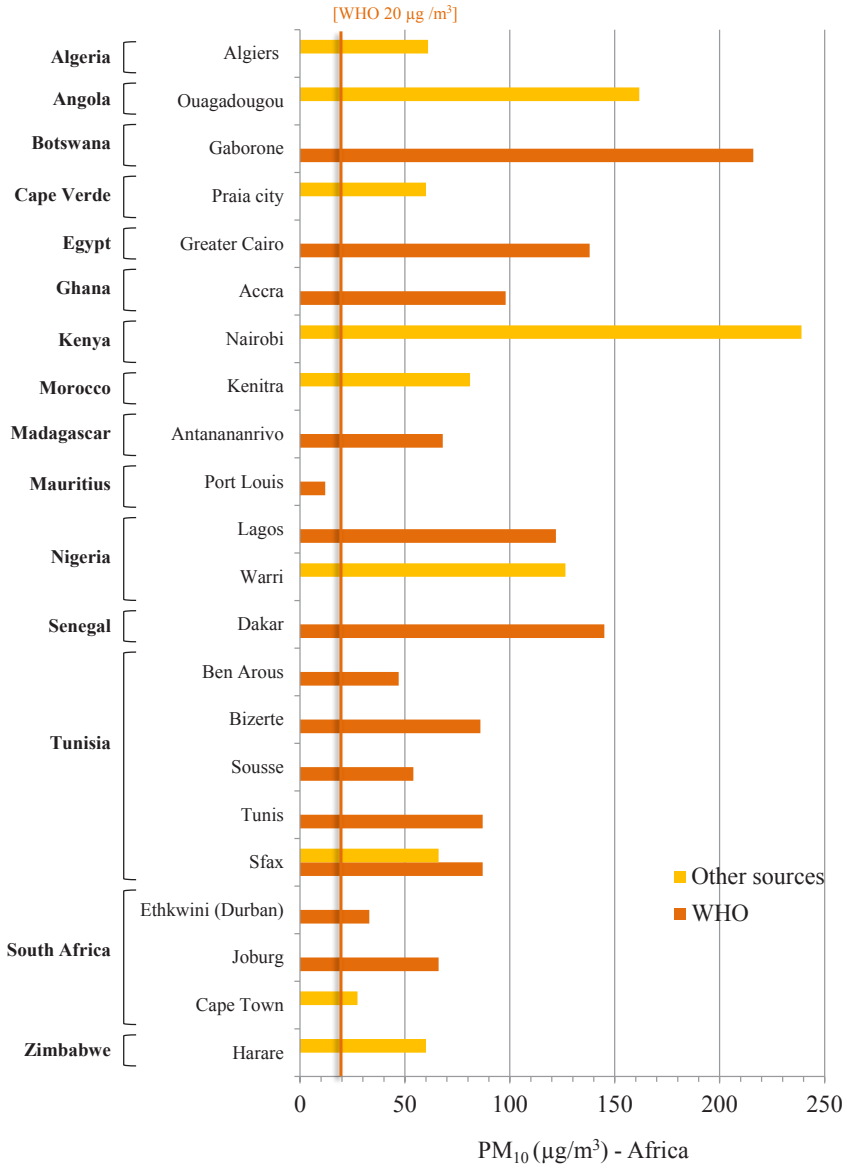
Measurements of air pollution in Africa are limited, and environmental agencies do not exist in all countries. World agencies provide some aggregate information for the continent, which can be complemented by local research, as air quality data in Africa are scarce.

Fig. 1.36 and Fig. 1.37 present the mean concentrations for PM measured with at least 2 months of monitoring coverage in selected African cities. The limited data show that the concentrations range from 7 μg/m³ to more than 100 μg/m³ for $PM_{2.5}$ and from 12 μg/m³ to more than 230 μg/m³ for PM_{10} in the African cities studied. Among the reported air pollution measurement campaigns, Dionisio *et al.* reported the geometric mean concentrations of $PM_{2.5}$ and PM_{10} along the mobile monitoring path [street-level monitoring] of 21 μg/m³ and 49 μg/m³, respectively, in the neighbourhood with the highest socioeconomic status and 39 μg/m³ and 96 μg/m³, respectively, in the neighbourhood with the lowest socioeconomic status and the highest population density in Accra, Ghana. The factors that had the largest effects on local PM pollution were nearby wood and charcoal stoves, congested and heavy traffic, loose-surface dirt roads, and trash burning (Dionisio et al., 2010a).

(ii) South America

Continuous measurements of air pollution are available in more than half of the South American countries. However, the spatial distribution of air monitoring stations in South America is not balanced. For instance, in Brazil monitoring stations are located mostly in large metropolitan regions and do not cover the remaining areas of Brazil; only 8 out of 27 Brazilian states (including the Federal District) have set up air monitoring networks. Fig 1.38 and Fig. 1.39 summarize the most recent data on PM concentrations in South American countries; concentrations ranged from

Fig. 1.36 PM_{10} concentrations (µg/m³) in selected African cities

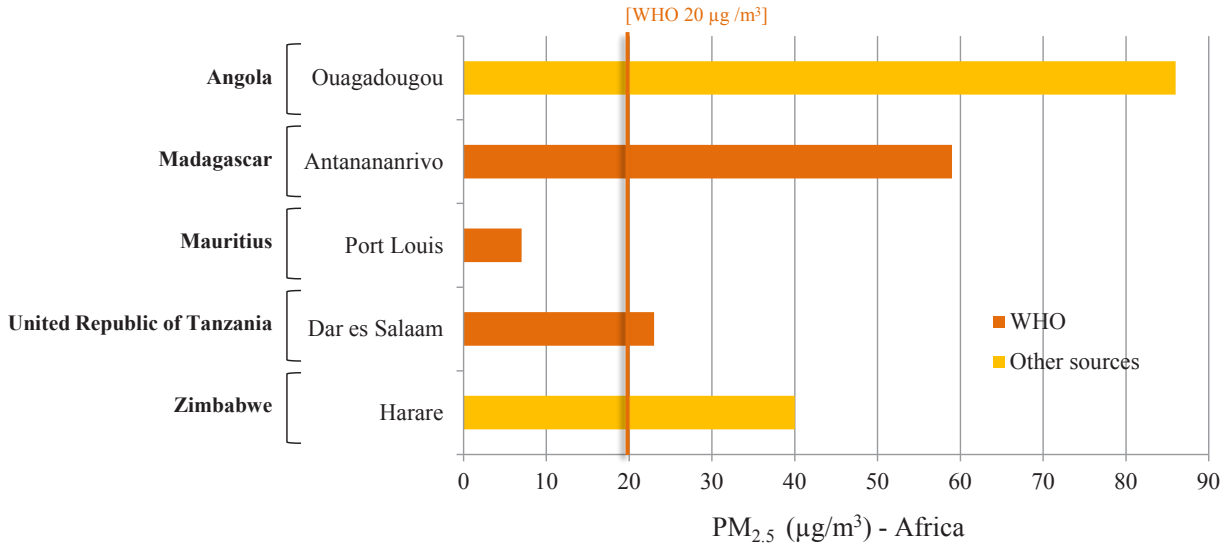


PM_{10}, particulate matter with particles of aerodynamic diameter < 10 µm.
Compiled by the Working Group with data from Lindén et al. (2012), WHO (2011), Tchuente et al. (2013), Almeida-Silva et al. (2013), Petkova et al. (2013), Laïd et al. (2006), WHO (2011), Abu-Allaban et al. (2007), Dionisio et al. (2010a, b), Arku et al. (2008), Mkoma et al. (2009, 2010), Wichmann & Voyi (2012), and Kuvarega & Taru (2008).

22 µg/m³ to 70 µg/m³ for PM_{10} and from 7 µg/m³ to 35 µg/m³ for $PM_{2.5}$.

Besides high PM concentrations measured in South American cities, high concentrations of formaldehyde were reported in some countries, such as Brazil. In downtown Rio de Janeiro, mean formaldehyde concentrations rose 4-fold from 1998 to 2002, to 96 µg/m³ (with peak 2-hour concentrations as high as 138 µg/m³) (Corrêa & Arbilla, 2005). A further 10-fold increase in formaldehyde concentrations was reported in Rio de Janeiro from 2001 to 2004, as a consequence

Fig. 1.37 $PM_{2.5}$ concentrations (μg/m³) in selected African cities



$PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 μm.
Compiled by the Working Group with data from Boman et al. (2009), Tchuente et al. (2013), Abu-Allaban et al. (2007), Dionisio et al. (2010a, b), Arku et al. (2008), Kinney et al. (2011), van Vliet & Kinney (2007), WHO (2011), Petkova et al. (2013), Mkoma et al. (2010), Worobiec et al. (2011), and Kuvarega & Taru (2008).

of the introduction of compressed natural gas vehicles in 2000 (Martins et al., 2007).

(iii) The Middle East

WHO (2011) depicts air monitoring information for 39% of the Middle East countries. Air pollution monitoring coverage in the Middle East is similar to that in South American countries – 67% of both regions have some type of air quality data available; however, the air pollution monitoring sites are not evenly distributed across Middle East countries. Fig 1.40 and Fig. 1.41 depict PM concentrations across the Middle East; concentrations mostly ranged from 25 μg/m³ to 100 μg/m³ for PM_{10} and from 50 μg/m³ to 300 μg/m³ for $PM_{2.5}$.

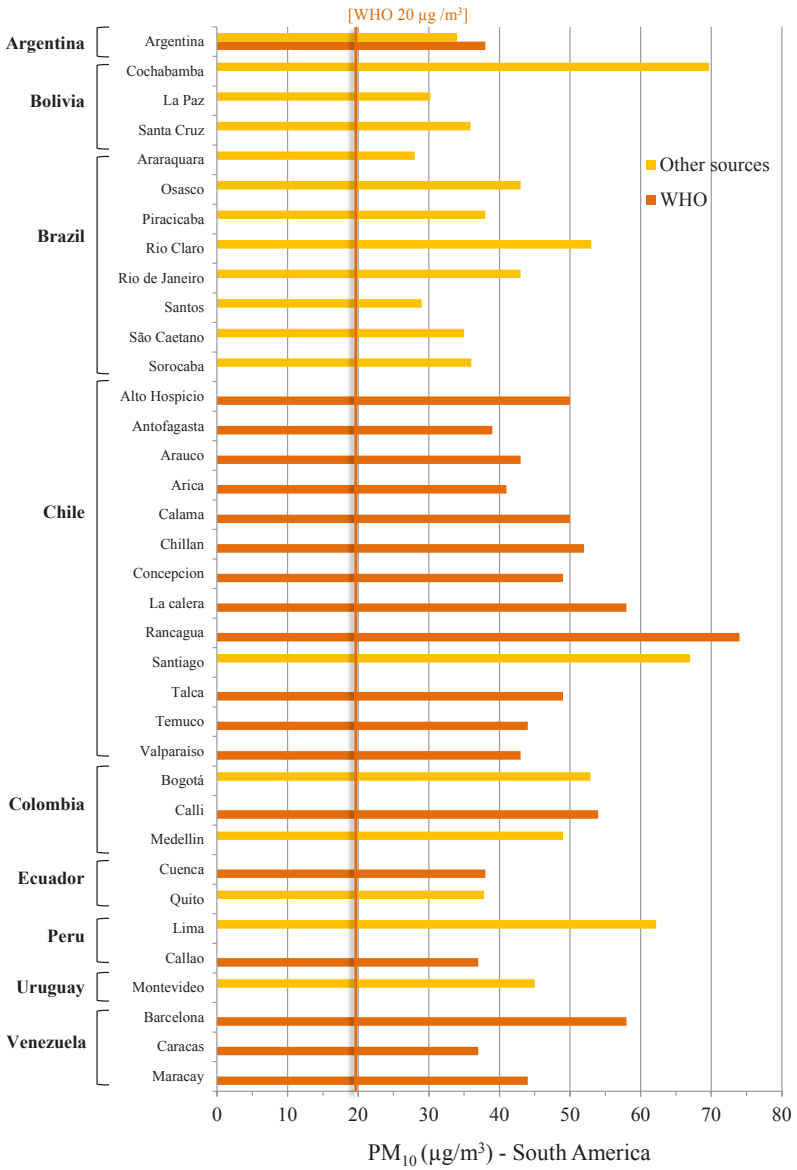
(iv) Australia

Between 1999 and 2008, there were significant decreases in the levels of air pollution in Australia. Levels of CO, NO_2, SO_2, and lead in urban areas declined to levels significantly below the national air quality standards. However, levels of PM and ozone did not decrease significantly over the time period. Between 1999 and 2008, the median 1-hour and 4-hour ozone levels varied between 0.02 ppm and 0.04 ppm in most Australian cities; the higher levels (~0.04 ppm) were observed in some areas including South East Queensland and Toowoomba. For PM, the median annual levels of PM_{10} remained at 15–20 μg/m³ and the $PM_{2.5}$ levels were 5–10 μg/m³ in most Australian cities in 2008 (Australian Government, 2010).

1.4.2 Exposure assessment in epidemiological studies

Epidemiological studies of relationships between air pollution exposure and cancer require long periods of observation and large populations. Therefore, it is virtually impossible with currently available approaches to assess exposure via personal monitoring (which is here distinguished from biomarkers of exposure, which are discussed in Section 1.4.3). Accordingly, epidemiological studies use outdoor air pollution concentrations as the primary basis for exposure

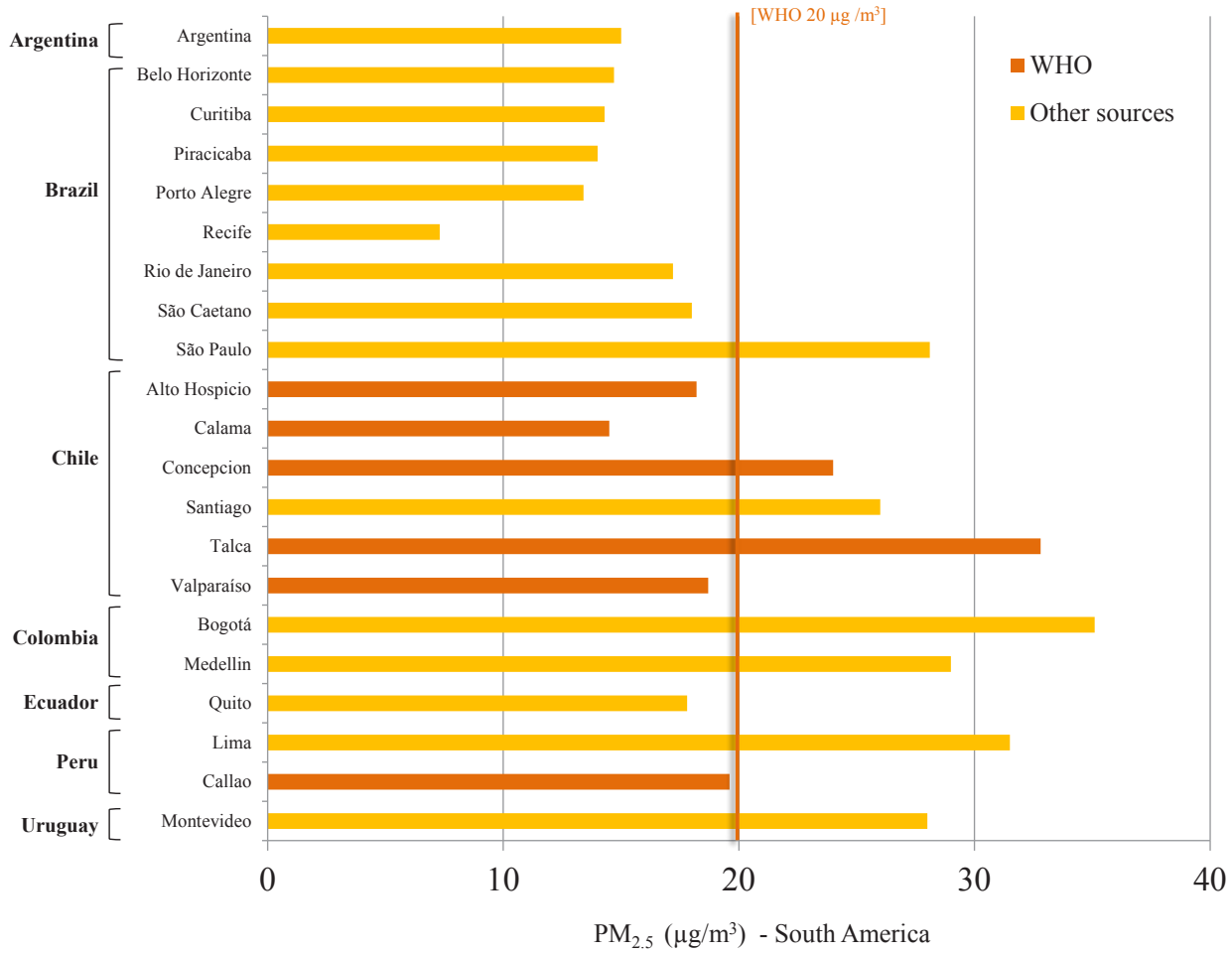
Fig. 1.38 PM_{10} concentrations (µg/m³) in selected South American cities



PM_{10}, particulate matter with particles of aerodynamic diameter < 10 µm.
Compiled by the Working Group with data from WHO (2011), Arkouli et al. (2010), Clean Air Institute (2012), CETESB (2013), FEAM (2011), IEMA (2007), de Miranda et al. (2012); INEA (2009), and RFF (2005).

estimation. Given that air quality monitoring is typically limited to measurements of a relatively small number of indicator pollutants collected at a limited number of discrete locations, epidemiological studies and risk assessments have typically used several approaches to estimate exposures of study subjects. Of particular importance for assessment of cancer is the ability to assess exposures over long time periods. An ideal assessment of long-term exposure requires both residential histories for the study population of interest and estimates of outdoor air pollution concentrations for periods of 20–30 years (life course). Prospective cohort studies following

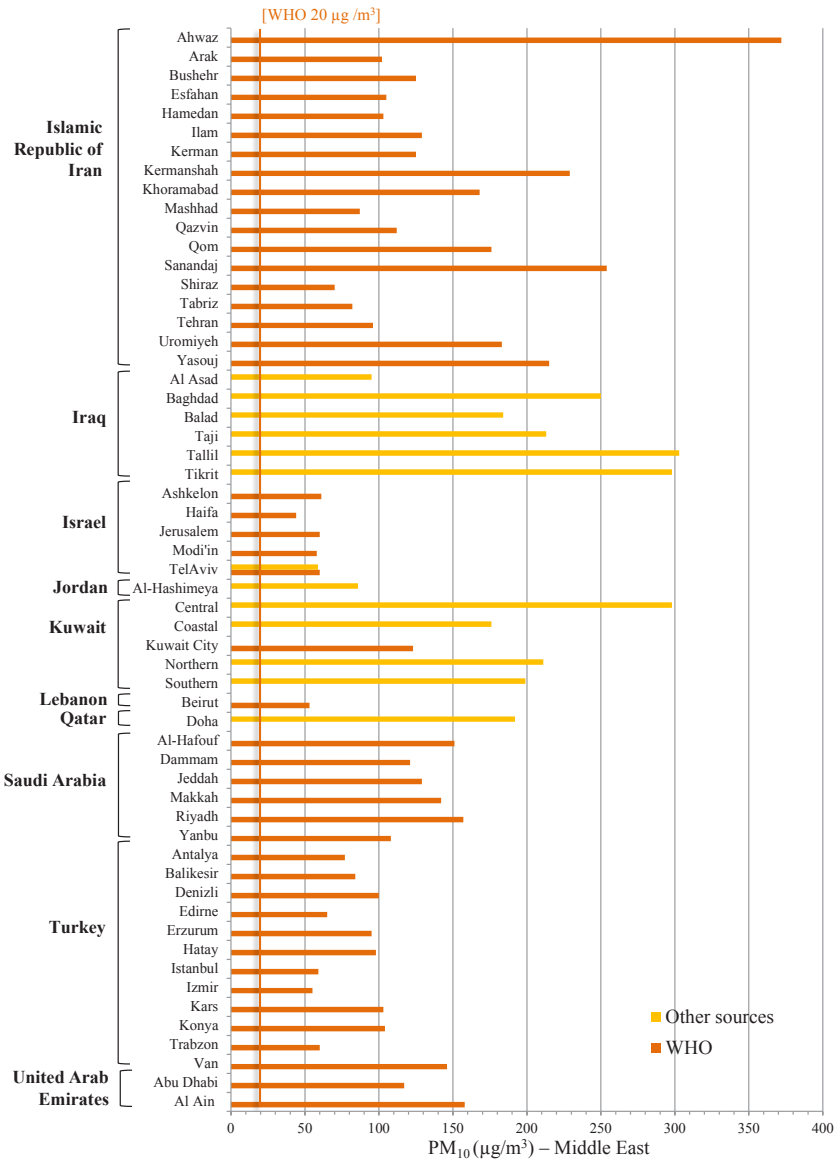
Fig. 1.39 $PM_{2.5}$ concentrations (μg/m³) in selected South America cities



$PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 μm.
Compiled by the Working Group with data from de Miranda et al. (2012), CETESB (2013), INEA (2009), WHO (2011), and Clean Air Institute (2012).

populations over long time periods with a focus on air pollution are rare; therefore, most studies require a retrospective exposure assessment approach. The ability to assign exposures retrospectively is often limited by the availability of historical exposure information or by the lack of residential histories. Several studies have evaluated the extent to which spatial patterns in measurements of NO_2 remain stable over time by repeating spatial measurement campaigns separated by periods of 7–18 years (Eeftens et al., 2011; Cesaroni et al., 2012; Gulliver et al., 2013; Wang et al., 2013). These studies suggest that although concentrations may change dramatically over time, the spatial patterns in concentrations remain quite similar. This suggests that studies of spatial contrasts in pollution based on information collected to represent one time period may be applied to other time periods using temporal trends, derived for example from a limited number of monitoring sites within the study area (Hystad et al., 2012). However, caution is needed in making extrapolations over longer periods of time, for more dynamic study areas, or for sites where major air pollution interventions took place.

Fig. 1.40 PM_{10} concentrations (µg/m³) in selected Middle East cities

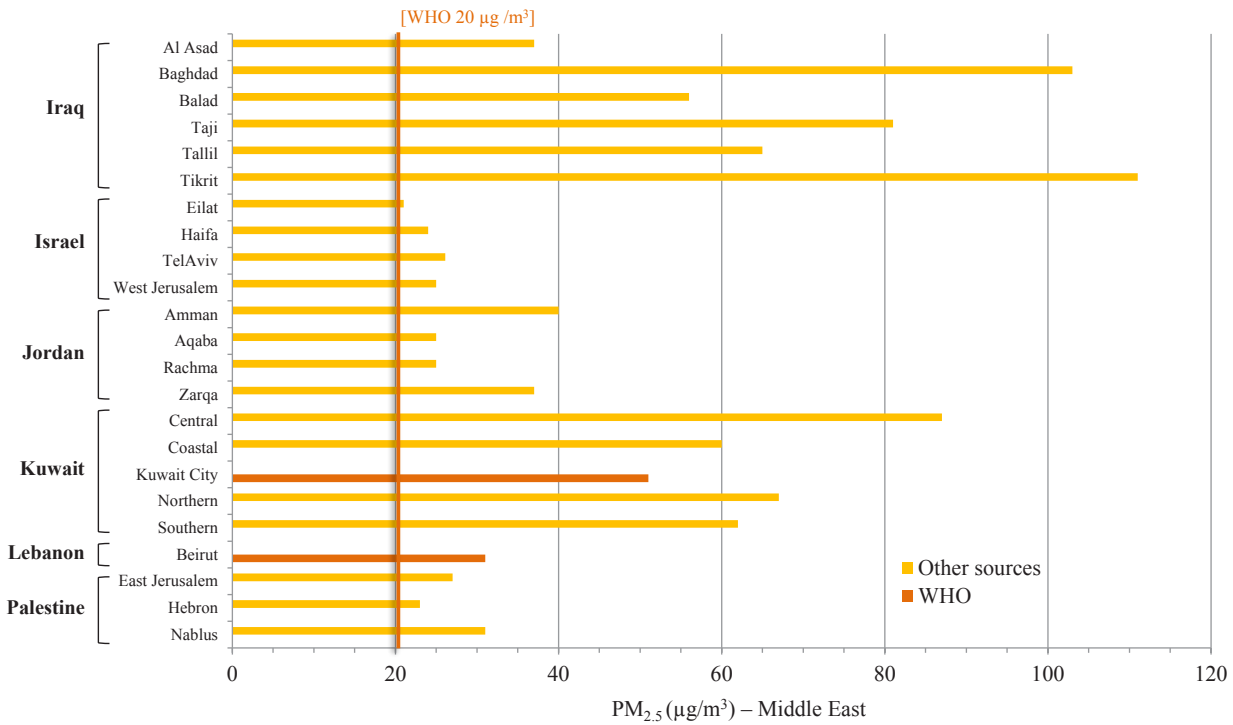


PM_{10}, particulate matter with particles of aerodynamic diameter < 10 µm.
Compiled by the Working Group with data from Vahlsing & Smith (2012), Khamdan et al. (2009), Naddafi et al. (2012), Brajer et al. (2012), WHO (2011), Mansourian et al. (2010), Engelbrecht et al. (2009), Agay-Shay et al. (2013), Israel Ministry of Environmental Protection (2010), Alnawaiseh et al. (2012), Saffarini & Odat (2008), Abu-Allaban et al. (2006), Al-Salem (2013), Alolayan et al. (2013), Saliba et al. (2010), Massoud et al. (2011), Qatar General Secretariat for Development Planning (2011), Al-Jeelani (2013), Rushdi et al. (2013), Khodeir et al. (2012), Munir et al. (2013), Meslmani (2004), Kara et al. (2013), Bayraktar et al. (2010), Kuzu et al. (2013), and Al Jallad et al. (2013).

(a) Outdoor air quality monitoring

The most traditional approach to estimate exposure is based on assignment of measured outdoor air pollutant concentrations to the study populations. Only rarely are these measurements specifically designed for the purposes of exposure assessment. One prominent exception is the Harvard Six Cities Study, in which air quality measurements in each study community were initiated at subject enrolment and continued in some form for much of the prospective follow-up

Fig. 1.41 $PM_{2.5}$ concentrations (μg/m³) in selected Middle East cities



$PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 μm.
Compiled by the Working Group with data from Khamdan et al. (2009), Brajer et al. (2012), Engelbrecht et al. (2009), von Schneidemesser et al. (2010), Sarnat et al. (2010), Agay-Shay et al. (2013), Alolayan et al. (2013), WHO (2011), Saliba et al. (2010), Massoud et al. (2011), Al-Jeelani (2013), Rushdi et al. (2013), Khodeir et al. (2012), Aburas et al. (2011), and Bayraktar et al. (2010).

period (Lepeule et al., 2012). In this case, the exposure assignment was based on a centrally located monitor in each community, and no adjustments were made for participants who changed addresses within each community as all subjects within a specific community were assigned the same exposure. A similar approach was applied in a Japanese cohort study where exposure was assigned based on address at study entry, and the analysis was restricted to those subjects who had resided in the study area for at least 10 years before enrolment and remained in the area during a 10-year follow-up period (Katanoda et al., 2011). In that study, the primary exposure metric of interest, $PM_{2.5}$, was estimated based on measured SPM levels using a subanalysis in which $PM_{2.5}$:SPM ratios were measured. Although this ratio was developed only for a specific time period and differed somewhat between study locations, a single ratio was applied to all areas. In the American Cancer Society's Cancer Prevention Study II (CPS-II) cohort (Turner et al., 2011), a single community-based monitor or the average of multiple monitors within each study community was used for exposure assignment. In that study, residential history was not considered because exposure assignment was based on the residential location at study entry. An identical method of assignment was used by Cao et al. (2011) in their assessment of air pollution and lung cancer in China. [Although these examples of exposure based on centrally located air quality

monitors do not include within-city variation in concentrations, this approach to estimating exposure may be valid if the within-city variability in concentrations is less than the between-city variability, as might be the case for $PM_{2.5}$ but is less likely to be so for NO_2. Where individual exposures are imputed from central monitors, there will be resulting measurement error, which will have an impact on the bias and variance of subsequent effect size estimates. The importance of these errors will be greater if the inter-monitor variance is small relative to total inter-individual variance.]

Other approaches using community-based air quality monitors allow some level of individual-level exposure assignment based on within-area variability in pollutant concentrations, by assigning exposures based on the nearest monitor to the residential address of each study participant (Heinrich et al., 2013) or using geostatistical averaging such as inverse-distance weighting of measurements from available monitors within a defined study area (Lipsett et al., 2011). [All of these approaches do provide highly accurate descriptions of temporal variation at fine resolution and allow assessment of exposures during specific time windows.]

(b) Proximity measures

Although the above-mentioned approaches provide quantitative information on exposures to specific pollutants, they are limited in their ability to evaluate impacts of specific sources and are limited to areas with available outdoor pollution monitoring. In particular, many studies exclude subjects who reside beyond a specific distance from an available air monitoring site. Furthermore, there is increasing interest in evaluating differences within populations that may reside in the same community. One of the simplest approaches to estimating individual exposures is to measure proximity to specific pollutant sources, such as major roads (Heinrich et al., 2013) or industrial point sources (López-Cima et al., 2011). These examples estimate exposure by the distance (which may be described by linear or nonlinear functions) between a subject and a source. Source intensity measures, such as traffic counts over time or within a defined area, have also been used (Beelen et al., 2008; Raaschou-Nielsen et al., 2011). If subject residential histories are available, then such proximity estimates can be limited to specific time periods of interest or weighted over the full period of follow-up. As described in Section 1.4.1a, deterministic concentrations gradients based on proximity to major roads and industrial sources have been used to estimate exposure to several carcinogenic air pollutants in outdoor air in Canada (CAREX Canada, 2013; Setton et al., 2013). For each of these compounds, maps of estimated outdoor annual average concentrations allow exposure assignment at the individual level.

[Although proximity measures are simple to implement, often reflect gradients in measured concentrations, and allow studies of within-area exposure variation related to specific sources or source sectors, the relationship between proximity and levels of pollution will differ between studies conducted in different locations or at different times. This limits comparability of studies and does not allow quantification of adverse impacts in relation to pollutant concentrations. Furthermore, while the proximity measure is assumed to be a surrogate of exposure to air pollution, it may also reflect variation in other exposures (e.g. noise, in the case of traffic proximity) and in other potential determinants of health (e.g. socioeconomic status). Finally, proximity estimates generally have an overly simplistic representation of the physical processes related to pollutant fate and transport.]

(c) Atmospheric transport models

Given the understanding of a relatively high degree of variability in exposure within urban areas, often associated with motor vehicle traffic, several epidemiological studies have used

dispersion models to estimate concentrations of specific air pollutants over space and time. In this approach, estimates of emissions and meteorological data are used (typically in a Gaussian dispersion model framework) to estimate the dispersion of pollutants within an airshed. Simple models do not consider any chemical transformation and are therefore most appropriate for non-reactive pollutants (e.g. CO); more sophisticated chemical transport models also incorporate a large number of chemical reactions and are designed to simulate atmospheric fate and transport, for example the production of secondary pollutants (Cesaroni et al., 2013). These models are designed for purposes other than health effects research, so their use in epidemiological studies has been opportunistic. In most cases, this approach has focused on estimating individual exposures to traffic-related pollutants within a single study area (Nyberg et al., 2000; Bellander et al., 2001; Gram et al., 2003; Nafstad et al., 2004; Naess et al., 2007; Raaschou-Nielsen et al., 2010, 2011), although there are examples of applications at the national level (Carey et al., 2013).

The Danish cohort studies (Raaschou-Nielsen et al., 2010, 2011) focus on traffic influences on NO_x and NO_2 combined with urban and regional background concentrations and have the notable advantages of both individual estimates of exposure and detailed residential histories, so that exposure estimates are a time-weighted average of outdoor concentrations at all addresses for each participant during the 34-year study period. The models include time-varying inputs on traffic levels and emissions and adjustments for street-canyon effects with time-varying information on building geometry. This approach also allows the estimation of exposure for different time windows, although estimates for the time of enrolment were strongly correlated ($r = 0.86$) with estimated exposures over the full period of follow-up (Raaschou-Nielsen et al., 2011).

The studies conducted in Oslo, Norway (Gram et al., 2003; Nafstad et al., 2003) incorporate emissions information for both traffic and point sources (industrial and space heating) to estimate individual-level exposures to SO_2 and NO_x for each year over a 25-year period. Deterministic gradients were used for subjects living in proximity to specific streets with the highest levels of traffic, and persons who moved to outside of Oslo were assigned a regional value for each year. Subjects moving from outside of Oslo were also assigned regional exposure values based on available outdoor monitoring network data. Subsequent analyses in Oslo have included estimates for $PM_{2.5}$ and PM_{10} (Naess et al., 2007) and incorporated emissions information from a larger set of source categories (traffic, road dust, wood burning) but were restricted to more recent and shorter time periods.

A very similar approach was used in a case–control analysis of lung cancer in Stockholm County, Sweden, in which individual exposures to SO_2, NO_2, and NO_x were estimated for each year over a 40-year period (Nyberg et al., 2000; Bellander et al., 2001). As in the Danish studies, the approaches applied in Oslo and Stockholm County allow individual exposure estimates covering different time windows.

The detailed data needed for dispersion modelling are seldom available at the national level. However, in a study in the United Kingdom, Carey et al. (2013) used emissions-based dispersion models to assign annual average concentrations of PM_{10}, $PM_{2.5}$, SO_2, NO_2, and ozone for 1-km grid squares to the nearest postal code at the time of death. The model included emissions by source sector (e.g. power generation, domestic combustion, and road traffic), with pollutant concentrations estimated by summing pollutant-specific components, such as point and local area sources.

[Although dispersion models have a strong physical basis, even they are typically simplified representations of atmospheric transport that do

not incorporate the complex physical and chemical transformations that occur after emission. Given their reliance on emissions, such models also are limited by the quality of emissions data as well as the lack of microscale meteorological measurements. Furthermore, dispersion models require specialized expertise to run, and there has been relatively little evaluation of dispersion models with measurements or integration of available measurements into the modelling effort. All of the above-mentioned examples are also limited to individual urban areas, given the data requirements of dispersion models, and therefore this approach is typically only applied to studies of within-city variation, which are usually focused on a single source sector, such as traffic. Although Carey et al. (2013) applied dispersion modelling at a national scale, their approach did not account for residential history or temporal changes in exposure and has a larger spatial resolution (1 km) than those of the Danish and Oslo models (~5 m).]

Although it has not been applied to epidemiological studies and is used as a screening-level assessment approach, the NATA (described in Section 1.4.1a) provides concentration estimates for several HAPs throughout the USA using a combination of dispersion, chemical transport, and exposure models (EPA, 2011b).

(d) Geospatial/land-use regression models

Land-use regression models or other geospatial statistical models have increasingly been used to assess chronic exposures to air pollution. In a simple form, estimates of source density and proximity can be used to estimate source-specific exposures. For example, Raaschou-Nielsen *et al.* used as supplementary exposure measures the presence of a street with a traffic density of more than 10 000 vehicles per day within 50 m of a residence and the total number of kilometres driven by vehicles within 200 m of the residence each day in a cohort analysis of cancer incidence for residents of two cities in Denmark (Raaschou-Nielsen et al., 2011). Chang *et al.* used the density of petrol stations as an indicator of a subject's potential exposure to benzene and other pollutants associated with evaporative losses of petrol or to air emissions from motor vehicles in a study of lung cancer in Taiwan, China (Chang et al., 2009). Although no evaluation of the exposure metric was conducted in this study, inverse distance to the nearest petrol station was associated with outdoor concentrations of benzene and xylene compounds in the RIOPA study in the USA (Kwon et al., 2006).

Land-use regression models are more sophisticated geospatial models in which pollutant measurements are combined with geographical predictors in a spatial regression model (Hoek et al., 2008a). This model is then used to predict concentrations of the air pollutant at unmeasured locations. These models have been especially useful in the assessment of exposure to variability in traffic-related air pollutant concentrations within urban areas. Note that the measurements used to develop models may be limited to available measurements from outdoor monitoring networks (Yorifuji et al., 2010, 2013), which are unlikely to fully capture the variability in outdoor concentrations or predictor variables, or from measurement campaigns of shorter duration (Cesaroni et al., 2013). Although land-use regression models often explain a high proportion (60–80%) of the variability in spatial measurements of air pollutant concentrations in a study area, if spatial correlation in model residuals exists, universal kriging may also be used for estimating exposures (Mercer et al., 2011). Universal kriging is a more generalized form of spatial modelling in which information from nearby (spatially correlated) measurements influences predictions through an estimated correlation structure.

In some cases these models may also incorporate temporal variation derived from outdoor monitoring network data, but most typically they provide estimates of spatial variability only,

and it is assumed that this variability is stable over time – an assumption that has generally been supported by several measurement studies for periods of up to 18 years (Eeftens et al., 2011; Cesaroni et al., 2012; Gulliver et al., 2013; Wang et al., 2013). Models that do not rely on targeted measurement campaigns may also allow annual estimates to be made (Yorifuji et al., 2010, 2013).

Land-use regression estimates have also been combined with external monitoring data and proximity estimates in hybrid models. For example, Beelen et al. (2008) estimated exposure to outdoor air pollution at the home address at study entry as a function of regional, urban, and local components. The regional background concentrations were estimated using inverse-distance-weighted interpolation of measured concentrations at regional background outdoor monitoring sites. The urban component was estimated using land-use regression models developed using only regional and urban background monitoring site data, and the sum of the regional and urban contributions was defined as the background concentration. Background concentrations were estimated for NO_2, black smoke, and SO_2. Estimates were made for 5-year intervals during a 20-year study period. The local traffic contribution was based on several measures of traffic intensity and proximity. In addition, quantitative estimates for the local component were estimated with regression models incorporating field monitoring measurements and traffic variables. The local component was added to background concentrations for an overall exposure estimate for each pollutant. [Land-use regression models are relatively easy to implement and, given their use of pollutant measurements, are capable of providing reliable estimates of exposure to a large number of specific pollutants as well as source indicators (Jerrett et al., 2005). Confidence in model use depends on adequate geographical and pollutant monitoring data, especially the inclusion of targeted monitoring that characterizes variability both in air pollutant concentrations and in geographical predictors within the study area. Reliability can be quite high, especially with increasing numbers of observation locations.]

(e) Remote sensing

A more recent development for application to epidemiological studies has been the use of remote-sensing-based estimates of air pollution. For example, van Donkelaar et al. (2010) developed a global model of long-term average $PM_{2.5}$ concentration at a spatial resolution of about 10 × 10 km. This approach combines aerosol optical depth (AOD) (a measure of the scattered light from all aerosol within the total column between the Earth's surface and the satellite) with information from a chemical transport model on the vertical stratification of aerosol as well as its composition to estimate time- and location-specific factors to relate AOD to surface $PM_{2.5}$. Estimates derived from this approach were combined with surface monitoring data and estimates from a different chemical transport model to estimate exposures for the Global Burden of Disease Study 2010 (Brauer et al., 2012; Lim et al., 2012). Useful satellite retrievals have been available since about 2000 and have been combined with available surface monitoring data to provide backcasted spatially resolved estimates for earlier periods (Crouse et al., 2012; Hystad et al., 2013), as described in more detail below. Satellite-based estimates are available globally for a small group of pollutants, including $PM_{2.5}$, NO_2, ozone, and formaldehyde (Brauer et al., 2012; De Smedt et al., 2012; Lamsal et al., 2013).

[Remote-sensing-based estimates have the advantage of providing estimates of concentrations essentially anywhere in the world by a consistent approach, although they are best suited to between-location contrasts, given the currently available resolution on the order of 10 × 10 km.]

(f) Remote sensing and land-use regression hybrid models

Remote-sensing-based estimates have also been combined with land use and other geographical predictors in hybrid land-use regression-type models. Canadian researchers developed national estimates of long-term average concentrations of $PM_{2.5}$ and NO_2 in which satellite-based estimates were combined with deterministic gradients related to traffic and industrial point sources (Hystad et al., 2011). Although these models were only spatial and did not include a temporal component, in a subsequent effort (Hystad et al., 2012), which was applied to a cohort analysis of lung cancer with detailed residential histories (Hystad et al., 2013), spatial satellite-based estimates for $PM_{2.5}$ and NO_2 and chemical transport model estimates for ozone were adjusted retrospectively with annual air pollution monitoring data, using either spatiotemporal interpolation or linear regression to produce annual estimates for a 21-year period. In addition, proximity to major roads, incorporating a temporal weighting factor based on mobile-source emission trends, was used to estimate exposure to vehicle emissions, and industrial point source location proximity was used to estimate exposures to industrial emissions. In the USA, Novotny et al. (2011) developed a national spatiotemporal land-use regression model with 30 m spatial resolution and 1 hour temporal resolution based on a single year of available regulatory monitoring network data, satellite-based estimates, and geographical predictors (population density, land use based on satellite data, and distance to major and minor roads). To date, this model has not been applied in epidemiological analyses.

More recently, a novel spatiotemporal approach combining AOD and daily calibration to available monitoring network measurements with land-use data (Kloog et al., 2011) was applied to investigate the effect of long-term exposures to $PM_{2.5}$ on population mortality (Kloog et al., 2013).

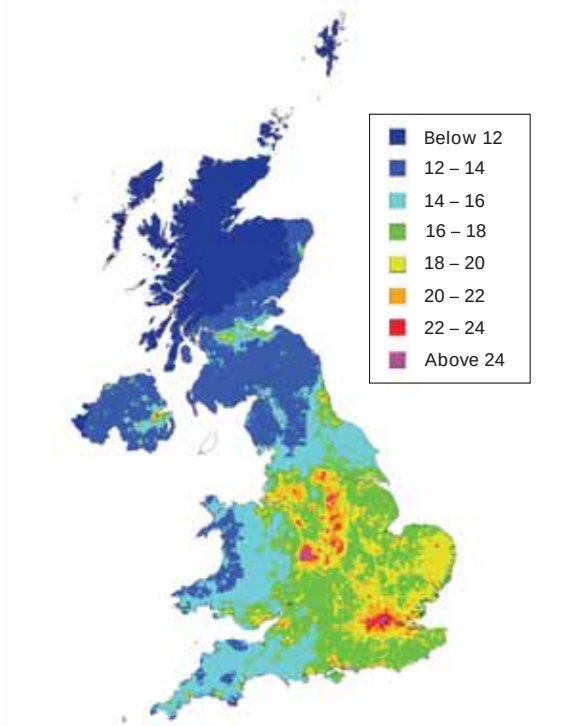
(g) Bioindicators (lichens/pine needles)

Although there are only limited examples of applications to epidemiological analyses, several approaches using environmental biomonitors such as lichens and pine needles (Augusto et al., 2010) as indicators of air pollution levels have been developed. For example, lichen biodiversity in north-eastern Italy was geographically correlated with both measurements of SO_2 and NO_3 and male lung cancer mortality, after correcting for spatial autocorrelation (Cislaghi & Nimis, 1997). In risk assessment, measures of PAHs and heavy metals in lichens have been used to estimate exposures (Augusto et al., 2012; Käffer et al., 2012) and cancer risk. Augusto *et al*. used measurements of multiple PAH species in lichens to develop a spatial model related to industrial point-source emissions of PAHs (Augusto et al., 2009). These approaches may prove to be useful in estimating historical exposures as the biomonitors can integrate deposited pollutant species over relatively long time periods.

1.4.3 Personal exposure and biomarkers

In recent decades a large number of studies have been published on personal exposure to major air pollutants (Wallace, 2000; Monn, 2001). Research conducted since the early 1980s has indicated that personal exposure may deviate significantly from concentrations measured at fixed sites in the outdoor environment. Subsequent research has identified factors that are responsible for differences between outdoor and personal exposure. In this section, the factors affecting personal exposure are summarized, followed by a discussion of validity studies in which indicators of exposure have been compared with actual measurements of personal exposure. There is also a brief discussion of the distinction between pollutants of outdoor origin and pollutants from indoor sources (Wilson et al., 2000; Ebelt et al., 2005; Wilson & Brauer, 2006).

Fig. 1.42 Estimated United Kingdom annual average background PM_{10} concentrations (µg/m³) during 2002



PM_{10}, particulate matter with particles of aerodynamic diameter < 10 µm.
Reprinted from Air Quality Expert Group (2005). © Crown copyright 2005.

Personal monitoring studies have been conducted for most of the major air pollutants, including PM, NO_2, VOCs, and ozone (Monn, 2001). Studies measuring PM have often used integrated samplers sampling $PM_{2.5}$ or PM_{10}, but real-time instruments based on light scattering have been used as well. Recently, studies have also measured personal exposure to ultrafine particles (Wallace & Ott, 2011; Buonanno et al., 2014), focusing especially on commuters' exposures (Knibbs et al., 2011). Fewer studies have measured particle composition. Components that have been measured include EC or proxies of EC, aerosol acidity, PAHs, and elemental composition.

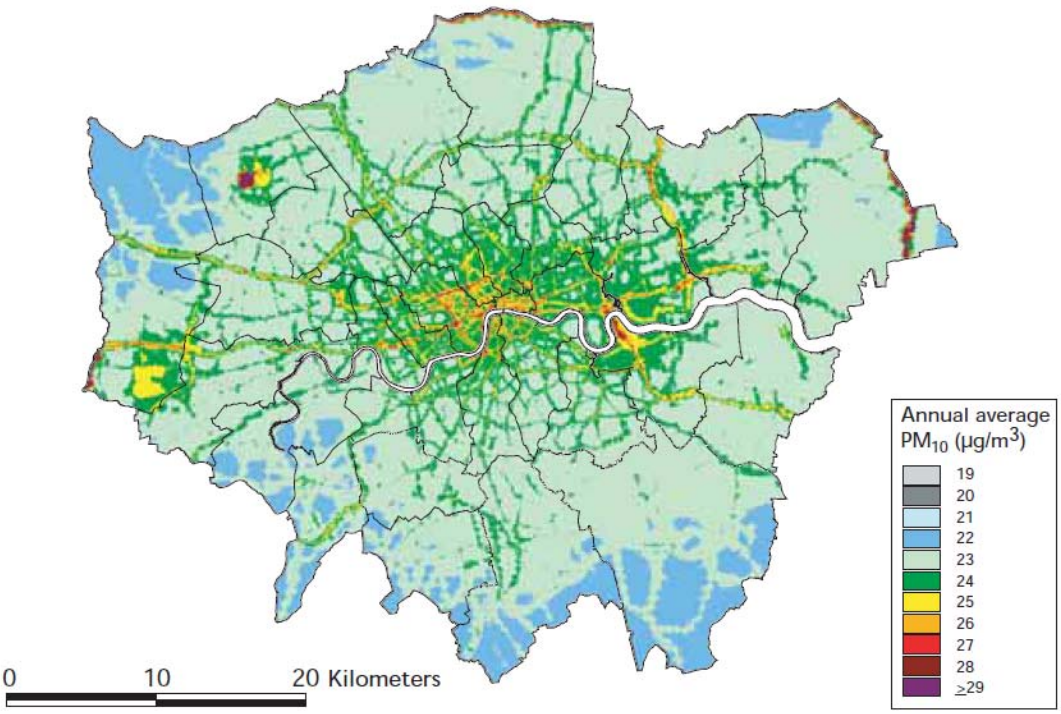
(a) Factors affecting personal exposure

For cancer, long-term average personal exposure is the biologically relevant exposure. Therefore, it is important to assess both the intensity of exposure and the duration. Exposure assessment in epidemiological studies of cancer and air pollution is often based on the residential address. Hence, residential history should be considered. A large number of studies have identified factors that affect the intensity of personal exposure to major air pollutants. These factors can be grouped into four broad groups: (i) concentration in outdoor air, at the residence and in the community; (ii) time–activity patterns, including residential history; (iii) infiltration of pollutants indoors; and (iv) indoor sources of pollutants. These factors are discussed further in the sections below, with a focus on air pollution including particles of outdoor origin.

(i) Concentration in outdoor air

People may be exposed to outdoor air pollutants directly while spending time outdoors. However, a significant fraction of the exposure to outdoor air pollutants occurs while spending time indoors, as people generally spend a large fraction of their time indoors and pollutants penetrate into the indoor environment. Because people spend a significant fraction of their time in or near their own home, exposure in epidemiological studies is often characterized based on the residential address. Residential address information is generally available from ongoing epidemiological studies designed for purposes other than studying air pollution effects. Most often the outdoor concentration at the address is characterized. A large number of studies have evaluated spatial variation of outdoor air pollution (Monn, 2001; HEI, 2010b). Spatial variation can be present at various scales, ranging from global to local (HEI, 2010b). Examples of the various scales of variation are illustrated in Fig. 1.42 and Fig. 1.43, and in Fig. 1.3 in Section 1.4.1a.

Fig. 1.43 Annual average PM_{10} concentrations (µg/m³) in London calculated for 2004



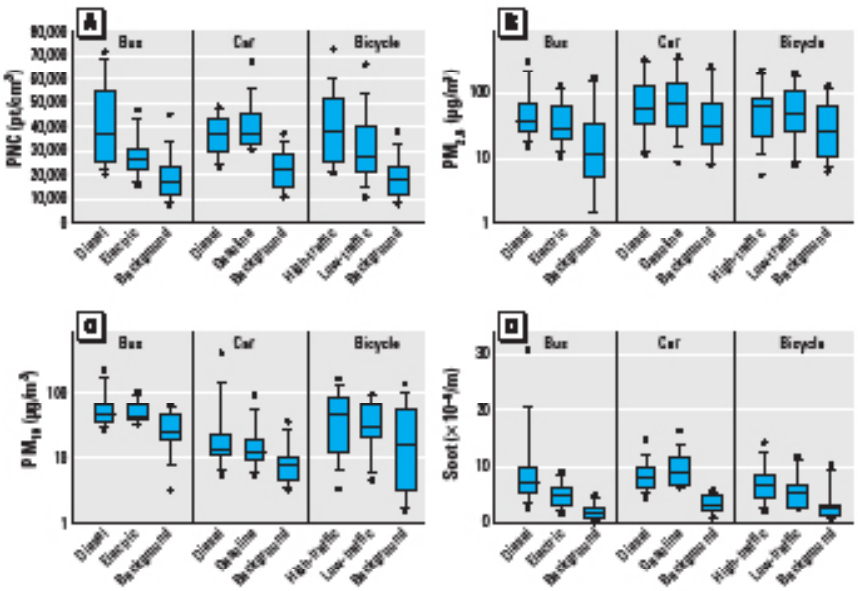
PM_{10}, particulate matter with particles of aerodynamic diameter < 10 µm.
Reprinted from Air Quality Expert Group (2005). © Crown copyright 2005.

Contrasts across countries within a continent are discussed further in Section 1.4.1.

As Fig. 1.43 illustrates, within urban areas, significant spatial variation is present related to proximity to major roads. Large gradients with distance to major roads have been identified for traffic-related pollutants, including NO_2, CO, benzene and other VOCs, EC, and ultrafine particles (HEI, 2010b). Gradients are relatively small for $PM_{2.5}$ and PM_{10} compared with, for example, EC (HEI, 2010b; Janssen et al., 2011). A summary of studies measuring both $PM_{2.5}$ or PM_{10} and BC reported an average ratio of 2 for BC and 1.2 for PM concentrations at street sites compared with urban background levels (Janssen et al., 2011). Spatial gradients vary significantly by pollutant and are nonlinear near major roads, with steep decreases in the first 50–100 m and smaller decreases up to about 300–500 m (HEI, 2010b). In compact urban areas, gradients from major roads are much smaller.

A growing number of studies have documented significant exposures to a range of traffic-related air pollutants, including fine and ultrafine particles, EC, and VOCs, while in transit, including walking, cycling, car and

Fig. 1.44 Concentrations in modes of transportation and at the urban background location on corresponding sampling days



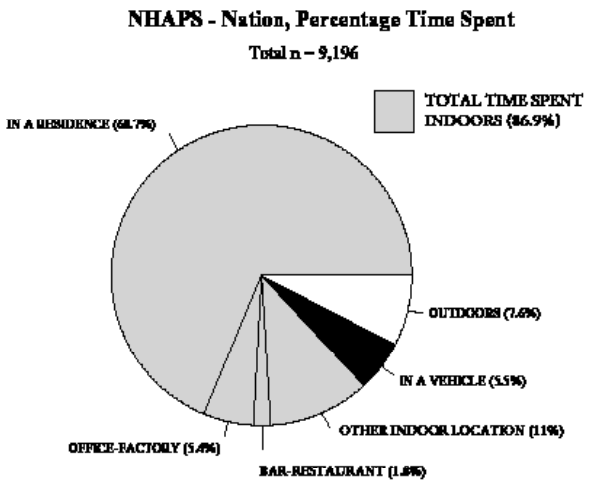
PM_{10}, particulate matter with particles of aerodynamic diameter < 10 µm; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 µm; PNC, particle number concentration.
Reproduced from *Environmental Health Perspectives* (Zuurbier et al., 2010).

bus driving, and underground (Fig. 1.44; Kaur et al., 2007; de Hartog et al., 2010; Zuurbier et al., 2010; de Nazelle et al., 2011). Commuters' exposures further differ significantly with route, and despite the relatively short time typically spent in traffic, significant contributions to average personal exposure may occur (Marshall et al., 2006; Kaur et al., 2007; Van Roosbroeck et al., 2008; de Nazelle et al., 2013; Dons et al., 2012, 2013). Van Roosbroeck et al. (2008) found that time spent in traffic was a significant predictor of 48-hour personal exposure to soot and $PM_{2.5}$ in elderly adults in the Netherlands. A study in 62 volunteers in Belgium reported that 6% of time was spent in traffic, but the contribution to the measured 24-hour average personal exposure to BC was 21%, and to calculated inhaled doses was 30% (Dons et al., 2012). Home-based activities, including sleep, accounted for 65% of time, 52% of exposure, and 36% of inhaled dose (Dons et al., 2012). For volunteers in Barcelona, Spain, in-transit exposures accounted for 6% of time, 11% of NO_2 exposure, and 24% of inhaled dose (de Nazelle et al., 2013). Setton and co-workers documented that ignoring residential mobility in epidemiological studies using individual-level air pollution may (modestly) bias exposure response functions towards the null (Setton et al., 2011).

(ii) Time–activity patterns

A range of surveys in developed countries have shown that most people spend a large fraction of their time indoors. An example is shown from the large National Human Activity Pattern Survey (NHAPS) in the USA (Fig. 1.45; Klepeis et al., 2001). On average, subjects spent 87% of their time indoors, of which a large fraction was spent in their own residence. Time spent outdoors accounted for about 2 hours of the day. These broad patterns have been found in other surveys as well (Jenkins et al., 1992; Leech et al., 2002).

Fig. 1.45 Time spent in various microenvironments by subjects in the USA



Reprinted from Klepeis et al. (2001) by permission from Macmillan Publishers Ltd: *Journal of Exposure Science and Environmental Epidemiology*, Klepeis NE, Nelson WC, Ott WR, Robinson JP, Tsang AM, Switzer P et al. The National Human Activity Pattern Survey (NHAPS): a resource for assessing exposure to environmental pollutants, Volume 11, Issue 3, pages 231–252, copyright (2001).

However, individual time–activity patterns differ substantially, related to factors such as age, employment, and socioeconomic status. A recent survey showed that German children spent on average 15.5 hours per day in their own home (65% of time), 4.75 hours in other indoor locations (for a total of 84% of time spent indoors), and 3.75 hours outdoors (16% of time) (Conrad et al., 2013). The German survey did not distinguish between "outdoors" and "in traffic," which may be partly responsible for the share of time spent outdoors.

Time–activity patterns vary significantly over the day, as does the air pollution concentration, supporting the use of more dynamic exposure estimates (Beckx et al., 2009). Time–activity patterns may thus differ across population groups (related to age, sex, employment status, socioeconomic position, and other factors), contributing to contrasts in exposure between population groups beyond contrasts in outdoor concentrations. A study in Delhi, India, showed a high proportion of time spent indoors, with significant variability across population groups (Saksena et al., 2007).

The contribution to time-weighted average exposure is a function of the time spent in a microenvironment and the concentration in that microenvironment. Thus, for pollutants that infiltrate poorly indoors, the relatively short time spent outdoors, including in transit, may nevertheless amount to a significant fraction of total exposure.

Because of the large fraction of time spent in the home, residential history is an important determinant of long-term average exposure to air pollution. In epidemiological studies, air pollution exposure is often assigned based on the most recent address or the address at recruitment into the (cohort) study. Because a significant number of subjects may change address before inclusion in the study or during follow-up, misclassification of exposure may occur. This is particularly problematic because limited information is available about the critical window of exposure. In a study in California of children with leukaemia, residential mobility differed with age and socioeconomic status, and accounting for residential mobility significantly affected the assigned neighbourhood socioeconomic status and urban/rural status (Urayama et al., 2009). A case–control study in Canada reported that in the 20-year exposure period, 40% of the population lived at the same address (Hystad et al., 2012). The correlation between air pollution exposure estimates with and without residential history was 0.70, 0.76, and 0.72 for $PM_{2.5}$, NO_2, and ozone, respectively. About 50% of individuals were classified into a different $PM_{2.5}$, NO_2, and ozone exposure quintile when using study-entry postal codes and spatial pollution surfaces, compared with exposures derived from residential histories and spatiotemporal air pollution models (Hystad et al., 2012). Recall bias was reported for self-reported residential history, with lung cancer cases reporting more residential addresses than

controls (Hystad et al., 2012). In a Danish cohort study, exposure was characterized as the average concentration of all addresses 20–25 years before enrolment and during follow-up weighted with the time lived at an address (Raaschou-Nielsen et al., 2011). People moved on average 2.4 times before enrolment and 0.3 times during follow-up. Exposure estimates from different periods were highly correlated (Section 1.4.2).

(iii) Infiltration of pollutants indoors

Because people generally spend a large fraction of their time indoors and outdoor air pollution infiltrates indoors, this section examines relationships between outdoor and indoor pollutant levels.

Mass-balance models have been used extensively to describe the concentration in indoor air as a function of outdoor air and indoor sources. The indoor concentration of an air pollutant can be expressed simply as $C_{ai} = F_{inf} C_a$, where C_{ai} = is the indoor pollutant concentration originating from outdoors, F_{inf} is defined as the infiltration factor, and C_a is the ambient (outdoor) concentration. The infiltration factor describes the fraction of outdoor pollution that penetrates indoors and remains suspended. Penetration efficiency depends on several factors, including the air velocity, the dimensions of the opening, and the particle size, with ultrafine and especially coarse particles penetrating less efficiently (Liu & Nazaroff, 2001).

Hänninen et al. (2011) evaluated the original data of European studies of indoor–outdoor relationships for $PM_{2.5}$. The overall average infiltration factor was 0.55, illustrating significant infiltration of outdoor fine particles. A review including European and North American studies reported infiltration factors of 0.3–0.82 for $PM_{2.5}$ (Chen & Zhao, 2011). Since people in Europe and North America spend a large fraction of their time indoors, human exposure to fine particles of outdoor origin occurs mostly indoors. Infiltration factors were consistently higher in the summer than in the winter (Hänninen et al., 2011). A study in seven cities in the USA included in the MESA Air study also reported high infiltration factors in the warm season (Allen et al., 2012). The implication is that for the same outdoor concentration, the actual human exposure is higher in the summer than in the winter. Higher infiltration factors in the summer are explained by higher air exchange rates in the summer than in the winter.

In the four European cities included in the RUPIOH study, infiltration factors for ultrafine particles assessed by total particle number counts were somewhat lower than those for $PM_{2.5}$ (Table 1.13; Hoek et al., 2008b) but higher than those for coarse particles. A large study in Windsor, Ontario, Canada, that measured total particle number counts reported infiltration factors of 0.16–0.26, with a large variability for individual homes (Kearney et al., 2011). The lower infiltration of ultrafine particles is consistent with lower penetration and higher decay rates due to diffusion losses compared with accumulation mode particles. Studies in the USA that measured particle size distributions have also found lower infiltration factors, on the order of 0.5 for particles in the ultrafine range and up to 0.7 for $PM_{2.5}$ (Abt et al., 2000; Long et al., 2001; Sarnat et al., 2006). A study conducted in a Helsinki, Finland, office found that indoor particle number concentrations tracked outdoor concentrations well but were only 10% of the outdoor concentrations (Koponen et al., 2001). A study in two empty hospital rooms in Erfurt, Germany, reported a high correlation between indoor and outdoor concentrations of $PM_{2.5}$, black smoke, and particle number concentration and an indoor–outdoor ratio of 0.42 for total number concentration, compared with 0.79 for $PM_{2.5}$ (Cyrys et al., 2004). There is thus a large range in reported infiltration factors, related to differences in air exchange rates and building characteristics, and likely also to differences in measurement methods across studies.

Table 1.13 Infiltration factors estimated as regression slope for the relationships between indoor and outdoor 24-hour average concentrations of different particle metrics from the RUPIOH study

Pollutant	Helsinki, Finland	Athens, Greece	Amsterdam, Netherlands	Birmingham, United Kingdom
$PM_{2.5}$	0.48	0.42	0.39	0.34
$PM_{10} - PM_{2.5}$	0.14	0.16	0.11	0.13
PNC	0.42	0.42	0.19	0.22
Soot	0.63	0.84	0.78	0.71
Sulfate	0.59	0.61	0.78	0.61

PM_{10}, particulate matter with particles of aerodynamic diameter < 10 μm; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 μm; PNC, particle number concentration.
Data from Hoek et al. (2008b).

The composition of particles infiltrated indoors also differs from the outdoor composition. Infiltration factors for EC exceeded those for $PM_{2.5}$ significantly (Fig. 1.46). EC is concentrated in submicrometre particles, is non-volatile, and has few indoor sources (Noullett et al., 2010). Although smoking affects EC levels, the impact is less than on $PM_{2.5}$ concentrations (Götschi et al., 2002). A detailed analysis of the RIOPA study showed that 92% of the indoor EC concentration was due to outdoor EC, whereas the corresponding contribution for $PM_{2.5}$ was 53% (Meng et al., 2009).

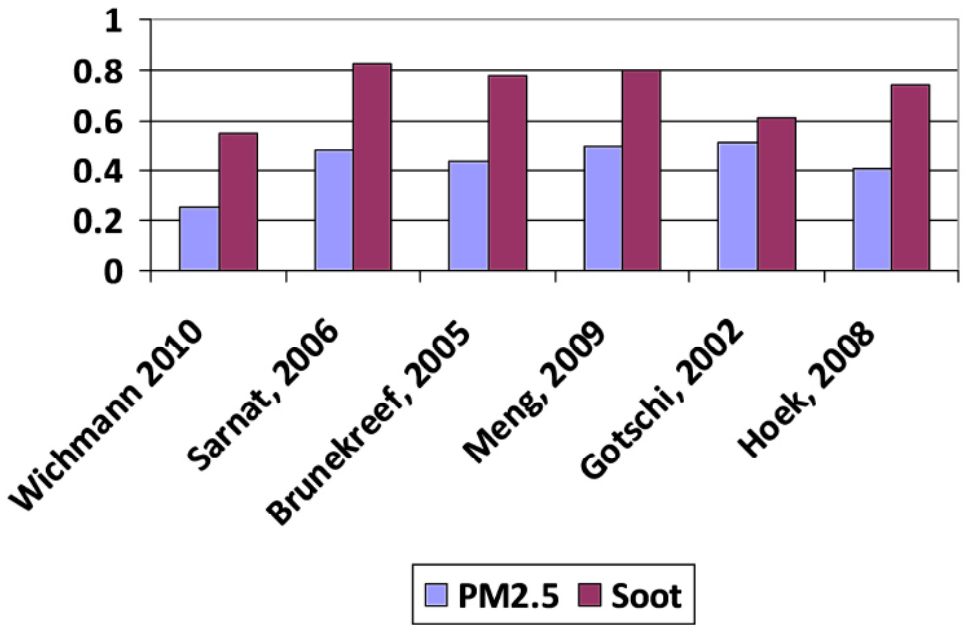
Sulfates have few indoor sources and high infiltration factors (Noullett et al., 2010). Indoor concentrations of SO_2 in the absence of indoor sources (e.g. unvented kerosene heaters) are typically low, related to large losses to indoor surfaces (Koutrakis et al., 2005).

Nitrates typically show low infiltration factors, ranging from 0.05 to 0.2 in studies in Europe and the USA (Sarnat et al., 2006; Hoek et al., 2008b). Indoor concentrations of NO_2 in the absence of indoor sources (e.g. gas cooking, unvented heaters) are substantially lower than outdoor concentrations (Monn, 2001). In a recent review of studies of personal and outdoor NO_2 exposure, the overall average personal–outdoor regression slope was between 0.14 and 0.40, depending on the study type (Meng et al., 2012a). A study in Spain reported indoor–outdoor slopes of 0.20 and 0.45 for two cities, after adjusting for the large influence of gas cookers and gas heaters (Valero et al., 2009). Personal exposure may be affected by more factors, but studies have shown that the indoor concentration is the dominant factor, with large heterogeneity observed between studies (Monn, 2001; Meng et al., 2012a).

Indoor ozone concentrations are typically low because ozone is a highly reactive component with a high decay rate and no indoor sources in residences (Monn, 2001). Indoor–outdoor ratios of between 0.2 and 0.8 were reported in previous studies, depending on air exchange rates (Monn, 2001). A recent analysis of the DEARS study in Detroit, USA, reported a personal–outdoor regression slope of 0.03 in summer and 0.002 in winter (Meng et al., 2012b), even lower than that for NO_2 and much lower than that for $PM_{2.5}$.

In large-scale epidemiological studies, indoor measurements of infiltration factors are not feasible. Hystad and co-workers developed a model for $PM_{2.5}$ infiltration based on measurements in 84 North American homes and publicly available predictor variables, including meteorology and housing stock characteristics (Hystad et al., 2009). A model including season, temperature, low building value, and heating with forced air predicted 54% of the variability in measured infiltration factors (Hystad et al., 2009). Low building value increased infiltration factors, increasing exposure contrasts across different

Fig. 1.46 Infiltration factors for $PM_{2.5}$ and soot (EC, BC) measured in the same study



BC, black carbon; EC, elemental carbon; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 μm.
Compiled by the Working Group with data from Wichmann et al. (2010), Sarnat et al. (2006), Brunekreef et al. (2005), Meng et al. (2009), Götschi et al. (2002), and Hoek et al. (2008b).

socioeconomic groups. Other modelling studies in North America reported similar results, with a substantial fraction of the variability of infiltration factors explained by factors including window opening, air exchange rate, and presence or use of central air conditioning and forced air heating, with indications that predictors differ by season (Clark et al., 2010; Allen et al., 2012).

(iv) Indoor sources of pollutants

Numerous indoor sources, including tobacco smoking, cooking, heating, appliances, consumer products, building construction, and activities such as vacuum cleaning, have been identified to affect indoor concentrations and personal exposure for a wide range of air pollutants (Weschler, 2009).

Indoor sources affect different pollutants to a different degree. As noted above, sulfate and EC are affected more by outdoor air pollution than by indoor sources. Sulfate has therefore been used to evaluate the personal or indoor exposure to particles of outdoor origin (Sarnat et al., 2002).

(b) Pollutants from both indoor and outdoor sources

Several authors have stressed the importance of distinguishing between personal exposure from all sources and exposure indoors to pollutants from indoor and outdoor sources (Wilson et al., 2000; Ebelt et al., 2005; Wilson & Brauer, 2006). The discussion was initiated in the framework of temporal studies of $PM_{2.5}$ showing often modest correlations between total personal $PM_{2.5}$ and outdoor $PM_{2.5}$ concentrations. Scientific reasons to separate the two sources include that particle composition differs significantly depending on the source and that different particle composition might influence health effects. Furthermore, if the interest is in evaluating the health effects of outdoor pollution, then exposure to the same pollutant from indoor sources should be treated

as a potential confounder. The implication is that to assess agreement between often used exposure metrics and personal exposure, personal exposure to pollutants of outdoor origin should be evaluated. It may also be important to distinguish pollution exposures originating from outdoor versus indoor sources for policy purposes.

(c) Validation studies

In this context, validation studies are studies that compare exposure metrics used in epidemiological studies (e.g. modelled outdoor concentration) with personal exposure monitoring, which is usually considered as a more valid method of individual exposure assessment. A critical issue is that the correct comparison must be made between exposure metrics and personal exposure, depending on the epidemiological study design and the health outcome of interest. For time-series studies of acute events, the interest is in the longitudinal (within-subject) variation in exposure levels, whereas for cohort studies assessing long-term exposures, the interest is in the between-subject variation of long-term averages.

Very few studies have assessed the validity of long-term outdoor exposure estimates as used in epidemiological studies for estimating long-term average personal exposure, in contrast to the large literature on the temporal correlation of outdoor and personal exposure over shorter time intervals (Avery et al., 2010). It is challenging to collect sufficient personal exposure data to represent a long-term average exposure in a large group of subjects. Consequently, most of the personal monitoring studies discussed previously rely on a single or a few 24-hour measurements. First, studies evaluating fine-spatial-scale outdoor exposure metrics are discussed. Next, studies assessing differences in personal exposure between cities are discussed.

A study in Amsterdam reported significantly higher outdoor concentrations of $PM_{2.5}$, soot, PAHs, and benzene measured near high-traffic homes compared with low-traffic homes (Fischer et al., 2000). These contrasts were also found for indoor concentrations; for example, for soot, concentration ratios of 1.8 for high- versus low-traffic homes were found for both indoor and outdoor measurements (Fischer et al., 2000). Another study in Amsterdam reported ratios of soot concentrations for high- versus low-traffic homes of 1.19 to 1.26 for 24-hour measurements indoors and of 1.29 for personal exposure (Wichmann et al., 2005). A study in Utrecht comparing air pollution exposures of elderly adults living near major roads versus minor roads found larger differences for soot than for $PM_{2.5}$ and NO_2 using both personal and environmental measurements (Van Roosbroeck et al., 2008).

A study among volunteers in Helsinki, Barcelona, and Utrecht found a significant correlation between long-term average residential outdoor soot concentrations estimated by city-specific land-use regression models and measured average personal exposure (Montagne et al., 2013). Within the individual cities, no consistent association was found between land-use regression-modelled NO_2 and $PM_{2.5}$ concentrations and personal exposures, but modelled and measured exposures to all pollutants were highly correlated when all data from all three cities were combined. The finding of strong correlations between modelled and measured exposures in the combined data from the three cities may be relevant for studies exploiting exposure contrasts across cities.

Two Dutch studies in children reported significant correlation between NO_2 exposure measured at school and personal exposure, which remained after accounting for indoor sources including gas cooking (Rijnders et al., 2001; van Roosbroeck et al., 2007). In contrast, a Canadian study where the 72-hour personal NO_2 exposure of elderly adults was measured in three seasons found no relationship between the modelled long-term average outdoor concentration and the

personal exposure measurements (Sahsuvaroglu et al., 2009).

Two studies reported consistently higher population average personal exposures in European cities with higher outdoor concentrations (Monn et al., 1998; Georgoulis et al., 2002). Personal NO_2 exposure was highly correlated with outdoor concentration in a study in eight Swiss cities and towns with large contrasts in outdoor NO_2 concentration (Monn et al., 1998). The correlation between community average outdoor concentration and personal exposure was $R^2 = 0.965$ (Fig. 1.47; Monn, 2001).

(d) Social inequalities in air pollution exposure

There is a large literature that has evaluated contrasts in air pollution exposures in association with socioeconomic status (O'Neill et al., 2003). In general, higher outdoor air pollution concentrations have been observed for subjects with lower socioeconomic status, related to residential location (O'Neill et al., 2003). However, the contrast in air pollution exposures across socioeconomic groups differs significantly between study areas and spatial scales, with several studies showing higher concentrations for individuals with higher socioeconomic status (Deguen & Zmirou-Navier, 2010). A study in Rome, Italy, reported that subjects living close to major roads had a higher socioeconomic position than subjects living further away from major roads (Cesaroni et al., 2010).

Most studies of air pollution and socioeconomic status have evaluated outdoor pollutant concentrations with little attention to time–activity patterns and indoor exposures. Higher indoor concentrations were reported in low-income subjects, related to outdoor concentrations, indoor sources, and housing characteristics (Adamkiewicz et al., 2011). A study in Vancouver, Canada, reported higher wood smoke exposures and intake fractions in low-income neighbourhoods (Ries et al., 2009).

(e) Biomarkers of exposures

Biomarkers of exposure to outdoor air pollution have not been commonly used as the main method of exposure assessment in large-scale epidemiological studies of outdoor air pollution and cancer. However, associations between biomarkers of exposure and biomarkers of effect have been evaluated in smaller studies with tens to hundreds of subjects (see Section 4). In this context, biomarkers can contribute to elucidating the pathway from exposure to cancer. Biomarkers could additionally be useful in retrospective exposure assessment, if appropriate biological material has been stored; however, a limitation of many biomarkers for this purpose is their relatively short half-life (Scheepers, 2008).

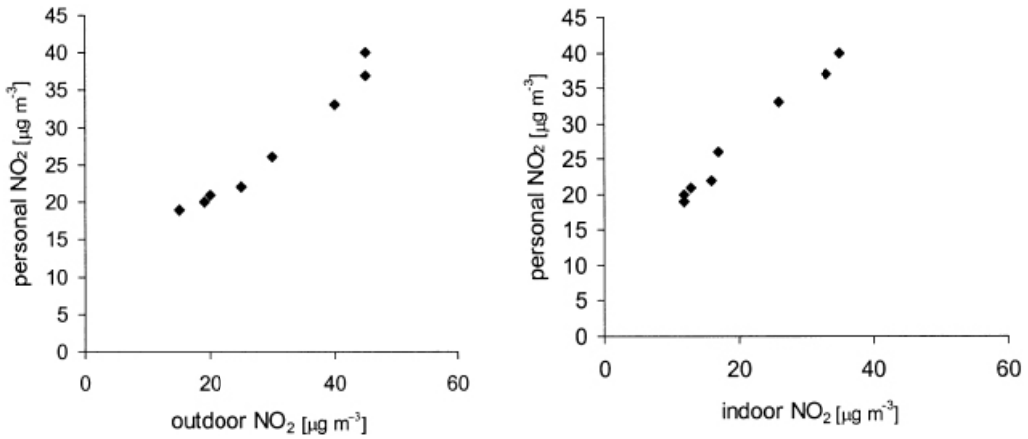
Associations of biomarkers with exposure to air pollution have been described in several recent reviews (Barbato et al., 2010; Møller & Loft, 2010; Demetriou et al., 2012; DeMarini, 2013; Rylance et al., 2013). Demetriou et al. (2012) specifically considered the utility of potential biomarkers of exposure to air pollution in a systematic review. The evidence of an association with external exposure was considered to be strong for 1-hydroxypyrene (1-OHP), DNA adducts, and oxidized nucleobases, particularly 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG). Studies in a wide variety of populations, including children, mail carriers, traffic police, and professional drivers, have repeatedly found increases in 1-OHP and in the frequency of DNA adducts in more exposed subjects (Demetriou et al., 2012).

It should be noted that the same markers can often be interpreted as indicators of early biological effects, as well as of exposure (DeMarini, 2013). Studies using these biomarkers and other markers of effect are reviewed in detail in Section 4.

1.4.4 Occupational exposure of outdoor workers

See Table 1.14.

Fig. 1.47 Scatterplot for outdoor–personal (R^2 = 0.965) and indoor–personal (R^2 = 0.983) NO_2 ratios of aggregated data (annual mean estimates) in eight Swiss cities



N (indoor) = 1501, *N* (outdoor) = 1544, *N* (personal data) = 1494; NO_2, nitrogen dioxide.
Reprinted from Monn (2001). *Atmospheric Environment*, Volume 35, Monn C, Exposure assessment of air pollutants: a review on spatial heterogeneity and indoor/outdoor/personal exposure to suspended particulate matter, nitrogen dioxide and ozone, Pages 1–32, Copyright (2001), with permission from Elsevier.

Workers who spend significant amounts of time outdoors may be occupationally exposed to outdoor air pollution. Although workers such as farmers, miners, and construction workers can face exposure to polluted air, emissions related to their work processes are the primary concern (e.g. diesel exposure in miners). Outdoor air pollution becomes an occupational exposure for workers who spend most or all of their working hours in polluted outdoor environments. Exposures for professional drivers, urban traffic police, mail carriers, toll booth operators, municipal workers, street vendors, service workers, and other outdoor occupations are often influenced by traffic-related emissions. Exposures from microenvironments influenced by polluted air can also be important for specialized groups of workers such as subway/underground metro workers and wildfire firefighters; the contribution of outdoor air pollution to occupational exposure in these instances can be substantial. However, few studies are designed to capture this contribution. Relying on fixed outdoor air quality monitors without exposure monitoring or reconstruction often fails to capture the range of exposures for such workers. This section describes the range of exposures to outdoor air pollution in occupational situations experienced by workers in selected jobs, as listed above. See Table 1.14.

(a) Traffic police

Urban traffic police are constantly exposed to traffic-related emissions while controlling traffic, and they may also be regarded as a model for worst-case exposures for air toxics. Many studies of traffic police have relied on outdoor air quality monitoring for criteria pollutants to highlight the potential for high occupational exposures directly attributable to the outdoor environment.

A review of traffic-related exposures (Han & Naeher, 2006) cited additional studies that reported high levels of outdoor exposures for VOCs including benzene, xylene, and toluene in the Republic of Korea (Jo & Song, 2001), India (Mukherjee et al., 2003), and Italy (Bono et al., 2003).

Traffic police on duty at the roadside had significantly higher environmental exposures to PAHs compared with police on office

Table 1.14 Exposure of outdoor workers to air pollutants

Occupation	Exposure measure	Outdoor air concentration (range, if provided)	Location	Comments	Reference
Traffic police	Personal exposure to respirable particulate matter (PM_5)	113–878 μg/m³; average, 322 μg/m³	Greater Mumbai, India	Similar levels have been reported in Nepal (Majumder et al., 2012)	Kulkarni & Patil (1999)
	Corresponding outdoor air PM_{10} concentration at the nearest air quality monitor	170–320 μg/m³; average, 143 μg/m³			
	Breath CO concentrations in non-smoking police officers after work shift	0.46–2.95 ppm	Ankara, Turkey		Atimtay et al. (2000)
	Breath CO concentrations in non-smoking police officers before work shift	0.7–3.37 ppm			
	Corresponding outdoor air concentrations	6.26–23.89 ppm			
	TWA exposure to benzene in traffic police	Geometric mean, 6.8 μg/m³	Rome, Italy		Crebelli et al. (2001)
	TWA exposure to benzene in indoor workers	Geometric mean, 3.5 μg/m³			
	PAH exposure for traffic police on active duty at the roadside	74.25 ng/m³	Thailand	Traffic police on active duty at the roadside had significantly higher environmental exposures to PAHs compared with police on office duty	Ruchirawat et al. (2002)
	PAH exposure for police on office duty	3.11 ng/m³			
	1-OHP in traffic police on active duty at the roadside	0.181 ± 0.078 μmol/mol creatinine	Thailand		Ruchirawat et al. (2002)
	1-OHP in police on office duty	0.173 ± 0.151 μmol/mol creatinine			
Automobile drivers	Benzene	55.6 (± 9.3) μg/m³	Manila, Philippines	Jeepney drivers	Balanay & Lungu (2009)
	Toluene	196.6 (± 75.0) μg/m³			
	Ethylbenzene	17.9 (± 9.0) μg/m³			
	m,*p*-xylene	72.5 (± 21.1) μg/m³			
	o-xylene	88.5 (± 26.5) μg/m³			
	Benzene in urban air	11.8 (± 2.2) μg/m³			
	Toluene in urban air	83.7 (± 40.5) μg/m³			
	o-xylene in urban air	38.0 (± 12.1) μg/m³			
	Toluene in rural air	14.0 (± 6.0) μg/m³			
	o-xylene in rural air	24.7 (± 11.9) μg/m³			

Table 1.14 (continued)

Occupation	Exposure measure	Outdoor air concentration (range, if provided)	Location	Comments	Reference
Street vendors/ small business operators	Total PAHs on main roads	7.10–83.04 ng/m^3	Bangkok, Thailand	Different occupations in 5 traffic-congested areas of Bangkok	Ruchirawat et al. (2005)
	Benzene levels on main roads	16.35–49.25 ppb			
	Total PAHs at nearby temples (control sites)	1.67–3.04 ng/m^3			
	Benzene levels at nearby temples (control sites)	10.16–16.25 ppb			
	Total PAHs in street vendors	16.07 ± 1.64 ng/m^3			
	Benzene in street vendors	21.97 ± 1.50 ppb			
	Total PAHs in monks and nuns from nearby temples	5.34 ± 0.65 ng/m^3			
	Benzene in monks and nuns from nearby temples	13.69 ± 0.77 ppb			
	Afternoon urinary 1-OHP levels (creatinine) in clothes vendors	0.12 µmol/mol creatinine			
	Afternoon urinary 1-OHP levels (creatinine) in grilled-meat vendors	0.15 µmol/mol creatinine			
	Afternoon urinary 1-OHP levels (creatinine) in controls	0.04 µmol/mol creatinine			
	Afternoon urinary *t*,*t*-MA levels in both groups of street vendors	0.12 mg/g creatinine			
	Afternoon urinary *t*,*t*-MA levels in controls	0.08 mg/g creatinine			
	Benzene in street vendors	83.7 ± 45.0 µg/m^3	Mexico City		Meneses et al. (1999)
	Benzene in office workers	45.2 ± 13.3 µg/m^3			

CO, carbon monoxide; 1-OHP, 1-hydroxypyrene; PAHs, polycyclic aromatic hydrocarbons; PM_{10}, particulate matter with particles of aerodynamic diameter < 10 µm; PM_5, particulate matter with particles of aerodynamic diameter < 5 µm; *t*,*t*-MA, *trans*,*trans*-muconic acid; TWA, time-weighted average.

duty (74.25 ng/m^3 vs 3.11 ng/m^3) in Thailand (Ruchirawat et al., 2002). Similar observations were reported from another study in Thailand (Arayasiri et al., 2010), which measured benzene and 1,3-butadiene exposures.

(b) Professional drivers

Research from around the world indicates that concentrations of particles and other air toxics in transportation microenvironments on and near roadways and inside vehicles often exceed nearby outdoor levels.

Such exposures are of concern for professional vehicle drivers, especially in developing-country settings, given the rapid increases in high-emitting vehicle fleets, vehicle use, and long exposure durations in and near traffic. For example, a 1997 study in Delhi, India, reported that concentrations of $PM_{5.0}$ and CO inside vehicles exceeded the high urban background concentrations by 1.5–10 times depending on vehicle type (Saksena et al., 2007). Although relatively few studies have been able to characterize outdoor air pollution exposures for automobile drivers, the ratio of reported in-vehicle concentrations to outdoor concentrations indicates the potential for extreme exposures (Apte et al., 2011; Fig. 1.48).

High in-vehicle concentrations would lead to high time-integrated exposures, as reported in the Delhi study (Apte et al., 2011). For example, a typical time-integrated exposure during an average daily commute (1.9 hours/day for auto-rickshaw users; Saksena et al., 2007) is nearly 2-fold higher than entire-day PM exposures for urban California residents (Fruin et al., 2008), the average in-home exposure contributions for residents of seven San Francisco Bay Area single-family homes (Bhangar et al., 2011), and the average for occupants of Beijing high-rise apartments (Mullen et al., 2011). During a typical daily work shift (10–16 hours; Harding & Hussein, 2010), auto-rickshaw drivers may receive very high PM exposures, up to an order of magnitude higher than those experienced during the average daily commute.

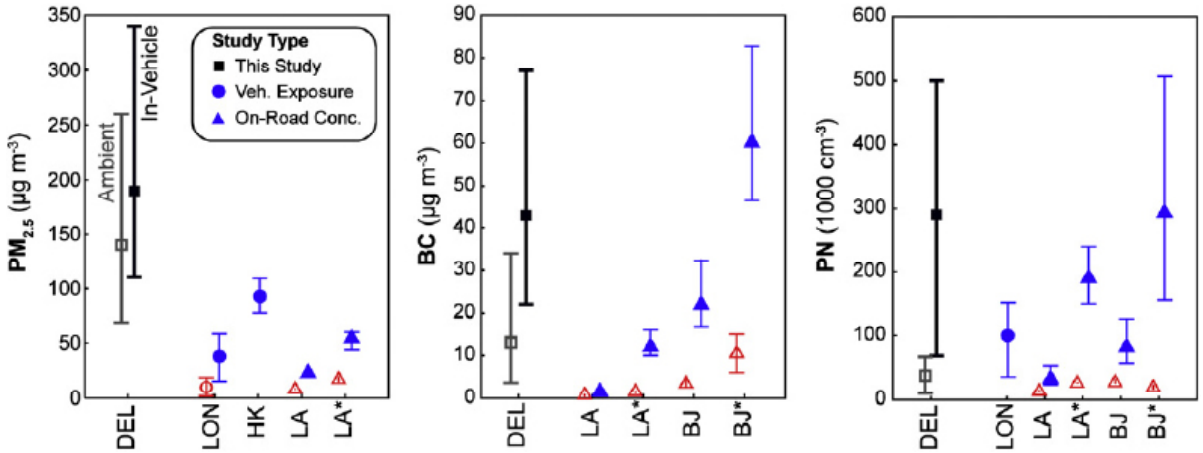
In a study that assessed the occupational exposure of jeepney drivers to selected VOCs in Manila, Philippines (Balanay & Lungu, 2009), personal sampling was conducted on 15 jeepney drivers. Area sampling was conducted to determine the background concentration of VOCs in Manila compared with that in a rural area. Both personal and area samples were collected for 5 working days. Samples were obtained using diffusive samplers and were analysed for VOCs including benzene, toluene, ethylbenzene, *m*,*p*-xylene, and *o*-xylene. The personal samples of drivers (collected for work-shift durations of 12–16 hours) had significantly higher concentrations for all selected VOCs than the urban area samples. Among the area samples, the urban concentrations of benzene and toluene were significantly higher than the rural concentrations. The personal exposures for all the target VOCs were not significantly different among the jeepney drivers.

A recent report (HEI, 2010a) that addressed contributions from mobile-source exposures to air toxics to exposures found that in-vehicle concentrations substantially exceeded outdoor concentrations for 1,3-butadiene, benzene, acrolein, formaldehyde, polycyclic organic matter, and diesel exhaust. This indicates substantial potential for high occupational exposures for many workers who spend long hours in vehicles.

(c) Street vendors/small business operators

Small-scale businesses, commonly street vending, operate primarily outdoors in many developing countries, especially in tropical countries, where weather poses fewer restrictions on spending time outdoors. Furthermore, in the absence of resources for air conditioning or other means of insulation from dust and heat, the work environment in many such small businesses is affected significantly by the prevailing outdoor air quality conditions. Traffic and industrial

Fig. 1.48 Comparison of in-vehicle concentrations in Delhi with those reported in other cities



BC, black carbon mass concentration; BJ, Beijing, China; DEL, Delhi, India; HK, Hong Kong Special Administrative Region; LA, Los Angeles, USA; LON, London, United Kingdom; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 µm; PN, ultrafine particle number concentration.
Plots indicate the mean and range of concentrations.
Reprinted from Apte et al. (2011). *Atmospheric Environment*, Volume 45, Apte JS, Kirchstetter TW, Reich AH, Deshpande SJ, Kaushik G, Chel A *et al*., Concentrations of fine, ultrafine, and black carbon particles in auto-rickshaws in New Delhi, India, Pages 4470–4480, Copyright (2011), with permission from Elsevier.

emissions thus become a source of occupational exposure. In a study conducted across various susceptible groups of the population with different occupations in five traffic-congested areas of Bangkok (Ruchirawat et al., 2005), the levels of total PAHs on the main roads at various sites were much higher than the outdoor levels in nearby temples (control sites).

In Mexico City, a significant proportion of the labour force works in informal markets, where many vendors spend long hours outdoors. Many workers in the service and transportation sectors experience similar conditions. In Mexico City, about 200 000 people work as taxi and bus drivers and more than 100 000 work as street vendors (SETRAVI, 2007); they have direct exposures to mobile-source emissions on high-traffic-density streets (Ortiz et al., 2002). Compared with indoor workers, these outdoor workers have higher exposures to PM, above the Mexican standard of 65 µg/m^3, and 2 or more times higher exposures to ozone, benzene, toluene, methyl *tert*-butyl ether, and 11-pentane (Tovalin-Ahumada & Whitehead, 2007). A survey among outdoor workers found a relationship between their exposure to selected VOCs, ozone, and $PM_{2.5}$ and the presence of severe DNA damage (Tovalin et al., 2006).

1.5 Guidelines and regulations

In many countries around the world, air quality standards are in place for ozone, SO_2, NO_2, CO, PM, and lead (Pegues et al., 2012; Vahlsing & Smith, 2012). Table 1.15 provides a summary of the air quality standards for some example countries. Within countries that have air quality regulations, there is not a consistent approach to regulating important air pollutants. In the USA, these pollutants are referred to as criteria pollutants and NAAQS are established for these pollutants at the national level. The EU has parallel limits for these pollutants but also has air quality limits for benzene, arsenic, cadmium, nickel, and PAHs. National standards in Japan are not set for lead but are set for

Table 1.15 Air quality standards in selected countries (in µg/m³)[a]

Country	SO_2	NO_2	O_3	$PM_{2.5}$	Lead	PAHs[b]	Benzene	Arsenic
Australia[c]								
1-hour	200 ppb [564]	120 ppb [243]	100 ppb [211]					
4-hour			80 ppb [169]					
1-day	80 ppb [226]			25				
Annual	20 ppb [56.4]	30 ppb [60.8]		8	0.50			
China (Class 2 areas)[d]								
1-hour	500	120	160					
24-hour	150	80		75				
Annual	60	40		35	1.0			
European Union[e]								
1-hour	350	200						
8-hour			120					
24-hour	125							
Annual		40		25	0.5	1 ng/m³	5	6 ng/m³
India (residential areas)[f]								
1-hour			180					
8-hour			100					
24-hour	80	80		60	1			
Annual	50	40		40	0.5		5	6 ng/m³
Japan[g]								
1-hour	100 ppb [282]		60 ppb [127]					
8-hour								
24-hour	40 ppb [113]	40–60 ppb [81–122]		35				
Annual				15			3	
USA[h]								
1-hour	75 ppb [212]	100 ppb [203]						
8-hour			75 ppb [159]					
24-hour				35				
Annual		53 ppb [107]		12	0.15			
WHO[i]								
10-minute	500							
1-hour		200						
8-hour			100					
24-hour	20			25				
Annual		40		10				

NO_2, nitrogen dioxide; O_3, ozone; PAHs, polycyclic aromatic hydrocarbons; PM_{10}, particulate matter with particles of aerodynamic diameter < 10 µm; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 µm; SO_2, sulfur dioxide; TSP, total suspended particles.

[a] Air quality standards are in µg/m³ unless otherwise specified; conversion from ppb into µg/m³ is given in square brackets.

Table 1.15 (continued)

[b] Expressed as concentration of benzo[*a*]pyrene.
[c] http://www.environment.gov.au/topics/environment-protection/air-quality/air-quality-standards#air
[d] http://www.mep.gov.cn/image20010518/5298.pdf; standards also exist for TSP, PM_{10}, benzo[*a*]pyrene, carbon monoxide, and fluorine.
[e] http://ec.europa.eu/environment/air/quality/standards.htm; standards also exist for carbon monoxide, PM_{10}, cadmium, and nickel.
[f] http://cpcb.nic.in/National_Ambient_Air_Quality_Standards.php; standards also exist for PM_{10}, carbon monoxide, ammonia, benzo[*a*]pyrene, and nickel.
[g] http://www.env.go.jp/en/air/aq/aq.html; standards also exist for TSP, carbon monoxide, trichloroethylene, tetrachloroethylene, dichloromethane, and dioxin.
[h] http://www.epa.gov/air/criteria.html; standards also exist for carbon monoxide.
[i] http://www.who.int/mediacentre/factsheets/fs313/en/ and WHO (2006).

benzene, trichloroethylene, tetrachloroethylene, dichloromethane, and dioxins. Similar lists of air pollutants are regulated in China and India with direct air quality standards. In some locations where air quality standards have not been developed, the WHO guidelines are used as a reference for air quality management. In many locations around the world, compliance with air quality standards and the WHO guidelines is not achieved.

Given the importance of specific industrial sectors on air pollution, sector-based regulations for emission controls have been developed (Lioy & Georgopoulos, 2011). Important examples are mandated controls on mobile sources, including gasoline-powered motor vehicles and diesel-powered vehicles (see the Annex of IARC, 2013a), stationary power generation, and Portland cement manufacturing. In the case of diesel engines, there are standards for new vehicles in all regions of the world that limit emissions of PM, NO_x, VOCs, and in some countries standards for gas-phase air toxic compounds such as benzene, formaldehyde, acetaldehyde, and butadiene (Diaz-Robles et al., 2013). Likewise, sector-based controls on coal-fired power plants are used to limit emissions of SO_2, NO_x, and mercury. These sector-based control requirements are established at both the national and the regional level, depending on the importance of specific sectors and the importance of the pollutants to local air quality problems. Some sector-based controls are also directed at consumer products and consumables used in industry. Examples include reformulated gasoline, reformulated paints, and replacement of environmental persistent chemicals in consumer goods.

Sector-based controls can take three forms: (1) risk-based (based on risk, not on every source); (2) technology-based (based on the "best" technology for all sources, regardless of risk; e.g. Maximum Achievable Control Technology standards, New Source Performance Standards, or Reasonably Available Control Technology standards); or (3) market-based (cap and trade, emissions taxes, and/or fees) (Farrell & Lave, 2004; Sovacool, 2011). A good example of a regulation or control strategy is that related to HAPs established by the USA: the National Emissions Standards for Hazardous Air Pollutants (NESHAPs) (EPA, 2013f) identify specific pollutants and emissions limits relevant to a wide range of industries.

References

Abt E, Suh HH, Allen G, Koutrakis P (2000). Characterization of indoor particle sources: A study conducted in the metropolitan Boston area. *Environ Health Perspect*, 108(1):35–44. doi:10.1289/ehp.0010835 PMID:10620522

Abu-Allaban M, Hamasha S, Gertler A (2006). Road dust resuspension in the vicinity of limestone quarries in Jordan. *J Air Waste Manag Assoc*, 56(10):1440–4. doi:10.1080/10473289.2006.10464546 PMID:17063866

Abu-Allaban M, Lowenthal DH, Gertler AW, Labib M (2007). Sources of PM(10) and PM(2.5) in Cairo's ambient air. *Environ Monit Assess*, 133(1-3):417–25. doi:10.1007/s10661-006-9596-8 PMID:17268919

Aburas HM, Zytoon MA, Abdulsalam MI (2011). Atmospheric lead in $PM_{2.5}$ after leaded gasoline

phase-out in Jeddah City, Saudi Arabia. *Clean Soil Water*, 39(8):711–9. doi:10.1002/clen.201000510

Adamkiewicz G, Zota AR, Fabian MP, Chahine T, Julien R, Spengler JD et al. (2011). Moving environmental justice indoors: understanding structural influences on residential exposure patterns in low-income communities. *Am J Public Health*, 101(S1):Suppl 1: S238–45. doi:10.2105/AJPH.2011.300119 PMID:21836112

Agay-Shay K, Friger M, Linn S, Peled A, Amitai Y, Peretz C (2013). Air pollution and congenital heart defects. *Environ Res*, 124:28–34. doi:10.1016/j.envres.2013.03.005 PMID:23623715

Air Quality Expert Group (2005). Particulate matter in the UK: summary. London: Department for the Environment, Food and Rural Affairs. Available from: uk-air.defra.gov.uk/assets/documents/reports/aqeg/pm-summary.pdf.

Al Jallad F, Al Katheeri E, Al Omar M (2013). Concentrations of particulate matter and their relationships with meteorological variables. *Sustain Environ Res*, 23(3):191–8.

Al-Jeelani HA (2013). The impact of traffic emission on air quality in an urban environment. *J Environ Prot (Irvine Calif)*, 4(02):205–17. doi:10.4236/jep.2013.42025

Al-Salem SM (2013). An overview of the PM_{10} pollution problem in Fahaheel urban area, Kuwait. *Emirates J Eng Res*, 13:1–9.

Allen RW, Adar SD, Avol E, Cohen M, Curl CL, Larson T et al. (2012). Modeling the residential infiltration of outdoor PM(2.5) in the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air). *Environ Health Perspect*, 120(6):824–30. doi:10.1289/ehp.1104447 PMID:22534026

Almeida-Silva M, Almeida SM, Freitas MC, Pio CA, Nunes T, Cardoso J (2013). Impact of Sahara dust transport on Cape Verde atmospheric element particles. *J Toxicol Environ Health A*, 76(4-5):240–51. doi:10.1080/15287394.2013.757200 PMID:23514066

Alnawaiseh NA, Hashim JH, Md Isa Z (2012). Relationship between vehicle count and particulate air pollution in Amman, Jordan. *Asia Pac J Public Health*, 27(2):NP1742–51. doi:10.1177/1010539512455046 PMID:22899706

Alolayan MA, Brown KW, Evans JS, Bouhamra WS, Koutrakis P (2013). Source apportionment of fine particles in Kuwait City. *Sci Total Environ*, 448:14–25. doi:10.1016/j.scitotenv.2012.11.090 PMID:23270730

Amador-Muñoz O, Bazan-Torija S, Villa-Ferreira SA, Villalobos-Pietrini R, Bravo-Cabrera JL, Munive-Colín Z et al. (2013). Opposing seasonal trends for polycyclic aromatic hydrocarbons and PM_{10}: health risk and sources in southwest Mexico City. *Atmos Res*, 122:199–212. doi:10.1016/j.atmosres.2012.10.003

Anttila P, Tuovinen J-P, Niemi JV (2011). Primary NO_2 emissions and their role in the development of NO_2 concentrations in a traffic environment. *Atmos Environ*, 45(4):986–92. doi:10.1016/j.atmosenv.2010.10.050

Apte JS, Kirchstetter TW, Reich AH, Deshpande SJ, Kaushik G, Chel A et al. (2011). Concentrations of fine, ultrafine, and black carbon particles in auto-rickshaws in New Delhi, India. *Atmos Environ*, 45(26):4470–80. doi:10.1016/j.atmosenv.2011.05.028

Arayasiri M, Mahidol C, Navasumrit P, Autrup H, Ruchirawat M (2010). Biomonitoring of benzene and 1,3-butadiene exposure and early biological effects in traffic policemen. *Sci Total Environ*, 408(20):4855–62. doi:10.1016/j.scitotenv.2010.06.033 PMID:20627202

Arkouli M, Ulke AG, Endlicher W et al. (2010). Distribution and temporal behavior of particulate matter over the urban area of Buenos Aires. *Atmos Pollut Res*, 1:1–8. doi:10.5094/APR.2010.001

Arku RE, Vallarino J, Dionisio KL, Willis R, Choi H, Wilson JG et al. (2008). Characterizing air pollution in two low-income neighborhoods in Accra, Ghana. *Sci Total Environ*, 402(2-3):217–31. doi:10.1016/j.scitotenv.2008.04.042 PMID:18565573

ASTM (2013). American Society for Testing and Materials. Conshohocken (PA): American Society for Testing Materials International.

Atimtay AT, Emri S, Bagci T, Demir AU (2000). Urban CO exposure and its health effects on traffic policemen in Ankara. *Environ Res*, 82(3):222–30. doi:10.1006/enrs.1999.4031 PMID:10702329

Augusto S, Máguas C, Matos J, Pereira MJ, Branquinho C (2010). Lichens as an integrating tool for monitoring PAH atmospheric deposition: a comparison with soil, air and pine needles. *Environ Pollut*, 158(2):483–9. doi:10.1016/j.envpol.2009.08.016 PMID:19782448

Augusto S, Máguas C, Matos J, Pereira MJ, Soares A, Branquinho C (2009). Spatial modeling of PAHs in lichens for fingerprinting of multisource atmospheric pollution. *Environ Sci Technol*, 43(20):7762–9. doi:10.1021/es901024w PMID:19921891

Augusto S, Pereira MJ, Máguas C, Soares A, Branquinho C (2012). Assessing human exposure to polycyclic aromatic hydrocarbons (PAH) in a petrochemical region utilizing data from environmental biomonitors. *J Toxicol Environ Health A*, 75(13-15):819–30. doi:10.1080/15287394.2012.690685 PMID:22788369

Australian Government (2010). State of the Air in Australia Report 1999–2008. Department of Sustainability, Environment, Water, Population and Communities. Available from: http://www.environment.gov.au/protection/air-quality/publications/state-of-the-air-1999-2008.

Avery CL, Mills KT, Williams R, McGraw KA, Poole C, Smith RL et al. (2010). Estimating error in using ambient $PM_{2.5}$ concentrations as proxies for personal exposures: a review. *Epidemiology*, 21(2):215–23. doi:10.1097/EDE.0b013e3181cb41f7 PMID:20087191

Balanay JA, Lungu CT (2009). Exposure of jeepney drivers in Manila, Philippines, to selected volatile organic compounds (VOCs). *Ind Health*, 47(1):33–42. doi:10.2486/indhealth.47.33 PMID:19218755

Barbato D, Tomei G, Tomei F, Sancini A (2010). Traffic air pollution and oxidatively generated DNA damage: can urinary 8-oxo-7,8-dihydro-2-deoxiguanosine be considered a good biomarker? A meta-analysis. *Biomarkers*, 15(6):538–45. doi:10.3109/1354750X.2010.493974 PMID:20545462

Battye W, Aneja VP, Roelle PA (2003). Evaluation and improvement of ammonia emissions inventories. *Atmos Environ*, 37(27):3873–83. doi:10.1016/S1352-2310(03)00343-1

Bayraktar H, Turalioğlu FS, Tuncel G (2010). F. S Turaliog¢lu, and G. Tuncel. Average mass concentrations of TSP, PM_{10} and $PM_{2.5}$ in Erzurum urban atmosphere, Turkey. *Stochastic Environ Res Risk Assess*, 24(1):57–65. doi:10.1007/s00477-008-0299-2

Beckx C, Int Panis L, Van De Vel K, Arentze T, Lefebvre W, Janssens D et al. (2009). The contribution of activity-based transport models to air quality modelling: a validation of the ALBATROSS-AURORA model chain. *Sci Total Environ*, 407(12):3814–22. doi:10.1016/j.scitotenv.2009.03.015 PMID:19344931

Beelen R, Hoek G, van den Brandt PA, Goldbohm RA, Fischer P, Schouten LJ et al. (2008). Long-term effects of traffic-related air pollution on mortality in a Dutch cohort (NLCS-AIR study). *Environ Health Perspect*, 116(2):196–202. doi:10.1289/ehp.10767 PMID:18288318

Belis CA, Karagulian F, Larsen BR, Hopke PK (2013). Critical review and meta-analysis of ambient particulate matter source apportionment using receptor models in Europe. *Atmos Environ*, 69:94–108. doi:10.1016/j.atmosenv.2012.11.009

Bellander T, Berglind N, Gustavsson P, Jonson T, Nyberg F, Pershagen G et al. (2001). Using geographic information systems to assess individual historical exposure to air pollution from traffic and house heating in Stockholm. *Environ Health Perspect*, 109(6):633–9. doi:10.1289/ehp.01109633 PMID:11445519

Bergamaschi P, Hein R, Heimann M, Crutzen PJ (2000). Inverse modeling of the global CO cycle 1. Inversion of CO mixing ratios. *J Geophys Res Atmos*, 105:D2: 1909–27. doi:10.1029/1999JD900818

Bhanarkar AD, Rao PS, Gajghate DG, Nema P (2005). Inventory of SO_2, PM and toxic metals emissions from industrial sources in Greater Mumbai, India *Atmos Environ*, 39(21):3851–64. doi:10.1016/j.atmosenv.2005.02.052

Bhangar S, Mullen NA, Hering SV, Kreisberg NM, Nazaroff WW (2011). Ultrafine particle concentrations and exposures in seven residences in northern California. *Indoor Air*, 21(2):132–44. doi:10.1111/j.1600-0668.2010.00689.x PMID:21029183

Billionnet C, Sherrill D, Annesi-Maesano I; GERIE study (2012). Estimating the health effects of exposure to multi-pollutant mixture. *Ann Epidemiol*, 22(2):126–41. doi:10.1016/j.annepidem.2011.11.004 PMID:22226033

Boman J, Lindén J, Thorsson S, Holmer B, Eliasson I (2009). A tentative study of urban and suburban fine particles ($PM_{2.5}$) collected in Ouagadougou, Burkina Faso. *XRay Spectrom*, 38(4):354–62. doi:10.1002/xrs.1173

Bond TC, Streets DG, Yarber KF et al. (2004). A technology-based global inventory of black and organic carbon emissions from combustion *J Geophys Res Atmos*, 109:D14: D14203. doi:10.1029/2003JD003697

Bono R, Scursatone E, Schilirò T, Gilli G (2003). Ambient air levels and occupational exposure to benzene, toluene, and xylenes in northwestern Italy. *J Toxicol Environ Health A*, 66(6):519–31. doi:10.1080/15287390306357 PMID:12712594

Brajer V, Hall J, Rahmatian M (2012). Air pollution, its mortality risk, and economic impacts in Tehran, Iran. *Iran J Public Health*, 41(5):31–8. PMID:23113175

Brauer M, Amann M, Burnett RT, Cohen A, Dentener F, Ezzati M et al. (2012). Exposure assessment for estimation of the global burden of disease attributable to outdoor air pollution. *Environ Sci Technol*, 46(2):652–60. doi:10.1021/es2025752 PMID:22148428

Brimblecombe P (1987). The big smoke: a history of air pollution in London since medieval times. London: Methuen & Co. Ltd.

Brown AS, Brown RJ, Coleman PJ, Conolly C, Sweetman AJ, Jones KC et al. (2013). Twenty years of measurement of polycyclic aromatic hydrocarbons (PAHs) in UK ambient air by nationwide air quality networks. *Environ Sci Process Impacts*, 15(6):1199–215. doi:10.1039/c3em00126a PMID:23636622

Brunekreef B, Janssen NA, de Hartog JJ, Oldenwening M, Meliefste K, Hoek G et al. (2005). Personal, indoor, and outdoor exposures to $PM_{2.5}$ and its components for groups of cardiovascular patients in Amsterdam and Helsinki. *Res Rep Health Eff Inst*, (127):1–70, discussion 71–9. PMID:15916017

Buonanno G, Stabile L, Morawska L (2014). Personal exposure to ultrafine particles: the influence of time-activity patterns. *Sci Total Environ*, 468–469:903–7. doi:10.1016/j.scitotenv.2013.09.016 PMID:24080417

Cao J, Yang C, Li J, Chen R, Chen B, Gu D et al. (2011). Association between long-term exposure to outdoor air pollution and mortality in China: a cohort study. *J Hazard Mater*, 186(2–3):1594–600. doi:10.1016/j.jhazmat.2010.12.036 PMID:21194838

Cao JJ, Shen ZX, Chow JC, Watson JG, Lee SC, Tie XX et al. (2012). Winter and summer $PM_{2.5}$ chemical compositions in fourteen Chinese cities. *J Air Waste Manag Assoc*, 62(10):1214–26. doi:10.1080/10962247.2012.701193 PMID:23155868

Cardenas B, Ferrrion J, Byrne C et al. (2011). Baseline ambient concentrations of dioxins and furans in

Mexico: 2008–2010 operation of the American Dioxin Air Monitoring Network (MDAMN). *Organohalogen Compd*, 73:1030–2.

CAREX Canada (2013). Profiles and estimates. Available from: http://www.carexcanada.ca/en/profiles_and_estimates, accessed 29 January 2015.

Carey IM, Atkinson RW, Kent AJ, van Staa T, Cook DG, Anderson HR (2013). Mortality associations with long-term exposure to outdoor air pollution in a national English cohort. *Am J Respir Crit Care Med*, 187(11):1226–33. doi:10.1164/rccm.201210-1758OC PMID:23590261

Carslaw DC, Beevers SD, Bell MC (2007). Risks of exceeding the hourly EU limit value for nitrogen dioxide resulting from increased road transport emissions of primary nitrogen dioxide. *Atmos Environ*, 41(10):2073–82. doi:10.1016/j.atmosenv.2006.10.074

Carslaw DC, Beevers SD, Tate JE, Westmoreland EJ, Williams ML (2011). Recent evidence concerning higher NO_x emissions from passenger cars and light duty vehicles. *Atmos Environ*, 45(39):7053–63. doi:10.1016/j.atmosenv.2011.09.063

CEN (2013). CEN/TC 264 – Air Quality. Published standards. Brussels, Belgium: European Committee for Standardization. Available from: http://www.cen.eu/cen/Sectors/TechnicalCommitteesWorkshops/CENTechnicalCommittees/Pages/Standards.aspx?param=6245&title=CEN/TC%20264, accessed 27 March 2014.

Cesaroni G, Badaloni C, Gariazzo C, Stafoggia M, Sozzi R, Davoli M et al. (2013). Long-term exposure to urban air pollution and mortality in a cohort of more than a million adults in Rome. *Environ Health Perspect*, 121(3):324–31. doi:10.1289/ehp.1205862 PMID:23308401

Cesaroni G, Badaloni C, Romano V, Donato E, Perucci CA, Forastiere F (2010). Socioeconomic position and health status of people who live near busy roads: the Rome Longitudinal Study (RoLS). *Environ Health*, 9(1):41 doi:10.1186/1476-069X-9-41 PMID:20663144

Cesaroni G, Porta D, Badaloni C, Stafoggia M, Eeftens M, Meliefste K et al. (2012). Nitrogen dioxide levels estimated from land use regression models several years apart and association with mortality in a large cohort study. *Environ Health*, 11(1):48 doi:10.1186/1476-069X-11-48 PMID:22808928

CETESB (2013). Qualidade do ar no estado de São Paulo [in Portuguese]. São Paulo, Brazil: Companhia Ambiental do Estado de São Paulo. Available from: http://www.cetesb.sp.gov.br/ar/qualidade-do-ar/31-publicacoes-e-relatorios, accessed 29 January 2015.

Chan CK, Yao X (2008). Air pollution in mega cities in China. *Atmos Environ*, 42(1):1–42. doi:10.1016/j.atmosenv.2007.09.003

Chang CC, Tsai SS, Chiu HF, Wu TN, Yang CY (2009). Traffic air pollution and lung cancer in females in Taiwan: petrol station density as an indicator of disease development. *J Toxicol Environ Health A*, 72(10):651–7. doi:10.1080/15287390902733515 PMID:19308850

Chen C, Zhao B (2011). Review of relationship between indoor and outdoor particles: I/O ratio, infiltration factor and penetration factor. *Atmos Environ*, 45(2):275–88. doi:10.1016/j.atmosenv.2010.09.048

Chen R, Li Y, Ma Y, Pan G, Zeng G, Xu X et al. (2011a). Coarse particles and mortality in three Chinese cities: the China Air Pollution and Health Effects Study (CAPES). *Sci Total Environ*, 409(23):4934–8. doi:10.1016/j.scitotenv.2011.08.058 PMID:21925709

Chen R, Pan G, Kan H, Tan J, Song W, Wu Z et al. (2010). Ambient air pollution and daily mortality in Anshan, China: a time-stratified case-crossover analysis. *Sci Total Environ*, 408(24):6086–91. doi:10.1016/j.scitotenv.2010.09.018 PMID:20889186

Chen R, Pan G, Zhang Y, Xu Q, Zeng G, Xu X et al. (2011b). Ambient carbon monoxide and daily mortality in three Chinese cities: the China Air Pollution and Health Effects Study (CAPES). *Sci Total Environ*, 409(23):4923–8. doi:10.1016/j.scitotenv.2011.08.029 PMID:21908017

Cheung K, Daher N, Kam W, Shafer MM, Ning Z, Schauer JJ et al. (2011). Spatial and temporal variation of chemical composition and mass closure of ambient coarse particulate matter ($PM_{10-2.5}$) in the Los Angeles area. *Atmos Environ*, 45(16):2651–62. doi:10.1016/j.atmosenv.2011.02.066

Chow JC (1995). Measurement methods to determine compliance with ambient air quality standards for suspended particles. *J Air Waste Manag Assoc*, 45(5):320–82. doi:10.1080/10473289.1995.10467369 PMID:7773805

Chow JC, Doraiswamy P, Watson JG, Chen LW, Ho SS, Sodeman DA (2008). Advances in integrated and continuous measurements for particle mass and chemical composition. *J Air Waste Manag Assoc*, 58(2):141–63. doi:10.3155/1047-3289.58.2.141 PMID:18318335

Chow JC, Engelbrecht JP, Watson JG, Wilson WE, Frank NH, Zhu T (2002). Designing monitoring networks to represent outdoor human exposure. *Chemosphere*, 49(9):961–78. doi:10.1016/S0045-6535(02)00239-4 PMID:12492160

Chow JC, Watson J (2011). Air quality management of multiple pollutants and multiple effects. *Air Qual Clim Chang*, 45(3):26–32.

Chow JC, Watson JG (2002). Review of $PM_{2.5}$ and PM_{10} apportionment for fossil fuel combustion and other sources by the chemical mass balance receptor model. *Energy Fuels*, 16(2):222–60. doi:10.1021/ef0101715

Chow JC, Watson JG (2012). Chemical analyses of particle filter deposits. In: Ruzer L, Harley NH, editors. Aerosols handbook: measurement, dosimetry, and health effects, 2nd ed. New York: CRC Press/Taylor & Francis; pp. 179–204. doi:10.1201/b12668-8

Chow JC, Watson JG, Park K, Lowenthal DH, Robinson NF, Park K et al. (2006). Comparison of particle light scattering and fine particulate matter mass in central California. *J Air Waste Manag Assoc*, 56(4):398–410. doi:10.1080/10473289.2006.10464515 PMID:16681205

Christian TJ, Yokelson RJ, Cárdenas B, Molina LT, Engling G, Hsu S-C (2010). Trace gas and particle emissions from domestic and industrial biofuel use and garbage burning in central Mexico. *Atmos Chem Phys*, 10(2):565–84. doi:10.5194/acp-10-565-2010

Cislaghi C, Nimis PL (1997). Lichens, air pollution and lung cancer. *Nature*, 387(6632):463–4. doi:10.1038/387463a0 PMID:9168106

Clark NA, Allen RW, Hystad P, Wallace L, Dell SD, Foty R et al. (2010). Exploring variation and predictors of residential fine particulate matter infiltration. *Int J Environ Res Public Health*, 7(8):3211–24. doi:10.3390/ijerph7083211 PMID:20948956

Clean Air Asia (2010). Air quality in Asia: status and trends – 2010 edition. Pasig City, Philippines: Clean Air Initiative for Asian Cities (CAI-Asia) Center. Available from: http://cleanairasia.org/portal/system/files/Air_Quality_in_Asia_-_Status_and_Trends_2010_Ed._0.pdf.

Clean Air Institute (2012). Air quality in Latin America: an overview. Available from: http://www.cleanairinstitute.org/calidaddelaireamericalatina/cai-report-english.pdf, accessed 29 January 2015.

Clemitshaw KC (2004). A review of instrumentation and measurement techniques for ground-based and airborne field studies of gas-phase tropospheric chemistry. *Crit Rev Environ Sci Technol*, 34(1):1–108. doi:10.1080/10643380490265117

Cohan DS, Hakami A, Hu Y, Russell AG (2005). Nonlinear response of ozone to emissions: source apportionment and sensitivity analysis. *Environ Sci Technol*, 39(17):6739–48. doi:10.1021/es048664m PMID:16190234

Cohen BS, McCammon CSJ (2001). Air sampling instruments for evaluation of atmospheric contaminants. 4th ed. Cincinnati (OH): American Conference of Governmental Industrial Hygienists.

Committee on Japan's Experience in the Battle Against Air Pollution (1997). Japan's experience in the battle against air pollution. Tokyo, Japan: The Pollution-Related Health Damage Compensation and Prevention Association.

Conrad A, Seiwert M, Hünken A, Quarcoo D, Schlaud M, Groneberg D (2013). The German Environmental Survey for Children (GerES IV): reference values and distributions for time-location patterns of German children. *Int J Hyg Environ Health*, 216(1):25–34. doi:10.1016/j.ijheh.2012.02.004 PMID:22410199

Cooper MJ, Martin RV, van Donkelaar A, Lamsal L, Brauer M, Brook JR (2012). A satellite-based multi-pollutant index of global air quality. *Environ Sci Technol*, 46(16):8523–4. doi:10.1021/es302672p PMID:22853810

Corbett JJ, Winebrake JJ, Green EH, Kasibhatla P, Eyring V, Lauer A (2007). Mortality from ship emissions: a global assessment. *Environ Sci Technol*, 41(24):8512–8. doi:10.1021/es071686z PMID:18200887

Corrêa SM, Arbilla G (2005). Formaldehyde and acetaldehyde associated with the use of natural gas as a fuel for light vehicles. *Atmos Environ*, 39(25):4513–8. doi:10.1016/j.atmosenv.2005.03.042

CPCB (2009a). Comprehensive environmental assessment of industrial clusters. New Delhi, India: Central Pollution Control Board, Ministry of Environment and Forests. Available from: http://cpcb.nic.in/divisionsofheadoffice/ess/NewItem_152_Final-Book_2.pdf, accessed 4 November 2014.

CPCB (2009b). National ambient air quality standards. New Delhi, India: Central Pollution Control Board, Ministry of Environment and Forests. Available from: http://cpcb.nic.in/National_Ambient_Air_Quality_Standards.php, accessed 29 January 2015.

CPCB (2011). Air quality monitoring, emission inventory and source apportionment study for Indian cities. New Delhi, India: Central Pollution Control Board.

CPCB (2012). National ambient air quality status and trends in India 2010. New Delhi, India: Central Pollution Control Board. Available from: www.cpcb.nic.in/upload/NewItems/NewItem_192_NAAQSTI.pdf.

Crebelli R, Tomei F, Zijno A, Ghittori S, Imbriani M, Gamberale D et al. (2001). Exposure to benzene in urban workers: environmental and biological monitoring of traffic police in Rome. *Occup Environ Med*, 58(3):165–71. doi:10.1136/oem.58.3.165 PMID:11171929

Crouse DL, Peters PA, van Donkelaar A, Goldberg MS, Villeneuve PJ, Brion O et al. (2012). Risk of nonaccidental and cardiovascular mortality in relation to long-term exposure to low concentrations of fine particulate matter: a Canadian national-level cohort study. *Environ Health Perspect*, 120(5):708–14. doi:10.1289/ehp.1104049 PMID:22313724

Cyrys J, Eeftens M, Heinrich J, Ampe C, Armengaud A, Beelen R et al. (2012). Variation of NO_2 and NO_x concentrations between and within 36 European study areas: results from the ESCAPE study. *Atmos Environ*, 62:374–90. doi:10.1016/j.atmosenv.2012.07.080

Cyrys J, Pitz M, Bischof W, Wichmann HE, Heinrich J (2004). Relationship between indoor and outdoor levels of fine particle mass, particle number concentrations and black smoke under different ventilation conditions. *J Expo Anal Environ Epidemiol*, 14(4):275–83. doi:10.1038/sj.jea.7500317 PMID:15254474

Dai H, Song W, Gao X, Chen L (2004). Study on relationship between ambient PM_{10}, $PM_{2.5}$ pollution and daily mortality in a district in Shanghai [in Chinese]. *Wei Sheng Yan Jiu*, 33(3):293–7. PMID:15211795

de Foy B, Krotkov NA, Bei N, Herndon SC, Huey LG, Martínez A-P et al. (2009). Hit from both sides: tracking industrial and volcanic plumes in Mexico City with surface measurements and OMI SO_2 retrievals during the MILAGRO field campaign. *Atmos Chem Phys*, 9(24):9599–617. doi:10.5194/acp-9-9599-2009

de Hartog J, Boogaard H, Nijland H, Hoek G (2010). Do the health benefits of cycling outweigh the risks? *Environ Health Perspect*, 118(8):1109–16. doi:10.1289/ehp.0901747 PMID:20587380

de Hoogh K, Wang M, Adam M, Badaloni C, Beelen R, Birk M et al. (2013). Development of land use regression models for particle composition in twenty study areas in Europe. *Environ Sci Technol*, 47(11):5778–86. doi:10.1021/es400156t PMID:23651082

de Miranda RM, de Fatima Andrade M, Fornaro A, Astolfo R, de Andre PA, Saldiva P (2012). Urban air pollution: a representative survey of PM(2.5) mass concentrations in six Brazilian cities. *Air Qual Atmos Health*, 5(1):63–77. doi:10.1007/s11869-010-0124-1 PMID:22408694

de Nazelle A, Nieuwenhuijsen MJ, Antó JM, Brauer M, Briggs D, Braun-Fahrlander C et al. (2011). Improving health through policies that promote active travel: a review of evidence to support integrated health impact assessment. *Environ Int*, 37(4):766–77. doi:10.1016/j.envint.2011.02.003 PMID:21419493

de Nazelle A, Seto E, Donaire-Gonzalez D, Mendez M, Matamala J, Nieuwenhuijsen MJ et al. (2013). Improving estimates of air pollution exposure through ubiquitous sensing technologies. *Environ Pollut*, 176:92–9. doi:10.1016/j.envpol.2012.12.032 PMID:23416743

De Smedt I, Van Roozendael M, Stavrakou T, Müller J-F, Lerot C, Theys N et al. (2012). Improved retrieval of global tropospheric formaldehyde columns from GOME-2/MetOp-A addressing noise reduction and instrumental degradation issues. *Atmos Meas Tech*, 5(11):2933–49. doi:10.5194/amt-5-2933-2012

Deguen S, Zmirou-Navier D (2010). Social inequalities resulting from health risks related to ambient air quality–A European review. *Eur J Public Health*, 20(1):27–35. doi:10.1093/eurpub/ckp220 PMID:20081212

DeMarini DM (2013). Genotoxicity biomarkers associated with exposure to traffic and near-road atmospheres: a review. *Mutagenesis*, 28(5):485–505. doi:10.1093/mutage/get042 PMID:23945473

Demetriou CA, Raaschou-Nielsen O, Loft S, Møller P, Vermeulen R, Palli D et al. (2012). Biomarkers of ambient air pollution and lung cancer: a systematic review. *Occup Environ Med*, 69(9):619–27. doi:10.1136/oemed-2011-100566 PMID:22773658

Diaz-Robles LA, Fu JS, Reed GD (2013). Emission scenarios and the health risks posed by priority mobile air toxics in an urban to regional area: an application in Nashville, Tennessee. *Aerosol Air Qual Res*, 13:795–803.

Dionisio KL, Arku RE, Hughes AF, Vallarino J, Carmichael H, Spengler JD et al. (2010b). Air pollution in Accra neighborhoods: spatial, socioeconomic, and temporal patterns. *Environ Sci Technol*, 44(7):2270–6. doi:10.1021/es903276s PMID:20205383

Dionisio KL, Rooney MS, Arku RE, Friedman AB, Hughes AF, Vallarino J et al. (2010a). Within-neighborhood patterns and sources of particle pollution: mobile monitoring and geographic information system analysis in four communities in Accra, Ghana. *Environ Health Perspect*, 118(5):607–13. doi:10.1289/ehp.0901365 PMID:20056591

Docherty KS, Stone EA, Ulbrich IM, DeCarlo PF, Snyder DC, Schauer JJ et al. (2008). Apportionment of primary and secondary organic aerosols in southern California during the 2005 study of organic aerosols in riverside (SOAR-1). *Environ Sci Technol*, 42(20):7655–62. doi:10.1021/es8008166 PMID:18983089

Dons E, Int Panis L, Van Poppel M, Theunis J, Wets G (2012). Personal exposure to black carbon in transport microenvironments. *Atmos Environ*, 55:392–8. doi:10.1016/j.atmosenv.2012.03.020

Dons E, Temmerman P, Van Poppel M, Bellemans T, Wets G, Int Panis L (2013). Street characteristics and traffic factors determining road users' exposure to black carbon. *Sci Total Environ*, 447:72–9. doi:10.1016/j.scitotenv.2012.12.076 PMID:23376518

Ebelt ST, Wilson WE, Brauer M (2005). Exposure to ambient and nonambient components of particulate matter: a comparison of health effects. *Epidemiology*, 16(3):396–405. doi:10.1097/01.ede.0000158918.57071.3e PMID:15824557

EEA (2007). Air pollution in Europe 1990–2004. European Environment Agency Report 2/2007. Luxembourg: Office for Official Publications of the European Union. Available from: http://www.eea.europa.eu/publications/eea_report_2007_2, accessed 22 January 2015.

EEA (2012). Air quality in Europe – 2012 report. European Environment Agency Report 4/2012. Luxembourg: Office for Official Publications of the European Union. Available from: http://www.eea.europa.eu/publications/air-quality-in-europe-2012, accessed 22 January 2015.

EEA (2013). European Union emission inventory report 1990–2011 under the UNECE Convention on Long-range Transboundary Air Pollution (LRTAP). European Environmental Agency Technical Report 10/2013. Luxembourg: Office for Official Publications of the European Union. Available from: http://www.eea.europa.eu/publications/eu-emission-inventory-report-lrtap, accessed 9 October 2014.

EEA (2014). AirBase – the European air quality database. Available from: http://www.eea.europa.eu/data-and-maps/data/airbase-the-european-air-quality-database-7, accessed 4 November 2014.

Eeftens M, Beelen R, Fischer P, Brunekreef B, Meliefste K, Hoek G (2011). Stability of measured and modelled

spatial contrasts in NO(2) over time. *Occup Environ Med*, 68(10):765–70. doi:10.1136/oem.2010.061135 PMID:21285243

Eeftens M, Tsai M-Y, Ampe C, Anwander B, Beelen R, Bellander T et al. (2012). Spatial variation of $PM_{2.5}$, PM_{10}, $PM_{2.5}$ absorbance and PM_{coarse} concentrations between and within 20 European study areas and the relationship with NO_2 – results of the ESCAPE project. *Atmos Environ*, 62:303–17. doi:10.1016/j.atmosenv.2012.08.038

Engelbrecht JP, McDonald EV, Gillies JA, Jayanty RK, Casuccio G, Gertler AW (2009). Characterizing mineral dusts and other aerosols from the Middle East–Part 1: ambient sampling. *Inhal Toxicol*, 21(4):297–326. doi:10.1080/08958370802464273 PMID:19235610

Environment Canada (2010). National air pollution surveillance. Available from: http://www.ec.gc.ca/rnspa-naps/default.asp?lang=En&n=77FECF05-1#reports, accessed 22 January 2015.

Environment of Tokyo (2013). Results of air pollution concentrations at general sites in Tokyo. Available from: http://www.kankyo.metro.tokyo.jp/air/air_pollution/result_measurement.html, accessed 29 December 2014.

EPA (1997). Guidance for network design and optimum site exposure for PM2.5 and PM10. EPA-454/R-99–022. Research Triangle Park (NC): US Environmental Protection Agency.

EPA (1998). Locating and estimating air emissions from sources of polycyclic organic matter. EPA-454/R-98–014. Research Triangle Park (NC): US Environmental Protection Agency.

EPA (2006). Expanding and updating the master list of compounds emitted from mobile sources – phase III. R420-R-06–005. Research Triangle Park (NC): US Environmental Protection Agency.

EPA (2010). Ambient concentrations of lead. Research Triangle Park (NC): US Environmental Protection Agency. Available from: http://www.epa.gov/air/airtrends/lead.html, accessed 17 September 2014.

EPA (2011a). The ambient air monitoring program. Research Triangle Park (NC): US Environmental Protection Agency. Available from: http://www.epa.gov/air/oaqps/qa/monprog.html, accessed 22 January 2015.

EPA (2011b). An overview of methods for EPA's National-Scale Air Toxics Assessment. Research Triangle Park (NC): US Environmental Protection Agency. Available from: http://www.epa.gov/ttn/atw/nata2005/05pdf/nata_tmd.pdf, accessed 29 January 2015.

EPA (2012a). Technology Transfer Network Ambient Monitoring Technology Information Center. Air Toxics. Research Triangle Park (NC): US Environmental Protection Agency. Available from: http://www.epa.gov/ttn/amtic/airtoxpg.html, accessed 22 January 2015.

EPA (2012b). Air Toxics – National Air Toxics Trends Stations. Research Triangle Park (NC): US Environmental Protection Agency. Available from: http://www.epa.gov/ttnamti1/natts.html, accessed 22 January 2015.

EPA (2012c). Air quality monitoring information. Research Triangle Park (NC): US Environmental Protection Agency. Available from: http://www.epa.gov/airtrends/factbook.html, accessed 22 January 2015.

EPA (2012d). 2010 National Monitoring Programs Annual Report (UATMP, NATTS, CSATAM). Research Triangle Park (NC): US Environmental Protection Agency. Available from: http://www.epa.gov/ttn/amtic/files/ambient/airtox/2010NMPAnnualReportVol1.pdf, accessed 22 January 2015.

EPA (2012e). 2005 National-Scale Air Toxics Assessment. Research Triangle Park (NC): US Environmental Protection Agency. Available from: http://www.epa.gov/ttn/atw/nata2005/, accessed 22 January 2015.

EPA (2013a). List of designated reference and equivalent methods. Research Triangle Park (NC): US Environmental Protection Agency. Available from: http://www.epa.gov/ttn/amtic/files/ambient/criteria/reference-equivalent-methods-list.pdf, accessed 27 March 2014.

EPA (2013b). Air monitoring methods. Research Triangle Park (NC): US Environmental Protection Agency. Available from: http://www.epa.gov/ttn/amtic/methods.html, accessed 27 March 2014.

EPA (2013c). Download detailed AQS data. Research Triangle Park (NC): US Environmental Protection Agency. Available from: http://www.epa.gov/ttn/airs/airsaqs/detaildata/downloadaqsdata.htm, accessed 27 March 2014.

EPA (2013d). Air emission sources. Research Triangle Park (NC): US Environmental Protection Agency. Available from: http://www.epa.gov/air/emissions/index.htm, accessed 9 October 2014.

EPA (2013e). Chemical speciation – general information. Research Triangle Park (NC): US Environmental Protection Agency. Available from: http://www.epa.gov/ttn/amtic/specgen.html, accessed 22 January 2015.

EPA (2013f). Title 40, Part 63 – National emission standards for hazardous air pollutants for source categories. Code of Federal Regulations. Research Triangle Park (NC): US Environmental Protection Agency. Available from: http://www.ecfr.gov/cgi-bin/retrieveECFR?gp=&SID=58ca7d63cbd732624780bdb648af1159&r=PART&n=40y10.0.1.1.1, accessed 22 January 2015.

EPA (2014). Air quality models. Research Triangle Park (NC): US Environmental Protection Agency. Available from: www.epa.gov/ttn/scram/aqmindex.htm, accessed 9 October 2014.

EU (2008). Directive 2008/50/EC of the European Parliament and of the Council of 21 May 2008 on ambient air quality and cleaner air for Europe. Off J Eur Union. L 152:1–44. Available from: http://eur-lex.

europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:152:0001:0044:EN:PDF, accessed 4 November 2014.

European Commission (2014). European guide on air pollution source apportionment with receptor models. Joint Research Centre Reference Report. Luxembourg: Office for Official Publications of the European Union. Available from: http://source-apportionment.jrc.ec.europa.eu/Docu/EU_guide_on_SA.pdf, accessed 6 October 2014.

Farrell AE, Lave LB (2004). Emission trading and public health. *Annu Rev Public Health*, 25(1):119–38. doi:10.1146/annurev.publhealth.25.102802.124348 PMID:15015915

FEAM (2011). Monitoramento da qualidade do ar na região metropolitana de Belo Horizonte no ano base de 2011 [in Portuguese]. Belo Horizonte, Brazil: Fundação Estadual do Meio Ambiente. Available from: http://www.feam.br/images/stories/arquivos/mudnacaclimatica/2013/relatorio_de_qualidade_do-ar_2011_final.pdf, accessed 6 October 2014.

Fehsenfeld FC, Hastie D, Chow JC, Solomon PA (2004). Particle and gas measurements. In: McMurry PH, Shepherd MF, Vickery JS, editors. Particulate matter science for policy makers, a NARSTO assessment. Cambridge, UK: Cambridge University Press; pp. 159–89.

Finlayson-Pitts BJ, Pitts JN, editors (2000a). Chemistry of the upper and lower atmosphere. San Diego (CA): Academic Press.

Finlayson-Pitts BJ, Pitts JN (2000b). Analytical methods and typical atmospheric concentrations for gases and particles. Chapter 11. In: Finlayson-Pitts BJ, Pitts JN, editors. Chemistry of the upper and lower atmosphere. San Diego (CA): Academic Press; pp. 547–656. doi:10.1016/B978-012257060-5/50013-7

Fischer PH, Hoek G, van Reeuwijk H, Briggs DJ, Lebret E, van Wijnen JH et al. (2000). Traffic-related differences in outdoor and indoor concentrations of particles and volatile organic compounds in Amsterdam. *Atmos Environ*, 34(22):3713–22. doi:10.1016/S1352-2310(00)00067-4

Forster C, Wandinger U, Wotawa G, James P, Mattis I, Althausen D et al. (2001). Transport of boreal forest fire emissions from Canada to Europe. *J Geophys Res Atmos*, 106:D19: 22887–906. doi:10.1029/2001JD900115

Fraser MP, Cass GR (1998). Detection of excess ammonia emissions from in-use vehicles and the implications for fine particle control. *Environ Sci Technol*, 32(8):1053–7. doi:10.1021/es970382h

Fruin S, Westerdahl D, Sax T, Sioutas C, Fine PM (2008). Measurements and predictors of on-road ultrafine particle concentrations and associated pollutants in Los Angeles. *Atmos Environ*, 42(2):207–19. doi:10.1016/j.atmosenv.2007.09.057

Fu S, Yang ZZ, Li K, Xu XB (2010). Spatial characteristics and major sources of polycyclic aromatic hydrocarbons from soil and respirable particulate matter in a mega-city, China. *Bull Environ Contam Toxicol*, 85(1):15–21. doi:10.1007/s00128-010-0026-9 PMID:20440470

Gandolfi I, Bertolini V, Ambrosini R, Bestetti G, Franzetti A (2013). Unravelling the bacterial diversity in the atmosphere. *Appl Microbiol Biotechnol*, 97(11):4727–36. doi:10.1007/s00253-013-4901-2 PMID:23604562

Gao H, Chen J, Wang B, Tan S-C, Lee CM, Yao X et al. (2011). A study of air pollution of city clusters. *Atmos Environ*, 45(18):3069–77. doi:10.1016/j.atmosenv.2011.03.018

Gentner DR, Isaacman G, Worton DR, Chan AW, Dallmann TR, Davis L et al. (2012). Elucidating secondary organic aerosol from diesel and gasoline vehicles through detailed characterization of organic carbon emissions. *Proc Natl Acad Sci USA*, 109(45):18318–23. doi:10.1073/pnas.1212272109 PMID:23091031

George BJ, Schultz BD, Palma T, Vette AF, Whitaker DA, Williams RW (2011). An evaluation of EPA's National-Scale Air Toxics Assessment (NATA): comparison with benzene measurements in Detroit, Michigan. *Atmos Environ*, 45(19):3301–8. doi:10.1016/j.atmosenv.2011.03.031

Georgoulis LB, Hänninen O, Samoli E, Katsouyanni K, Künzli N, Polanska L et al. (2002). Personal carbon monoxide exposure in five European cities and its determinants. *Atmos Environ*, 36(6):963–74. doi:10.1016/S1352-2310(01)00473-3

Götschi T, Oglesby L, Mathys P, Monn C, Manalis N, Koistinen K et al. (2002). Comparison of black smoke and $PM_{2.5}$ levels in indoor and outdoor environments of four European cities. *Environ Sci Technol*, 36(6):1191–7. doi:10.1021/es010079n PMID:11944668

Gram F, Nafstad P, Håheim LL (2003). Estimating residential air pollution exposure among citizens in Oslo 1974–1998 using a geographical information system. *J Environ Monit*, 5(4):541–6. doi:10.1039/b303500j PMID:12948224

Grice S, Stedman J, Kent A, Hobson M, Norris J, Abbott J et al. (2009). Recent trends and projections of primary NO_2 emissions in Europe. *Atmos Environ*, 43(13):2154–67. doi:10.1016/j.atmosenv.2009.01.019

Gulliver J, de Hoogh K, Hansell A, Vienneau D (2013). Development and back-extrapolation of NO_2 land use regression models for historic exposure assessment in Great Britain. *Environ Sci Technol*, 47(14):7804–11. doi:10.1021/es4008849 PMID:23763440

Han X, Naeher LP (2006). A review of traffic-related air pollution exposure assessment studies in the developing world. *Environ Int*, 32(1):106–20. doi:10.1016/j.envint.2005.05.020 PMID:16005066

Hänninen O, Hoek G, Mallone S, Chellini E, Katsouyanni K, Gariazzo C et al. (2011). Seasonal patterns of outdoor PM infiltration into indoor environments: review and meta-analysis of available studies from different climatological zones in Europe. *Air Qual Atmos Health*, 4(3–4):221–33. doi:10.1007/s11869-010-0076-5

Harding S, Hussein A (2010). On the road to nowhere? Auto-rickshaws in Delhi: the system, problems and recommendations. Informal Labour portfolio. New Delhi, India: Aman Public Charitable Trust.

Harrison RM, Stedman J, Derwent D (2008). New directions: Why are PM_{10} concentrations in Europe not falling? *Atmos Environ*, 42(3):603–6. doi:10.1016/j.atmosenv.2007.11.023

Hazenkamp-von Arx ME, Götschi T, Ackermann-Liebrich U et al. (2004). $PM_{2.5}$ and NO_2 assessment in 21 European study centres of ECRHS II: annual means and seasonal differences. *Atmos Environ*, 38(13):1943–53. doi:10.1016/j.atmosenv.2004.01.016

Heard MJ (2006). Analytical techniques for atmospheric measurement. Oxford, UK: Blackwell Publishing. doi:10.1002/9780470988510

HEI (2007). Mobile-source air toxics: a critical review of the literature on exposure and health effects. Special report 16. Boston (MA): Health Effects Institute. Available from: http://pubs.healtheffects.org/view.php?id=282, accessed 22 January 2015.

HEI (2010a). Traffic-related air pollution: a critical review of the literature on emissions, exposure, and health effects. HEI Special report 17. Boston (MA): Health Effects Institute. Available from: http://pubs.healtheffects.org/view.php?id=334, accessed 30 September 2014.

HEI (2010b). Outdoor air pollution and health in the developing countries of Asia: a comprehensive review. HEI Special report 18. Boston (MA): Health Effects Institute.

HEI (2013). Understanding the health effects of ambient ultrafine particles. *Perspectives*, 3. Boston (MA): Health Effects Institute. Available from: http://pubs.healtheffects.org/view.php?id=394, accessed 22 January 2015.

Heinrich J, Thiering E, Rzehak P, Krämer U, Hochadel M, Rauchfuss KM et al. (2013). Long-term exposure to NO2 and PM10 and all-cause and cause-specific mortality in a prospective cohort of women. *Occup Environ Med*, 70(3):179–86. doi:10.1136/oemed-2012-100876 PMID:23220504

Heo J, Dulger M, Olson MR, McGinnis JE, Shelton BR, Matsunaga A et al. (2013). Source apportionments of $PM_{2.5}$ organic carbon using molecular marker positive matrix factorization and comparison of results from different receptor models. *Atmos Environ*, 73:51–61. doi:10.1016/j.atmosenv.2013.03.004

Hidy GM, Brook JR, Chow JC, Green M, Husar RB, Lee C et al. (2009). Remote sensing of particulate pollution from space: have we reached the promised land?: Critical review discussion. *J Air Waste Manage Assoc*, 59(10):1130–9. doi:10.3155/1047-3289.59.10.1130

Hill ASG (1936). Measurement of the optical densities of smokestains of filter papers. *Trans Faraday Soc*, 32:1125–31. doi:10.1039/tf9363201125

Hoek G, Beelen R, De Hoogh K, Vienneau D, Gulliver J, Fischer P et al. (2008a). A review of land-use regression models to assess spatial variation of outdoor air pollution. *Atmos Environ*, 42(33):7561–78. doi:10.1016/j.atmosenv.2008.05.057

Hoek G, Forsberg B, Borowska M, Hlawiczka S, Vaskövi E, Welinder H et al. (1997). Wintertime PM_{10} and black smoke concentrations across Europe: results from the PEACE study. *Atmos Environ*, 31(21):3609–22. doi:10.1016/S1352-2310(97)00158-1

Hoek G, Kos G, Harrison R, de Hartog J, Meliefste K, ten Brink H et al. (2008b). Indoor-outdoor relationships of particle number and mass in four European cities. *Atmos Environ*, 42(1):156–69. doi:10.1016/j.atmosenv.2007.09.026

Hoff RM, Christopher SA (2009). Remote sensing of particulate pollution from space: have we reached the promised land? *J Air Waste Manag Assoc*, 59(6):645–75, discussion 642–4. doi:10.3155/1047-3289.59.6.645 PMID:19603734

Holloway T, Levy H 2nd, Kasibhatla P (2000). Global distribution of carbon monoxide. *J Geophys Res Atmos*, 105:D10: 12123–47. doi:10.1029/1999JD901173

Hou B, Dai L, Wang Z et al. (2011). Time-series analysis of acute mortality effects of air pollution in Xi'an [in Chinese]. *J Environ Health*, 28:1039–1043.

Houthuijs D, Breugelmans O, Hoek G, Vaskövi É, Miháliková E, Pastuszka JS et al. (2001). PM_{10} and $PM_{2.5}$ concentrations in central and eastern Europe: results from the CESAR study. *Atmos Environ*, 35(15):2757–71. doi:10.1016/S1352-2310(01)00123-6

Huang W, Cao J, Tao Y, Dai L, Lu SE, Hou B et al. (2012a). Seasonal variation of chemical species associated with short-term mortality effects of PM(2.5) in Xi'an, a Central City in China. *Am J Epidemiol*, 175(6):556–66. doi:10.1093/aje/kwr342 PMID:22323403

Huang W, Tan J, Kan H, Zhao N, Song W, Song G et al. (2009). Visibility, air quality and daily mortality in Shanghai, China. *Sci Total Environ*, 407(10):3295–300. doi:10.1016/j.scitotenv.2009.02.019 PMID:19275954

Huang XL, Dai LZ, Lu P, Shang Y, Li Y, Tao YB et al. (2012b). Time-series analysis on the acute mortality affected by air pollution, in the city of Guangzhou, 2004–2008 [in Chinese]. *Zhonghua Liu Xing Bing Xue Za Zhi*, 33(2):210–4. PMID:22575146

Hystad P, Demers PA, Johnson KC, Brook J, van Donkelaar A, Lamsal L et al. (2012). Spatiotemporal air pollution exposure assessment for a Canadian population-based lung cancer case-control study. *Environ Health*, 11(1):22. doi:10.1186/1476-069X-11-22 PMID:22475580

Hystad P, Demers PA, Johnson KC, Carpiano RM, Brauer M (2013). Long-term residential exposure to air pollution and lung cancer risk. *Epidemiology*, 24(5):762–72. doi:10.1097/EDE.0b013e3182949ae7 PMID:23676262

Hystad P, Setton E, Cervantes A, Poplawski K, Deschenes S, Brauer M et al. (2011). Creating national air pollution

models for population exposure assessment in Canada. *Environ Health Perspect*, 119(8):1123–9. doi:10.1289/ehp.1002976 PMID:21454147

Hystad PU, Setton EM, Allen RW, Keller PC, Brauer M (2009). Modeling residential fine particulate matter infiltration for exposure assessment. *J Expo Sci Environ Epidemiol*, 19(6):570–9. doi:10.1038/jes.2008.45 PMID:18716606

IARC (1995). Dry cleaning, some chlorinated solvents and other industrial chemicals. IARC Monogr Eval Carcinog Risks Hum, 63:1–551. PMID:9139128. Available from: http://monographs.iarc.fr/ENG/Monographs/vol63/index.php.

IARC (1999). Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide. *IARC Monogr Eval Carcinog Risks Hum*, 71:1–315. PMID:10507919. Available from: http://monographs.iarc.fr/ENG/Monographs/vol71/index.php.

IARC (2006). Inorganic and organic lead compounds. *IARC Monogr Eval Carcinog Risks Hum*, 87:1–471. PMID:17191367. Available from: http://monographs.iarc.fr/ENG/Monographs/vol87/index.php.

IARC (2008). 1,3-Butadiene, ethylene oxide and vinyl halides (vinyl fluoride, vinyl chloride and vinyl bromide). *IARC Monogr Eval Carcinog Risks Hum*, 97:1–510. PMID:20232717. Available from: http://monographs.iarc.fr/ENG/Monographs/vol97/index.php.

IARC (2010a). Some non-heterocyclic polycyclic aromatic hydrocarbons and some related exposures. *IARC Monogr Eval Carcinog Risks Hum*, 92:1–853. PMID:21141735. Available from: http://monographs.iarc.fr/ENG/Monographs/vol92/index.php.

IARC (2010b). Household use of solid fuels and high-temperature frying. *IARC Monogr Eval Carcinog Risks Hum*, 95:1–430. PMID:20701241. Available from: http://monographs.iarc.fr/ENG/Monographs/vol95/index.php.

IARC (2012a). Arsenic, metals, fibres, and dusts. *IARC Monogr Eval Carcinog Risks Hum*, 100C:1–499. PMID:23189751. Available from: http://monographs.iarc.fr/ENG/Monographs/vol100C/index.php.

IARC (2012b). Chemical agents and related occupations. *IARC Monogr Eval Carcinog Risks Hum*, 100F:1–599. PMID:23189753. Available from: http://monographs.iarc.fr/ENG/Monographs/vol100F/index.php.

IARC (2012c). Personal habits and indoor combustions. *IARC Monogr Eval Carcinog Risks Hum*, 100E:1–575. PMID:23193840. Available from: http://monographs.iarc.fr/ENG/Monographs/vol100E/index.php.

IARC (2013a). Diesel and gasoline engine exhausts and some nitroarenes. *IARC Monogr Eval Carcinog Risks Hum*, 105:1–704. Available from: http://monographs.iarc.fr/ENG/Monographs/vol105/index.php.

IARC (2013b). Some chemicals present in industrial and consumer products, food and drinking-water. *IARC Monogr Eval Carcinog Risks Hum*, 101:9–549. PMID:24772663. Available from: http://monographs.iarc.fr/ENG/Monographs/vol101/index.php.

IARC (2014a). Trichloroethylene and some chlorinated agents. *IARC Monogr Eval Carcinog Risks Hum*, 106:1–514. Available from: http://monographs.iarc.fr/ENG/Monographs/vol106/index.php.

IARC (2014b). Polychlorinated biphenyls and polybrominated biphenyls. *IARC Monogr Eval Carcinog Risks Hum*, 107:1–502. Available from: http://monographs.iarc.fr/ENG/Monographs/vol107/index.php.

IEMA; Instituto Estadual do Meio Ambiente (2007). Relatório da qualidade do ar na Região da grande Vitória [in Portuguese]. Available from: http://www.meioambiente.es.gov.br/download/Relatorio_Qualidade_do_Ar_2007.pdf, accessed 29 January 2015.

IMPROVE (2012). Interagency monitoring of protected visual environments. Available from: http://vista.cira.colostate.edu/IMPROVE/, accessed 22 January 2015.

INEA (2009). Relatório Anual da Qualidade do Ar do Estado do Rio de Janeiro [in Portuguese]. Available from: http://www.cetesb.sp.gov.br/ar/qualidade-do-ar/31-publicacoes-e-relatorios, accessed 22 January 2015.

Isaacman G, Chan AWH, Nah T, Worton DR, Ruehl CR, Wilson KR et al. (2012). Heterogeneous OH oxidation of motor oil particles causes selective depletion of branched and less cyclic hydrocarbons. *Environ Sci Technol*, 46(19):10632–40. doi:10.1021/es302768a PMID:22947099

ISO (2013). International Organization for Standardization. Geneva, Switzerland: International Organization for Standardization. Available from: http://www.iso.org/iso/home.html, accessed 22 January 2015.

Israel Ministry of Environmental Protection (2010). State of the environment in Israel: indicators, data and trends 2010. Bar-Or Y, Matzner O, editors. Available from: http://www.sviva.gov.il/InfoServices/ReservoirInfo/DocLib2/Publications/P0601-P0700/p0607.pdf, accessed 29 January 2015.

Janssen NA, Hoek G, Simic-Lawson M, Fischer P, van Bree L, ten Brink H et al. (2011). Black carbon as an additional indicator of the adverse health effects of airborne particles compared with PM_{10} and $PM_{2.5}$. *Environ Health Perspect*, 119(12):1691–9. doi:10.1289/ehp.1003369 PMID:21810552

Jenkins PL, Phillips TJ, Mulberg EJ, Hui SP (1992). Activity patterns of Californians: use of and proximity to indoor pollutant sources. *Atmos Environ A Gen Topics*, 26(12):2141–8. doi:10.1016/0960-1686(92)90402-7

Jerrett M, Arain A, Kanaroglou P, Beckerman B, Potoglou D, Sahsuvaroglu T et al. (2005). A review and evaluation of intraurban air pollution exposure models. *J Expo Anal Environ Epidemiol*, 15(2):185–204. doi:10.1038/sj.jea.7500388 PMID:15292906

Jo WK, Song KB (2001). Exposure to volatile organic compounds for individuals with occupations associated with potential exposure to motor vehicle exhaust and/or gasoline vapor emissions. *Sci Total Environ*, 269(1-3):25–37. doi:10.1016/S0048-9697(00)00774-9 PMID:11305341

Käffer MI, Lemos AT, Apel MA, Rocha JV, Martins SM, Vargas VM (2012). Use of bioindicators to evaluate air quality and genotoxic compounds in an urban environment in Southern Brazil. *Environ Pollut*, 163:24–31. doi:10.1016/j.envpol.2011.12.006 PMID:22325427

Kam W, Delfino RJ, Schauer JJ, Sioutas C (2013). A comparative assessment of $PM_{2.5}$ exposures in light-rail, subway, freeway, and surface street environments in Los Angeles and estimated lung cancer risk. *Environ Sci Process Impacts*, 15(1):234–43. doi:10.1039/C2EM30495C PMID:24592440

Kan H, Chen B (2003). Air pollution and daily mortality in Shanghai: a time-series study. *Arch Environ Health*, 58(6):360–7. PMID:14992311

Kan H, London SJ, Chen G, Zhang Y, Song G, Zhao N et al. (2007). Differentiating the effects of fine and coarse particles on daily mortality in Shanghai, China. *Environ Int*, 33(3):376–84. doi:10.1016/j.envint.2006.12.001 PMID:17229464

Kan H, London SJ, Chen G, Zhang Y, Song G, Zhao N et al. (2008). Season, sex, age, and education as modifiers of the effects of outdoor air pollution on daily mortality in Shanghai, China: The Public Health and Air Pollution in Asia (PAPA) Study. *Environ Health Perspect*, 116(9):1183–8. doi:10.1289/ehp.10851 PMID:18795161

Kara E, Özdilek HG, Kara EE (2013). Ambient air quality and asthma cases in Niğde, Turkey. *Environ Sci Pollut Res Int*, 20(6):4225–34. doi:10.1007/s11356-012-1376-0 PMID:23247525

Karner AA, Eisinger DS, Niemeier DA (2010). Near-roadway air quality: synthesizing the findings from real-world data. *Environ Sci Technol*, 44(14):5334–44. doi:10.1021/es100008x PMID:20560612

Katanoda K, Sobue T, Satoh H, Tajima K, Suzuki T, Nakatsuka H et al. (2011). An association between long-term exposure to ambient air pollution and mortality from lung cancer and respiratory diseases in Japan. *J Epidemiol*, 21(2):132–43. doi:10.2188/jea.JE20100098 PMID:21325732

Kaur S, Nieuwenhuijsen MJ, Colvile RN (2007). Fine particulate matter and carbon monoxide exposure concentrations in urban street transport microenvironments. *Atmos Environ*, 41(23):4781–810. doi:10.1016/j.atmosenv.2007.02.002

Kearney J, Wallace L, MacNeill M, Xu X, VanRyswyk K, You H et al. (2011). Residential indoor and outdoor ultrafine particles in Windsor, Ontario. *Atmos Environ*, 45(40):7583–93. doi:10.1016/j.atmosenv.2010.11.002

Keuken M, Roemer M, van den Elshout S (2009). Trend analysis of urban NO_2 concentrations and the importance of direct NO_2 emissions versus ozone/NO_x equilibrium. *Atmos Environ*, 43(31):4780–3. doi:10.1016/j.atmosenv.2008.07.043

Khamdan SA, Al Madany IM, Buhussain E (2009). Temporal and spatial variations of the quality of ambient air in the Kingdom of Bahrain during 2007. *Environ Monit Assess*, 154(1-4):241–52. doi:10.1007/s10661-008-0392-5 PMID:18581244

Khodeir M, Shamy M, Alghamdi M, Zhong M, Sun H, Costa M et al. (2012). Source apportionment and elemental composition of $PM_{2.5}$ and PM_{10} in Jeddah City, Saudi Arabia. *Atmos Pollut Res*, 3(3):331–40. PMID:24634602

Kim Oanh NT, Upadhyay N, Zhuang Y-H, Hao Z-P, Murthy DVS, Lestari P et al. (2006). Air pollution in six Asian cities: spatial and temporal distributions, and associated sources. *Atmos Environ*, 40(18):3367–80. doi:10.1016/j.atmosenv.2006.01.050

Kinney PL, Gichuru MG, Volavka-Close N, Ngo N, Ndiba PK, Law A et al. (2011). Traffic impacts on $PM_{2.5}$ air quality in Nairobi, Kenya. *Environ Sci Policy*, 14(4):369–78. doi:10.1016/j.envsci.2011.02.005 PMID:21779151

Kitayama K, Murao N, Hara H (2010). PMF analysis of impacts of SO_2 from Miyakejima and Asian continent on precipitation sulfate in Japan. *Atmos Environ*, 44(1):95–105. doi:10.1016/j.atmosenv.2009.09.011

Klepeis NE, Nelson WC, Ott WR, Robinson JP, Tsang AM, Switzer P et al. (2001). The National Human Activity Pattern Survey (NHAPS): a resource for assessing exposure to environmental pollutants. *J Expo Anal Environ Epidemiol*, 11(3):231–52. doi:10.1038/sj.jea.7500165 PMID:11477521

Kloog I, Koutrakis P, Coull BA, Lee HJ, Schwartz J (2011). Assessing temporally and spatially resolved $PM_{2.5}$ exposures for epidemiological studies using satellite aerosol optical depth measurements. *Atmos Environ*, 45(35):6267–75. doi:10.1016/j.atmosenv.2011.08.066

Kloog I, Ridgway B, Koutrakis P, Coull BA, Schwartz JD (2013). Long- and short-term exposure to $PM_{2.5}$ and mortality: using novel exposure models. *Epidemiology*, 24(4):555–61. doi:10.1097/EDE.0b013e318294beaa PMID:23676266

Knibbs LD, Cole-Hunter T, Morawska L (2011). A review of commuter exposure to ultrafine particles and its health effects. *Atmos Environ*, 45(16):2611–22. doi:10.1016/j.atmosenv.2011.02.065

Koponen IK, Asmi A, Keronen P, Puhto K, Kulmala M (2001). Indoor air measurement campaign in Helsinki, Finland 1999 – the effect of outdoor air pollution on indoor air. *Atmos Environ*, 35:1465–77. doi:10.1016/S1352-2310(00)00338-1

Kot-Wasik A, Zabiegała B, Urbanowicz M, Dominiak E, Wasik A, Namieśnik J (2007). Advances in passive sampling in environmental studies. *Anal Chim Acta*, 602(2):141–63. doi:10.1016/j.aca.2007.09.013 PMID:17933599

Koutrakis P, Suh HH, Sarnat JA et al. (2005). Characterization of particulate and gas exposures of sensitive subpopulations living in Baltimore and Boston. Report 131, 2005–01–01. Boston (MA): Health Effects Institute.

Kreyling WG, Tuch T, Peters A et al. (2003). Diverging long-term trends in ambient urban particle mass and number concentrations associated with emission changes caused by the German unification. *Atmos Environ*, 37(27):3841–8. doi:10.1016/S1352-2310(03)00457-6

Kulkarni MM, Patil RS (1999). Monitoring of daily integrated exposure of outdoor workers to respirable particulate in an urban region in India. *Environ Monit Assess*, 56(2):129–46. doi:10.1023/A:1005947301971

Kulkarni P, Baron PA, Willeke K (2011). Aerosol measurement principles, techniques and applications. 3rd ed. Hoboken (NJ): John Wiley & Sons. doi:10.1002/9781118001684

Kurokawa J, Ohara T, Morikawa T, Hanayama S, Greet JM, Fukui T et al. (2013). Emissions of air pollutants and greenhouse gases over Asian regions during 2000–2008: Regional Emission inventory in ASia (REAS) version 2. *Atmos Chem Phys Discuss*, 13(4):10049–123. doi:10.5194/acpd-13-10049-2013

Kuvarega AT, Taru P (2008). Ambiental dust speciation and metal content variation in TSP, PM 10 and PM 2.5 in urban atmospheric air of Harare (Zimbabwe). *Environ Monit Assess*, 144(1-3):1–14. doi:10.1007/s10661-008-0436-x PMID:18633721

Kuzu SL, Saral A, Demir S, Summak G, Demir G (2013). A detailed investigation of ambient aerosol composition and size distribution in an urban atmosphere. *Environ Sci Pollut Res Int*, 20(4):2556–68. doi:10.1007/s11356-012-1149-9 PMID:22968673

Kwon J, Weisel CP, Turpin BJ, Zhang J, Korn LR, Morandi MT et al. (2006). Source proximity and outdoor-residential VOC concentrations: results from the RIOPA study. *Environ Sci Technol*, 40(13):4074–82. doi:10.1021/es051828u PMID:16856719

Laïd Y, Atek M, Oudjehane R, Filleul L, Baough L, Zidouni N et al. (2006). Health effects of PM10 air pollution in a low-income country: the case of Algiers. *Int J Tuberc Lung Dis*, 10(12):1406–11. PMID:17167960

Lamsal LN, Martin RV, Parrish DD, Krotkov NA (2013). Scaling relationship for NO2 pollution and urban population size: a satellite perspective. *Environ Sci Technol*, 47(14):7855–61. doi:10.1021/es400744g PMID:23763377

Landsberger S, Creatchman M (1999). *Elemental analysis of airborne particles*. Newark (NJ): Gordon and Breach.

Lee C, Martin RV, van Donkelaar A, O'Byrne G, Krotkov N, Richter A et al. (2009). Retrieval of vertical columns of sulfur dioxide from SCIAMACHY and OMI: air mass factor algorithm development and validation. *J Geophys Res*, 114:D22: D22303. doi:10.1029/2009JD012123

Leech JA, Nelson WC, Burnett RT, Aaron S, Raizenne ME (2002). It's about time: a comparison of Canadian and American time-activity patterns. *J Expo Anal Environ Epidemiol*, 12(6):427–32. doi:10.1038/sj.jea.7500244 PMID:12415491

Lepeule J, Laden F, Dockery D, Schwartz J (2012). Chronic exposure to fine particles and mortality: an extended follow-up of the Harvard Six Cities study from 1974 to 2009. *Environ Health Perspect*, 120(7):965–70. doi:10.1289/ehp.1104660 PMID:22456598

Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H et al. (2012). A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*, 380(9859):2224–60. doi:10.1016/S0140-6736(12)61766-8 PMID:23245609

Lindén J, Boman J, Holmer B, Thorsson S, Eliasson I (2012). Intra-urban air pollution in a rapidly growing Sahelian city. *Environ Int*, 40:51–62. doi:10.1016/j.envint.2011.11.005 PMID:22280928

Lioy PJ, Georgopoulos PG (2011). New Jersey: a case study of the reduction in urban and suburban air pollution from the 1950s to 2010. *Environ Health Perspect*, 119(10):1351–5. doi:10.1289/ehp.1103540 PMID:21622086

Lipsett MJ, Ostro BD, Reynolds P, Goldberg D, Hertz A, Jerrett M et al. (2011). Long-term exposure to air pollution and cardiorespiratory disease in the California teachers study cohort. *Am J Respir Crit Care Med*, 184(7):828–35. doi:10.1164/rccm.201012-2082OC PMID:21700913

Liu D-L, Nazaroff W (2001). Modeling pollutant penetration across building envelopes. *Atmos Environ*, 35(26):4451–62. doi:10.1016/S1352-2310(01)00218-7

Liu S, Ahlm L, Day DA et al. (2012). Secondary organic aerosol formation from fossil fuel sources contribute majority of summertime organic mass at Bakersfield. *J Geophys Res Atmos*, 117:21.

Liu Y, Zhu L, Shen X (2001). Polycyclic aromatic hydrocarbons (PAHs) in indoor and outdoor air of Hangzhou, China. *Environ Sci Technol*, 35(5):840–4. doi:10.1021/es001354t PMID:11351525

Liu YN, Tao S, Dou H, Zhang TW, Zhang XL, Dawson R (2007). Exposure of traffic police to Polycyclic aromatic hydrocarbons in Beijing, China. *Chemosphere*, 66(10):1922–8. doi:10.1016/j.chemosphere.2006.07.076 PMID:16996563

Long CM, Suh HH, Catalano PJ, Koutrakis P (2001). Using time- and size-resolved particulate data to quantify indoor penetration and deposition behavior. *Environ Sci Technol*, 35(10):2089–99. doi:10.1021/es001477d PMID:11393992

López-Cima MF, García-Pérez J, Pérez-Gómez B, Aragonés N, López-Abente G, Tardón A et al. (2011). Lung cancer risk and pollution in an industrial region of Northern Spain: a hospital-based case-control

study. *Int J Health Geogr*, 10(1):10. doi:10.1186/1476-072X-10-10 PMID:21266041

Lu H, Wen W, Cai Q et al. (2008). Source apportionment and pollution of BTEX in indoor and outdoor air of Guangzhou hospitals [in Chinese]. *China Environ Sci*, 28:1127–1132.

Luo J, Hendryx M (2011). Environmental carcinogen releases and lung cancer mortality in rural-urban areas of the United States. *J Rural Health*, 27(4):342–9. doi:10.1111/j.1748-0361.2010.00357.x PMID:21967377

Majumder AK, Nazmul Islam KM, Bajracharya RM, Carter WS (2012). Assessment of occupational and outdoor air quality of traffic police personnel of the Kathmandu valley, Nepal; in view of atmospheric particulate matter concentrations (PM_{10}) *Atmos Pollut Res*, 3(1):132–42. doi:10.5094/APR.2012.013

Manolopoulos H, Snyder DC, Schauer JJ, Hill JS, Turner JR, Olson ML et al. (2007). Sources of speciated atmospheric mercury at a residential neighborhood impacted by industrial sources. *Environ Sci Technol*, 41(16):5626–33. doi:10.1021/es0700348 PMID:17874765

Mansourian M, Javanmard SH, Poursafa P, Kelishadi R (2010). Air pollution and hospitalization for respiratory diseases among children in Isfahan, Iran. *Ghana Med J*, 44(4):138–43. PMID:21416047

Marć M, Zabiegala B, Namiesnik J (2012). Mobile systems (portable, handheld, transportable) for monitoring air pollution. *Crit Rev Anal Chem*, 42(1):2–15. doi:10.1080/10408347.2011.607079

Marshall JD, Granvold PW, Hoats AS, McKone TE, Deakin E, W Nazaroff W (2006). Inhalation intake of ambient air pollution in California's South Coast Air Basin. *Atmos Environ*, 40(23):4381–92. doi:10.1016/j.atmosenv.2006.03.034

Martin RV et al. (2003). Global inventory of nitrogen oxide emissions constrained by space-based observations of NO_2 columns *J Geophys Res Atmos*, 108:D17:4537. doi:10.1029/2003JD003453

Martins EM, Arbilla G, Bauerfeldt GF, de Paula M (2007). Atmospheric levels of aldehydes and BTEX and their relationship with vehicular fleet changes in Rio de Janeiro urban area. *Chemosphere*, 67(10):2096–103. doi:10.1016/j.chemosphere.2006.09.088 PMID:17257646

Massoud R, Shihadeh AL, Roumié M, Youness M, Gerard J, Saliba NB et al. (2011). Intraurban variability of PM_{10} and $PM_{2.5}$ in an Eastern Mediterranean city. *Atmos Res*, 101(4):893–901. doi:10.1016/j.atmosres.2011.05.019

Mavroidis I, Chaloulakou A (2011). Long-term trends of primary and secondary NO_2 production in the Athens area. Variation of the NO_2/NO_x ratio. *Atmos Environ*, 45(38):6872–9. doi:10.1016/j.atmosenv.2010.11.006

McMurry PH (2000). A review of atmospheric aerosol measurements. *Atmos Environ*, 34(12–14):1959–99. doi:10.1016/S1352-2310(99)00455-0

Meneses F, Romieu I, Ramirez M, Colome S, Fung K, Ashley D et al. (1999). A survey of personal exposures to benzene in Mexico City. *Arch Environ Health*, 54(5):359–63. doi:10.1080/00039899909602501 PMID:10501154

Meng Q, Williams R, Pinto JP (2012b). Determinants of the associations between ambient concentrations and personal exposures to ambient $PM_{2.5}$, NO_2, and O_3 during DEARS. *Atmos Environ*, 63:109–16. doi:10.1016/j.atmosenv.2012.09.019

Meng QY, Spector D, Colome S, Turpin B (2009). Determinants of indoor and personal exposure to $PM_{2.5}$ of indoor and outdoor origin during the RIOPA study. *Atmos Environ (1994)*, 43(36):5750–8. doi:10.1016/j.atmosenv.2009.07.066 PMID:20339526

Meng QY, Svendsgaard D, Kotchmar DJ, Pinto JP (2012a). Associations between personal exposures and ambient concentrations of nitrogen dioxide: a quantitative research synthesis. *Atmos Environ*, 57:322–9. doi:10.1016/j.atmosenv.2012.04.035

MEPPRC (2012). Ambient air quality standards, GB 3095–2012. Beijing, China: Ministry of Environmental Protection of the People's Republic of China. Available from: http://kjs.mep.gov.cn/hjbhbz/bzwb/dqhjbh/dqhjzlbz/201203/t20120302_224165.htm, accessed 10 July 2012.

Mercer LD, Szpiro AA, Sheppard L, Lindström J, Adar SD, Allen RW et al. (2011). Comparing universal kriging and land-use regression for predicting concentrations of gaseous oxides of nitrogen (NO_x) for the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air). *Atmos Environ (1994)*, 45(26):4412–20. doi:10.1016/j.atmosenv.2011.05.043 PMID:21808599

Meslmani Y (2004). Some trends related to air pollution in Damascus. *Manag Environ Qual*, 15(4):353–63. doi:10.1108/14777830410540108

Mestrot A, Uroic MK, Plantevin T, Islam MR, Krupp EM, Feldmann J et al. (2009). Quantitative and qualitative trapping of arsines deployed to assess loss of volatile arsenic from paddy soil. *Environ Sci Technol*, 43(21):8270–5. doi:10.1021/es9018755 PMID:19924955

Ministry of the Environment of Japan (2011). Air pollution situation in the fiscal year of 2011. Available from: http://www.env.go.jp/air/osen/jokyo_h23/index.html, accessed 29 December 2014.

Mkoma SL, Chi X, Maenhaut W (2010). Characteristics of carbonaceous aerosols in ambient PM_{10} and $PM_{2.5}$ particles in Dar es Salaam, Tanzania. *Sci Total Environ*, 408(6):1308–14. doi:10.1016/j.scitotenv.2009.10.054 PMID:19906404

Mkoma SL, Maenhaut W, Chi X, Wang W, Raes N (2009). Characterisation of PM_{10} atmospheric aerosols for the wet season 2005 at two sites in East Africa. *Atmos Environ*, 43(3):631–9. doi:10.1016/j.atmosenv.2008.10.008

Møller P, Loft S (2010). Oxidative damage to DNA and lipids as biomarkers of exposure to air pollution. *Environ Health Perspect*, 118(8):1126–36. doi:10.1289/ehp.0901725 PMID:20423813

Monn C (2001). Exposure assessment of air pollutants: a review on spatial heterogeneity and indoor/outdoor/personal exposure to suspended particulate matter, nitrogen dioxide and ozone. *Atmos Environ*, 35(1):1–32. doi:10.1016/S1352-2310(00)00330-7

Monn C, Brändli O, Schindler C, Ackermann-Liebrich U, Leuenberger P; Swiss Study on Air Pollution and Lung Diseases in Adults (1998). Personal exposure to nitrogen dioxide in Switzerland. SAPALDIA team. *Sci Total Environ*, 215(3):243–51. doi:10.1016/S0048-9697(98)00124-7 PMID:9606945

Montagne D, Hoek G, Nieuwenhuijsen M, Lanki T, Pennanen A, Portella M et al. (2013). Agreement of land use regression models with personal exposure measurements of particulate matter and nitrogen oxides air pollution. *Environ Sci Technol*, 47(15):8523–31. PMID:23786264

Moon HS, Lee JH, Kwon K, Jung HI (2012). Review of recent progress in micro-systems for the detection and analysis of airborne microorganisms. *Anal Lett*, 45(2–3):113–29. doi:10.1080/00032719.2011.633189

Mukherjee A, Bhattacharya S, Ahmed S, Roy SK, Roychowdhury A, Sen S (2003). Exposure of drivers and conductors to noise, heat, dust and volatile organic compounds in the state transport special buses of Kolkata city. *Transp Res Part D Transp Environ*, 8(1):11–9. doi:10.1016/S1361-9209(02)00015-9

Mullen NA, Liu C, Zhang Y, Wang S, Nazaroff WW (2011). Ultrafine particle concentrations and exposures in four high-rise Beijing apartments. *Atmos Environ*, 45(40):7574–82. doi:10.1016/j.atmosenv.2010.07.060

Munir S, Habeebullah TM, Seroji AR et al. (2013). Modeling particulate matter concentrations in Makkah, applying a statistical modeling approach. *Aerosol Air Quality Research*, 13:901–10.

Naddafi K, Hassanvand MS, Yunesian M, Momeniha F, Nabizadeh R, Faridi S et al. (2012). Health impact assessment of air pollution in megacity of Tehran, Iran. *Iran J Environ Health Sci Eng*, 9(1):28 doi:10.1186/1735-2746-9-28 PMID:23369114

Naess Ø, Nafstad P, Aamodt G, Claussen B, Rosland P (2007). Relation between concentration of air pollution and cause-specific mortality: four-year exposures to nitrogen dioxide and particulate matter pollutants in 470 neighborhoods in Oslo, Norway. *Am J Epidemiol*, 165(4):435–43. doi:10.1093/aje/kwk016 PMID:17135427

Nafstad P, Håheim LL, Oftedal B, Gram F, Holme I, Hjermann I et al. (2003). Lung cancer and air pollution: a 27 year follow up of 16 209 Norwegian men. *Thorax*, 58(12):1071–6. doi:10.1136/thorax.58.12.1071 PMID:14645978

Nafstad P, Håheim LL, Wisløff T, Gram F, Oftedal B, Holme I et al. (2004). Urban air pollution and mortality in a cohort of Norwegian men. *Environ Health Perspect*, 112(5):610–5. doi:10.1289/ehp.6684 PMID:15064169

National Bureau of Statistics of China (2011). *China Statistical Yearbook*. Beijing, China: China Statistics Press.

National Bureau of Statistics of China (2012). *China Statistical Yearbook*. Beijing, China: China Statistics Press.

Niu Y, He L, Hu M, Zhang J, Zhao Y (2006). Pollution characteristics of atmospheric fine particles and their secondary components in the atmosphere of Shenzhen in summer and in winter. *Sci China Ser B*, 49(5):466–74. doi:10.1007/s11426-006-2010-0

Noullett M, Jackson PL, Brauer M (2010). Estimation and characterization of children's ambient generated exposure to $PM_{2.5}$ using sulphate and elemental carbon as tracers. *Atmos Environ*, 44(36):4629–37. doi:10.1016/j.atmosenv.2010.08.004

Novotny EV, Bechle MJ, Millet DB, Marshall JD (2011). National satellite-based land-use regression: NO2 in the United States. *Environ Sci Technol*, 45(10):4407–14. doi:10.1021/es103578x PMID:21520942

Nyberg F, Gustavsson P, Järup L, Bellander T, Berglind N, Jakobsson R et al. (2000). Urban air pollution and lung cancer in Stockholm. *Epidemiology*, 11(5):487–95. doi:10.1097/00001648-200009000-00002 PMID:10955399

O'Neill MS, Jerrett M, Kawachi I, Levy JI, Cohen AJ, Gouveia N et al.; Workshop on Air Pollution and Socioeconomic Conditions (2003). Health, wealth, and air pollution: advancing theory and methods. *Environ Health Perspect*, 111(16):1861–70. doi:10.1289/ehp.6334 PMID:14644658

Oderbolz DC, Aksoyoglu S, Keller J, Barmpadimos I, Steinbrecher R, Skjøth CA et al. (2013). A comprehensive emission inventory of biogenic volatile organic compounds in Europe: improved seasonality and land-cover *Atmos Chem Phys*, 13(4):1689–712. doi:10.5194/acp-13-1689-2013

Ortiz E, Alemón E, Romero D, Arriaga JL, Olaya P, Guzmán F et al. (2002). Personal exposure to benzene, toluene and xylene in different microenvironments at the Mexico City metropolitan zone. *Sci Total Environ*, 287(3):241–8. doi:10.1016/S0048-9697(01)00986-X PMID:11993966

Ozkurt N, Sari D, Akalin N, Hilmioglu B (2013). Evaluation of the impact of SO_2 and NO_2 emissions on the ambient air-quality in the Çan-Bayramiç region of northwest Turkey during 2007–2008. *Sci Total Environ*, 456–457:254–66. doi:10.1016/j.scitotenv.2013.03.096 PMID:23602979

Pachon JE, Balachandran S, Hu Y, Mulholland JA, Darrow LA, Sarnat JA et al. (2012). Development of outcome-based, multipollutant mobile source indicators. *J Air*

Waste Manag Assoc, 62(4):431–42. doi:10.1080/10473289.2012.656218 PMID:22616285

Pacyna EG, Pacyna JM, Sundseth K, Munthe J, Kindbom K, Wilson S et al. (2010). Global emission of mercury to the atmosphere from anthropogenic sources in 2005 and projections to 2020. *Atmos Environ*, 44(20):2487–99. doi:10.1016/j.atmosenv.2009.06.009

Pan X, Yang M, Fan T (2008). Time-series analysis of air pollution and cardiovascular mortality in Beijing, China. *Epidemiology*, 19:S170–S171.

Parrish DD, Singh HB, Molina L, Madronich S (2011). Air quality progress in North American megacities: a review. *Atmos Environ*, 45(39):7015–25. doi:10.1016/j.atmosenv.2011.09.039

Pegues AH, Cohan DS, Digar A, Douglass C, Wilson RS (2012). Efficacy of recent state implementation plans for 8-hour ozone. *J Air Waste Manag Assoc*, 62(2):252–61. doi:10.1080/10473289.2011.646049 PMID:22442941

Peltier RE, Hsu SI, Lall R, Lippmann M (2009). Residual oil combustion: a major source of airborne nickel in New York City. *J Expo Sci Environ Epidemiol*, 19(6):603–12. doi:10.1038/jes.2008.60 PMID:18841166

Petkova EP, Jack DW, Volavka-Close NH, Kinney PL (2013). Particulate matter pollution in African cities. *Air Qual Atmos Health,* 6(3):603–14.

Putaud J, Raes F, Van Dingenen R, Brüggemann E, Facchini M-C, Decesari S et al. (2004). A European aerosol phenomenology – 2: chemical characteristics of particulate matter at kerbside, urban, rural and background sites in Europe. *Atmos Environ*, 38(16):2579–95. doi:10.1016/j.atmosenv.2004.01.041

Putaud JP, Van Dingenen R, Alastuey A, Bauer H, Birmili W, Cyrys J et al. (2010). A European aerosol phenomenology – 3: physical and chemical characteristics of particulate matter from 60 rural, urban, and kerbside sites across Europe. *Atmos Environ*, 44(10):1308–20. doi:10.1016/j.atmosenv.2009.12.011

Puustinen A, Hämeri K, Pekkanen J, Kulmala M, de Hartog J, Meliefste K et al. (2007). Spatial variation of particle number and mass over four European cities. *Atmos Environ*, 41(31):6622–36. doi:10.1016/j.atmosenv.2007.04.020

Qatar General Secretariat for Development Planning (2011). Qatar National Development Strategy 2011–2016. Doha, Qatar: Qatar General Secretariat for Development Planning. Available from: www.gsdp.gov.qa/gsdp_vision/docs/NDS_EN.pdf, accessed 7 July 2015.

Qian Z, He Q, Lin H-M, Kong L, Liao D, Yang N et al. (2007). Short-term effects of gaseous pollutants on cause-specific mortality in Wuhan, China. *J Air Waste Manag Assoc*, 57(7):785–93. doi:10.3155/1047-3289.57.7.785 PMID:17687993

Quass U, Fermann M, Bröker G (2004). The European dioxin air emission inventory project–final results. *Chemosphere*, 54(9):1319–27. doi:10.1016/S0045-6535(03)00251-0 PMID:14659425

Querol X, Viana M, Alastuey A, Amato F, Moreno T, Castillo S et al. (2007). Source origin of trace elements in PM from regional background, urban and industrial sites of Spain. *Atmos Environ*, 41(34):7219–31. doi:10.1016/j.atmosenv.2007.05.022

Raaschou-Nielsen O, Andersen ZJ, Hvidberg M, Jensen SS, Ketzel M, Sørensen M et al. (2011). Lung cancer incidence and long-term exposure to air pollution from traffic. *Environ Health Perspect*, 119(6):860–5. doi:10.1289/ehp.1002353 PMID:21227886

Raaschou-Nielsen O, Bak H, Sørensen M, Jensen SS, Ketzel M, Hvidberg M et al. (2010). Air pollution from traffic and risk for lung cancer in three Danish cohorts. *Cancer Epidemiol Biomarkers Prev*, 19(5):1284–91. doi:10.1158/1055-9965.EPI-10-0036 PMID:20447920

Ratafia-Brown JA (1994). Overview of trace element partitioning in flames and furnaces of utility coal-fired boilers. *Fuel Process Technol*, 39(1–3):139–57. doi:10.1016/0378-3820(94)90177-5

Reff A, Bhave PV, Simon H, Pace TG, Pouliot GA, Mobley JD et al. (2009). Emissions inventory of $PM_{2.5}$ trace elements across the United States. *Environ Sci Technol*, 43(15):5790–6. doi:10.1021/es802930x PMID:19731678

Ren Y, Li X, Jing M et al. (2007). The case-crossover studies of air particulate matter pollution and cardiovascular disease death [in Chinese]. *China Environ Sci*, 27:657–660.

RFF (2005). Assessment of Colombia's national environmental system (SINA), 64. Washington (DC): Resources for the Future. Available from: http://www.rff.org/rff/documents/rff-rpt-sina.pdf, accessed 29 January 2015.

Ries FJ, Marshall JD, Brauer M (2009). Intake fraction of urban wood smoke. *Environ Sci Technol*, 43(13):4701–6. doi:10.1021/es803127d PMID:19673254

Rijnders E, Janssen NA, van Vliet PH, Brunekreef B (2001). Personal and outdoor nitrogen dioxide concentrations in relation to degree of urbanization and traffic density. *Environ Health Perspect*, 109(s3):Suppl 3: 411–7. doi:10.1289/ehp.01109s3411 PMID:11429326

Ruchirawat M, Mahidol C, Tangjarukij C, Pui-ock S, Jensen O, Kampeerawipakorn O et al. (2002). Exposure to genotoxins present in ambient air in Bangkok, Thailand–particle associated polycyclic aromatic hydrocarbons and biomarkers. *Sci Total Environ*, 287(1–2):121–32. doi:10.1016/S0048-9697(01)01008-7 PMID:11883753

Ruchirawat M, Navasumrit P, Settachan D, Tuntaviroon J, Buthbumrung N, Sharma S (2005). Measurement of genotoxic air pollutant exposures in street vendors and school children in and near Bangkok. *Toxicol Appl Pharmacol*, 206(2):207–14. doi:10.1016/j.taap.2004.11.025 PMID:15967210

Rushdi AI, Al-Mutlaq KF, Al-Otaibi M, El-Mubarak AH, Simoneit BRT (2013). Air quality and elemental

enrichment factors of aerosol particulate matter in Riyadh City, Saudi Arabia. *Arab J Geosci*, 6(2):585–99. doi:10.1007/s12517-011-0357-9

Ryerson TB, Buhr MP, Frost GJ, Goldan PD, Holloway JS, Hübler G et al. (1998). Emissions lifetimes and ozone formation in power plant plumes. *J Geophys Res Atmos*, 103:D17: 22569–83. doi:10.1029/98JD01620

Rylance J, Gordon SB, Naeher LP, Patel A, Balmes JR, Adetona O et al. (2013). Household air pollution: a call for studies into biomarkers of exposure and predictors of respiratory disease. *Am J Physiol Lung Cell Mol Physiol*, 304(9):L571–8. doi:10.1152/ajplung.00416.2012 PMID:23457186

Saffarini G, Odat O (2008). Time series analysis of air pollution in Al-Hashimeya Town Zarqa, Jordan. *Jordan J Earth Environ Sci*, 1(2):63–72.

Sahsuvaroglu T, Su JG, Brook J, Burnett R, Loeb M, Jerrett M (2009). Predicting personal nitrogen dioxide exposure in an elderly population: integrating residential indoor and outdoor measurements, fixed-site ambient pollution concentrations, modeled pollutant levels, and time-activity patterns. *J Toxicol Environ Health A*, 72(23):1520–33. doi:10.1080/15287390903129408 PMID:20077226

Saksena S, Prasad R, Shankar V (2007). Daily exposure to air pollutants in indoor, outdoor and in-vehicle micro-environments: a pilot study in Delhi. *Indoor Built Environ*, 16(1):39–46. doi:10.1177/1420326X06074715

Saliba NA, El Jam F, El Tayar G, Obeid W, Roumie M (2010). Origin and variability of particulate matter (PM_{10} and $PM_{2.5}$) mass concentrations over an Eastern Mediterranean city. *Atmos Res*, 97(1–2):106–14. doi:10.1016/j.atmosres.2010.03.011

Sarnat JA, Long CM, Koutrakis P, Coull BA, Schwartz J, Suh HH (2002). Using sulfur as a tracer of outdoor fine particulate matter. *Environ Sci Technol*, 36(24):5305–14. doi:10.1021/es025796b PMID:12521154

Sarnat JA, Moise T, Shpund J, Liu Y, Pachon JE, Qasrawi R et al. (2010). Assessing the spatial and temporal variability of fine particulate matter components in Israeli, Jordanian, and Palestinian cities. *Atmos Environ*, 44(20):2383–92. doi:10.1016/j.atmosenv.2010.04.007

Sarnat SE, Coull BA, Ruiz PA, Koutrakis P, Suh HH (2006). The influences of ambient particle composition and size on particle infiltration in Los Angeles, CA, residences. *J Air Waste Manag Assoc*, 56(2):186–96. doi:10.1080/10473289.2006.10464449 PMID:16568802

Schauer C, Niessner R, Pöschl U (2003). Polycyclic aromatic hydrocarbons in urban air particulate matter: decadal and seasonal trends, chemical degradation, and sampling artifacts. *Environ Sci Technol*, 37(13):2861–8. doi:10.1021/es034059s PMID:12875387

Schauer JJ, Lough GC, Shafer MM, Christensen WF, Arndt MF, DeMinter JT et al. (2006). Characterization of metals emitted from motor vehicles. *Res Rep Health Eff Inst*, 133(133):1–76, discussion 77–88. PMID:16669575

Schauer JJ, Rogge WF, Hildemann LM, Mazurek MA, Cass GR, Simoneit BRT (1996). Source apportionment of airborne particulate matter using organic compounds as tracers. *Atmos Environ*, 30(22):3837–55. doi:10.1016/1352-2310(96)00085-4

Scheepers PT (2008). The use of biomarkers for improved retrospective exposure assessment in epidemiological studies: summary of an ECETOC workshop. *Biomarkers*, 13(7):734–48. doi:10.1080/13547500802528630 PMID:18985470

Secretaría del Medio Ambiente (2013). SIMAT. Available from: http://www.sedema.df.gob.mx/, accessed 31 October 2014.

Seinfeld JH, Pandis S (2006). Atmospheric chemistry and physics. 2nd ed. Hoboken (NJ): John Wiley.

SETRAVI (2007). Informe SETRAVI. Enero-agosto de 2007. Mexico City: Secretaría de Transportes y Vialidad (SETRAVI), Gobierno del Distrito Federal Mexico D.F.

Setton E, Hystad P, Poplawski K, Cheasley R, Cervantes-Larios A, Keller CP et al. (2013). Risk-based indicators of Canadians' exposures to environmental carcinogens. *Environ Health*, 12(1):15 doi:10.1186/1476-069X-12-15 PMID:23398723

Setton E, Marshall JD, Brauer M, Lundquist KR, Hystad P, Keller P et al. (2011). The impact of daily mobility on exposure to traffic-related air pollution and health effect estimates. *J Expo Sci Environ Epidemiol*, 21(1):42–8. doi:10.1038/jes.2010.14 PMID:20588325

Shang Y, Sun Z, Cao J, Wang X, Zhong L, Bi X et al. (2013). Systematic review of Chinese studies of short-term exposure to air pollution and daily mortality. *Environ Int*, 54:100–11. doi:10.1016/j.envint.2013.01.010 PMID:23434817

Sheesley RJ, Schauer JJ, Zheng M, Wang B (2007). Sensitivity of molecular marker-based CMB models to biomass burning source profiles. *Atmos Environ*, 41(39):9050–63. doi:10.1016/j.atmosenv.2007.08.011

Shen H, Huang Y, Wang R, Zhu D, Li W, Shen G et al. (2013). Global atmospheric emissions of polycyclic aromatic hydrocarbons from 1960 to 2008 and future predictions. *Environ Sci Technol*, 47(12):6415–24. PMID:23659377

SINAICA (2011). Dirección de Investigación sobre la Calidad del Aire. Instituto National de ecologia y Cambio climatico. Mexico City: National Information System for Air Quality (SINAICA). Available from: http://sinaica.ine.gob.mx/, accessed 22 January 2015.

Smith SJ, van Aardenne J, Klimont Z, Andres RJ, Volke A, Delgado Arias S (2011). Anthropogenic sulfur dioxide emissions: 1850–2005. *Atmos Chem Phys*, 11(3):1101–16. doi:10.5194/acp-11-1101-2011

Snyder DC, Rutter AP, Collins R, Worley C, Schauer JJ (2009a). Insights into the origin of water soluble organic carbon in atmospheric fine particulate matter. *Aerosol Sci Technol*, 43(11):1099–107. doi:10.1080/02786820903188701

Snyder DC, Schauer JJ, Gross DS, Turner JR (2009b). Estimating the contribution of point sources to atmospheric metals using single-particle mass spectrometry. *Atmos Environ*, 43(26):4033–42. doi:10.1016/j.atmosenv.2009.05.011

Sovacool BK (2011). The policy challenges of tradable credits: a critical review of eight markets. *Energy Policy*, 39(2):575–85. doi:10.1016/j.enpol.2010.10.029

Stedman JR, Vincent KJ, Campbell GW, Goodwin JWL, Downing CEH (1997). New high resolution maps of estimated background ambient NO_x and NO_2 concentrations in the UK. *Atmos Environ*, 31(21):3591–602. doi:10.1016/S1352-2310(97)00159-3

Steinle S, Reis S, Sabel CE (2013). Quantifying human exposure to air pollution–moving from static monitoring to spatio-temporally resolved personal exposure assessment. *Sci Total Environ*, 443:184–93. doi:10.1016/j.scitotenv.2012.10.098 PMID:23183229

Stetzenbach LD, Buttner MP, Cruz P (2004). Detection and enumeration of airborne biocontaminants. *Curr Opin Biotechnol*, 15(3):170–4. doi:10.1016/j.copbio.2004.04.009 PMID:15193322

Stone EA, Schauer JJ, Pradhan BB, Dangol PM, Habib G, Venkataraman C et al. (2010). Characterization of emissions from South Asian biofuels and application to source apportionment of carbonaceous aerosol in the Himalayas. *J Geophys Res Atmos*, 115:D6:D06301. doi:10.1029/2009JD011881

Stone EA, Snyder DC, Sheesley RJ, Sullivan AP, Weber RJ, Schauer JJ (2008). Source apportionment of fine organic aerosol in Mexico City during the MILAGRO experiment 2006. *Atmos Chem Phys*, 8(5):1249–59. doi:10.5194/acp-8-1249-2008

Tao Y, Zhong L, Huang X, Lu SE, Li Y, Dai L et al. (2011). Acute mortality effects of carbon monoxide in the Pearl River Delta of China. *Sci Total Environ*, 410–411:34–40. doi:10.1016/j.scitotenv.2011.09.004 PMID:21978618

Tchuente SYF, Saidou S, Yakum NY, Kenmoe NX, Abdourahimi A (2013). Monitoring of particulate matter and analysis of black carbon and some particle containing toxic trace in the city of Yaoundé, Cameroon. *Asian J Atmos Environ*, 7(2):120–8. doi:10.5572/ajae.2013.7.2.120

Tian H, Gao J, Lu L, Zhao D, Cheng K, Qiu P (2012). Temporal trends and spatial variation characteristics of hazardous air pollutant emission inventory from municipal solid waste incineration in China. *Environ Sci Technol*, 46(18):10364–71. PMID:22920612

Tørseth K, Aas W, Breivik K, Fjæraa AM, Fiebig M, Hjellbrekke AG et al. (2012). Introduction to the European Monitoring and Evaluation Programme (EMEP) and observed atmospheric composition change during 1972–2009. *Atmos Chem Phys*, 12(12):5447–81. doi:10.5194/acp-12-5447-2012

Tovalin H, Valverde M, Morandi MT, Blanco S, Whitehead L, Rojas E (2006). DNA damage in outdoor workers occupationally exposed to environmental air pollutants. *Occup Environ Med*, 63(4):230–6. doi:10.1136/oem.2005.019802 PMID:16556741

Tovalin-Ahumada H, Whitehead L (2007). Personal exposures to volatile organic compounds among outdoor and indoor workers in two Mexican cities. *Sci Total Environ*, 376(1-3):60–71. doi:10.1016/j.scitotenv.2007.01.063 PMID:17306862

Turner MC, Krewski D, Pope CA 3rd, Chen Y, Gapstur SM, Thun MJ (2011). Long-term ambient fine particulate matter air pollution and lung cancer in a large cohort of never-smokers. *Am J Respir Crit Care Med*, 184(12):1374–81. doi:10.1164/rccm.201106-1011OC PMID:21980033

UNEP (2008). The global atmospheric mercury assessment: sources, emissions and transport. Geneva, Switzerland: United Nations Environment Programme, Chemicals Branch. Available from: http://www.unep.org/chemicalsandwaste/Portals/9/Mercury/Documents/Publications/UNEP_GlobalAtmosphericMercuryAssessment_May2009.pdf, accessed 18 June 2015.

Unger N, Bond TC, Wang JS, Koch DM, Menon S, Shindell DT et al. (2010). Attribution of climate forcing to economic sectors. *Proc Natl Acad Sci USA*, 107(8):3382–7. doi:10.1073/pnas.0906548107 PMID:20133724

Urayama KY, Von Behren J, Reynolds P, Hertz A, Does M, Buffler PA (2009). Factors associated with residential mobility in children with leukemia: implications for assigning exposures. *Ann Epidemiol*, 19(11):834–40. doi:10.1016/j.annepidem.2009.03.001 PMID:19364662

Vahlsing C, Smith KR (2012). Global review of national ambient air quality standards for PM(10) and SO(2) (24 h). *Air Qual Atmos Health*, 5(4):393–9. doi:10.1007/s11869-010-0131-2 PMID:23205158

Valero N, Aguilera I, Llop S, Esplugues A, de Nazelle A, Ballester F et al. (2009). Concentrations and determinants of outdoor, indoor and personal nitrogen dioxide in pregnant women from two Spanish birth cohorts. *Environ Int*, 35(8):1196–201. doi:10.1016/j.envint.2009.08.002 PMID:19740538

Van Dingenen R, Raes F, Putaud J, Baltensperger U, Charron A, Facchini M-C et al. (2004). A European aerosol phenomenology-1: physical characteristics of particulate matter at kerbside, urban, rural and background sites in Europe. *Atmos Environ*, 38(16):2561–77. doi:10.1016/j.atmosenv.2004.01.040

van Donkelaar A, Martin RV, Brauer M, Kahn R, Levy R, Verduzco C et al. (2010). Global estimates of ambient fine particulate matter concentrations from satellite-based aerosol optical depth: development and application. *Environ Health Perspect*, 118(6):847–55. doi:10.1289/ehp.0901623 PMID:20519161

Van Roosbroeck S, Hoek G, Meliefste K, Janssen NA, Brunekreef B (2008). Validity of residential traffic intensity as an estimate of long-term personal exposure

to traffic-related air pollution among adults. *Environ Sci Technol*, 42(4):1337–44. doi:10.1021/es0712827 PMID:18351114

van Roosbroeck S, Jacobs J, Janssen NAH, Oldenwening M, Hoek G, Brunekreef B (2007). Long-term personal exposure to $PM_{2.5}$, soot and NO_x in children attending schools located near busy roads, a validation study. *Atmos Environ*, 41(16):3381–94. doi:10.1016/j.atmosenv.2006.12.023

van Vliet EDS, Kinney PL (2007). Impacts of roadway emissions on urban particulate matter concentrations in sub-Saharan Africa: new evidence from Nairobi, Kenya. *Environ Res Lett*, 2(4):1–5. doi:10.1088/1748-9326/2/4/045028

Venners SA, Wang B, Xu Z, Schlatter Y, Wang L, Xu X (2003). Particulate matter, sulfur dioxide, and daily mortality in Chongqing, China. *Environ Health Perspect*, 111(4):562–7. doi:10.1289/ehp.5664 PMID:12676616

Vestreng V, Myhre G, Fagerli H, Reis S, Tarrasón L (2007). Twenty-five years of continuous sulphur dioxide emission reduction in Europe. *Atmos Chem Phys*, 7(13):3663–81. doi:10.5194/acp-7-3663-2007

Vestreng V, Ntziachristos L, Semb A, Reis S, Isaksen ISA, Tarrasón L (2009). Evolution of NO_x emissions in Europe with focus on road transport control measures. *Atmos Chem Phys*, 9(4):1503–20. doi:10.5194/acp-9-1503-2009

von Schneidemesser E, Zhou JB, Stone EA, Schauer JJ, Qasrawi R, Abdeen Z et al. (2010). Seasonal and spatial trends in the sources of fine particle organic carbon in Israel, Jordan, and Palestine. *Atmos Environ*, 44(30):3669–78. doi:10.1016/j.atmosenv.2010.06.039

Wallace L (2000). Correlations of personal exposure to particles with outdoor air measurements: a review of recent studies. *Aerosol Sci Technol*, 32(1):15–25. doi:10.1080/027868200303894

Wallace L, Ott W (2011). Personal exposure to ultrafine particles. *J Expo Sci Environ Epidemiol*, 21(1):20–30. doi:10.1038/jes.2009.59 PMID:20087407

Wang J, Zhu LZ, Liu YJ (2002). Pattern of polycyclic aromatic hydrocarbons (PAHs) pollution in communication air of Hangzhou, China. *J Environ Sci (China)*, 14(2):145–50. PMID:12046280

Wang R, Henderson SB, Sbihi H, Allen RW, Brauer M (2013). Temporal stability of land use regression models for traffic-related air pollution. *Atmos Environ*, 64:312–9. doi:10.1016/j.atmosenv.2012.09.056

Wang X, Bi X, Sheng G, Fu J (2006). Chemical composition and sources of PM_{10} and $PM_{2.5}$ aerosols in Guangzhou, China. *Environ Monit Assess*, 119(1-3):425–39. doi:10.1007/s10661-005-9034-3 PMID:16741816

Wang Y, Qi F, Lun X, Sun D (2010). Temporal and spatial distribution rule of volatile organic compounds in ambient air around urban traffic roads in Beijing [in Chinese]. *Res Environ Sci.*, 23(5):596–600.

Wang Y, Turnbull AB, Harrison RM (1997). Concentrations, phase partitioning and deposition of specific alkyl-lead compounds in the atmosphere. *Appl Organomet Chem*, 11(10–11):889–901. doi:10.1002/(SICI)1099-0739(199710/11)11:10/11<889::AID-AOC657>3.0.CO;2-T

Watson JG (2002). Visibility: science and regulation. *J Air Waste Manag Assoc*, 52(6):628–713. doi:10.1080/10473289.2002.10470813 PMID:12074426

Watson JG, Chow JC, Lowenthal DH, Magliano KL (2008). Estimating aerosol light scattering at the Fresno Supersite. *Atmos Environ*, 42(6):1186–96. doi:10.1016/j.atmosenv.2007.10.040

Watson JG, Chow JC, Tropp RJ, Wang X, Kohl SD, Chen LWA (2013). Standards and traceability for air quality measurements: flow rates and gaseous pollutants. *Mapan-J Metrol Soc India*, 28(3):167–79

Wei E, Wang Y, Shi T, Yin Y, Li L, Wu Y (2011). Study on the pollution characteristic of VOCs in ambient air of Anshan [in Chinese]. *Environ Pollut Control*, 33(6):61–70.

Wei S, Teng M, Fu Q, Zhang Y (2007). Pollution characteristic and source analysis of BTEX in ambient air of Olympic Gymnasium before and after traffic restriction [in Chinese]. *Environ Monit China*, 23:48–52.

Weschler CJ (2009). Changes in indoor pollutants since the 1950s. *Atmos Environ*, 43(1):153–69. doi:10.1016/j.atmosenv.2008.09.044

Wexler AS, Johnston MV (2008). What have we learned from highly time-resolved measurements during EPA's Supersites Program and related studies? *J Air Waste Manag Assoc*, 58(2):303–19. doi:10.3155/1047-3289.58.2.303 PMID:18318343

WHO (2006). Air quality guidelines for particulate matter, ozone, nitrogen dioxide and sulfur dioxide. Global update 2005. Summary of risk assessment. WHO/SDE/PHE/OEH/06.02. Geneva, Switzerland: World Health Organization. Available from: http://www.euro.who.int/__data/assets/pdf_file/0005/78638/E90038.pdf, accessed 17 December 2014.

WHO (2011). Urban outdoor air pollution database. Geneva, Switzerland: World Health Organization, Department of Public Health and Environment. Available from: http://www.who.int/phe/health_topics/outdoorair/databases/en/index.html, accessed 29 January 2015.

Wichmann J, Janssen N, Vanderzee S, Brunekreef B (2005). Traffic-related differences in indoor and personal absorption coefficient measurements in Amsterdam, the Netherlands. *Atmos Environ*, 39(38):7384–92. doi:10.1016/j.atmosenv.2005.09.015

Wichmann J, Lind T, Nilsson MA-M, Bellander T (2010). $PM_{2.5}$, soot and NO_2 indoor-outdoor relationships at homes, pre-schools and schools in Stockholm, Sweden. *Atmos Environ*, 44(36):4536–44. doi:10.1016/j.atmosenv.2010.08.023

Wichmann J, Voyi K (2012). Ambient air pollution exposure and respiratory, cardiovascular and cerebrovascular mortality in Cape Town, South Africa: 2001–2006. *Int J Environ Res Public Health*, 9(11):3978–4016. doi:10.3390/ijerph9113978 PMID:23202828

Williams ML, Carslaw DC (2011). New directions: Science and policy – out of step on NO_x and NO_2? *Atmos Environ*, 45(23):3911–2. doi:10.1016/j.atmosenv.2011.04.067

Wilson WE, Brauer M (2006). Estimation of ambient and non-ambient components of particulate matter exposure from a personal monitoring panel study. *J Expo Sci Environ Epidemiol*, 16(3):264–74. doi:10.1038/sj.jes.7500483 PMID:16617313

Wilson WE, Chow JC, Claiborn C, Fusheng W, Engelbrecht J, Watson JG (2002). Monitoring of particulate matter outdoors. *Chemosphere*, 49(9):1009–43. doi:10.1016/S0045-6535(02)00270-9 PMID:12492163

Wilson WE, Mage DT, Grant LD (2000). Estimating separately personal exposure to ambient and nonambient particulate matter for epidemiology and risk assessment: why and how. *J Air Waste Manag Assoc*, 50(7):1167–83. doi:10.1080/10473289.2000.10464164 PMID:10939210

Wong C-M, Ou C-Q, Chan K-P, Chau YK, Thach TQ, Yang L et al. (2008a). The effects of air pollution on mortality in socially deprived urban areas in Hong Kong, China. *Environ Health Perspect*, 116(9):1189–94. doi:10.1289/ehp.10850 PMID:18795162

Wong C-M, Vichit-Vadakan N, Kan H, Qian Z (2008b). Public Health and Air Pollution in Asia (PAPA): a multicity study of short-term effects of air pollution on mortality. *Environ Health Perspect*, 116(9):1195–202. doi:10.1289/ehp.11257 PMID:18795163

Wong T-W, Tam WS, Yu T-S, Wong AHS (2002). Associations between daily mortalities from respiratory and cardiovascular diseases and air pollution in Hong Kong, China. *Occup Environ Med*, 59(1):30–5. doi:10.1136/oem.59.1.30 PMID:11836466

Worobiec A, Potgieter-Vermaak SS, Berghmans P, Winkler H, Burger R, Van Grieken R (2011). Air particulate emissions in developing countries: a case study in South Africa. *Anal Lett*, 44(11):1907–24. doi:10.1080/00032719.2010.539734

Yang C, Peng X, Huang W, Chen R, Xu Z, Chen B et al. (2012a). A time-stratified case-crossover study of fine particulate matter air pollution and mortality in Guangzhou, China. *Int Arch Occup Environ Health*, 85(5):579–85. doi:10.1007/s00420-011-0707-7 PMID:21960028

Yang C, Yang H, Guo S, Wang Z, Xu X, Duan X et al. (2012b). Alternative ozone metrics and daily mortality in Suzhou: the China Air Pollution and Health Effects Study (CAPES). *Sci Total Environ*, 426:83–9. doi:10.1016/j.scitotenv.2012.03.036 PMID:22521098

Yeo HG, Kim JH (2002). SPM and fungal spores in the ambient air of west Korea during the Asian dust (yellow sand) period. *Atmos Environ*, 36(35):5437–42. doi:10.1016/S1352-2310(02)00672-6

Yin JX, Harrison RM (2008). Pragmatic mass closure study for $PM_{1.0}$, $PM_{2.5}$ and PM_{10} at roadside, urban background and rural sites. *Atmos Environ*, 42(5):980–8. doi:10.1016/j.atmosenv.2007.10.005

Yorifuji T, Kashima S, Tsuda T, Ishikawa-Takata K, Ohta T, Tsuruta K et al. (2013). Long-term exposure to traffic-related air pollution and the risk of death from hemorrhagic stroke and lung cancer in Shizuoka, Japan. *Sci Total Environ*, 443:397–402. doi:10.1016/j.scitotenv.2012.10.088 PMID:23208275

Yorifuji T, Kashima S, Tsuda T, Takao S, Suzuki E, Doi H et al. (2010). Long-term exposure to traffic-related air pollution and mortality in Shizuoka, Japan. *Occup Environ Med*, 67(2):111–7. doi:10.1136/oem.2008.045542 PMID:19773277

Yu ITS, Zhang YH, Tam WWS, Yan QH, Xu Y, Xun X et al. (2012). Effect of ambient air pollution on daily mortality rates in Guangzhou, China. *Atmos Environ*, 46:528–35. doi:10.1016/j.atmosenv.2011.07.055

Zabiegała B, Kot-Wasik A, Urbanowicz M, Namieśnik J (2010). Passive sampling as a tool for obtaining reliable analytical information in environmental quality monitoring. *Anal Bioanal Chem*, 396(1):273–96. doi:10.1007/s00216-009-3244-4 PMID:19924407

Zhang B, Xu H, Yu JC (2002). Determination of total gaseous selenium in atmosphere by honeycomb denuder/differential pulse cathodic stripping voltammetry. *Talanta*, 57(2):323–31. doi:10.1016/S0039-9140(02)00025-5 PMID:18968633

Zhang DH, Ma YL, He KB, Duan FK, Jia YT, Okuda T et al. (2006a). Characteristics of polycyclic aromatic hydrocarbons (PAHS) on airborne particulates in Beijing [in Chinese]. *Huan Jing Ke Xue*, 27(7):1269–75. PMID:16881293

Zhang G, Du S, Liu Z et al. (2010a). Regional background value investigation and health risk evaluation of PAHs in Shandong province atmospheric particles. In: Proceedings: 2010 International Conference on Digital Manufacturing and Automation (ICDMA 2010). Piscataway (NJ): The Institute of Electrical and Electronics Engineers; pp. 145–8.

Zhang J, Guo Y, Meng H et al. (2010b). Time-series analysis on relationship between air pollution and daily mortality in Chaoyang District, Beijing [in Chinese]. *J Environ Health*, 27:797–800.

Zhang J, Wang Y, Wu F, Wang S (2009b). Difference between workday and non-workday of BTEX concentration in Beijing urban area [in Chinese]. *Environ Chem*, 28:112–116.

Zhang Q, Jimenez JL, Canagaratna MR, Allan JD, Coe H, Ulbrich I et al. (2007). Ubiquity and dominance of oxygenated species in organic aerosols in anthropogenically-influenced Northern Hemisphere

midlatitudes. *Geophys Res Lett*, 34(13):L13801. doi:10.1029/2007GL029979

Zhang Y, Huang W, London SJ, Song G, Chen G, Jiang L et al. (2006b). Ozone and daily mortality in Shanghai, China. *Environ Health Perspect*, 114(8):1227–32. doi:10.1289/ehp.9014 PMID:16882530

Zhang Y, Sheesley RJ, Schauer JJ, Lewandowski M, Jaoui M, Offenberg JH et al. (2009a). Source apportionment of primary and secondary organic aerosols using positive matrix factorization (PMF) of molecular markers. *Atmos Environ*, 43(34):5567–74. doi:10.1016/j.atmosenv.2009.02.047

Zhang YS, Zhou MG, Jia YP, Hu YS, Zhang JL, Jiang GH et al. (2010c). Time-series analysis of association between inhalable particulate matter and daily mortality among urban residents in Tianjin [in Chinese]. *Zhonghua Liu Xing Bing Xue Za Zhi*, 31(5):544–8. PMID:21163034

Zhao Y, Kreisberg NM, Worton DR, Isaacman G, Weber RJ, Liu S et al. (2013). Insights into secondary organic aerosol formation mechanisms from measured gas/particle partitioning of specific organic tracer compounds. *Environ Sci Technol*, 47(8):3781–7. doi:10.1021/es304587x PMID:23448102

Zheng M, Cass GR, Schauer JJ, Edgerton ES (2002). Source apportionment of $PM_{2.5}$ in the Southeastern United States using solvent-extractable organic compounds as tracers. *Environ Sci Technol*, 36(11):2361–71. doi:10.1021/es011275x PMID:12075791

Zheng M, Salmon LG, Schauer JJ, Zeng L, Kiang CS, Zhang Y et al. (2005). Seasonal trends in $PM_{2.5}$ source contributions in Beijing, China. *Atmos Environ*, 39(22):3967–76. doi:10.1016/j.atmosenv.2005.03.036

Zhou YM, Hao ZP, Wang HL (2011). Pollution and source of atmospheric volatile organic compounds in urban-rural juncture belt area in Beijing [in Chinese]. *Huan Jing Ke Xue*, 32(12):3560–5. PMID:22468518

Zhu L, Lu H, Chen S, Amagai T (2009). Pollution level, phase distribution and source analysis of polycyclic aromatic hydrocarbons in residential air in Hangzhou, China. *J Hazard Mater*, 162(2-3):1165–70. doi:10.1016/j.jhazmat.2008.05.150 PMID:18640778

Zou SC, Lee SC, Chan CY, Ho KF, Wang XM, Chan LY et al. (2003). Characterization of ambient volatile organic compounds at a landfill site in Guangzhou, South China. *Chemosphere*, 51(9):1015–22. doi:10.1016/S0045-6535(03)00004-3 PMID:12697192

Zuurbier M, Hoek G, Oldenwening M, Lenters V, Meliefste K, van den Hazel P et al. (2010). Commuters' exposure to particulate matter air pollution is affected by mode of transport, fuel type, and route. *Environ Health Perspect*, 118(6):783–9. doi:10.1289/ehp.0901622 PMID:20185385

2. CANCER IN HUMANS

2.1 Cancer of the lung

2.1.1 Cohort studies in North America

See Table 2.1.

To date, the association of exposure to outdoor air pollution with lung cancer risk has been assessed in six North American cohort studies: the Harvard Six Cities Study, the American Cancer Society study, the Adventist Health Study on Smog, the Trucking Industry Particle Study, the California Teachers Study, and the Ontario Tax Cohort Study. However, there have been multiple publications from the first three studies, representing different periods of follow-up and/or selected subsets of the population.

(a) Harvard Six Cities Study

The Harvard Six Cities Study was designed specifically to evaluate exposures to outdoor air pollution and their association with health among 8111 White adults aged 25–74 years recruited from six cities in the eastern USA representing a range of air pollution exposures: Steubenville, Ohio, and St. Louis, Missouri (high exposure); Watertown, Massachusetts, and Kingston-Harriman, Tennessee (medium exposure); and Portage (including Wyocena and Pardeeville), Wisconsin, and Topeka, Kansas (low exposure). Follow-up began between 1975 and 1977 in each city, and each participant completed a baseline questionnaire. Active follow-up, including information on vital status, continued by mail until 1991 (Dockery et al., 1993). In addition, the cohort was followed up through searches of the National Death Index, with the last update in 2009 (Lepeule et al., 2012).

Three follow-ups of the Harvard Six Cities Study have been published: through 1989 or 1991 (determined by the last date of search of the National Death Index or the ending date of the study, respectively) (Dockery et al., 1993), through 1998 (Laden et al., 2006), and through 2009 (Lepeule et al., 2012). Between 1979 and 1986–1988 (depending on the city) the researchers measured outdoor concentrations of total suspended particles (TSP), sulfur dioxide (SO_2), ozone, suspended sulfates, and particulate matter (PM) with particles of aerodynamic diameter less than 2.5 μm ($PM_{2.5}$), less than 15 μm (PM_{15}) (before 1984), and less than 10 μm (PM_{10}) (after 1984) at central site air-monitoring stations in each community (Dockery et al., 1993; Laden et al., 2006). Measurements of PM_{10} from routine air-quality monitoring stations are available from monitors located near the original central sites in each community starting in 1985, and measurements of $PM_{2.5}$ are available starting in 1999. For follow-up after 1999, these measurements were used to obtain city-specific annual average $PM_{2.5}$ concentrations from representative monitors within 80 km of the original sampling locations (Lepeule et al., 2012). For the period between the end of the original monitoring activity and 1999, the authors predicted city-specific annual average $PM_{2.5}$ based on PM_{10} concentrations from the monitors, extinction

Table 2.1 Cohort studies of lung cancer and outdoor air pollution in North America

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Harvard Six Cities Study									
Lepeule et al. (2012) USA	8096 total	1974–2009	City-specific annual average $PM_{2.5}$ from study monitors and monitors in the US EPA AIRS (Air Quality System) database	Lung	1–3-year moving average $PM_{2.5}$ per 10 µg/m³; range, city-specific annual mean ~40–8 µg/m³ during follow-up	351 never-smokers NR former smokers NR current smokers NR	1.37 (1.07–1.75) 1.25 (0.54–2.89) 1.96 (1.29–2.99) 1.25 (0.95–1,64)	Pack-years of past smoking, less than high school education, and linear and quadratic terms for BMI	Mortality; update of Laden et al. (2006) and Dockery et al. (1993)
American Cancer Society study (ACS CPS-II)									
Krewski et al. (2009) USA	351 338	1982–2000	Metropolitan Statistical Area averages from US EPA air quality monitoring databases	Lung	$PM_{2.5}$ (1979–1983) per 10 µg/m³; range, 10.8–30.1; mean (var), 21.2 (21.4)		1.08 (1.03–1.14)	44 individual-level covariates, including age, sex, race, smoking, education level, marital status, alcohol consumption, occupational exposure, and diet	Update of Pope et al. (1995, 2002); adjustment for ecological covariates did not materially change results
	499 968				$PM_{2.5}$ (1999–2000) per 10 µg/m³; range, 5.8–22.2; mean (var), 14.0 (9.1)		1.11 (1.04–1.18)		
	572 312				Sulfate (1980) per 5 µg/m³; range, 1.4–15.6; mean (var), 6.5 (7.9)		1.05 (1.02–1.09)		
	268 336				Sulfate (1990) per 5 µg/m³; range, 2.0–10.7; mean (var), 6.2 (3.9)		1.04 (0.97–1.11)		
	513 450				SO_2 (1980) per 5 ppb; range, 0.02–29.3; mean (var), 9.7 (23.7)		1.00 (0.98–1.02)		
	531 826				O_3 (1980) per 10 ppb; range, 10.4–41.1; mean (var), 22.9 (21.5)		1.00 (0.96–1.04)		

Table 2.1 (continued)

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Krewski et al. (2009) USA (cont.)	406 917				NO_2 (1980) per 10 ppb; range, 7.8–51.1; mean (var), 27.9 (85.3)		0.99 (0.97–1.01)		
	508 538				CO (1980) per 1 ppm; range, 0.2–4.0; mean (var), 1.7 (0.4)		0.99 (0.97–1.03)		
Subgroup in New York City, New York	44 056	1982–2000	Monthly average $PM_{2.5}$ LUR at the postal-code level		$PM_{2.5}$ per 1.5 μg/m³ (interdecile range); mean, 14.3; SD, 1.78; range, 10.8–18.6	853	0.96 (0.84–1.09)		
Jerrett et al. (2005) Los Angeles, California, USA	22 905	1982–2000	Monthly average $PM_{2.5}$ kriging at the postal-code level	Lung	$PM_{2.5}$ per 10 μg/m³; range, 9.0–27.1 μg/m³	434	1.44 (0.98–2.11)	Same as Krewski et al. (2009)	Results were attenuated but still elevated after addition of ecological covariates; kriging results also presented in Krewski et al. (2005), along with similar results from LUR models
Turner et al. (2011) USA, never-smokers	188 699	1982–2008	Metropolitan Statistical Area average $PM_{2.5}$ from US EPA air quality databases	Lung		1100		Sex, age, race, education level, marital status, BMI, passive smoking, diet, alcohol consumption, occupational exposure, and county-level radon	Never-smokers; extended follow-up of Krewski et al. (2009) and Pope et al. (2002)
					1979–1983 average $PM_{2.5}$ per 10 μg/m³; range, 10.3–37.8; mean (SD), 21.1 (4.7)	772	1.15 (0.99–1.35)		
					1999–2000 average $PM_{2.5}$ per 10 μg/m³; range, 5.8–22.2; mean (SD), 14 (3)	1042	1.27 (1.03–1.56)		
					Average of 2 time periods; range, 9.0–27.7; mean (SD), 17.6 (3.7)	714	1.19 (0.97–1.47)		
	50 805 men				1999–2000 average $PM_{2.5}$ per 10 μg/m³	334	1.19 (0.83–1.73)		

Table 2.1 (continued)

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
	126 947 women					708	1.30 (1.01–1.68)		
Jerrett et al. (2013) California, USA	73 711	1982–2000	Residence-level average $PM_{2.5}$, NO_2, and O_3 from US EPA air quality database; satellite data also used for $PM_{2.5}$ (LUR for $PM_{2.5}$ and NO_2; inverse-distance weighting for O_3)	Lung	1998–2002 average $PM_{2.5}$ per 5.30 µg/m³; range, 4.3–25.1; mean (var), 14.1 (12.4) 1988–2002 average NO_2 per 4.12 ppb; range, 3.0–21.9; mean (var), 12.3 (8.5) 1988–2002 average O_3 per 24.18 ppb; range, 17.1–89.3; mean (var), 50.4 (212.2)	1481	1.06 (0.95–1.18) 1.11 (1.02–1.21) 0.86 (0.75–0.99)	42 individual-level covariates [including those listed for Pope et al. (2002)], 5 consolidated Metropolitan Statistical Area indicators, and 7 ecological covariates	Results are presented per IQR of each pollutant; in multipollutant models, associations with NO_2 persisted, while estimates for $PM_{2.5}$ were reduced to unity The authors considered NO_2 a possible marker of traffic, but it appears model included other sources
Adventist Health Study on Smog (AHSMOG)									
Beeson et al. (1998) California, USA	6340 2278 men	1977–1992	Residential and workplace postal code centroid cumulative averages for 1973–1992 from fixed monitors	Lung	PM_{10} per 24 µg/m³ (IQR) cumulative average with 3-year lag SO_2 per 3.7 ppb (IQR) cumulative average with 3-year lag NO_2 per 19.8 ppb (IQR) cumulative average with 3-year lag 8-h average O_3 per 12.0 ppb (IQR) cumulative average with 3-year lag	16 16 16 16	5.21 (1.94–13.99) 2.66 (1.62–4.39) 1.45 (0.67–3.14) 2.23 (0.79–6.34)	Attained age, pack-years of past smoking, years of education, and current alcohol consumption	Incident cases; update of Abbey et al. (1991a) and Mills et al. (1991); also present HRs for days above exceedance cut-off points, but these are not presented here
	4060 women				SO_2 per 3.7 ppb (IQR) cumulative average with 3-year lag	20	2.14 (1.36–3.37)	Attained age, pack-years of past smoking, and years of education	

Table 2.1 (continued)

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Abbey et al. (1999) California, USA	6340 2278 men	1977–1992	Residential and workplace postal code centroid cumulative averages for 1973–1992 from fixed monitors	Lung	PM_{10} per 24 μg/m³ (IQR) cumulative average with 3-year lag	17	3.36 (1.57–7.19)	Attained age, pack-years of past smoking, years of education, and current alcohol consumption	Mortality; update of Abbey et al. (1991a) and Mills et al. (1991); also presented HRs for days above exceedance cut-off points, but these are not presented here
					SO_2 per 3.7 ppb (IQR) cumulative average with 3-year lag	17	1.99 (1.24–3.20)		
					NO_2 per 19.8 ppb (IQR) cumulative average with 3-year lag	17	1.82 (0.93–3.57)		
					8-h average O_3 per 12.0 ppb (IQR) cumulative average with 3-year lag	17	2.10 (0.99–4.44)		
	4060 women				PM_{10} per 24 μg/m³ (IQR) cumulative average with 3-year lag	12	1.08 (0.55–2.13)	Attained age, education level, and smoking	
					SO_2 per 3.7 ppb (IQR) cumulative average with 3-year lag	12	3.01 (1.88–4.84)		
					NO_2 per 19.8 ppb (IQR) cumulative average with 3-year lag	12	2.81 (1.15–6.89)		
					8-h average O_3 per 12.0 ppb (IQR) cumulative average with 3-year lag	12	0.77 (0.37–1.61)		

Table 2.1 (continued)

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
McDonnell et al. (2000) California, USA	1228 men	1977–1992	Average $PM_{2.5}$ for the airshed of residence, predicted from visibility, relative humidity, and season	Lung	Average $PM_{2.5}$ per 24.3 μg/m³ (IQR)	13	2.23 (0.56–8.94)	Attained age, pack-years of past smoking, years of education, and current alcohol consumption	Mortality; results for 2422 women not presented
			Postal code centroid cumulative averages for 1973–1992 from fixed monitors		Average PM_{10} per 29.5 μg/m³ (IQR)		1.84 (0.59–5.67)		
			PM_{10} – $PM_{2.5}$		Average $PM_{2.5}$ – PM_{10} per 9.7 μg/m³ (IQR)		1.25 (0.63–2.49)		
Trucking Industry Particle Study (TrIPS)									
Hart et al. (2011) USA	53 814 men in the trucking industry in the USA	1985–2000	Residence-level geospatial model for PM_{10}, SO_2, and NO_2; nearest monitor for $PM_{2.5}$	Lung	2000 annual average $PM_{2.5}$ per 4 μg/m³ (IQR); mean (SD), 14.1 (4.0)	800	1.02 (0.95–1.10)	Age at entry, decade of hire, calendar year, race, region, healthy worker survivor effect, and occupational exposures	Results are presented per IQR of each pollutant
					1985–2000 average PM_{10} per 6 μg/m³ (IQR); mean (SD), 26.8 (6.0)	800	0.99 (0.92–1.08)		
					1985–2000 average SO_2 per 4 ppb (IQR); mean (SD), 4.8 (2.9)	800	1.09 (0.98–1.21)		
					1985–2000 average NO_2 per 8 ppb (IQR); mean (SD), 14.2 (7.1)	800	1.06 (0.97–1.15)		

Table 2.1 (continued)

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Hart et al. (2011) USA (cont.)	39 948				2000 annual average $PM_{2.5}$ per 4 μg/m³ (IQR)	475	1.07 (0.97–1.17)		Excluding long-haul drivers who work away from home
					1985–2000 average PM_{10} per 6 μg/m³ (IQR)		1.05 (0.94–1.17)		
					1985–2000 average SO_2 per 4 ppb (IQR)		1.09 (0.95–1.25)		
					1985–2000 average NO_2 per 8 ppb (IQR)		1.07 (0.96–1.20)		
California Teachers Study									
Lipsett et al. (2011) California, USA	101 784 women	1997–2005	Monthly pollutant surfaces of PM_{10}, $PM_{2.5}$, SO_2, NO_2, CO, O_3, and NO_x calculated from fixed monitoring network; assigned to participant's residence using 250 m grids	Lung	Cumulative average $PM_{2.5}$ per 10 μg/m³; range, 3.1–28.4; mean (SD), 15.6 (4.5)	234	0.95 (0.70–1.28)	Age, race, smoking, BMI, marital status, alcohol consumption, second-hand smoke exposure, diet, physical activity, menopausal status, hormone therapy, family history of myocardial infarction/ stroke, use of blood pressure medication, aspirin use, and neighbourhood SES variables	Mortality; follow-up for $PM_{2.5}$ began in 2000 due to availability of data
					Cumulative average PM_{10} per 10 μg/m³; range, 9.2–82.6; mean (SD), 29.2 (9.7)	275	0.93 (0.81–1.07)		
					Cumulative average O_3 per 11.02 ppb (IQR); range, 25.4–82.6; mean (SD), 48.1 (8.7)	433	0.96 (0.84–1.09)		
					Cumulative average NO_x per 48.31 ppb (IQR); range, 7.3–221.4; mean (SD), 95.6 (34.5)	70	0.92 (0.60–1.40)		
					Cumulative average NO_2 per 10.29 ppb (IQR); range, 5.2–67.2; mean (SD), 33.6 (9.6)	67	1.00 (0.75–1.33)		
					Cumulative average CO per 0.49 ppm (IQR); range,0.3–3.3; mean (SD), 1.1 (0.4)	52	0.89 (0.57–1.39)		

Table 2.1 (continued)

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Lipsett et al. (2011) California, USA (cont.)	83 491				Cumulative average $PM_{2.5}$ per 10 μg/m³	50	1.62 (0.83–3.16)		
					Cumulative average PM_{10} per 10 μg/m³	62	1.00 (0.75–1.31)		
					Cumulative average O_3 per 11.02 ppb (IQR)	103	0.98 (0.76–1.27)		
					Cumulative average NO_x per 49.31 ppb (IQR)	22	0.89 (0.41–1.92)		
					Cumulative average NO_2 per 10.29 ppb (IQR)	20	0.96 (0.54–1.71)		
					Cumulative average CO per 0.49 ppm (IQR)	15	0.37 (0.13–1.06)		
Ontario Tax Cohort Study									
Villeneuve et al. (2013) Toronto, Canada	58 760	1982–2004	LUR surfaces of VOCs (benzene, *n*-hexane, and total hydrocarbons) and NO_2 linked to baseline home address	Lung	Benzene per 0.13 μg/m³ (IQR)	1470	1.05 (0.96–1.14)	Age; sex; family income; marital status; census area measures of income, immigration, and unemployment; and NO_2; indirect adjustment for smoking and BMI	Mortality; splines indicated linearity for benzene–lung cancer exposure–response function; results for all cancers also presented; effect estimates stronger when follow-up restricted to first 5 years HR unadjusted for VOCs is presented in a figure; does not appear markedly different
					n-Hexane per 1.20 μg/m³ (IQR)		1.03 (0.97–1.10)		
					Total hydrocarbons per 9.02 μg/m³ (IQR)		1.04 (0.98–1.10)		
					NO_2 per 5.9 ppb (IQR)		0.96 (0.89–1.03)		

BMI, body mass index; CI, confidence interval; CO, carbon monoxide; h, hour or hours; HR, hazard ratio; IQR, interquartile range; LUR, land-use regression; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; O_3, ozone; PM_{10}, particulate matter with particles of aerodynamic diameter < 10 μm; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 μm; SD, standard deviation; SES, socioeconomic status; SO_2, sulfur dioxide; US EPA, United States Environmental Protection Agency; var, variance; VOCs, volatile organic compounds.

coefficients (humidity-corrected visibility data from the local airport), and indicators of season (Laden et al., 2006).

Publications on the first and second follow-ups of the cohort (Dockery et al., 1993; Laden et al., 2006) reported positive associations of lung cancer mortality with sulfate and $PM_{2.5}$, respectively. In the most recent follow-up of the full cohort, through 2009, 4495 deaths (7.8% from lung cancer) were identified. In adjusted models, the hazard ratio (HR) was 1.37 (95% confidence interval [CI], 1.07–1.75) for each 10 μg/m^3 increase in $PM_{2.5}$ averaged over the past 1–3 years (determined as the averaging period with the best fit). Analyses of penalized splines indicated a linear relationship. (The city-specific annual average $PM_{2.5}$ ranged from approximately 40 μg/m^3 to 8 μg/m^3 over the course of the entire follow-up period.) Other modelling options were also considered, with similar results (Lepeule et al., 2012). In stratified analyses, relative risks were elevated for never-smokers, current smokers, and former smokers, with former smokers appearing to have the highest risk compared with never-smokers or current smokers; however, the *P*-value for interaction was not statistically significant. In time-period-specific analyses, the hazard ratio for the past 8 years of follow-up (2001–2009) was the strongest (HR, 2.84; 95% CI, 1.06–7.59), but again the *P*-value for interaction was not significant. Because of the high correlation of exposures over time, the critical exposure window could not be determined (Lepeule et al., 2012).

[A limitation of the Harvard Six Cities Study is that it relied on central site monitoring for each city. Since all participants in the same city were assigned the same exposure value, there was no ability to assess intra-city spatial variation in exposures. In Dockery et al. (1993), a city-specific average value for each pollutant was created for 3–8 years during the late 1970s or the 1980s, depending on the pollutant; therefore, there was also no assessment of variation of air pollution over time. Furthermore, in some cases the measurements may actually have occurred after the relevant death. In the subsequent analyses, an annual average for $PM_{2.5}$ for each city was created and assigned to the follow-up time by calendar year; thus, temporal variation was accounted for. Other limitations are that there is no information on whether a person moved out of the city in which they were recruited during the follow-up period, and that only baseline information on covariates was included in the final analyses. However, in a reanalysis of the Dockery et al. (1993) study, Krewski and colleagues (HEI, 2000) found that the results were robust to updates of the covariates and changes in address. The strengths of the study are the detailed exposure monitoring, the assessment of different modelling options in the most recent follow-up, the prospective follow-up, and the control for potential confounders at the individual level: age, sex, body mass index (BMI), smoking status and pack-years of smoking, and education level.]

(b) American Cancer Society study

Six analyses of the association of measures of air pollution with lung cancer mortality have relied on data collected by the American Cancer Society (ACS) as part of the Cancer Prevention Study II (CPS-II) (Pope et al., 1995, 2002; Jerrett et al., 2005, 2013; Krewski et al., 2009; Turner et al., 2011). The ACS CPS-II is an ongoing prospective mortality study of approximately 1.2 million adults aged at least 30 years at enrolment in 1982 and residing throughout the USA. Before 1989, vital status was obtained from the study volunteers who enrolled the participants. After 1989, searches of the National Death Index were conducted. Individual-level risk factor information was available through a baseline questionnaire. The original analysis included 7 years of follow-up, through 1989 (Pope et al., 1995). Subsequent publications on the nationwide cohort included follow-up through 1998 (16 years) (Pope et al., 2002), through 2000 (18 years) (Krewski et al., 2009), and through

2008 (26 years), with the most recent follow-up restricted to never-smokers (Turner et al., 2011). Jerrett et al. (2005, 2013) and Krewski et al. (2009) conducted analyses focused on Los Angeles, New York City, and the state of California.

Analyses of air pollution effects in the ACS CPS-II took advantage of existing national monitoring networks to quantify air pollution exposures. Therefore, the study population was restricted to participants who resided in United States Metropolitan Statistical Areas (MSAs) with available pollution data (approximately 300 000–500 000 participants, depending on the follow-up and pollutants measured). Baseline average $PM_{2.5}$ levels were quantified by MSA of residence for 1979–1983 using data from the Inhalable Particle Monitoring Network. TSP and different size fractions of PM (PM_{15}, $PM_{15–2.5}$) were available for that time period as well. PM_{10} concentrations for 1982–1998 and $PM_{2.5}$ beginning in 1999 were available from the United States Environmental Protection Agency (US EPA) AIRS database. Average outdoor $PM_{2.5}$ concentrations from 1999–2000 were used to quantify exposures towards the end of the follow-up period, and an average of the two time periods was considered as an estimate of exposure over the course of the study. Sulfate concentrations were available for 1980–1981, and SO_2, nitrogen dioxide (NO_2), carbon monoxide (CO), and ozone levels were available for 1980 and 1982–1998. Ranges and/or means of exposure for all pollutants in each follow-up are presented in Table 2.1 when available (Pope et al., 2002; Krewski et al., 2009; Turner et al., 2011).

Reports of the first two follow-ups of the ACS CPS-II cohort (Pope et al., 1995, 2002) provided data on the association of lung cancer mortality with concentrations of $PM_{2.5}$ and sulfate. Positive associations were observed for both indicators. The second report also included data for SO_2, NO_2, CO, and ozone (Pope et al., 2002).

In the most recent analysis of the cohort, with 2 more years of follow-up and additional adjustment for individual-level covariates from the baseline questionnaire, hazard ratios were 1.08 (95% CI, 1.03–1.14) and 1.11 (95% CI, 1.04–1.18) for $PM_{2.5}$ in 1979–1983 and 1999–2000, respectively, and 1.05 (95% CI, 1.02–1.11) and 1.04 (95% CI, 0.97–1.11) for sulfate in 1980 and 1990, respectively (Krewski et al., 2009). No association with lung cancer was observed for ozone, SO_2, NO_2, or CO. Additional adjustment for ecological covariates derived at the postal code and MSA level did not materially change the results. Spatial autocorrelation was also included in sensitivity analyses, but results specific to lung cancer are not presented. No clear patterns emerged from analyses of time windows of exposure.

[The nationwide assessments of the ACS CPS-II rely on MSA-specific measurements from at most two time periods (near the beginning and near the end of the follow-up). There is no assessment of intra-city variability, which could enhance contrasts in exposure but should not hamper interpretation of the results that were obtained. Furthermore, there is no accounting for whether a participant moved out of their baseline location, which could contribute to measurement error. Covariates were not updated over time, potentially reducing the ability to control confounding. However, strengths of the studies are the assessment of a linear trend, the prospective follow-up, and that individual-level covariates are controlled for in both analyses. Krewski et al. (2009) also included a large battery of ecological covariates and assessment of autocorrelation.]

In the analysis with the longest follow-up period to date (26 years), Turner et al. (2011) assessed the association of $PM_{2.5}$ with lung cancer mortality among 188 699 lifetime non-smokers in the ACS CPS-II cohort. In Cox proportional hazard models adjusting for the same covariates as in the Pope et al. (2002) study with the addition of dietary variables, additional measures of occupational exposures, and mean county-level residential radon concentrations, each 10 μg/m^3

increase in $PM_{2.5}$ was associated with a 15–27% increase in lung cancer mortality, depending on the time window in which the $PM_{2.5}$ concentration was assessed. The fully adjusted hazard ratios were modestly attenuated compared with those not adjusted for residential radon. A plot of adjusted hazard ratios in relation to quartiles of $PM_{2.5}$ (1999–2000) suggests a linear trend, but a formal test was not presented. [The strengths and limitations of Turner et al. (2011) are the same as those described for Pope et al. (2002) and Krewski et al. (2009). The restriction of this study to never-smokers is a major additional strength, as is the control for other potential confounders – diet, occupation, and residential radon – as covariates in the models. Both features reduce the potential for confounding, although among the additional covariates considered, only radon had a notable effect on the association with $PM_{2.5}$.]

The ACS investigators also performed specific analyses in Los Angeles, the state of California, and New York City, where they had the ability to describe intra-city variability in exposure using land-use regression exposure models. In Los Angeles, the hazard ratio controlling for 44 individual-level covariates was 1.44 (95% CI, 0.98–2.11) per 10 μg/m³ increase in $PM_{2.5}$ estimated for each individual's postal code centroid. This was attenuated to 1.20 (95% CI, 0.79–1.82) when statistically significant contextual covariates were included (Jerrett et al., 2005). Results using a slightly different statistical technique to predict exposures were similar (Krewski et al., 2009). In equivalent analyses in New York City, the hazard ratio adjusted for individual-level covariates was 0.96 (95% CI, 0.84–1.09) per 1.5 μg/m³ increase in $PM_{2.5}$ (the interdecile range) (Krewski et al., 2009). Jerrett et al. (2013) modelled monthly averaged $PM_{2.5}$, NO_2, and ozone at the baseline residential address for all 73 711 ACS CPS-II participants residing in California. Monitoring data for $PM_{2.5}$ and NO_2 were supplemented with data from satellites. Exposure metrics were determined as averages for 1988–2002 for NO_2 and ozone and as averages for 1998–2002 for $PM_{2.5}$. In models adjusted for 42 individual-level covariates, as well as indicators of the MSAs and 7 ecological covariates, hazard ratios for lung cancer were elevated for an interquartile range (IQR) increase in $PM_{2.5}$ (HR, 1.06; 95% CI, 0.95–1.18) and NO_2 (HR, 1.11; 95% CI, 1.02–1.21) but not for ozone (HR, 0.86; 95% CI, 0.75–0.99). Analyses representing exposure with splines showed no evidence of nonlinearity. Associations with NO_2 remained statistically significant in two pollutant models that additionally included $PM_{2.5}$ and ozone, while estimates for $PM_{2.5}$ were reduced to unity. [The authors described NO_2 as a marker for traffic-related air pollution. However, since other exposure sources (i.e. heating and industrial) were included in the models, their contributions to the modelled concentrations cannot be ruled out. The results for NO_2 are more consistent with the European studies, which also assessed intra-city variability, than with the full-country ACS analysis, which assessed variation across larger areas.]

[The strengths of the three area-specific analyses of the ACS CPS-II (Los Angeles, New York City, and California) are the detailed adjustment for baseline and ecological confounders and the ability to consider intra-city variability and temporal variability.]

(c) Adventist Health Study on Smog

The Adventist Health Study on Smog (AHSMOG) cohort consists of 6340 Seventh-Day Adventists who were participants in the Adventist Health Study. They were non-Hispanic Whites residing in California, currently non-smokers, who had lived for at least 10 years within 5 miles (8 km) of their baseline residence and were aged 25 years to more than 80 years when they completed the baseline questionnaire in 1977 (Abbey et al., 1991a).

Monthly outdoor concentrations of TSP, PM_{10}, SO_2, NO_2, and ozone were estimated for each participant starting in 1966 from fixed-site

monitors maintained by the California Air Resources Board. Exposure predictions were restricted to postal code centroids within 50 km of a monitoring station and were not allowed to cross topographical obstructions or other barriers to air flow (Abbey et al., 1991b). Before 1987, PM_{10} was estimated from TSP, and before 1972, total oxidants were measured as opposed to ozone. For each pollutant, both means and exceedance frequencies (the sum of hours for gaseous pollutants or of days for particulate pollutants above a specified cut-off based on federal and California standards at the time) were used as exposure metrics in the majority of the epidemiological analyses. Cancer incidence was ascertained from linkage with cancer registries and medical record review of self-reported hospitalizations, and mortality was ascertained from linkage with the California death certificate file, the National Death Index, and the Seventh-Day Adventist church records (Mills et al., 1991).

In the initial follow-up through 1982, elevated hazard ratios were reported for the associations of lung cancer with TSP and total oxidants (Abbey et al., 1991a; Mills et al., 1991).

Results for associations of lung cancer with air pollution with follow-up extended through 1992 have been presented in three separate publications (Beeson et al., 1998; Abbey et al., 1999; McDonnell et al., 2000). In addition to exceedance frequencies, cumulative annual averages from January 1973 until 3 years before the date of the case defining the risk set (i.e. a 3-year lag) were estimated for PM_{10}, SO_2, and 8-hour average ozone. Among men, positive associations were observed for incident lung cancer (n = 16) after adjustment for age, years of education, pack-years of smoking, and alcohol consumption, for each 24 μg/m^3 (IQR) increase in PM_{10} (HR, 5.21; 95% CI, 1.94–13.99), each 3.7 ppb (IQR) increase in SO_2 (HR, 2.66; 95% CI, 1.62–4.39), each 19.8 ppb (IQR) increase in NO_2 (HR, 1.45; 95% CI, 0.67–3.14), and each 12.0 ppb (IQR) increase in 8-hour average ozone (2.23; 95% CI, 0.79–6.34). Among women (cases = 20), the equivalent hazard ratios were elevated only for SO_2 (HR, 2.14; 95% CI, 1.36–3.37) (Beeson et al., 1998). Among men, the equivalent hazard ratios for lung cancer mortality (n = 17) were 3.36 (95% CI, 1.57–7.19) for PM_{10}, 1.99 (95% CI, 1.24–3.20) for SO_2, 1.82 (95% CI, 0.93–3.57) for NO_2, and 2.10 (95% CI, 0.99–4.44) for 8-hour average ozone. Among women, the hazard ratios for lung cancer mortality (n = 12) were 1.08 (95% CI, 0.55–2.13) for PM_{10}, 3.01 (95% CI, 1.88–4.84) for SO_2, 2.81 (95% CI, 1.15–6.89) for NO_2, and 0.77 (95% CI, 0.37–1.61) for 8-hour average ozone (Abbey et al., 1999). [The Working Group noted a discrepancy in the IQRs for NO_2 and ozone as reported in the papers by Abbey et al. (1999), where the IQRs are given as 19.8 ppb and 12.03 ppb, respectively, and Beeson et al. (1998), where they are reported as 1.98 ppb and 2.12 ppb, respectively. The Working Group was unable to obtain clarification from the authors. Therefore, the former figures, which are of the same magnitude as those reported in other papers based on the same population, are assumed to be the correct ones.]

$PM_{2.5}$ data were available for a subcohort residing within an airshed adjacent to one of nine airports located throughout California (n = 1347 men, 2422 women) during the study baseline period (McDonnell et al., 2000). Visibility and $PM_{2.5}$ were measured concurrently at the nine airports from 1979 to 1993. These data were used to predict daily $PM_{2.5}$ concentrations for 1966–1993 using linear regression controlling for season and relative humidity, and monthly average $PM_{2.5}$ concentrations were calculated for each airshed. Monthly average $PM_{2.5-10}$ values were calculated as the monthly mean PM_{10} (modelled as in earlier publications) minus the monthly mean $PM_{2.5}$ value for each participant. In addition, monthly ozone, SO_2, and NO_2 for 1966–1992 and SO_4 for 1977–1992 were interpolated to the postal code centroid of the participants' residential and work addresses. Among the 1228 men with $PM_{2.5}$ data, 13 deaths

from lung cancer were identified. Hazard ratios adjusted for age, pack-years of smoking, years of education, and current alcohol consumption were elevated with wide confidence intervals for all size fractions of PM using the average for the baseline years 1973–1977. In models including $PM_{2.5}$ and $PM_{2.5–10}$ simultaneously, the magnitude of the hazard ratio for $PM_{2.5–10}$ was attenuated. Results for women were not presented but were described as weak or inverse. Numbers of deaths from lung cancer in the subcohort were too small to assess the other pollutants.

[The strengths of the AHSMOG studies are the long prospective follow-up, the detailed information on long-term work and home addresses, the control for individual covariates, and the ability to assess incidence as well as mortality. Major limitations are the very small sample size, the non-standard exposure assessment, and the lack of clarity and consistency in the published reports of the results.]

(d) Trucking Industry Particle Study

The Trucking Industry Particle Study (TrIPS) was a retrospective occupational cohort study of men in the trucking industry across the USA, which was originally designed to examine the association of occupational exposures to vehicle exhaust with lung cancer. The investigators subsequently examined the effect of annual outdoor exposures to PM_{10}, SO_2, and NO_2 on lung cancer mortality (Hart et al., 2009, 2011). Exposures to PM_{10} and NO_2 were estimated by modelling data obtained from the US EPA Air Quality System for 1985–2000 (Hart et al., 2009), and $PM_{2.5}$ was estimated based on the nearest Air Quality System monitor in 2000. (Mean concentrations for all pollutants are presented in Table 2.1.) In models stratified by age at entry, decade of hire, and calendar year, and adjusted for race, census region of residence, the healthy worker survivor effect, and occupational exposures, the hazard ratios for annual average (1985–2000) SO_2 and NO_2 were elevated in the full cohort. When long-haul drivers who spend days away from home were excluded, elevated hazard ratios were also observed for PM_{10}. The hazard ratio for a 4 μg/m³ (IQR) increase in $PM_{2.5}$ in 2000 was 1.02 (95% CI, 0.95–1.10) in the full cohort and 1.07 (95% CI, 0.97–1.17) in the cohort excluding long-haul drivers (Hart et al., 2011). In supplemental analyses using information from a survey administered to a sample of currently employed and recently retired workers in the industry, the authors evaluated the potential impact of not controlling for smoking and BMI. Current smoking, but not BMI, was associated with small increases in the hazard ratio for PM_{10} and NO_2 ($PM_{2.5}$ was not evaluated). Therefore, not adjusting for smoking may have led to inflation of the effect estimates.

[The limitations of this study are the lack of control for potential confounding by individual-level risk factors such as smoking history and the reliance on the most recent address to predict exposure. The strengths are the control for occupational exposures and the availability of time-varying residence-level predictions for most of the pollutants.]

(e) California Teachers Study

The California Teachers Study is a prospective cohort study of 133 479 female current and former public school professionals participating in the California State Teachers' Retirement System. All participants completed a baseline questionnaire in 1995. Subsequent questionnaires were mailed in 1997 and 2000, and name and residential address were updated annually. Cause-specific mortality data were obtained from record linkage with California state registries, the United States Social Security Administration, and the National Death Index. Monthly surfaces of $PM_{2.5}$, PM_{10}, ozone, nitrogen oxides (NO_x), NO_2, CO, and SO_2 in 250 m grids were estimated using inverse-distance weighting of data from monitors maintained by the state. (Ranges and means [standard deviations] for

each pollutant are presented in Table 2.1.) Individual monthly exposures were estimated by linking each residential address to the gridded pollutant surface, and cumulative averages were calculated for each risk set to represent long-term exposure. The final analytical data set included 101 784 women with available air pollution data (73 489 for $PM_{2.5}$, since monitoring began later). In adjusted multivariable models, there was no evidence of a positive association of any of the pollutants considered with lung cancer mortality risk (Lipsett et al., 2011). However, in analyses restricted to never-smokers, the hazard ratio for a 10 μg/m^3 increase in $PM_{2.5}$ was 1.62 (95% CI, 0.83–3.16).

[The strengths of this study are the spatially and temporally resolved air pollution measurements and the control for time-varying confounding by individual-level lung cancer risk factors. The limitations are that there were only 5.6 years of follow-up for the analyses of $PM_{2.5}$ and that $PM_{2.5}$ data were only available concurrently or for the 12 months before the start of follow-up. Therefore, there was no ability to look at truly long-term exposures, which might be necessary for assessment of an association with lung cancer risk.]

(f) Ontario Tax Cohort Study

Villeneuve et al. (2013) conducted a cohort study of intra-urban variations in volatile organic compounds (VOCs) and NO_2 and cause-specific mortality in Toronto, Canada. The population consisted of 58 760 residents of Toronto in 1982 who were part of the larger Ontario Tax Cohort Study, a cohort randomly selected from income tax filings of Canadians residing in one of 10 urban areas in the province of Ontario. Residential addresses at baseline were linked by postal code centroid to estimated exposure surfaces of benzene, *n*-hexane, total hydrocarbons, and NO_2 modelled from measurements (obtained in 2006 for the VOCs and in 2002 and 2004 for NO_2) and spatial covariates. Deaths were identified by linkage to the Canadian Mortality Database. Individual-level information on household income and marital status was obtained from the income tax return, and contextual measures of unemployment, average household income, and immigration were obtained from the 1981 Canadian census. Data from the 2001 Canadian Community Health Survey were used to indirectly adjust for smoking and obesity, using the spatial association between smoking, BMI, and pollution measurements.

The participants ranged in age from 35 to 85 years in 1982 (mean, 51.7 years). Through 2004, 1470 deaths from lung cancer were identified among 18 020 deaths. In Cox proportional hazards models adjusted for age, sex, the socioeconomic variables described above, and NO_2, the hazard ratios for all VOCs were elevated. After indirect adjustment for smoking and BMI, the effect estimates were attenuated. No independent association was observed of NO_2 with lung cancer mortality (Villeneuve et al., 2013).

[This study is the only cohort study to date to assess residential exposure to VOCs as well as other urban air pollutants. Individual-level information on smoking was not available, but the measurements of socioeconomic status that were obtained are a strength and could help to control indirectly for smoking.]

2.1.2 Cohort studies in Europe

The association between exposure to outdoor air pollution and the risk of lung cancer has been evaluated in several prospective cohort studies in Europe, which are summarized in Table 2.2. The table summarizes features of the study design, the exposure metrics used, and the main results after adjustment for relevant confounders. Several European countries have been included. The largest study is a pooled analysis of 17 European cohorts from the ESCAPE study, which included areas in Austria, Denmark, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the

Table 2.2 Cohort studies of lung cancer and outdoor air pollution in Europe

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Nafstad et al. (2003) Norway	16 209	1972–1998	Assessment at home addresses based on area emissions, dispersion modelling, and local traffic	Lung cancer incidence	NO_x (per 10 μg/m³; home address) 1974–1998 SO_2 (per 10 μg/m³)	418	1.08 (1.02–1.15) 1.01 (0.94–1.08)	Age, smoking habits, and length of education	Men only in Oslo, aged 40–49 yr
Filleul et al. (2005) PAARC Study	14 284	1974–2000	24 areas; exposure based on daily measurements for 1974–1976 at central site station in each area	Lung cancer mortality	Total suspended particulate (per 10 μg/m³); range, 45–243 μg/m³ Black smoke (per 10 μg/m³) NO (per 10 μg/m³) NO_2 (per 10 μg/m³); range, 12–61 μg/m³ SO_2 (per 10 μg/m³)	178	0.97 (0.94–1.01) 0.97 (0.93–1.01) 0.97 (0.94–1.01) 0.97 (0.85–1.10) 0.99 (0.92–1.07)	Age, sex, BMI, smoking, occupational exposure, and education level	Adults aged 25–59 yr, subjects enrolled in 1974; frailty models used to account for spatial correlation
Vineis et al. (2006) Gen-Air Study	197 cases, 556 controls (nested)	1993–1998	Exposure assessment for NO_2, SO_2, and PM_{10} for 1990–1994 or 1995–1999 from nearest stationary monitor; residence near heavy-traffic roads	Lung cancer incidence	PM_{10} (10 μg/m³ increase) NO_2 (10 μg/m³ increase) SO_2 (10 μg/m³ increase) Proximity of residence to major road (exposed vs non-exposed)	197	0.91 (0.70–1.18) 1.14 (0.78–1.67) 1.08 (0.89–1.30) 1.31 (0.82–2.09)	Age, BMI, education level, sex, smoking, alcohol consumption, intake of meat, intake of fruit and vegetables, time since recruitment, country, occupational index, and cotinine	Nested, never-smokers or ex-smokers; 10 European countries
Naess et al. (2007)	143 842 residents of Oslo	1992–1998	Air dispersion model for concentrations in 1992–1995	Lung cancer mortality	*Men, aged 51–70 yr* NO_2 (1 quartile) PM_{10} (1 quartile) $PM_{2.5}$ (1 quartile)	449	 1.07 (0.97–1.18) 1.07 (0.97–1.18) 1.07 (0.97–1.18)	Adjustment for age, occupation, and education level	Age range, 51–90 yr Quartile values for pollutants not reported

Table 2.2 (continued)

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Naess et al. (2007) (cont.)					*Women, aged 51–70 yr*	295			
					NO_2 (1 quartile)		1.23 (1.10–1.38)		
					PM_{10} (1 quartile)		1.27 (1.13–1.43)		
					$PM_{2.5}$ (1 quartile)		1.27 (1.13–1.43)		
					Men, aged 71–90 yr	424			
					NO_2 (1 quartile)		1.09 (0.98–1.20)		
					PM_{10} (1 quartile)		1.08 (0.98–1.20)		
					$PM_{2.5}$ (1 quartile)		1.07 (0.97–1.18)		
					Women, aged 71–90 yr	285			
					NO_2 (1 quartile)		1.12 (0.98–1.27)		
					PM_{10} (1 quartile)		1.17 (1.03–1.33)		
					$PM_{2.5}$ (1 quartile)		1.16 (1.02–1.32)		
Beelen et al. (2008a)	111 816	1986–1997	LUR models	Lung cancer incidence	Black smoke (per 10 μg/m³); range, 8.7–35.8; mean (SD), 16.5 (3.5)	1940	0.96 (0.83–1.11)	Age, sex, smoking status, and area-level SES	Netherlands cohort study
					$PM_{2.5}$ (per 10 μg/m³); range, 22.9–36.8; mean (SD), 28.2 (2.1)		0.81 (0.63–1.04)		
					NO_2 (per 30 μg/m³); range, 14.6–66.7; mean, 36.9		0.86 (0.70–1.07)		
					SO_2 (per 20 μg/m³); range, 4.4–33.8; mean (SD), 13.7 (5.1)		0.9 (0.72–1.11)		
					Traffic intensity on nearest road		1.05 (0.94–1.16)		
					Living near a major road		1.11 (0.91–1.34)		
					Black smoke by tobacco smoking status				
					Never-smokers	252	1.47 (1.01–2.16)		
					Ex-smokers	500	0.91 (0.68–1.23)		
					Current smokers	1188	0.85 (0.70–1.03)		

Table 2.2 (continued)

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Beelen et al. (2008b)	117 528	1987–1996	See Beelen et al. (2008a)	Lung cancer mortality	Black smoke (per 10 μg/m³)	1935	1.03 (0.88–1.20)	Age, sex, smoking status, and area-level SES	Adults aged 55–69 yr
					NO_2 (per 30 μg/m³)		0.91 (0.72–1.15)		
					$PM_{2.5}$ (per 10 μg/m³)		1.06 (0.82–1.38)		
					SO_2 (per 20 μg/m³)		1.00 (0.79–1.26)		
					Traffic intensity (increase of 10 000 motor vehicles/day)		1.07 (0.96–1.19)		
					Never-smokers				
					Black smoke (per 10 μg/m³)		1.47 (1.01–2.16)		
Raaschou-Nielsen et al. (2010)	Total 679 cases, 3481 controls (nested)	1993–2001	Dispersion modelling at all addresses since 1971	Lung cancer incidence	NO_x (30–72 μg/m³ vs < 30 μg/m³)	298 incident cases	1.30 (1.07–1.57)	Smoking, education level, BMI, alcohol consumption, sex, cohort, and birth cohort	
					NO_x (> 72 μg/m³ vs < 30 μg/m³)	87	1.45 (1.12–1.88)		
					NO_x at residence (per 100 μg/m³ increase); mean, 37.6 μg/m³	679 incident cases	1.37 (1.06–1.76)		
Raaschou-Nielsen et al. (2011a)	Total 52 970	1993–2006	Dispersion modelling at all addresses since 1971 and traffic indicators	Lung cancer incidence	NO_x at residence (per 100 μg/m³ increase)	592 incident cases	1.09 (0.79–1.51)	Age, smoking, second-hand smoke, length of school attendance, fruit intake, employment, and sex	Enrolment, 1993–1997; database on exposure in 1960–2005; residential addresses from 1971
					NO_x				
					17.2–21.8 μg/m³	NR	1.09 (0.84–1.40)		
					21.8–29.7 μg/m³	NR	0.93 (0.73–1.18)		
					> 29.7 μg/m³	NR	1.30 (1.05–1.61)		
					Per 1000 vehicle-km/day traffic load within 200 m of the residence	592	1.03 (0.90–1.19)		
					Major road within 50 m	NR	1.21 (0.95–1.55)		

Table 2.2 (continued)

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Raaschou-Nielsen et al. (2013) ESCAPE Study	312 944		LUR models and traffic indicators	Lung cancer incidence	PM_{10} (per 10 μg/m³), all lung cancers	2095	1.22 (1.03–1.45)	Sex, calendar time, age (time axis), smoking status, smoking intensity, smoking duration, time since quitting smoking, second-hand smoke, occupation, fruit intake, marital status, education level, employment status, and SES	17 European cohorts in 9 countries
					Adenocarcinomas		1.51 (1.10–2.08)		
					Squamous cell		0.84 (0.50–1.40)		
					$PM_{2.5}$ (per 10 μg/m³), all lung cancers		1.18 (0.96–1.46)		
					Adenocarcinomas		1.55 (1.05–2.29)		
					Squamous cell		1.46 (0.43–4.90)		
					PM coarse (per 5 μg/m³), all cases		1.09 (0.88–1.33)		
					Absorbance $PM_{2.5}$ (per 10^{-5}/m)		1.12 (0.88–1.42)		
					NO_2 (per 10 μg/m³)		0.99 (0.93–1.06)		
					NO_x (per 20 μg/m³)		1.01 (0.95–1.07)		
					Traffic density on nearest road (5000 vehicles/day)		1.00 (0.97–1.04)		
					Traffic load on major roads within 100 m		1.09 (0.99–1.21)		
Heinrich et al. (2013)	4 752 women	1980–2008	Nearest monitoring station and proximity to a major road; PM_{10} estimated from TSP	Lung cancer mortality	PM_{10} (per 7 μg/m³)	41	1.84 (1.23–2.74)	Smoking status and age	Women only
					NO_2 (per 16 μg/m³)		1.46 (0.92–2.32)		
Cesaroni et al. (2013)	1 265 058	2001–2010	LUR model	Lung cancer mortality	NO_2 (per 10 μg/m³)	12 208	1.04 (1.02–1.07)	Sex, age, marital status, place of birth, education level, occupation, and SES	Age ≥ 30 yr
					NO_2 ≤ 36.5 μg/m³	2008	1.00 (ref)		
					36.5–42.7	2187	1.07 (1.01–1.14)		
					42.7–46.2	2568	1.09 (1.03–1.16)		
					46.2–50.4	2610	1.09 (1.03–1.16)		
					> 50.4	2835	1.11 (1.05–1.18)		P_{trend} = 0.002

Table 2.2 (continued)

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Cesaroni et al. (2013) (cont.)					$PM_{2.5}$ (per 10 μg/m³)	12 208	1.05 (1.01–1.10)		
					$PM_{2.5} \leq 19.4$ μg/m³	2090	1.00 (ref)		
					19.4–22.5	2268	1.04 (0.98–1.10)		
					22.5–24.8	2397	1.09 (1.02–1.15)		
					24.8–26.8	2610	1.07 (1.01–1.13)		
					> 26.8	2842	1.08 (1.02–1.15)		$P_{trend} = 0.006$
					Distance to high-traffic road, *P* for trend		0.9		
					Quintiles of traffic intensity within 150 m, *P* for trend		0.3		
Carey et al. (2013)	835 607 patients from general practitioners in the United Kingdom	2003–2007	Emissions inventory combined with dispersion modelling	Lung cancer mortality	PM_{10} (per 3 μg/m³); mean (SD), 19.7 (2.3); range, 12.6–29.8	5244	1.03 (0.98–1.08)	Age, sex, smoking, BMI, and education level	Age range, 40–89 yr
					$PM_{2.5}$ (per 1.9 μg/m³); mean (SD), 12.9 (1.4); range, 8.5–20.2	5244	1.04 (0.99–1.09)		
					NO_2 (per 10.7 μg/m³); mean (SD), 22.5 (7.4); range, 4.5–60.8	5241	1.11 (1.05–1.17)		
					SO_2 (per 2.2 μg/m³); mean (SD), 3.9 (2.1); range, 0.1–24.2	5192	1.03 (0.99–1.06)		
					O_3 (per 3.0 μg/m³); mean (SD), 51.7 (2.4); range, 44.5–63.0	5210	0.94 (0.90–0.98)		

BMI, body mass index; CI, confidence interval; LUR, land-use regression; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; NR, not reported; O_3, ozone; PM_{10}, particulate matter with particles of aerodynamic diameter < 10 μm; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 μm; ref, reference; SD, standard deviation; SES, socioeconomic status; SO_2, sulfur dioxide; TSP, total suspended particles; yr, year.

United Kingdom, with large differences in exposure levels. Both incidence and mortality have been considered in European studies. In the case of lung cancer the two are almost equivalent, since lung cancer is a highly lethal disease. However, incidence registration is usually more reliable than mortality registration, since the latter is affected by some degree of misclassification due to lung metastases.

Nafstad et al. (2003) conducted a study among 16 209 male residents of Oslo (1972–1998). Exposure to NO_x and SO_2 at home addresses was estimated for 1974–1995 based on area emissions, dispersion modelling, and an additional contribution from busy streets near the home. Traffic was the main source of NO_x and heating was the main source of SO_2 in Oslo. After controlling for age, smoking habits, and education level, the authors found a relative risk (RR) of 1.08 (95% CI, 1.02–1.15) for every 10 μg/m^3 increment in NO_x exposure and of 1.01 (95% CI, 0.94–1.08) for every 10 μg/m^3 increment in SO_2.

Filleul et al. (2005) studied 14 284 young adults (aged 25–59 years), enrolled in 1974, living in 24 areas of France (PAARC Study). Concentrations of TSP, black smoke, nitrogen oxide (NO), NO_2, and SO_2 were measured at one monitoring station in each area during 1974–1976. After a follow-up of 26 years, they identified 178 deaths from lung cancer, with no excess risk for any of the air pollutants. Using the ratio between NO and NO_2, the authors identified six monitoring stations located close to traffic and therefore considered less representative for the population in the area. A subanalysis based on the 18 other areas showed a mortality rate ratio of 1.48 (95% CI, 1.05–2.06) in association with a 10 μg/m^3 increase in NO_2 but no significant association with any of the other pollutants. [The population was particularly young, so the number of cases was small. Determinants of lung cancer in young subjects may differ from those in the elderly. Cumulative exposure may have been limited.]

Vineis et al. (2006) conducted a nested case–control study on lung cancer within the large European Prospective Investigation into Cancer and Nutrition (EPIC) cohort recruited in 1993–1998. Cases accrued after a median follow-up of 7 years among the ex-smokers (who had stopped smoking at least 10 years previously) and never-smokers. Three controls per case were matched by sex, age, smoking status, country, and time elapsed between recruitment and diagnosis. Residence in proximity to heavy-traffic roads was used as an indicator of exposure to air pollution. In addition, exposure to air pollutants (NO_2, PM_{10}, and SO_2) was assessed using concentration data from the routine monitoring station nearest to the address at the time of enrolment. Exposure data for single pollutants were limited by the relatively small number of monitoring stations. Exposure estimates were available for 197 cases and 556 controls. Cotinine was measured in plasma as an indicator of second-hand smoke exposure. There was a non-significant association between lung cancer and residence near heavy-traffic roads (odds ratio [OR], 1.31; 95% CI, 0.82–2.09). For NO_2, the odds ratio was 1.14 (95% CI, 0.78–1.67) for each increment of 10 μg/m^3, and 1.37 (95% CI, 1.06–1.75) for concentrations greater than 30 μg/m^3 after adjustment for cotinine and additional potential confounders, including occupational exposures. No clear association was found with other pollutants. [The restriction of the study to never-smokers and former smokers is a notable strength. The lack of information on traffic and single pollutants for some cases and controls may have introduced some misclassification of exposure. Follow-up was relatively short.]

Naess et al. (2007) investigated the concentration–response relationship between air pollution (NO_2, PM_{10}, and $PM_{2.5}$) and cause-specific mortality. The population included all inhabitants of Oslo, Norway, aged 51–90 years, with follow-up of deaths from 1992 to 1998. An air dispersion model was used to estimate exposure levels in

1992–1995. Several hazard ratios were reported for lung cancer mortality and different levels of NO_2, PM_{10}, and $PM_{2.5}$ exposure, and smoothed concentration–response curves were shown in figures. After adjustment for confounders (age, occupation, and education level), increased risks were found among women. The relative risks for an IQR increase in exposure to NO_2, PM_{10}, and $PM_{2.5}$ were 1.23 (95% CI, 1.10–1.38), 1.27 (95% CI, 1.13–1.43), and 1.27 (95% CI, 1.13–1.43), respectively, in women aged 51–70 years and 1.12 (95% CI, 0.98–1.27), 1.17 (95% CI, 1.03–1.33), and 1.16 (95% CI, 1.02–1.32), respectively, in women aged 71–90 years. Relative risks for men were lower (1.07–1.09) and not statistically significant. There was no direct adjustment for smoking at the individual level, but three indirect methods were used to assess the potential for confounding: (i) a health survey indicating that the correlation between residence in polluted areas and smoking was $r = 0.06$; (ii) adjustment for occupation and education level as proxies for smoking; and (iii) analyses of a separate cohort in the same area, which found no attenuation of estimates after adjustment for smoking. [The Working Group noted the lack of direct adjustment for smoking; however, indirect adjustment provides some reassurance that there was no significant confounding by smoking. Identical relative risks for $PM_{2.5}$, PM_{10}, and NO_2 were also noted in several analyses, implying very strong correlations between these pollutant indices.]

Beelen et al. (2008a, 2008b) investigated the association of lung cancer incidence and mortality with several indicators of exposure to air pollution in a prospective cohort study of more than 120 000 subjects in the Netherlands. Exposure assessment for the home address at the time of enrolment was based on regional background monitoring of black smoke, NO_2, and SO_2 during 1976–1996, land-use regression models for estimating intra-urban differences, and traffic intensity near the residence and field monitoring of black smoke, NO_2, and $PM_{2.5}$ for the very local contribution. Background $PM_{2.5}$ concentrations were estimated from PM_{10} using a conversion factor.

The incidence study (Beelen et al., 2008a) included 111 816 subjects with valid address data and no prevalent cancer at baseline. In the 11 years of follow-up, 1940 incident lung cancer cases were identified, giving relative risks adjusted for age, sex, smoking, and area indicators of socioeconomic status of 0.96 (95% CI, 0.83–1.11) per 10 μg/m³ of black smoke, 0.81 (95% CI, 0.63–1.04) per 10 μg/m³ of $PM_{2.5}$, 0.86 (95% CI, 0.70–1.07) per 30 μg/m³ of NO_2, and 0.90 (95% CI, 0.72–1.11) per 20 μg/m³ of SO_2. More detailed analyses were conducted for the association of lung cancer with a 10 μg/m³ increment in black smoke among never-smokers (RR, 1.47; 95% CI, 1.01–2.16; 252 cases), ex-smokers (RR, 0.91; 95% CI, 0.68–1.23; 500 cases), and current smokers (RR, 0.85; 95% CI, 0.70–1.03; 1188 cases). Relative risks for traffic intensity and proximity to a major road were elevated but not statistically significant. Case–cohort analyses with adjustment for additional covariates gave qualitatively similar results.

Analyses of the association of lung cancer mortality with air pollution including 117 528 individuals from the same cohort were reported by Beelen et al. (2008b). Further details of the study methods and analyses of mortality from non-cancer outcomes, as well as identical results for lung cancer, were also reported by Brunekreef et al. (2009). After adjustment for age, sex, smoking, and socioeconomic status, relative risks were 1.03 (95% CI, 0.88–1.20) per 10 μg/m³ of black smoke, 1.06 (95% CI, 0.82–1.38) per 10 μg/m³ of $PM_{2.5}$, 0.91 (95% CI, 0.72–1.15) per 30 μg/m³ of NO_2, and 1.00 (95% CI, 0.79–1.26) per 20 μg/m³ of SO_2. A slightly increased but not statistically significant relative risk was found with black smoke and traffic intensity. Relative risks for black smoke by tobacco smoking status were shown in a figure: in never-smokers the relative risk for an increment of 10 μg/m³ in black smoke was approximately 1.5 (95% CI,

approximately 1.0–2.2), whereas no association was indicated in current or former smokers.

Raaschou-Nielsen et al. (2010) conducted a case–cohort study nested within three Danish cohorts that were initiated at different times between 1970 and 1993 and followed up until 2001. Baseline data on tobacco smoking and other risk factors were obtained by self-administered questionnaire. Exposure to NO_x was estimated with the validated Danish AirGIS dispersion modelling system estimating traffic-related air pollution at all residential addresses of the study participants from 1971 to 2001. The study included 679 incident cases and 3481 people in a subcohort (comparison group). After controlling for sex, cohort, birth cohort, smoking, education level, BMI, and alcohol consumption, the relative risk was 1.30 (95% CI, 1.07–1.57) for exposure to NO_x between 30 μg/m³ and 72 μg/m³ and 1.45 (95% CI, 1.12–1.88) for NO_x > 72 μg/m³, corresponding to a relative risk of 1.37 (95% CI, 1.06–1.76) per 100 μg/m³ increase in NO_x. The rate ratio was higher among never-smokers, but there was no significant difference among never-smokers, former smokers, or current smokers. [The Working Group noted the short follow-up as a limitation of this study.]

The study of Raaschou-Nielsen et al. (2011a) is based on a cohort of 52 970 individuals followed up until 2006 and included 592 incident lung cancer cases (241 of these were also included in the 2010 study). NO_x concentrations at each home address from 1971 onwards were assessed for each cohort member with the AirGIS modelling system for traffic-related air pollution, and indicators of proximity to major roads and traffic load within 200 m were estimated. There were no estimates of exposure to PM or other air pollutants. After adjustment for age, smoking, second-hand smoke, education level, and dietary variables, the relative risk for an increment of 100 μg/m³ in NO_x was 1.09 (95% CI, 0.79–1.51). Analysis by quartile of NO_x showed an elevated relative risk in the highest exposure category, with NO_x > 29.7 μg/m³ (RR, 1.30; 95% CI, 1.05–1.61), but no increase at intermediate levels of exposure. Elevated risks were found in particular in association with proximity to a major road (RR, 1.21; 95% CI, 0.95–1.55).

The ESCAPE study (Raaschou-Nielsen et al., 2013) includes 17 European cohorts, for which exposure assessment was carefully standardized with a campaign of measurements, the creation of a common database of exposure data and covariates, and a common script for statistical analysis. Two cohorts had been published separately before: Raaschou-Nielsen et al. (2011a) and EPIC. For the former, only the Copenhagen part of the cohort was included and the follow-up was extended to 2010; 397 lung cancer cases were included in both studies. Part of the EPIC cohort was also included in Vineis et al. (2006) but included only never-smokers and ex-smokers, after a shorter follow-up and with different exposure assessment. In the ESCAPE study, exposures to air pollution were estimated using land-use regression models with the same methodology in all the areas. Estimates of exposure were generated for PM_{10}, $PM_{2.5}$, coarse particles, NO_2, NO_x, and two indicators of traffic. The overall population was 312 944, and 2095 incident cases of lung cancer were identified. After adjustment for potential individual-level confounders, including several indicators of smoking, and socioeconomic status at an area level (Table 2.2), the relative risks for lung cancer were 1.22 (95% CI, 1.03–1.45) for an increment of 10 μg/m³ of PM_{10} and 1.18 (0.96–1.46) per 10 μg/m³ of $PM_{2.5}$. Addition of the smoking variables to the models decreased the relative risks for PM_{10} and $PM_{2.5}$ from about 1.3 to about 1.2. The risk was particularly elevated for adenocarcinomas, rather than squamous cell carcinomas. No increase in lung cancer risk was observed for exposure to NO_2, NO_x, or indicators of traffic.

There was no evidence of heterogeneity between the hazard ratios for the 17 cohorts, since the *P*-values based on the Q statistics were

close to 1.0 for PM_{10} and $PM_{2.5}$ and the I^2 values (indicating the proportion of observed variation reflecting a real difference in effect size) were zero for both PM_{10} and $PM_{2.5}$. Furthermore, the 95% confidence interval of each cohort-specific hazard ratio in relation to PM_{10} and $PM_{2.5}$ enclosed the combined hazard ratio for all cohorts. [The Working Group regarded this as a highly informative study, for the wide range of exposures included, the quality of exposure assessment and degree of standardization in procedures, the large sample size, and the careful control for confounding by smoking and other factors.]

Heinrich et al. (2013) studied 4752 women and identified 41 deaths from lung cancer. Exposure was assessed at the baseline address using pollutant measurements from the nearest monitoring station and proximity to a major road. The PM_{10} concentration was estimated from measured TSP using a conversion factor. Elevated relative risks for lung cancer were found for an IQR increase in PM_{10} (RR, 1.84; 95% CI, 1.23–2.74) and NO_2 (RR, 1.46; 95% CI, 0.92–2.32). [The Working Group noted the very small sample size and expressed concern about potential publication bias affecting small studies.]

Cesaroni et al. (2013) investigated the association of lung cancer mortality with air pollution among 1 265 058 people in Rome, Italy, whose exposure was characterized with land-use regression models for NO_2 and dispersion models for $PM_{2.5}$. After adjustment for sex, age, marital status, place of birth, education level, occupation, and socioeconomic status, they found relative risks of 1.05 (95% CI, 1.01–1.10) for a 10 μg/m³ increment in $PM_{2.5}$ and 1.04 (95% CI, 1.02–1.07) for a 10 μg/m³ increment in NO_2. Tests for trend in analyses based on quintiles of exposure were statistically significant ($P < 0.01$) for both pollutants. An association was not observed for indicators of distance to heavy-traffic roads. The association of smoking with exposure to $PM_{2.5}$ was evaluated among a subgroup of 7845 SIDRIA cohort members. Smoking and exposure to air pollutants were not associated, and no change in results for total mortality was observed when adjusting for smoking status in the subcohort. However, this finding was for total mortality, not specifically lung cancer. [This was a very large study with good exposure assessment based on land-use regression models.]

Carey et al. (2013) conducted a study on a large (n = 835 607) cohort of primary care patients in the United Kingdom. Annual mean concentrations of PM_{10}, $PM_{2.5}$, NO_2, SO_2, and ozone were assessed at 1 km² resolution by an emissions inventory combined with dispersion modelling. Covariates were obtained from electronic patient records. The estimated hazard ratios were derived from emission-based models. They found elevated hazard ratios for lung cancer in particular in association with NO_2 after adjustment for age, sex, smoking, BMI, and education level (HR, 1.11; 95% CI, 1.05–1.17 for a 10.7 μg/m³ increment). The hazard ratios for the association of lung cancer with SO_2 and PM were modestly elevated with adjustment for the same covariates: 1.03 (95% CI, 0.99–1.06) per 2.2 μg/m³ increment in SO_2, 1.03 (95% CI, 0.98–1.09) per 3 μg/m³ of PM_{10}, and 1.04 (95% CI, 0.99–1.09) per 1.9 μg/m³ of $PM_{2.5}$. With adjustment for income instead of education level, the associations for PM and NO_2 were slightly weaker and not statistically significant, whereas the association for SO_2 was stronger (HR, 1.05; 95% CI, 1.01–1.08). [The particular nature of this cohort derived from a primary care database and the sensitivity of the associations to adjustment for different markers of social position makes the interpretation of the results difficult.]

2.1.3 Cohort studies in other regions

See Table 2.3.

Cao et al. (2011) examined the association of outdoor air pollution with mortality using the China National Hypertension Survey, a

Table 2.3 Cohort studies of lung cancer and outdoor air pollution in other regions

Reference and study location	Total no. of subjects	Follow-up period	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Cao et al. (2011) China National Hypertension Survey, China	70 947	1991–1999/ 2000	Annual average TSP, SO_2, and NO_x concentrations between 1991 and 2000 measured at 103 fixed-site monitoring stations in 31 cities Conversion factors (PM_{10}/TSP ≈ 0.5 and $PM_{2.5}/PM_{10}$ ≈ 0.65) were used to estimate RRs for $PM_{2.5}$	Lung	Per 10 μg/m³ increase in TSP; mean, 289; range, 113–499	624	1.01 (1.00–1.02)	Age, sex, BMI, physical activity, education level, occupation, smoking status, age at starting to smoke, years smoked, cigarettes per day, alcohol consumption, and hypertension	Multipollutant models were considered (the effects of SO_2 remained even after adjustment for TSP or NO_x, whereas the effects of TSP were attenuated after adjustment for SO_2 or NO_x); during 1991–2000
					Per 10 μg/m³ increase in SO_2; mean, 73; range, 11–174	624	1.04 (1.02–1.06)		
					Per 10 μg/m³ increase in NO_x; mean, 50; range, 19–122	624	1.03 (0.99–1.07)		
					Per 10 μg/m³ increase in $PM_{2.5}$	624	1.03 (1.00–1.07)		
Katanoda et al. (2011) Three-Prefecture Cohort Study, Japan	63 520	1983–1985	Annual mean concentrations of SPM, SO_2, and NO_2 during 1974–1983 measured at monitoring stations in or near each study area; $PM_{2.5}$ concentrations converted from SPM using a ratio of 0.7	Lung	Per 10 μg/m³ increase in SPM; range, 24.0–59.9	518	1.16 (1.08–1.25)	Sex, age, smoking status (current, former, never), pack-years of smoking, smoking status of family members living together, daily green and yellow vegetable consumption, daily fruit consumption, and use of indoor charcoal or briquette braziers for heating	
					Per 10 μg/m³ increase in $PM_{2.5}$; range, 16.8–41.9	518	1.24 (1.12–1.37)		
					Per 10 ppb increase in SO_2; range, 2.4–19.0	518	1.26 (1.07–1.48)		
					Per 10 ppb increase in NO_2; range, 1.2–33.7	518	1.17 (1.10–1.26)		
					Male current smokers	292	1.35 (1.20–1.52)	Age, pack-years of smoking, smoking status of family members living together, daily green and yellow vegetable consumption, daily fruit consumption, and use of indoor charcoal or briquette braziers for heating	The same tendency was observed for other pollutants (SPM, SO_2, and NO_2); other strata were not considered due to small number of the participants
					Male former smokers (per 10 μg/m³ increase in $PM_{2.5}$)	90	1.11 (0.77–1.60)		
					Female never-smokers (per 10 μg/m³ increase in $PM_{2.5}$)	73	1.16 (1.02–1.33)		

Table 2.3 (continued)

Reference and study location	Total no. of subjects	Follow-up period	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Hales et al. (2012) New Zealand Census–Mortality Study, New Zealand	1 065 645	1996–1999	Estimated exposure to PM_{10} for census area units modelled by a LUR model (developed for Christchurch)	Lung	Per 1 μg/m³ increase in PM_{10}; mean (SD), 8.3 (8.4) μg/m³	1686	1.02 (1.00–1.03)	Age, sex, ethnicity, social deprivation, income, education level, smoking history, and average minimum temperature	The validity of exposure modelling was examined by Kingham et al. (2008); the atmospheric dispersion model was developed for one city (Christchurch) and extrapolated to urban census units throughout the country
Yorifuji et al. (2013) Shizuoka Elderly Cohort, Japan	13 412	1999–2009	Traffic-related air pollution (indexed by NO_2) modelled by using a LUR model, assigned as concentration in the year of the outcome	Lung	All participants NO_2 (per 10 μg/m³ increase); mean (SD), 3.11 (12.10); range, 9.40–77.08 μg/m³	116	1.20 (1.03–1.40)	Age, sex, smoking, BMI, hypertension, diabetes, financial capability, and area mean taxable income	Update of Yorifuji et al. (2010); individual exposure assessment was conducted; the validity of exposure modelling was examined by Kashima et al. (2009) Loss to follow-up, 57%
					Never-smokers (per 10 μg/m³ increase)	NR	1.30 (0.98–1.71)		
					Ex/current smokers (per 10 μg/m³ increase)	NR	1.18 (0.98–1.43)		

BMI, body mass index; CI, confidence interval; LUR, land-use regression; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; NR, not reported; PM_{10}, particulate matter with particles of aerodynamic diameter < 10 μm; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 μm; RR, relative risk; SD, standard deviation; SO_2, sulfur dioxide; SPM, suspended particulate matter; TSP, total suspended particles.

prospective cohort of approximately 160 000 adults enrolled in 1991 from 17 provinces in China. They limited the analysis to participants living in urban areas, due to a lack of air pollution exposure data in rural areas, leaving 70 947 participants in 31 cities. Baseline data on demographic characteristics, medical history, and lifestyle-related factors (including smoking variables) were obtained in 1991, and follow-up examinations were conducted in 1999 and 2000. During the follow-up period, there were 624 deaths from lung cancer. Annual average TSP, SO_2, and NO_x concentrations measured at a total of 103 fixed-site monitoring stations in the 31 cities were calculated for 1991–2000 and were assigned to the participants living in the cities. PM_{10}, $PM_{2.5}$, NO_2, and ozone were not measured. After adjustment for smoking, socioeconomic status (education level and occupation), and other potential confounders, the rate ratios per 10 μg/m³ increase in each pollutant were 1.01 (95% CI, 1.00–1.02) for TSP, 1.04 (95% CI, 1.02–1.06) for SO_2, and 1.03 (95% CI, 0.99–1.07) for NO_x. The effects of SO_2 remained even after adjustment for TSP or NO_x, whereas the effects of TSP were attenuated after adjustment for SO_2 or NO_x. Using conversion factors (PM_{10}/TSP ≈0.5 and $PM_{2.5}/PM_{10}$ ≈0.65), the estimated rate ratio per 10 μg/m³ increase in $PM_{2.5}$ was 1.03 (95% CI, 1.00–1.07). [Exposure assessment was conducted at the central monitoring sites in the cities and did not account for variations within each city. No information about loss to follow-up was provided. The lack of direct measurements of PM_{10} or $PM_{2.5}$ is a limitation. The authors used a single set of conversion factors recommended by the China Ministry of Environmental Protection for all areas.]

Katanoda et al. (2011) examined the associations between long-term exposure to air pollution and lung cancer in the Three-Prefecture Cohort Study in Japan. Each prefecture had one polluted (urban) area and one to three non-polluted (rural) areas. The participants were residents in these areas aged 40 years or older and were enrolled into the cohort between 1983 and 1985. Among 100 615 respondents, the authors restricted the analysis to 63 520 participants who had lived in the study areas for more than 10 years and had complete data for potential confounders. Annual mean concentrations of suspended PM (SPM), SO_2, and NO_2 during the period 1974–1983 measured at monitoring stations were assigned. $PM_{2.5}$ concentrations were estimated from SPM using a ratio of 0.7, which was assumed considering local data obtained in study areas during several periods between 1974 and 2005. During the 10-year follow-up, there were 518 deaths from lung cancer. The relative risks for lung cancer mortality associated with a 10-unit increase in SPM (μg/m³), $PM_{2.5}$ (μg/m³), SO_2 (ppb), and NO_2 (ppb) were 1.16 (95% CI, 1.08–1.25), 1.24 (95% CI, 1.12–1.37), 1.26 (95% CI, 1.07–1.48), and 1.17 (95% CI, 1.10–1.26), respectively, after adjustment for tobacco smoking and other confounding factors. Men had slightly higher effect estimates than women. The effect estimates were larger for male current smokers; for example, the relative risks for $PM_{2.5}$ were 1.35 (95% CI, 1.20–1.52) for male current smokers, 1.11 (95% CI, 0.77–1.60) for male former smokers, and 1.16 (95% CI, 1.02–1.33) for female never-smokers. [This study included adjustments for a wide range of risk factors, which could be expected to account for most confounding. The study is notable for having adjusted for indoor sources of air pollution. The Working Group questioned the validity of the factors used to estimate $PM_{2.5}$ from SPM.]

Hales et al. (2012) used the New Zealand Census–Mortality Study to examine the association between PM_{10} exposure and mortality. Records from the 1996 New Zealand census (n = 3 732 000) were anonymously and probabilistically linked to mortality data for the next 3 years, creating a cohort study with 3 years of follow-up. There were 1 065 645 adults aged 30–74 years living in urban areas for which data were available on all covariates. A land-use

regression model developed and evaluated for census area units in Christchurch was extrapolated to urban census area units throughout the country to estimate exposure to PM_{10} in 1996, which was validated by Kingham et al. (2008). Four PM_{10} exposure categories (0.1, 7, 14, and 19 μg/m³) were assigned to the participants and analysed as a linear term. The odds ratio for lung cancer mortality was 1.015 (95% CI, 1.004–1.026) per 1 μg/m³ increase in PM_{10} after adjustment for smoking history, socioeconomic status, and other potential confounders. [This study includes a very large and representative sample of the New Zealand population. This study also has the strength of modelling PM_{10} at the level of a small census unit, which includes approximately 2300 people. There is a concern that a land-use regression model developed for Christchurch was extrapolated to urban census area units throughout the country.]

Yorifuji et al. (2013) studied the association between long-term exposure to traffic-related air pollution and cause-specific mortality. This study is an update of an earlier study of the same cohort (Yorifuji et al., 2010). Individual data were extracted from an ongoing cohort study of elderly residents in Shizuoka Prefecture, Japan (the Shizuoka Elderly Cohort). In December 1999, 22 200 residents were randomly selected from all 74 municipalities in Shizuoka, by stratifying both sex and age group (65–74 years and 75–84 years). In the updated study, Yorifuji et al. (2013) extended the follow-up period by 3 years and evaluated the lung cancer risk associated with traffic-related air pollution. A total of 13 412 individuals completed questionnaires and were eligible to participate, of whom 7650 were lost to follow-up from December 1999 to January 2009. Annual individual exposure to NO_2, as an index of traffic-related exposure, was assessed for 1996 to 2009 using a land-use regression model and assigned to the participants. Participants were assigned an estimated NO_2 exposure in the fiscal year of the outcome. The relative risk for lung cancer mortality associated with a 10 μg/m³ increase in NO_2 was 1.20 (95% CI, 1.03–1.40) after adjustment for smoking, socioeconomic status, and other potential confounders. The relative risk among never-smokers was 1.30 (95% CI, 0.98–1.71), whereas among ex-smokers and current smokers it was 1.18 (95% CI, 0.98–1.43). [The never-smoker category was described as non-smokers in the paper.]

Analyses using other windows of exposure (the preceding 1, 2, or 3 years before the outcome) gave similar results, and assigning the average concentration from the first year of the study slightly attenuated the relative risk (RR, 1.16; 95% CI, 0.97–1.39). Restricting the analysis to participants living within 10 km of sampling sites increased the relative risk to 1.27 (95% CI, 1.07–1.50). [The strength of this study is the exposure assessment at the individual level and the use of individual NO_2 exposure as an index of traffic-related exposure. A somewhat stronger association was found after restricting the participants to those living within 10 km of sampling sites, presumably reducing measurement error. Although there is considerable loss to follow-up, the Working Group concluded that this was unlikely to have resulted in significant bias.]

2.1.4 Case–control studies

See Table 2.4.

The case–control studies investigating the role of air pollution in lung cancer are presented below according to the main type of exposure under study: all sources, including traffic-related air pollution, or specific industrial sources. The studies focused on all sources of air pollution have been divided according to the methodology – qualitative or quantitative – used for exposure assessment. In fact, the main development in the design of the studies is the evolution of exposure assessment methods from the rather crude classification of urban areas and air pollution zones (Vena, 1982; Samet et al., 1987), proximity to

Table 2.4 Case–control studies of lung cancer and outdoor air pollution

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Studies with qualitative or semiquantitative exposure assessment										
Vena (1982) New York, USA, 1957–1965	417 incident cases	752	Hospital	Interviewer-administered questionnaire; town of residence classified according to 2-year average TSP levels; duration of residence considered	Lung	Duration of residence in zones with high or medium air pollution 0–29 yr 30–49 yr ≥ 50 yr ≥ 50 yr	 54 114 249 249	 1 1.32 (NR), $P > 0.05$ 1.58 (1.09–2.29) 1.26 (NR), $P > 0.05$	Age and occupation Adding adjustment for smoking	Men only; response rate NR
Samet et al. (1987) New Mexico, USA, 1980–1982	422 incident cases	727	Population	Interviewer-administered standardized questionnaire to the cases or relatives; duration of residence in areas with different urbanization levels and industry	Lung	Duration of residence in counties with > 500 000 residents *Non-Hispanic Whites* 1–10 yr ≥ 11 yr *Hispanic Whites* ≥ 1 yr		 0.9 (0.6–1.4) 1.1 (0.8–1.7) 0.9 (0.4–2.1)	Age, smoking, and occupation	Response rate: 91% for cases and 81.3% for controls
Katsouyanni et al. (1991) Athens, Greece, 1987–1989	101 incident cases	89	Hospital	Interviewer-administered questionnaire; area of residence classified according to 1983–1985 average smoke and NO_2 levels; inverse of distance from fixed monitors was considered	Lung	Quartile of air pollution exposure		1.22 (0.91–1.63) 1.09 (NR)	Age, education level, and interviewer Smoking	Women only; response rate: 96% for cases and 90.6% for controls

Table 2.4 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Jöckel et al. (1992) Germany	194 incident cases	194 hospital and 194 population controls	Both	Interviewer-administered questionnaire; area of residence classified according to SO_2 emission for 1955–1980 and a semiquantitative index based on TSP, SO_2, and B[*a*]P	Lung	Air pollution exposure Emission index high Semiquantitative index high	 39 44	 1.01 (0.53–1.91) 1.16 (0.64–2.13)	Age, smoking, and occupation	Response rate NR for cases or hospital controls, 40.7% for population controls
Barbone et al. (1995) Trieste, Italy, 1979–1981, 1985–1986	755 deaths	755 (from the Autopsy Department)	Population	Interviewer-administered questionnaire to next of kin; distance from 4 pollution sources (city centre, shipyard, iron foundry, incinerator); data from 28 PM deposition meters linked to each residential address	Lung	Level of particulate deposition (g/m²/day) < 0.175 0.176–0.298 > 0.298 *P* for trend	 188 256 311	 1 1.1 (0.8–1.5) 1.4 (1.1–1.8) 0.022	Age, smoking, occupation, and social status	Men only; response rate: 80.6% for cases and 83% for controls. Deceased cases and controls. Relative risks were also increased for those living in the city centre and close to the iron foundry and the incinerator
Gupta et al. (2001) Chandigarh, India, 1995–1997	265 incident cases	525	Hospital	Interviewer-administered questionnaire; lifetime (> 75%) residence in urban, mixed, or rural area	Lung	Residence in urban, mixed, or rural area *Men* Rural Mixed Urban	 153 36 45	 1 0.89 (0.62–1.64) 0.82 (0.53–1.27)	Age, smoking, religion, and education level	Response rates NR

Table 2.4 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Gupta et al. (2001) Chandigarh, India, 1995–1997 (cont.)						*Women*				
						Rural	5	1		
						Mixed	1	0.08 (0.01–0.78)		
						Urban	24	0.29 (0.07–1.17)		
Edwards et al. (2006) Teesside, England, 2000–2004	204 incident cases	339	Population	Interviewer-administered questionnaire; residential addresses classified in three exposure zones on the basis of proximity to heavy industry	Lung	Duration of residence in areas close to heavy industry (adjusted for latency)			Age, smoking, asbestos exposure, marital status, and type of job	Response rate: 82.3% for cases and 47.8% for controls
						0 yr	45	1		
						1–25 yr	60	0.83 (0.43–1.60)		
						> 25 yr	99	1.85 (0.80–4.24)		
						Per 10 yr of exposure		1.21 (0.99–1.47)		
Chiu et al. (2006) Taiwan, China, 1994–2003	962 deaths	972 deaths	Population	Municipality-based composite index of air pollution exposure based on fixed monitors for PM_{10}, SO_2, NO_2, O_3, and CO	Lung	*Air pollution exposure index*			Age and urbanization index	Only housewives according to the death certificate were included. No interview was conducted
						0.62–0.74	312	1.11 (0.88–1.40)		
						≥ 0.75	345	1.28 (1.02–1.61)		
Liu et al. (2008a) Taiwan, China, 1995–2005	1676 deaths	1676 deaths	Population	Municipality-based composite index of air pollution exposure based on fixed monitors for NO_2 and CO	Lung	*Air pollution exposure index*			Age, urbanization index, and marital status	No interview was conducted. No smoking status available. Women only
						Medium	710	1.24 (1.03–1.50)		
						High	547	1.46 (1.18–1.81)		
						P for trend		< 0.001		

Table 2.4 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Chang et al. (2009) Taiwan, China, 1997–2006	4087 deaths	4087 deaths	Population	Municipality-based index of petrol-station density	Lung	Petrol-station density (per km²)			Age and urbanization index	Only housewives according to the death certificate were included. No interview was conducted
						0.159–0.444	1417	1.14 (1.01–1.30)		
						0.452–2.692	1552	1.19 (1.02–1.38)		
López-Cima et al. (2011) Asturias, Spain, 2000–2008	626 incident cases	626	Hospital	Interviewer-administered questionnaire; last residential addresses geocoded using GIS; distance from city centre and industry estimated	Lung	*Residence area*			Age, sex, smoking, hospital area, occupation, and family history of cancer	Residents near industry: increased risk of small cell carcinoma (RR, 2.23; 95% CI, 1.01–4.92). Residents in urban areas: increased risk of adenocarcinoma (RR, 1.92; 95% CI, 1.09–3.38)
						Urban	63	1.33 (0.86–2.06)		
						Semi-urban	63	1.34 (0.86–2.07)		
						Industrial	63	1.49 (0.93–2.39)		
Studies of exposure to industrial pollution										
Brown et al. (1984) Pennsylvania, USA, 1974–1977	335 deaths	332	Population (death certificates)	Interviewer-administered questionnaire to next of kin; metals in soil and proximity to a zinc plant used for exposure assessment	Lung	Heavy arsenic	16	2.3 (1.0–5.4)	Age, smoking, and occupation	Men only; response rate: 96% for cases and 94% for controls
						Heavy cadmium	16	2.0 (0.9–4.6)		
						Far from the zinc smelter	292	1		
						Middle distance	26	1.2 (0.6–2.1)		
						Near distance	16	1.6 (0.6–4.3)		
Pershagen (1985) Sweden, 1961–1979	212 deaths	424 deaths	Population (death certificates)	Mailed questionnaire to next of kin; subjects living in parishes close to an arsenic-emitting smelter were "exposed"	Lung	Residence in exposed parishes			Age, smoking, and occupation	Men only; response rate: 96% for cases and 91% for controls. All subjects were deceased
						Yes	42	2.0 (1.2–3.4)		

Table 2.4 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Xu et al. (1989) Shenyang, China, 1985–1987	1249 incident cases	1345	Population	Interviewer-administered standardized questionnaire; perceived smokiness of outdoor environment; duration of residence close to industrial factories	Lung	*Smokiness of outdoor environment* Men Somewhat/slightly smoky Smoky Women Somewhat/slightly smoky Smoky	 190 262 118 161	 1.5 (1.2–2.0) 2.3 (1.7–2.9) 1.4 (1.1–2.0) 2.5 (1.8–3.5)	Age, education level, smoking, and indoor air pollution	Response rate: 95% for cases and 99.8% for controls. Subsequent analysis (Xu et al., 1991) indicated an OR of 3.0 (95% CI, 1.6–6.0) for men living within 1 km of the large smelter plant
Ko et al. (1997) Kaohsiung, Taiwan, China, 1992–1993	117 incident cases	117	Hospital	Interviewer-administered questionnaire; residence for at least 5 yr within 3 km of a major industrial site	Lung	Residence close to an industrial site 0–20 yr ≥ 20 yr	 7 20	 0.8 (0.2–3.9) 2.7 (0.9–7.8)	Age, date of interview (matched), SES, residential area, education level, cooking fuels, tuberculosis, use of fume extractor, and consumption of vegetables	Women only; analyses for residence close to an industrial site were restricted to non-smokers; response rate: 91% for cases and 94% for controls
Yang et al. (1999) Taiwan, China, 1990–1994	399 deaths	399	Population	Proportion of a municipality's total population employed in the petrochemical industry	Lung	Proportion employed in petrochemical industries 0.07–0.50 ≥ 0.51	 141 148	 1.50 (1.03–2.17) 1.66 (1.05–2.61)	Sex, year of birth, year of death (matched), non-petrochemical air pollution index, marital status, and urbanization of residence	Only housewives according to the death certificate were included. No interview was conducted

Table 2.4 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Petrauskaite et al. (2002) Lithuania, 1981–1991	277 deaths	1108	Population	Questionnaire mailed to next of kin; area of residence classified according to distance from a chemical plant	Lung	Distance from the plant < 5 km	96	1.02 (0.76–1.38)	Age, smoking, and occupation	Men only; response rate: 81.6% for cases and 80% for controls
Bessö et al. (2003) Sweden, 1961–1990	316 deaths	727	Population	Mailed questionnaire to next of kin; duration of residence in the area close to the smelter was the exposure under study	Lung	*Residence in the smelter area* Men Ever < 20 yr > 20 yr Women Ever < 20 yr > 20 yr	 19 37 10 15	 1.38 (0.89–2.14) 1.65 (0.80–3.38) 1.28 (0.77–2.12) 0.88 (0.48–1.62) 0.72 (0.29–1.80) 1.00 (0.48–2.12)	Age, smoking, and occupation	Response rate: 94% for cases and 91% for controls

Table 2.4 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Pisani et al. (2006) Lampang Province, Thailand, 1993–1995	211 incident cases	202 controls (set 1) and 211 controls (set 2)	Set 1: population; set 2: hospital	Interviewer-administered questionnaire; air pollution exposure index incorporating linear distance from power plants, SO_2, NO_2, or TSP emissions, and the percentage of wind from the plants	Lung	Cumulative index of exposure to air pollutants (tons per km^2 per yr) SO_2 or NO_2 1808–3507 > 3507 Suspended particulate 214–392 > 392	 86 71 84 71	 1.3 (0.8–2.1) 1.2 (0.7–2.0) 1.2 (0.7–2.0) 1.1 (0.7–1.8)	Age, sex (matched), and cumulative number of cigarettes smoked	Only the results with population control are shown; response rate: 81% for cases and 81% for controls (set 1), 77% for controls (set 2)
Studies with quantitative exposure assessment										
Jedrychowski et al. (1990) Cracow, Poland, 1980–1985	1099 deaths	1073	Population (death certificates)	Mailed questionnaire to next of kin; measured levels of TSP and SO_2 were used, and isopleths were estimated	Lung	*Air pollution index* Men Low (TSP < 150 µg/m³ and SO_2 < 104 µg/m³) Medium (TSP > 150 µg/m³ or SO_2 > 104 µg/m³ but not both) High (TSP > 150 µg/m³ and SO_2 > 104 µg/m³) Women Low Medium and high combined	 650 129 122 124 74	 1 1.0 (0.75–1.83) 1.46 (1.06–1.99) 1 1.17 (0.70–1.96)	Age, smoking, and occupation	Response rate: 70.7% for male cases, 65.1% for female cases, 73.5% for male controls, and 64.0% for female controls

Table 2.4 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Nyberg et al. (2000) Stockholm, Sweden, 1985–1990	1042 incident cases	2364 population controls, 1090 deaths controls	Population	Mailed questionnaire to the subjects and next of kin; dispersion models used for annual mean levels of SO_2 and NO_2; annual levels of SO_2 and NO_2 were estimated for each year from 1950 to 1990 (Bellander et al., 2001)	Lung	NO_2 for traffic air pollution and SO_2 for air pollution related to heating (10-yr average, lagged 20 yr)			Age, smoking, occupation, social status, and radon	Men only; response rate: 87% for cases, 88% for population controls, and 82% for deceased controls
						NO_2 from traffic air pollution (effect per 10 μg/m³)		1.10 (0.97–1.23)		
						≥ 12.78–17.35 μg/m³	264	1.15 (0.91–1.46)		
						≥ 17.35–23.17 μg/m³	250	1.01 (0.79–1.29)		
						≥ 23.17–29.26 μg/m³	165	1.07 (0.81–1.42)		
						≥ 29.26 μg/m³	120	1.44 (1.05–1.99)		
						SO_2 from heating (effect per 10 μg/m³)		1.01 (0.98–1.03)		
						≥ 66.20–87.60 μg/m³	270	1.16 (0.91–1.47)		
						≥ 87.60–110.30 μg/m³	259	1.00 (0.79–1.27)		
						≥ 110.30–129.10 μg/m³	151	0.92 (0.70–1.21)		
						≥ 129.10 μg/m³	123	1.21 (0.89–1.66)		

Table 2.4 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Hystad et al. (2013) Canada, 1994–1997	2390 incident cases	3507 population controls	Population	Mailed questionnaire to the subjects and next of kin; national spatial surface estimates using satellite ($PM_{2.5}$ and NO_2) or chemical transport model (O_3); annual pollutant concentrations and residential histories were used (Hystad et al., 2012)	Lung	Effects per 10-unit increase in $PM_{2.5}$, NO_2, and O_3			Individual (age, sex, smoking, occupation, SES, etc.) and a large set of geographical confounders	Response rate: 62% for cases and 67% for population controls
						Exposure from national spatial model				
						$PM_{2.5}$ (per 10 μg/m³)	2154	1.29 (0.95–1.76)		
						NO_2 (per 10 ppb)	2154	1.11 (1.00–1.24)		
						O_3 (per 10 ppb)	2154	1.09 (0.85–1.39)		
						Exposure from fixed monitors within 50 km of residential address				
						$PM_{2.5}$ (per 10 μg/m³)	1200	1.33 (0.82–2.15)		
						NO_2 (per 10 ppb)	983	1.34 (1.07–1.69)		
						O_3 (per 10 ppb)	1015	1.11 (0.79–1.54)		

B[*a*]P, benzo[*a*]pyrene; CI, confidence interval; CO, carbon monoxide; GIS, geographic information system; NO_2, nitrogen dioxide; NR, not reported; O_3, ozone; OR, odds ratio; PM, particulate matter; PM_{10}, particulate matter with particles of aerodynamic diameter < 10 μm; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 μm; RR, relative risk; SES, socioeconomic status; SO_2, sulfur dioxide; TSP, total suspended particles; yr, year.

industry (Brown et al., 1984; Pershagen, 1985), and proximity to traffic (Vineis et al., 2006) to more advanced use of fixed-monitor data (Jedrychowski et al., 1990), exposure modelling (Nyberg et al., 2000), and national spatiotemporal air pollution maps (Hystad et al., 2012, 2013).

(a) Studies with qualitative or semiquantitative assessment of air pollutant exposure

Vena (1982) conducted a hospital-based case–control study in Erie County, New York, USA. Retrospective data on residential and employment history and on smoking were obtained from 417 White male lung cancer patients and 752 controls with non-respiratory, non-neoplastic diseases, admitted from 1957 to 1965. Two-year TSP data and a historical review of point sources of air pollution were used to define air pollution zones. Subjects were classified by duration of residence in zones with medium or high air pollution levels. The results did not show a clear association of lung cancer with air pollution alone; the relative risk for exposure of 50 years or longer in medium- or high-pollution zones went from 1.58 (95% CI, 1.09–2.29) after adjustment for age and occupation to 1.26 (CI not reported; $P > 0.05$) after adjustment also for smoking. There was a suggestion of effect modification for air pollution as there was increased risk from smoking and occupational exposures if there was also long-term exposure to air pollution. The risk for heavy smokers with heavy exposure to air pollution was more than 4 times that of men with none of the high-exposure conditions. [Exposure assessment was rather crude. No response rates by case–control status were provided.]

Samet et al. (1987) conducted a population-based case–control study of lung cancer in New Mexico, USA, between 1980 and 1982, including 422 cases and 727 controls. Subjects were asked to identify all locations where they had resided for 6 months or longer and were interviewed about other personal characteristics, including smoking and occupation. The residential data were coded at the county and state levels and combined with county-level socioeconomic data from population censuses to generate indices of time lived in counties or metropolitan areas of different sizes, degrees of urbanization, and extents of employment in manufacturing industries. Residential history patterns were the same in cases and controls. There was no association of the residential history variables with lung cancer risk; relative risks were constantly close to unity. [Exposure assessment was rather crude in this study.]

Katsouyanni et al. (1991) conducted a case–control study exploring the role of smoking and outdoor air pollution in the causation of lung cancer. The study was undertaken in Athens, Greece, between 1987 and 1989 and included women only; 101 women with lung cancer and 89 comparison women with fractures or other orthopaedic conditions were included. Smoking habits were ascertained through interviews, whereas lifetime exposure to air pollution was assessed by linking lifelong residential and employment addresses with objectively estimated or presumed air pollution levels. Pollution isopleths were based on smoke and NO_2 levels measured at fixed-monitor stations in the period 1983–1985. Air pollution levels were associated with increased risk of lung cancer with an odds ratio of 1.22 (95% CI, 0.91–1.63) per quartile of exposure, which was reduced to 1.09 (CI not reported) after adjustment for tobacco smoking. The *P*-value for the interaction of air pollution and tobacco smoking was 0.10. There was no effect of air pollution among non-smokers [crude OR, 0.7], but the relative risk contrasting extreme quartiles of air pollution among smokers of 30 years' duration was 2.23 (CI not reported). [Detailed information on occupational exposure and smoking was available, but the size of the study is limited.]

Jöckel et al. (1992) conducted a hospital-based case–control study in five cities in Germany, including 194 lung cancer cases, 194 hospital

controls, and 194 population controls (only a sample of all hospitals was included). Subjects were interviewed for their smoking, occupational, and residential history by trained interviewers, using a standardized questionnaire. For the quantification of occupational exposure to known carcinogens of the lung, an approach was developed with exposure information obtained by supplemental questionnaires. Quantification of air pollution was based on emission data for SO_2 and a semiquantitative index. After adjustment for smoking and occupational exposures, relative risks of 1.01 (95% CI, 0.53–1.91) for the emission index and 1.16 (95% CI, 0.64–2.13) for the semiquantitative index were obtained. [Exposure assessment was rather crude, on a county basis, and the statistical power was rather low.]

Barbone et al. (1995) investigated the relationship between air pollution and lung cancer with a case–control study among men who had died in Trieste, Italy, from 1979 to 1981 and from 1985 to 1986. From an autopsy registry, 755 cases and 755 controls were identified, and information on smoking, occupation, and residence was obtained from the next of kin. Air pollution at the residence of each subject was estimated from the average value of total PM deposition at the nearest monitoring station. After adjustment for age, smoking habits, likelihood of exposure to occupational carcinogens, and social group, the risk of lung cancer increased with increasing level of air pollution for all types of lung cancer combined ($P = 0.022$; RR, 1.4; 95% CI, 1.1–1.8 for the highest exposure category vs the lowest), for small cell carcinoma ($P = 0.016$), and for large cell carcinoma ($P = 0.049$). Compared with inhabitants of the residential area, the relative risk was 1.5 (95% CI, 1.0–2.2) for residents of the centre of the city and 1.4 (95% CI, 1.0–2.1) for residents of the industrial area. The increased relative risk of the industrial area was mainly due to exposure to an iron foundry (RR, 1.7; 95% CI, 0.7–4.1) and an incinerator (RR, 2.6; 95% CI, 1.3–5.1).

Gupta et al. (2001) conducted a case–control study on lung cancer in Chandigarh, northern India, involving 265 lung cancer cases and 525 hospital controls matched by age and sex. Data were collected in face-to-face interviews. The exposure assessment of air pollution was based on lifetime residence in areas classified by the investigators as predominantly urban, rural, or mixed. Residence in urban areas was not associated with increased risk of lung cancer: the odds ratio for men living in urban areas was 0.82 (95% CI, 0.53–1.27) and for women living in urban areas it was 0.29 (95% CI, 0.07–1.17). [Response rates were not reported. Exposure assessment was crude, and the precision was rather low.]

Edwards et al. (2006) conducted a case–control study of lung cancer among women in the highly industrialized area of Teesside, in north-eastern England. A total of 204 women aged 80 years or younger with incident primary lung cancer and 339 age-matched community controls were recruited for a population-based case–control study. Life-course residential, occupational, and active and passive smoking histories were obtained using an interviewer-administered questionnaire. The adjusted odds ratio for lung cancer among women living near (within 0–5 km of) heavy industry in Teesside or elsewhere was 1.85 (95% CI, 0.80–4.24) for more than 25 years' residence versus 0 years, or 1.21 (95% CI, 0.99–1.47) for each period of 10 years living near industry (latency was allowed for by disregarding residential exposures within the past 20 years). [A low response rate among controls (47.8%) is noted.]

Chiu et al. (2006) investigated the relationship between air pollution and lung cancer among women in a matched case–control study on deaths (972 cases) that occurred in Taiwan, China, from 1994 to 2003. The control group consisted of women who had died from causes other than cancer or respiratory diseases (972 controls), pair-matched to the cases by sex, year of birth, and year of death. A municipality-based

aggregate index of long-term exposure to air pollution was created by dividing the annual average of the measured values for each pollutant by the National Ambient Air Quality Standard for that pollutant. The ratios for each pollutant were scaled to a 100-point scale and then averaged together to generate an index value representing the net burden of these pollutants. Women who lived in municipalities with the highest levels of the air pollution exposure index had a statistically significant increased risk of lung cancer compared with those living in municipalities with the lowest air pollution exposure index after controlling for the urbanization index (RR, 1.28; 95% CI, 1.02–1.61). [Only housewives according to the death certificate were included. Since only deceased subjects were in the controls and exposure to air pollution is linked with increased cardiorespiratory mortality, exposure to air pollution may have been overrepresented in the control group, with underestimation of the effect. In addition, controlling for urbanization, which is likely to be a predictor of pollution levels, could result in overadjustment. No smoking data were available, although smoking was rare among women in Taiwan, China.]

Using the same design as Chiu et al. (2006), Liu et al. (2008a) investigated the relationship between air pollution and lung cancer in a matched case–control study on deaths among women (1676 cases and 1676 controls) that occurred in Taiwan, China, from 1995 to 2005. The classification of exposure was based on the measured levels of PM_{10}, SO_2, NO_2, and CO. NO_2 and CO levels were used to classify subjects' areas of residence into tertiles of pollutant concentrations. An urbanization index and marital status were considered in the analyses in addition to the matching factors. Among individual pollutants, positive associations were observed only for NO_2 and CO. A composite index based on these two pollutants yielded adjusted odds ratios of 1.24 (95% CI, 1.03–1.50) and 1.46 (95% CI, 1.18–1.81) for groups with medium and high exposure, respectively, compared with the group with low exposure, with a statistically significant trend. [The study shares the methodology and the limitations of the initial study by Chiu et al. (2006), and there may be a partial overlap in the study populations.]

Chang et al. (2009) investigated the relationship between exposure to traffic-related air pollution and development of lung cancer in women in Taiwan, China, using the density of petrol stations as a surrogate measure of exposure. A matched case–control study was based on lung cancer deaths among women (4087 cases and 4087 controls) from 1997 to 2006, using the same design as Chiu et al. (2006). Data on the number of petrol stations in study municipalities were collected from the two major petroleum supply companies. The petrol-station density per square kilometre for each municipality was used as an indicator of exposure. There was a statistically significant exposure–response relationship between the tertile of petrol-station density and the risk of lung cancer in women after controlling for possible confounders. [The study shares the methodology and the limitations of the studies by Chiu et al. (2006) and Liu et al. (2008a), and there may be an overlap in the study populations.]

López-Cima et al. (2011) conducted a hospital-based case–control study in Asturias, Spain. The study area included a large industrial setting. A total of 626 lung cancer patients and 626 controls were recruited and matched by ethnicity, hospital, age, and sex. Distances from the respective participants' residential locations to industrial facilities and city centres were used as a metric of exposure to urban and industrial air pollution. Odds ratios for distance to pollution sources were estimated with adjustment for sex, age, hospital area, tobacco smoking, family history of cancer, and occupation. Individuals living near industries had an excess risk of lung cancer (RR, 1.49; 95% CI, 0.93–2.39). The relative risk was higher for small cell carcinoma (RR, 2.23; 95% CI, 1.01–4.92). Residents in urban areas

showed a statistically significant increased risk of adenocarcinoma (RR, 1.92; 95% CI, 1.09–3.38) compared with those in rural areas.

(b) Studies of exposure to industrial pollution

Brown et al. (1984) reported the results of a case–control study on lung cancer deaths among residents near a zinc smelter and a steel manufacturing plant in Pennsylvania, USA. Lifetime residential, occupational, and smoking histories were obtained from the next of kin of 335 White male lung cancer cases and 332 White male controls. Relative risks were estimated according to the distance of the residence from the zinc smelter and the steel plant, and according to levels of several metals (arsenic, copper, lead, manganese, zinc, and cadmium) measured in soil samples. Twofold risks of lung cancer were associated with residence in areas with heavy levels of arsenic (RR, 2.3; 95% CI, 1.0–5.4) and cadmium (RR, 2.0; 95% CI, 0.9–4.6). Usual residence near the zinc plant was associated with an increased risk (RR, 1.6; 95% CI, 0.6–4.3), although the number of individuals living in the higher exposure area was small. These increases remained after accounting for cigarette smoking and employment in the zinc or steel industry. No excess risk was associated with living near the steel plant.

Pershagen (1985) studied 212 male lung cancer cases and 424 control men who had died between 1961 and 1979 in an industrialized county in northern Sweden. Data on smoking, occupation, and residence were obtained from the next of kin. A relative risk of 2.0 (95% CI, 1.2–3.4) for lung cancer was seen among men who had lived within 20 km of a large copper smelter that emitted arsenic.

Xu et al. (1989) conducted a case–control study in Shenyang, China, with data collected in interviews with 1249 patients with lung cancer and 1345 population-based controls. After adjustment for smoking, the relative risks were twice as high among those who reported living in smoky outdoor environments (RR, 2.3; 95% CI, 1.7–2.9 in men, and RR, 2.5; 95% CI, 1.8–3.5 in women) compared with subjects living in an environment that was not smoky. There were also associations with duration of residence within 200 m of industrial factories such as chemical and rubber plants, cement, glass, and asbestos factories, and ferrous and non-ferrous smelters in men, and wood and paper plants and ferrous and non-ferrous smelters in women.

In a subsequent publication on the case–control study of Xu et al. (1989), Xu et al. (1991) performed an additional analysis on residential distance from the industrial area. Soil levels of arsenic and other metals rose with increasing proximity to the Shenyang copper smelter, and elevated risks of lung cancer were found among men, but not women, living within 1 km of the smelter (OR, 3.0; 95% CI, 1.6–6.0).

Biggeri et al. (1996) used the data collected by Barbone et al. (1995) to better investigate the relationship of lung cancer with the four sources of air pollution (shipyard, iron foundry, incinerator, and city centre). Spatial models were used to evaluate the effect of sources of pollution on lung cancer adjusted for age, smoking habits, exposure to occupational carcinogens, and levels of PM. The excess relative risk at the city centre was 2.2 (P = 0.0098; CI not reported). At the incinerator source, the excess relative risk was 6.7 (P = 0.0098; CI not reported). [This is a rather large study with improved exposure assessment relative to earlier studies and detailed information on occupational exposure and smoking.]

A case–control study involving interviews with 117 women with lung cancer and 117 matched hospital controls was conducted in Taiwan, China, from 1992 to 1993 (Ko et al., 1997). Information on cigarette smoking and suspected risk factors for lung cancer, including residential distance from industrial plants, was collected by interview. Only a small proportion (9.4%) of female cases had smoked. Among non-smoking women, the odds ratio for the association of lung

cancer with living near an industrial district for 20 years or longer was 2.7 (95% CI, 0.9–7.8) after adjustment for several covariates, including indoor air pollution from cooking. [This is a relatively small study with a rather crude exposure assessment.]

To investigate the relationship between petrochemical air pollution and lung cancer, Yang et al. (1999) conducted a matched case–control study among women who had died in Taiwan, China, from 1990 to 1994, using a similar design to Chiu et al. (2006); 399 lung cancer cases and 399 controls were matched by sex, year of birth, and year of death. The proportion of a municipality's total population employed in the petrochemical manufacturing industry was used as an indicator of exposure to air emissions from this industry. For women who lived in municipalities with the highest level of petrochemical industry employment, the odds ratio was 1.66 (95% CI, 1.05–2.61) compared with women who lived in municipalities with the lowest petrochemical industry employment level after controlling for possible confounders. [The study shares the methodology and the limitations of the studies by Chiu et al. (2006) and Liu et al. (2008a).]

Petrauskaite et al. (2002) conducted a case–control study on lung cancer near an industry producing sulfuric acid and fertilizers in central Lithuania. Between 1967 and 1973, the levels of sulfuric acid exceeded 500 μg/m^3 within 2 km of the industry and 100 μg/m^3 more than 5 km away. A total of 277 men diagnosed with lung cancer during 1981–1991 and 1108 deceased controls, excluding deaths from respiratory cancer, were included. Information on residential history since 1960, smoking habits, and lifetime occupations and workplaces was obtained from questionnaires mailed to the next of kin. The relative risk of lung cancer associated with living within approximately 5 km of the plant was 1.02 (95% CI, 0.76–1.38) compared with never having lived in the area. No relationship with distance or with duration of residence was observed. [Since only deceased subjects were in the control group and exposure to air pollution is linked with increased cardiorespiratory mortality, exposure to air pollution may have been overrepresented in the control group, with underestimation of the effect. The Working Group noted a minor discrepancy in the odds ratios reported in the abstract and tables of this paper; the odds ratio from the abstract is shown here.]

Bessö et al. (2003) evaluated the association of exposure to industrial air pollution and lung cancer risk in a case–control study in the vicinity of a non-ferrous metal smelter in Sweden. The work was an extension of the study previously conducted by Pershagen (1985). The smelter started operations in 1930 and had very high emissions of arsenic and SO_2 in the early years. Among people who had died in 1961–1990 in the municipality where the smelter was located and who had not worked at the smelter, 316 lung cancer cases were identified and matched by sex and year of birth to 727 controls. Information on smoking habits, occupations, and residences was collected from questionnaires mailed to the next of kin and from registry data. Living close to the smelter was associated with a relative risk for lung cancer of 1.38 (95% CI, 0.89–2.14) among men after adjustment for smoking and occupational exposures. For women, however, no overall increased risk of lung cancer was observed (OR, 0.88; 95% CI, 0.48–1.62).

Pisani et al. (2006) conducted a case–control study in Lampang Province, Thailand, to assess the risk of lung cancer associated with exposures in the area, including power plants and coal mines, and to investigate possible interactions with genetic susceptibility. A total of 211 cases of lung cancer diagnosed in 1993–1995 among residents of the province were recruited at the provincial hospital. Community (n = 202) and hospital (n = 211) controls were frequency-matched to the cases by sex and age. Sociodemographic information, complete residential history, and characteristics of the household related to cooking

and heating, occupational history, and history of tobacco smoking were obtained by interview. An air pollution exposure index was calculated for each village or township reported in residential histories, based on the linear distance from the power plants, the annual SO_2, NO_2, and TSP emissions from the power plant, and the percentage of time that wind blew from the power plant centre. For the highest category of estimated cumulative exposure to SO_2 and NO_2 emissions versus the lowest category, the overall odds ratio was 1.2 (95% CI, 0.7–2.0). The cumulative index of exposure to PM was not associated with lung cancer. [The controls included individuals hospitalized for causes related to air pollution exposure, such as cardiovascular disease, with a possibility of a bias to the null.]

(c) Studies with quantitative assessment of air pollutant exposure

Jedrychowski et al. (1990) reported the results of a case–control study of 1099 lung cancer deaths and 1073 age- and sex-matched control deaths from other, non-respiratory causes that occurred in 1980–1985 in Cracow, Poland. Information on occupation, smoking habits, and residency was collected from the next of kin. Exposure to outdoor air pollution was estimated from levels of TSP and SO_2 measured by an urban monitoring network from 1973 to 1980. In men exposed to the highest air pollution level (TSP > 150 μg/m³ and SO_2 > 104 μg/m³), the relative risk was 1.46 (95% CI, 1.06–1.99). In women exposed in the combined medium and high air pollution categories, the relative risk was 1.17 (95% CI, 0.70–1.96). The joint action of the risk factors of smoking, occupational exposure, and air pollution was found to fit a multiplicative model. [This is a large study with detailed information on occupational exposure and smoking, and improved exposure assessment relative to earlier case–control studies, which did not quantify exposure.]

Nyberg et al. (2000) conducted a population-based case–control study among men aged 40–75 years with incident lung cancer in 1985–1990 in Stockholm County, Sweden. A total of 1042 cases and 2364 controls were studied, with a response rate of more than 85%. Local annual source-specific air pollution levels were estimated by dispersion modelling of emission data for NO_x/NO_2 and SO_2 and linked to residential addresses. More details on the exposure assessment are available from Bellander et al. (2001). Average traffic-related NO_2 exposure over 10 years (lagged 20 years) was associated with a relative risk of 1.10 (95% CI, 0.97–1.23) for each 10 μg/m³ increase in NO_2. The relative risk for the top decile of NO_2 exposure was 1.44 (95% CI, 1.05–1.99). In contrast, no association was found for SO_2 from heating: the relative risk was 1.01 (0.98–1.03) for each 10 μg/m³ increase in SO_2. All the risk estimates were adjusted for age, year, tobacco smoking, socioeconomic status, residential radon, and occupational exposures. The relative risk for never-smokers exposed to NO_2 above the 90th percentile (> 29.3 μg/m³) versus below the first quartile (< 12.7 μg/m³) was 1.68 (95% CI, 0.67–4.19). [This is a large study with high-quality historical exposure assessment and detailed information on smoking.]

Hystad et al. (2013) investigated lung cancer incidence in relation to long-term exposure to outdoor air pollutants and proximity to major roads in a population-based case–control study. Annual residential exposure to fine PM ($PM_{2.5}$), NO_2, and ozone over a 20-year period was compared among 2390 incident lung cancer cases and 3507 population controls in eight Canadian provinces from 1994 to 1997. Residential exposure to air pollutants was estimated using self-reported residential histories from 1975 to 1994 and national spatial surfaces of outdoor air pollution compiled from satellite-based estimates (for $PM_{2.5}$ and NO_2) and a chemical transport model (for ozone) and then adjusted with historical annual air pollution monitoring data. Details

of the exposure assessment are presented by Hystad et al. (2012). Hierarchical logistic regression models incorporated a comprehensive set of individual and geographical covariates. There was an increase in lung cancer incidence, with relative risks of 1.29 (95% CI, 0.95–1.76) with a 10-unit increase in $PM_{2.5}$ (μg/m³), 1.11 (95% CI, 1.00–1.24) with a 10-unit increase in NO_2 (ppb), and 1.09 (95% CI, 0.85–1.39) with a 10-unit increase in ozone (ppb). A subanalysis conducted in urban centres using exposures derived from fixed-site air pollution monitors supported the national results, with larger associations for NO_2 (RR, 1.34; 95% CI, 1.07–1.69) and $PM_{2.5}$ (RR, 1.33; 95% CI, 0.82–2.15) per 10-unit increase. An elevated relative risk was found among those living within 50 m of highways (RR, 1.23; 95% CI, 0.76–1.98) but not among those living near major roads. There was an increased risk of adenocarcinoma with an increase of 10 ppb in NO_2 exposure (OR, 1.17; 95% CI, 1.01–1.35) and an increased but non-significant risk with an increase of 10 μg/m³ in $PM_{2.5}$ exposure (OR, 1.27; 95% CI, 0.84–1.90). The odds ratio for $PM_{2.5}$ among never-smokers was 0.95 (95% CI, 0.38–2.34) based on 120 cases. [This is a large study, and notable strengths are the historical exposure estimation at an individual level, data for lung cancer subtypes, and adjustment for an extensive list of potential confounders, including known lung cancer risk factors. Despite the large size, the study had limited power to examine associations among never-smokers.]

2.1.5 Studies of outdoor workers and cancer of the lung

See Table 2.5.

Outdoor air pollution can be an occupational exposure for workers in polluted outdoor environments. Studies have been conducted on workers exposed to urban air pollution or specific sources of pollution, such as diesel and gasoline engine emissions. This group of studies was previously analysed in the *IARC Monograph* on diesel and gasoline engine exhausts (IARC, 2013). Therefore, there is an overlap between the present volume and the previous *IARC Monograph* on diesel and gasoline engine exhausts, since these two sources are important contributors to urban air pollution. On this basis, occupational cohorts and case–control studies considering professional drivers, traffic police, mail carriers, and filling station attendants are reviewed here, as the occupation can be considered an estimator of air pollution exposure shared with the general population. The studies on occupations with specific exposure to diesel exhaust, such as underground miners and railway workers, have already been reviewed in the *IARC Monograph* on the carcinogenicity of diesel and gasoline engine exhausts, and they are not considered in detail here.

(a) Cohort studies

(i) Professional drivers (bus drivers, taxi drivers, and lorry drivers)

Balarajan & McDowall (1988) studied a total of 3392 male professional drivers in London, United Kingdom, with a retrospective mortality study. The cohort was enrolled from the National Health Service Central Register with occupational information since 1939. Subjects whose occupational description was bus, coach, lorry, or taxi driver were enrolled and followed up for mortality during the period 1950–1984. During the follow-up period, there were significantly fewer deaths (n = 2182) than expected (in England and Wales) from all causes (standardized mortality ratio [SMR], 0.91; [95% CI, 0.87–0.95]). Overall, the standardized mortality ratio for lung cancer was 1.47 [95% CI, 1.32–1.64]. Lorry drivers showed excess deaths from lung cancer (SMR, 1.59; [95% CI, 1.41–1.79]), a pattern not evident among taxi drivers. [No estimate of air pollution exposure was available in the study. No measure of duration of exposure was available. No individual information on smoking habits was available.]

Table 2.5 Lung cancer in cohort studies of professional drivers, urban police officers, mail carriers, and filling station attendants

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Professional drivers									
Balarajan & McDowall (1988) London, United Kingdom. Professional drivers	3392	1950–1984	Occupational history from the National Health Service Central Register: bus, coach, lorry, and taxi drivers	Lung	All drivers Taxi drivers Bus and coach drivers Lorry drivers	328 30 18 280	1.47 [0.32–1.64] 0.86 [0.58–1.23] 1.42 [0.84–2.24] 1.59 [1.41–1.79]	Age	SMRs. Men only. Air pollution levels not known. No information on duration of exposure or on smoking habits
Carstensen et al. (1988) Sweden. Professional drivers	1.6 million (total cohort)	1961–1979	Swedish Cancer–Environment Register: all subjects employed and aged 30–64 yr in 1960; professional drivers	Lung	All drivers	1021 cases	1.14 (1.03–1.25)	Age and smoking	SIRs. Men only. Air pollution levels not known. No information on duration of exposure
Paradis et al. (1989) Montreal, Canada. Bus drivers	2134	1962–1985	Subjects employed by the Montreal Urban Community Transit Commission	Lung	Bus drivers *Employment duration* < 30 yr ≥ 30 yr	78 34 44	0.92 (0.73–1.14) 1.01 (0.70–1.38) 0.85 (0.62–1.13)	Age	SMRs. Men only. Air pollution levels not known. No information on smoking habits
Rafnsson & Gunnarsdóttir (1991) Reykjavik, Iceland. Truck and taxi drivers	868 truck drivers; 726 taxi drivers	1951–1988	Membership rolls of the Truck Drivers' Union and the Cooperative Taxi Agency	Lung	Truck drivers Taxi drivers	24 12	2.14 (1.37–3.18) 1.39 (0.72–2.43)	Age	Men only. Air pollution levels not known. Smoking status known for a sample of the cohort
Gubéran et al. (1992) Geneva, Switzerland. Professional drivers	1726	1949–1986 (1970–1986 for cancer incidence)	Licensing Authority, Canton of Geneva	Lung	Professional drivers (lorry, taxi, bus, and coach)	77 64	1.50 (1.23–1.81) 1.61 (1.29–1.98)	Age	SMR. 15 yr latency. Men only. Air pollution levels not known. No information on smoking habits SIR. 15 yr latency

Table 2.5 (continued)

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Borgia et al. (1994) Rome, Italy. Taxi drivers	2311	1965–1988	Rome taxi cooperatives; taxi drivers	Lung	All	76	1.23 (0.97–1.54)	Age	SMR. Men only. Air pollution levels not known. Smoking status known for a sample of the cohort
Jakobsson et al. (1997) Sweden. Professional drivers	96 438	1971–1984	Swedish national census; bus drivers, taxi drivers, long-distance and short-distance lorry drivers	Lung	*All Sweden*				RRs. Men only. Air pollution levels not known. No information on duration of exposure. Indirect adjustment for smoking
					Bus drivers	52 cases	0.9 (0.7–1.2)	Age and region	
					Taxi drivers	104 cases	1.2 (1.0–1.4)	Age, region, and smoking	
					Long-distance lorry drivers	304 cases	1.1 (0.9–1.2)	Age, region, and smoking	
					Short-distance lorry drivers	144 cases	1.2 (1.0–1.4)	Age, region, and smoking	
					Stockholm County only				
					Taxi drivers	42 cases	1.3 (1.0–1.8)	Age and smoking	
					Long-distance lorry drivers	76 cases	1.4 (1.1–1.8)	Age and smoking	
					Short-distance lorry drivers	50 cases	1.7 (1.3–2.3)	Age and smoking	

Table 2.5 (continued)

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Soll-Johanning et al. (1998) Copenhagen, Denmark. Bus drivers and tramway employees	18 174	1943–1992	Copenhagen Traffic Company; bus and tramway employees	Lung	Bus drivers and tramway workers	473	1.6 (1.5–1.8) men	Age and sex (men only)	SIRs. Air pollution levels not known. No information on duration of exposure. Confounding by smoking unlikely. In a subsequent case–control study on lung cancer within the cohort (Soll-Johanning & Bach, 2004), OR for high vs low air pollution index was 0.99 (95% CI, 0.36–2.75)
						15	2.6 (1.5–4.3) women	Age and sex (women only)	
					Time since first employment				
					0–14 yr	35 male cases; 3 female cases	1.2 [0.84–1.67] men; 1.3 [0.27–3.80] women		
					15–29 yr	77 male cases; 10 female cases	1.5 [1.18–1.87] men; 3.5 [1.68–6.44] women		
					≥ 30 yr	361 male cases; 2 female cases	1.7 [1.53–1.88] men; 3.8 [0.46–13.73] women		
Soll-Johanning et al. (2003) Copenhagen, Denmark. Bus drivers and tramway employees	18 174	1900–1994	Employment records for all bus drivers and tramway employees employed in 1900–1994	Lung	Air pollution index: Low	14	1.00 (ref)	Smoking	RRs for lag time of > 10 yr. Nested case–control study that overlaps with Soll-Johanning et al. (1998)
					High	39	0.99 (0.36–2.75)		
					Cumulative employment				
					< 3 months	4	0.50 (0.14–1.81)		
					3 months to < 2 yr	27	1.00		
					2 yr to < 10 yr	45	1.03 (0.54–1.95)		
					10 yr to < 20 yr	22	1.34 (0.65–2.77)		
					≥ 20 yr	43	0.54 (0.28–1.03)		

Table 2.5 (continued)

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Pukkala et al. (2009) Nordic countries. Several occupations	15 million	1960–1990	Job history reported through self-administered census questionnaires	Lung	Drivers (men)	12 882	1.28 (1.26–1.31)	Country, sex, age, and time period	SIR
					Drivers (women)	210	1.46 (1.27–1.67)		
					Postal workers (men)	1783	0.95 (0.90–0.99)		
					Postal workers (women)	962	1.01 (0.95–1.08)		
Petersen et al. (2010) Copenhagen, Aarhus, and Odense, Denmark. Bus drivers	2037	1979–2003	Baseline responses to mailed questionnaires (1978) to bus drivers	Lung	Bus drivers (men)	100	1.2 (1.0–1.4)	Age	SIRs. Men only
					Employment (yr)			Age, calendar time, city, bus route, and smoking	Internal survival analysis
					< 15	49	1		
					> 15–24	24	0.89 (0.59–1.48)		
					> 24	25	0.95 (0.55–1.63)		
					P for trend		0.79		
Merlo et al. (2010) Genoa, Italy. Bus drivers	9267 men (6510 bus drivers; 2073 maintenance workers; 601 white-collar workers)	1970–2005	Bus company records	Lung	Bus drivers	235	1.11 (0.98–1.26)	Age	RR. Men only. No information on smoking habits
Urban police officers, mail carriers, and filling station attendants									
Forastiere et al. (1994) Rome, Italy. Urban police officers	3868	1972–1991	Local Council of Rome; urban police officers including traffic wardens, car drivers, motorcyclists, and office workers	Lung	All urban police officers	82	1.05 (0.84–1.30)	Age	SMR. Men only. No association of lung cancer with job category
					Employment duration				
					≥ 30 yr	18	0.86 (0.51–1.36)		
					Latency since first employment				
					≥ 30 yr	56	1.11 (0.84–1.45)		

Table 2.5 (continued)

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Soll-Johanning & Bach (2004) Copenhagen, Denmark. Mail carriers	17 233	1898–1996	Post Denmark files; mail carriers	Lung	All mail carriers (men) All mail carriers (women)	298 6	0.96 (0.86–1.08) 1.28 (0.47–2.79)	Age	SIRs. No smoking data. No association with time since first employment. Overlaps with Soll-Johanning et al. (1998)
Lagorio et al. (1994) Lazio, Italy. Filling station attendants	2665	1981–1992	National Survey of Service Stations; shelf managers	Lung	All filling station attendants (men)	29	0.87 (0.64–1.23)	Age	SMR. No smoking data. No information on duration of employment

CI, confidence interval; OR, odds ratio; ref, reference; RR, relative risk; SIR, standardized incidence ratio; SMR, standardized mortality ratio; yr, year.

Carstensen et al. (1988) reported the results of an occupational morbidity analysis based on the Swedish Cancer–Environment Register to evaluate the relationship between occupation and lung cancer incidence during the period 1961–1979 in 1.6 million men aged 30–64 years in 1960. By adding information about smoking habits from a sample of 1% of the Swedish population, smoking-adjusted [indirect adjustment] standardized incidence ratios (SIRs) were estimated for different occupational categories according to the population census of 1960. Smoking-adjusted excess risks ($P < 0.01$) were found in assemblers and machine erectors, professional drivers, miners, packers, and longshoremen as well as in sheet metal workers. The smoking-adjusted standardized incidence ratio for professional drivers, based on 1021 lung cancer cases, was 1.14 (95% CI, 1.03–1.25). [The number of subjects in the category "Drivers, road transport" was not given.]

Paradis et al. (1989) studied 2134 male bus drivers in Montreal, Canada, employed for at least 5 years as of January 1962 and followed up until 31 December 1985. They were compared with the male population of the Greater Montreal area. The number of deaths observed was 804. The overall mortality was somewhat lower than expected (SMR, 0.97). No excesses were observed for lung cancer (SMR, 0.92; 95% CI, 0.73–1.14), and no excess was found among those with a longer duration of employment (≥ 30 years; SMR, 0.85; 95% CI, 0.62–1.13). [No measure of air contamination was available. No information on smoking habits was available.]

Rafnsson & Gunnarsdóttir (1991) studied the mortality of truck drivers and taxi drivers in Reykjavik, Iceland. The subjects were enrolled from the membership rolls of the Truck Drivers' Union and the Cooperative Taxi Agency. The cohort was assembled in 1951, and the follow-up lasted until 1 December 1988. The national mortality rate was used for comparison. The 868 truck drivers had an excess of lung cancer deaths (SMR, 2.14; 95% CI, 1.37–3.18) but fewer deaths than expected from respiratory diseases (15 observed vs 30.1 expected). The standardized mortality ratio from lung cancer did not steadily increase as the duration of employment increased, nor did it change with the length of follow-up. The standardized mortality ratio for lung cancer among the 726 taxi drivers was 1.39 (95% CI, 0.72–2.43). Information on smoking was available from a subset of the cohorts participating in a cross-sectional survey. A slightly higher prevalence of ever-smokers among truck drivers than among taxi drivers or the entire surveyed population was found. [No measure of air contamination was available.]

Gubéran et al. (1992) conducted a historical prospective cohort study of 6630 drivers from the Canton of Geneva, Switzerland, to evaluate cancer mortality and incidence in this occupation. The study population was all men (of all occupations) who held in 1949 a special licence for driving lorries, taxis, buses, or coaches; all new licence holders in the period 1949–1961 were also included. According to the occupation registered on their licence, the 6630 drivers were divided into three groups: (i) professional drivers ($n = 1726$), (ii) non-professional drivers "more exposed" to exhaust gas and fumes (this group included occupations such as vehicle mechanic, police officer, and road sweeper; $n = 712$), and (iii) non-professional drivers "less exposed," composed of all other occupations ($n = 4192$). The cohort was followed up from 1949 to December 1986. Compared with the general population living in the Canton of Geneva, professional drivers experienced significant excess risks, taking into account 15 years of latency, for all causes of death (SMR, 1.15; 90% CI, 1.07–1.23) and for all malignant neoplasms (SMR, 1.25; 90% CI, 1.12–1.40; SIR, 1.28; 90% CI, 1.15–1.42). Cause-specific analysis showed significant excesses for lung cancer (SMR, 1.50; 90% CI, 1.23–1.81; SIR, 1.61; 90% CI, 1.29–1.98). Risk of lung cancer increased significantly with

time from first exposure. Among non-professional drivers, no significant excess risk was found except for lung cancer mortality among the "less exposed" group (SMR, 1.21; 90% CI, 1.03–1.40) and for lung cancer incidence among the "more exposed" group (SIR, 1.61; 90% CI, 1.11–2.27). [No measure of air contamination was available. No information on smoking habits was available.]

Borgia et al. (1994) conducted a historical cohort study to evaluate the mortality patterns of taxi drivers in Rome, Italy. A total of 2311 male subjects registered as taxi drivers between 1950 and 1975 with the local taxi cooperatives were followed up from 1965 to 1988. The overall mortality was lower than expected on the basis of the regional reference rates (692 deaths; SMR, 0.89; 95% CI, 0.82–0.96), whereas the number of recorded deaths for malignant neoplasms was about the expected number (205 deaths; SMR, 0.99; 95% CI, 0.86–1.13). Mortality from circulatory and respiratory diseases was lower than expected [suggesting that smoking was of less importance in the cohort]. An increased standardized mortality ratio was seen for respiratory cancer (SMR, 1.23; 95% CI, 0.98–1.50), mainly due to lung cancer (observed = 76; SMR, 1.23; 95% CI, 0.97–1.54); two pleural cancers were also recorded. The excess of lung cancer deaths was present only among those enrolled in the most recent period (1965–1975) (45 deaths; SMR, 1.40; 95% CI, 1.02–1.87), especially among those of younger age (< 65 years; SMR, 1.86); there was no relationship between lung cancer mortality and latency since first enrolment in the cooperatives or duration of membership. A survey among 400 currently employed taxi drivers at the time of the study indicated that the age-adjusted prevalence of current (55.8%) and former (18.8%) smokers among taxi drivers was slightly higher than that of the general population (50.8% and 9.3%, respectively). [No measure of air contamination was available. Exposure to second-hand smoke and the higher prevalence of smoking among taxi drivers are possible sources of confounding.]

Jakobsson et al. (1997) studied the risk of lung cancer in different subgroups of professional drivers in urban and rural areas of Sweden. Information on occupation and geographical region was obtained from the Swedish census of 1970, and data on the incidence of lung cancer between 1971 and 1984 from the Swedish Cancer Registry. Professional drivers were separated into bus drivers, taxi drivers, and long- and short-distance lorry drivers. Comparisons of cumulative incidence of lung cancer were made between each particular group of drivers and all employed men in the same region. After indirect adjustment for differences in smoking habits (based on the 1963 Swedish survey on smoking habits), the relative risks were significantly increased for taxi drivers (RR, 1.3; 95% CI, 1.0–1.8), long-distance lorry drivers (RR, 1.4; 95% CI, 1.1–1.8), and short-distance lorry drivers (RR, 1.7; 95% CI, 1.3–2.3) in Stockholm but not for other groups of drivers in mainly rural areas of Sweden (counties other than Stockholm, Gothenburg/Bohus, and Malmöhus): taxi drivers (RR, 0.9; 95% CI, 0.6–1.2), short-distance lorry drivers (RR, 1.0; 95% CI, 0.7–1.2), and long-distance lorry drivers (RR, 0.9; 95% CI, 0.8–1.1).

Soll-Johanning et al. (1998) conducted a retrospective cohort study of 18 174 bus drivers and tramway employees (of both sexes) in Copenhagen, Denmark, who were employed during the period 1900–1994. The follow-up was conducted for the period 1943–1992. Cancer rates were compared with the general population of Denmark by linkage to the Danish Cancer Registry and the National Death Index to identify cancers that occurred since 1943. The standardized incidence ratio of lung cancer among those employed for 3 months or longer was 1.6 (95% CI, 1.5–1.8; 473 cases) for men and 2.6 (95% CI, 1.5–4.3; 15 cases) for women. In both men and women, there was a greater risk of lung cancer with greater time since first employment.

There was no trend in lung cancer risk based on the period of predominantly gasoline or diesel vehicle use, and the risks were similarly elevated for workers starting before, at the onset of, or during the use of diesel buses. [There was no specific exposure information. Compared with other men in Copenhagen, the smoking rates among the bus drivers were slightly greater during some time periods, suggesting the possibility of some confounding by smoking, but this is unlikely to explain the elevated risks found.]

The same investigators (Soll-Johanning et al., 2003) conducted a nested case–control study of 153 lung cancer cases included in the previous cohort of bus drivers and tramway employees (Soll-Johanning et al., 1998). The cases and controls or their next of kin were interviewed about smoking history. Deaths were excluded from the control group if the person had died of cancer or non-neoplastic respiratory disease. Cases and controls were matched by date of birth as well as vital status. One of the main exposure variables was an air pollution index, estimated on the basis of a predicted estimate of air pollution along each segment along the bus lines when considering the local traffic, the street configuration, and the urban background. Both 10-year-lag and no-lag models based on employment duration were assessed, adjusting for smoking history in seven categories based on pack-years. There was no consistent elevation in lung cancer risk based on categories of employment duration in either lag model. The risk increased, although the increase was not statistically significant, with more years of employment, but then decreased for a duration of 20 years or longer. The odds ratio for lung cancer associated with the high versus the low air pollution index was 0.99 (95% CI, 0.36–2.75), with a lag time of more than 10 years. [This study also reported results for several other cancers, including bladder cancer and leukaemia.]

Pukkala et al. (2009) conducted a cohort study with linkage of individual records in all the Nordic countries. The study covers the 15 million people aged 30–64 years in the 1960–1990 censuses in five countries and the 2.8 million incident cancer cases diagnosed in these people in a follow-up until about 2005. In the censuses, information on occupation for each person was provided through free text in self-administered questionnaires. The original occupational codes were reclassified into 53 occupational categories, including professional drivers and postal workers. The observed number of cancer cases in each group of people defined by country, sex, age, period, and occupation was compared with the expected number calculated from the stratum-specific person-years and the incidence rates for the national population. The standardized incidence ratios for lung cancer in men were 1.28 (95% CI, 1.26–1.31; 12 882 cases) for drivers and 0.95 (95% CI, 0.90–0.99; 1783 cases) for postal workers. The corresponding standardized incidence ratios for women were 1.46 (95% CI, 1.27–1.67; 210 cases) for drivers and 1.01 (95% CI, 0.95–1.08; 962 cases) for postal workers. [This study may partially overlap with other studies previously described in the Nordic countries.]

Petersen et al. (2010) reported on cancer incidence in a cohort of 2037 male urban bus drivers in Denmark that was established in 1978, with a 25-year follow-up period from 1979 to 2003. In 1978, public bus drivers in the three largest cities in Denmark were sent a mailed questionnaire, which requested an occupational history and information regarding bus route and smoking habits. Information on incident cases of cancer through 2003 was obtained by linkage to the Danish Cancer Registry. Using external rates from the men in the three cities, the standardized incidence ratio for lung cancer among bus drivers was 1.2 (95% CI, 1.0–1.4; 100 cases), and 1.3 (95% CI, 1.0–1.8) with employment of 15 years or longer. A Cox regression model was used to assess the relationship between risk and employment duration. After adjustment for smoking, city of employment, and usual type of

bus route operated (urban or rural), in addition to age and calendar time, no overall increased risk was observed for lung cancer per year of extra employment as a bus driver (RR, 1.00; 95% CI, 0.98–1.03). Compared with drivers employed for less than 15 years, the incidence rate ratios (IRRs) were 0.89 (95% CI, 0.59–1.48) for those employed for 15–24 years and 0.95 (95% CI, 0.55–1.63) for those employed for 25 years or longer. There was no change in the estimates in a 10-year-lag model. [These data indicate that when adjusted for smoking and other risk factors and using an internal comparison group, there was little to no increased risk of lung cancer in bus drivers with increasing duration of work. This finding is in contrast to the elevated risks for bus drivers suggested by the standardized incidence ratio results also reported. This study partially overlaps with Pukkala et al. (2009). Data were reported for several other cancer sites, including the bladder.]

Merlo et al. (2010) conducted a historical mortality cohort study among public transportation workers ever employed between 1949 and 1980 in Genoa, Italy. They estimated overall and cause-specific mortality from January 1970 to December 2005. A total of 9267 men were studied, including 6510 bus drivers. Standardized mortality ratios were computed by applying Italian and regional male death rates to person-years of observation for the entire cohort. An analysis by longest held job title, length of employment, and time since first employment was done using the Poisson regression model. The standardized mortality ratio for lung cancer was 1.16 (95% CI, 1.05–1.28; 386 deaths), and 1.11 (95% CI, 0.98–1.26; 235 deaths) among bus drivers. [No smoking information was available. Data were reported for several other cancers.]

(ii) Urban police officers

Forastiere et al. (1994) evaluated a total of 3868 urban police officers (including traffic wardens, car drivers, motorcyclists, and office workers) in Rome, Italy, through a historical cohort study with emphasis on mortality from cardiovascular disease and cancer. Male subjects employed as of 31 December 1972 (or subsequently hired through 1975) as urban police officers were followed up until 1991. Mortality from all causes, cardiovascular disease, respiratory conditions, digestive and genitourinary diseases, and accidents was lower than expected. The standardized mortality ratio for lung cancer mortality was 1.05 (95% CI, 0.84–1.30; 82 deaths). Analysis for lung cancer by duration of employment and time since employment did not reveal increased lung cancer mortality among those in the longest duration category (≥ 30 years; 18 deaths; SMR, 0.86; 95% CI, 0.51–1.36) and in the last latency category (≥ 30 years since hiring; 56 deaths; SMR, 1.11; 95% CI, 0.84–1.45). In nested case–control analyses conducted to evaluate lung cancer mortality risk by police officers' job category while considering smoking habits, no significant associations were observed (81 lung cancer cases; 405 controls). [The length of follow-up might be considered insufficient to detect an increase of lung cancer. No smoking data were available for the cohort analysis. Data for several other cancers were also reported.]

(iii) Mail carriers

Soll-Johanning & Bach (2004) evaluated cancer incidence among mail carriers in Copenhagen, Denmark. The retrospective cohort study included 17 233 people who had been mail carriers for Post Denmark during the period 1898–1996. Data on employment were obtained from company files, and cancer incidence was obtained from the Danish Cancer Registry. Male mail carriers employed for longer than 3 months had a standardized incidence ratio for cancer of 0.92 (95% CI, 0.88–0.97) and for lung cancer of 0.96 (95% CI, 0.86–1.08; 298 cases). [Data were also reported for other cancers.]

(iv) Filling station attendants

Lagorio et al. (1994) evaluated the mortality of a cohort of 2665 filling station managers from the Latium region, Italy. Only self-employed individuals were available for study (about 50% of the whole workforce). The follow-up period extended from 1981 to 1992. The mortality of the cohort was compared with that of the regional population. The overall analysis showed a significantly decreased mortality from all causes, mainly due to a deficit of cardiovascular diseases and malignant neoplasms. Mortality due to lung cancer (SMR, 0.87; 95% CI, 0.64–1.23; 29 deaths) was lower than expected. [No analysis was reported by duration or time since first employment. No smoking data were available. Data were reported for several other cancers.]

(b) Case–control studies

Several case–control studies of lung cancer have evaluated risks among professional drivers and other outdoor occupations potentially exposed to air pollution. The case–control studies of truck drivers exposed to diesel exhaust have been reviewed in the *IARC Monograph* on diesel and gasoline engine exhausts (IARC, 2013), whereas the studies on other drivers (including broad groupings of drivers that sometimes included truck drivers) and other outdoor workers are briefly reviewed here.

Hansen et al. (1998) conducted a nationwide case–control study (1970–1989) based on employees, including 28 744 men with primary lung cancer and incidence density sampled matched controls (1:1 match). Employment histories were reconstructed back to 1964 for each study subject from the records of a nationwide pension scheme with compulsory membership, and socioeconomic status was derived from the individual job title taken from the national population registry. The adjusted odds ratio for lung cancer was 1.6 (95% CI, 1.2–2.2; 277 cases) for taxi drivers (considered to be the most highly exposed to outdoor air pollution), 1.3 (95% CI, 1.2–1.5; 972 cases) for bus and lorry drivers, and 1.4 (95% CI, 1.3–1.5; 1002 cases) for unspecified drivers. The risk of lung cancer increased significantly with increasing duration of employment as a driver.

Brüske-Hohlfeld et al. (1999) conducted a pooled analysis of two case–control studies of lung cancer in Germany on 3498 male cases with histologically or cytologically ascertained lung cancer and 3541 male population controls. Information about lifelong occupational and smoking history was obtained by interview. The group of professional drivers (e.g. trucks, buses, and taxis) showed an increased risk in western Germany (OR, 1.44; 95% CI, 1.18–1.76) but not in eastern Germany (OR, 0.83; 95% CI, 0.60–1.14) after adjustment for smoking and asbestos exposure.

Menvielle et al. (2003) investigated all lung cancer cases diagnosed between January 1993 and December 1995 (228 lung cancers) in New Caledonia and 305 population controls. Information on lifetime job history, smoking, and other potential risk factors was collected by interview. Among men, an excess risk of lung cancer was found for bus, lorry, and van drivers (OR, 2.7; 95% CI, 1.1–7.0; 13 exposed cases) after adjustment for age, ethnicity, and smoking.

Consonni et al. (2010) examined the relationship between occupation and lung cancer in a case–control study (2002–2005) in the Lombardy region of northern Italy, including 2100 incident lung cancer cases and 2120 randomly selected population controls. The odds ratio for bus and truck drivers was 1.23 (95% CI, 0.90–1.68) after adjustment for area of residence, age, smoking, and number of jobs held.

(c) Meta-analyses

Tsoi & Tse (2012) conducted a systematic review on the association between professional drivers and lung cancer, taking into consideration the potential confounding effect of

cigarette smoking. They systematically searched all published cohort and case–control studies in English from January 1996 to January 2011. A total of 19 studies were included in the meta-analysis (8 cohort studies and 11 case–control studies), and a significantly increased risk of lung cancer (pooled smoking-adjusted RR, 1.18; 95% CI, 1.05–1.33) among professional drivers was observed after combining 4 cohort studies and 9 case–control studies. A higher pooled relative risk was observed among smoking-adjusted studies reporting 10 years or longer of employment (RR, 1.19; 95% CI, 1.06–1.34) compared with the study reporting shorter duration of employment (6 years; RR, 1.00; 95% CI, 0.92–1.09). [There was no information on never-smokers or non-smokers.]

2.2 Cancer of the urinary bladder

Compared with studies focusing on lung cancer, there are a limited number of studies considering cancers of the urinary bladder as an outcome of exposure to outdoor air pollution. Some studies addressed occupations preferentially exposed to specific components of urban outdoor air pollution, such as diesel and gasoline engine emissions. Fewer studies focused on the general population, using population density or measures of specific pollutants as estimates of exposure. This section presents a summary of the studies that assessed the association between exposure to outdoor air pollution and bladder cancer, stratified by exposure scenario or occupation and also by adjustment for smoking, a potential confounder and an important risk factor for bladder cancer. Stratification by study design was not informative, due to few studies of case–control or cohort design within the analyses stratified by smoking and occupation. Another important consideration is that among several studies from Taiwan, China, not all assessed arsenic exposure, an important risk factor for bladder cancer.

Details of occupational studies that assessed bladder cancer as well as lung cancer have been described above in the section on studies of lung cancer in outdoor workers (Section 2.1.4).

2.2.1 Ecological studies

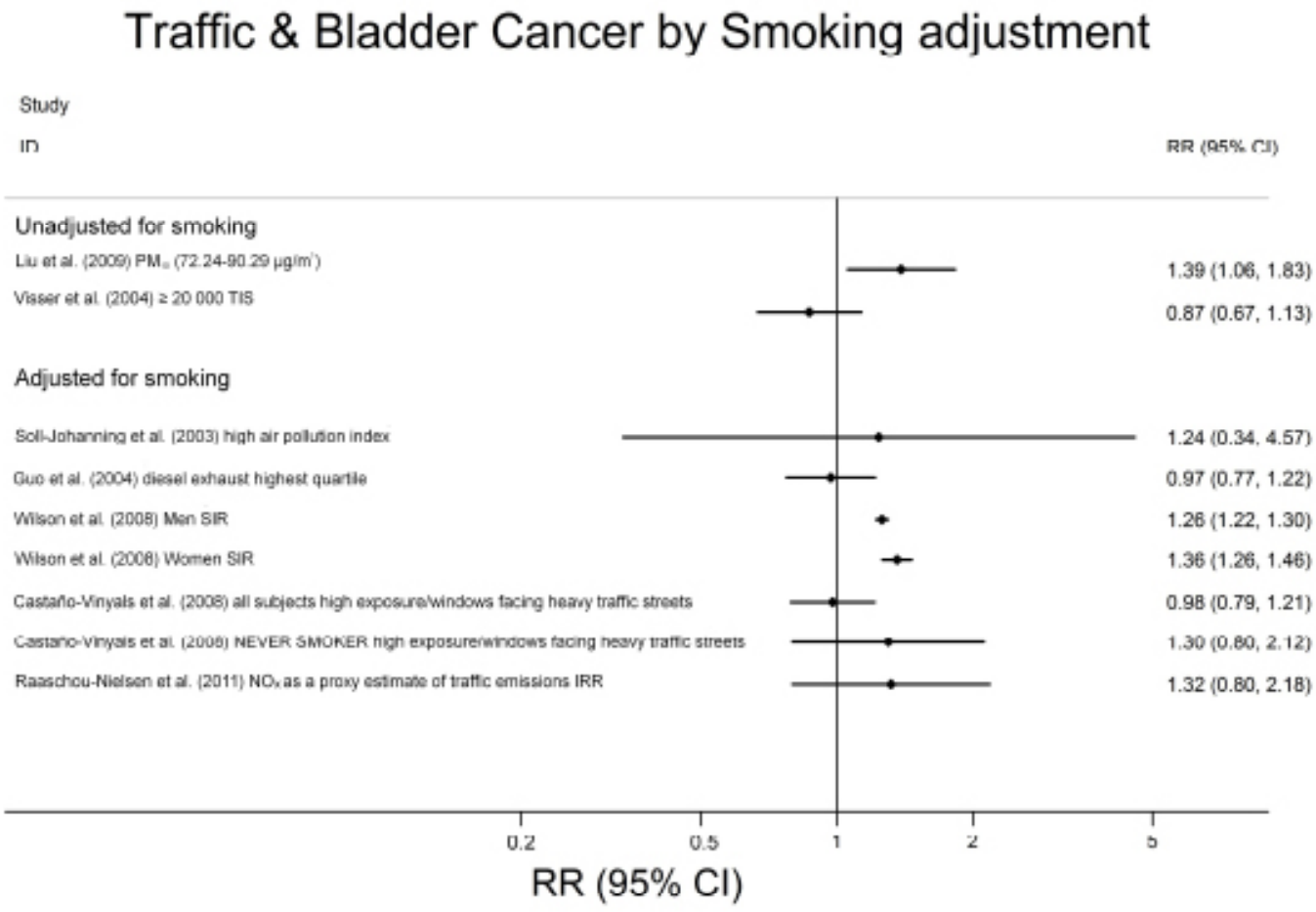
Ecological studies in the USA reported increased mortality from bladder cancer among people living in urban areas compared with rural areas. Blot & Fraumeni (1978) reported increased age-adjusted mortality during 1950–1969 in people living in urban areas compared with rural areas within 3056 counties of the contiguous USA after controlling for several variables in the multivariate regression models, such as ethnicity, occupation, income, and education level. Considering population density as a proxy estimate of urban air pollution (traffic and industrial pollution), Colli et al. (2012) reported significant increases in bladder cancer mortality rates with increases in population density (in quartiles) in 2248 counties of the USA during the period 1950–1994. [The Working Group noted that the interpretation of these findings is limited by the ecological design, the aggregate level of information on exposure to air pollution, and a limited ability to assess the importance of potential confounders, such as smoking. However, there was evidence of increasing risk with increasing population density in the study of Colli et al. (2012).]

2.2.2 Exposure to traffic

See Fig. 2.1

Several studies have examined the association between exposure to outdoor air pollution from traffic, using various metrics, and the risk of bladder cancer. Most studies adjusted for smoking (Soll-Johanning et al., 2003; Guo et al., 2004; Castaño-Vinyals et al., 2008; Wilson et al., 2008; Raaschou-Nielsen et al., 2011b), although two studies did not adjust for smoking (Visser et al., 2004; Liu et al., 2009). All but three studies

Fig. 2.1 Exposure to outdoor air pollution from traffic indicators and the risk of bladder cancer, stratified by adjustment for smoking



Compiled by the Working Group.

observed an increased risk of bladder cancer (25–40% increase) associated with various metrics of traffic exposure.

2.2.3 Taxi drivers

See Fig. 2.2

The studies that evaluated the association between occupation as a taxi driver and the risk of bladder cancer are presented in Fig. 2.2. Both the studies that adjusted for smoking (Schoenberg et al., 1984; Jensen et al., 1987; Silverman et al., 1989a, b; Colt et al., 2004, 2011; Gaertner et al., 2004; Guo et al., 2004; Band et al., 2005; Dryson et al., 2008; Samanic et al., 2008) and those that did not adjust for smoking (Decouflé et al., 1977; Rafnsson & Gunnarsdóttir, 1991; Dolin & Cook-Mozaffari, 1992; Borgia et al., 1994) generally showed an increased risk of bladder cancer.

2.2.4 Bus drivers

See Fig. 2.3

The studies that evaluated the association between occupation as a bus driver and the risk of bladder cancer are presented in Fig. 2.3. The results of studies that did not adjust for smoking (Decouflé et al., 1977; Wynder et al., 1985; Paradis et al., 1989; Dolin & Cook-Mozaffari, 1992; Soll-Johanning et al., 1998) as well as those that adjusted for smoking (Schoenberg et al., 1984; Jensen et al., 1987; Silverman et al., 1989a; Hrubec et al., 1992; Colt et al., 2004; Gaertner et al., 2004; Guo et al., 2004; Dryson et al., 2008; Samanic et al., 2008; Petersen et al., 2010) were inconsistent.

2.2.5 Truck drivers

See Fig. 2.4

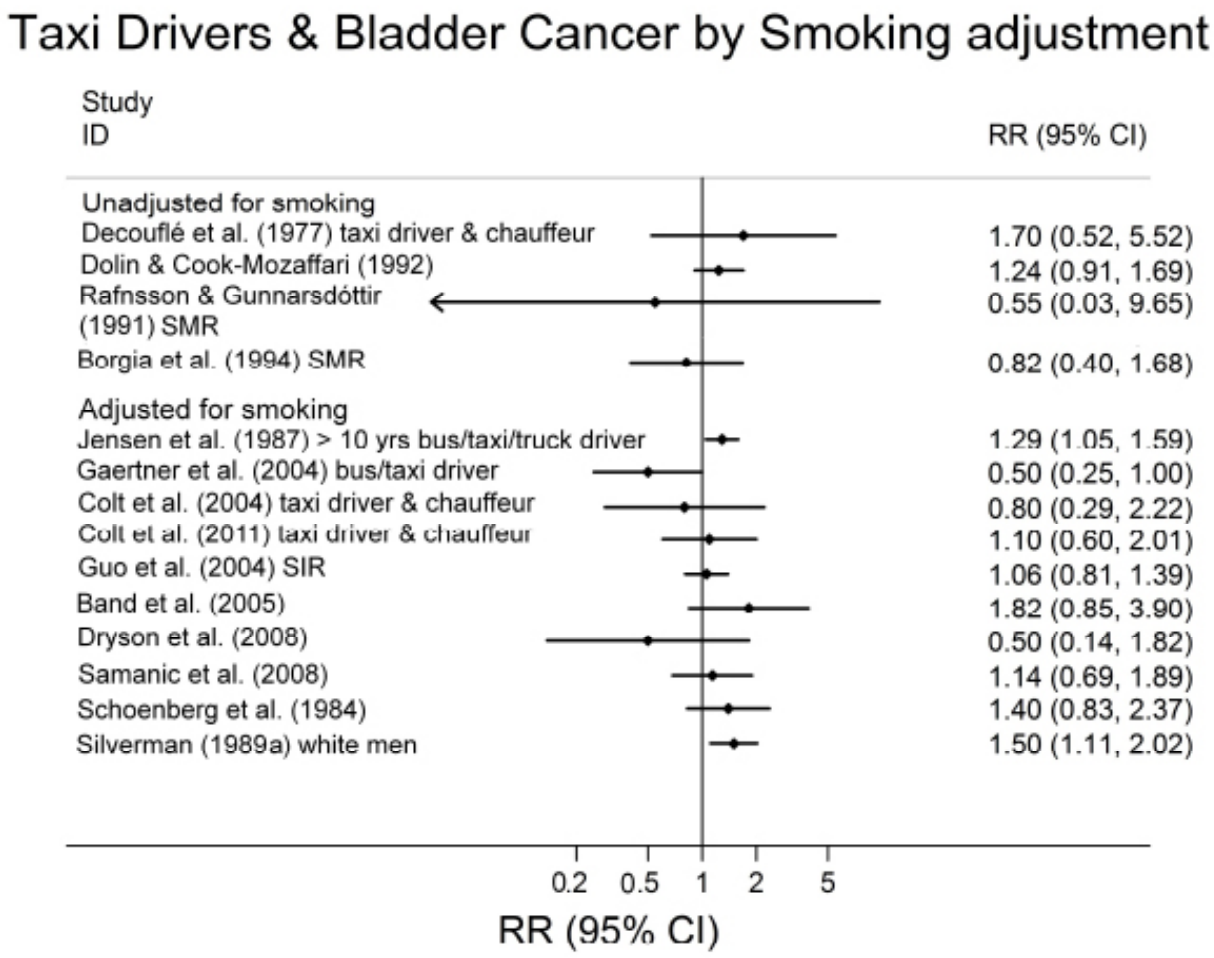
The studies that evaluated the association between occupation as a truck driver and the risk of bladder cancer are presented in Fig. 2.4. Both the studies that did not adjust for smoking (Decouflé et al., 1977; Vineis & Magnani, 1985; Wynder et al., 1985; Steenland et al., 1987; Rafnsson & Gunnarsdóttir, 1991; Dolin & Cook-Mozaffari, 1992) and those that adjusted for smoking (Schoenberg et al., 1984; Hoar & Hoover, 1985; Coggon et al., 1986; Brownson et al., 1987; Jensen et al., 1987; Schifflers et al., 1987; Claude et al., 1988; Bonassi et al., 1989; Silverman et al., 1989a; Iyer et al., 1990; Hrubec et al., 1992; Kunze et al., 1992; Siemiatycki et al., 1994; Porru et al., 1996; Colt et al., 2004, 2011; Gaertner et al., 2004; Guo et al., 2004; Band et al., 2005; Dryson et al., 2008; Samanic et al., 2008; Cassidy et al., 2009) generally demonstrated an increased risk of bladder cancer.

2.2.6 Other jobs with high exposure to outdoor air pollution

See Fig. 2.5

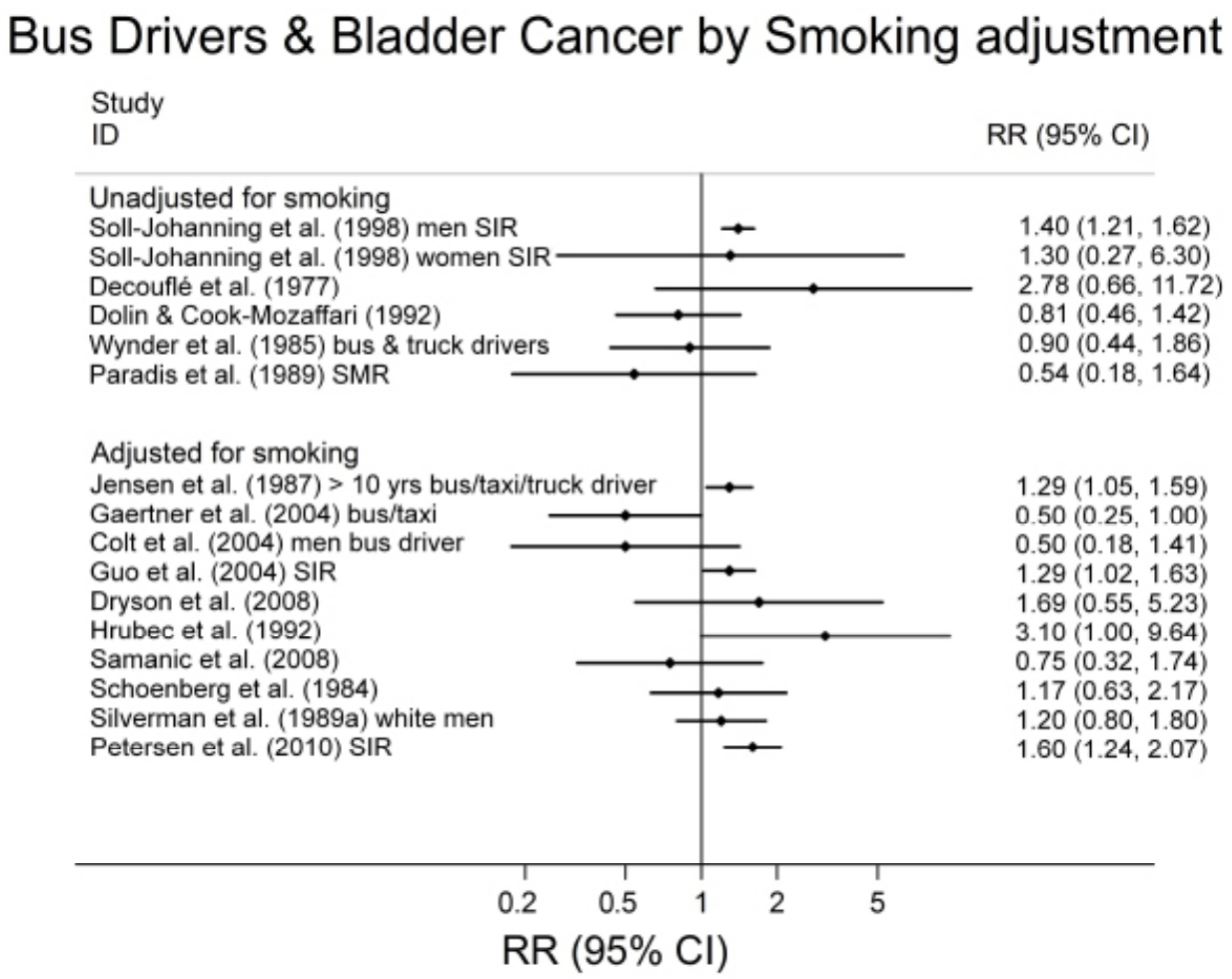
There were several studies that evaluated the association between other jobs with a priori higher exposure to outdoor air pollution than the general population and the risk of bladder cancer (see Fig. 2.5). Many other jobs were included in this category, including mail carrier, driver, urban police officer, and service station attendant. Both the studies that did not adjust for smoking (Balarajan & McDowall, 1988; Gubéran et al., 1992; Forastiere et al., 1994; Lagorio et al., 1994; Soll-Johanning & Bach, 2004; Pukkala et al., 2009) and those that adjusted for smoking (Jensen et al., 1987; Risch et al., 1988; Burns & Swanson, 1991; Cordier et al., 1993; Porru et al., 1996; Pesch et al., 2000; Kogevinas et al., 2003; Colt et al., 2004; Gaertner et al., 2004; Kellen et al., 2007; Reulen et al., 2007; Wilson et al., 2008) generally demonstrated an increased risk of bladder cancer.

Fig. 2.2 Risk of bladder cancer in taxi drivers, stratified by adjustment for smoking



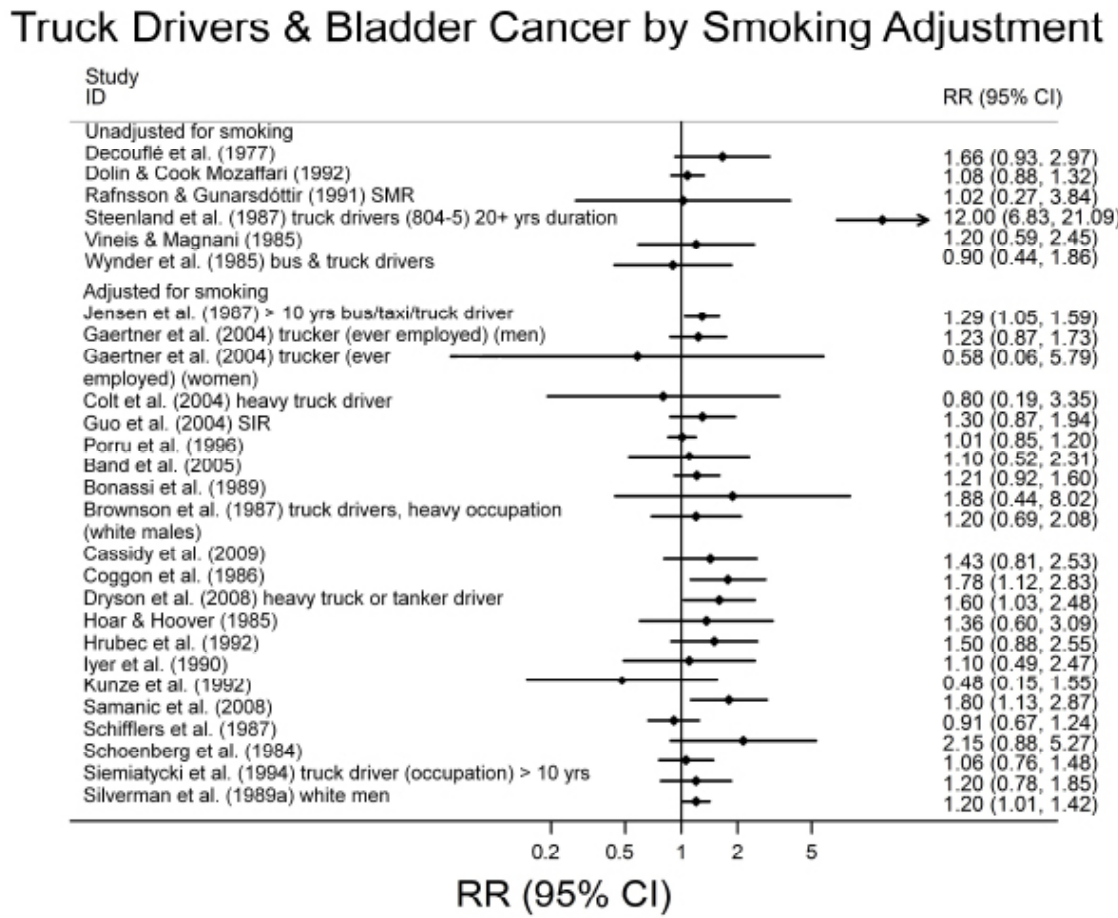
Compiled by the Working Group.

Fig. 2.3 Risk of bladder cancer in bus drivers, stratified by adjustment for smoking



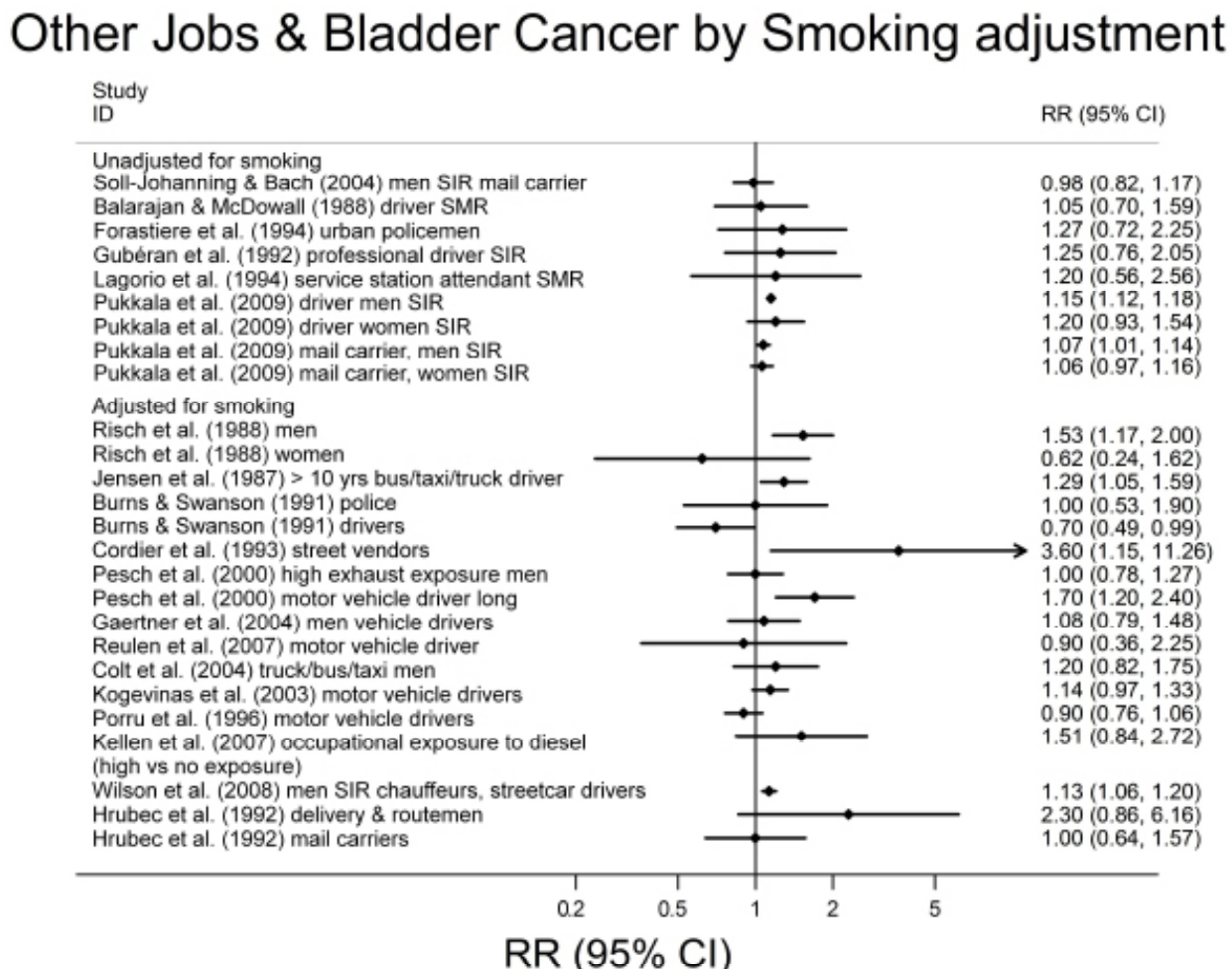
Compiled by the Working Group.

Fig. 2.4 Risk of bladder cancer in truck drivers, stratified by adjustment for smoking



Compiled by the Working Group.

Fig. 2.5 Risk of bladder cancer in other jobs with higher exposure to outdoor air pollution, stratified by adjustment for smoking



Compiled by the Working Group.

2.3 Cancer of the breast

2.3.1 Outdoor air pollution, including traffic emissions

(a) Cohort studies

See Table 2.6.

One of the outcomes evaluated in the AHSMOG study (a prospective cohort study of 6340 adults) by Mills et al. (1991) was incidence of breast cancer among women. The cohort was followed up between April 1977 and December 1982, with a follow-up rate of 99%. (For more study details, see Section 2.1.1c.) During the follow-up, there were 65 new cases of breast cancer. Education level and total years of past smoking were adjusted for in the model. For 1000 hours per year in excess of 200 μg/m^3 of TSP, the risk of breast cancer was elevated, and the relative risk was 1.51 (95% CI, 0.92–2.47). The relative risk with mean concentration of TSP was elevated but was not significant (data not shown in the paper). [A strength of the study is the high follow-up rate, but the study is limited by a lack of control for known breast cancer risk factors.]

Visser et al. (2004) used a population-based regional cancer registry in Amsterdam (n = 718 000 in January 1998) and examined the association between cancer incidence in 1989–1997 and residential traffic intensity. Data on daily traffic intensity in Amsterdam in 1986, 1991, and 1993 were obtained, and a daily traffic intensity score (TIS) was calculated for each of the three available years (passenger cars counted as 1, and trucks, with their larger emissions, were assigned 10). Roads with a TIS of 10 000 or higher for at least one of the three available years were considered as main roads, and those with a TIS of less than 10 000 in all three available years or with residential traffic only were considered as other roads. About 15% of the total number of addresses in Amsterdam (373 157 addresses) were classified as main road addresses (55 719 addresses). Subsequently, cancer registry data were linked to the data on traffic intensity for individual addresses. Annual population data according to sex and 5-year age group were obtained for each year of the study period. Data on smoking and socioeconomic status were obtained in a separate survey of a sample of 2693 people consisting of residents living along main roads and those living along other roads. The survey showed that smoking history did not differ across resident groups but that socioeconomic status was higher among the residents living along the main roads than among the residents living along other roads. Using the age- and sex-specific cancer incidence rate in the population living along other roads as the reference, standardized incidence ratios for the population living along the main roads were calculated. During 1989–1997, 459 new cases of breast cancer were identified. The standardized incidence ratio for breast cancer was not elevated (SIR, 1.00; 95% CI, 0.91–1.09). [The lack of information on potential confounders poses a limitation to the validity of the findings.]

Raaschou-Nielsen et al. (2011b) examined the associations between air pollution from traffic and cancers other than lung cancer. During 1993–1997, 57 053 participants aged 50–64 years living in the Copenhagen and Aarhus areas in Denmark were recruited to the Danish Diet, Cancer, and Health cohort. After a baseline examination was conducted, each cohort member was followed up until June 2006 to investigate occurrence of 20 selected cancers. The participants' residential addresses were traced from 1971 onwards, and outdoor concentrations of NO_x were calculated for each year at the residential address of each participant with the Danish AirGIS modelling system. The mean and median of NO_x concentrations were 28.4 μg/m^3 and 21.9 μg/m^3 (5th–95th percentile, 14.8–69.4), respectively. Then, the time-weighted average NO_x concentrations at all addresses were calculated and used as a time-dependent variable. In addition, two indicators of the amount of traffic near the residence (at the

Table 2.6 Cohort studies of breast cancer and outdoor air pollution

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Outdoor air pollution, including traffic emissions								
Mills et al. (1991) California, USA	6340	1977–1982	Interpolations using inverse-distance weighting from fixed-site monitoring stations to postal code centroids	Annual average exceedance frequency above 200 µg/m^3 of TSP during 1973–1977 (1000 h/y)	65	1.51 (0.92–2.47)	Education level and smoking	Response rate to baseline questionnaire: 87%; follow-up rate of participants: 99%; lack of control for known breast cancer risk factors. Incident cases
Visser et al. (2004) Amsterdam, Netherlands	718 000	1989–1997	Residence along main roads (TIS ≥ 10 000)	*Adult women* TIS ≥ 10 000 10 000 ≤ TIS < 20 000 TIS ≥ 20 000	459 228 231	1.00 (0.91–1.09) 0.98 (0.86–1.12) 1.01 (0.89–1.15)	Age and sex	Reference: residence along other roads; lack of control for potential confounders
Raaschou-Nielsen et al. (2011b) Copenhagen and Aarhus, Denmark	57 053	1993–2006	Outdoor concentrations of NO_x at the residential addresses derived from the Danish AirGIS modelling system	Per 100 µg/m^3 increase in NO_x Major street within 50 m (yes vs no) Per 10^4 vehicle-km/day traffic load within 200 m of the residence	987 incidences 987 incidences 987 incidences	1.16 (0.89–1.51) 0.98 (0.78–1.22) 0.98 (0.88–1.10)	BMI, education level, alcohol consumption, number of births, age at first birth, lactation, HRT use, benign breast disease, physical activity, and occupation	Two traffic indicators were not associated with the outcome: street with a traffic density > 10 000 vehicles/day within 50 m of the residence, and total number of kilometres driven by vehicles within 200 m of the residence/day

Table 2.6 (continued)

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Emissions from waste incinerators, industrial facilities, or other sources								
Ranzi et al. (2011) Forlì, Italy	31 347	1990–2003	Atmospheric Dispersion Model System software used to model concentrations of heavy metals (annual average) as indicators of pollution from incinerators	Lowest quartile exposure category (< 0.5 ng/m³)	21 deaths	1.00 (ref)	Age and area-based SES	Rate ratios for breast cancer incidence were not elevated; concerns are residual confounding and multiple comparisons; in Table 5, the ICD-9 code of breast cancer is shown as "175" but it would be incorrect
				Second quartile (0.5–1 ng/m³)	22 deaths	1.33 (0.73–2.43)		
				Third quartile (1–2 ng/m³)	18 deaths	1.02 (0.55–1.92)		
				Highest quartile (> 2 ng/m³)	13 deaths	2.00 (1.00–3.99)		
				Lowest quartile exposure category (< 0.5 ng/m³)	125 incident cases	1.00 (ref)		
				Second quartile (0.5–1 ng/m³)	90 incident cases	0.89 (0.68–1.17)		
				Third quartile (1–2 ng/m³)	81 incident cases	0.78 (0.59–1.03)		
				Highest quartile (> 2 ng/m³)	30 incident cases	0.76 (0.51–1.13)		

BMI, body mass index; CI, confidence interval; ICD, International Classification of Diseases; HRT, hormone replacement therapy; NO_x, nitrogen oxides; NR, not reported; ref, reference; SES, socioeconomic status; TIS, traffic intensity score; TSP, total suspended particles.

time of enrolment) were obtained: the presence of a street with a traffic density of more than 10 000 vehicles per day within 50 m of the residence, and the total number of kilometres driven by vehicles within 200 m of the residence per day. Cox proportional hazards models were used to estimate incidence rate ratios per 100 μg/m^3 increase in NO_x. A total of 54 304 cohort members were included in the analysis. During the follow-up, there were 987 new breast cancer cases. The crude incidence rate ratio per 100 μg/m^3 increase in NO_x was 1.39 (95% CI, 1.09–1.77) but was attenuated (IRR, 1.16; 95% CI, 0.89–1.51) after adjustment for BMI, education level, alcohol consumption, number of births, age at first birth, lactation, hormone replacement therapy use, benign breast disease, physical activity, and occupation. The two traffic indicators were not associated with the outcome. [Strengths of this study include a 10-year prospective follow-up of a relatively large cohort with complete follow-up for vital status. This study also has the strength of modelling exposure since 1971. This study shows the necessity of adjustment for known breast cancer risk factors in evaluating the association between air pollution and breast cancer risk.]

(b) Case–control studies

See Table 2.7.

Lewis-Michl et al. (1996) conducted a population-based case–control study in Nassau and Suffolk counties in New York State, USA. A total of 1420 cases of breast cancer in women aged 20–79 years diagnosed in 1984–1986 at any hospital and 1420 age- and county-matched controls identified through driver's license records were included. The response rates were 88% for cases (1436 of 1616 contacted) and 67% for controls (1420 of 2097 contacted). After restricting to participants with continuous residence for 20 years, address information, and driver's license, there were 793 cases and 966 controls. Geographically based exposure indices of industrial concentration (chemical and other facilities) in 1965 and 1975 and traffic density in 1990–1992 were obtained and assigned to the participants based on 1 km^2 grid cells of residence. Although the industrial data were obtained on 1 km^2 grid cells, the traffic data (i.e. vehicle count data) were originally aggregated for 25 km^2 grid cells and resampled to produce 1 km^2 grid cells. Multiple logistic regression was used to control for family history of breast cancer, history of benign breast disease, age at first live birth, years of education, and attained age. Residence in a grid cell with a chemical facility (i.e. one or more facilities, for 1 year or longer) increased the risk of breast cancer among postmenopausal women in both counties: the odds ratios were 1.61 (95% CI, 1.06–2.43) in Nassau County and 1.58 (95% CI, 0.71–3.51) in Suffolk County. However, proximity to other facilities or to traffic (100 000 vehicles per mile of highway) did not increase the risk. No meaningful associations were found among premenopausal women either. [A strength of the study is the adjustment for several known breast cancer risk factors. However, the traffic data were originally aggregated for 25 km^2 grid cells and resampled to produce 1 km^2 grid cells; thus, the geographical units of that size are probably too large to reflect meaningful differences of traffic exposure, which may induce exposure misclassification. Selection bias is another concern, due to a relatively low response rate of controls.]

Bonner et al. (2005) conducted a population-based case–control study among women living in Erie and Niagara counties in western New York State, USA, during 1996–2001 (Western New York Exposures and Breast Cancer [WEB] study). Cases included 1166 women aged 35–79 years with histologically confirmed primary incident breast cancer. Controls (n = 2105) were frequency-matched to cases by age, race, and county of residence. The response rates were 71% for cases (1166 of 1638) and 62% for controls (2105 of 3396). TSP, a measure of outdoor air pollution, was used as a proxy for exposure to polycyclic aromatic hydrocarbons

Table 2.7 Case–control studies of breast cancer and outdoor air pollution

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Outdoor air pollution, including traffic emissions									
Lewis-Michl et al. (1996) Nassau and Suffolk counties, New York, USA, 1984–1986	793	966	Population	Geographically based exposure indices of industrial concentration (chemical and other facilities) in 1965 and 1975, and traffic density (> 100 000 vehicle miles of travel) in 1990–1992	*Postmenopausal women in Nassau County* Proximity (i.e. residence in a grid cell) to chemical or other facilities	127	1.11 (0.83–1.48)	Family history of breast cancer, history of benign breast disease, age at first live birth, years of education, and attained age	Response rate: 88% of contacted cases and 67% of contacted controls; the adjusted ORs for premenopausal women in both counties are not provided because no meaningful associations were found in the crude models
					Proximity to chemical facilities	58	1.61 (1.06–2.43)		
					Proximity to other facilities	NR	1.08 (0.80–1.46)		
					Proximity to traffic	33	1.29 (0.77–2.15)		
					Postmenopausal women in Suffolk County Proximity to chemical or other facilities	44	1.12 (0.72–1.74)		
					Proximity to chemical facilities	14	1.58 (0.71–3.51)		
					Proximity to other facilities	NR	0.99 (0.62–1.56)		
					Proximity to traffic	11	0.89 (0.40–1.99)		

Table 2.7 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Bonner et al. (2005) New York, USA, 1996–2001	1166	2105	Population	Prediction maps of historical TSP (at birth, at menarche, at first birth, and cumulative) generated using inverse-distance-squared-weighted interpolation	*Premenopausal women: TSP (μg/m³) at birth* < 84	5	1.00 (ref)	Age, education level, and parity	Response rate: 71% for cases and 62% for controls; lifetime cumulative exposure was associated with an increased risk of postmenopausal breast cancer but not with that of premenopausal breast cancer.
					84–114	26	1.96 (0.64–3.01)		
					115–140	64	2.23 (0.77–6.44)		
					> 140	69	1.78 (0.62–5.10)		
					P for trend		0.38		
					Postmenopausal women: TSP (μg/m³) at birth < 84	7	1.00 (ref)		
					84–114	52	2.32 (0.89–6.10)		
					115–140	142	1.94 (0.77–4.86)		
					> 140	156	2.42 (0.97–6.09)		
					P for trend		0.01		
					Premenopausal women: TSP (μg/m³) at menarche < 84	32	1.00 (ref)		
					84–114	53	0.98 (0.56–1.70)		
					115–140	62	1.25 (0.71–2.23)		
					> 140	57	0.66 (0.38–1.16)		
					P for trend		0.21		

Table 2.7 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Bonner et al. (2005) New York, USA, 1996–2001 (cont.)					*Postmenopausal women: TSP (μg/m³) at menarche* < 84	14	1.00 (ref)		
					84–114	81	1.36 (0.67–2.77)		
					115–140	171	1.20 (0.61–2.36)		
					> 140	203	1.45 (0.74–2.87)		
					P for trend		0.18		
					Premenopausal women: TSP (μg/m³) at first birth < 84	147	1.00 (ref)		
					84–114	19	1.06 (0.55–2.02)		
					115–140	5	0.41 (0.14–1.67)		
					> 140	10	0.52 (0.22–1.20)		
					P for trend		0.04		
					Postmenopausal women: TSP (μg/m³) at first birth < 84	54	1.00 (ref)		
					84–114	89	1.30 (0.83–2.03)		
					115–140	142	1.28 (0.83–1.97)		
					> 140	150	1.33 (0.87–2.06)		
					P for trend		0.61		

Table 2.7 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Crouse et al. (2010) Montreal, Canada, 1996–1997	383	416	Hospital	LUR model to predict outdoor concentrations of NO_2 across Montreal for 2006; in addition, the estimates for 1985 and 1996 were back-extrapolated by combining the observed concentrations and the predicted estimates of NO_2 for 2006	Outdoor concentrations of NO_2 (per 5 ppb increase)			Hospital of diagnosis; mother or sister with breast cancer; oophorectomy; years of education; ethnicity; age at menarche; age at first full-term pregnancy; breastfeeding history; oral contraceptive use; hormone replacement therapy use; with reactive metabolites, extremely low magnetic fields, CO, and PAHs; and two neighbourhood ecological covariates (median household income and percentage of adults without a high school diploma)	Postmenopausal breast cancer; response rate: 81.1% for cases and 75.7% for controls; NO_2 was used as a continuous variable *Extrapolated using observed concentrations of NO_2 at each fixed-site monitoring station **Extrapolated using predicted concentrations of NO_2 derived from the LUR model for 2006 at each fixed-site monitoring station
					Exposure surface in 2006	383	1.35 (0.94–1.94)		
					Exposure surface in 1996*	383	1.36 (0.99–1.88)		
					Exposure surface in 1985*	383	1.17 (0.91–1.50)		
					Exposure surface in mean of 1996 and 1985*	383	1.25 (0.94–1.65)		
					Exposure surface in 1996**	383	1.31 (1.00–1.71)		
					Exposure surface in 1985**	383	1.16 (0.94–1.42)		
					Exposure surface in mean of 1996 and 1985**	383	1.22 (0.97–1.54)		

B[*a*]P, benzo[*a*]pyrene; BMI, body mass index; CI, confidence interval; CO, carbon monoxide; LUR, land-use regression; NO_2, nitrogen dioxide; NR, not reported; OR, odds ratio; PAHs, polycyclic aromatic hydrocarbons, ref, reference; TSP, total suspended particles; yr, year.

(PAHs). Prediction maps of TSP (in the 1960s and 1970–1997) were generated using inverse-distance-squared-weighted interpolation, and historical exposure (at birth, at menarche, at first birth, and lifetime cumulative exposure) was assigned to the participants. The interpolated concentrations in the 1960s were also used for TSP concentrations before 1960. Age, race, education level, age at first birth, age at menarche, parity, previous benign breast disease, family history of breast cancer, BMI, and age at menopause were first considered as potential confounders, but the final models presented include only age, education level, and parity because other variables did not alter the effect estimates by more than 10%. In postmenopausal women, exposure to high concentrations of TSP (> 140 μg/m^3) at birth was associated with an increased risk (OR, 2.42; 95% CI, 0.97–6.09) compared with exposure to low concentrations (< 84 μg/m^3). On a continuous scale, the odds ratio with each increase of 30 μg/m^3 in TSP concentration at birth was 1.20 (95% CI, 1.04–1.38) for postmenopausal women. The odds ratios for other exposure periods were elevated but lower than those at birth. The results for premenopausal women were equivocal. [A strength of the study is that the study predicted historical exposure (at birth, at menarche, at first birth, and lifetime cumulative exposure) at each participant's address using geographic information system (GIS) data. The low response rate of controls and the assumption that TSP concentrations before 1960 were equal to those in the 1960s hamper interpretation. Another concern is potential residual confounding, although it is stated that adjustment for other variables did not alter effect estimates by more than 10%.]

Crouse et al. (2010) used data from a hospital-based case–control study conducted in Montreal, Canada, in 1996–1997. The cases were 383 women aged 50–75 years with incident invasive breast cancer, and the controls were 416 women with other incident, malignant cancers, excluding those potentially associated with selected occupational exposures. The response rates were 81.1% for cases and 75.7% for controls. The controls were matched by hospital and approximately frequency-matched by age. Concentrations of NO_2 were used as a marker for traffic-related pollution. A land-use regression model was developed to predict concentrations of NO_2 across Montreal for 2006 (Crouse et al., 2009). The estimates in 1985 and 1996 were back-extrapolated in two methods by combining the observed concentrations and the predicted estimates of NO_2 for 2006: the first method was extrapolation using observed concentrations at each fixed-site monitoring station, and the second method was extrapolation using predicted concentrations from the land-use regression model at each fixed-site monitoring station. These estimates were linked to addresses of residences of subjects at the time of the interview. Several known and suspected breast cancer risk factors (e.g. age at menarche, age at first full-term pregnancy, breastfeeding history, oral contraceptive use, hormone replacement therapy use, and BMI), occupational exposures, and neighbourhood ecological covariates were adjusted for in the model. The odds ratios with each increase of 5 ppb in NO_2 in 2006 were 1.15 (95% CI, 0.89–1.48) in the age-adjusted model and 1.35 (95% CI, 0.94–1.94) in the fully adjusted model. For two NO_2 estimates (obtained from extrapolation using observed concentrations or predicted concentrations) in 1996, the corresponding fully adjusted odds ratios were 1.36 (95% CI, 0.99–1.88) and 1.31 (95% CI, 1.00–1.71), respectively. [The historical exposure prediction at an individual level is an advantage of this study but also introduces uncertainty. An adjustment for an extensive list of potential confounders, including known breast cancer risk factors, is a strength.]

2.3.2 Emissions from waste incinerators, industrial facilities, or other sources

(a) Ecological studies

Cambra et al. (2011) examined the association between proximity to air polluting industries and mortality in small geographical areas in the Basque Country, Spain, from 1996 to 2003. Breast cancer mortality was higher within 2 km of mineral industries. Amaral et al. (2006) compared age-standardized rates of cancer incidence between an area affected by volcanic activity and an area without volcanic activity, both in the Azores, Portugal. They showed higher breast cancer incidence in the area with volcanic activity. [Because these studies cannot account for individual potential confounding and are limited by multiple testing, the findings should be considered preliminary.]

(b) Cohort studies

Ranzi et al. (2011) evaluated the health effects of emissions from two incineration plants located near Forlì, Italy, in a pilot cohort study. The study area was defined as the area of radius 3.5 km around the two incinerators. Subjects who lived in the study area in January 1990 or who subsequently became residents until December 2003 were enrolled in the study (n = 31 347), and their cancer mortality and morbidity were followed up from 1990 to 2003. Atmospheric Dispersion Model System software was used to simulate the impact of the different emission sources; modelled concentrations of heavy metals (annual average) were considered as the indicators of pollution from incinerators. In addition, NO_2 concentration was modelled as an indicator of air pollution from other sources. [Waste incinerators also generate NO_2.] Each subject in the cohort was assigned a value of estimated concentrations of heavy metals and NO_2 based on the residential address. Rate ratios were estimated with Poisson regression, using the lowest quartile exposure category to heavy metals as a reference, and adjusted for age and area-based socioeconomic status. During the follow-up, there were 326 incident cases and 74 deaths from breast cancer. The rate ratios for breast cancer mortality were elevated in the highest exposure category (RR, 2.00; 95% CI, 1.00–3.99). The result did not change substantially even after adjustment for NO_2. The rate ratios for breast cancer incidence were not elevated. [Strengths of the study are exposure modelling of emissions from the incinerators and the relatively large sample size. However, multiple comparisons and residual confounding are potential weaknesses of this study. A positive association with breast cancer mortality but not with incidence in the highest exposure category (RR, 0.76; 95% CI, 0.51–1.13) hampers interpretation of the study findings.]

2.4 Haematological malignancies: leukaemia and lymphoma

2.4.1 Outdoor air pollution, including traffic emissions

(a) Cohort studies

See Table 2.8

Mixed results were reported in several studies that assessed associations of exposure to air pollution or occupations involving exposure to outdoor air pollution with all haematopoietic cancers combined (Forastiere et al., 1994; Pukkala & Pönkä, 2001; Visser et al., 2004; Ranzi et al., 2011). One study in Italy reported an increased risk of Hodgkin lymphoma in bus drivers, white-collar workers, and maintenance workers (Merlo et al., 2010). Mixed results were reported in several studies for non-Hodgkin lymphoma (Forastiere et al., 1994; Lagorio et al., 1994; Soll-Johanning & Bach, 2004; Merlo et al., 2010; Raaschou-Nielsen et al., 2011b; Ranzi et al., 2011).

The incidence of leukaemia and lymphoma was one of the outcomes evaluated in the AHSMOG study (Mills et al., 1991) (see

Section 2.1.1c for a more detailed study description). During the follow-up, there were 12 incident cases of leukaemia (6 women, 6 men) and 15 incident cases of lymphoma (6 women, 9 men). Education level, total years of past smoking, and past or present employment in occupations that involved exposure to airborne contaminants (only for men) were adjusted for in the model. For 1000 hours per year in excess of 200 μg/m^3 of TSP, the risk of leukaemia and lymphoma combined was not elevated among women (HR, 1.05; 95% CI, 0.33–3.37). The hazard ratio for men was not elevated either (data not shown). [The strength of the study is the high follow-up rate. Assessing the risk of leukaemia and lymphoma as a combined measure may not be appropriate because they have different and poorly understood etiologies.]

One of the outcomes evaluated by Visser et al. (2004) was haematological malignancies (see Section 2.3.1a for a more detailed study description). During 1989–1997, 122 and 148 new haematological malignancies were identified for adult men and women, respectively. Using the age group- and sex-specific cancer incidence rates in the population living along other roads as the reference, standardized incidence ratios for the population living along the main roads were calculated. The standardized incidence ratio for haematological malignancies was 0.98 (95% CI, 0.81–1.17) for adult men and 1.23 (95% CI, 1.04–1.44) for adult women. The standardized incidence ratios for specific types of haematological malignancies among adult women were 1.23 (95% CI, 0.97–1.54) for non-Hodgkin lymphoma, 1.33 (95% CI, 0.90–1.90) for multiple myeloma, and 1.60 (95% CI, 1.01–2.40) for myeloid leukaemia. However, the standardized incidence ratio for haematological malignancies among adult women was higher in residents living along less-busy main roads (10 000 ≤ TIS < 20 000) (SIR, 1.41; 95% CI, 1.13–1.73) than for residents living along the busiest main roads (TIS ≥ 20 000) (SIR, 1.03; 95% CI, 0.78–1.32). [An increased risk was noted only in the intermediate category of exposure, and this could suggest a chance finding.]

Two of the outcomes evaluated by Raaschou-Nielsen et al. (2011b) were non-Hodgkin lymphoma and leukaemia (see Section 2.3.1a for a more detailed study description). During the follow-up, there were 197 incident cases of non-Hodgkin lymphoma and 117 incident cases of leukaemia. The incidence rate ratios per 100 μg/m^3 increase in NO_x were 1.11 (95% CI, 0.61–2.03) for non-Hodgkin lymphoma after adjustment for education level and occupation, and 0.47 (95% CI, 0.16–1.39) for leukaemia after adjustment for smoking status and occupation. The two traffic indicators were not associated with either outcome. [Strengths of this study include a 10-year prospective follow-up of a relatively large cohort with complete follow-up for vital status, modelling exposure since 1971, and adjustment for potential confounders.]

2.4.2 Emissions from waste incinerators

Cohort studies

See Table 2.8

Ranzi et al. (2011) evaluated the effects of emissions from two incineration plants located near Forlì, Italy, on multiple outcomes, including non-Hodgkin lymphoma and leukaemia, in a pilot cohort study (see Section 2.3.2b for a more detailed study description). Rate ratios were estimated with Poisson regression, using the lowest quartile exposure category to heavy metals as a reference, and adjusted for age and area-based socioeconomic status. During the follow-up, there were 43 deaths and 93 incident cases of non-Hodgkin lymphoma and 46 deaths and 48 incident cases of leukaemia. The rate ratios for non-Hodgkin lymphoma mortality were elevated among women with the highest exposure category (RR, 2.03; 95% CI, 0.48–8.67) but were not elevated among men for incident non-Hodgkin lymphoma or leukaemia. The results did not change substantially even after adjustment for NO_2 (data not shown), and rate ratios for NO_2 were not shown either. [Strengths of the study

Table 2.8 Cohort studies of leukaemia and lymphoma and outdoor air pollution

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Outdoor air pollution, including traffic emissions									
Mills et al. (1991) California, USA	6340	1977–1982	Interpolations using inverse-distance weighting from fixed-site monitoring stations to postal code centroids	Leukaemia and lymphoma combined (ICD code: NR)	Annual average hours in excess of 200 µg/m³ of TSP during 1973–1977 (1000 h/y)	20 incident cases for leukaemia; 26 incident cases for lymphoma	1.05 (0.33–3.37) for women	Education level, total years of past smoking, and past or present employment in occupations that involved exposure to airborne contaminants (only for men)	There was no association for men
Visser et al. (2004) Amsterdam, Netherlands	718 000	1989–1997	Residence along main roads (TIS ≥ 10 000)	Haematological malignancies (ICD-10 code: C81–95)	*Adult men* Other roads	NR	1.00 (ref)	Age and sex	
					Main roads (TIS ≥ 10 000)	122	0.98 (0.81–1.17)		
					Main roads (10 000 ≤ TIS < 20 000)	57	0.92 (0.70–1.20)		
					Main roads (TIS ≥ 20 000)	65	1.03 (0.80–1.32)		
					Adult women Other roads	NR	1.00 (ref)		
					Main roads (TIS ≥ 10 000)	148	1.23 (1.04–1.44)		
					Main roads (10 000 ≤ TIS < 20 000)	89	1.41 (1.13–1.73)		
					Main roads (TIS ≥ 20 000)	59	1.03 (0.78–1.32)		

Table 2.8 (continued)

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Raaschou-Nielsen et al. (2011b) Copenhagen and Aarhus, Denmark	57 053	1993–2006	Outdoor concentration of NO_x at the residential addresses derived from the Danish AirGIS modelling system	Non-Hodgkin lymphoma (ICD-7 code: 200, 202)	Per 100 µg/m³ increase in NO_x	197 incident cases	1.11 (0.61–2.03)	Education level and occupation (rubber industry)	Two traffic indicators (major street within 50 m, and total number of kilometres driven by vehicles within 200 m of the residence/ day) were not associated with non-Hodgkin lymphoma and leukaemia
					Major street within 50 m: No	NR	1.00 (ref)		
					Yes	NR	0.90 (0.54–1.51)		
					Per 10^4 vehicle-km/day traffic load within 200 m of the residence	197 incident cases	1.06 (0.83–1.35)		
				Leukaemia	Per 100 µg/m³ increase in NO_x	117 incident cases	0.47 (0.16–1.39)	Smoking status and occupation (chemical industry [oil refinery] and rubber industry)	
					Major street within 50 m: No	NR	1.00 (ref)		
					Yes	NR	0.81 (0.39–1.66)		
					Per 10^4 vehicle-km/day traffic load within 200 m of the residence	117 incident cases	0.75 (0.51–1.11)		

Table 2.8 (continued)

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Emissions from waste incinerators									
Ranzi et al. (2011) Forlì, Italy	31 347	1990–2003	Atmospheric Dispersion Model System software used to model heavy metals concentrations (annual average) as indicators of pollution from incinerators	Non-Hodgkin lymphoma (200, 202)	Women: Lowest quartile of heavy metals air concentration (< 0.5 ng/m^3)	7 deaths	1.00 (ref)	Age and area-based SES	Rate ratios for mortality in men and for incidences in both sexes were not elevated
					Second quartile (0.5–1 ng/m^3)	7 deaths	0.83 (0.27–2.56)		
					Third quartile (1–2 ng/m^3)	2 deaths	0.47 (0.09–2.44)		
					Highest quartile (> 2 ng/m^3)	3 deaths	2.03 (0.48–8.67)		
				Leukaemia (204–208)	Women: Lowest quartile of heavy metals air concentration (< 0.5 ng/m^3)	5 deaths	1.00 (ref)	Age and area-based SES	
					Second quartile (0.5–1 ng/m^3)	6 deaths	1.82 (0.54–6.19)		
					Third quartile (1–2 ng/m^3)	7 deaths	1.69 (0.52–5.55)		
					Highest quartile (> 2 ng/m^3)	2 deaths	1.31 (0.25–6.95)		

CI, confidence interval; ICD, International Classification of Diseases; NO_x, nitrogen oxides; NR, not reported; ref, reference; SES, socioeconomic status; TIS, traffic intensity score; TSP, total suspended particles.

are exposure modelling of emissions from the incinerators and the relatively large sample size.]

2.4.3 Emissions from petrochemical plants or other industries

(a) Ecological studies

Sans et al. (1995) included a general population sample of 115 721 people living within 7.5 km of the petrochemical plant in southern Wales. Leukaemia or lymphoma incidence and mortality were examined within distances of 7.5 km and 3 km from the plant, standardized for age, sex, and index of deprivation, and adjusted for region. There was no increased risk of leukaemia or lymphoma. Wilkinson et al. (1999) examined the incidence of lymphohaematopoietic malignancy from 1974 to 1991 within 7.5 km of all 11 oil refineries in Great Britain. After standardization for age, sex, and index of deprivation, there was no increased risk of the diseases. [These studies suffer from multiple testing and imprecise exposure assessment.]

(b) Case–control studies

See Table 2.9.

Linos et al. (1991) conducted a population-based case–control study to evaluate the association of residential proximity to industrial plants and incident cases of leukaemia and non-Hodgkin lymphoma among men living in Iowa and Minnesota in the USA. Cases included 622 people with non-Hodgkin lymphoma and 578 people with leukaemia diagnosed from 1980 to 1983. Controls were 1245 people frequency-matched to cases by year of birth, vital status, and state of residence (and year of death if the case was deceased). The response rates were 87% for non-Hodgkin lymphoma, 86% for leukaemia, and 81% for controls. Interviews were conducted of the subjects or their next of kin, and residential history with proximity to the factory and type of the factory was queried. Polychotomous logistic regression was conducted to estimate odds ratios adjusting for age, state of residence, vital status, and several risk factors for the cancers. Living within 0.8 km of any type of factory, compared with living in an unexposed area (> 3.2 km from the factory, or with no factory), was associated with odds ratios of 1.5 (95% CI, 1.1–1.9) for non-Hodgkin lymphoma and 1.1 (95% CI, 0.9–1.5) for leukaemia. In an analysis stratified by type of factory, the elevated risks of non-Hodgkin lymphoma were associated with living near stone, clay, or glass industry facilities; the odds ratio for living within 3.2 km of a factory was 1.6 (95% CI, 1.0–2.7; 31 exposed cases). In addition, the risk of leukaemia was greater among people who lived within 3.2 km of either a chemical plant (OR, 1.7; 95% CI, 1.0–3.0) or a petroleum plant (OR, 2.0; 95% CI, 1.0–4.2). [The interpretation of this study is difficult because of imprecise exposure assessment, which asked the subjects to recall their residential proximity to the factory and its type (i.e. potential for recall bias). Matching on year of death, as well as year of birth, may have overmatched in this study.]

Shore et al. (1993) used an existing population-based case–control study to evaluate the association between residential proximity to industrial plants and the risk of acute leukaemia. Cases were 712 patients aged 18–79 years who were residents of either the USA or Canada and were diagnosed during a 3.5-year period starting in 1986. Controls were 637 people who were selected by random telephone sampling and frequency-matched by age categories (10 years), race, sex, and region of residence. Cases (or their next of kin) were interviewed within 2 days of diagnosis, and controls were interviewed between June 1989 and January 1990. The response rates were 86% for cases and 80% for controls. In the interview, the subjects were asked whether they had lived near a factory before 2 years before the interview and the name and location of the factory. Logistic regression was used to estimate odds ratios adjusting for age, race, sex, region, level of schooling, smoking, and use of hair dye.

Table 2.9 Case–control studies of leukaemia and lymphoma and outdoor air pollution

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Emissions from petrochemical plant, oil refineries, and oil spill										
Belli et al. (2004) Brindisi, Italy	31	170	Population (deceased residents due to other causes)	Distance between the central point of the petrochemical plant and the residence of each subject	Lymphohaematopoietic malignancies (leukaemia, non-Hodgkin lymphoma, multiple myeloma, and Hodgkin lymphoma)	Distance: > 5 km 4–5 km 3–4 km 2–3 km ≤ 2 km	 10 5 5 7 4	 1.00 (ref) 0.57 (0.14–2.4) 0.26 (0.06–1.1) 0.39 (0.10–1.6) 2.7 (0.45–17)	Age, sex, smoking, and education level	Response rate: 98%
Yu et al. (2006) Kaohsiung, Taiwan, China	40	96	Population	Cumulative exposure score to petrochemicals considering proximity to the petrochemicals, monthly prevailing wind, subjects' mobility, and length of stay at each residence	Leukaemia (204–208)	Never lived in an exposed area Ever lived in an exposed area Per 1-unit increase in log-transformed exposure score	26 14 40	1.00 (ref) 4.56 (1.66–12.54) 1.54 (1.14–2.09)	Educational status of the subject; smoking status was further adjusted. Age (± 1 yr) and sex matched	Response rate: 91% for cases and 53% for controls; only results for those aged 20–29 yr are shown in this table
Emissions from other industrial facilities										
Linos et al. (1991) Iowa and Minnesota, USA	622 non-Hodgkin lymphoma cases and 578 leukaemia cases	1245	Population	Residential history (proximity to the factory and type of the factory)	Non-Hodgkin lymphoma (ICD code: NR) *Leukaemia*	Distance: > 3.2 km 0.8–3.2 km < 0.8 km Distance: > 3.2 km 0.8–3.2 km < 0.8 km	 272 304 182 272 248 142	 1.0 (ref) 1.4 (1.0–1.8) 1.5 (1.1–1.9) 1.0 (ref) 1.2 (0.9–1.9) 1.1 (0.9–1.5)	Age, state of residence, vital status, high-risk occupations, social class, smoking, use of hair dye, exposure to pesticides, and family history of cancer	Response rate: 87% for non-Hodgkin lymphoma, 86% for leukaemia, and 81% for controls; the results given refer to "any type of factory"

Table 2.9 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Shore et al. (1993) USA and Canada	712	637	Population	Residential history (proximity to the factory and types of the factory)	Leukaemia (ICD code: NR)	Distance: > 8 km < 8 km Distance: > 5 miles 2–5 miles ≤ 1 mile	 NR 117 NR 41 76	 1.0 (ref) 1.4 (1.0–1.9) 1.0 (ref) 1.0 (0.7–1.6) 1.7 (1.2–2.6)	Age, race, sex, region, level of schooling, smoking, and use of hair dye	Response rate: 86% for cases and 80% for controls; the results given refer to "any type of factory" (5 miles = 8 km)
Johnson et al. (2003) Canada	1499	5039	Population	Residential history (proximity to the factory and type of the factory)	Non-Hodgkin lymphoma (ICD code: NR)	Distance: > 3.2 km ≤ 3.2 km 0.8–3.2 km < 0.8 km	 1026 473 435 71	 1.00 (ref) 1.11 (0.97–1.26) 1.08 (0.95–1.24) 1.16 (0.87–1.54)	Age, sex, province, income adequacy level, education level, pack-years of smoking, alcohol consumption, urban/rural residential history, chemical exposure, and occupational exposure	Response rate: 62% for cases and 63% for controls; the results given refer to "any type of factory"
De Roos et al. (2010) 4 SEER regions, USA	864	684	Population	Residential history (proximity to the factory and type of the factory)	Non-Hodgkin lymphoma (ICD code: NR)	Distance: > 2 miles ≤ 2 miles > 1–2 miles > 0.5–1 miles ≤ 0.5 miles *P* for trend	 295 569 233 218 118	 1.0 (ref) 1.0 (0.8–1.2) 0.9 (0.7–1.2) 1.1 (0.8–1.4) 1.1 (0.8–1.5) 0.54	Age, sex, race, education level, and study site	Response rate: 59% for cases and 44% for controls (in the original study), and 76% for cases and 52% for controls (among eligible participants); the results given refer to "any type of factory" (5 miles = 8 km)

BMI, body mass index; CI, confidence interval; ICD, International Classification of Diseases; ICD-O, International Classification of Diseases for Oncology; NR, not reported; ref, reference; SEER, Surveillance, Epidemiology, and End Results; TEQ, toxic equivalence quotient; US EPA, United States Environmental Protection Agency; WHO, World Health Organization; yr, year.

Living within 8 km of any type of factory was associated with increased risk (OR, 1.4; 95% CI, 1.0–1.9) compared with living more than 8 km from the factory. In addition, the odds ratio for living within 1.6 km of the factory was 1.7 (95% CI, 1.2–2.6) and for living within 3.2–8 km of the factory was 1.0 (95% CI, 0.7–1.6). Confounder adjustment was not conducted due to the small number of cases. [This study is limited due to exposure assessment that depends on subjects' recall of their residential proximity to the factory and its type (i.e. potential for recall bias).]

Johnson et al. (2003) conducted a population-based case–control study to investigate the association between residential proximity to seven major types of industry (copper smelter, lead smelter, nickel smelter, steel production plant, petroleum refinery, kraft pulp plant, and sulfite pulp plant) and the risk of non-Hodgkin lymphoma. Cases were 1499 people diagnosed between April 1994 and December 1996 in 8 of the 10 Canadian provinces, and 5039 controls were randomly selected. The response rates were 62% for cases and 63% for controls. Questionnaires were used to collect detailed information as well as a lifetime Canadian residential history (exact address). Then, residential proximity to the seven major types of industry was calculated from 1960 to 5 years before the questionnaire was completed. Unconditional logistic regression was conducted to estimate odds ratios adjusting for age, sex, province, income adequacy level, education level, pack-years of smoking, alcohol consumption, urban/rural residential history, chemical exposure, and occupational exposure. Compared with living more than 3.2 km from the plants, the odds ratios were 1.11 (95% CI, 0.97–1.26) for having lived within 3.2 km of the plants, 1.08 (95% CI, 0.95–1.24) for having lived 0.8–3.2 km from the plants, and 1.16 (95% CI, 0.87–1.54) for having lived within 0.8 km of the plants. Increased risk of follicular non-Hodgkin lymphoma was observed among women who had lived within 3.2 km of a plant (OR, 1.48; 95% CI, 1.10–1.99). Proximity to copper smelters (within 3.2 km) (OR, 5.13; 95% CI, 1.49–17.71) and sulfite pulp mills (within 0.8 km) (OR, 3.71; 95% CI, 1.46–9.42) was associated with increased risk. [Strengths of this study are the large sample size and the control for several potential confounders. Multiple testing and small numbers of cases in analyses for types of industries hamper interpretation of the results.]

Belli et al. (2004) investigated cancer mortality and residential proximity to the petrochemical plant located in Brindisi, Italy. Cases included all residents in Brindisi and in three neighbouring municipalities who had died in the study area from 1996 to 1997 from lung cancer, pleural neoplasm, bladder cancer, and lymphohaematopoietic malignancies (i.e. leukaemia, non-Hodgkin lymphoma, multiple myeloma, and Hodgkin lymphoma) (n = 144, including 31 lymphohaematopoietic malignant cases). Controls were randomly selected from the residents in the study area who had died during the same period from any cause except those listed for the cases (n = 170). Distance between the central point of the plant and the residence of each subject was calculated. Logistic regression was used to estimate odds ratios adjusting for age, sex, smoking, and education level. The risk of lymphohaematopoietic malignancies was elevated for residents living within 2 km of the plant (OR, 2.7; 95% CI, 0.45–17). [The small number of cases poses threats to the validity of findings. Combining leukaemia and lymphoma cases may not be appropriate because they have different and poorly understood etiologies.]

Yu et al. (2006) conducted a population-based case–control study to examine the associations between residential exposure to petrochemical complexes and the risk of leukaemia among subjects aged 29 years and younger in Kaohsiung, Taiwan, China. There were four petrochemical complexes in the study area. Cases included 171 incident primary leukaemia cases during the period from November 1997 to January 2003

who were residents of the study area at diagnosis (response rate, 91%). Controls were 410 subjects randomly selected from the study area, matched by age (± 1 year) and sex (response rate, 53%). Based on information on residential history obtained by interview, a cumulative exposure score to petrochemicals was calculated for each individual, considering proximity to the petrochemical plants, monthly prevailing wind, subjects' mobility, and length of stay at each residence. Conditional logistic regression models were used to estimate odds ratios further adjusting for educational status and smoking status. For subjects aged 20–29 years, there were 40 cases and 96 controls, and the risk of leukaemia was elevated among the subjects who had ever lived in an exposed area (i.e. within an area of radius 3 km around the complexes) (OR, 4.56; 95% CI, 1.66–12.54) compared with those who had never lived in an exposed area. For the subjects aged 20–29 years, the odds ratio per 1-unit increase in log-transformed exposure score was 1.54 (95% CI, 1.14–2.09). [The study has the strength of exposure modelling but is limited due to the low response rate among controls. There is potential for selection bias in this study as controls appeared to vary in several characteristics of socioeconomic status: more controls completed college or above (56%) compared with cases (30%) among the subjects aged 20–29 years.]

De Roos et al. (2010) used an existing population-based case–control study to examine the association between proximity to industrial facilities (15 types of industry) and the risk of non-Hodgkin lymphoma in four United States SEER registry areas. Cases included 1321 patients with non-Hodgkin lymphoma, and controls were 1057 people identified by random-digit dialling. The overall response rate was 59% for cases and 44% for controls. Residential history was queried by interviewer-administered questionnaire, and residential proximity to industrial facilities during a 10-year period before diagnosis or reference year was calculated. Analyses were limited to participants with more than 70% of their person-years during the 10-year exposure period with reliable residential information, which yielded 864 cases and 684 controls. Unconditional logistic regression was used to estimate odds ratios adjusting for age, sex, race, education level, and study site. Having lived within 3.2 km of any type of industrial facility was not associated with the risk of non-Hodgkin lymphoma (OR, 1.0; 95% CI, 0.8–1.2). There was no dose–response relationship in terms of the proximity or the number of years of residence. Increased risk of non-Hodgkin lymphoma was observed for living within 3.2 km of several industries, including lumber and wood products (OR, 1.4; 95% CI, 0.9–2.1), chemical (OR, 1.2; 95% CI, 0.9–1.6), petroleum (OR, 1.1; 95% CI, 0.8–1.5), and primary metal (OR, 1.3; 95% CI, 1.0–1.6) industries. However, the findings were inconsistent in terms of distance or duration of residence. [Although the study had a large sample size, it had inconsistent results and a low response rate.]

2.5 Childhood cancer

Initial interest in the hypothesis that air pollution causes childhood cancer was prompted by two independent case–control studies of wire configuration and electromagnetic fields near the homes of children with cancer, which considered proximity to high-density road traffic as a potential confounder. Both studies found positive associations with metrics of heavy traffic near the residence (Wertheimer & Leeper, 1979; Savitz et al. 1988, Savitz & Feingold 1989).

Subsequent studies of air pollution and childhood cancer have consisted primarily of ecological/geographical studies and case–control studies. Ecological/geographical studies have compared the density of childhood cancer cases, for example incidence and mortality rates, in areas with higher and low air pollution levels, estimated for example by proximity to industry

or density of streets and cars, providing mixed results (Knox, 1994; Lyons et al., 1995; Sans et al., 1995; Alexander et al., 1996; Knox & Gilman, 1997; Nordlinder & Järvholm, 1997; Gilman & Knox, 1998; Harrison et al., 1999; Reynolds et al., 2002, 2003; Visser et al., 2004; Knox, 2005a, b, 2006; Thompson et al., 2008; Whitworth et al., 2008). Ecological studies are not reviewed here because of the limitations for causal inference. Case–control studies have explored differences in various metrics of exposure to outdoor air pollution at addresses of childhood cancer cases and control children, for example traffic density, modelled concentrations, neighbouring automotive repair garages, petrol stations, and refuelling of a car.

Several studies that addressed parental occupational exposure to motor-vehicle-related exhausts and the risk of cancer in the offspring showed associations with childhood leukaemia (Colt & Blair, 1998; IARC, 2013). However, these studies were not reviewed in detail because the Working Group believed that the exposures assessed could be relevant to engine exhausts but were not informative for outdoor air pollution. Furthermore, the results were not consistent and several common methodological limitations were identified related to the quality of the exposure assessment (usually just a job title), the small number of exposed cases, multiple comparisons, and possible bias towards reporting of positive results.

2.5.1 Case–control studies

See Table 2.10 for results for all cancers combined, Table 2.11 for leukaemia, Table 2.12 for acute leukaemia, Table 2.13 for lymphoma, Table 2.14 for central nervous system (CNS) tumours, and Table 2.15 for other cancers. (Note that some studies reported data for several cancer sites.)

(a) All cancers combined

See Table 2.10.

Wertheimer & Leeper (1979) considered traffic at the residence as a potential confounder in their study of wire configuration and the risk of childhood cancer mortality in the Denver, Colorado, area, USA. No risk estimates for traffic were provided, but based on the given numbers an odds ratio of 1.6 (95% CI, 1.1–2.3) for all cancers combined in association with 5000 vehicles per day or more at a street within 40 m of the home could be calculated (Feychting et al., 1998). [This study was limited by its use of mortality as a surrogate for the incidence of childhood cancer because a large proportion of children with cancer (e.g. acute lymphoblastic leukaemia) survive their disease. Other limitations were that only a crude exposure estimate and only odds ratios for all cancer types combined were presented. The odds ratio was based not on counts of cases and controls but on counts of case and control addresses, where each child could contribute with both an address at birth and an address at diagnosis.]

Savitz et al. (1988) and Savitz & Feingold (1989) identified 328 cases of all types of childhood cancer from the Colorado Central Cancer Registry and area hospitals and used random-digit dialling to select 262 controls from the population (response rate, 75%), who were matched to cases by age, sex, and area. The amount of traffic at the address at the time of diagnosis was provided by Highway Planning authorities. The study reported an odds ratio of 3.1 (95% CI, 1.2–8.0) for all incident cancers combined. Further adjustment for several covariates in a subset of study participants had little effect on the risk estimates. [The Working Group noted several limitations to this study, including that the random-digit dialling method for selection of controls could potentially result in selection bias, that the exposure assessment was crude, and that there were small numbers of exposed cases for specific types of cancer.]

Table 2.10 Case–control studies of all childhood cancers combined and outdoor air pollution

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Savitz & Feingold (1989) Denver, Colorado, USA, 1976–1983	280	262	Population; random-digit dialling	Traffic counts at home address at time of diagnosis	All cancers	< 500 vehicles/day		1.0 (ref)	Matched by age, sex, and area	Incidence. 0–14 yr. Adjustment in a subset for sex, age, year of diagnosis, type of residence, location at birth, mother's age, father's education level, per capita income, and wire configuration had little effect on the risk estimates. Also see Savitz et al. (1988)
						≥ 500 vehicles/day	48	1.7 (1.0–2.8)		
						≥ 5000 vehicles/day	29	1.8 (0.9–3.3)		
						≥ 10 000 vehicles/day	18	3.1 (1.2–8.0)		
Feychting et al. (1998) Sweden	63	550	Population; randomly selected among children living within 300 m of high-voltage power lines	Modelled peak concentrations of NO_2 (99th percentile of 1-h means); based on latest address within the power line corridor	All cancers	≤ 39 μg/m³		1.0 (ref)	Matched by calendar time, geographical area, and residence near same power line	Incidence. Cases: 0–15 yr; identified among children living within 300 m of high-voltage power lines. Adjustment for electromagnetic fields and socioeconomic position did not materially change the results. Similar effects for boys and girls
						40–49 μg/m³	35	1.3 (0.4–4.3)		
						≥ 50 μg/m³	44	2.7 (0.9–8.5)		
						≥ 80 μg/m³	8	3.8 (1.2–12.1)		

Table 2.10 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Raaschou-Nielsen et al. (2001) Denmark, 1968–1991	1989	5506	Randomly selected from whole population	Traffic density and modelled NO_2 and benzene at home addresses from time of conception to time of diagnosis	Leukaemia, CNS tumours, and lymphoma (3 main types of childhood cancer together)	NO_2 (in 1000 ppb-days) during childhood*			Matched by sex, age, and calendar time. Adjustment for urban development, geographical region, type of residence, electromagnetic fields, mother's age, and birth order	Incidence. Cases: 0–14 yr. Cumulative air pollution exposure over addresses during childhood. Similar results for exposure of mother during pregnancy. *Cut-off points for exposure categories were set at the 50th, 90th, and 99th percentiles
						< 11.5	955	1.0 (ref)		
						11.5–29.4	679	1.1 (0.9–1.3)		
						29.4–57.8	145	1.1 (0.8–1.5)		
						≥ 57.8	17	1.2 (0.6–2.3)		
						Number of vehicles/ day during childhood (time-weighted average)				
						< 500	1142	1.0 (ref)		
						≥ 10 000	27	1.0 (0.7–1.6)		
Reynolds et al. (2004) California, USA, 1988–1997	4369	8730	Population; birth certificates	Road density (miles) and traffic density (vehicle miles travelled per square mile) within 152 m of address at time of birth	All cancers	Quartile 1 Road density		1.0 (ref)	Matched by age and sex. Adjustment for race and ethnicity. Little effect of further adjustment for mother's age, birth weight, neighbourhood income, or county-level benzene emissions	Incidence. Cases: 0–4 yr. Successful validation of the exposure assessment method reported
						≥ 90th percentile		0.87 (0.75–1.00)		
						Traffic density				
						≥ 90th percentile		0.92 (0.80–1.06)		

CI, confidence interval; CNS, central nervous system; CO, carbon monoxide; h, hour or hours; IQR, interquartile range; NO_2, nitrogen dioxide; NR, not reported; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 μm; ref, reference; SES, socioeconomic status; yr, year.

(b) Childhood leukaemia and lymphoma

See Table 2.11, Table 2.12, and Table 2.13.

Savitz et al. (1988) and Savitz & Feingold (1989) (see description in Section 2.5.1a) reported odds ratios of 3.1 (95% CI, 1.2–8.0) for all cancers combined and 4.7 (95% CI, 1.6–13.5) for leukaemia in association with 10 000 vehicles or more per day, compared with fewer than 500 vehicles per day, and 0.7 (95% CI, 0.2–3.0) for lymphoma.

A total of 142 cases of all types of childhood cancer were identified in the Swedish Cancer Registry among 127 000 children living within 300 m of transmission lines in Sweden (Feychting et al., 1998). Among the children living within the power line corridor, identified by the Swedish Population Registry, 550 controls were randomly selected and matched to cases by calendar time, geographical area, and residence near the same power line. The study used information on traffic density, street type, traffic speed, street width, and distance between the house and the street to model NO_2 at the latest home addresses within the power line corridor. The study noted elevated risk of incident childhood cancers among children living at addresses with high concentrations of NO_2. When NO_2 concentrations of 50 μg/m^3 or more were compared with concentrations of less than 40 μg/m^3, the odds ratios were 2.7 (95% CI, 0.9–8.5) for all cancers combined, 2.7 (95% CI, 0.3–20.6) for leukaemia, and 5.1 (95% CI, 0.4–61.2) for CNS tumours; NO_2 concentrations of 80 μg/m^3 or more were associated with an odds ratio for all cancers of 3.8 (95% CI, 1.2–12.1). There was indication of a linear exposure–response relationship. Further adjustment for electromagnetic fields and socioeconomic position had little impact on the results. [A strength of this study was the use of an air pollution model. Limitations included imprecise risk estimates due to the relatively few cases and no validation of the exposure model (i.e. no comparison between modelled and measured concentration).]

In a population-based study, Raaschou-Nielsen et al. (2001) identified 1989 cases of leukaemia, lymphoma, and CNS tumours in the Danish Cancer Registry and randomly selected 5506 controls from among the whole Danish childhood population using the Danish Population Registry. Controls were matched to cases by sex, age, and calendar time. The residential history of each child was traced from 9 months before birth to the time of diagnosis. NO_2 and benzene concentrations were calculated from a validated model based on traffic and the configuration of the street and buildings at the address, emission factors of the Danish car fleet, meteorological variables, and the background air pollution concentration. The analyses adjusted for urban development, geographical region, type of residence, electromagnetic fields, mother's age, and birth order. For exposure to NO_2 between the 90th and 99th percentile or above the 99th percentile compared with below the 50th percentile, the respective relative risks were 1.1 (95% CI, 0.8–1.5) and 1.2 (95% CI, 0.6–2.3) for all three cancer types combined, 1.3 (95% CI, 0.8–2.3) and 0.4 (95% CI, 0.1–1.3) for leukaemia, 0.8 (95% CI, 0.5–1.5) and 1.0 (95% CI, 0.3–3.1) for CNS tumours, and 1.8 (95% CI, 0.7–4.3) and 4.7 (95% CI, 1.2–17.6) for lymphomas. The results also indicated no associations with exposure to benzene concentrations or traffic density either in utero or during childhood. [The Working Group noted several strengths of this study, including the large sample size, assessment of cumulative exposure over all addresses during pregnancy and childhood, successful validation of the exposure assessment method, and a low potential for bias.]

Langholz et al. (2002) evaluated the amount of traffic near the residence of children (0–10 years) who developed leukaemia (n = 212) and controls (n = 202) from an earlier study of electromagnetic fields (London et al., 1991) in the Los Angeles area, which has some of the heaviest traffic loads in the USA. Cases were ascertained

by the Los Angeles County Cancer Surveillance Programme, and controls, matched to cases by age and sex, were either friends or identified by random-digit dialling. Exposure was assessed as a distance-weighted metric of the total amount of traffic within 457 m (1500 feet) of the home address where the child had lived for the longest time. Although an increased risk of leukaemia was observed in the upper quintile compared with the lowest quintile (RR, 1.4; 95% CI, 0.7–3.0; adjustment for wire coding), no exposure–response association was observed; the second quintile was associated with the highest risk. Further adjustment for magnetic fields and other variables had little impact on the results. (The "other variables" were not specified in the article, which referred to an Interim Report from the Electric Power Research Institute; EPRI EN-7464.) [Several weaknesses were noted, including the selection of controls and friends, which could lead to selection bias, and the use of a crude exposure measure.]

A small study of leukaemia incidence was undertaken in Varese, Italy (Crosignani et al., 2004). A total of 120 cases were identified in the population-based Lombardy Cancer Registry, and 480 population controls were selected from the population-based Health Service Archives and matched to cases by age and sex. Benzene concentration at the address at diagnosis was calculated on the basis of traffic density on surrounding roads and the distances from the home address to roads with heavy traffic. When benzene concentrations of more than 10 μg/m^3 were compared with concentrations of less than 0.1 μg/m^3, the relative risk was 3.9 (95% CI, 1.4–11.3; 7 exposed cases; adjusted for socioeconomic status of the municipality) and there was a trend across the three exposure categories. [The exposure model was a strength of the study. Limitations included a small number of cases and the lack of validation of the exposure model.]

A large, state-wide study in California, USA, evaluated risk relationships for incident cancers among young children (0–4 years) (Reynolds et al., 2004). A total of 4369 cases of all types of cancer were identified in the population-based Californian Cancer Registry, and 8730 population controls were selected using birth certificates. Controls were matched to cases by age and sex. Road and traffic density was assessed within 152 m of the address at the time of birth. For leukaemia, the odds ratio was 0.79 (95% CI, 0.63–1.00) in association with road density and 0.92 (95% CI, 0.73–1.15) in association with traffic density, for the upper 10% compared with the lowest quartile. Similarly, no association was found for all cancers combined or for CNS tumours. Thus, the study found no evidence for an association with traffic near the mother's residence at the time of the child's birth, after adjustment for race and ethnicity. Further adjustment for mother's age, birth weight, neighbourhood income, or county-level benzene emissions had little effect on the results. The exposure assessment method was successfully validated against benzene measurements. [Strengths of this study are that it was large and state-wide, that it had a low potential for bias, and that the exposure assessment method was successfully validated.]

Von Behren et al. (2008) studied the incidence of acute lymphocytic leukaemia among children in northern and central California, USA, in association with traffic load at the residence at the time of birth, at the time of diagnosis, and a time-weighted average over all addresses during childhood. A total of 310 cases were recruited at hospitals, and 396 population controls were selected from birth certificates and matched to cases by age, sex, Hispanic ethnicity, mother's race, and county of birth. Exposure was defined as the total number of vehicle miles travelled within 152 m of the residence. After adjustment for household income, for the upper quartile of exposure compared with the "no road traffic" category, the odds ratio was 1.1 (95% CI, 0.7–1.8) for the address at birth, 1.2 (95% CI, 0.8–1.8) for the address at diagnosis, and 1.2 (95% CI, 0.7–2.1)

for all addresses. The exposure assessment method was successfully validated against measurements. [Strengths of this study include the use of all addresses in the exposure assessment and the validation of the exposure measurements.]

Steffen et al. (2004) identified 280 cases of acute leukaemia at hospitals in France and used 285 children hospitalized for acute pathologies as controls. Controls were matched to cases by age, sex, ethnic origin, hospital centre, and urban or rural setting. Mothers of case and control children were interviewed about heavy-traffic roads near addresses during childhood, neighbouring automotive repair garages or petrol stations, and many other potential risk factors. The odds ratios were 4.0 (95% CI, 1.5–10.3) for living neighbouring a repair garage or petrol station and 1.3 (95% CI, 0.6–2.9) for living near a motorway. Adjustment for family history of solid tumours or haematological neoplasms, early infections, day-care attendance, breastfeeding, and high-traffic roads did not modify the association. [Several limitations of the study were noted, including potential selection bias resulting from the use of hospital-based controls, potential recall bias resulting from the interview-based exposure assessment, and the lack of certainty as to how the crude exposure measures relate to air pollution exposure.]

Brosselin et al. (2009) further investigated the hypothesis of an association between acute leukaemia and residence near petrol stations and automotive repair garages in a new independent nationwide study in France including 765 cases of acute leukaemia from hospitals and 1681 controls selected from national telephone lists (landlines only). Mothers of case and control children were interviewed about proximity of the home to automotive repair garages, petrol stations, and other businesses, and many other potential risk factors during childhood. The study showed an increased risk for living neighbouring a repair garage or petrol station (OR, 1.6; 95% CI, 1.2–2.2) after adjustment for age, sex, number of children in the household, degree of urban development, and type of housing. [A strength of the study is its large sample size. Limitations include potential recall bias resulting from the interview-based exposure assessment, the use of a crude exposure measure, and potential selection bias due to the fact that lists of landline telephones would probably not cover the total base population. This study overlaps with Amigou et al. (2011).]

Amigou et al. (2011) assessed the association between acute leukaemia and traffic or NO_2 near the residence using many of the same methods as Brosselin et al. (2009) but applying objective approaches for NO_2 assessment in local 4 km^2 grids, proximity to roads, and road density within 500 m of the address at diagnosis. Controls were matched to cases by age and sex, and the results were adjusted for socioeconomic status. The study found positive associations between all three measures for air pollution and acute leukaemia; the odds ratios were 2.0 (95% CI, 1.0–3.6) for a high score on the index for proximity to main roads compared with the unexposed category, 2.2 (95% CI, 1.1–4.2) for a high score on the index for heavy-traffic roads within 500 m compared with the unexposed category, and 1.2 (95% CI, 1.0–1.5) for traffic-related NO_2 of 16.2 $\mu g/m^3$ or more compared with less than 12.2 $\mu g/m^3$. Further adjustment for degree of urban development, type of housing, birth order, infections, pesticide use, and parental smoking did not change the results. [The large sample size is a strength of this study. Limitations include potential selection bias resulting from the fact that lists of landline telephones would probably not cover the total base population, the use of crude exposure measures, and the lack of validation of the NO_2 model.]

Associations of childhood leukaemia with several indicators of exposure to air pollution were reported in several papers from Taiwan, China. Weng et al. (2008b) studied leukaemia mortality in association with the same industry index at the municipality level (405 cases and

405 controls), petrol-station density, defined as number of petrol stations divided by the area of the municipality (729 cases and 729 controls) (Weng et al., 2009), and NO_2 measured at monitoring stations in 64 municipalities (308 cases and 308 controls) (Weng et al., 2008a). Controls were selected from among all people who had died due to non-neoplastic, non-respiratory diseases and were matched to cases by sex, year of birth, and year of death. Results were adjusted for the urbanization level of the municipality. Among those aged 0–19 years, the odds ratio was 1.75 (95% CI, 1.00–3.06) for the highest quartile of 226 more-rural municipalities compared with the lowest quartile of scores for the petrochemical air pollution index and 1.26 (95% CI, 0.70–2.26) for the non-petrochemical industry index (Weng et al., 2008b). The two industrial indices were mutually adjusted. [Limitations of the study are the use of mortality and the uncertainty as to how the air pollution indices relate to concentrations at participants' addresses since no validation is presented.]

The highest tertile of the municipality petrol-station density index was associated with a significantly higher risk of death due to leukaemia among children aged 0–14 years (OR, 1.91; 95% CI, 1.29–2.82) (Weng et al., 2009). [The study is large but is limited by the use of mortality and the uncertainty as to how the petrol-station density index relates to concentrations at participants' addresses since no validation is presented.]

A related paper (Weng et al., 2008a) reported leukaemia mortality among children aged 0–14 years to be associated with the highest tertile of annual mean concentrations of NO_2 at municipal monitoring stations compared with the lowest tertile of municipalities (OR, 2.29; 95% CI, 1.44–3.64). [This study is limited by the use of mortality, the lack of information on location (street or background) of the monitoring stations, and the uncertainty as to how the concentrations monitored in the different municipalities reflect population exposure.]

In another study from Taiwan, China, Yu et al. (2006) studied incidence of leukaemia among children aged 0–19 years in metropolitan Kaohsiung. Cases (n = 131) were identified at the large hospitals in the area, and controls were selected from a population registry and matched to cases by age and sex. Assessment of exposure to petrochemical air pollution was improved over previous methods by using an exposure opportunity score based on the assessment of all addresses held for more than 1 year for distance to petrochemical plant(s), prevailing wind direction, and multiple sources of petrochemical pollution. The odds ratios for an association with the exposure opportunity score were 1.04 (95% CI, 0.79–1.38) for all leukaemias and 1.21 (95% CI, 0.89–1.65) for acute lymphocytic leukaemia. Further adjustment for parental occupation in the petrochemical industry had little impact on the results. [This study is limited by the small sample size. The Working Group noted that although the exposure assessment method is more sophisticated compared with the simple petrochemical index used in other studies, it is uncertain how the exposure opportunity score relates to concentrations at participants' addresses since no validation is presented.]

In Australia, Bailey et al. (2011) studied parental non-occupational refuelling of a car the year before and during pregnancy, as a surrogate for exposure to benzene, a potential risk factor for childhood acute lymphoblastic leukaemia. A total of 389 cases were ascertained from the Australian paediatric oncology centres, and population controls were selected using random-digit dialling. Information about exposure was collected by questionnaire. The odds ratios for acute lymphoblastic leukaemia in the offspring were 0.82 (95% CI, 0.57–1.20) for refuelling by the mother (ever vs never) and 1.56 (95% CI, 0.65–3.77) for refuelling by the father (ever vs never) after adjustment for age, sex, state, and education level. Further adjustment for income, ethnicity, birth order, parental age, birth defects,

and paternal smoking had little impact on the results. [The Working Group noted that the use of random-digit dialling for selection of controls could lead to selection bias, the assessment of exposure by questionnaire could lead to recall bias, the exposure measures were crude, and there was uncertainty as to how these related to the exposure of participants.]

In the Emilia-Romagna region, in northern Italy, Vinceti et al. (2012) identified 83 incident cases of acute leukaemia among children aged 0–14 years in the population-based cancer registry of the Italian Association of Paediatric Haematology and Oncology and selected 332 population controls individually matched to cases by sex, year of birth, and province of residence. Traffic-related benzene and PM_{10} concentrations were estimated by the CALINE4 dispersion model at the addresses at the time of diagnosis. Modelled concentrations were validated against those measured at fixed-site monitoring stations. For the highest compared with the lowest exposure categories, the odds ratios were 1.8 (95% CI, 0.9–3.7) for benzene and 1.8 (95% CI, 0.8–3.9) for PM_{10}. Stronger, statistically significant results were found for children younger than 5 years. [A strength of this study was the use of a validated exposure model. A limitation was the small sample size, resulting in wide confidence intervals.]

In a nationwide case–control study in Italy, Badaloni et al. (2013) studied leukaemia among children aged 0–10 years in association with traffic and air pollutants at the residence. A total of 747 eligible cases from 14 out of 20 Italian regions were identified through the national childhood cancer registry of the Italian Association of Paediatric Haematology and Oncology and the National Paediatric Oncology Task Force, and 1509 controls were randomly selected from the population and matched to cases by birth data, sex, and region; 91% of the cases and 69% of the controls participated. Information about residential history and individual-level potential confounders was collected by face-to-face interviews. $PM_{2.5}$ concentration was estimated by a national dispersion model with 4 km × 4 km resolution. Concentrations of NO_2, PM_{10}, and ozone were estimated by land-use regression models with 100 m × 100 m resolution. Increased risks for leukaemia were not found regardless of the exposure measure applied: the odds ratio for the highest quartile compared with the lowest quartile was 0.85 (95% CI, 0.61–1.18) for NO_2 and 1.00 (95% CI, 0.70–1.41) for PM_{10}. Similar negative results were found in several sensitivity analyses. [Strengths of this study include the large sample size, the nationwide coverage, and a detailed exposure assessment that was successfully validated. However, this study may be affected by selection bias due to the large difference in participation rate between cases and controls.]

(c) Other childhood cancers

Data for childhood CNS tumours are presented in Table 2.14; data for other childhood cancers are presented in Table 2.15.

Associations of childhood CNS tumours with indicators of exposure to air pollution were investigated in the previously cited studies by Savitz & Feingold (1989) and Feychting et al. (1998). No significant association was found.

In a large study in Los Angeles County, California, USA, Ghosh et al. (2013) investigated incident cancer among children aged 0–5 years in association with exposure to NO, NO_2, and NO_x during pregnancy. A total of 4015 cases of all types of cancer diagnosed between 1988 and 2008 were identified in the California Cancer Registry that could be linked to birth certificates (11% of identified cases could not be linked and were excluded), and 80 658 population controls were selected using birth certificates. Land-use regression models were successfully validated and used to calculate the annual mean levels of NO, NO_2, and NO_x at the address at birth. Monthly variation was estimated from data from

the nearest monitoring station. Risk of childhood cancer was analysed per linear increase of 25 ppb during pregnancy. Among 19 types of childhood cancer assessed, only rare bilateral retinoblastoma showed a statistically significant result for exposure during the third trimester. For acute lymphoblastic leukaemia, the odds ratios were 1.08 (95% CI, 1.01–1.16) for NO_x, 1.23 (95% CI, 0.98–1.53) for NO_2, and 1.09 (95% CI, 1.01–1.18) for NO. For acute myeloid leukaemia, the odds ratios were 0.88 (95% CI, 0.73–1.07) for NO_x, 0.71 (95% CI, 0.39–1.30) for NO_2, and 0.84 (95% CI, 0.65–1.09) for NO. The results were adjusted for sex, year of birth, mother's age, race/ethnicity, education level, parity, prenatal care, insurance type, and socioeconomic score of the census block. Further adjustment for prenatal care, mother's birthplace, father's race, father's education level, child's birth weight, and birth season had little impact on the results. [Strengths of this study include the large sample size and the validated exposure assessment method. Limitations include the possibility of chance findings resulting from multiple testing and the potential for selection bias if the 11% of cases that were excluded differed from the included cases with respect to air pollution exposure.]

Heck et al. (2013) used the California Cancer Registry to identify incident childhood (0–5 years) cancer cases born and diagnosed in 1998–2007; 3590 cases (89%) that could be matched to California birth certificates were included, and 80 224 controls were randomly selected directly from the California birth rolls. Concentrations of CO, NO_x, and $PM_{2.5}$, considered markers of the traffic-related air pollution mix, were modelled by the validated CALINE4 dispersion model. The exposure metrics assessed included residence of the child within 8 km of a fixed-site monitoring station, $PM_{2.5}$ concentrations from these monitors, and traffic density within 500 m of the residence. The analyses were adjusted for year of birth, parental race/ethnicity, mother's education level, mother's county of birth, method of payment for prenatal care, and neighbourhood socioeconomic status index. Among the 16 different types of childhood cancer assessed, the odds ratios for an IQR increase in exposure during pregnancy of CO and $PM_{2.5}$, respectively, were 1.05 (95% CI, 1.01–1.10) and 1.10 (95% CI, 0.92–1.30) for acute lymphoblastic leukaemia, 1.16 (95% CI, 1.02–1.33) and 1.46 (95% CI, 0.70–3.06) for bilateral retinoblastoma, and 1.26 (95% CI, 1.12–1.41) and 0.77 (95% CI, 0.36–1.68) for germ cell tumours of the teratoma type. The odds ratios for acute lymphoblastic leukaemia in association with CO were similar for Los Angeles County (1.06; 95% CI, 1.00–1.12) and the rest of the state (1.08; 95% CI, 0.99–1.17). For acute myeloid leukaemia, the odds ratios for an IQR increase in exposure during pregnancy were 0.85 (95% CI, 0.73–0.98) for CO and 0.85 (95% CI, 0.57–1.27) for $PM_{2.5}$. There was some consistency with the results presented by Ghosh et al. (2013) since both studies showed increased risk of acute lymphoblastic leukaemia and retinoblastoma and decreased risk of acute myeloid leukaemia. [About one third of the study population overlapped with that investigated by Ghosh et al. (2013) (Julia Heck, personal communication), and the results from these two studies are therefore not independent, except for the acute lymphoblastic leukaemia result for California excluding Los Angeles County, where no overlap in study population existed. Strengths of this study include the large sample size, the statewide enrolment, and a validated exposure model. Limitations include the possibility of chance findings resulting from multiple testing, the small numbers of rare cancers, and the potential for selection bias if the 11% of cases that could not be matched to birth certificates differed from the included cases with respect to air pollution exposure.]

Table 2.11 Case–control studies of childhood leukaemia and outdoor air pollution

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Savitz & Feingold (1989) Denver, Colorado, USA, 1976–1983	328	262	Population; random-digit dialling	Traffic counts at home address at time of diagnosis	Leukaemia	≥ 500 vehicles/day ≥ 5000 vehicles/day ≥ 10 000 vehicles/day	17 13 8	2.1 (1.1–4.0) 2.7 (1.3–5.9) 4.7 (1.6–13.5)	Matched by age, sex, and area	Incidence. 0–14 yr. Adjustment in a subset for sex, age, year of diagnosis, type of residence, location at birth, mother's age, father's education level, per capita income, and wire configuration had little effect on the risk estimates
Feychting et al. (1998) Sweden	142	550	Population; randomly selected from among children living within 300 m of high-voltage power lines	Modelled peak concentrations of NO_2 (99th percentile of 1-h means). Based on latest address within the power line corridor	Leukaemia	40–49 μg/m³ ≥ 50 μg/m³	7 9	1.7 (0.2–14.6) 2.7 (0.3–20.6)	Matched by calendar time, geographical area, and residence near same power line	Incidence. Cases: 0–15 yr; identified among children living within 300 m of high-voltage power lines. Similar effects for boys and girls

Table 2.11 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Raaschou-Nielsen et al. (2001) Denmark, 1968–1991	1989	5506	Randomly selected from whole population	Traffic density and modelled NO_2 and benzene at home addresses from time of conception to time of diagnosis	Leukaemia, CNS tumours, and lymphoma	NO_2 (in 1000 ppb-days) during childhood*			Matched by sex, age, and calendar time. Adjustment for urban development, geographical region, type of residence, electromagnetic fields, mother's age, and birth order	Incidence. Cases: 0–14 yr. Cumulative air pollution exposure over addresses during childhood. Similar results for exposure of mother during pregnancy. Successful validation of the exposure assessment method was reported *Cut-off points for exposure categories were set at the 50th, 90th, and 99th percentiles
						< 11.5	585	1.0 (ref)		
						11.5–29.4	237	0.9 (0.7–1.3)		
						29.4–57.8	58	1.3 (0.8–2.3)		
						≥ 57.8	3	0.4 (0.1–1.3)		
						Number of vehicles/ day during childhood (time-weighted average)				
						< 500	566	1.0 (ref)		
						≥ 10 000	14	1.1 (0.6–2.2)		
Langholz et al. (2002) Los Angeles County, California, USA, 1978–1984	212	202	Population; a friend, or selected by random-digit dialling	Sum of traffic counts (vehicles/ day) at all streets within 457 m of home address at which the child had resided the longest; a distance-weighted metric was used	Leukaemia	< 2301	35	1.0 (ref)	Matched by age and sex. Adjustment for wire coding	Incidence. Cases: 0–10 yr. Quintiles were used for cut-off points between exposure categories. Overlaps with London et al. (1991)
						2301–5997	45	1.6 (0.8–3.6)		
						5997–13 264	43	1.1 (0.5–2.4)		
						13 264–28 497	43	1.1 (0.5–2.2)		
						≥ 28 497	46	1.4 (0.7–3.0)		

Table 2.11 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Crosignani et al. (2004) Province of Varese, Italy, 1978–1997	120	480	Population; Health Service archives	Modelled concentration of benzene (μg/m³) outside the residence at time of diagnosis	Leukaemia	< 0.1 0.1–10 > 10	88 25 7	1.0 (ref) 1.5 (0.9–2.5) 3.9 (1.4–11.3)	Matched by age and sex. Adjustment for SES of the municipality	Incidence. Cases: 0–14 yr. P_{trend} = 0.005
Reynolds et al. (2004) California, USA, 1988–1997	4369	8730	Population; birth certificates	Road density (miles) and traffic density (vehicle miles travelled per square mile) within 152 m of address at time of birth	Leukaemia	Quartile 1 Road density ≥ 90th percentile Traffic density ≥ 90th percentile		1.0 (ref) 0.79 (0.63–1.00) 0.92 (0.73–1.15)	Matched by age and sex. Adjustment for race and ethnicity. Little effect of further adjustment for mother's age, birth weight, neighbourhood income, or county-level benzene emissions	Incidence. Cases: 0–4 yr.
Yu et al. (2006) Kaohsiung, Taiwan, China, 1997–2003	131	314	Population register	Exposure opportunity score based on distance to petrochemical plant(s), prevailing wind direction, and multiple petrochemical pollution sources. Based on all addresses held for >1 yr	Leukaemia	Log-linear analyses (i.e. relative risk per 1-unit increase in the log-transformed exposure opportunity score)		All leukaemias 1.04 (0.79–1.38)	Matched by age and sex. Adjustment for mother's educational status	Incidence. Cases: 0–19 yr.

Table 2.11 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Weng et al. (2008a) Taiwan, China, 1995–2005	308	308	Selected from among all who had died due to non-neoplastic, non-respiratory diseases	Mean NO_2 concentrations measured in 1995–2005 in 64 municipalities with monitoring stations. Residence at time of death was used	Leukaemia	≤ 20.9 ppb ≥ 26.3 ppb	88 117	1.00 (ref) 2.29 (1.44–3.64)	Matched by sex, year of birth, and year of death. Adjustment for urbanization level of municipality	Mortality. Cases: 0–14 yr. Location (street or background) of the monitoring stations is not described. Tertiles of NO_2 concentration used in analyses. P_{trend} < 0.001. Overlaps with Weng et al. (2008b)
Weng et al. (2008b) Taiwan, China, 1995–2005	405	405	Selected from among all who had died due to non-neoplastic, non-respiratory diseases	Number of workers in, respectively, petrochemical industry and non-petrochemical manufacturing divided by the total population of the municipality. Residence at time of death was used	Leukaemia	Petrochemical air pollution index ≤ 25th percentile > 75th percentile Non-petrochemical air pollution index ≤ 25th percentile > 75th percentile	 96 116 88 109	 1.00 (ref) 1.75 (1.00–3.06) 1.00 (ref) 1.26 (0.70–2.26)	Matched by sex, year of birth, and year of death. Adjustment for urbanization level of municipality. Results for petrochemical air pollution were adjusted for non-petrochemical air pollution and vice versa	Mortality. Cases: 0–19 yr. Study included 226 more-rural municipalities out of 361 municipalities of Taiwan, China. Overlaps with Weng et al. (2008a)

Table 2.11 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Weng et al. (2009) Taiwan, China, 1996–2006	729	729	Selected from among all who had died due to non-neoplastic, non-respiratory diseases	Petrol-station density of municipality (i.e. number of petrol stations divided by the area of the municipality). Residence at time of death was used	Leukaemia	Lowest tertile Highest tertile	179 312	1.00 (ref) 1.91 (1.29–2.82)	Matched by sex, year of birth, and year of death. Adjustment for urbanization level of municipality	Mortality. Cases: 0–14 yr.
Badaloni et al. (2013) Italy, 1998–2001	620	957	Population	(i) Distance to main roads and length of main roads within 100 m; (ii) $PM_{2.5}$ from national dispersion model (4 km × 4 km resolution); (iii) NO_2, PM_{10}, and O_3 from LUR models (100 m × 100 m resolution). Birth address used for primary analyses	Leukaemia	Distance from main road > 150 m 50–149 m < 50 m Main road distance < 100 m No main roads 1st tertile 2nd tertile 3rd tertile	 209 190 221 296 122 94 108	 1.00 1.05 (0.80–1.36) 0.80 (0.62–1.02) 1.00 1.07 (0.80–1.41) 0.69 (0.51–0.92) 0.91 (0.68–1.21)	Age, sex, region, and parental education level	Incidence. Cases: 0–10 yr.

Table 2.11 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Badaloni et al. (2013) Italy, 1998–2001 (cont.)						NO_2				
						1st quartile	158	1.00		
						2nd quartile	160	1.09 (0.81–1.46)		
						3rd quartile	161	1.03 (0.76–1.39)		
						4th quartile	141	0.85 (0.61–1.18)		
						$PM_{2.5}$				
						1st quartile	155	1.00		
						2nd quartile	171	1.18 (0.88–1.59)		
						3rd quartile	136	0.75 (0.54–1.04)		
						4th quartile	158	1.00 (0.72–1.39)		

CI, confidence interval; CNS, central nervous system; h, hour or hours; LUR, land-use regression; NO_2, nitrogen dioxide; O_3, ozone; PM_{10}, particulate matter with particles of aerodynamic diameter < 10 μm; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 μm; ref, reference; SES, socioeconomic status; yr, year.

Table 2.12 Case–control studies of childhood acute leukaemia and outdoor air pollution

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Steffen et al. (2004) Nancy, Lille, Lyon, and Paris, France, 1995–1999	280	285	Hospital; among children with acute pathologies	Interview with mothers about heavy-traffic road within 50 m of the residence, neighbouring automotive repair garage or petrol station, etc. All addresses until diagnosis were used	Acute leukaemia	Motorway < 50 m No Yes Neighbouring business No Yes, repair garage or petrol station	 14 249 17	 1.0 (ref) 1.3 (0.6–2.9) 1.0 (ref) 4.0 (1.5–10.3)	Matched by age, sex, ethnic origin, hospital centre, and urban or rural setting	Incidence. Cases: 0–14 yr.
Yu et al. (2006) Kaohsiung, Taiwan, China, 1997–2003	131	314	Population register	Exposure opportunity score based on distance to petrochemical plant(s), prevailing wind direction, and multiple petrochemical pollution sources. Based on all addresses held for > 1 yr	Acute lymphocytic leukaemia	Log-linear analyses (i.e. relative risk per 1-unit increase in the log-transformed exposure opportunity score)		1.21 (0.89–1.65)	Matched by age and sex. Adjustment for mother's educational status	Incidence. Cases: 0–19 yr.

Table 2.12 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Von Behren et al. (2008) Northern and central California, USA, 1995–2002	310	396	Population; birth certificate files	Vehicle miles travelled within 152 m of the address at birth, the address at diagnosis, and a time-weighted average over all addresses during childhood. Based on all addresses during childhood	Acute lymphocytic leukaemia	*Address at birth* No road traffic ≥ 75th percentile *Address at diagnosis* No road traffic ≥ 75th percentile *All addresses* No road traffic ≥ 75th percentile	 93 56 129 70 63 52	 1.0 (ref) 1.1 (0.7–1.8) 1.0 (ref) 1.2 (0.8–1.8) 1.0 (ref) 1.2 (0.7–2.1)	Matched by age, sex, Hispanic ethnicity, mother's race, and county of birth. Adjustment for household income	Incidence. Cases: 0–14 yr.
Brosselin et al. (2009) France, 2003–2004	765	1681	Population; French national telephone directory	Interview with mothers about proximity of the home to automotive repair garages, petrol stations, other businesses, etc. All addresses until diagnosis were used	Acute leukaemia	Address next to automotive repair garage or petrol station Never Ever	 689 76	 1.0 (ref) 1.6 (1.2–2.2)	Adjustment for age, sex, number of children in the household, degree of urban development, and type of housing	Incidence. Cases: 0–14 yr. Overlaps with Amigou et al. (2011)

Table 2.12 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Amigou et al. (2011) France, 2003–2004	762	1681	Population; national telephone lists (landlines)	Traffic indicators: indices based on function classes of roads within 500 m of the residence. NO_2: national smoothed maps of NO_2 in 4 km^2 grids, modelled from road, transportation, and emission data. Inverse-distance-weighted average of concentrations at grid-square centres within 3 km of each address. Address at diagnosis was used	Acute leukaemia	Index for proximity to main roads			Matched by age and sex. Adjustment for SES	Incidence. Cases: 0–14 yr. Results persisted after exclusion of children with Down syndrome, those having lived closed to a gas station, and with poor precision in geocoding of the address. Overlaps with Brosselin et al. (2009)
						Unexposed	282	1.0 (ref)		
						High	22	2.0 (1.0–3.6)		
						Index for length of heavy-traffic roads within 500 m				
						Unexposed	547	1.0 (ref)		
						High	19	2.2 (1.1–4.2)		
						Traffic-related NO_2				
						< 12.2 µg/m	337	1.0 (ref)		
						≥ 16.2 µg/m^3	204	1.2 (1.0–1.5)		

Table 2.12 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Bailey et al. (2011) Australia, 2003–2007	389	876	Population; random-digit dialling	Information about frequency of refuelling a vehicle the year before and during pregnancy	Acute lymphocytic leukaemia	Refuelling of vehicle by mother in the year before or during pregnancy			Adjustment for age, sex, state, and education level	Incidence. Cases: 0–14 yr. No associations appeared in subanalyses by frequency of refuelling and type of fuel (petrol, diesel, liquefied petroleum gas).
						Never		1.00 (ref)		
						Ever		0.82 (0.57–1.20)		
						Refuelling of vehicle by father in the year before pregnancy				
						Never		1.00 (ref)		
						Ever		1.56 (0.65–3.77)		
Vinceti et al. (2012) Emilia-Romagna region, northern Italy, 1998–2009	83	332	Population; registry	CALINE4 dispersion model estimating exposure to benzene and PM_{10} from road traffic. Based on address at diagnosis	Acute leukaemia	Average benzene level ($\mu g/m^3$)			Matched by sex, year of birth, and province of residence	Incidence. Cases: 0–14 yr. Linear trends were not statistically significant. Stronger (and statistically significant) associations for children < 5 yr
						< 0.10	16	1.0 (ref)		
						0.10–0.25	18	1.1 (0.5–2.3)		
						0.25–0.50	17	1.2 (0.5–2.7)		
						> 0.50	32	1.8 (0.9–3.7)		
						Average PM_{10} level ($\mu g/m^3$)				
						< 2.5	18	1.0 (ref)		
						2.5–5.0	16	1.1 (0.5–2.3)		
						5.0–7.5	21	1.6 (0.8–3.4)		
						> 7.5	28	1.8 (0.8–3.9)		

Table 2.12 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Ghosh et al. (2013) Los Angeles County, California, USA, 1988–2008	4015	80 658	Population; birth records	Modelled NO, NO_2, and NO_x at address at birth. Monthly variation was estimated from data from the nearest monitoring station to create "seasonalized" exposure measures for the pregnancy period and for each trimester	Acute lymphoblastic leukaemia (n = 1346)	Linear analyses per 25 ppb increment during pregnancy (seasonalized exposure measure)			Adjustment for sex, year of birth, mother's age, race/ethnicity, education level, parity, prenatal care, insurance type, and socioeconomic score of the census block	Incidence. Cases: 0–5 yr. Among analyses of 15 other types of childhood cancer, only bilateral retinoblastoma showed a statistical significant result, and only so for exposure during the third trimester. No association was found with acute lymphoblastic leukaemia (ALL) when using the unseasonalized exposure measure.
						NO		1.09 (1.01–1.18)		
						NO_2		1.23 (0.98–1.53)		
						NO_x		1.08 (1.01–1.16)		
					Acute myeloid leukaemia (n = 217)					
						NO		0.84 (0.65–1.09)		
						NO_2		0.71 (0.39–1.30)		
						NO_x		0.88 (0.73–1.07)		

Table 2.12 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Heck et al. (2013) California, USA, 1998–2007	3590	80 224	Population; randomly selected from California birth rolls	Exposure estimated during pregnancy and during first year of life. CO estimated with dispersion model using traffic < 1.5 km as input. $PM_{2.5}$ during pregnancy estimated from central monitors within 8 km. Traffic density within 500 m of the residence was estimated. Birth address used in exposure assessment	Acute lymphoblastic leukaemia	CO	1280	1.05 (1.01–1.10)	Year of birth, parental race/ethnicity, mother's education level, mother's county of birth, method of payment for prenatal care, and neighbourhood SES index	Incidence, 0–5 yr, statewide study. High correlations between air pollution during all trimesters; only results for 1st trimester presented. Results were provided for 16 types of childhood cancer. Only types showing significant results in the fully adjusted model are shown in this table
						$PM_{2.5}$	397	1.10 (0.92–1.30)		
						Traffic density	1243	1.03 (1.00–1.07)		
					Acute myeloid leukaemia	CO	229	0.85 (0.73–0.98)		
						$PM_{2.5}$	82	0.85 (0.57–1.27)		
						Traffic density	224	0.89 (0.79–1.00)		

CI, confidence interval; CO, carbon monoxide; NO, nitrogen oxide; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; PM_{10}, particulate matter with particles of aerodynamic diameter < 10 μm; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 μm; ref, reference; SES, socioeconomic status; yr, year.

Table 2.13 Case–control studies of childhood lymphoma and outdoor air pollution

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Savitz & Feingold (1989) Denver, Colorado, USA, 1976–1983	328	262	Population; random-digit dialling	Traffic counts at home address at time of diagnosis	Lymphoma	≥ 500 vehicles/day	2	0.7 (0.2–3.0)	Matched by age, sex, and area	Incidence. 0–14 yr. Adjustment in a subset for sex, age, year of diagnosis, type of residence, location at birth, mother's age, father's education level, per capita income, and wire configuration had little effect on the risk estimates
Raaschou-Nielsen et al. (2001) Denmark, 1968–1991	1989	5506	Randomly selected from whole population	Traffic density and modelled NO_2 and benzene at home addresses from time of conception to time of diagnosis	Leukaemia, CNS tumours, and lymphoma	NO_2 (in 1000 ppb-days) during childhood*			Matched by sex, age, and calendar time. Adjustment for urban development, geographical region, type of residence, electromagnetic fields, mother's age, and birth order	Incidence. Cases: 0–14 yr. Cumulative air pollution exposure over addresses during childhood. Similar results for exposure of mother during pregnancy. *Cut-off points for exposure categories were set at the 50th, 90th, and 99th percentiles
						< 11.5	75	1.0 (ref)		
						11.5–29.4	134	1.7 (1.0–3.0)		
						29.4–57.8	30	1.8 (0.7–4.3)		
						≥ 57.8	8	4.7 (1.2–17.6)		
						Number of vehicles/day during childhood (time-weighted average)				
						< 500	152	1.0 (ref)		
						≥ 10 000	3	1.3 (0.4–4.8)		

Table 2.13 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Ghosh et al. (2013) Los Angeles County, California, USA, 1988–2008	4015	80 658	Population; birth records	Modelled NO, NO_2, and NO_x at address at birth. Monthly variation was estimated from data from the nearest monitoring station to create "seasonalized" exposure measures for the pregnancy period and for each trimester	Non-Hodgkin lymphoma (n = 109)	Linear analyses per 25 ppb increment during pregnancy (seasonalized exposure measure) NO_x		0.98 (0.75–1.27)	Adjustment for sex, year of birth, mother's age, race/ethnicity, education level, parity, prenatal care, insurance type, and socioeconomic score of the census block	Incidence. Cases: 0–5 yr.

CI, confidence interval; CNS, central nervous system; NO, nitrogen oxide; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; ref, reference.

Table 2.14 Case–control studies of childhood central nervous system tumours and outdoor air pollution

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Savitz & Feingold (1989) Denver, Colorado, USA, 1976–1983	328	262	Population; random-digit dialling	Traffic counts at home address at time of diagnosis	CNS tumours	≥ 500 vehicles/day	9	1.7 (0.8–3.9)	Matched by age, sex, and area	Incidence. 0–14 yr.
Feychting et al. (1998) Sweden	142	550	Population; randomly selected from among children living within 300 m of high-voltage power lines	Modelled peak concentrations of NO_2 (99th percentile of 1-h means). Based on latest address within the power line corridor	CNS tumours	40–49 µg/m³ ≥ 50 µg/m³	6 11	1.0 (0.1–12.7) 5.1 (0.4–61.2)	Matched by calendar time, geographical area, and residence near same power line	Incidence. Cases: 0–15 yr; identified among children living within 300 m of high-voltage power lines. Similar effects for boys and girls

Table 2.14 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Raaschou-Nielsen et al. (2001) Denmark, 1968–1991	1989	5506	Randomly selected from whole population	Traffic density and modelled NO_2 and benzene at home addresses from time of conception to time of diagnosis	CNS tumours	NO_2 (in 1000 ppb-days) during childhood*			Matched by sex, age, and calendar time. Adjustment for urban development, geographical region, type of residence, electromagnetic fields, mother's age, and birth order	Incidence. Cases: 0–14 yr. Cumulative air pollution exposure over addresses during childhood.
						< 11.5	295	1.0 (ref)		
						11.5–29.4	308	1.1 (0.8–1.5)		
						29.4–57.8	57	0.8 (0.5–1.5)		
						≥ 57.8	6	1.0 (0.3–3.1)		
						Number of vehicles/ day during childhood (time-weighted average)				
						< 500	424	1.0 (ref)		
						≥ 10 000	10	0.9 (0.4–1.8)		
						Road density				
						≥ 90th percentile		1.03 (0.75–1.43)		
						Traffic density				
						≥ 90th percentile		1.22 (0.87–1.70)		

Table 2.14 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Liu et al. (2008b) Taiwan, China, 1995–2005	340	340	Selected from among all who had died due to non-neoplastic, non-respiratory diseases	Number of workers in, respectively, petrochemical industry and non-petrochemical manufacturing divided by the total population of the municipality. Residence at time of death	Brain	Petrochemical air pollution index Lowest tertile Highest tertile Non-petrochemical air pollution index Lowest tertile Highest tertile	 93 127 94 129	 1.00 (ref) 1.65 (1.00–2.73) 1.00 (ref) 1.41 (0.84–2.38)	Matched by sex, year of birth, and year of death. Adjustment for urbanization level of municipality. Results for petrochemical air pollution were adjusted for non-petrochemical air pollution and vice versa	Mortality. Cases: 0–29 yr. About half of cases were < 15 yr. Municipalities divided into tertiles
Ghosh et al. (2013) Los Angeles County, California, USA, 1988–2008	4015	80 658	Population; birth records	Modelled NO, NO_2, and NO_x at address at birth. Monthly variation was estimated from data from the nearest monitoring station to create "seasonalized" exposure measures for the pregnancy period and for each trimester	CNS tumours (n = 709)	Linear analyses per 25 ppb increment during pregnancy (seasonalized exposure measure) NO_x		0.96 (0.87–1.07)	Adjustment for sex, year of birth, mother's age, race/ethnicity, education level, parity, prenatal care, insurance type, and socioeconomic score of the census block	Incidence. Cases: 0–5 yr.

CI, confidence interval; CNS, central nervous system; h, hour or hours; IQR, interquartile range; NO, nitrogen oxide; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; PAHs, polycyclic aromatic hydrocarbons; ref, reference; yr, year.

Table 2.15 Case–control studies of other childhood cancers and outdoor air pollution

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Heck et al. (2013) California, USA, 1998–2007	3590	80 224	Population; randomly selected from California birth rolls	Exposure estimated during pregnancy and during first year of life. CO estimated with dispersion model using traffic < 1.5 km as input. $PM_{2.5}$ during pregnancy was estimated from central monitors within 8 km. Traffic density within 500 m of the residence was estimated. Birth address used in exposure assessment	Bilateral retinoblastoma	CO	87	1.16 (1.02–1.33)	Year of birth, parental race/ethnicity, mother's education level, mother's county of birth, method of payment for prenatal care, and neighbourhood SES index	Incidence, 0–5 yr, statewide study.
						$PM_{2.5}$	22	1.46 (0.70–3.06)		
						Traffic density	81	1.09 (0.97–1.24)		
					Germ cell tumours of the teratoma type	CO	72	1.26 (1.12–1.41)		
						$PM_{2.5}$	23	0.77 (0.36–1.68)		
						Traffic density	71	1.16 (1.04–1.30)		

CI, confidence interval; CO, carbon monoxide; IQR, interquartile range; NO_2, nitrogen dioxide; PAHs, polycyclic aromatic hydrocarbons; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 μm; SES, socioeconomic status; yr, year.

Table 2.16 Cohort studies of outdoor air pollution and risk estimates for cancers of the bladder, breast, colon, stomach, brain, and pancreas

Reference, study, location and period	Exposure	Relative risk (95% CI)					
		Bladder	Breast	Colon	Stomach	Brain	Pancreas
North America							
Harvard Six Cities Study							
McKean-Cowdin et al. (2009) USA	$PM_{2.5}$					0.91 (0.74–1.11)	
	PM_{10}					0.92 (0.82–1.03)	
	SO_2					0.82 (0.67–0.99)	
	NO_2					0.88 (0.81–0.96)	
	CO					0.81 (0.68–0.95)	
	O_3					1.02 (0.75–1.41)	
AHSMOG							
Beeson et al. (1998) USA	TSP > 200 µg/m³		1.51 (0.92–2.47)				
Mills et al. (1991) USA	TSP > 200 µg/m³		1.51 (0.92–2.47)				
Paradis et al. (1989) Canada	Bus drivers (SMR)	0.54 (0.15–1.38)					
Europe							
Raaschou-Nielsen et al. (2011b) Denmark	NO_x	1.32 (0.80–2.19)	1.16 (0.89–1.51)	0.93 (0.60–1.46)	0.65 (0.21–2.02)	2.28 (1.25–4.19)	0.64 (0.24–1.71)
	Major street within 50 m	0.94 (0.60–1.48)	0.98 (0.78–1.22)	0.89 (0.41–1.95)	0.92 (0.42–1.98)	1.89 (1.07–3.36)	0.79 (0.38–1.63)
	Per 10^4 vehicle-km/day traffic load within 200 m of the residence	1.09 (0.87–1.35)	0.98 (0.88–1.10)	0.99 (0.66–1.47)	1.00 (0.70–1.48)	1.27 (0.93–1.75)	0.73 (0.49–1.09)
Visser et al. (2004) Netherlands; SIR	TIS ≥ 10 000	1.05 (0.87–1.20)	1.00 (0.91–1.09)				
	10 000 ≤ TIS < 20 000	1.16 (0.93–1.43)	0.98 (0.86–1.12)				
	TIS ≥ 20 000	0.87 (0.66–1.12)	1.01 (0.89–1.15)				

Table 2.16 (continued)

Reference, study, location and period	Exposure	Relative risk (95% CI)					
		Bladder	Breast	Colon	Stomach	Brain	Pancreas
Ranzi et al. (2011) Italy	Heavy metal concentrations from incinerators, quartiles; lowest quartile used as a reference						
	Incidence in men						
	Smoking not adjusted for						
	Second quartile (0.5–1 ng/m³)	0.83 (0.53–1.29)			1.18 (0.69–2.00)		
	Third quartile (1–2 ng/m³)	0.76 (0.48–1.18)			1.47 (0.89–2.42)		
	Highest quartile (> 2 ng/m³)	0.78 (0.43–1.42)			1.24 (0.64–2.40)		
	Incidence in women						
	Second quartile (0.5–1 ng/m³)	1.49 (0.55–4.01)	0.89 (0.68–1.17)		1.02 (0.57–1.81)		
	Third quartile (1–2 ng/m³)	0.85 (0.27–2.68)	0.78 (0.59–1.03)		1.54 (0.91–2.63)		
	Highest quartile (> 2 ng/m³)	2.30 (0.73–7.24)	0.76 (0.51–1.13)		1.09 (0.49–2.44)		
Balarajan & McDowall (1988) United Kingdom	Professional drivers (SMR)	1.05			1.30 ($P < 0.05$)		
Forastiere et al. (1994) Italy	Urban police officers, male [SMR (no adjustment)]	1.27 (0.67–2.1)	14.36 (1.73–51)	1.47 (0.84–2.30)	1.09 (0.70–1.60)	0.52 (0.13–1.20)	0.87 (0.35–1.70)
Soll-Johanning et al. (1998) Denmark	Bus drivers and tramway employees, male	1.4 (1.2–1.6)			1.0 (0.8–1.3)		
	Retrospective cohort						
	Bus drivers and tramway employees, female	1.3 (0.2–4.7)	1.1 (0.8–1.6)				
	SIR (no adjustment)						
Guo et al. (2004) Finland	Exposure to diesel exhausts, highest quartile vs none; men	0.97 (0.77–1.21)					
	Exposure to gasoline exhausts, highest quartile vs none; men	0.93 (0.71–1.23)					
Soll-Johanning & Bach (2004) Denmark	Mail carriers, male (SIR)	0.98 (0.82–1.16)					
	Mail carriers, female (SIR)		0.84 (0.48–1.37)				
Petersen et al. (2010) Denmark	Bus drivers (SIR)	1.6 (1.2–2.0)					

Table 2.16 (continued)

Reference, study, location and period	Exposure	Relative risk (95% CI)					
		Bladder	Breast	Colon	Stomach	Brain	Pancreas
Rafnsson & Gunnarsdóttir (1991) Iceland	Truck drivers (SMR)	1.02 (0.21–2.97)		1.25 (0.50–2.58)	0.92 (0.55–1.43)	1.40 (0.29–4.10)	1.50 (0.65–2.96)
Gubéran et al. (1992) Switzerland	*Men only* Professional drivers; mortality (SMR)	1.43 (0.80–2.36)		0.92 (0.50–1.56)	1.79 (1.17–2.63)		0.91 (0.43–1.71)
	Professional drivers; incidence (SIR)	1.25 (0.74–1.99)		1.11 (0.67–1.74)	2.33 (1.56–3.36)		
Lagorio et al. (1994) Italy	Service station attendants (SMR)	1.20 (0.52–2.36)	1.04 (0.18–3.28)	1.02 (0.44–2.01)	0.60 (0.26–1.18)		0.76 (0.21–1.95)
Pukkala & Pönkä (2001) Finland	Households built close to a former industrial and household waste dump (SIR)		1.12 (0.60–1.91)			1.55 (0.42–3.97)	1.52 (0.61–3.13)

CI, confidence interval; CO, carbon monoxide; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; O_3, ozone; PM_{10}, particulate matter with particles of aerodynamic diameter < 10 μm; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 μm; SIR, standardized incidence ratio; SMR, standardized mortality ratio; SO_2, sulfur dioxide; TIS, traffic intensity score; TSP, total suspended particles.

2.6 All cancers combined and cancers of other sites

Few studies have reported the association between exposure to air pollution and all cancers combined or cancers at sites other than the lung, bladder, breast, or haematopoietic system, or childhood cancers. The sparse data limit a formal evaluation. Furthermore, the interpretation of all cancer sites combined is difficult because different cancer sites have different etiologies and different potential confounders.

2.6.1 All cancers combined

The group of studies that investigated all cancer sites combined have different designs, including ecological studies (Nasca et al., 1980; Robertson, 1980; Howe, 2005; Visser et al., 2005; García-Pérez et al., 2013) and cohort studies (Forastiere et al., 1994; Soll-Johanning et al., 1998; Pukkala & Pönkä, 2001; Soll-Johanning & Bach, 2004; Ranzi et al., 2011). These studies focused on different sources, such as "general urban mixture of air pollutants," as well as specific point sources, such as waste disposal facilities, industries, and airports. [The Working Group noted that combining all cancer sites in studies that assessed air pollution renders them uninterpretable due to the different etiologies and the lack of control for the appropriate potential confounders.]

2.6.2 Cancers of other sites

(a) Case–control studies

Liu et al. (2008b) investigated the relationship between petrochemical air pollution and brain cancer death in Taiwan, China, using a matched case–control study (see Table 2.14). Cases were 340 deaths from brain cancer (ICD-9 code: 191) aged 29 years or younger registered between 1995 and 2005. About half of the cases were younger than 15 years. A total of 340 controls were selected from among all people who had died due to non-neoplastic, non-respiratory diseases in the same period and were pair-matched to cases by sex, year of birth, and year of death. A surrogate measure of exposure to petrochemical air pollution was defined as the proportion of workers working in the petrochemical manufacturing industry per municipality. Subjects were assigned to tertiles of the petrochemical air pollution index according to their residential municipality. Conditional logistic regression models were used with adjustment for age, sex, urbanization level of residence, and non-petrochemical air pollution exposure level. The odds ratio for living in a municipality with high petrochemical air pollution index compared with low index was 1.65 (95% CI, 1.00–2.73). A dose–response relationship was observed, with increasing exposure to petrochemical air pollutants in a residential municipality associated with a greater odds ratio (P-value from test for trend < 0.01). [Limitations of the study are the use of mortality, an indirect measure of air pollution, and the lack of adjustment for other potential confounding factors, such as exposure to ionizing radiation.]

Chiu et al. (2011) conducted a matched case–control study to examine the association between petrol-station density and death from gastric cancer in Taiwan, China. Cases included 358 deaths from gastric cancer (ICD-9 code: 151), aged 50–69 years, registered from 2004 to 2008. Control subjects were 358 non-cancer or gastrointestinal disorder-related deaths, pair-matched by sex, year of birth, and year of death. Petrol-station density was calculated by summing the total number of petrol stations in each municipality, divided by the total area (km^2). Participants were assigned to tertiles of exposure according to levels of petrol-station density within their residential municipality. Conditional logistic regression models were applied with adjustment for marital status and urbanization level. The adjusted odds ratio for living in a municipality

with high petrol-station density compared with low petrol-station density was 1.26 (95% CI, 1.04–1.53). A dose–response relationship was observed, with increasing petrol-station density in a residential municipality related to a greater odds ratio (*P*-value from test for trend < 0.001). [Limitations of the study are the use of mortality, an indirect measure of air pollution, and the lack of adjustment for other potential confounding factors, such as smoking and diet.]

Parent et al. (2013) conducted a case–control study based on incident cases (803 cases) in Montreal, Canada, to estimate associations between exposure to modelled ground-level NO_2 concentration, a marker for traffic-related air pollution, and incidence of prostate cancer. For each increase of 5 ppb in NO_2, the odds ratio was 1.27 (95% CI, 1.03–1.58), adjusted for age, first-degree family history of prostate cancer, ancestry, attained level of education, and three ecological covariates from the 1996 Canadian census: percentage of adults who did not complete high school, median household income, and percentage of recent immigrants. [The study modelled ground-level NO_2 concentration as an estimator of traffic-related pollution.]

(b) Cohort studies

See Table 2.16.

Selected other cancer sites reported in cohort studies that assessed exposure to air pollution or occupations involving exposure to outdoor air pollution are summarized in Table 2.16. Mixed results were reported in several studies for colon cancer (Rafnsson & Gunnarsdóttir, 1991; Gubéran et al., 1992; Forastiere et al., 1994; Lagorio et al., 1994; Raaschou-Nielsen et al., 2011b). Of the cohort studies that assessed stomach cancer (Rafnsson & Gunnarsdóttir, 1991; Gubéran et al., 1992; Forastiere et al., 1994; Lagorio et al., 1994; Soll-Johanning et al., 1998; Raaschou-Nielsen et al., 2011b; Ranzi et al., 2011) and brain cancer (Rafnsson & Gunnarsdóttir, 1991; Gubéran et al., 1992; Forastiere et al., 1994; Pukkala & Pönkä, 2001; McKean-Cowdin et al., 2009; Raaschou-Nielsen et al., 2011b), many reported risk estimates greater than 1. All except two cohort studies reported a decreased risk of pancreatic cancer, although none of the associations reported were statistically significant (Raaschou-Nielsen et al., 2011b; Forastiere et al., 1994; Rafnsson & Gunnarsdóttir, 1991; Gubéran et al., 1992; Lagorio et al., 1994; Pukkala & Pönkä, 2001). A large cohort study (Raaschou-Nielsen et al. 2011b) in Denmark reported increased risks of cervical cancer associated with proximity to a major road at both 50 m (IRR, 4.36; 95% CI, 2.12–8.95) and 200 m (IRR, 1.70; 95% CI, 1.12–2.58) and exposure to NO_x (IRR, 2.45; 95% CI, 1.01–5.93, per 100 μg/m^3 increase in NO_x, adjusted for smoking, education level, and oral contraceptive use). [This study did not adjust for human papillomavirus (HPV) status, an important risk factor for cervical cancer. Chance findings are possible given the number of cancer sites considered.]

References

Abbey DE, Mills PK, Petersen FF, Beeson WL (1991a). Long-term ambient concentrations of total suspended particulates and oxidants as related to incidence of chronic disease in California Seventh-Day Adventists. *Environ Health Perspect*, 94:43–50. doi:10.2307/3431291 PMID:1954938

Abbey DE, Moore J, Petersen F, Beeson L (1991b). Estimating cumulative ambient concentrations of air pollutants: description and precision of methods used for an epidemiological study. *Arch Environ Health*, 46(5):281–7. doi:10.1080/00039896.1991.9934388 PMID:1953035

Abbey DE, Nishino N, McDonnell WF, Burchette RJ, Knutsen SF, Lawrence Beeson W et al. (1999). Long-term inhalable particles and other air pollutants related to mortality in nonsmokers. *Am J Respir Crit Care Med*, 159(2):373–82. doi:10.1164/ajrccm.159.2.9806020 PMID:9927346

Alexander FE, Leon DA, Cartwright RA (1996). Isolation, car ownership, and small area variation in incidence of acute lymphoblastic leukaemia in

children. *Paediatr Perinat Epidemiol*, 10(4):411–7. doi:10.1111/j.1365-3016.1996.tb00066.x PMID:8931055

Amaral A, Rodrigues V, Oliveira J, Pinto C, Carneiro V, Sanbento R et al. (2006). Chronic exposure to volcanic environments and cancer incidence in the Azores, Portugal. *Sci Total Environ*, 367(1):123–8. doi:10.1016/j.scitotenv.2006.01.024 PMID:16540151

Amigou A, Sermage-Faure C, Orsi L, Leverger G, Baruchel A, Bertrand Y et al. (2011). Road traffic and childhood leukemia: the ESCALE study (SFCE). *Environ Health Perspect*, 119(4):566–72. doi:10.1289/ehp.1002429 PMID:21147599

Badaloni C, Ranucci A, Cesaroni G, Zanini G, Vienneau D, Al-Aidrous F et al.; SETIL Study Group (2013). Air pollution and childhood leukaemia: a nationwide case-control study in Italy. *Occup Environ Med*, 70(12):876–83. doi:10.1136/oemed-2013-101604 PMID:24142970

Bailey HD, de Klerk NH, Fritschi L, Attia J, Daubenton JD, Armstrong BK et al.; Aus-ALL Consortium (2011). Refuelling of vehicles, the use of wood burners and the risk of acute lymphoblastic leukaemia in childhood. *Paediatr Perinat Epidemiol*, 25(6):528–39. doi:10.1111/j.1365-3016.2011.01224.x PMID:21980942

Balarajan R, McDowall ME (1988). Professional drivers in London: a mortality study. *Br J Ind Med*, 45(7):483–6. PMID:3395584

Band PR, Le ND, MacArthur AC, Fang R, Gallagher RP (2005). Identification of occupational cancer risks in British Columbia: a population-based case-control study of 1129 cases of bladder cancer. *J Occup Environ Med*, 47(8):854–8. PMID:16093936

Barbone F, Bovenzi M, Cavallieri F, Stanta G (1995). Air pollution and lung cancer in Trieste, Italy. *Am J Epidemiol*, 141(12):1161–9. PMID:7771454

Beelen R, Hoek G, van den Brandt PA, Goldbohm RA, Fischer P, Schouten LJ et al. (2008a). Long-term exposure to traffic-related air pollution and lung cancer risk. *Epidemiology*, 19(5):702–10. doi:10.1097/EDE.0b013e318181b3ca PMID:18633326

Beelen R, Hoek G, van den Brandt PA, Goldbohm RA, Fischer P, Schouten LJ et al. (2008b). Long-term effects of traffic-related air pollution on mortality in a Dutch cohort (NLCS-AIR study). *Environ Health Perspect*, 116(2):196–202. doi:10.1289/ehp.10767 PMID:18288318

Beeson WL, Abbey DE, Knutsen SF; Adventist Health Study on Smog (1998). Long-term concentrations of ambient air pollutants and incident lung cancer in California adults: results from the AHSMOG study. *Environ Health Perspect*, 106(12):813–22. doi:10.2307/3434125 PMID:9831542

Bellander T, Berglind N, Gustavsson P, Jonson T, Nyberg F, Pershagen G et al. (2001). Using geographic information systems to assess individual historical exposure to air pollution from traffic and house heating in Stockholm. *Environ Health Perspect*, 109(6):633–9. doi:10.1289/ehp.01109633 PMID:11445519

Belli S, Benedetti M, Comba P, Lagravinese D, Martucci V, Martuzzi M et al. (2004). Case-control study on cancer risk associated to residence in the neighbourhood of a petrochemical plant. *Eur J Epidemiol*, 19(1):49–54. doi:10.1023/B:EJEP.0000013395.38701.c2 PMID:15012022

Bessö A, Nyberg F, Pershagen G (2003). Air pollution and lung cancer mortality in the vicinity of a nonferrous metal smelter in Sweden. *Int J Cancer*, 107(3):448–52. doi:10.1002/ijc.11412 PMID:14506746

Biggeri A, Barbone F, Lagazio C, Bovenzi M, Stanta G (1996). Air pollution and lung cancer in Trieste, Italy: spatial analysis of risk as a function of distance from sources. *Environ Health Perspect*, 104(7):750–4. doi:10.1289/ehp.96104750 PMID:8841761

Blot WJ, Fraumeni JF Jr (1978). Geographic patterns of bladder cancer in the United States. *J Natl Cancer Inst*, 61(4):1017–23. PMID:279707

Bonassi S, Merlo F, Pearce N, Puntoni R (1989). Bladder cancer and occupational exposure to polycyclic aromatic hydrocarbons. *Int J Cancer*, 44(4):648–51. doi:10.1002/ijc.2910440415 PMID:2793238

Bonner MR, Han D, Nie J, Rogerson P, Vena JE, Muti P et al. (2005). Breast cancer risk and exposure in early life to polycyclic aromatic hydrocarbons using total suspended particulates as a proxy measure. *Cancer Epidemiol Biomarkers Prev*, 14(1):53–60. PMID:15668476

Borgia P, Forastiere F, Rapiti E, Rizzelli R, Magliola ME, Perucci CA et al. (1994). Mortality among taxi drivers in Rome: a cohort study. *Am J Ind Med*, 25(4):507–17. doi:10.1002/ajim.4700250405 PMID:7516624

Brosselin P, Rudant J, Orsi L, Leverger G, Baruchel A, Bertrand Y et al. (2009). Acute childhood leukaemia and residence next to petrol stations and automotive repair garages: the ESCALE study (SFCE). *Occup Environ Med*, 66(9):598–606. doi:10.1136/oem.2008.042432 PMID:19213757

Brown LM, Pottern LM, Blot WJ (1984). Lung cancer in relation to environmental pollutants emitted from industrial sources. *Environ Res*, 34(2):250–61. doi:10.1016/0013-9351(84)90093-8 PMID:6745227

Brownson RC, Chang JC, Davis JR (1987). Occupation, smoking, and alcohol in the epidemiology of bladder cancer. *Am J Public Health*, 77(10):1298–300. doi:10.2105/AJPH.77.10.1298 PMID:3631363

Brunekreef B, Beelen R, Hoek G, Schouten L, Bausch-Goldbohm S, Fischer P et al. (2009). Effects of long-term exposure to traffic-related air pollution on respiratory and cardiovascular mortality in the Netherlands: the NLCS-AIR study. *Res Rep Health Eff Inst*, 139(139):5–71, discussion 73–89. PMID:19554969

Brüske-Hohlfeld I, Möhner M, Ahrens W, Pohlabeln H, Heinrich J, Kreuzer M et al. (1999). Lung cancer risk in

male workers occupationally exposed to diesel motor emissions in Germany. *Am J Ind Med*, 36(4):405–14. doi:10.1002/(SICI)1097-0274(199910)36:4<405::AID-AJIM1>3.0.CO;2-W PMID:10470005

Burns PB, Swanson GM (1991). Risk of urinary bladder cancer among Blacks and Whites: the role of cigarette use and occupation. *Cancer Causes Control*, 2(6):371–9. doi:10.1007/BF00054297 PMID:1764561

Cambra K, Martínez-Rueda T, Alonso-Fustel E, Cirarda FB, Ibáñez B, Esnaola S et al. (2011). Mortality in small geographical areas and proximity to air polluting industries in the Basque Country (Spain). *Occup Environ Med*, 68(2):140–7. doi:10.1136/oem.2009.048215 PMID:20852305

Cao J, Yang C, Li J, Chen R, Chen B, Gu D et al. (2011). Association between long-term exposure to outdoor air pollution and mortality in China: a cohort study. *J Hazard Mater*, 186(2-3):1594–600. doi:10.1016/j.jhazmat.2010.12.036 PMID:21194838

Carey IM, Atkinson RW, Kent AJ, van Staa T, Cook DG, Anderson HR (2013). Mortality associations with long-term exposure to outdoor air pollution in a national English cohort. *Am J Respir Crit Care Med*, 187(11):1226–33. doi:10.1164/rccm.201210-1758OC PMID:23590261

Carstensen JM, Pershagen G, Eklund G (1988). Smoking-adjusted incidence of lung cancer among Swedish men in different occupations. *Int J Epidemiol*, 17(4):753–8. doi:10.1093/ije/17.4.753 PMID:3265699

Cassidy A, Wang W, Wu X, Lin J (2009). Risk of urinary bladder cancer: a case-control analysis of industry and occupation. *BMC Cancer*, 9(1):443. doi:10.1186/1471-2407-9-443 PMID:20003537

Castaño-Vinyals G, Cantor KP, Malats N, Tardon A, Garcia-Closas R, Serra C et al. (2008). Air pollution and risk of urinary bladder cancer in a case-control study in Spain. *Occup Environ Med*, 65(1):56–60. doi:10.1136/oem.2007.034348 PMID:17634245

Cesaroni G, Badaloni C, Gariazzo C, Stafoggia M, Sozzi R, Davoli M et al. (2013). Long-term exposure to urban air pollution and mortality in a cohort of more than a million adults in Rome. *Environ Health Perspect*, 121(3):324–31. doi:10.1289/ehp.1205862 PMID:23308401

Chang CC, Tsai SS, Chiu HF, Wu TN, Yang CY (2009). Traffic air pollution and lung cancer in females in Taiwan: petrol station density as an indicator of disease development. *J Toxicol Environ Health A*, 72(10):651–7. doi:10.1080/15287390902733515 PMID:19308850

Chiu HF, Cheng MH, Tsai SS, Wu TN, Kuo HW, Yang CY (2006). Outdoor air pollution and female lung cancer in Taiwan. *Inhal Toxicol*, 18(13):1025–31. doi:10.1080/08958370600904561 PMID:16966302

Chiu HF, Tsai SS, Chen PS, Liao YH, Liou SH, Wu TN et al. (2011). Traffic air pollution and risk of death from gastric cancer in Taiwan: petrol station density as an indicator of air pollutant exposure. *J Toxicol Environ Health A*, 74(18):1215–24. doi:10.1080/15287394.2011.590100 PMID:21797773

Claude JC, Frentzel-Beyme RR, Kunze E (1988). Occupation and risk of cancer of the lower urinary tract among men. A case-control study. *Int J Cancer*, 41(3):371–9. doi:10.1002/ijc.2910410309 PMID:3346100

Coggon D, Pannett B, Osmond C, Acheson ED (1986). A survey of cancer and occupation in young and middle aged men. II. Non-respiratory cancers. *Br J Ind Med*, 43(6):381–6. PMID:3718882

Colli J, Lee BR, Thomas R (2012). Population densities in relation to bladder cancer mortality rates in America from 1950 to 1994. *Int Urol Nephrol*, 44(2):443–9. doi:10.1007/s11255-011-0018-7 PMID:21701802

Colt JS, Baris D, Stewart P, Schned AR, Heaney JA, Mott LA et al. (2004). Occupation and bladder cancer risk in a population-based case-control study in New Hampshire. *Cancer Causes Control*, 15(8):759–69. doi:10.1023/B:CACO.0000043426.28741.a2 PMID:15456989

Colt JS, Blair A (1998). Parental occupational exposures and risk of childhood cancer. *Environ Health Perspect*, 106:Suppl 3: 909–25. doi:10.1289/ehp.98106909 PMID:9646055

Colt JS, Karagas MR, Schwenn M, Baris D, Johnson A, Stewart P et al. (2011). Occupation and bladder cancer in a population-based case-control study in Northern New England. *Occup Environ Med*, 68(4):239–49. doi:10.1136/oem.2009.052571 PMID:20864470

Consonni D, De Matteis S, Lubin JH, Wacholder S, Tucker M, Pesatori AC et al. (2010). Lung cancer and occupation in a population-based case-control study. *Am J Epidemiol*, 171(3):323–33. doi:10.1093/aje/kwp391 PMID:20047975

Cordier S, Clavel J, Limasset JC, Boccon-Gibod L, Le Moual N, Mandereau L et al. (1993). Occupational risks of bladder cancer in France: a multicentre case-control study. *Int J Epidemiol*, 22(3):403–11. doi:10.1093/ije/22.3.403 PMID:8359955

Crosignani P, Tittarelli A, Borgini A, Codazzi T, Rovelli A, Porro E et al. (2004). Childhood leukemia and road traffic: a population-based case-control study. *Int J Cancer*, 108(4):596–9. doi:10.1002/ijc.11597 PMID:14696126

Crouse DL, Goldberg MS, Ross NA (2009). A prediction-based approach to modelling temporal and spatial variability of traffic-related air pollution in Montreal, Canada. *Atmos Environ*, 43(32):5075–84. doi:10.1016/j.atmosenv.2009.06.040

Crouse DL, Goldberg MS, Ross NA, Chen H, Labrèche F (2010). Postmenopausal breast cancer is associated with exposure to traffic-related air pollution in Montreal, Canada: a case-control study. *Environ Health Perspect*, 118(11):1578–83. doi:10.1289/ehp.1002221 PMID:20923746

De Roos AJ, Davis S, Colt JS, Blair A, Airola M, Severson RK et al. (2010). Residential proximity to industrial facilities and risk of non-Hodgkin lymphoma. *Environ Res*, 110(1):70–8. doi:10.1016/j.envres.2009.09.011 PMID:19840879

Decouflé P, Stanislawczyk K, Houten L (1977). A retrospective survey of cancer in relation to occupation. NIOSH Publication No. 77-178. Cincinnati (OH): Department of Health, Education, and Welfare.

Dockery DW, Pope CA 3rd, Xu X, Spengler JD, Ware JH, Fay ME et al. (1993). An association between air pollution and mortality in six U.S. cities. *N Engl J Med*, 329(24):1753–9. doi:10.1056/NEJM199312093292401 PMID:8179653

Dolin PJ, Cook-Mozaffari P (1992). Occupation and bladder cancer: a death-certificate study. *Br J Cancer*, 66(3):568–78. doi:10.1038/bjc.1992.316 PMID:1520596

Dryson E, 't Mannetje A, Walls C, McLean D, McKenzie F, Maule M et al. (2008). Case-control study of high risk occupations for bladder cancer in New Zealand. *Int J Cancer*, 122(6):1340–6. doi:10.1002/ijc.23194 PMID:18027852

Edwards R, Pless-Mulloli T, Howel D, Chadwick T, Bhopal R, Harrison R et al. (2006). Does living near heavy industry cause lung cancer in women? A case-control study using life grid interviews. *Thorax*, 61(12):1076–82. doi:10.1136/thx.2005.057620 PMID:17040935

Feychting M, Svensson D, Ahlbom A (1998). Exposure to motor vehicle exhaust and childhood cancer. *Scand J Work Environ Health*, 24(1):8–11. doi:10.5271/sjweh.272 PMID:9562395

Filleul L, Rondeau V, Vandentorren S, Le Moual N, Cantagrel A, Annesi-Maesano I et al. (2005). Twenty five year mortality and air pollution: results from the French PAARC survey. *Occup Environ Med*, 62(7):453–60. doi:10.1136/oem.2004.014746 PMID:15961621

Forastiere F, Perucci CA, Di Pietro A, Miceli M, Rapiti E, Bargagli A et al. (1994). Mortality among urban policemen in Rome. *Am J Ind Med*, 26(6):785–98. doi:10.1002/ajim.4700260607 PMID:7892829

Gaertner RR, Trpeski L, Johnson KC; Canadian Cancer Registries Epidemiology Research Group (2004). A case-control study of occupational risk factors for bladder cancer in Canada. *Cancer Causes Control*, 15(10):1007–19. doi:10.1007/s10552-004-1448-7 PMID:15801485

García-Pérez J, Fernández-Navarro P, Castelló A, López-Cima MF, Ramis R, Boldo E et al. (2013). Cancer mortality in towns in the vicinity of incinerators and installations for the recovery or disposal of hazardous waste. *Environ Int*, 51:31–44. doi:10.1016/j.envint.2012.10.003 PMID:23160082

Ghosh JK, Heck JE, Cockburn M, Su J, Jerrett M, Ritz B (2013). Prenatal exposure to traffic-related air pollution and risk of early childhood cancers. *Am J Epidemiol*, 178(8):1233–9. doi:10.1093/aje/kwt129 PMID:23989198

Gilman EA, Knox EG (1998). Geographical distribution of birth places of children with cancer in the UK. *Br J Cancer*, 77(5):842–9. doi:10.1038/bjc.1998.137 PMID:9514068

Gubéran E, Usel M, Raymond L, Bolay J, Fioretta G, Puissant J (1992). Increased risk for lung cancer and for cancer of the gastrointestinal tract among Geneva professional drivers. *Br J Ind Med*, 49(5):337–44. PMID:1376139

Guo J, Kauppinen T, Kyyrönen P, Heikkilä P, Lindbohm ML, Pukkala E (2004). Risk of esophageal, ovarian, testicular, kidney and bladder cancers and leukemia among Finnish workers exposed to diesel or gasoline engine exhaust. *Int J Cancer*, 111(2):286–92. doi:10.1002/ijc.20263 PMID:15197784

Gupta D, Boffetta P, Gaborieau V, Jindal SK (2001). Risk factors of lung cancer in Chandigarh, India. *Indian J Med Res*, 113:142–50. PMID:11558323

Hales S, Blakely T, Woodward A (2012). Air pollution and mortality in New Zealand: cohort study. *J Epidemiol Community Health*, 66(5):468–73. doi:10.1136/jech.2010.112490 PMID:20966448

Hansen J, Raaschou-Nielsen O, Olsen JH (1998). Increased risk of lung cancer among different types of professional drivers in Denmark. *Occup Environ Med*, 55(2):115–8. doi:10.1136/oem.55.2.115 PMID:9614396

Harrison RM, Leung PL, Somervaille L, Smith R, Gilman E (1999). Analysis of incidence of childhood cancer in the West Midlands of the United Kingdom in relation to proximity to main roads and petrol stations. *Occup Environ Med*, 56(11):774–80. doi:10.1136/oem.56.11.774 PMID:10658564

Hart JE, Garshick E, Dockery DW, Smith TJ, Ryan L, Laden F (2011). Long-term ambient multipollutant exposures and mortality. *Am J Respir Crit Care Med*, 183(1):73–8. doi:10.1164/rccm.200912-1903OC PMID:20656944

Hart JE, Yanosky JD, Puett RC, Ryan L, Dockery DW, Smith TJ et al. (2009). Spatial modeling of PM_{10} and NO_2 in the continental United States, 1985–2000. *Environ Health Perspect*, 117(11):1690–6. PMID:20049118

HEI (2000). Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of particulate air pollution and mortality: a special report of the Institute's Particle Epidemiology Reanalysis Project. Boston (MA): Health Effects Institute. Available from: http://pubs.healtheffects.org/getfile.php?u=273.

Heck JE, Wu J, Lombardi C, Qiu J, Meyers TJ, Wilhelm M et al. (2013). Childhood cancer and traffic-related air pollution exposure in pregnancy and early life. *Environ Health Perspect*, 121(11):(12):1385–91. doi:10.1289/ehp.1306761 PMID:24021746

Heinrich J, Thiering E, Rzehak P, Krämer U, Hochadel M, Rauchfuss KM et al. (2013). Long-term exposure to NO_2 and PM_{10} and all-cause and cause-specific mortality in a prospective cohort of women. *Occup*

Environ Med, 70(3):179–86. doi:10.1136/oemed-2012-100876 PMID:23220504

Hoar SK, Hoover R (1985). Truck driving and bladder cancer mortality in rural New England. *J Natl Cancer Inst*, 74(4):771–4. PMID:3857373

Howe HL (2005). Urban-rural gradients in cancer incidence and mortality in the United States. Springfield (IL): North American Association of Central Cancer Registries.

Hrubec Z, Blair AE, Vaught E, Rogot J (1992). Mortality risks by occupation among U.S. veterans of known smoking status 1954-1980. NIH Publication No. 92-3407. Bethesda (MD): National Cancer Institute.

Hystad P, Demers PA, Johnson KC, Brook J, van Donkelaar A, Lamsal L et al. (2012). Spatiotemporal air pollution exposure assessment for a Canadian population-based lung cancer case-control study. *Environ Health*, 11(1):22. doi:10.1186/1476-069X-11-22 PMID:22475580

Hystad P, Demers PA, Johnson KC, Carpiano RM, Brauer M (2013). Long-term residential exposure to air pollution and lung cancer risk. *Epidemiology*, 24(5):762–72. doi:10.1097/EDE.0b013e3182949ae7 PMID:23676262

IARC (2013). Diesel and gasoline engine exhausts and some nitroarenes. IARC Monogr Eval Carcinog Risks Hum, 105:1–704. Available from: http://monographs.iarc.fr/ENG/Monographs/vol105/index.php.

Iyer V, Harris RE, Wynder EL (1990). Diesel exhaust exposure and bladder cancer risk. *Eur J Epidemiol*, 6(1):49–54. doi:10.1007/BF00155549 PMID:1693120

Jakobsson R, Gustavsson P, Lundberg I (1997). Increased risk of lung cancer among male professional drivers in urban but not rural areas of Sweden. *Occup Environ Med*, 54(3):189–93. doi:10.1136/oem.54.3.189 PMID:9155780

Jedrychowski W, Becher H, Wahrendorf J, Basa-Cierpialek Z (1990). A case-control study of lung cancer with special reference to the effect of air pollution in Poland. *J Epidemiol Community Health*, 44(2):114–20. doi:10.1136/jech.44.2.114 PMID:2370498

Jensen OM, Wahrendorf J, Knudsen JB, Sørensen BL (1987). The Copenhagen case-referent study on bladder cancer. Risks among drivers, painters and certain other occupations. *Scand J Work Environ Health*, 13(2):129–34. doi:10.5271/sjweh.2070 PMID:3602967

Jerrett M, Burnett RT, Beckerman BS, Turner MC, Krewski D, Thurston G et al. (2013). Spatial analysis of air pollution and mortality in California. *Am J Respir Crit Care Med*, 188(5):593–9. doi:10.1164/rccm.201303-0609OC PMID:23805824

Jerrett M, Burnett RT, Ma R, Pope CA 3rd, Krewski D, Newbold KB et al. (2005). Spatial analysis of air pollution and mortality in Los Angeles. *Epidemiology*, 16(6):727–36. doi:10.1097/01.ede.0000181630.15826.7d PMID:16222161

Jöckel KH, Ahrens W, Wichmann HE, Becher H, Bolm-Audorff U, Jahn I et al. (1992). Occupational and environmental hazards associated with lung cancer. *Int J Epidemiol*, 21(2):202–13. doi:10.1093/ije/21.2.202 PMID:1428471

Johnson KC, Pan S, Fry R, Mao Y; Canadian Cancer Registries Epidemiology Research Group (2003). Residential proximity to industrial plants and non-Hodgkin lymphoma. *Epidemiology*, 14(6):687–93. PMID:14569184

Kashima S, Yorifuji T, Tsuda T, Doi H (2009). Application of land use regression to regulatory air quality data in Japan. *Sci Total Environ*, 407(8):3055–62. doi:10.1016/j.scitotenv.2008.12.038 PMID:19185904

Katanoda K, Sobue T, Satoh H, Tajima K, Suzuki T, Nakatsuka H et al. (2011). An association between long-term exposure to ambient air pollution and mortality from lung cancer and respiratory diseases in Japan. *J Epidemiol*, 21(2):132–43. doi:10.2188/jea.JE20100098 PMID:21325732

Katsouyanni K, Trichopoulos D, Kalandidi A, Tomos P, Riboli E (1991). A case-control study of air pollution and tobacco smoking in lung cancer among women in Athens. *Prev Med*, 20(2):271–8. doi:10.1016/0091-7435(91)90026-Z PMID:2057473

Kellen E, Zeegers M, Paulussen A, Vlietinck R, Vlem EV, Veulemans H et al. (2007). Does occupational exposure to PAHs, diesel and aromatic amines interact with smoking and metabolic genetic polymorphisms to increase the risk on bladder cancer? The Belgian case control study on bladder cancer risk. *Cancer Lett*, 245(1-2):51–60. doi:10.1016/j.canlet.2005.12.025 PMID:16504378

Kingham S, Fisher G, Hales S, Wilson I, Bartie P (2008). An empirical model for estimating census unit population exposure in areas lacking air quality monitoring. *J Expo Sci Environ Epidemiol*, 18(2):200–10. doi:10.1038/sj.jes.7500584 PMID:17668011

Knox EG (1994). Leukaemia clusters in childhood: geographical analysis in Britain. *J Epidemiol Community Health*, 48(4):369–76. doi:10.1136/jech.48.4.369 PMID:7964336

Knox EG (2005a). Childhood cancers and atmospheric carcinogens. *J Epidemiol Community Health*, 59(2):101–5. doi:10.1136/jech.2004.021675 PMID:15650139

Knox EG (2005b). Oil combustion and childhood cancers. *J Epidemiol Community Health*, 59(9):755–60. doi:10.1136/jech.2004.031674 PMID:16100313

Knox EG (2006). Roads, railways, and childhood cancers. *J Epidemiol Community Health*, 60(2):136–41. doi:10.1136/jech.2005.042036 PMID:16415262

Knox EG, Gilman EA (1997). Hazard proximities of childhood cancers in Great Britain from 1953–80. *J Epidemiol Community Health*, 51(2):151–9. doi:10.1136/jech.51.2.151 PMID:9196644

Ko YC, Lee CH, Chen MJ, Huang CC, Chang WY, Lin HJ et al. (1997). Risk factors for primary lung cancer

among non-smoking women in Taiwan. *Int J Epidemiol*, 26(1):24–31. doi:10.1093/ije/26.1.24 PMID:9126500

Kogevinas M, 't Mannetje A, Cordier S, Ranft U, González CA, Vineis P et al. (2003). Occupation and bladder cancer among men in Western Europe. *Cancer Causes Control*, 14(10):907–14. doi:10.1023/B:CACO.0000007962.19066.9c PMID:14750529

Krewski D, Burnett R, Jerrett M, Pope CA, Rainham D, Calle E et al. (2005). Mortality and long-term exposure to ambient air pollution: ongoing analyses based on the American Cancer Society cohort. *J Toxicol Environ Health A*, 68(13-14):1093–109. doi:10.1080/15287390590935941 PMID:16024490

Krewski D, Jerrett M, Burnett RT, Ma R, Hughes E, Shi Y et al. (2009). Extended follow-up and spatial analysis of the American Cancer Society study linking particulate air pollution and mortality. *Res Rep Health Eff Inst*, 140(140):5–114, discussion 115–36. PMID:19627030

Kunze E, Chang-Claude J, Frentzel-Beyme R (1992). Life style and occupational risk factors for bladder cancer in Germany. A case-control study. *Cancer*, 69(7):1776–90. doi:10.1002/1097-0142(19920401)69:7<1776::AID-CNCR2820690721>3.0.CO;2-P PMID:1551063

Laden F, Schwartz J, Speizer FE, Dockery DW (2006). Reduction in fine particulate air pollution and mortality: extended follow-up of the Harvard Six Cities study. *Am J Respir Crit Care Med*, 173(6):667–72. doi:10.1164/rccm.200503-443OC PMID:16424447

Lagorio S, Forastiere F, Iavarone I, Rapiti E, Vanacore N, Perucci CA et al. (1994). Mortality of filling station attendants. *Scand J Work Environ Health*, 20(5):331–8. doi:10.5271/sjweh.1389 PMID:7863296

Langholz B, Ebi KL, Thomas DC, Peters JM, London SJ (2002). Traffic density and the risk of childhood leukemia in a Los Angeles case-control study. *Ann Epidemiol*, 12(7):482–7. doi:10.1016/S1047-2797(01)00317-9 PMID:12377426

Lepeule J, Laden F, Dockery D, Schwartz J (2012). Chronic exposure to fine particles and mortality: an extended follow-up of the Harvard Six Cities study from 1974 to 2009. *Environ Health Perspect*, 120(7):965–70. doi:10.1289/ehp.1104660 PMID:22456598

Lewis-Michl EL, Melius JM, Kallenbach LR, Ju CL, Talbot TO, Orr MF et al. (1996). Breast cancer risk and residence near industry or traffic in Nassau and Suffolk counties, Long Island, New York. *Arch Environ Health*, 51(4):255–65. doi:10.1080/00039896.1996.9936024 PMID:8757405

Linos A, Blair A, Gibson RW, Everett G, Van Lier S, Cantor KP et al. (1991). Leukemia and non-Hodgkin's lymphoma and residential proximity to industrial plants. *Arch Environ Health*, 46(2):70–4. doi:10.1080/00039896.1991.9937431 PMID:2006896

Lipsett MJ, Ostro BD, Reynolds P, Goldberg D, Hertz A, Jerrett M et al. (2011). Long-term exposure to air pollution and cardiorespiratory disease in the California Teachers Study cohort. *Am J Respir Crit Care Med*, 184(7):828–35. doi:10.1164/rccm.201012-2082OC PMID:21700913

Liu CC, Chen CC, Wu TN, Yang CY (2008b). Association of brain cancer with residential exposure to petrochemical air pollution in Taiwan. *J Toxicol Environ Health A*, 71(5):310–4. doi:10.1080/15287390701738491 PMID:18214804

Liu CC, Tsai SS, Chiu HF, Wu TN, Chen CC, Yang CY (2009). Ambient exposure to criteria air pollutants and risk of death from bladder cancer in Taiwan. *Inhal Toxicol*, 21(1):48–54. doi:10.1080/08958370802207326 PMID:18923949

Liu CC, Tsai SS, Chiu HF, Wu TN, Yang CY (2008a). Ambient exposure to criteria air pollutants and female lung cancer in Taiwan. *Inhal Toxicol*, 20(3):311–7. doi:10.1080/08958370701866107 PMID:18300049

London SJ, Thomas DC, Bowman JD, Sobel E, Cheng TC, Peters JM (1991). Exposure to residential electric and magnetic fields and risk of childhood leukemia. *Am J Epidemiol*, 134(9):923–37. PMID:1843457

López-Cima MF, García-Pérez J, Pérez-Gómez B, Aragonés N, López-Abente G, Tardón A et al. (2011). Lung cancer risk and pollution in an industrial region of Northern Spain: a hospital-based case-control study. *Int J Health Geogr*, 10(1):10. doi:10.1186/1476-072X-10-10 PMID:21266041

Lyons RA, Monaghan SP, Heaven M, Littlepage BN, Vincent TJ, Draper GJ (1995). Incidence of leukaemia and lymphoma in young people in the vicinity of the petrochemical plant at Baglan Bay, South Wales, 1974 to 1991. *Occup Environ Med*, 52(4):225–8. doi:10.1136/oem.52.4.225 PMID:7795736

McDonnell WF, Nishino-Ishikawa N, Petersen FF, Chen LH, Abbey DE (2000). Relationships of mortality with the fine and coarse fractions of long-term ambient PM_{10} concentrations in nonsmokers. *J Expo Anal Environ Epidemiol*, 10(5):427–36. doi:10.1038/sj.jea.7500095 PMID:11051533

McKean-Cowdin R, Calle EE, Peters JM, Henley J, Hannan L, Thurston GD et al. (2009). Ambient air pollution and brain cancer mortality. *Cancer Causes Control*, 20(9):1645–51. doi:10.1007/s10552-009-9412-1 PMID:19685148

Menvielle G, Luce D, Févotte J, Bugel I, Salomon C, Goldberg P et al. (2003). Occupational exposures and lung cancer in New Caledonia. *Occup Environ Med*, 60(8):584–9. doi:10.1136/oem.60.8.584 PMID:12883019

Merlo DF, Stagi E, Fontana V, Consonni D, Gozza C, Garrone E et al. (2010). A historical mortality study among bus drivers and bus maintenance workers exposed to urban air pollutants in the city of Genoa, Italy. *Occup Environ Med*, 67(9):611–9. doi:10.1136/oem.2009.050377 PMID:20576925

Mills PK, Abbey D, Beeson WL, Petersen F (1991). Ambient air pollution and cancer in California Seventh-Day

Adventists. *Arch Environ Health*, 46(5):271–80. doi:10.1080/00039896.1991.9934387 PMID:1953034

Naess Ø, Nafstad P, Aamodt G, Claussen B, Rosland P (2007). Relation between concentration of air pollution and cause-specific mortality: four-year exposures to nitrogen dioxide and particulate matter pollutants in 470 neighborhoods in Oslo, Norway. *Am J Epidemiol*, 165(4):435–43. doi:10.1093/aje/kwk016 PMID:17135427

Nafstad P, Håheim LL, Oftedal B, Gram F, Holme I, Hjermann I et al. (2003). Lung cancer and air pollution: a 27 year follow up of 16 209 Norwegian men. *Thorax*, 58(12):1071–6. doi:10.1136/thorax.58.12.1071 PMID:14645978

Nasca PC, Burnett WS, Greenwald P, Brennan K, Wolfgang P, Carlton K (1980). Population density as an indicator of urban-rural differences in cancer incidence, upstate New York, 1968–1972. *Am J Epidemiol*, 112(3):362–75. PMID:7424884

Nordlinder R, Järvholm B (1997). Environmental exposure to gasoline and leukemia in children and young adults – an ecology study. *Int Arch Occup Environ Health*, 70(1):57–60. doi:10.1007/s004200050186 PMID:9258708

Nyberg F, Gustavsson P, Järup L, Bellander T, Berglind N, Jakobsson R et al. (2000). Urban air pollution and lung cancer in Stockholm. *Epidemiology*, 11(5):487–95. doi:10.1097/00001648-200009000-00002 PMID:10955399

Paradis G, Theriault G, Tremblay C (1989). Mortality in a historical cohort of bus drivers. *Int J Epidemiol*, 18(2):397–402. doi:10.1093/ije/18.2.397 PMID:2475446

Parent ME, Goldberg MS, Crouse DL, Ross NA, Chen H, Valois MF et al. (2013). Traffic-related air pollution and prostate cancer risk: a case-control study in Montreal, Canada. *Occup Environ Med*, 70(7):511–8. doi:10.1136/oemed-2012-101211 PMID:23531743

Pershagen G (1985). Lung cancer mortality among men living near an arsenic-emitting smelter. *Am J Epidemiol*, 122(4):684–94. PMID:4025308

Pesch B, Haerting J, Ranft U, Klimpel A, Oelschlägel B, Schill W; MURC Study Group (2000). Occupational risk factors for urothelial carcinoma: agent-specific results from a case-control study in Germany. *Int J Epidemiol*, 29(2):238–47. doi:10.1093/ije/29.2.238 PMID:10817119

Petersen A, Hansen J, Olsen JH, Netterstrøm B (2010). Cancer morbidity among Danish male urban bus drivers: a historical cohort study. *Am J Ind Med*, 53(7):757–61. PMID:20583138

Petrauskaite R, Pershagen G, Gurevicius R (2002). Lung cancer near an industrial site in Lithuania with major emissions of airway irritants. *Int J Cancer*, 99(1):106–11. doi:10.1002/ijc.10314 PMID:11948500

Pisani P, Srivatanakul P, Randerson-Moor J, Vipasrinimit S, Lalitwongsa S, Unpunyo P et al. (2006). *GSTM1* and *CYP1A1* polymorphisms, tobacco, air pollution, and lung cancer: a study in rural Thailand. *Cancer Epidemiol Biomarkers Prev*, 15(4):667–74. doi:10.1158/1055-9965.EPI-05-0667 PMID:16614107

Pope CA 3rd, Burnett RT, Thun MJ, Calle EE, Krewski D, Ito K et al. (2002). Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *JAMA*, 287(9):1132–41. doi:10.1001/jama.287.9.1132 PMID:11879110

Pope CA 3rd, Thun MJ, Namboodiri MM, Dockery DW, Evans JS, Speizer FE et al. (1995). Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. *Am J Respir Crit Care Med*, 151(3 Pt 1):669–74. doi:10.1164/ajrccm/151.3_Pt_1.669 PMID:7881654

Porru S, Aulenti V, Donato F, Boffetta P, Fazioli R, Cosciani Cunico S et al. (1996). Bladder cancer and occupation: a case-control study in northern Italy. *Occup Environ Med*, 53(1):6–10. doi:10.1136/oem.53.1.6 PMID:8563860

Pukkala E, Martinsen JI, Lynge E, Gunnarsdottir HK, Sparén P, Tryggvadottir L et al. (2009). Occupation and cancer – follow-up of 15 million people in five Nordic countries. *Acta Oncol*, 48(5):646–790. doi:10.1080/02841860902913546 PMID:19925375

Pukkala E, Pönkä A (2001). Increased incidence of cancer and asthma in houses built on a former dump area. *Environ Health Perspect*, 109(11):1121–5. doi:10.1289/ehp.011091121 PMID:11712996

Raaschou-Nielsen O, Andersen ZJ, Beelen R, Samoli E, Stafoggia M, Weinmayr G et al. (2013). Air pollution and lung cancer incidence in 17 European cohorts: prospective analyses from the European Study of Cohorts for Air Pollution Effects (ESCAPE). *Lancet Oncol*, 14(9):813–22. doi:10.1016/S1470-2045(13)70279-1 PMID:23849838

Raaschou-Nielsen O, Andersen ZJ, Hvidberg M, Jensen SS, Ketzel M, Sørensen M et al. (2011a). Lung cancer incidence and long-term exposure to air pollution from traffic. *Environ Health Perspect*, 119(6):860–5. doi:10.1289/ehp.1002353 PMID:21227886

Raaschou-Nielsen O, Andersen ZJ, Hvidberg M, Jensen SS, Ketzel M, Sørensen M et al. (2011b). Air pollution from traffic and cancer incidence: a Danish cohort study. *Environ Health*, 10(1):67. doi:10.1186/1476-069X-10-67 PMID:21771295

Raaschou-Nielsen O, Bak H, Sørensen M, Jensen SS, Ketzel M, Hvidberg M et al. (2010). Air pollution from traffic and risk for lung cancer in three Danish cohorts. *Cancer Epidemiol Biomarkers Prev*, 19(5):1284–91. doi:10.1158/1055-9965.EPI-10-0036 PMID:20447920

Raaschou-Nielsen O, Hertel O, Thomsen BL, Olsen JH (2001). Air pollution from traffic at the residence of children with cancer. *Am J Epidemiol*, 153(5):433–43. doi:10.1093/aje/153.5.433 PMID:11226975

Rafnsson V, Gunnarsdóttir H (1991). Mortality among professional drivers. *Scand J Work Environ Health*, 17(5):312–7. doi:10.5271/sjweh.1697 PMID:1947916

Ranzi A, Fano V, Erspamer L, Lauriola P, Perucci CA, Forastiere F (2011). Mortality and morbidity among

people living close to incinerators: a cohort study based on dispersion modeling for exposure assessment. *Environ Health*, 10(1):22. doi:10.1186/1476-069X-10-22 PMID:21435200

Reulen RC, Kellen E, Buntinx F, Zeegers MP (2007). Bladder cancer and occupation: a report from the Belgian case-control study on bladder cancer risk. *Am J Ind Med*, 50(6):449–54. doi:10.1002/ajim.20469 PMID:17450546

Reynolds P, Von Behren J, Gunier RB, Goldberg DE, Hertz A (2004). Residential exposure to traffic in California and childhood cancer. *Epidemiology*, 15(1):6–12. doi:10.1097/01.ede.0000101749.28283.de PMID:14712141

Reynolds P, Von Behren J, Gunier RB, Goldberg DE, Hertz A, Smith D (2002). Traffic patterns and childhood cancer incidence rates in California, United States. *Cancer Causes Control*, 13(7):665–73. doi:10.1023/A:1019579430978 PMID:12296514

Reynolds P, Von Behren J, Gunier RB, Goldberg DE, Hertz A, Smith DF (2003). Childhood cancer incidence rates and hazardous air pollutants in California: an exploratory analysis. *Environ Health Perspect*, 111(4):663–8. doi:10.1289/ehp.5986 PMID:12676632

Risch HA, Burch JD, Miller AB, Hill GB, Steele R, Howe GR (1988). Occupational factors and the incidence of cancer of the bladder in Canada. *Br J Ind Med*, 45(6):361–7. PMID:3395572

Robertson LS (1980). Environmental correlates of intercity variation in age-adjusted cancer mortality rates. *Environ Health Perspect*, 36:197–203. doi:10.1289/ehp.8036197 PMID:6159211

Samanic CM, Kogevinas M, Silverman DT, Tardón A, Serra C, Malats N et al. (2008). Occupation and bladder cancer in a hospital-based case-control study in Spain. *Occup Environ Med*, 65(5):347–53. doi:10.1136/oem.2007.035816 PMID:17951336

Samet JM, Humble CG, Skipper BE, Pathak DR (1987). History of residence and lung cancer risk in New Mexico. *Am J Epidemiol*, 125(5):800–11. PMID:3565355

Sans S, Elliott P, Kleinschmidt I, Shaddick G, Pattenden S, Walls P et al. (1995). Cancer incidence and mortality near the Baglan Bay petrochemical works, South Wales. *Occup Environ Med*, 52(4):217–24. doi:10.1136/oem.52.4.217 PMID:7795735

Savitz DA, Feingold L (1989). Association of childhood cancer with residential traffic density. *Scand J Work Environ Health*, 15(5):360–3. doi:10.5271/sjweh.1848 PMID:2477895

Savitz DA, Wachtel H, Barnes FA, John EM, Tvrdik JG (1988). Case-control study of childhood cancer and exposure to 60-Hz magnetic fields. *Am J Epidemiol*, 128(1):21–38. PMID:3164167

Schifflers E, Jamart J, Renard V (1987). Tobacco and occupation as risk factors in bladder cancer: a case-control study in southern Belgium *Int J Cancer*, 39(3):287–92. doi:10.1002/ijc.2910390304 PMID:6585596

Schoenberg JB, Stemhagen A, Mogielnicki AP, Altman R, Abe T, Mason TJ (1984). Case-control study of bladder cancer in New Jersey. I. Occupational exposures in white males. *J Natl Cancer Inst*, 72(5):973–81. PMID:6585596

Shore DL, Sandler DP, Davey FR, McIntyre OR, Bloomfield CD (1993). Acute leukemia and residential proximity to potential sources of environmental pollutants. *Arch Environ Health*, 48(6):414–20. doi:10.1080/00039896.1993.10545963 PMID:8250593

Siemiatycki J, Dewar R, Nadon L, Gérin M (1994). Occupational risk factors for bladder cancer: results from a case-control study in Montreal, Quebec, Canada. *Am J Epidemiol*, 140(12):1061–80. PMID:7998589

Silverman DT, Levin LI, Hoover RN (1989b). Occupational risks of bladder cancer in the United States: II. Nonwhite men. *J Natl Cancer Inst*, 81(19):1480–3. doi:10.1093/jnci/81.19.1480 PMID:2778835

Silverman DT, Levin LI, Hoover RN, Hartge P (1989a). Occupational risks of bladder cancer in the United States: I. White men. *J Natl Cancer Inst*, 81(19):1472–80. doi:10.1093/jnci/81.19.1472 PMID:2778834

Soll-Johanning H, Bach E (2004). Occupational exposure to air pollution and cancer risk among Danish urban mail carriers. *Int Arch Occup Environ Health*, 77(5):351–6. doi:10.1007/s00420-004-0510-9 PMID:15108001

Soll-Johanning H, Bach E, Jensen SS (2003). Lung and bladder cancer among Danish urban bus drivers and tramway employees: a nested case-control study. *Occup Med (Lond)*, 53(1):25–33. doi:10.1093/occmed/kqg004 PMID:12576562

Soll-Johanning H, Bach E, Olsen JH, Tüchsen F (1998). Cancer incidence in urban bus drivers and tramway employees: a retrospective cohort study. *Occup Environ Med*, 55(9):594–8. doi:10.1136/oem.55.9.594 PMID:9861180

Steenland K, Burnett C, Osorio AM (1987). A case-control study of bladder cancer using city directories as a source of occupational data. *Am J Epidemiol*, 126(2):247–57. doi:10.1093/aje/126.2.247 PMID:3605053

Steffen C, Auclerc MF, Auvrignon A, Baruchel A, Kebaili K, Lambilliotte A et al. (2004). Acute childhood leukaemia and environmental exposure to potential sources of benzene and other hydrocarbons; a case-control study. *Occup Environ Med*, 61(9):773–8. doi:10.1136/oem.2003.010868 PMID:15317919

Talbott EO, Xu X, Youk AO, Rager JR, Stragand JA, Malek AM (2011). Risk of leukemia as a result of community exposure to gasoline vapors: a follow-up study. *Environ Res*, 111(4):597–602. doi:10.1016/j.envres.2011.03.009 PMID:21453914

Thompson JA, Carozza SE, Zhu L (2008). Geographic risk modeling of childhood cancer relative to county-level crops, hazardous air pollutants and population density

characteristics in Texas. *Environ Health*, 7(1):45. doi:10.1186/1476-069X-7-45 PMID:18817548

Tsoi CT, Tse LA (2012). Professional drivers and lung cancer: a systematic review and meta-analysis. *Occup Environ Med*, 69(11):831–6. doi:10.1136/oemed-2012-100666 PMID:22767869

Turner MC, Krewski D, Pope CA 3rd, Chen Y, Gapstur SM, Thun MJ (2011). Long-term ambient fine particulate matter air pollution and lung cancer in a large cohort of never-smokers. *Am J Respir Crit Care Med*, 184(12):1374–81. doi:10.1164/rccm.201106-1011OC PMID:21980033

Vena JE (1982). Air pollution as a risk factor in lung cancer. *Am J Epidemiol*, 116(1):42–56. PMID:7102655

Viel JF, Arveux P, Baverel J, Cahn JY (2000). Soft-tissue sarcoma and non-Hodgkin's lymphoma clusters around a municipal solid waste incinerator with high dioxin emission levels. *Am J Epidemiol*, 152(1):13–9. doi:10.1093/aje/152.1.13 PMID:10901325

Villeneuve PJ, Jerrett M, Su J, Burnett RT, Chen H, Brook J et al. (2013). A cohort study of intra-urban variations in volatile organic compounds and mortality, Toronto, Canada. *Environ Pollut*, 183:30–9. doi:10.1016/j.envpol.2012.12.022 PMID:23369806

Vinceti M, Rothman KJ, Crespi CM, Sterni A, Cherubini A, Guerra L et al. (2012). Leukemia risk in children exposed to benzene and PM_{10} from vehicular traffic: a case-control study in an Italian population. *Eur J Epidemiol*, 27(10):781–90. doi:10.1007/s10654-012-9727-1 PMID:22892901

Vineis P, Hoek G, Krzyzanowski M, Vigna-Taglianti F, Veglia F, Airoldi L et al. (2006). Air pollution and risk of lung cancer in a prospective study in Europe. *Int J Cancer*, 119(1):169–74. doi:10.1002/ijc.21801 PMID:16463382

Vineis P, Magnani C (1985). Occupation and bladder cancer in males: a case-control study. *Int J Cancer*, 35(5):599–606. doi:10.1002/ijc.2910350506 PMID:3997281

Visser O, van Wijnen JH, van Leeuwen FE (2004). Residential traffic density and cancer incidence in Amsterdam, 1989–1997. *Cancer Causes Control*, 15(4):331–9. doi:10.1023/B:CACO.0000027480.32494.a3 PMID:15141134

Visser O, van Wijnen JH, van Leeuwen FE (2005). Incidence of cancer in the area around Amsterdam Airport Schiphol in 1988–2003: a population-based ecological study. *BMC Public Health*, 5(1):127. doi:10.1186/1471-2458-5-127 PMID:16332253

Von Behren J, Reynolds P, Gunier RB, Rull RP, Hertz A, Urayama KY et al. (2008). Residential traffic density and childhood leukemia risk. *Cancer Epidemiol Biomarkers Prev*, 17(9):2298–301. doi:10.1158/1055-9965.EPI-08-0338 PMID:18768496

Weng HH, Tsai SS, Chen CC, Chiu HF, Wu TN, Yang CY (2008a). Childhood leukemia development and correlation with traffic air pollution in Taiwan using nitrogen dioxide as an air pollutant marker. *J Toxicol Environ Health A*, 71(7):434–8. doi:10.1080/15287390701839042 PMID:18306090

Weng HH, Tsai SS, Chiu HF, Wu TN, Yang CY (2008b). Association of childhood leukemia with residential exposure to petrochemical air pollution in Taiwan. *Inhal Toxicol*, 20(1):31–6. doi:10.1080/08958370701758734 PMID:18236219

Weng HH, Tsai SS, Chiu HF, Wu TN, Yang CY (2009). Childhood leukemia and traffic air pollution in Taiwan: petrol station density as an indicator. *J Toxicol Environ Health A*, 72(2):83–7. doi:10.1080/15287390802477338 PMID:19034797

Wertheimer N, Leeper E (1979). Electrical wiring configurations and childhood cancer. *Am J Epidemiol*, 109(3):273–84. PMID:453167

Whitworth KW, Symanski E, Coker AL (2008). Childhood lymphohematopoietic cancer incidence and hazardous air pollutants in southeast Texas, 1995–2004. *Environ Health Perspect*, 116(11):1576–80. doi:10.1289/ehp.11593 PMID:19057714

Wilkinson P, Thakrar B, Walls P, Landon M, Falconer S, Grundy C et al. (1999). Lymphohaematopoietic malignancy around all industrial complexes that include major oil refineries in Great Britain. *Occup Environ Med*, 56(9):577–80. doi:10.1136/oem.56.9.577 PMID:10615289

Wilson RT, Donahue M, Gridley G, Adami J, El Ghormli L, Dosemeci M (2008). Shared occupational risks for transitional cell cancer of the bladder and renal pelvis among men and women in Sweden. *Am J Ind Med*, 51(2):83–99. doi:10.1002/ajim.20522 PMID:18067176

Wynder EL, Dieck GS, Hall NE, Lahti H (1985). A case-control study of diesel exhaust exposure and bladder cancer. *Environ Res*, 37(2):475–89. doi:10.1016/0013-9351(85)90129-X PMID:2410250

Xu ZY, Blot WJ, Li G, Fraumeni JF Jr, Zhao DZ, Stone BJ et al. (1991). Environmental determinants of lung cancer in Shenyang, China. *IARC Sci Publ*, 105:460–5. PMID:1855896

Xu ZY, Blot WJ, Xiao HP, Wu A, Feng YP, Stone BJ et al. (1989). Smoking, air pollution, and the high rates of lung cancer in Shenyang, China. *J Natl Cancer Inst*, 81(23):1800–6. doi:10.1093/jnci/81.23.1800 PMID:2555531

Yang CY, Cheng MF, Chiu JF, Tsai SS (1999). Female lung cancer and petrochemical air pollution in Taiwan. *Arch Environ Health*, 54(3):180–5. doi:10.1080/00039899909602257 PMID:10444039

Yorifuji T, Kashima S, Tsuda T, Ishikawa-Takata K, Ohta T, Tsuruta K et al. (2013). Long-term exposure to traffic-related air pollution and the risk of death from hemorrhagic stroke and lung cancer in Shizuoka, Japan. *Sci Total Environ*, 443:397–402. doi:10.1016/j.scitotenv.2012.10.088 PMID:23208275

Yorifuji T, Kashima S, Tsuda T, Takao S, Suzuki E, Doi H et al. (2010). Long-term exposure to traffic-related air pollution and mortality in Shizuoka, Japan. *Occup Environ Med*, 67(2):111–7. doi:10.1136/oem.2008.045542 PMID:19773277

Yu CL, Wang SF, Pan PC, Wu MT, Ho CK, Smith TJ et al.; Kaohsiung Leukemia Research Group (2006). Residential exposure to petrochemicals and the risk of leukemia: using geographic information system tools to estimate individual-level residential exposure. *Am J Epidemiol*, 164(3):200–7. doi:10.1093/aje/kwj182 PMID:16754633

3. CANCER IN EXPERIMENTAL ANIMALS

3.1 Studies of components of outdoor air pollution in previous *IARC Monographs*

3.1.1 Introduction

Outdoor air pollution is a complex mixture of multiple pollutants originating from a myriad of natural and anthropogenic sources. This includes transportation-related pollution – the overall mixture of various exhaust emissions, which themselves are source-specific complex mixtures of particulate matter (PM), gases, and volatile and semivolatile substances, and very often contain organic and inorganic substances classified as IARC Group 1 or Group 2 carcinogens (Section 1, Table 1.2) – as well as contributions from other sources. The evaluation of the carcinogenic potential of outdoor air pollution should be based on investigations using polluted outdoor air or on studies of emissions that contribute substantially to air pollution.

In experimental animals, only inhalation experiments are able to investigate complex mixtures of airborne gases, volatile substances, and aerosols, and the primary target organ of air pollutants is the respiratory tract. Therefore, studies in experimental animals using inhalation, intratracheal instillation, or lung implantation were the most informative studies to evaluate the carcinogenicity of air pollutants or of fractions thereof collected using special devices. Skin application or subcutaneous injection of PM, condensates, and extracts of PM, all contained in outdoor air and in exhaust emissions, were also used to assess the carcinogenic potential of exhaust emissions and therefore also of outdoor air pollution.

One class of carcinogens that has been widely identified in outdoor air pollution – because it is generated by high-temperature incomplete combustion of organic material like oil, oil-derived products, coal, and wood – comprises non-heterocyclic polycyclic aromatic hydrocarbons (PAHs), nitroarenes, and some related compounds. In outdoor air, these compounds are attached primarily to outdoor PM. Some examples of PAH-containing emissions are those from household combustion of coal or wood and exhaust emissions from diesel and gasoline engines (see Section 1).

The carcinogenic effects in experimental animals of PAHs, of related compounds, and of mixtures containing two or more representatives of these agents have been evaluated previously in the *IARC Monographs*, in Volume 3 (IARC, 1973), Volume 32 (IARC, 1983), Volume 92 (IARC, 2010a), and Volume 100F (IARC, 2012b), as well as in Volume 95 (IARC, 2010b) and Volume 100E (IARC, 2012a) (both of which deal with emissions from combustion of coal or wood) and Volume 105 (IARC, 2013) (which deals with diesel and gasoline engine exhausts and some nitroarenes).

3.1.2 Emissions from household combustion of coal or wood

See Table 3.1, Table 3.2, Table 3.3, Table 3.4, Table 3.6, and Table 3.7.

In two studies in mice and one study in rats, inhalation exposure to emissions from incomplete combustion of coal caused high incidences of malignant lung tumours (IARC, 2012a). In one study in mice, exposure to high emissions from incomplete combustion of wood caused an increased incidence of lung tumours (mainly adenocarcinomas) after 15 months of exposure. A study in rats with a similar design was negative after 19 months of exposure (IARC, 2010b).

The previous *IARC Monographs* Working Groups concluded that there was *sufficient evidence* in experimental animals for the carcinogenicity of emissions from combustion of coal (IARC, 2012a) but only *limited evidence* in experimental animals for the carcinogenicity of emissions from combustion of wood (IARC, 2010b).

In addition, four skin application or subcutaneous injection studies using coal-derived soot extracts in mice (IARC, 2012a) and two subcutaneous injection studies using wood smoke extracts in mice (IARC, 2010b) showed increased incidences of lung cancers or skin tumours.

The *IARC Monographs* Working Groups concluded that there was *sufficient evidence* in experimental animals for the carcinogenicity of coal-derived soot extracts (IARC, 2012a) and *sufficient evidence* in experimental animals for the carcinogenicity of wood smoke extracts (IARC, 2010b).

Since the above-mentioned previous *IARC Monographs* evaluations, only one new skin application study using wood smoke extract in mice [inadequate for the evaluation] (Lewtas, 1993; Cupitt et al., 1994) and no new studies on emissions from combustion of coal were available to the Working Group.

3.1.3 Exhaust emissions from diesel engines and gasoline engines

See Table 3.1, Table 3.2, Table 3.3, Table 3.4, Table 3.5, and Table 3.6.

It has been shown in 11 studies in rats that whole diesel engine exhaust from engines produced before 2000 caused an increased incidence of benign and/or malignant lung tumours after long-term inhalation exposure to sufficiently high concentrations of particles contained in whole diesel engine exhaust. All studies in mice were negative except one, which showed inconsistent results. No increase in the incidence of lung tumours was observed in three studies in hamsters exposed to whole diesel engine exhaust. The gas phase of diesel engine exhaust (i.e. without diesel engine exhaust particles) did not cause an increase in lung tumours in studies in mice, rats, or hamsters. Diesel engine exhaust particles caused malignant lung tumours in rats after intratracheal instillation, and extracts of these particles caused malignant lung tumours in rats after intrapulmonary implantation and caused malignant fibrous histiocytomas in mice after subcutaneous injection (IARC, 2013).

No lung tumours were observed in rats, hamsters, or dogs after inhalation exposure to whole gasoline engine exhaust. However, gasoline engine exhaust condensates induced malignant tumours of the skin in three skin application studies in mice, malignant lung tumours in one intrapulmonary implantation study in rats, and pulmonary adenomas in one intratracheal instillation study in hamsters (IARC, 2013).

The Working Group of Volume 105 of the *IARC Monographs* concluded that there was *sufficient evidence* in experimental animals for the carcinogenicity of whole diesel engine exhaust, of diesel engine exhaust PM, and of extracts of diesel engine exhaust particles. With respect to gasoline engine exhaust, the Working Group concluded that there was *sufficient evidence* in experimental animals for the carcinogenicity of only the condensates of the exhaust (IARC, 2013).

Table 3.1 Studies of carcinogenicity in experimental animals of components of outdoor air pollution by inhalation or whole-body exposure

Species, strain (sex) Duration Reference	Test materials/ Type of samples	Dosing regimen Animals/group at start	Incidence of tumours	Statistical significance	Comments
Coal smoke and soot from household combustion of coal					
Mouse, Buffalo (NR) Up to 19 mo Seeling & Benignus (1936), IARC (2010b, 2012a)	Coal soot as bedding in the cages	Shaking the cage, 2–3 ×/d 50 (controls) 100 (exposed)	Lung adenocarcinoma: 1/50 (control), 8/100	NS	Age at start: 3 mo Unusually high mortality in controls, and lack of reporting on skin tumours
Mouse, NR (M, F) 2 yr Campbell (1939), IARC (2010b, 2012a)	"Moderate" cloud soot in inhalation chamber	1 h/d, 5 d/wk, 12 mo "moderate" dose Number of animals NR	No increase in the incidence of lung tumours, and no skin tumours	NS	Age at start: 3 mo
Mouse, Kunming (M, F) 2 yr Lin et al. (1995), IARC (2010b, 2012a)	Amounts of coal chosen to simulate normal indoor air conditions for humans in Harbin City, China. Exposure assumed to be daily exposure	Control, clean air Smoke, 60 g of coal, daily Smoke, 105 g of coal, daily Smoke, 160 g of coal, daily 30 M + 30 F	Lung cancer: 3.6% (control), 9.4%, 12.8%*, 24.3%*	*$P < 0.05$	Purity NR; age at start NR; weight, 13 ± 1 g
Mouse, Kunming (M, F) 15 mo Liang et al. (1988), IARC (2010b, 2012a)	Bituminous coal was incompletely combusted to simulate indoor air in Xuanwei County, China Total suspended particles: 0.91 mg/m³ (control, clean air), 14.38 mg/m³ (coal smoke) B[*a*]P: 0.15 µg/m³ (control, clean air), 50.5 µg/m³ (coal smoke)	Control, clean air Coal smoke 113 M + 58 F (control) 160 M + 50 F (coal smoke)	Lung cancer: 29/171 (all adenocarcinoma); 188/210* (119/210, adenocarcinoma; 45/210, adenosquamous carcinoma; 24/210, squamous cell carcinoma)	*$P < 0.001$	Age at start NR; weight, 21 g

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Test materials/ Type of samples	Dosing regimen Animals/group at start	Incidence of tumours	Statistical significance	Comments
Rat, Wistar (M, F) 19 mo Liang et al. (1988), IARC (2010b, 2012a)	Room with indoor air pollution and a round, shallow pit in the centre where bituminous coal was incompletely combusted to simulate indoor air in Xuanwei County, China Total suspended particles: 0.91 mg/m³ (control, clean air), 14.38 mg/m³ (coal smoke) B[*a*]P: 0.15 µg/m³ (control, clean air), 50.5 µg/m³ (coal smoke)	Control, clean air Coal smoke 59 M + 51 F (control) 62 M + 63 F (coal smoke)	Lung cancer: 1/110 (adenocarcinoma), 84/125* (all squamous cell carcinoma)	*$P < 0.001$	Age at start NR; weight, 105 g
Wood smoke					
Mouse, Kunming (M, F) Mouse, Beijing (M) 15 mo Liang et al. (1988), IARC (2010b)	Incompletely combusted wood smoke from a fire pit in the centre of a room: PM, 14.99 mg/m³; B[*a*]P: 43.1 µg/10 m³ (control: PM, 0.91 mg/m³; B[*a*]P, 1.47 µg/10 m³) Simulation of indoor air in Xuanwei County, China	12 h/d, 15 mo Kunming: 58 M, 59 F Beijing: 60 M Similar number of controls	Lung tumours: Exposed groups: 81/177 (45.8%) (sex and strain combined) Control groups: 29/171 (17.0%) Highest tumour incidence with F Kunming mice in exposed group (49.3%) and control group (26.9%), followed by M Kunming mice (exposed, 37.9%; controls, 13.2%)	NR [$P < 0.05$]	Age at start NR; weight, 21 g Tumours were mainly adenocarcinomas
Mouse, A/J (M, F) 12 mo Reed et al. (2006), IARC (2010b)	Whole hardwood smoke emissions	6 h/d, 7 d/wk, 6 mo; 6 mo follow-up PM: 0, 30, 100, 300, or 1000 µg/m³ 20 M + 20 F	Lung tumours: 47–59% (both sexes combined)	NS (no differences in lung tumour incidence or multiplicity between exposure groups and control group)	Age at start: 6 wk No exposure-related mortality

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Test materials/ Type of samples	Dosing regimen Animals/group at start	Incidence of tumours	Statistical significance	Comments
Rat, Wistar (M, F) 19 mo Liang et al. (1988), IARC (2010b)	Incompletely combusted wood smoke from a fire pit in the centre of a room: PM, 14.99 mg/m^3; B[*a*]P, 43.1 µg/10 m^3 (control: PM, 0.91 mg/m^3; B[*a*]P, 1.47 µg/10 m^3) Simulation of indoor air in Xuanwei County, China	12 h/d, 19 mo 55 M, 55 F Similar number of controls	1 pulmonary tumour in controls; 0 in wood smoke-exposed rats	NS	Age at start NR; weight, 105 g
Diesel engine exhaust					
Mouse, NMRI (F) Lifetime (up to 120 wk) IARC (2013), Heinrich et al. (1986a, b)	Filtered or unfiltered exhaust from a 1.6 L diesel engine (diluted 1 : 17; particles, 4.24 mg/m^3); control: clean air	19 h/d, 5 d/wk, lifetime 96 animals/group	Lung adenocarcinoma: Unfiltered exhaust: 18/93 (19%)* Filtered exhaust: 13/76 (17%)* Control: 2/84 (2%)	*$P < 0.05$	Age at start: 8–10 wk Incidence of lung tumours in "historical controls" in this laboratory reported to reach 32% in untreated controls and 12.5% in inhalation controls
Mouse, NMRI (F) 23 mo Mouse, C57BL/6N (F) 30 mo IARC (2013), Heinrich et al. (1995)	Exhaust from a 1.6 L diesel engine operated according to US-72 FTP driving cycle or under constant load conditions (diluted 1 : 9; particles, 7.0 mg/m^3); exhaust from a 1.6 L diesel engine (diluted 1 : 15; particles, 4.5 mg/m^3); particle-free exhaust; control: clean air	18 h/d, 5 d/wk, 13.5 mo; then kept untreated for 9.5 mo 18 h/d, 5 d/wk; 24 mo; then kept untreated for 6 mo 80 animals/group	No increase in the number of animals with lung tumours in groups of particle-exposed animals	NS	Age at start: 7 wk
Mouse, CD1 (M, F) 24 mo IARC (2013), Mauderly et al. (1996)	Exhaust from a 1980 model 5.7 L V8 diesel engine; different levels of NO_2 and soot concentrations	6 h/d, 5 d/wk, 24 mo 0.35, 3.5, or 7.0 mg soot/m^3 (0.1 ± 0.1, 0.3 ± 0.2, or 0.7 ± 0.5 ppm NO_2) Number of animals NR	No increase in the incidence of lung tumours in exposed animals	NS	Age at start: 17 wk No effects on survival or bw

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Test materials/ Type of samples	Dosing regimen Animals/group at start	Incidence of tumours	Statistical significance	Comments
Mouse, C57BL/N (newborn) (M, F) Mouse, ICR (M, F) 24 mo IARC (2013), Takemoto et al. (1986)	Exhaust from a 269 cm^3 small diesel engine at idling speed (diluted 1 : 2 or 1 : 4 with clean air; PM, 1–4 mg/m^3; NO_2, 2–4 ppm) Control group: clean air	4 h/d, 4 d/wk, 24 mo Number of exposed and control animals (combined): 225 M, 225 F (C57BL/N); 205 M, 205 F (ICR)	Low incidence of lung adenoma and/or adenocarcinoma in exposed and control animals of both strains	NS	
Rat, Wistar (M) 20 mo IARC (2013), Karagianes et al. (1981)	Soot from exhaust from a 3-cylinder, 43 hp diesel engine driving a 15 kW electric generator (diluted 1 : 35); soot from diesel exhaust plus coal dust	6 h/d, 20 mo Clean air (control) 8.3 ± 2.0 mg/m^3 soot 8.3 ± 2.0 mg/m^3 soot + 5.8 ± 3.5 mg/m^3 coal dust 8.3 ± 2.0 mg/m^3 soot + 6.6 ± 1.9 mg/m^3 coal dust 8.3 ± 2.0 mg/m^3 soot + 14.9 ± 6.2 mg/m^3 coal dust 14.9 ± 6.2 mg/m^3 coal dust only 24 animals/group	One bronchioloalveolar adenoma in diesel-only exposed group and one in diesel + coal dust-exposed group No lung tumours in control group and coal dust-only exposed group	NS	Age at start: 18 wk Increased incidence of non-neoplastic lesions of the respiratory tract, with severity related to duration of exposure
Rat, Wistar (F) Lifetime IARC (2013), Heinrich et al. (1986a)	Filtered or unfiltered exhaust from a 1.6 L diesel engine (diluted 1 : 17; particles, 4.24 mg/m^3) Control group: clean air	19 h/d, 5 d/wk, lifetime 96 animals/group	Bronchioloalveolar adenomas and lung squamous cell tumours (combined): Unfiltered diesel exhaust: 17/95 (18%)* Filtered diesel exhaust: 0/96 Control group: 0/96	*[$P < 0.0001$]	Age at start: 8–10 wk

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Test materials/ Type of samples	Dosing regimen Animals/group at start	Incidence of tumours	Statistical significance	Comments
Rat, F344 (M, F) 30 mo IARC (2013), Ishinishi et al. (1986)	Exhaust with particles from a light-duty 4-cylinder, 1.8 L diesel engine or a heavy-duty 6-cylinder, 11 L diesel engine (different particle concentrations and NO_x concentrations tested) Control group: clean air	16 h/d, 6 d/wk, 30 mo 64 M, 61 F	Lung carcinoma: Heavy-duty engine exhaust: 5/64* (M, highest-dose group; particles, 2.32 mg/m³) 3/60* (F, highest-dose group; particles, 2.32 mg/m³) Control group: 0/64 (M) 1/59 (F)	*$P < 0.05$ (M + F combined)	Age at start: 5 wk No significant increase in incidence of lung tumours in groups exposed to light-duty diesel engine exhaust Lung carcinomas were adenocarcinomas, squamous cell carcinomas, or adenosquamous cell carcinomas
Rat, F344 (F) 30 mo IARC (2013), Iwai et al. (1986)	Diluted exhaust and diluted filtered exhaust from a 2.4 L diesel truck engine (particles, 4.9 ± 1.6 mg/m³) Control group: clean air	8 h/d, 7 d/wk, 24 mo; 6 mo follow-up 24 animals/group	Lung tumours: Unfiltered diesel: 8/19* (5 malignant tumours) Filtered diesel: 0/16 Control group: 1/22	*$P < 0.01$	Age at start: 7 wk
Rat, F344 (F) 24 mo IARC (2013), Takemoto et al. (1986)	Exhaust from a 269 cm³ small diesel engine (diluted 1 : 2 to 1 : 4 with clean air; PM, 2–4 mg/m³) Control group: clean air	4 h/d, 4 d/wk, 24 mo 15 (exposed animals) 12 (control animals)	No lung tumours	NS	Age at start: 5 wk
Rat, F344 (M, F) 30 mo IARC (2013), Mauderly et al. (1986, 1987)	3 concentrations of exhaust from a 1980 model 5.7 L V8 diesel engine	7 h/d, 5 d/wk, 30 mo 0.35, 3.5, 7.0 mg/m³ (measured as soot) Controls: filtered air 221–230 M + F	Lung tumours: 1.3%, 3.6%*, 12.8%*, 0.9% (control) Lung adenocarcinoma or squamous cell carcinoma (combined): 1.3%, 0.5%, 7.5%*, 0.9% (control)	*$P < 0.05$	Age at start: 17 wk Lung tumours were bronchioloalveolar adenoma, adenocarcinoma, squamous cyst, or squamous cell carcinoma

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Test materials/ Type of samples	Dosing regimen Animals/group at start	Incidence of tumours	Statistical significance	Comments
Rat, F344 (M, F) 24 mo IARC (2013), Lewis et al. (1986, 1989)	Exhaust from a 7.0 L, 4-cycle Caterpillar model 3304 diesel engine (diluted 1 : 27) with specific limits on gaseous/vapour constituents, coal dust, coal dust + diesel exhaust, control (clean air)	7 h/d, 5 d/wk, 24 mo Controls 2 mg/m^3 coal dust 2 mg/m^3 diesel exhaust particles 1 mg/m^3 coal dust + 1 mg/m^3 diesel exhaust particles 72 M, 72 F	No statistically significant differences in incidence of lung tumours	NS	Age at start: 8–10 wk
Rat, F344 (M, F) 30 mo IARC (2013), Brightwell et al. (1989)	3 concentrations of exhaust from a 1.5 L VW Rabbit diesel engine, filtered or unfiltered; diluted with a constant volume of 800 m^3 of air; further dilutions: 1 : 3 and 1 : 9 Control groups: clean air	16 h/d, 5 d/wk, 2 yr; 6 mo follow-up Particle concentration of unfiltered fraction: 0.9, 2.7, or 8.2 mg/m^3 72 M, 72 F Control groups: 144 F, 144 M	Lung tumours (all) in controls: M, 2/134; F, 1/126 Lung tumours in high-dose group: M, 16/71*; F, 39/72* Lung tumours in high-dose group animals that survived 24 mo: M, 12/27 (10/27 malignant); F, 24/25 (19/25 malignant)	NR *[$P < 0001$] No increase in the incidence of respiratory tract tumours in groups exposed to filtered exhaust	Age at start: 6–8 wk
Rat, F344 (M, F) Duration NR IARC (2013), Takaki et al. (1989)	Exhaust from a 1.8 L light-duty diesel engine or from a 11 L heavy-duty diesel engine	16 h/d, 5 d/wk, duration NR Particle concentrations from 1.8 L engine: 0, 0.1, 0.4, 1.1, or 2.3 mg/m^3 Particle concentrations from 11 L engine: 0, 0.5, 1.0, 1.8, or 3.7 mg/m^3 64 M, 59 F	No significant increase in the incidence of lung adenoma or lung carcinoma in exposed groups	NS	Age at start: 5 wk
Rat, F344/N (M, F) 24 mo IARC (2013), Mauderly et al. (1994)	Exhaust from a light-duty diesel engine	16 h/d, 5 d/wk, 24 mo Particle concentration in engine exhaust: 0 (clean air), 2.44, or 6.33 mg/m^3 140 F, 140 M	Bronchioloalveolar adenoma: M: 0.8%, 0.9%, 2.6% F: 0%, 2.6%, 17%* Bronchioloalveolar adenocarcinoma: M: 0.8%, 1.8%, 3.5% F: 0%, 4.4%, 16%*	*[$P < 0.0001$]	Age at start: 8 wk

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Test materials/ Type of samples	Dosing regimen Animals/group at start	Incidence of tumours	Statistical significance	Comments
Rat, Wistar (F) 30 mo IARC (2013), Heinrich et al. (1995)	Diluted exhaust soot from a 1.6 L VW diesel engine; dilution: 1 : 80, 1 : 27, or 1 : 9	18 h/d, 5 d/wk, 24 mo; 6 mo follow-up Control group: clean air Concentration of diesel soot particles: 0.8, 2.5, or 7.0 mg/m^3 100–220 animals	Lung tumours (all): 1/217, 0/198, 11/200*, 22/100* Bronchioloalveolar adenoma: 0/217, 0/198, 2/200, 4/100** Lung adenocarcinoma: 1/217, 1/217, 0/198, 1/200, 5/100***	*[$P < 0.005$] **$P < 0.01$ ***$P < 0.05$	Age at start: 7 wk
Rat, F344 (M, F) 30 mo IARC (2013), Nikula et al. (1995)	Exhaust soot from two 1988 model LH6 General Motors 6.2 L V8 diesel engines, diluted in filtered conditioned air	16 h/d, 5 d/wk, 24 mo; 6 mo follow-up 0 (control), 2.5, or 6.5 mg/m^3 105–109 animals (M, F)	Bronchioloalveolar adenocarcinoma: M: 1/109, 1/105, 3/106 F: 0/105, 3/105, 19/106*	*[$P < 0.0001$]	Age at start: 7–9 wk
Rat, F344 (F) 30 mo IARC (2013), Iwai et al. (1997)	Diluted filtered or unfiltered exhaust from a 2.4 L diesel truck engine (particles, 9.4 mg/m^3) either directly or after particle exclusion through a HEPA filter	8 h/d, 7 d/wk, 24 mo; 6 mo follow-up Clean air (control group) Diluted filtered or unfiltered diesel engine exhaust 120 (control group or filtered exhaust) and 24 (unfiltered exhaust) animals	Lung tumours (all): Controls: 5/121 Unfiltered engine exhaust: 8/19* Filtered engine exhaust: 4/108	*$P < 0.01$	Age at start: 8 wk Tumours were mainly adenomas and adenocarcinomas
Rat, F344 (F) 30 mo IARC (2013), Iwai et al. (1997)	Diluted filtered or unfiltered exhaust from a 2.4 L diesel truck engine (particles, 3.2 mg/m^3) either directly or after particle exclusion through a HEPA filter	8 h/d, 6 d/wk, 24 mo; 6 mo follow-up Clean air (control group) Diluted filtered or unfiltered diesel engine exhaust 120 (control group or filtered diesel exhaust) and 48 (unfiltered diesel exhaust) animals	Lung tumours (all): Controls: 5/121 Unfiltered engine exhaust: 5/43* Filtered engine exhaust: 4/108	*$P < 0.01$	Age at start: 8 wk Tumours were mainly adenomas and adenocarcinomas

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Test materials/ Type of samples	Dosing regimen Animals/group at start	Incidence of tumours	Statistical significance	Comments
Rat, F344 (F) 30 mo IARC (2013), Iwai et al. (1997)	Diluted filtered or unfiltered exhaust from a 2.4 L diesel truck engine (particles, 5.1 mg/m^3) either directly or after particle exclusion through a HEPA filter	18 h/d, 3 d/wk, 24 mo; 6 mo follow-up Clean air (control group) Diluted filtered or unfiltered diesel engine exhaust 120 (control group or filtered diesel exhaust) and 96 (unfiltered diesel exhaust) animals	Lung tumours (all): Controls: 5/121 Unfiltered engine exhaust: 40/96* Filtered engine exhaust group: 4/108	*$P < 0.01$	Age at start: 8 wk Tumours were mainly adenomas and adenocarcinomas
Rat, F344 (F) 30 mo IARC (2013), Iwai et al. (2000)	Diluted filtered exhaust from a 2.4 L diesel truck engine (particles, 3.5 ± 1.4 mg/m^3) Controls: clean air	17 h/d, 3 d/wk, for 0 (control), 3, 6, 9, or 12 mo; follow-up to termination at 30 mo 48–50 animals/group	Lung tumours (all): 1/48, 0/48, 6/43, 19/47*, 10/44* Types of tumours: bronchioloalveolar adenoma (14 rats) or adenocarcinoma (22 rats), squamous cell carcinoma (3 rats), adenosquamous carcinoma (1 rat), and sarcoma (1 rat) Controls: 1/48	*$P < 0.01$	Age at start: 8 wk
Hamster, Syrian golden (F) Lifetime IARC (2013), Heinrich et al. (1982)	Filtered or unfiltered exhaust from a 1.6 L Daimler-Benz diesel engine (dilution: 1 : 7; particles, 4.24 mg/m^3)	7–8 h/d, 5 d/wk, lifetime Controls: clean air 48 animals/group	No lung tumours	NS	Age at start: 8 wk No effects on survival
Hamster, Syrian golden (M, F) Lifetime IARC (2013), Heinrich et al. (1986a)	Filtered or unfiltered exhaust from a 1.6 L Daimler-Benz diesel engine (dilution: 1 : 17; particles, 4.24 mg/m^3)	19 h/d, 5 d/wk, lifetime Controls: clean air 48 M, 48 F/group	No lung tumours	NS	Age at start: 8–10 wk No effects on survival

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Test materials/ Type of samples	Dosing regimen Animals/group at start	Incidence of tumours	Statistical significance	Comments
Hamster, Syrian golden (M, F) 24 mo IARC (2013), Brightwell et al. (1989)	Filtered or unfiltered exhaust from a VW Rabbit 1.5 L diesel engine (dilution to give a particle concentration of 0.7, 2.2, or 6.6 mg/m^3)	16 h/d, 5 d/wk Controls: clean air 104 M, 104 F/exposure group 208 M, 208 F/control group	No lung tumours	NS	Age at start: 6–8 wk No effects on survival
Monkey, Cynomolgus (M) 24 mo IARC (2013), Lewis et al. (1989)	Exhaust from a 7.0 L Caterpillar model 3304 diesel engine, diluted 1 : 27 (particle concentration, 4.98 ± 0.82 mg/m^3); coal dust at 2.00 ± 0.41 mg/m^3; or coal dust at 2.02 ± 0.30 mg/m^3 + diesel engine exhaust	7 h/d, 5 d/wk, 24 mo Controls: clean air 15 M/group	No differences in tumour incidence	NS	Age at start NR
Gasoline engine exhaust					
Mouse, NR (M, F) 25 mo IARC (2013), Campbell (1936)	Exhaust from a 4-cylinder, 23 hp (unleaded) gasoline car engine or a 6-cylinder, 24 hp (leaded) gasoline car engine	7 h/d, 5 d/wk, 25 mo Controls: clean air 37–38 animals/group	Lung tumours (all) in M + F combined: Unleaded gasoline exhaust: 9/75 (12%) Controls: 8/74 (11%) Leaded gasoline exhaust: 12/75 (16%) Controls: 6/70 (9%)	NS	Age at start: 3 mo Study poorly reported; no details provided on survival and pathology
Mouse, ICR (F) 12 mo IARC (2013), Yoshimura (1983)	Exhaust from a small gasoline engine diluted with clean air to give concentration of 0.1 mg/m^3	2 h/d, 3 d/wk, 6–12 mo	Lung tumours: 2/15 (13%) (no malignant tumours)	—	Age NR Study poorly reported Lack of controls
Rat, Bor:WISW (F) 30 mo IARC (2013), Heinrich et al. (1986c)	Exhaust from a 1.6 L (leaded) gasoline engine operated according to US-72 FTP driving cycle, diluted 1 : 27 or 1 : 61 with clean air Controls: clean air	18–19 h/d, 5 d/wk, 24 mo; 6 mo follow-up 80–83 animals/group	Lung tumours: 1 : 61 dilution: 1/83 (squamous cell carcinoma) 1 : 27 dilution: 3/78 (squamous cell carcinoma, adenoma) Controls: 1/78 (adenoma)	NS	Age at start: 10–12 wk

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Test materials/ Type of samples	Dosing regimen Animals/group at start	Incidence of tumours	Statistical significance	Comments
Rat, F344 (M, F) 30 mo IARC (2013), Brightwell et al. (1989)	Exhaust from a Renault R18 1.6 L (unleaded) gasoline engine, operated with or without a 3-way catalytic converter, diluted with a constant volume of 800 m^3 of air, or further diluted 1 : 3 Controls: clean air	16 h/d, 5 d/wk, 24 mo; additional 6 mo clean air 72 animals/group	No increase in lung tumours	NS	Age at start: 6–8 wk
Hamster, Syrian golden (F) 24 mo IARC (2013), Heinrich et al. (1986c)	Exhaust from a 1.6 L (leaded) gasoline engine operated according to US-72 FTP driving cycle, diluted 1 : 27 or 1 : 61 with clean air Controls: clean air	18–19 h/d, 5 d/wk, 24 mo 80–83 animals/group	0/83 (control), 3/80 (1 : 61), 1/75 (1 : 27)	NS	Age at start: 10–12 wk No effects on survival
Hamster, Syrian golden (M, F) 24 mo IARC (2013), Brightwell et al. (1989)	Exhaust from a Renault R18 1.6 L (unleaded) gasoline engine, operated with or without a 3-way catalytic converter, diluted with a constant volume of 800 m^3 of air, or further diluted 1 : 3 Controls: clean air	18–19 h/d, 5 d/wk, 24 mo 104 animals/group Control: 208 M and 208 F animals Half of the animals were treated with NDEA 3 d before start of exposure	No increase in lung tumours	NS	Age at start: 6–8 wk No effects on survival
Dog, Beagle (F) 104 mo IARC (2013), Stara et al. (1980)	Exposure to exhaust from a 6-cylinder, 2.4 L (leaded) gasoline engine, operated to simulate urban driving, and/or to specific air pollutants Pb concentration: 14–26 µg/m^3	16 h/d, 68 mo, 36 mo follow-up 12–20 animals/group Controls: 17 animals	No lung tumours observed in 41 surviving dogs from groups exposed to engine exhaust or in 17 surviving controls	[NS]	

B[*a*]P, benzo[*a*]pyrene; bw, body weight; d, day or days; F, female; h, hour or hours; HEPA, high-efficiency particulate air; hp, horse power; M, male; mo, month or months; NDEA, *N*-nitrosodiethylamine; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; NR, not reported; NS, not significant; Pb, lead; PM, particulate matter; VW, Volkswagen; wk, week or weeks; yr, year or years

Table 3.2 Studies of carcinogenicity in experimental animals of components of outdoor air pollution by intratracheal administration, intratracheal instillation, or intrapulmonary implantation

Species, strain (sex) Duration Reference	Test materials/ Type of samples	Dosing regimen Animals/group at start	Incidence of tumours	Statistical significance	Comments
Coal smoke and soot from household combustion of coal					
Mouse, Kunming (M) 18 mo IARC (2010b, 2012a), Yin et al. (1984)	Coal fume extracts from coal smoke collected from an area of Xuanwei County, China, in an aqueous solution of Tween 80 and 0.1 mL of vehicle solution (12.5 mg soot/mL)	Intratracheal instillation once/10 d for an average period of 100 d; follow-up to termination at 18 mo 43 controls and 72 exposed animals	Lung adenoma or adenocarcinoma (combined): 25.6% (vehicle control), 52.8%* Lung adenocarcinoma: 16.3% (vehicle control), 40.3%*	*$P < 0.01$	Age at start NR
Diesel engine exhaust					
Mouse, ICR (M) 12 mo IARC (2013), Ichinose et al. (1997)	Exhaust emissions from a 1.5 L diesel engine (2740 cm^3 exhaust volume), collected on a glass filter, suspended in 50 mM phosphate-buffered 0.9% saline (pH 7.4) containing 0.05% Tween 80	Intratracheal instillation once/wk for 10 wk; follow-up to termination at 12 mo 0, 0.05, 0.1, or 0.2 mg/mouse 34 animals/group	No increase in incidence of lung adenoma, lung adenocarcinoma, or lymphoma	NS	Age at start: 4 wk
Rat, Osborne-Mendel (F) 24–140 wk IARC (2013), Grimmer et al. (1987)	Vehicle alone (control); condensate from exhaust from a diesel car engine (3.0 L, Daimler-Benz 300D), separated into hydrophilic (6.7 mg) and hydrophobic (20 mg) fractions; hydrophobic fraction separated by column chromatography into several subfractions: (A) non-aromatic compounds plus PAHs with 2 or 3 rings (19.22 mg), (B) PAHs with 4–7 rings (0.21 mg), (C) polar PAHs (0.29 mg), and (D) nitro-PAHs (0.19 mg), or a hydrophobic fraction reconstituted from subfractions A–D (19.9 mg) in beeswax:trioctanoin (1 : 1)	Single intrapulmonary implantation of each fraction or subfraction 35 animals/group	Lung squamous cell carcinoma: 0/35 (control), 5/35 (hydrophobic)*, 6/35 (PAHs with 4–7 rings)*, 1/35 (nitro-PAHs), 7/35 (reconstituted hydrophobic)*, 0/35 (other fractions)	*[$P < 0.05$]	Age at start: 3 mo Study poorly reported; details of results, including pathology and dosing regimen, not clear; results summarized in a general manner and difficult to interpret
Rat, F344 (M, F) 30 mo IARC (2013), Iwai et al. (1997)	Diesel particulate suspension collected from the exhaust of a 2.4 L diesel truck engine, suspended in Tween 80 or DMSO phosphate buffer (pH 7.4)	Intratracheal instillation of 2, 4, 8, or 10 mg of diesel particulate suspension Once/wk for 2–10 wk; follow-up to termination at 30 mo 50 animals/group	Lung tumours (all): 6% (2% malignant), 20% (13% malignant), 43% (34% malignant), 74% (48% malignant)	NR [dose-related increase]	Age at start: 8 wk Results of study poorly reported; unclear whether there was a control group

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Test materials/ Type of samples	Dosing regimen Animals/group at start	Incidence of tumours	Statistical significance	Comments
Hamster, Syrian golden (M, F) Lifetime IARC (2013), Kunitake et al. (1986)	Suspension of tar from exhaust from a heavy-duty V6 11 L diesel engine, suspended in 0.1 mL of Tween 60, ethanol, and phosphate buffer solution	Intratracheal instillation of 0, 0.1, 0.5, or 1.0 mg of tar Control group: vehicle only 59–62 animals/group	No significant differences in the incidence of tumours of the lung, trachea, or larynx between treated groups and untreated controls	NS	Age at start: 8 wk Dose-related decrease in survival: 98% (control), 95%, 92%, 71%
Gasoline engine exhaust					
Rat, Osborne-Mendel (F) Lifetime IARC (2013), Grimmer et al. (1984)	Condensate from exhaust emission from a 1.5 L gasoline car engine (operated on the European test cycle)	Single intrapulmonary implantation of 0 (control), 5.0, or 10.0 mg (A1, A2) condensate, or one of several fractions: 4.36, 8.73, or 17.45 mg PAH-free (B1, B2, B3); 0.50, 0.99, or 1.98 mg PAHs with 2 or 3 rings (C1, C2, C3); or 0.14, 0.28, or 0.56 mg PAHs with > 3 rings (D1, D2, D3) in beeswax:trioctanoin (1 : 1) into the left lobe of the lung 34–35 animals/group	Lung carcinoma: 0/34, 3/35 (9%; A1), 20/35 (57%; A2)**, 0/34 (B1), 3/34 (9%; B2), 1/34 (3%; B3), 0/35 (C1), 0/35 (C2), 3/35 (9%; C3), 3/35 (9%; D1), 15/34 (44%; D2)*, 24/35 (69%; D3)** Lung sarcoma: 0/34, 4/35 (11%; A1), 0/35 (A2), 0/34 (B1), 3/34 (9%; B2), 2/34 (6%; B3), 0/35 (C1), 0/35 (C2), 3/35 (9%; C3), 1/35 (3%; D1), 2/34 (6%; D2), 0/35 (D3)	[*$P = 0.0002$, **$P < 0.001$]	Age at start: 3 mo Mean survival times: 80–11 wk No tumours in untreated or vehicle controls The authors reported that a lung tumour dose–response relationship was obtained with the total condensate and with the fraction of PAHs with > 3 rings
Hamster, Syrian golden (M) Lifetime IARC (2013), Mohr et al. (1976), Reznik-Schüller and Mohr (1977)	Condensate from exhaust emission from a German gasoline car engine (operated on the European test cycle), containing 340 µg/g B[*a*]P, dissolved in 0.2 mL of Tris-HCl and EDTA	Intratracheal instillation of 0 (control), 2.5 or 5.0 mg; every other wk for life 6 animals/group	Pulmonary adenoma: 0/6, 6/6*, 6/6*	*[$P < 0.05$]	Age at start: 12 wk Survival range: 30–60 wk Study poorly described
Hamster, Syrian golden (M) Lifetime IARC (2013), Künstler (1983)	Condensate from exhaust emission from a VW 1500 Otto gasoline engine	Single intratracheal instillation of 0 (control), 0.5, 1.0, or 2.1 mg of exhaust condensate in Tris-buffer/ saline 30 animals/group	No lung tumours observed	NS	Age at start: 16 wk Survival range: 68–87 wk

B[*a*]P, benzo[*a*]pyrene; d, day or days; DMSO, dimethyl sulfoxide; EDTA, ethylenediaminetetraacetic acid; F, female; M, male; mo, month or months; NR, not reported; NS, not significant; PAHs, polycyclic aromatic hydrocarbons; VW, Volkswagen; wk, week or weeks

Table 3.3 Studies of carcinogenicity in experimental animals of components of outdoor air pollution by skin application

Species, strain (sex) Duration Reference	Test materials/ Type of samples	Dosing regimen Animals/group at start	Incidence of tumours	Statistical significance	Comments
Coal smoke and soot from household combustion of coal					
Mouse, SENCAR (F) 77 wk IARC (2010b, 2012a), Mumford et al. (1990)	Exposure to organic extracts of indoor air particles (< 10 µm) from burned smoky coal in Xuanwei County, China (B[*a*]P, 19.3 µg/m^3 air) Indoor air particles collected during cooking periods in Xuanwei homes. Smoky coal: 0.9% sulfur, high heating value (27.1 MJ/kg), 20% ash content	1 mg of smoky coal extract in 0.2 mL of acetone, twice/wk, 52 wk Acetone control 40 animals/ group	Skin carcinoma: Acetone control: no skin carcinoma at 52 wk (100% survival) or at 77 wk (78% survival) Smoky coal-exposed: 38%* (multiplicity, 1.3) at 52 wk (88% survival); 88%* (multiplicity, 1.1) at 77 wk (10% survival)	NR, *[significant]	Age at start: 7–9 wk
Wood smoke					
Mouse, NR (M, F) 2 yr IARC (2010b), Sulman & Sulman (1946)	Ethanol extract of wood (eucalyptus) soot	Daily application on the neck skin, 2 yr 10 exposed animals 20 controls	No skin tumours observed Two exposed mice with para-urinary bladder sarcoma, after 5 mo and 12 mo, and one exposed mouse with bladder sarcoma, after 21 mo	NS	Age at start NR, "adult" mice Dose NR
Mouse, SENCAR (F) 74 wk IARC (2010b), Mumford et al. (1990)	Wood (pine) smoke extract in acetone (PM < 10 µm), collected from homes in Xuanwei County, China High-volume sampling onto fibreglass filters	Skin application of 1 mg/kg bw extract twice/wk, 52 wk; further observation for 25 wk Positive control: 50 mg of B[*a*]P Acetone control group 40 animals/group	Skin carcinoma: Wood smoke extract-treated mice: 5% Acetone control group: 0% Positive control group: 100%	NS	Age at start: 7–9 wk
Mouse, SENCAR (F) NR IARC (2010b), Lewtas (1993)	Extracts of particle emissions of a mixture of softwoods (e.g. pine) and of a mixture of hardwoods (e.g. oak) burned in a wood stove	1, 2, 5, 10, or 20 mg of dichloromethane extracts in 0.2 mL of acetone 40 animals/group	Skin papilloma (slope of dose–response curve) Particles from softwoods (0.046 papillomas/mouse/mg) more tumorigenic than those from hardwoods (0.009 papillomas/ mouse/mg)	—	Age at start NR No controls

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Test materials/ Type of samples	Dosing regimen Animals/group at start	Incidence of tumours	Statistical significance	Comments
Mouse, SENCAR (F) NR IARC (2010b), Lewtas (1993), Cupitt et al. (1994)	Sample A: composite outdoor air sample from Boise, Idaho, USA, of a mixture of 78% wood smoke, 11% mobile sources, and 11% residual unidentified mass Sample B: composite outdoor air sample of a mixture of 51% wood smoke, 33% mobile sources, and 16% residual unidentified mass	Skin application of 1, 2, 5, 10, or 20 mg of dichloromethane extract in 0.2 mL of acetone 40 animals/group	Skin papilloma (slope of dose–response curve) Sample A: 0.095 papillomas/mouse/mg Sample B: 0.21 papillomas/mouse/mg	—	Age at start NR No controls
Diesel engine exhaust					
Mouse, CBA (M, F) C57BL/Gr (M, F) A/Grf (M, F) GFF (M, F) GFF_f (F) 13.5 mo Clemo et al. (1955)	Two fractions of diesel engine exhaust extracts in benzene; controls received benzene only	Dermal application, 3 ×/wk 1–6 mice/strain/group	Lung nodules [not further described]: Fraction A: 5/21 Fraction B: 0/17 Controls: 1/21	[NS]	M and F mice of all strains combined Small number of animals. Poor study design
Mouse, SENCAR (M, F) 50–52 wk IARC (2013), Nesnow et al. (1983)	Dichloromethane extracts of particles from the emission of a Nissan Datsun 220C diesel engine, dissolved in acetone	0 (control), 0.1, 0.5, 1.0, 2.0, or 4.0 mg/mouse Application once/wk for 50–52 wk (4 mg dose given as 2 mg twice/wk) 40 animals/group	Skin carcinoma: 0–2.0 mg-treated groups: 0% (M), 0% (F) 4 mg-treated group: 3% (M), 5% (F)	NS	Age at start: 7–9 wk Pathology poorly described
Gasoline engine exhaust					
Mouse, C57BL (NR) NR [> 390 d] IARC (2013), Kotin et al. (1954a)	Extract of filtered exhaust from an overhauled Ford V8 gasoline engine, in benzene	Dose [NR] in benzene of an oil residue of the benzene extract Application "at frequent but irregular intervals" to the skin Controls: 42 Treated: 86	Skin tumours (all): 0/42, 38/86* Skin squamous cell carcinoma: 0/42, 22/86*	*[$P < 0.0005$]	Age at start NR Study poorly reported

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Test materials/ Type of samples	Dosing regimen Animals/group at start	Incidence of tumours	Statistical significance	Comments
Mouse, Swiss (F) Up to 18 mo IARC (2013), Wynder & Hoffmann (1962)	Oil residue of benzene extract of condensed and filtered exhaust from a V8 gasoline engine in acetone	3 ×/wk, 15 mo; 3 mo follow-up Skin application of 0%, 5%, 10%, 25%, 33%, or 50% of an oil residue of benzene extract 30–50 animals/group	Skin papilloma: 0%, 4%, 50%, 60%, 60%, 70% Skin carcinoma: 0%, 4%, 32%, 48%, 54%, 4%	NR, [significant]	Age at start: 6 wk All animals in the highest-dose group had died by 10 mo Study poorly designed
Mouse, Swiss (F) 18 mo IARC (2013), Hoffmann et al. (1965)	Tar (in acetone) from exhaust of a a V8 gasoline engine, using 0.3 L engine oil/100 km (A) or 0.04 L engine oil/100 km (B)	[Frequency and method of skin application NR] 50 animals/group	Skin tumours (all): A: 60% (48% carcinoma) B: 84% (52% carcinoma)	—	Age at start NR Study poorly designed. No control group
Mouse, CFLP (F) Lifetime IARC (2013), Brune et al. (1978)	Different doses of exhaust condensate from a 1.5 L VW Otto gasoline engine in DMSO:acetone (3 : 1)	Application twice/wk for life of 0, 0, 0.5, 1.6, or 4.7 µg of exhaust condensate to the shaved interscapular region 80 animals/group in Hamburg laboratory 40 animals/group in Heidelberg laboratory	Hamburg laboratory study: Skin squamous cell tumours (all): 0/76, 1/76 (1%), 3/77 (4%), 26/74 (35%)*, 60/78 (77%)* Skin squamous cell carcinoma: 0/76, 0/76, 1/77 (1%), 22/74 (30%)*, 56/78 (72%)* Heidelberg laboratory study: Skin squamous cell tumours (all): 0/30, 0/37, 1/31 (3%), 3/37 (8%), 19/38 (50%)** Skin squamous cell carcinoma: 0/30, 0/37, 1/31 (3%), 2/37 (5%), 18/38 (47%)* Lung tumours (all): 3/40 (7%), 3/40 (7%), 3/40 (7%), 8/40 (20%)***, 9/40 (22%)***	[*$P < 0.0001$, **$P = 0.0002$, ***$P = 0.001$]	Age at start: 12 wk Two control groups

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Test materials/ Type of samples	Dosing regimen Animals/group at start	Incidence of tumours	Statistical significance	Comments
Mouse, CFLP (F) Lifetime IARC (2013), Grimmer et al. (1983a, b)	Exhaust condensate from a 1.5 L gasoline car engine (50 hp); PAH-free fraction and PAH-containing fraction; mixture of PAHs simulating those in exhaust from gasoline automobile engine. Solution in DMSO:acetone (3 : 1)	Twice/wk, 104 wk; lifetime follow-up Application of 0.1 mL of solution of: 0 (control), 0.29, 0.87, or 2.6 mg/animal of exhaust condensate; 0.97 or 2.9 mg/animal of PAH-free fraction (A); 0.152 or 0.455 mg/animal of PAH-containing fraction (2 or 3 rings) (B); 0.02 or 0.06 mg/animal of PAH-containing fraction (> 3 rings) (C); or mixture of 15 PAHs (0.003 or 0.009 mg/animal) 65 controls and 80 treated animals/group	Skin tumours (all): Exhaust condensate: 0/65 (control); 6/80 (7%)*; 34/80 (42%)**, 65/80 (81%)** Fraction A: 4/80 (5%), 11/80 (14%)*** Fraction C: 7/80 (9%)*, 50/80 (62%)** Mixture of 15 PAHs: 1/80 (1%), 29/80 (36%)** Fraction B: no significant increase in skin tumours	[*$P < 0.05$, **$P < 0.0001$, ***$P = 0.003$]	Age at start: 7 wk Tumours were mainly squamous cell carcinomas

B[*a*]P, benzo[*a*]pyrene; bw, body weight; DMSO, dimethyl sulfoxide; F, female; hp, horse power; M, male; mo, month or months; NR, not reported; NS, not significant; PAHs, polycyclic aromatic hydrocarbons; PM, particulate matter; VW, Volkswagen; wk, week or weeks; yr, year or years

Table 3.4 Studies of carcinogenicity in experimental animals of components of outdoor air pollution by subcutaneous injection or implantation

Species, strain (sex) Duration Reference	Test materials/ Type of samples	Dosing regimen Animals/group at start	Incidence of tumours	Statistical significance	Comments
Coal smoke and soot from household combustion of coal					
Mouse, Hybrid F1 (C57BlxCBA) (M) 55 wk IARC (2010b, 2012a), Khesina et al. (1977)	Olive oil containing coal soot extracts collected from individual houses that were heated with brown coal	5 subcutaneous injections of 2.5 mL of olive oil containing coal soot extracts over 8 wk (total of 0.2 mg of B[*a*]P/animal); follow-up to 55 wk Vehicle group (olive oil) 30 animals/group	Subcutaneous tumours: Coal soot extract-treated group: 5/30 (17%)*, first tumour at 15 wk Controls: 0/30, no mortality at 55 wk	*[$P < 0.05$]	Age at start: 1.5–2 mo Tumour type NR
Mouse, Kunming (M) 10 mo IARC (2010b, 2012a), Liang et al. (1983)	Cyclohexane extracts of coal soot from Xuanwei County, China, dissolved in Tween 80 and saline solution	Injection of 0.1 mL into the back of the neck, once/wk, 10 wk; follow-up to 10 mo 0 mg (vehicle control) 500 mg of coal soot extract (total dose) 1000 mg of coal soot extract (total dose) 38–57 animals/group	Lung cancer: 1/38 (2.6%), 44/57 (77.2%)*, 36/56 (64.3%)*	*$P < 0.001$	Age at start NR; weight, 18–26 g Lung cancers were squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma
Mouse, Kunming (M) 311 d IARC (2010b, 2012a), Liang et al. (1984)	Extracts of coal soot from Xuanwei County, China, dissolved in Tween 80 and saline solution	Injection of 0.1 mL into the back of the neck, once/wk, 10 wk; follow-up to 311 d 0 mg (vehicle control) 119 mg of soot extract (total dose) containing 0.15 µg of B[*a*]P 400 mg of soot extract (total dose) containing 0.52 µg of B[*a*]P ~60 animals/group	Lung cancer: 6/60 (10%) (all adenocarcinomas), 52/58 (89.5%)*, 39/59 (66.1%)*	*$P < 0.001$	Age at start NR; weight, 18–22 g Lung cancers were mainly squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma (one fibrosarcoma in the low-dose group)
Wood smoke					
Mouse, Hybrid F1 (C57BlxCBA) (M) 55 wk IARC (2010b), Khesina et al. (1977)	Olive oil containing soot extracts from a wood-fired wood-working atelier	5 subcutaneous injections of 2.5 mL of olive oil containing soot extract over 8 wk (total of 0.2 mg of B[*a*]P/animal); follow-up to 55 wk Vehicle control group (olive oil) 30 animals/group	Subcutaneous tumours Wood soot extract-treated group: 5/30 (17%)*, first tumour at 15 wk Controls: 0/30, no mortality at 55 wk	*[$P < 0.05$]	Age at start: 1.5–2 mo Tumour type NR

Table 3.4 (continued)

Species, strain (sex) Duration Reference	Test materials/ Type of samples	Dosing regimen Animals/group at start	Incidence of tumours	Statistical significance	Comments
Mouse, Kunming (M) 311 d IARC (2010b), Liang et al. (1984)	Extract of wood smoke generated from a fire pit in the centre of a room to mimic that of rural inhabitants in Xuanwei County, China, in Tween 80 and saline solution	Injection of 0.1 mL into the back of the neck, once/wk, 10 wk; follow-up to 311 d 0 mg (vehicle control) 148 mg of extract (total dose) containing 0.074 µg of B[*a*]P 296 mg of extract (total dose) containing 0.15 µg of B[*a*]P ~60 animals/group	Lung cancer (all adenocarcinomas): 6/60 (10%), 31/60 (51.7%)*, 36/58 (62.1%)*	*$P < 0.001$	Age at start NR; weight, 18–22 g
Rat, NR (M, F) 2.5 yr IARC (2010b), Sulman & Sulman (1946)	Fragments of wood (eucalyptus) soot from the smoking chamber of a sausage factory	Implantation of 5–20 mg fragments near the right axilla and in the scrotal sac 18 M,18 F Controls (untreated): 18 M,18 F	Local sarcomas: Exposed animals: M: 0/18; F: 3/18 Controls: M: 0/18; F: 0/18	[NS]	Age at start NR; weight, 120–150 g Small number of animals Inadequate control group The 3 sarcomas had latency periods of 12, 17, and 14 mo
Diesel engine exhaust					
Mouse, C57BL/6N (F) 18 mo IARC (2013), Kunitake et al. (1986)	Residue from dichloromethane extraction of particles collected from a V6 11 L heavy-duty diesel engine	Injection into the interscapular region, once/wk for 5 wk, follow-up to 18 mo, of a total dose of 0 (control), 10, 25, 50, 100, 200, or 500 mg/kg bw of residue in olive oil containing DMSO 15–50 animals/group	Malignant fibrous histiocytomas: 0/38 (control), 0/15, 1/15, 2/14, 3/30, 1/15, 5/22*	*$P < 0.01$	Age at start: 6 wk
Mouse, ICR (newborn) (M, F) 24 mo IARC (2013), Kunitake et al. (1986)	Residue from dichloromethane extraction of particles collected from a V6 11 L heavy-duty diesel engine	Single subcutaneous injection 24 h after birth of 0, 2.5, 5, or 10 mg/mouse of residue in olive oil containing DMSO 12–36 animals/group	Malignant lymphoma: 2/14 (control), 4/12 (10 mg/mouse) No significant increase in hepatoma, malignant lymphoma, lung, mammary gland, or other tumours	[NS]	Newborn C57BL mice were also injected with doses of 0 (control) or 5 mg/mouse, and no increase in the incidence of tumours was observed in treated vs control animals

Table 3.4 (continued)

Species, strain (sex) Duration Reference	Test materials/ Type of samples	Dosing regimen Animals/group at start	Incidence of tumours	Statistical significance	Comments
Gasoline engine exhaust					
Mouse, NMRI (F) NR IARC (2013), Pott et al. (1977)	Different doses of gasoline engine [type NR] exhaust condensate	Single subcutaneous injection of 0 (control), 20, or 60 mg of exhaust condensate in 0.5 mL of tricaprylin 87–88 animals/group Fourth group: 3 injections of 60 mg dose 45 animals/group	Local fibrosarcomas: Control: 3/89 (3%) Condensate-treated groups: 10/87 (11%), 6/88 (7%), 5/45 (11%)	NR [NS]	Age at start NR Decrease of survival as a function of dose. Survival time in the low- and mid-dose group: 80–88 wk (in the range of the control group); in the high-dose group: 57 wk Study poorly reported; no details provided on histopathology

B[*a*]P, benzo[*a*]pyrene; bw, body weight; d, day or days; DMSO, dimethyl sulfoxide; F, female; h, hour or hours; M, male; mo, month or months; NR, not reported; NS, not significant; wk, week or weeks; yr, year or years

Table 3.5 Studies of administration in experimental animals of components of outdoor air pollution with known carcinogens or modifying factors

Species, strain (sex) Duration Reference	Test materials/ Type of samples	Dosing regimen Animals/group at start	Incidence of tumours	Statistical significance	Comments
Diesel engine exhaust					
Mouse, NMRI (F) Lifetime (up to 120 wk) IARC (2013), Heinrich et al. (1986a)	B[*a*]P or DB[*a*,*h*]A, followed by exposure to filtered or unfiltered exhaust from a 1.6 L VW diesel engine, diluted (1 : 17) with air (particles, 4.24 mg/m^3)	19 h/d, 5 d/wk, lifetime Initial intratracheal instillation with 50 or 100 µg of B[*a*]P for 20 or 10 wk, respectively, or 50 µg of DB[*a*,*h*]A for 10 wk, followed by exposure to clean air, or filtered or unfiltered exhaust Controls: DB[*a*,*h*]A + clean air or B[*a*]P + clean air 64–96 mice/group	Lung tumours: Inconsistent results for the various treatments B[*a*]P: 71% lung tumour rate B[*a*]P + diesel exhaust: only 41% lung tumour rate (not reproduced)	NS	Age at start: 8–10 wk
Mouse, NMRI (newborn) (F) 6 mo IARC (2013), Heinrich et al. (1986a)	DB[*a*,*h*]A, followed by exposure to filtered or unfiltered exhaust from a 1.6 L VW diesel engine, diluted (1 : 17) with air (particles, 4.24 mg/m^3)	19 h/d, 5 d/wk, 6 mo Initial subcutaneous injection of 5 or 10 µg of DB[*a*,*h*]A, followed by exposure to clean air, or filtered or unfiltered exhaust Control: DB[*a*,*h*]A + clean air 96 mice/group	Lung tumours: Incidence NR. The various treatments gave erratic and inconsistent results	NS	
Rat, F344 (F) Up to 24 mo IARC (2013), Takemoto et al. (1986)	Exhaust from a 269 cm^3 small diesel engine (diluted 1 : 2 to 1 : 4 with clean air), followed by DIPN	4 h/d, 4 d/wk, 24 mo; after 1 mo, the exposure group was injected with 1 g/kg bw DIPN once/wk for 3 wk Control: DIPN + clean air 20–35 animals/group	Lung carcinoma: 4/21 (control), 7/18 Lung adenoma: 10/21 (control), 12/18	NS	Age at start: 5 wk Small number of animals
Gasoline engine exhaust					
Mouse, NMRI (F) 93 wk IARC (2013), Heinrich et al. (1986c)	B[*a*]P or DB[*a*,*h*]A, followed by inhalation exposure to exhaust from a 1.6 L gasoline engine (leaded fuel) diluted 1 : 27 or 1 : 61 with air	18–19 h/d, 5 d/wk, 53 wk; 40 wk follow-up Initial treatment with 10 intratracheal instillations of 100 µg of B[*a*]P, 20 intratracheal instillations of 50 µg of B[*a*]P, or 10 intratracheal instillations of 50 µg of DB[*a*,*h*]A, followed by inhalation exposure to clean air (control) or dilutions of gasoline exhaust 60 animals/group	Similar lung tumour incidences in control groups and exhaust-exposed groups	NS	Age at start: 8–10 wk

Table 3.5 (continued)

Species, strain (sex) Duration Reference	Test materials/ Type of samples	Dosing regimen Animals/group at start	Incidence of tumours	Statistical significance	Comments
Mouse, NMRI (newborn) (M, F) 6 mo IARC (2013), Heinrich et al. (1986c)	DB[*a*,*h*]A, followed by inhalation exposure of exhaust from a 1.6 L gasoline engine (leaded fuel) diluted 1 : 27 or 1 : 61 with air	Single injection of 4 µg or 10 µg of DB[*a*,*h*]A, followed by inhalation exposure to clean air (control) or dilutions of gasoline exhaust for 6 mo 61–83 animals/group	Number of lung tumours per animal was not significantly different from that in controls	NS	
Mouse, NMRI (F) NR IARC (2013), Pott et al. (1977)	B[*a*]P alone or together with exhaust condensate from a gasoline engine [type NR] in tricaprylin	Single subcutaneous injection of 10, 30, 90, or 270 µg of B[*a*]P alone or together with 6.6, 20, or 60 mg of condensate in 0.5 mL of tricaprylin 87–88 animals/group	Significant reduction of the dose–response relationship for local fibrosarcoma incidence produced by B[*a*]P by addition of the condensate	—	Age at start NR Study poorly reported
Rat, Sprague-Dawley (F) 6–12 mo IARC (2013), Yoshimura (1983)	DIPN alone or together with exhaust emissions from a small gasoline engine (diluted 1 : 250 with clean air)	2 h/d, 3 d/wk, 6 or 12 mo 0.01% DIPN in drinking-water, alone (control) or with 0.1 mg/m^3 exhaust emission Numbers NR	Lung tumours: DIPN control: 2/24 (8%) DIPN + exhaust: 11/37 (30%)* (10 undifferentiated carcinomas, squamous cell carcinomas, adenocarcinomas, or mixed tumours, and 1 adenoma)	*[$P < 0.05$]	Age at start NR
Rat, Bor:WISW (F) 30 mo IARC (2013), Heinrich et al. (1986c)	NDPA, followed by inhalation exposure to clean air or exhaust from a 1.6 L gasoline engine (leaded fuel) operated according to US-72 FTP driving cycle, diluted 1 : 27 or 1 : 61 with clean air	18–19 h/d, 5 d/wk, 24 mo; 6 mo follow-up Subcutaneous injection of 0.25 or 0.5 g/kg bw NDPA, once/d for 25 d, followed by exposure to clean air (control) or exhaust 60 animals/group	Decrease in the incidence of benign or malignant (combined) lung tumours	—	Age at start: 10–12 wk
Hamster, Syrian golden (F) 24 mo IARC (2013), Heinrich et al. (1986c)	NDEA or B[*a*]P, followed by inhalation exposure to clean air or exhaust from a 1.6 L gasoline engine (leaded fuel) operated according to US-72 FTP driving cycle, diluted 1 : 27 or 1 : 61 with air	18–19 h/d, 5 d/wk, 24 mo Single subcutaneous injection of 3 mg/kg bw NDEA or 20 intratracheal instillations of 0.25 mg of B[*a*]P, followed by exposure to clean air (control) or exhaust 80–81 animals/group	Basic rates of NDEA- or B[*a*]P-induced benign respiratory tract tumours were 12.8% and 6.5%, respectively; tumour rates in NDEA- and B[*a*]P-treated animals exposed to the 1 : 27 dilution were ~50% lower than those in treated animals exposed to the 1 : 61 dilution or clean air	—	Age at start: 10–12 wk

B[*a*]P, benzo[*a*]pyrene; bw, body weight; d, day or days; DB[*a*,*h*]A, dibenz[*a*,*h*]anthracene; DIPN, *N*-nitrosodiisopropanolamine; F, female; h, hour or hours; M, male; NDEA, *N*-nitrosodiethylamine; NDPA, *N*-nitrosodipentylamine; NR, not reported; NS, not significant; VW, Volkswagen

Table 3.6 Initiation–promotion studies in experimental animals of components of outdoor air pollution

Species, strain (sex) Duration Reference	Test materials/ Type of samples	Dosing regimen Animals/group at start	Incidence of tumours	Statistical significance	Comments
Wood smoke					
Mouse, Kunming (F) 32 wk IARC (2010b), Liang & Wang (1987)	Extracts of inhalable particles (< 10 µm) of indoor wood smoke collected from Xuanwei County, China	Skin application of 1, 5, 10, or 20 mg of inhalable particles of indoor wood smoke in acetone; promotion with TPA (application of 2 µg/mouse, twice/wk, 26 wk); further observation for 6 wk TPA control group 40 animals/group	Skin tumours (at 26 wk): TPA + wood smoke extract-treated group: 12.5–41%* TPA control group: 10%	*$P < 0.01$	Age at start NR; weight, ~28.7 g Time to first tumour incidence decreased with increasing dose of extract Histopathology of skin tumours NR
Mouse, SENCAR (F) Up to 52 wk IARC (2010b), Mumford et al. (1990)	Wood (pine) smoke extract in acetone (PM < 10 µm); collected from homes in Xuanwei County, China High-volume sampling onto fibreglass filters	Skin application of two doses of 1, 2, 5, 10, or 20 mg of wood smoke extract/kg bw in 0.2 mL of acetone over 1–5 d and then 2 µg of TPA twice/wk for 26 wk TPA control group 40 animals/group	Skin papilloma (at 23 wk): TPA + wood smoke extract-treated groups: 40%*, 45%*, 70%*, 80%*, 90%* TPA control group: 10%	NR, *[significant]	Age at start: 7–9 wk
Coal smoke and soot from household combustion of coal					
Mouse, SENCAR (F) 27 wk IARC (2010b, 2012a), Mumford et al. (1990)	Exposure to organic extracts of indoor air particles (< 10 µm) from burned smoky coal in Xuanwei County, China (B[*a*]P, 19.3 µg/m^3 air) Indoor particles collected during cooking periods in Xuanwei homes. Smoky coal: 0.9% sulfur, high heating value (27.1 MJ/kg), 20% ash content	Initiation with skin application of smoky coal extract, followed 1 wk later by promotion with TPA (application of 2 µg/mouse, twice/wk, 26 wk) Initiation dose: 0 (acetone control), 1, 2, 5, 10, or 20 mg in 0.2 mL of acetone 40 animals/group	Skin papilloma: 15%, 80%*, 90%*, > 90%*, > 90%*, 100%*	NR, *[significant]	Age at start: 7–9 wk Tumour incidences estimated from graphical presentation of data
Mouse, Kunming (M) 32 wk IARC (2010b, 2012a), Liang & Wang (1987)	Extracts of particles (< 10 µm) from smoky coal soot from Xuanwei County, China	Initiation with skin application of 1, 5, 10, or 20 mg of smoky coal soot extract in acetone; promotion with TPA (application of 2 µg/mouse, twice/wk, 26 wk); further observation for 6 wk Control group (TPA only) 40 animals/group	Skin tumours (at 26 wk): Smoky coal extract-treated groups: 25%, 54%*, 60%*, 40%* TPA control group: 10%	*[$P < 0.05$]	Age at start NR; weight, ~28.7 g Histopathology of skin tumours NR

Table 3.6 (continued)

Species, strain (sex) Duration Reference	Test materials/ Type of samples	Dosing regimen Animals/group at start	Incidence of tumours	Statistical significance	Comments
Diesel engine exhaust					
Mouse, ICR (F) [29 wk] IARC (2013), Kunitake et al. (1986)	Extracts of particles from a V6 11 L heavy-duty diesel engine, dissolved in acetone	Skin application every other d for 20 d of 0 (acetone control), 0.5, 1.5, or 4.5 mg/animal, followed by treatment with 2.5 µg of TPA in 0.1 mL of acetone 3 ×/wk for 25 wk 50 animals/group	Skin papilloma: 0/50, 0/49, 1/48, 4/50 No skin "cancers"	[NS]	Age at start: 8–9 wk Study poorly described
Mouse, SENCAR (M, F) 26 wk IARC (2013), Nesnow et al. (1982a, b)	Extracts of diesel engine exhaust particles from emissions of (A) a 1973 Nissan Datsun 220C, (B) a 1978 Oldsmobile 350, (C) a prototype VW turbo-charged Rabbit, or (D) a 1972 heavy-duty Caterpillar 3304; collected on Teflon-coated fibreglass filters, extracted with dichloromethane, and dissolved in acetone	Application of 0 (control), 0.1, 0.5, 1.0, 2.0, or 10.0 mg of extract/mouse in 0.2 mL of acetone to shaved dorsal surface, followed 1 wk later by treatment with 2 µg of TPA in 0.2 mL of acetone, twice/wk for 25 wk Positive control: B[*a*]P 40 animals/group	Diesel engine A: Skin papillomas/mouse: M: 0.08 (control), 0, 0.34, 0.38, 1.1, 5.5 F: 0.05 (control), 0.03, 0.39, 0.53, 1.6, 5.7 Skin squamous cell carcinoma: M: 0/37 (control) vs 12/38* (31%), high dose F: 1/38 (control) vs 14/38* (36%), high dose Diesel engines B, C, and D: Skin papillomas/mouse: M + F: 0.1–0.5 vs 0.05–0.08 in TPA controls	*[$P < 0.001$]	Age at start: 7–9 wk
Gasoline engine exhaust					
Mouse, SENCAR (M, F) 25 wk IARC (2013), Nesnow et al. (1982a,b, 1983)	Dichloromethane extract of gasoline engine exhaust particles from the emission of a 1977 Ford Mustang II-302 V8 engine with catalyst, collected on Teflon-coated fibreglass filters and dissolved in acetone	Single dose on shaved dorsal surface of 0 (control), 0.1, 0.5, 1.0, 2.0, or 3.0 mg of extract in 0.2 mL of acetone, followed 1 wk later by skin application of 2.0 µg of TPA in 0.2 mL of acetone, twice/wk for 25 wk 40 animals/group	Skin papilloma: M: 0% (control), 5%, 13%, 18%, 22%, 18% F: 5% (control), 13%, 18%, 10%, 21%, 23% Skin carcinoma: F: 0% (control), 20% (3.0 mg)	NR The authors stated that the responses at the higher doses were significantly higher than those in controls	Age at start: 7–9 wk

B[*a*]P, benzo[*a*]pyrene; bw, body weight; d, day or days; F, female; M, male; NR, not reported; NS, not significant; PM, particulate matter; TPA, 12-*O*-tetradecanoylphorbol-13-acetate; VW, Volkswagen; wk, week or weeks

Table 3.7 Veterinary epidemiology studies of components of outdoor air pollution

Species, strain (sex) Duration Reference	Test materials/ Type of samples	Dosing regimen Animals/group at start	Incidence of tumours	Statistical significance	Comments
Coal smoke and soot from household combustion of coal					
Dog, pet dogs (sex NR) 5 yr IARC (2010b, 2012a), Bukowski et al. (1998)	Coal smoke	Exposure to coal smoke resulting from indoor use of coal Case–control study between 1989 and 1993 129 cases and 176 controls	Sinonasal cancer Odds ratio, 4.24 (95% CI, 1.30–16.52)	Indoor use of coal is a risk factor for sinonasal cancer	Histopathology database at the University of Pennsylvania School of Veterinary Medicine Data on exposure, confounders, and behaviour were obtained by questionnaire and by telephone from veterinarians and owners
Wood smoke					
Dog, pet dogs (sex NR) 5 yr IARC (2010b), Bukowski et al. (1998)	Wood fires	Exposure to wood fires within a residence Case–control study between 1989 and 1993 129 cases and 176 controls	Sinonasal cancer Odds ratio, 1.58 (95% CI, 0.81–3.09)	NS	Histopathology database at the University of Pennsylvania School of Veterinary Medicine Data on exposures, confounders, and behaviour were obtained by questionnaire and telephone from veterinarians and owners More than 220 cumulative occurrences of exposure to wood fires

CI, confidence interval; NR, not reported; NS, not significant; yr, year or years

3.2 Inhalation studies of exposure to outdoor air

See Table 3.8.

A series of studies was conducted in São Paulo, Brazil, to determine the effect of inhaled outdoor air on the initiation and promotion of lung tumours in Swiss mice treated with or without the known carcinogen urethane. A second series of studies was conducted in Los Angeles, USA, on the induction of lung tumours in several strains of mice and one rat strain exposed to outdoor air. Descriptions of these studies are given below.

3.2.1 Mice exposed to outdoor air in São Paulo, Brazil

Cury et al. (2000) studied Swiss mice aged 15 days [sex was not reported] that were injected intraperitoneally twice within 48 hours with 3 g/kg body weight (bw) of the carcinogen urethane. The animals were then housed in cages in either a low-pollution area (in a house in the rural region of Atibaia) or a high-pollution area (a church tower in São Paulo) for 6 months before being killed. The outdoor air pollution in São Paulo is mainly due to vehicular traffic. [Methanol and ethanol, besides gasoline and diesel, are used as vehicle fuels in Brazil; see Section 1.] The authors stated that the mean levels of pollutants in São Paulo between 1994 and 1997 were as follows: 63.8 μg/m^3 ozone, 66.2 μg/m^3 PM with particles of aerodynamic diameter less than 10 μm (PM_{10}), 125 μg/m^3 nitrogen dioxide (NO_2), 4.4 ppm carbon monoxide (CO), and 21 μg/m^3 sulfur dioxide (SO_2). [It is unclear whether the study was performed between 1994 and 1997.] Pollutant levels in the rural area were not reported. There was an increase (P = 0.002) in lung "atypical" adenoma multiplicity (number of tumours per tumour-bearing animal). [These lesions exhibited cytological and architectural atypia, but no metastasis or invasion was found.] There was no increase in the multiplicity of lung adenoma or lung hyperplasia. [The Working Group noted that the study was limited by the fact that lung tumour incidence was not provided, that there was no clean air control group, and that numerical values of tumour multiplicity were not tabulated but were shown on a graph.]

In a similar study, the same group of investigators (Reymão et al., 1997) used the same exposure protocol, both for administration of urethane and for geographical sites of outdoor air pollution exposure (São Paulo and Atibaia), to conduct two experiments. The relative contributions of the different sources of PM in São Paulo were 40% from automotive, 10% from industrial, and 50% from other sources.

The first experiment was designed to determine whether outdoor air pollution acts as an initiator and/or a promoter of lung cancer. Eight groups of 25–50 Swiss mice (half male, half female) were studied. For one set of four groups of mice (50 per group), each group was exposed to outdoor air in either São Paulo or Atibaia for 2 months with or without prior intraperitoneal injections of urethane. For another set of four groups of mice (25 per group), each group was exposed to outdoor air in either São Paulo or Atibaia for 6 months and then returned to the laboratory "vivarium" [animal house at the University of São Paulo] for 2 months before being killed; two groups of these mice, exposed to either São Paulo air or Atibaia air, were injected with urethane at the beginning of the 2-month holding period. Animals exposed only to air pollution were considered as being tested for initiation of lung tumours; animals exposed to both urethane and air pollution were being tested for promotion of lung tumours initiated by urethane.

In the 2-month initiation studies, the incidences of lung adenoma (both sexes combined) were 6/50 for mice exposed to São Paulo air and 0/50 for mice exposed to Atibaia air. In the 6-month initiation studies, the incidences were 11/21 for São Paulo air and 0/20 for Atibaia air. [The Working Group found both results to be

Table 3.8 Studies of cancer in experimental animals exposed to outdoor air by inhalation

Species, strain (sex) Duration References	Dosing regimen Animals/group at start	Results	Statistical significance	Comments
Studies in mice exposed to outdoor air in São Paulo, Brazil				
Mouse, Swiss (NR) 6 mo Cury et al. (2000)	Animals housed in high-pollution area (São Paulo, $n = 48$) or low-pollution area (Atibaia, $n = 43$) for 6 mo Animals aged 15 d, injected intraperitoneally twice within 48 h with 3 g/kg bw urethane Mean levels (μg/m^3) in São Paulo: ozone, 63.8; PM_{10}, 66.2; NO_2, 125; SO_2, 21 CO, 4.4 ppm Pollutants in Atibaia NR	Significant increase in lung "atypical" adenoma multiplicity No increase in multiplicity of lung adenoma or hyperplasia	$P = 0.002$	Limited study: no clean air control group; no lung tumour incidence provided; numerical values of tumour multiplicity were not given but were shown on a graph Lung "atypical" adenoma exhibited cytological and architectural atypia, but no metastasis or invasion was found
Mouse, Swiss (M, F) 2–8 mo Reymão et al. (1997)	Experiment 1: Animals aged 15 d, injected intraperitoneally twice within 48 h with 3 g/kg bw urethane One set of 4 groups of mice (50/group) was exposed for 2 mo to outdoor air in São Paulo or Atibaia with or without prior intraperitoneal injections of urethane Another set of 4 groups of mice (25/group) was exposed for 6 mo to outdoor air in São Paulo or Atibaia, with or without urethane injections at beginning of 2 mo follow-up Similar number of M and F mice in each group	Lung adenoma: Experiment 1: Incidence for initiation study (without urethane): 2-mo exposure, 6/50* for São Paulo air, 0/50 for Atibaia air; 6-mo exposure, 11/21* for São Paulo air, 0/20 for Atibaia air Incidence for promotion study (with urethane): 2-mo exposure, 43/50* for São Paulo air, 30/50 for Atibaia air; 6-mo exposure, 17/20 for São Paulo air, 14/20 for Atibaia air The authors also stated that there was statistical significance for tumour promotion ($P = 0.005$), based on increased tumour multiplicity	*[$P < 0.05$]	Relative contributions of the different sources of PM in São Paulo: 40% from automotive, 10% from industrial, and 50% from other sources No tumour multiplicity values were provided Small number of animals and short duration of exposure for some groups
	Experiment 2: 4 groups of 50 mice each, urethane-treated, were exposed for 15, 30, 45, or 60 d to outdoor air in São Paulo. Another group of 50 animals was exposed for 60 d to outdoor air in Atibaia Half M, half F	Experiment 2: The authors stated that there was dose-dependency, based on increasing duration of exposure to São Paulo air related to increasing promotion of lung adenomas in mice exposed to urethane [no statistics given]. Lung adenoma incidence after exposure for 15, 30, 45, or 60 d in São Paulo was 13/26, 15/27, 33/39, and 34/39, respectively. The animals exposed for 60 d in Atibaia had a tumour incidence of 28/41	[$P_{trend} < 0.005$, positive trend for increased incidence]	Many early deaths within 3 d of urethane injection

Table 3.8 (continued)

Species, strain (sex) Duration References	Dosing regimen Animals/group at start	Results	Statistical significance	Comments
Mouse, Swiss (F) 2 mo Pereira et al. (2011)	100 mice were divided into 4 groups of 25 animals and housed in one of two chambers in São Paulo for 2 mo; half were injected intraperitoneally with urethane (3 g/kg bw) São Paulo outdoor air: 24.5 µg/m³ PM_{10}, 1.93 ppm CO, 116.72 µg/m³ NO_2, 14.47 µg/m³ SO_2 67.5% of $PM_{2.5}$ due to traffic; 42–70% ratio of carbon black to organic carbon One of two chambers had HEPA-filtered outdoor air (3 filters) [The Working Group assumed that there was no PM_{10} left in the exposure atmosphere] Mean concentration of $PM_{2.5}$ in chambers: 4.54 µg/m³ (filtered outdoor air); 17.66 µg/m³ (unfiltered outdoor air)	Mean number of lung adenomas/animal in urethane-treated mice was higher in the chamber with unfiltered air (4.0 ± 3.0) than in the chamber with filtered air (2.0 ± 2.0) No lung adenomas were observed in groups of animals not exposed to urethane	$P = 0.02$	There were no clean air-exposed groups
Studies in mice exposed to outdoor air in Los Angeles, USA				
Mouse, A, A/J, and C57 (M, F) Up to 15 mo Gardner (1966), Wayne & Chambers (1968)	4 exposure sites were used: University of Southern California Medical School, Burbank, and the Hollywood Freeway (all with high pollution levels) and Azusa (lower pollution level) Exposures from age 6 wk for 6–15 mo continuously A group of control mice was exposed to air that had passed through an activated charcoal filter, which removed O_3, NO_2, and PM > 0.3 µm Subsets of 30 animals/group were killed at monthly intervals at age 7–16 mo and examined for lung tumours	No differences between sexes were observed for incidences of pulmonary adenoma; consequently, data for both sexes were pooled In one experiment in A mice, there was a significant increase in the incidence of pulmonary adenoma in mice older than 12 mo if data from the Burbank and Azusa sites were combined*. Incidence rates: Burbank site, 55/124 vs 32/116 controls; Azusa site, 46/120 vs 34/121 controls. This response was not repeated in a second experiment. There was no effect at the medical school site (35/129 vs 41/131 controls). Data from the Hollywood Freeway site were incomplete A/J mice developed more pulmonary adenomas than A mice, but there was no difference in incidence between outdoor air-exposed and control A/J mice C57 mice had a pulmonary adenoma incidence of only 4/381, but all tumours were observed in mice exposed to outdoor air (4/194 vs 0/187 controls)	*$P < 0.01$	Study performed beginning in 1962 No precise information on PM was provided. Concentrations of CO, NO, NO_2, O_3, "particulates", and hydrocarbons provided. Concentrations for all sites were not very different Limited reporting of the study and inconsistent results

Table 3.8 (continued)

Species, strain (sex) Duration References	Dosing regimen Animals/group at start	Results	Statistical significance	Comments
Rat, Sprague-Dawley (M, F) Up to 28 mo Gardner et al. (1969)	Exposures were at the same sites as in the Gardner (1966) study (see above) Exposures from age 6 wk for either 4–5 mo (35–36 M and 29–31 F/group) or 27–28 mo (4–11 M and 5 F/group)	No lung tumours were observed in 92 controls and 153 outdoor air-exposed rats	NS	Study performed beginning in 1962 No precise information on PM was provided. Concentrations of CO, NO, NO_2, O_3, "particulates", and hydrocarbons provided. Concentrations for all sites were not very different Limited reporting of the study

bw, body weight; CO, carbon monoxide; d, day or days; F, female; h, hour or hours; HEPA, high-efficiency particulate air; M, male; mo, month or months; NO, nitrogen oxide; NO_2, nitrogen dioxide; NR, not reported; NS, not significant; O_3, ozone; PM, particulate matter; PM_{10}, particulate matter with particles of aerodynamic diameter < 10 μm; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 μm; SO_2, sulfur dioxide; wk, week or weeks

statistically significant ($P < 0.05$), although the number of animals was small in the 6-month study and the duration of exposure was short.] In the 2-month promotion studies, the incidences in the urethane-injected mice were 43/50 for São Paulo air and 30/50 for Atibaia air. [The Working Group found this result to be statistically significant ($P < 0.05$) but noted the short duration of exposure.] In the 6-month promotion studies, the incidences in the urethane-injected mice were 17/20 for São Paulo air and 14/20 for Atibaia air [not significant]. The authors stated that the promotion arm of the experiment was positive, based on an increase in lung tumour multiplicity that was statistically significant ($P = 0.005$). [The Working Group noted that numerical values of tumour multiplicity were not given.]

The second experiment was designed to determine whether the effect of outdoor air pollution on urethane-induced lung adenomas was dose-dependent. A group of Swiss mice aged 15 days was divided into five groups of 25 male and 25 female mice, all treated with intraperitoneal injections of urethane as previously described. One group was then sent to Atibaia for the duration of the experiment (60 days). The other four groups were exposed to outdoor air in São Paulo for 15, 30, 45, or 60 days, respectively. At the end of the designated exposure period, the four groups of mice were shipped to Atibaia for the remainder of the 60-day study. Only 172 of the 250 mice that started the experiment survived, due to early deaths from urethane within 3 days of injection of the drug. The authors reported a dose-dependent increase [no statistics were given], based on increasing duration of exposure to São Paulo air related to increasing promotion of lung adenomas in mice exposed to urethane. The incidences of lung adenoma after 15, 30, 45, or 60 days of exposure to São Paulo air were 13/26, 15/27, 33/39, and 34/39, respectively [positive trend, $P < 0.005$]. The incidence in the group of animals exposed for 60 days in Atibaia was 28/41.

In a later study by Pereira et al. (2011), 100 female Swiss mice were divided into four groups of 25 animals and housed for 2 months in one of two chambers in São Paulo. PM_{10} concentration in the outdoor air was 24.5 μg/m³. Half of the animals were treated with intraperitoneal injections of urethane as described above, and half were not. One of the chambers had filtered outdoor air containing a mean of 4.54 μg/m³ PM with particles of aerodynamic diameter less than 2.5 μm ($PM_{2.5}$), and the other chamber had unfiltered outdoor air with 17.66 μg/m³ $PM_{2.5}$. The mean number of lung adenomas per animal in the urethane-treated mice was significantly higher ($P = 0.02$) in the chamber with unfiltered air (4.0 ± 3.0) than in the chamber with filtered air (2.0 ± 2.0). [No lung tumour incidences were reported.]

3.2.2 Mice exposed to outdoor air in Los Angeles, USA

One study has been performed on the effect of outdoor air in Los Angeles, USA, in mice (Gardner, 1966; Wayne & Chambers, 1968). Gardner (1966) investigated whether outdoor air could induce lung tumours in several strains of mice exposed to Los Angeles outdoor air for 6–15 months, beginning in 1962. [The Working Group noted the limited reporting of all the publications, and especially that no precise information on PM was provided.] In the report by Gardner (1966), the experimental design was described as using three strains of mice: the lung tumour-susceptible A and A/J strains and the lung tumour-resistant C57 strain. The authors stated that four exposure sites were used, three of which had high pollution levels (University of Southern California Medical School, Burbank, and the Hollywood Freeway) and one of which had lower pollution levels (Azusa). With respect to describing outdoor air pollution, only concentrations of CO, nitrogen oxide, NO_2, ozone, "particulates", and hydrocarbons were given;

the concentrations for all sites were not very different. Exposures began at age 6 weeks and lasted for 6–15 months continuously. There were 10 animals per cage, segregated by sex. The exposed mice were housed in rooms with ventilation from the outdoor air; the unexposed (control) mice were held in rooms with air that had passed through an activated charcoal filter, which removed ozone, PM > 0.3 μm, and NO_2. The number of mice used varied by strain, with almost 2000 mice of the A strain and 600 of the C57 strain.

Subsets of 30 animals were randomly chosen from each atmosphere to be killed at monthly intervals beginning at age 7 months. Lung tissue was examined for tumours. No difference between sexes in tumour incidence was noted in either the outdoor air-exposed or control groups, and consequently data for both sexes were pooled. In a first experiment in strain A mice, there was a significant ($P < 0.01$) increase in the incidence of pulmonary adenoma in the outdoor air-exposed groups of animals older than 12 months if data from the Burbank and Azusa sites were combined. However, there was no significant increase in the incidence of pulmonary adenoma in mice exposed to outdoor air at the medical school site. Pooled incidence data for animals observed after 12 months were as follows: medical school site, 35/129 (controls, 41/131); Azusa site, 46/120 (controls, 34/121); Burbank site, 55/124 (controls, 32/116). [Data from the Hollywood Freeway site were incompletely reported.] In an additional experiment conducted 2 years later, there was no significant difference between the exposed and control groups. Results with the A/J strain of mice indicated a higher incidence of pulmonary adenoma in both the outdoor air-exposed and control groups compared with the incidence in strain A mice, but there was no difference in the incidences between the outdoor air-exposed and control A/J mice. As expected, a low incidence of pulmonary adenoma was found in C57 mice, but all of the tumours were found in the mice exposed to outdoor air (exposed, 4/194; controls, 0/187) (Gardner, 1966; Wayne & Chambers, 1968). [The Working Group noted the limited reporting and the inconsistent results, and found this study difficult to interpret.]

3.2.3 Rats exposed to outdoor air in Los Angeles, USA

In a study designed similarly to the one described in Section 3.2.2, male and female Sprague-Dawley rats were exposed at the same sites to Los Angeles outdoor air for 6–15 months, beginning in 1962 (Gardner et al., 1969). Rats were exposed continuously beginning at age 6 weeks and were killed after either 4–5 months or 27–28 months of exposure. No differences were noted in lifespan, body weight at death, or histology of lung tissue between the outdoor air-exposed and control groups. The total number of rats exposed to outdoor air was 287, of which 153 were examined for lung tumours. Control rats were exposed to charcoal-filtered air. There were 161 controls, of which 92 were examined for lung tumours. No lung tumours were observed in either group of animals. [The Working Group noted that the sensitivity to PM-induced lung carcinogenesis in this strain is unknown.]

3.3 Non-inhalation studies of exposure to outdoor air

See Table 3.9.

3.3.1 Intratracheal instillation

Ito et al. (1997) collected PM from urban outdoor air in Tokyo, Japan, and extracted the tar with dichloromethane. The tar (25 mg) was mixed with 4.25 mg of carbon [not further described] and suspended in saline. Four groups of 5 male Fischer 344 rats (age, 5 weeks) were administered the tar–carbon mixture (1 mg in 0.2 mL of saline) once a week for 4 consecutive

Table 3.9 Non-inhalation carcinogenicity studies of outdoor air particulates and extracts in experimental animals

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	For each target organ: incidence (%) and/or multiplicity of tumours	Statistical significance	Comments
Intratracheal instillation				
Rat, F344 (M) 18 mo Ito et al. (1997)	Particulates were collected from urban outdoor air and tar was extracted with dichloromethane. 25 mg of tar extract was mixed with 4.25 mg of carbon and suspended in 0.8 mL of saline 4 groups of 5 rats (age, 5 wk) were administered the tar–carbon mixture (1 mg/0.2 mL) by intratracheal instillation once/wk for 4 wk and exposed to the following gases for 11 mo: group A, 6 ppm NO_2 + 4 ppm SO_2; group B, 6 ppm NO_2; group C, 4 ppm SO_2; group D, filtered air Group E (control) rats (n = 5) were injected intratracheally with 1 mg of carbon suspended in 0.2 mL of saline once/wk for 4 wk and housed in filtered air for 18 mo Group F (untreated control) rats (n = 5) were housed in filtered air for 18 mo	Mean incidence of PEC hyperplasia (number of lesions/lung volume): Group A: 378 ± 105/cm³ * Group B: 372 ± 104/cm³ * Group C: 349 ± 126/cm³ * Group D: 376 ± 146/cm³ * Group E: 200 ± 75/cm³ Group F: 194 ± 105/cm³ A few PEC papillomas were found in all groups of tar-treated rats and not in controls; however, the incidences (22–33/cm³) were not statistically significant	*$P < 0.05$ — —	Small number of animals The relevance of PEC hyperplasia and papilloma to cancer is not known No detailed information on outdoor air pollutants was reported
Subcutaneous injection				
Mouse, C3H (M) 12 mo Leiter et al. (1942)	Outdoor air particulates from 6 sites in the USA were suspended in saline. Mice received a single subcutaneous injection containing ~20 mg of dust 6 groups of 20 M C3H mice (age, 2–3 mo); 120 in total	For pooled exposed groups Pulmonary tumours: 5/60 (8%) Hepatoma: 8/60 (13%) No injection-site sarcomas	Tumour incidence in treated mice was not greater than the incidence in historical controls (see comments)	Study was poorly designed and reported. Old age of animals. Short duration Saline-injected controls were not included Tumour types were not further specified. Spontaneous tumour incidence NR No detailed information on outdoor air pollutants was reported

Table 3.9 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	For each target organ: incidence (%) and/or multiplicity of tumours	Statistical significance	Comments
Mouse, strain A (M, F) Mouse, C3H (M) 12 mo Leiter et al. (1942)	Outdoor air particulates from 6 sites in the USA were extracted with benzene, the benzene was removed, and the tar was suspended in tricaprylin. There were 8 tar extracts. 8 groups of 20 M C3H mice and 10 M and 10 F strain A mice received a single subcutaneous injection of extract containing 21–71 mg of tar 20 M C3H controls were injected with tricaprylin 30 strain A mice (sex NR) were kept as untreated controls	For pooled exposed groups Injection-site sarcoma: C3H (M): 10/154 (7%) Strain A (M, F): 4/126 (3%) Control C3H (M): 0/16 (0%) Pulmonary tumours: C3H (M): 5/81 (6%) Control C3H (M): 0/16 (0%) Strain A (M, F): 51/78 (65%) Control strain A: 5/10 (50%) Hepatoma: C3H (M): 21/81 (26%) Control C3H (M): 2/16 (13%)	[Fisher exact test, 1-tailed] [NS] [NS] — [NS] — [NS] — [NS] —	Study was poorly designed and reported. Old age of animals. Short duration Tumour types were not further specified Hepatoma incidence in treated M C3H mice (26%) was not greater than the incidence in M C3H historical controls No detailed information on outdoor air pollutants was reported
Mouse, C57BL/6 (M, F) Mouse, C3H (M) 24 mo Hueper et al. (1962)	Monthly subcutaneous injections of extracts of outdoor air dusts from 8 cities in the USA (Atlanta, Birmingham, Cincinnati, Detroit, Los Angeles, Philadelphia, New Orleans, San Francisco). C57 mice were injected with the crude benzene extract (4 mg) or the aromatic fraction (obtained from 4 mg); these doses were doubled after 11 mo. C57 and C3H mice received either oxygenated (0.5 mg) or aliphatic (1 mg) fractions Vehicle control (C57, 36/group/sex) Crude benzene extract (36/group/sex) Aromatic fraction (C57, 36/group/sex) Aliphatic fraction (C57 [sex NR] and C3H, 50/group) Oxygenated fraction (C57 [sex NR] and C3H, 50/group)	For pooled exposed groups Injection-site tumours: Vehicle control (pooled), C57: 0/31 (0%) Crude benzene, C57: 26/576 (4.5%)* Aromatic, C57: 12/576 (2.1%) Aliphatic, C57: 2/372 (0.5%) Aliphatic, C3H: 2/372 (0.5%) Oxygenated, C57: 5/392 (1.3%) Oxygenated, C3H: 7/392 (1.8%)	[Fisher exact test, 1-tailed] — *[$P < 0.05$] [NS] [NS] [NS]	Majority of tumours were sarcomas and fibrosarcomas Study poorly designed and reported No detailed information on outdoor air pollutants was reported No C3H mice controls

Table 3.9 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	For each target organ: incidence (%) and/or multiplicity of tumours	Statistical significance	Comments
Mouse, Swiss ICR/Ha (newborn) (M, F) 50–52 wk Epstein et al. (1966)	PM from outdoor air in 6 cities in the USA (Chicago, Cincinnati, Los Angeles, Philadelphia, New Orleans, Washington DC) was extracted with benzene 6 groups were injected subcutaneously with the extracts on d 1, 7, and 14 after birth *n* = 105–137/group (M + F) Tricaprylin vehicle control, *n* = 190 (M + F)	For pooled exposed groups Hepatoma: Control (M): 3/67 (4%) Treated (M): 37/85 (44%) Control (F): 0/68 (0%) Treated (F): 1/143 (0.7%) Pulmonary adenoma (multiple): Control (M): 0/67 (0%) Treated (M): 49/85 (58%) Control (F): 0/68 (0%) Treated (F): 55/143 (38%)	[Fisher exact test, 1-tailed] — [$P < 0.0001$] — [NS] — [$P < 0.0001$] — [$P < 0.0001$]	High mortality (29–61%) before weaning, due to acute toxicity Higher incidence of deaths after weaning in treated M mice than in controls, due to obstructive uropathy Due to lack of material, some animals of 2 groups received 2 injections only (15 mg) Tumour types were not further specified No detailed information on outdoor air pollutants was reported Short duration of the experiment Controls were untreated (*n* = 90) or injected with tricaprylin (*n* = 100)
Mouse, Swiss ICR/Ha (M, F) (pre-weaned) 49–52 wk Epstein et al. (1979)	Groups of mice were injected subcutaneously with 0.1 mL (10 mg), 0.1 mL (10 mg), and 0.2 mL (20 mg) of benzene extract of a composite of air particulates (from several cities in the USA, collected in 1962) on d 1, 7, and/or 14 after birth. Various dosing sequences were used. Total doses were 1.1–8.3 mg/g bw *n* = 89–233/group Tricaprylin vehicle controls, *n* = 100; untreated controls, *n* = 90	For pooled groups Pulmonary adenoma (single): Controls: M: 9/76 (12%) F: 4/73 (5%) Treated: M: 58/334 (17%) F: 39/304 (13%) Pulmonary adenoma (multiple): Controls: M: 0/76 (0%) F: 0/73 (0%) Treated: M: 28/334 (8%) F: 43/304 (13%)	[Fisher exact test, 1-tailed] — — [NS] [NS] — — [$P = 0.0026$] [$P < 0.0001$]	Treated mice aged 1 d and 7 d were generally more prone than treated mice aged 14 d to the development of pulmonary adenomas High mortality (13–61%) before weaning, due to acute toxicity. Relatively higher mortality in M mice, due to non-treatment-related obstructive uropathy No detailed information on outdoor air pollutants was reported. Short duration of the experiment No hepatocellular tumours in F mice

Table 3.9 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	For each target organ: incidence (%) and/or multiplicity of tumours	Statistical significance	Comments
Mouse, Swiss ICR/Ha (M, F) (pre-weaned) 49–52 wk Epstein et al. (1979) (cont.)		Pulmonary adenocarcinoma: Controls: M: 0/76 (0%) F: 0/73 (0%) Treated: M: 18/334 (5%) F: 14/304 (5%) Hepatocellular carcinomas and neoplastic nodules (combined): Controls (M): 3/76 (4%) Treated (M): 26/334 (8%)	 — — [$P = 0.0229$] [$P = 0.0463$] — [NS]	
Mouse, CFW white Swiss (sex NR) Up to 1 yr Rigdon & Neal (1971)	Samples ($n = 15$) of airborne PM were collected near a petrochemical industrial area in Texas City, Texas, USA, from 1965 to 1969. Samples ($n = 11$) were also collected from non-industrial areas. Benzene-soluble components were extracted from the samples. Mice (4–69/group) were injected subcutaneously with 1–20 mg of extracts in cottonseed oil. Vehicle controls ($n = 47$) received only cottonseed oil. Animals were killed when a tumour was observed	For pooled exposed groups Fibrosarcomas: Industrial-area samples (1965–1968): 4/269 (1.5%) Industrial-area samples (1969): 95/232 (41%) Non-industrial area samples (1966–1969): 4/359 (1.1%) Vehicle controls: 0/47 (0%)	 [Fisher exact test, 1-tailed] [NS] [$P < 0.0001$] [NS] —	Short duration of the experiment Non-industrial areas were mainly located in the state of Texas, USA.
Mouse, Swiss ICR/Ha (newborn) (M, F) 49–51 wk Asahina et al. (1972)	Airborne PM was collected on air-conditioner filters in New York City and extracted with benzene, and the crude extract was fractionated. Mice (44–73/group) were injected subcutaneously with the benzene extract or fractions suspended in tricaprylin (25, 50, or 100 mg/mL) on d 1, 7, and 14 after birth, resulting in total doses of 10, 20, or 40 mg/animal. Controls received tricaprylin ($n = 86$) or were not injected ($n = 81$). Surviving mice were necropsied at age 49–51 wk	For pooled exposed groups Any tumours: M mice: Untreated controls: 0/23 (0%) Vehicle controls: 5/31 (16.1%) Benzene extract: 11/39 (28.2%) Acidic fraction: 2/31 (6.5%) Basic fraction: 13/28 (46.4%) Neutral fraction: 13/68 (19.1%) Aliphatic fraction: 8/67 (11.9%)	 — — NS NS $P < 0.05$ NS NS	Study was compromised by high mortality after weaning in all M mice, due to non-treatment-related obstructive uropathy. High incidence of hepatomas [mainly hepatocellular tumours] in M mice in the basic fraction-treated group and slightly fewer in the benzene extract-treated group. High incidence of pulmonary adenoma in the basic, neutral, aromatic, and oxyneutral fraction-treated groups

Table 3.9 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	For each target organ: incidence (%) and/or multiplicity of tumours	Statistical significance	Comments
Mouse, Swiss ICR/Ha (newborn) (M, F) 49–51 wk Asahina et al. (1972) (cont.)		Aromatic fraction: 17/76 (22.4%)	NS	High mortality before weaning in high-dose groups treated with benzene extract and acidic and basic fractions. Short duration of the experiment
		Oxyneutral fraction 9%: 18/35 (32.7%)	NS	
		Oxyneutral fraction 12%: 17/72 (23.6%)	NS	
		Oxyneutral fraction 36%: 11/50 (22.0%)	NS	
		Insoluble fraction: 9/58 (15.5%)	NS	
		F mice:		
		Untreated controls: 1/23 (4.3%)	—	
		Vehicle controls: 3/35 (8.6%)	—	
		Benzene extract: 6/48 (12.5%)	NS	
		Acidic fraction: 0/23 (0%)	NS	
		Basic fraction: 10/23 (43.5%)	$P < 0.05$	
		Neutral fraction: 11/53 (20.8%)	NS	
		Aliphatic fraction: 21/66 (31.8%)	$P < 0.05$	
		Aromatic fraction: 33/81 (40.7%)	$P < 0.01$	
		Oxyneutral fraction 9%: 15/59 (25.4%)	NS	
		Oxyneutral fraction 12%: 23/65 (35.4%)	$P < 0.01$	
		Oxyneutral fraction 36%: 10/41 (24.4%)	NS	
		Insoluble fraction: 10/58 (17.2%)	NS	
Mouse, NMRI (F) Up to 24 mo Pott et al. (1980), Pott & Stöber (1983)	Benzene extracts of airborne PM from 3 urban sites (Duisburg-Neuenkamp, Duisburg-Hamborn, Düsseldorf) and one rural site (Krahm) in western Germany were injected subcutaneously once Doses were based on the B[*a*]P content of the extracts (0.16, 0.63, 2.5, and 10 µg/mouse). Controls were injected with tricaprylin vehicle 76–80/group	Injection-site tumours [sarcomas]: Duisburg-Neuenkamp: 18.3%, 31.7%, 65.5%, 68.3%; Duisburg-Hamborn: 10.3%, 31.7%, 53.3%, 61.0%; Düsseldorf: 16.7%, 25.9%, 46.7%, 39.0%; Krahm: 10.3%, 20.0%, 20.7%, 20.0% Tricaprylin controls, 1.7%		Exact numbers of mice per group NR Tumour incidences NR, only percentages Sampling period: winter 1975–1976 In the same study, a second experiment with an almost identical design in 3 urban sites and 2 rural sites in western Germany gave similar results

Table 3.9 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	For each target organ: incidence (%) and/or multiplicity of tumours	Statistical significance	Comments
Mouse, Jcl:ICR (M, F) (newborn) Up to 12 mo Sasaki et al. (1987)	Air particulates were collected from a central urban area of Tokyo and extracted with benzene–ethanol. Neutral, acidic, and basic fractions were obtained. The crude extract or the fractions (10 mg in olive oil) were injected subcutaneously into newborn mice. Controls were injected with olive oil. 90 M and 77 F mice were killed at age 3, 6, or 12 mo Initial number of mice per group NR	Pulmonary adenomas: Crude extract: M: 3/20 (15%) F: 1/5 (20%) Neutral fraction: M: 5/9 (56%) F: 2/16 (13%) Basic fraction: M: 1/6 (17%) F: 0/5 (0%) Acidic fraction: M: 0/10 (0%) F: 0/10 (0%) Vehicle controls: M: 1/22 (4.5%) F: 1/17 (6%)	[Fisher exact test, 1-tailed] [NS] [NS] [$P = 0.0039$] $P < 0.01$, χ^2 test [NS] [NS] [NS] [NS] — —	High mortality before weaning in all groups, especially mice injected with the acidic and basic fractions Low and variable numbers of surviving mice Short duration of the experiment No detailed information on outdoor air pollutants was reported
Skin application				
Mouse C57BL/6 (M, F) > 15 mo Kotin et al. (1954b)	Benzene extracts of outdoor air particulates Skin application, 3 ×/wk ($n = 76$) Benzene control ($n = 69$)	Skin papilloma: 0/37 (control); 13/31* (42%; 9/13 also had squamous carcinomas**)	[Fisher exact test, 1-tailed] *[$P < 0.0001$] **[$P < 0.001$]	Outdoor air particulates obtained in an industrial area during the smoggy season and in a high-traffic area during the non-smoggy season in Los Angeles County, USA M and F mice were combined. Exposed groups were pooled An unspecified number of mice died early due to toxicity and intercurrent infection

Table 3.9 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	For each target organ: incidence (%) and/or multiplicity of tumours	Statistical significance	Comments
Mouse, CBA (M, F) Mouse, C57BL/Gr (M, F) Mouse, A/Gr_f (M, F) Mouse, C57BL/How (M, F) Up to 13.5 mo Clemo et al. (1955)	3 fractions (A, B, C) of city smoke extract diluted to 1% in benzene. Controls received benzene only Skin application 3 ×/wk for 13.5 mo, or until malignant skin tumour was observed or animal died 1–6 mice/strain/group	For pooled groups Lung nodules [not further described]: Fraction A: 5/14 (36%) Fraction B: 6/15 (40%) Fraction C: 1/16 (6%) Benzene controls: 1/21 (5%) Skin papillomas: Fraction A: 0/14 (0%) Fraction B: 9/15 (60%) Fraction C: 5/16 (33%) Benzene controls: 0/21 (0%) Skin epitheliomas: Fraction A: 0/14 (0%) Fraction B: 5/15 (33%) Fraction C: 6/16 (38%) Benzene controls: 0/21 (0%)	 [Fisher exact test, 1-tailed] [$P = 0.0278$] [$P = 0.013$] [NS] — [$P = 0.0008$] [$P = 0.01$] — [$P = 0.008$] [$P = 0.0034$] —	M and F treated mice of all strains were combined M and F control mice of all strains were combined Small number of animals and poor study design. Use of old animals (aged 2.5–9.5 mo)

Table 3.9 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	For each target organ: incidence (%) and/or multiplicity of tumours	Statistical significance	Comments
Mouse, Kunming (F) 28 wk Guan et al. (1990)	Particle samples collected from outdoor air in Beijing, Taiyuan, and Xuanwei (China) in winter were separated into two fractions: ≥ 3.3 μm and < 3.3 μm. The particulates were extracted with dichloromethane Mice were treated with 5 mg of particle extracts (in acetone) by skin application once (5 mg group) or twice (10 mg group: 5 mg applied on d 1 and 2). From the second wk, mice were treated with 2.0 μg of TPA twice/wk for 26 wk and observed for skin papilloma development until experimental wk 28	Skin papillomas: Beijing samples: Samples with particles ≥ 3.3 μm: 5 mg group: 4/19 (21.1%) Samples with particles < 3.3 μm: 5 mg group: 16/40 (40.0%) 10 mg group: 20/36 (55.6%) Control group, acetone: 4/38 (10.5%) Taiyuan samples: Samples with particles ≥ 3.3 μm: 5 mg group: 9/30 (30.0%) Samples with particles < 3.3 μm: 5 mg group: 25/39 (64.1%) 10 mg group: 22/39 (56.4%) Control group, acetone: 4/38 (10.5%) Xuanwei samples: Samples with particles ≥ 3.3 μm: 5 mg group: 17/36 (47.2%) 10 mg group: 24/39 (61.5%) Samples with particles < 3.3 μm: 5 mg group: 25/39 (64.1%) 10 mg group: 26/39 (66.7%) Control group, acetone: 4/38 (10.5%)	 [Fisher exact test, 1-tailed] [NS] [$P = 0.015$] [$P < 0.0001$] — [$P = 0.0431$] [$P < 0.0001$] [$P < 0.0001$] — [$P = 0.0005$] [$P < 0.0001$] [$P < 0.0001$] [$P < 0.0001$] —	For all 3 locations, the first papilloma was observed at 10 wk for particles < 3.3 μm

Table 3.9 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	For each target organ: incidence (%) and/or multiplicity of tumours	Statistical significance	Comments
Mouse, BALB/c (M, F) 35 wk Zhao et al. (2003)	Skin application of dichloromethane extracts of outdoor air particulates from 4 sites in Shanghai 5 mg (single application) or 10 mg (2 mg/d for 5 d) Vehicle control: 0.2 mL of acetone (single application) From 1 wk after initiation, TPA (2 µg in 0.2 mL of acetone) was applied dermally twice/wk for 30 wk 20/group/sex/extract	Skin papilloma (M): Controls, acetone: 0/40 (0%) 5 mg dose: 1/79 (1.3%) 10 mg dose: 9/75 (12%) Positive controls: 11/18 (61%) Skin papilloma (F): Controls, acetone: 0/40 (0%) 5 mg dose: 1/79 (1.3%) 10 mg dose: 1/80 (1.2%)	[Fisher exact test, 1-tailed] — [NS] [$P = 0.0179$] [Fisher exact test, 1-tailed] — [NS] [NS]	Incidences were combined for the 4 extracts
Mouse, [Sv/129] $AhR^{+/+}$ or $AhR^{-/-}$ (F) 58 wk Matsumoto et al. (2007)	PM from outdoor air (from the city of Sapporo, Japan) by skin application once/wk; 6.4 mg of particulate extract in 200 µL of acetone $AhR^{+/+}$ ($n = 17$), $AhR^{-/-}$ ($n = 15$)	Skin squamous cell carcinoma: $AhR^{-/-}$: 0/15 (0%) $AhR^{+/+}$: 8/17 (47%)	— $P < 0.01$	The samples were stored from 1988 to 2007. No clean air-exposed control groups. Extracts contained B[*a*]P and other PAHs
Intravenous injection				
Mouse, strain A (sex NR) 4 mo Leiter et al. (1942)	Groups of mice received a single intravenous injection (tail vein) with outdoor air particulates from 6 sites in the USA. Dusts were suspended in saline (2.5 mg/0.25 mL). Controls were untreated Treated: 20–30/group Untreated controls: 20	Pulmonary tumours: Controls: 3/20 (15%) Treated: 15/138 (11%)	NS	The methods and results of this older study were poorly reported. Study duration was short. No detailed information on outdoor air pollutants was reported. Groups of treated mice were combined

Table 3.9 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	For each target organ: incidence (%) and/or multiplicity of tumours	Statistical significance	Comments
Intraperitoneal injection				
Mouse, NMRI (M) (newborn) 52 wk Heussen et al. (1996)	Outdoor air particulates from a non-industrial site (Wageningen, The Netherlands) were extracted with benzene, benzene was removed, and the extract was resuspended in propylene glycol. Mice were injected intraperitoneally on d 1, 8, and 15 after birth with 1.95 mg or 3.9 mg of extract. Controls were injected with propylene glycol Controls, *n* = 52 Extract (1.95 mg), *n* = 49 Extract (3.9 mg), *n* = 47	Bronchioloalveolar tumours: Controls: 16/52 (30.8%) 1.95 mg dose: 10/49 (20.4%) 3.9 mg dose: 17/47 (36.2%)	NS NS	No deaths occurred before weaning No significant difference in mortality between groups Short duration of the study. No detailed information on outdoor air pollutants was reported

AhR, aryl hydrocarbon receptor; B[*a*]P, benzo[*a*]pyrene; bw, body weight; d, day or days; F, female; h, hour or hours; M, male; mo, month or months; NO_2, nitrogen dioxide; NR, not reported; NS, not significant; PAHs, polycyclic aromatic hydrocarbons; PEC, pulmonary endocrine cell; PM, particulate matter; SO_2, sulfur dioxide; TPA, 12-*O*-tetradecanoylphorbol-13-acetate; wk, week or weeks; yr, year or years

weeks by intratracheal injection [instillation]. Groups of instilled rats were also exposed by inhalation for 11 months to (group A) a mixture of 6 ppm NO_2 + 4 ppm SO_2, (group B) 6 ppm NO_2, (group C) 4 ppm SO_2, or (group D) filtered air. A control group (n = 5) received an intratracheal instillation of carbon suspension (1 mg in saline) once a week for 4 weeks and was housed in filtered air for 18 months. Untreated control rats (n = 5) received no treatments and were housed in filtered air for 18 months. At 18 months, rats were killed and the incidence of pulmonary endocrine cell (PEC) hyperplasia and the incidence of PEC papilloma were estimated as the number of observed lesions per lung volume. The mean incidences of PEC hyperplasia were significantly greater ($P < 0.05$) in animals treated with tar (groups A–D) relative to both control groups. Exposure to NO_2 and/or SO_2 did not promote hyperplasia or papilloma formation. A few PEC papillomas were found in animals treated with the tar extract (groups A–D) (not statistically significant); no papillomas were detected in controls. [The relevance of PEC hyperplasia and papilloma to cancer is not known. The Working Group noted the small number of animals. The study was judged inadequate for the evaluation.]

3.3.2 Subcutaneous injection

PM from outdoor air was collected by various methods at six sites in the USA: in Chelsea, Massachusetts, in Pittsburgh, Pennsylvania, and at four sites in the Holland Tunnel, which connects New York City and Jersey City (Leiter et al., 1942). In six groups of 20 male C3H mice (age, 2–3 months), each mouse received a single subcutaneous injection in the right axilla with one of six dust samples (~20 mg) suspended in 0.9% saline containing a small amount of emulsifying agent (dioctyl ester of sodium sulfosuccinate). The study was terminated 12 months after injection. Of the initial 120 treated mice, 60 were alive at 12 months. Of the 60 treated mice, 5 (8%) had pulmonary tumours and 8 (13%) had hepatomas. [Tumour types were not further specified.] The authors stated that incidences of pulmonary tumours in treated mice were not higher than the incidence of spontaneous pulmonary tumours in untreated mice of a subline of C3H mice [spontaneous tumour incidence was not reported]. [No detailed information on outdoor air pollutants was reported. No saline-injected control group was included. The Working Group noted the old age of the animals at the start of the experiment and the short duration of the experiment. The study was judged inadequate for the evaluation.]

Leiter et al. (1942) also evaluated the carcinogenicity of eight tar fractions collected from the six outdoor air PM samples. The samples were extracted with benzene followed by ethyl ether. The solvents were removed by evaporation and the tar extract collected. Groups of 20 male C3H mice and 10 male and 10 female strain A mice (all aged 2–3 months) received a single subcutaneous injection of the tar extracts at doses ranging from 21 mg to 71 mg suspended in tricaprylin vehicle. [No attempt was made to use equal doses.] A vehicle control group of 20 male C3H mice received a single subcutaneous injection of tricaprylin. A group of 30 untreated strain A mice was kept for determining the spontaneous tumour incidence. The study was terminated 12 months after injection. Over the 12 months after injection of tars, 10 sarcomas were found in an effective total of 154 treated male C3H mice (7%), in contrast to 4 sarcomas in 126 treated strain A mice (3%). All sarcomas in strain A mice occurred in male mice. There were no injection-site sarcomas in vehicle controls. [Incidences of sarcomas in male C3H and strain A mice were not significantly different from the incidence in controls.] The incidence of pulmonary tumours [tumour type was not further specified] was 5/81 (6%) [not statistically significant] in treated C3H mice compared with 0/16 in C3H controls. Treated C3H mice (21/81 [26%]) also developed hepatomas [tumour type was not

further specified]; however, the incidence was not significantly different from that in vehicle control C3H mice (2/16 [13%]). The authors stated that the incidence of hepatomas in treated male C3H mice was not different from the incidence of spontaneous hepatomas in untreated male C3H mice [the incidence of spontaneous hepatomas was not reported]. Pulmonary tumours [tumour type was not further specified] were present in 51/78 (65%) strain A mice injected with tar extracts and in 5/10 (50%) untreated control strain A mice [not significantly different]. [This older study was not adequately designed and reported. No detailed information on outdoor air pollutants was reported. The Working Group noted the old age of the animals at the start of the experiment and the short duration of the experiment. The study was judged inadequate for the evaluation.]

Hueper et al. (1962) collected atmospheric dusts from eight cities in the USA and extracted the PM with benzol (benzene). The crude benzene extract was further fractionated to obtain aromatic, oxygenated, and aliphatic fractions. Groups of 36 male and 36 female C57BL/6 mice (age, 2 months) were injected subcutaneously (nape of the neck) once a month with either the crude extract (4 mg in 0.1 mL of tricaprylin) or the aromatic fraction obtained from 4 mg of crude extract (in 0.1 mL of tricaprylin vehicle). [The actual dose (mg) of the aromatic fraction was not reported.] These doses were doubled after 11 months. The oxygenated (0.5 mg in 0.1 mL of tricaprylin) and aliphatic (1.0 mg in 0.1 mL of ethyl laurate) fractions were also administered to groups of 50 C57BL/6 mice [sex was not reported] and 50 C3H mice [male] once a month by subcutaneous injection. Groups of 36 male and 36 female control C57BL/6 mice were injected subcutaneously with 0.1 mL of tricaprylin or ethyl laurate once a month. After 24 months, all the particulate extracts except one caused injection-site tumours (primarily sarcomas and fibrosarcomas). Compared with C57BL/6 controls, the tumour incidence was higher in C57BL/6 mice receiving the crude benzene extract (26/576 [4.5%]) [$P < 0.05$] and the aromatic fraction (12/576 [2.1%]) [not significant]. Tumour incidences in male and female C57BL/6 mice (combined) injected with the oxygenated or aliphatic fractions were 5/392 (1.3%) and 2/372 (0.5%), respectively [not significant]. In male and female C3H mice (combined), the tumour incidences were 7/392 (1.8%) with the oxygenated fraction and 2/372 (0.5%) with the aliphatic fraction. None of the C57BL/6 control mice (0/31) had tumours after 12 months. [Tumour incidences in mice treated with the oxygenated and aliphatic fractions were not statistically different from that in controls.] [The experiments were not well designed and reported. No detailed information on outdoor air pollutants was reported. There were no C3H control mice.]

Male and female newborn Swiss ICR/Ha mice (105–137 per group) were injected subcutaneously (nape of the neck) with benzene-soluble extracts of organic atmospheric particulates collected from six cities in the USA (Epstein et al., 1966). Mice received 5 mg of extract in 0.05 mL of tricaprylin on the day of birth, 10 mg in 0.1 mL on day 7, and 10 mg in 0.1 mL on day 14 after birth. Control mice (n = 190) were untreated (n = 90) or injected with the tricaprylin vehicle only (n = 100). The final injection was omitted for some animals of two groups because of a lack of material; these mice received only 15 mg. Mortality before weaning was high (29–61%) in all treated groups (16% in controls), and deaths after weaning were higher in treated males than in controls, due to obstructive uropathy. At age 50–52 weeks, the overall incidence of hepatomas [tumour type was not further specified] in treated male mice (37/85 [44%]) was significantly greater [$P < 0.0001$] than that in controls (3/67 [4%]), but the difference in incidence was not statistically significant in female mice. A significantly increased overall incidence of pulmonary adenoma (multiple) was observed in treated male

(49/85 [58%]) [$P < 0.0001$] and female (55/143 [38%) [$P < 0.0001$] mice relative to controls (male, 0/67; female, 0/68). In addition, there was a small incidence of lymphomas in groups of treated mice (up to 18.5%), compared with 0–1.5% in controls. [The Working Group noted the short duration of the experiment and the high mortality. No detailed information on outdoor air pollutants was reported.]

In a subsequent study (Epstein et al., 1979), atmospheric particulates collected in 1962 from several cities in the USA were combined and extracted with benzene, and the extracts were suspended in tricaprylin (100 mg/mL). Groups of pre-weaned male and female Swiss ICR/Ha mice were injected subcutaneously (nape of the neck) with 10 mg, 10 mg, and 20 mg of extract suspension on day 1, 7, and/or 14 after birth, respectively. Two control groups were either untreated ($n = 90$) or were injected subcutaneously with tricaprylin vehicle on days 1, 7, and 14 ($n = 100$). The animals were injected using various dosing sequences. Total doses were 1.1–8.3 mg/g bw. The study was terminated at 49–52 weeks. Mortality ranged from 13% to 61% in the various test groups. Groups injected on day 1 had the highest mortality. In addition, a relatively high mortality was observed in male mice, due to non-treatment-related obstructive uropathy. The tumour incidences in both sexes were dose-related in all test groups. The incidences of pulmonary adenoma (single) in all exposed groups combined were 58/334 (17%) in male mice [not statistically significant] and 39/304 (13%) in female mice [not statistically significant]; corresponding values for control groups were 9/76 (12%) in male mice and 4/73 (5%) in female mice. There was a significantly increased incidence of pulmonary adenoma (multiple) in treated male (28/334 [8%]) [$P = 0.0026$] and female (43/304 [13%]) [$P < 0.0001$] mice relative to controls (male, 0/76; female, 0/73). A significantly increased incidence of pulmonary adenocarcinoma was observed in treated male (18/334 [5%]) [$P = 0.0229$] and female (14/304 [5%]) [$P = 0.0463$] mice relative to controls (male, 0/76; female, 0/73). Hepatocellular tumours were observed only in male mice and were not dose-related. The incidence of hepatocellular carcinomas and neoplastic nodules (combined) in male mice of all exposed groups combined was 26/334 (8%) [not statistically significant] and in control male mice was 3/76 (4%). [The Working Group noted that the study duration was short. The study was compromised by the high mortality, due to acute toxicity in treated groups and non-treatment-related uropathy in male mice.]

Rigdon & Neal (1971) collected samples of airborne PM near a petrochemical industrial area in Texas City, Texas, USA, and from non-industrial areas at various times between 1965 and 1969. Benzene-soluble extracts were obtained from the samples. Groups of 4–69 CFW white Swiss mice ("usually 30 to 50 days old") [sex was not reported] were injected subcutaneously with 1–20 mg of the various benzene-soluble extracts in 0.5 mL of cottonseed oil vehicle. Controls ($n = 47$) were injected with 0.5 mL of cottonseed oil vehicle. Animals were kept for up to 1 year and were killed when a tumour was observed. After injection of industrial-area samples (1–10 mg) collected from 1965 to 1968, in mice of pooled exposed groups only 4/269 (1.5%) developed fibrosarcomas. The incidence was not significantly different from that in vehicle controls (0/47). Injection of industrial-area samples (2.5–10 mg) collected in 1969 resulted in a significantly increased [$P < 0.0001$] incidence of fibrosarcomas (pooled exposed groups; 95/232 [41%]) relative to that in vehicle controls. Benzene-soluble extracts of PM collected from non-industrial areas did not cause a statistically significant increase in fibrosarcomas (pooled exposed groups; 4/359 [1.1%]). [The Working Group noted the short duration of the experiment.]

In the study of Asahina et al. (1972), groups of 44–73 male and female newborn Swiss ICR/Ha mice were injected subcutaneously with extracts

of particulates collected on air-conditioner filters in New York City. Crude benzene extracts of the particulates were fractionated into acidic, basic, neutral, aliphatic, aromatic, water-ether insoluble, and oxygenated (oxyneutral, pentane-9%, -12%, or -36% ether) fractions. The extracts and fractions were resuspended in tricaprylin at concentrations of 25, 50, and 100 mg/mL. Mice aged 1, 7, and 14 days were injected with 0.1 mL (days 1 and 7) and 0.2 mL (day 14) of suspension, resulting in total doses of 10, 20, or 40 mg. Controls consisted of newborn mice injected with tricaprylin (0.1 mL on days 1 and 7 and 0.2 mL on day 14) (n = 86) and non-injected newborn mice (n = 81). Mice were necropsied at age 49–51 weeks. Mortality before weaning was high in neonates receiving high doses (40 mg) of the benzene-soluble extract (86%), acidic fraction (96%), and basic fraction (100%), and this precluded determining carcinogenicity in these groups. A large number of male mice in all groups (25–56%) developed non-treatment-related obstructive uropathy. Because of the small number of mice at risk at weaning, the numbers of tumour-bearing mice (all organs) were combined for all doses in each treatment group for purposes of comparison. The number of tumour-bearing male mice was significantly increased ($P < 0.05$) in groups injected with the basic fraction (13/28, 46.4%) relative to tricaprylin controls (5/31, 16.1%). The number of tumour-bearing female mice was significantly increased ($P < 0.05$) in groups injected with the basic (10/23, 43.5%), aliphatic (21/66, 31.8%), aromatic (33/81, 40.7%), and oxyneutral pentane-12% ether (23/65, 35.4%) fractions relative to tricaprylin controls (3/35, 8.6%). Tumours were not observed in any of the untreated male control mice. The highest incidences of lymphomas in male mice were found in the groups treated with the aliphatic, aromatic, oxyneutral pentane-9% ether, and insoluble fractions (7–13%). In female mice, the highest incidences of lymphomas were observed in the groups treated with the basic, insoluble, aliphatic, aromatic, and oxyneutral fractions (12–30%). Lymphomas were found in 1/23 (4%) untreated female controls and 2/35 (6%) female vehicle controls. A relatively high incidence of pulmonary adenoma (single) was found in male mice injected with oxyneutral pentane-9% ether (10/55, 18%) and female mice injected with the neutral fraction (7/53, 13%). Multiple pulmonary adenomas occurred most frequently in male and female mice injected with the aromatic (9% and 14%, respectively) and the oxyneutral pentane-12% ether (7% and 11%, respectively) fractions. No multiple adenomas were observed in either control group. The highest incidence of hepatomas [mainly hepatocellular tumours] occurred in male mice injected with the basic fraction (12/28, 43%) and the benzene extract (9/39, 23%). In controls, only 3/31 vehicle-treated male mice developed hepatomas. [The Working Group noted the short duration of the experiment and the high mortality.]

Pott et al. (1980) collected airborne PM from three urban sites and one rural site in western Germany during the winter of 1975–1976. The particulates were extracted with benzene and then partially fractionated and analysed for benzo[*a*]pyrene (B[*a*]P) and other PAHs. The extracts (in 0.5 mL of tricaprylin) were injected subcutaneously once into groups of 76–80 female NMRI mice aged 9–12 weeks at doses containing 0.16, 0.63, 2.5, or 10 μg of B[*a*]P per mouse. Controls were injected with the tricaprylin vehicle only. [The exact number of mice per group was not reported.] The animals were observed for up to 2 years. The percentage of mice with injection-site tumours [sarcomas] increased with increasing B[*a*]P content of the injected extract. [Tumour incidences were not reported, only percentages.] The tumour rate was 1.7% in tricaprylin-injected controls and reached up to 68.3% in mice treated with particulate extracts from the rural or urban sites. The extracts from the three urban sites showed a dose-dependent effect, and they showed a higher potency compared with extracts

from the rural site on the basis of the same B[*a*]P content. In the same study, a second experiment with an almost identical design, using samples from three urban sites and two rural sites in western Germany, gave similar results (Pott et al., 1980; Pott & Stöber, 1983).

Sasaki et al. (1987) collected outdoor air particulates from an urban site in Tokyo, Japan. The particulates were extracted with a benzene–ethanol mixture. A portion of the crude extract was fractionated into acidic, basic, and neutral fractions. Newborn male and female Jcl:ICR mice [initial number of mice per group was not reported] were injected subcutaneously (nape of the neck) with 10 mg of the crude extract or fraction suspended in 0.05 mL of olive oil. Control mice were injected subcutaneously with 0.05 mL of olive oil. Mortality was high in all groups before weaning, particularly in mice that received the acidic and basic fractions. Surviving mice (90 male, 77 female) were killed and necropsied 3, 6, or 12 months after treatment. Within 1 year of treatment with the crude extract, pulmonary adenomas were observed in male (3/20, 15%) [not statistically significant] and female (1/5, 20%) [not statistically significant] mice injected with the crude extract, and in male (5/9, 56%) [$P = 0.0039$] and female (2/16, 13%) ($P < 0.01$) mice injected with the neutral fraction. One male mouse and one female mouse that received the neutral fraction had multiple pulmonary adenomas. In mice injected with the basic fraction, one male mouse (1/6, 17%) [not significant] and no female mice (0/5) had pulmonary adenoma. No tumours were found in mice that received the acidic fraction. Pulmonary adenomas were found in one male mouse (1/22, 4.5%) and one female mouse (1/17, 6%) in the vehicle control groups. [The Working Group noted the low and variable numbers of surviving mice and the short duration of the experiment.]

3.3.3 Skin application

Kotin et al. (1954b) collected outdoor air particulates in Los Angeles County, USA, in an industrial area during the smoggy season, and also adjacent to an area of high traffic density during the non-smoggy season. Pyrene, B[*a*]P, and 1,12-benzoperylene were detected in both particulate samples, and both contained relatively low concentrations of B[*a*]P. The samples were extracted with benzene, and both extracts were resuspended in benzene. Groups of 76 C57BL/6 mice (age, 3 months) [the exact numbers of male and female mice were not reported] were treated by skin application (interscapular area) 3 times a week with the extracts [dose was not reported] in approximately 0.5 mL of benzene. A control group of 69 C57BL/6 mice received skin applications of benzene. At the time of appearance of the first tumour (~15 months after treatment), 31 treated (pooled exposed groups) and 37 control mice were alive. Of the 31 treated mice, 13 (42%) [$P < 0.0001$] developed skin papillomas, 9 of which also bore squamous carcinomas [$P < 0.001$]. No skin tumours were observed in controls. [The Working Group noted that the study was incomplete. This appears to be an interim report because the authors state that "this 42% figure of positive tumour production is subject to upward revision in view of the possibility of tumour demonstration in nine remaining mice." An unspecified number of mice died early due to toxicity and intercurrent infection.]

Groups of 1–6 male and female CBA, C57BL/Gr, A/Gr$_f$, or C57BL/How mice (age, 2.5–9.5 months) were treated by skin application with one of three fractions (A, B, C) of an extract of smoke from chimneys diluted to 1% in benzene (Clemo et al., 1955). [The Working Group assumed that particles were mainly from emissions from combustion of coal.] Fractions were applied to the interscapular region 3 times a week, using two strokes of a No. 4 brush, for up to 13.5 months, or until malignant skin tumours

appeared or the animal died. Control mice (21 of various strains, both sexes) received the benzene vehicle only. For each fraction, groups of male and female mice of all strains were pooled. A significantly increased incidence of lung nodules [not further described] was observed in mice treated with fraction A (5/14, 36%) [$P = 0.0278$] and fraction B (6/15, 40%) [$P = 0.013$] relative to controls (1/21, 5%). In mice treated with fraction C, lung nodules [not further described] were observed in only 1/16 (6%) mice [not significant]. Skin papillomas were observed in 9/15 (60%) [$P = 0.0008$] mice treated with fraction B and 5/16 (33%) [$P = 0.01$] mice treated with fraction C. Skin epitheliomas were observed in 5/15 (33%) [$P = 0.008$] mice treated with fraction B and 6/16 (38%) [$P = 0.0034$] mice treated with fraction C. Female A/Gr_f mice treated with fraction C were too old when the treatment started, and they survived only to 6.5–7.5 months of treatment. Of the C57BL/Gr mice treated with fraction C, all (6/6) developed skin epitheliomas and 5/6 developed skin papillomas. Of the 14 mice treated with fraction A, none survived more than 9.5 months of treatment, and no skin tumours were observed. Control mice did not develop skin tumours (0/21). [The Working Group judged this study inadequate due to several major design flaws, including the use of old mice of mixed strains.]

PM from outdoor air was collected in Beijing, Taiyuan, and Xuanwei (China) in winter using a multistage Andersen air sampler. Particle samples were separated into two fractions (≥ 3.3 μm and < 3.3 μm in diameter). Dichloromethane extracts of these particles were tested for skin tumour-initiating ability in a two-stage carcinogenesis assay (Guan et al., 1990). Female Kunming mice were treated with 5 mg of particle extracts (in acetone) by skin application once (5 mg group) or twice (10 mg group; 5 mg applied also on the second day). From the second week, mice were treated with 2.0 μg of the tumour promoter 12-*O*-tetradecanoylphorbol-13-acetate (TPA) twice a week for 26 weeks and observed for skin tumour development until experimental week 28. After 28 weeks, the extracts of outdoor air samples from Beijing with particles ≥ 3.3 μm induced skin papillomas with an incidence of 4/19 [not significant] in the 5 mg group, whereas the extracts with particles < 3.3 μm induced skin papillomas with an incidence of 16/40 [$P = 0.015$] in the 5 mg group and 20/36 [$P < 0.0001$] in the 10 mg group. Similarly, the extracts of outdoor air samples from Taiyuan with particles ≥ 3.3 μm induced skin papillomas with an incidence of 9/30 [$P < 0.0431$] in the 5 mg group, whereas the extracts with particles < 3.3 μm induced skin papillomas with an incidence of 25/39 [$P < 0.0001$] in the 5 mg group and 22/39 [$P < 0.0001$] in the 10 mg group. The extracts of outdoor air samples from Xuanwei with particles ≥ 3.3 μm induced skin papillomas with an incidence of 17/36 [$P = 0.0005$] in the 5 mg group and 24/39 [$P < 0.0001$] in the 10 mg group, whereas the extracts with particles < 3.3 μm induced skin papillomas with an incidence of 25/39 [$P < 0.0001$] in the 5 mg group and 26/39 [$P < 0.0001$] in the 10 mg group. The incidence of skin papilloma in the control group treated with acetone plus TPA was 4/38. For all three locations, the first skin papilloma was observed at 10 weeks for particles < 3.3 μm.

In a 24-month study, Hueper et al. (1962) collected atmospheric dusts from eight cities in the USA and extracted the PM with benzene. The crude benzene extract was further fractionated to obtain oxygenated and aliphatic fractions. Groups of male and female C57BL/6 mice and C3H mice received skin applications of the oxygenated or aliphatic fractions. [The limited reporting and poor design of the study, the weak response, and the lack of vehicle controls rendered this study inadequate for the evaluation.]

Groups of 20 male and 20 female BALB/c mice (age, 7–9 weeks) received skin applications of dichloromethane extracts of outdoor air particulates in 0.2 mL of acetone from four sites in Shanghai (samples A, E, I, or K) at a single

dose of 5 mg or at a dose of 2 mg per day for 5 days (cumulative dose of 10 mg) (Zhao et al., 2003). Vehicle control mice received 0.2 mL of acetone. From 1 week after initiation, the tumour promoter TPA was applied topically at 2 µg in 0.2 mL of acetone per mouse, twice a week for 30 weeks. None of the extracts produced skin cancers; however, all extracts initiated skin papillomas in 5% (1/20) to 17% (3/18) of male mice at the cumulative dose of 10 mg. Sample E initiated papillomas in male and female mice at all doses. Only sample E induced skin papillomas in female mice (1/20). The incidence of skin papillomas in male mice at the cumulative dose of 10 mg was significantly increased [9/75, $P = 0.0179$] compared with male controls (0/40). No skin papillomas were observed in female controls (0/40).

Matsumoto et al. (2007) investigated the role of aryl hydrocarbon receptor (AhR) signalling on carcinogenicity of airborne PM. Groups of 17 female [Sv/129] $AhR^{+/+}$ (wild-type) and 15 female [Sv/129] $AhR^{-/-}$ (knockout) mice (age, 6–8 weeks) were treated with extracts of outdoor air particulates (from the city of Sapporo, Japan) by skin application. Extracts were shown to contain B[*a*]P and other PAHs. [The Working Group noted that the samples were stored from 1988 to 2007.] Mice received skin applications of extract (6.4 mg in 200 µL of acetone) once a week until a skin tumour appeared, and mice were necropsied after experimental week 58. In $AhR^{+/+}$ mice, the first tumour appeared after 29 weeks of treatment, and after 58 weeks, 8/17 (47%) $AhR^{+/+}$ mice bore squamous cell carcinomas. No skin tumours developed in $AhR^{-/-}$ mice (0/15). The difference in skin tumour incidence between $AhR^{+/+}$ and $AhR^{-/-}$ mice was significant ($P < 0.01$). [The Working Group noted the lack of clean air control groups.]

3.3.4 Intravenous injection

Leiter et al. (1942) collected PM from outdoor air at six sites in the USA: in Chelsea, Massachusetts, in Pittsburgh, Pennsylvania, and at four sites in a road tunnel that connects New York City and Jersey City. Groups of 20–30 strain A mice (age, 2–3 months) [sex was not reported] were injected intravenously (tail vein) with the unextracted dusts suspended in saline (2.5 mg in 0.25 mL). Control mice were untreated. Four months after treatment, the incidence of pulmonary tumours in all dust-treated mice (15/138, 11%) [groups of treated mice were combined] was not increased compared with controls (3/20, 15%). [The methods and results of this older study were poorly reported. The study duration was short. No detailed information on outdoor air pollutants was reported.]

3.3.5 Intraperitoneal injection

Heussen et al. (1996) evaluated the carcinogenicity of outdoor air particulates collected over 2 years at a non-industrial site (Wageningen, The Netherlands). The particulates were extracted with benzene, benzene was removed by evaporation, and the extract was suspended in propylene glycol. Male newborn NMRI mice were injected intraperitoneally on days 1 (5 µL), 8 (10 µL), and 15 (20 µL) after birth with propylene glycol vehicle ($n = 52$), 1.95 mg of extract ($n = 49$), or 3.9 mg of extract ($n = 47$). No deaths occurred before weaning. [There was no significant difference in mortality between groups.] Mice were necropsied at experimental week 52, and lungs and liver were examined for tumours. Incidences of bronchioloalveolar tumours in mice treated with 3.9 mg of extract (17/47, 36.2%) and 1.95 mg of extract (10/49, 20.4%) were not significantly different from the incidence in vehicle controls (16/52, 30.8%). [The Working Group noted the short duration of the study. No detailed information on outdoor air pollutants was reported.]

References

Asahina S, Andrea J, Carmel A, Arnold E, Bishop Y, Joshi S et al. (1972). Carcinogenicity of organic fractions of particulate pollutants collected in New York City and administered subcutaneously to infant mice. *Cancer Res*, 32(10):2263–8. PMID:4343014

Brightwell J, Fouillet X, Cassano-Zoppi A-L, Bernstein D, Crawley F, Duchosal F et al. (1989). Tumours of the respiratory tract in rats and hamsters following chronic inhalation of engine exhaust emissions. *J Appl Toxicol*, 9(1):23–31. doi:10.1002/jat.2550090106 PMID:2466883

Brune H, Habs M, Schmähl D (1978). The tumor-producing effect of automobile exhaust condensate and fractions thereof. Part II: animal studies. *J Environ Pathol Toxicol*, 1(6):737–45. PMID:83348

Bukowski JA, Wartenberg D, Goldschmidt M (1998). Environmental causes for sinonasal cancers in pet dogs, and their usefulness as sentinels of indoor cancer risk. *J Toxicol Environ Health A*, 54(7):579–91. doi:10.1080/009841098158719 PMID:9726781

Campbell JA (1936). The effects of exhaust gases from internal combustion engines and of tobacco smoke upon mice, with special reference to incidence of tumours of the lung. *Br J Exp Pathol.*, 17(2):146–158.

Campbell JA (1939). Carcinogenic agents present in the atmosphere and incidence of primary lung tumours in mice. *Br J Exp Pathol.*, 20(2):122–132.

Clemo GR, Miller EW, Pybus FC (1955). The carcinogenic action of city smoke. *Br J Cancer*, 9(1):137–41. doi:10.1038/bjc.1955.10 PMID:14378498

Cupitt LT, Glen WG, Lewtas J (1994). Exposure and risk from ambient particle-bound pollution in an airshed dominated by residential wood combustion and mobile sources. *Environ Health Perspect*, 102:Suppl 4: 75–84. doi:10.1289/ehp.94102s475 PMID:7529707

Cury PM, Lichtenfels AJ, Reymão MS, Conceição GM, Capelozzi VL, Saldiva PH (2000). Urban levels of air pollution modifies the progression of urethane-induced lung tumours in mice. *Pathol Res Pract*, 196(9):627–33. doi:10.1016/S0344-0338(00)80006-0 PMID:10997738

Epstein SS, Fujii K, Asahina S (1979). Carcinogenicity of a composite organic extract of urban particulate atmospheric pollutants following subcutaneous injection in infant mice. *Environ Res*, 19(1):163–76. doi:10.1016/0013-9351(79)90044-6 PMID:510265

Epstein SS, Joshi S, Andrea J, Mantel N, Sawicki E, Stanley T et al. (1966). Carcinogenicity of organic particulate pollutants in urban air after administration of trace quantities to neonatal mice. *Nature*, 212(5068):1305–7. doi:10.1038/2121305a0

Gardner MB (1966). Biological effects of urban air pollution. 3. Lung tumors in mice. *Arch Environ Health*, 12(3):305–13. doi:10.1080/00039896.1966.10664377 PMID:5904509

Gardner MB, Loosli CG, Hanes B, Blackmore W, Teebken D (1969). Histopathologic findings in rats exposed to ambient and filtered air. *Arch Environ Health*, 19(5):637–47. doi:10.1080/00039896.1969.10666903 PMID:5350434

Grimmer G, Brune H, Deutsch-Wenzel R, Dettbarn G, Jacob J, Naujack KW et al. (1987). Contribution of polycyclic aromatic hydrocarbons and nitro-derivatives to the carcinogenic impact of diesel engine exhaust condensate evaluated by implantation into the lungs of rats. *Cancer Lett*, 37(2):173–80. doi:10.1016/0304-3835(87)90160-1 PMID:2445467

Grimmer G, Brune H, Deutsch-Wenzel R, Dettbarn G, Misfeld J (1984). Contribution of polycyclic aromatic hydrocarbons to the carcinogenic impact of gasoline engine exhaust condensate evaluated by implantation into the lungs of rats. *J Natl Cancer Inst*, 72(3):733–9. PMID:6199545

Grimmer G, Brune H, Deutsch-Wenzel R, Naujack KW, Misfeld J, Timm J (1983a). On the contribution of polycyclic aromatic hydrocarbons to the carcinogenic impact of automobile exhaust condensate evaluated by local application onto mouse skin. *Cancer Lett*, 21(1):105–13. doi:10.1016/0304-3835(83)90089-7 PMID:6196104

Grimmer G, Naujack K-W, Dettbarn G, Brune H, Deutsch-Wenzel R, Misfeld J (1983b). Characterization of polycyclic aromatic hydrocarbons as essential carcinogenic constituents of coal combustion and automobile exhaust using mouse-skin painting as a carcinogen-specific detector. *Toxicol Environ Chem*, 6(2):97–107. doi:10.1080/02772248309356998

Guan NY, Guo HE, Pan CQ (1990). A study of carcinogenicity skin of extracts from different size particles in air [in Chinese]. *Zhonghua Yu Fang Yi Xue Za Zhi*, 24(1):9–12. PMID:2340767

Heinrich U, Peters L, Mohr U, Bellman B, Fuhst R, Ketkar MB et al. (1986c). Investigation of subacute and chronic effects of gasoline engine exhaust on rodents [in German]. (FAT Series No. 55). Frankfurt am Main: Forschungsvereinigung Automobiltechnik.

Heinrich U, Fuhst R, Rittinghausen S, Creutzenberg O, Bellmann B, Koch W et al. (1995). Chronic inhalation exposure of Wistar rats and 2 different strains of mice to diesel-engine exhaust, carbon black, and titanium dioxide. *Inhal Toxicol*, 7(4):533–56. doi:10.3109/08958379509015211

Heinrich U, Muhle H, Takenaka S, Ernst H, Fuhst R, Mohr U et al. (1986a). Chronic effects on the respiratory tract of hamsters, mice and rats after long-term inhalation of high concentrations of filtered and unfiltered diesel engine emissions. *J Appl Toxicol*, 6(6):383–95. doi:10.1002/jat.2550060602 PMID:2433325

Heinrich U, Peters L, Funcke W, Pott F, Mohr U, Stöber W (1982). Investigation of toxic and carcinogenic effects of diesel exhaust in long-term inhalation

exposure of rodents. *Dev Toxicol Environ Sci*, 10:225–42. PMID:6176424

Heinrich U, Pott F, Mohr U, Fuhst R, König J (1986b). Lung tumours in rats and mice after inhalation of PAH-rich emissions. *Exp Pathol*, 29(1):29–34. doi:10.1016/S0232-1513(86)80003-2 PMID:3699126

Heussen GAH, van den Berg JH, Dreef-van der Meulen HC, Alink GM (1996). Carcinogenicity study of outdoor airborne particulate matter in newborn male NMRI mice. *Toxicol Lett*, 88(1-3):23–8. doi:10.1016/0378-4274(96)03713-7 PMID:8920712

Hoffmann D, Theisz E, Wynder EL (1965). Studies on the carcinogenicity of gasoline exhaust. *J Air Pollut Control Assoc*, 15(4):162–5. doi:10.1080/00022470.1965.10468353 PMID:14273615

Hueper WC, Kotin P, Tabor EC, Payne WW, Falk H, Sawicki E (1962). Carcinogenic bioassays on air pollutants. *Arch Pathol*, 74:89–116. PMID:14449727

IARC (1973). Certain polycyclic aromatic hydrocarbons and heterocyclic compounds. *IARC Monogr Eval Carcinog Risk Chem Man*, 3:1–271. Available from: http://monographs.iarc.fr/ENG/Monographs/vol1-42/mono3.pdf.

IARC (1983). Polynuclear aromatic compounds, Part 1, Chemical, environmental and experimental data. *IARC Monogr Eval Carcinog Risk Chem Hum*, 32:1–453. Available from: http://monographs.iarc.fr/ENG/Monographs/vol1-42/mono32.pdf. PMID:6586639

IARC (2010a). Some non-heterocyclic polycyclic aromatic hydrocarbons and some related exposures. *IARC Monogr Eval Carcinog Risks Hum*, 92:1–853.Available from: http://monographs.iarc.fr/ENG/Monographs/vol92/index.php. PMID:21141735

IARC (2010b). Household use of solid fuels and high-temperature frying. *IARC Monogr Eval Carcinog Risks Hum*, 95:1–430. Available from: http://monographs.iarc.fr/ENG/Monographs/vol95/index.php. PMID:20701241

IARC (2012a). Personal habits and indoor combustions. *IARC Monogr Eval Carcinog Risks Hum*, 100:E: 1–575. Available from: http://monographs.iarc.fr/ENG/Monographs/vol100E/index.php. PMID:23193840

IARC (2012b). Chemical agents and related occupations. *IARC Monogr Eval Carcinog Risks Hum*., 100F:1–599. Available from: http://monographs.iarc.fr/ENG/Monographs/vol100F/index.php. PMID:23189753

IARC (2013). Diesel and gasoline engine exhausts and some nitroarenes. *IARC Monogr Eval Carcinog Risks Hum*., 105:1–704. Available from: http://monographs.iarc.fr/ENG/Monographs/vol105/index.php

Ichinose T, Yajima Y, Nagashima M, Takenoshita S, Nagamachi Y, Sagai M (1997). Lung carcinogenesis and formation of 8-hydroxy-deoxyguanosine in mice by diesel exhaust particles. *Carcinogenesis*, 18(1):185–92. doi:10.1093/carcin/18.1.185 PMID:9054605

Ishinishi N, Kuwabara N, Nagase S, Suzuki T, Ishiwata S, Kohno T (1986). Long-term inhalation studies on effects of exhaust from heavy and light duty diesel engines on F344 rats. *Dev Toxicol Environ Sci*, 13:329–48. PMID:2435494

Ito T, Ohyama K, Kusano T, Usuda Y, Nozawa A, Hayashi H et al. (1997). Pulmonary endocrine cell hyperplasia and papilloma in rats induced by intratracheal injections of extract from particulate air pollutants. *Exp Toxicol Pathol*, 49(1):(2):65–70. doi:10.1016/S0940-2993(97)80066-8 PMID:9085076

Iwai K, Adachi S, Takahashi M, Möller L, Udagawa T, Mizuno S et al. (2000). Early oxidative DNA damages and late development of lung cancer in diesel exhaust-exposed rats. *Environ Res*, 84(3):255–64. doi:10.1006/enrs.2000.4072 PMID:11097799

Iwai K, Higuchi K, Udagawa T, Ohtomo K, Kawabata Y (1997). Lung tumor induced by long-term inhalation or intratracheal instillation of diesel exhaust particles. *Exp Toxicol Pathol*, 49(5):393–401. doi:10.1016/S0940-2993(97)80125-X PMID:9455688

Iwai K, Udagawa T, Yamagishi M, Yamada H (1986). Long-term inhalation studies of diesel exhaust on F344 SPF rats. Incidence of lung cancer and lymphoma. *Dev Toxicol Environ Sci*, 13:349–60. PMID:2435495

Karagianes MT, Palmer RF, Busch RH (1981). Effects of inhaled diesel emissions and coal dust in rats. *Am Ind Hyg Assoc J*, 42(5):382–91. doi:10.1080/15298668191419910 PMID:6164283

Khesina AIa, Gaevaia TIa, Linnik AB (1977). Polycyclic aromatic hydrocarbon content and carcinogenic activity of soot extracts from the heating systems [in Russian]. *Gig Sanit*, 8(8):107–9. PMID:590784

Kotin P, Falk HL, Mader P, Thomas M (1954b). Aromatic hydrocarbons. I. Presence in the Los Angeles atmosphere and the carcinogenicity of atmospheric extracts. *AMA Arch Ind Hyg Occup Med*, 9(2):153–63. PMID:13113748

Kotin P, Falk HL, Thomas M (1954a). Aromatic hydrocarbons. II. Presence in the particulate phase of gasoline-engine exhausts and the carcinogenicity of exhaust extracts. *AMA Arch Ind Hyg Occup Med*, 9(2):164–77. PMID:13113749

Kunitake E, Shimamura K, Katayama H, Takemoto K, Yamamoto A, Hisanaga A et al. (1986). Studies concerning carcinogenesis of diesel particulate extracts following intratracheal instillation, subcutaneous injection, or skin application. *Dev Toxicol Environ Sci*, 13:235–52. PMID:2435490

Künstler K (1983). Failure to induce tumors by intratracheal instillation of automobile exhaust condensate and fractions thereof in Syrian golden hamsters. *Cancer Lett*, 18(1):105–8. doi:10.1016/0304-3835(83)90123-4 PMID:6186363

Leiter J, Shimkin MB, Shear MJ (1942). Production of subcutaneous sarcomas in mice with tars extracted from atmospheric dusts *J Natl Cancer Inst*., 3:155–165.

Lewis TR, Green FHY, Moorman WJ, Burg JA, Lynch DW (1986). A chronic inhalation toxicity study of diesel engine emissions and coal dust, alone and combined. In: Ishinishi N, Koizumi A, McClellan R, Stöber W, editors. Carcinogenic and mutagenic effects of diesel engine exhaust: Proceedings of the International Satellite Symposium on Toxicological Effects of Emissions from Diesel Engines, held in Tsukuba, Japan, July 26–28, 1986. Amsterdam, The Netherlands: Elsevier; pp. 361–380.

Lewis TR, Green FHY, Moorman WJ, Burg JR, Lynch DW (1989). A chronic inhalation toxicity study of diesel engine emissions and coal dust, alone and combined. *Int J Toxicol*, 8(2):345–75. doi:10.3109/10915818909019560

Lewtas J (1993). Complex mixtures of air pollutants: characterizing the cancer risk of polycyclic organic matter. *Environ Health Perspect*, 100:211–8. doi:10.1289/ehp.93100211 PMID:8354169

Liang CK, Guan NY, Ma F ,Zhang Y, Wang EM, Yin XR (1984). Carcinogenicity of extract of soot from Xuan Wei County after administering subcutaneously to mice. *Environ Sci Res*., 31:826–827.

Liang CK, Guan NY, Ma F, Zhang Y, Wang EM, Yin XR (1983). Carcinogenicity in mice of soot extract collected from Xuan Wei County [in Chinese]. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao*, 5(5):307–10. PMID:6329534

Liang CK, Quan NY, Cao SR, He XZ, Ma F (1988). Natural inhalation exposure to coal smoke and wood smoke induces lung cancer in mice and rats. *Biomed Environ Sci*, 1(1):42–50. PMID:3268107

Liang C-K, Wang W (1987). Kunming mouse skin tumor-initiating activity of extracts of inhalable particles in indoor air [in Chinese]. *Zhonghua Yu Fang Yi Xue Za Zhi*, 21(6):316–8. PMID:3452506

Lin C, Dai X, Sun X (1995). Expression of oncogene and anti-oncogene in mouse lung cancer induced by coal-burning smoke [in Chinese]. *Zhonghua Zhong Liu Za Zhi*, 17(6):432–4. PMID:8697995

Matsumoto Y, Ide F, Kishi R, Akutagawa T, Sakai S, Nakamura M et al. (2007). Aryl hydrocarbon receptor plays a significant role in mediating airborne particulate-induced carcinogenesis in mice. *Environ Sci Technol*, 41(10):3775–80. doi:10.1021/es062793g PMID:17547212

Mauderly JL, Snipes MB, Barr EB, Belinsky SA, Bond JA, Brooks AL et al. (1994). Pulmonary toxicity of inhaled diesel exhaust and carbon black in chronically exposed rats. Research Report 68. Boston (MA): Health Effects Institute. PMID:7530965

Mauderly JL, Banas DA, Griffith WC, Hahn FF, Henderson RF, McClellan RO (1996). Diesel exhaust is not a pulmonary carcinogen in CD-1 mice exposed under conditions carcinogenic to F344 rats. *Fundam Appl Toxicol*, 30(2):233–42. doi:10.1006/faat.1996.0061 PMID:8812271

Mauderly JL, Jones RK, Griffith WC, Henderson RF, McClellan RO (1987). Diesel exhaust is a pulmonary carcinogen in rats exposed chronically by inhalation. *Fundam Appl Toxicol*, 9(2):208–21. doi:10.1016/0272-0590(87)90044-3 PMID:2443412

Mauderly JL, Jones RK, McClellan RO, Henderson RF, Griffith WC (1986). Carcinogenicity of diesel exhaust inhaled chronically by rats. *Dev Toxicol Environ Sci*, 13:397–409. PMID:2435498

Mohr U, Resnik-Schüller H, Reznik G, Grimmer G, Misfeld J (1976). Investigations on the carcinogenic burden by air pollution in man. XIV. Effects of automobile exhaust condensate on the Syrian golden hamster lung. *Zentralbl Bakteriol Orig B*, 163(5):(6):425–32. PMID:65878

Mumford JL, Helmes CT, Lee XM, Seidenberg J, Nesnow S (1990). Mouse skin tumorigenicity studies of indoor coal and wood combustion emissions from homes of residents in Xuan Wei, China with high lung cancer mortality. *Carcinogenesis*, 11(3):397–403. doi:10.1093/carcin/11.3.397 PMID:2311182

Nesnow S, Evans C, Stead A, Creason J, Slaga TJ, Triplett LL (1982b). Skin carcinogenesis studies of emission extracts. *Dev Toxicol Environ Sci*, 10:295–320. PMID:6176428

Nesnow S, Triplett LL, Slaga TJ (1982a). Comparative tumor-initiating activity of complex mixtures from environmental particulate emissions on SENCAR mouse skin. *J Natl Cancer Inst*, 68(5):829–34. PMID:6951092

Nesnow S, Triplett LL, Slaga TJ (1983). Mouse skin tumor initiation-promotion and complete carcinogenesis bioassays: mechanisms and biological activities of emission samples. *Environ Health Perspect*, 47:255–68. doi:10.1289/ehp.8347255 PMID:6825618

Nikula KJ, Snipes MB, Barr EB, Griffith WC, Henderson RF, Mauderly JL (1995). Comparative pulmonary toxicities and carcinogenicities of chronically inhaled diesel exhaust and carbon black in F344 rats. *Fundam Appl Toxicol*, 25(1):80–94. doi:10.1006/faat.1995.1042 PMID:7541380

Pereira FA, Lemos M, Mauad T, Assunção JV, Saldiva PH (2011). Urban, traffic- related particles and lung tumors in urethane treated mice. *Clinics (Sao Paulo)*, 66(6):1051–4. doi:10.1590/S1807-59322011000600022 PMID:21808874

Pott F, Stöber W (1983). Carcinogenicity of airborne combustion products observed in subcutaneous tissue and lungs of laboratory rodents. *Environ Health Perspect*, 47:293–303. doi:10.1289/ehp.8347293 PMID:6186480

Pott F, Tomingas R, Brockhaus A, Huth F (1980). Studies on the tumourigenicity of extracts and their fractions of airborne particulates with the subcutaneous test in the mouse [in German]. *Zentralbl Bakteriol B*, 170(1):(2):17–34. PMID:7424257

Pott F, Tomingas R, Misfeld J (1977). Tumours in mice after subcutaneous injection of automobile exhaust condensates. *IARC Sci Publ*, 16:79–87. PMID:68912

Reed MD, Campen MJ, Gigliotti AP, Harrod KS, McDonald JD, Seagrave JC et al. (2006). Health effects of subchronic exposure to environmental levels of hardwood smoke. *Inhal Toxicol*, 18(8):523–39. doi:10.1080/08958370600685707 PMID:16717024

Reymão MS, Cury PM, Lichtenfels AJ, Lemos M, Battlehner CN, Conceição GM et al. (1997). Urban air pollution enhances the formation of urethane-induced lung tumors in mice. *Environ Res*, 74(2):150–8. doi:10.1006/enrs.1997.3740 PMID:9339228

Reznik-Schüller H, Mohr U (1977). Pulmonary tumorigenesis in Syrian golden hamsters after intratracheal instillations with automobile exhaust condensate. *Cancer*, 40(1):203–10. doi:10.1002/1097-0142(197707)40:1<203::AID-CNCR2820400132>3.0.CO;2-L PMID:69482

Rigdon RH, Neal J (1971). Tumors in mice induced by air particulate matter from a petrochemical industrial area. *Tex Rep Biol Med*, 29(1):109–23. PMID:5570556

Sasaki Y, Kawai T, Ohyama K, Nakama A, Endo R (1987). Carcinogenicity of extract of airborne particles using newborn mice and comparative study of carcinogenic and mutagenic effect of the extract. *Arch Environ Health*, 42(1):14–8. doi:10.1080/00039896.1987.9935789 PMID:3566345

Seeling MG, Benignus EL (1936). Coal smoke soot and tumors of the lung and mice. *Am J Cancer*, 28:96–111.

Stara JF, Dungworth DL, Orthoefer JG, Tyler WS, editors (1980). Long-term effects of air pollutants: in canine species (EPA-600/8–80–014). Cincinnati (OH): US Environmental Protection Agency.

Sulman E, Sulman F (1946). The carcinogenicity of wood soot from the chimney of a smoked sausage factory. *Cancer Res*, 6:366. PMID:20987096

Takaki Y, Kitamura S, Kuwabara N, Fukuda Y (1989). Long-term inhalation studies of exhaust from the diesel engine in F-344 rats: the quantitative relationship between pulmonary hyperplasia and anthracosis. *Exp Pathol*, 37(1-4):56–61. doi:10.1016/S0232-1513(89)80013-1 PMID:2484033

Takemoto K, Yoshimura H, Katayama H (1986). Effects of chronic inhalation exposure to diesel exhaust on the development of lung tumors in di-isopropanol-nitrosamine-treated F344 rats and newborn C57BL and ICR mice. *Dev Toxicol Environ Sci*, 13:311–27. PMID:2435493

Wayne LG, Chambers LA (1968). Biological effects of urban air pollution. V. A study of effects of Los Angeles atmosphere on laboratory rodents. *Arch Environ Health*, 16(6):871–85. doi:10.1080/00039896.1968.10665168 PMID:4297588

Wynder EL, Hoffmann D (1962). A study of air pollution carcinogenesis. II. Carcinogenic activity of gasoline engine exhaust condensate. *Cancer*, 15(1):103–8. doi:10.1002/1097-0142(196201/02)15:1<103::AID-CNCR2820150114>3.0.CO;2-3 PMID:14008627

Yin XR, Guan NY, Liang CK, Zhang Y, Wang EM, Ma F (1984). Study on lung cancer in mice by intra-bronchial injection of Yiwei coal fume extracts [in Chinese]. *Wei Shen Yan Jin.*, 13:21–5.

Yoshimura H (1983). The influence of air pollution on the development of pulmonary cancer, with special reference to gasoline engine [in Japanese]. *Nippon Eiseigaku Zasshi*, 37(6):848–65. doi:10.1265/jjh.37.848 PMID:6191062

Zhao X, Wan Z, Zhu H, Chen R (2003). The carcinogenic potential of extractable organic matter from urban airborne particles in Shanghai, China. *Mutat Res*, 540(1):107–17. doi:10.1016/S1383-5718(03)00178-5 PMID:12972063

4. MECHANISTIC AND OTHER RELEVANT DATA

4.1 Toxicokinetic data

4.1.1 Introduction

The toxicokinetics of many of the major classes of compounds and industrial processes that contribute to outdoor air pollution have been described in previous *IARC Monograph* Volumes: carbon black, titanium dioxide, and talc (Volume 93; IARC, 2010a); household use of solid fuels and high-temperature frying (Volume 95; IARC, 2010b); non-heterocyclic polycyclic aromatic hydrocarbons (PAHs) (Volume 92; IARC, 2010c); diesel and gasoline engine exhausts (Volume 105; IARC, 2013); silica dust and asbestos (Volume 100C; IARC, 2012a); and benzene, butadiene, formaldehyde, coke production, iron and steel founding, and coal gasification (Volume 100F; IARC, 2012b).

4.1.2 Particulate matter

Some atmospheric particles are poorly soluble in water. As a consequence, after inhalation and deposition, they may remain present as particulate matter (PM) in the respiratory tract, and produce effects associated with particle toxicity.

The toxicokinetics, including deposition, clearance, and retention of poorly soluble particles and fibres, are discussed below for both humans and laboratory animals.

The deposition of *particles* within a region of the respiratory tract depends on the characteristics and physical factors that influence transport in the airways (e.g. air velocity and airway structure). The primary mechanisms for deposition of particles in the respiratory tract are sedimentation, impaction, and diffusion. Deposition by sedimentation and impaction depends on the aerodynamic diameter of the particle, whereas deposition by diffusion depends on the thermodynamic diameter of the particle (ICRP, 1994).

After inhalation, particles may either deposit in the extra-thoracic, tracheobronchial, or pulmonary/alveolar airways or remain in the airstream and be eliminated through exhalation. The deposition of particles in the respiratory tract depends primarily on the size of the inhaled particle, the route of breathing (i.e. through the nose and/or mouth), and the breathing pattern (i.e. volume and frequency). Particles of about 0.3 μm in diameter have minimal mobility in air; they are large enough that their diffusive mobility is minimal but are small enough that their sedimentation and impaction are also minimal. As a consequence, particles in this size range also have minimal deposition in the lung. In general, the deposition fraction for humans for most particle sizes smaller than 3–4 μm (aerodynamic diameter) is greater for the alveolar region than for the tracheobronchial airways. The deposition fraction decreases in the alveolar region for particles larger than 3–4 μm and smaller than 0.01 μm due to their removal in the extra-thoracic airways (particularly during nasal breathing) and tracheobronchial airways (NCRP, 1997; Maynard & Kuempel, 2005).

A few studies with human volunteers are available on the kinetics of clearance and retention of inhaled particles in the respiratory tract. Retention is determined by the balance between the rate of deposition and the rate of clearance. Particles that deposit in the tracheobronchial region are cleared by mucociliary clearance, which is relatively rapid (retention half-times of ~24–48 hours) (Oberdörster, 1988; ICRP, 1994), although some fraction of the particles that deposit in the airways is cleared more slowly than expected (Stahlhofen et al., 1995). For particles that deposit in the alveolar region, the primary mechanism of clearance is phagocytosis by alveolar macrophages, followed by migration of the macrophages to the terminal bronchioles and subsequent mucociliary clearance; the particles are eventually swallowed or expectorated. Particles that are cleared via the mucociliary escalator, whether from the tracheobronchial region or the alveolar region, and then swallowed will pass through the gastrointestinal tract and are subsequently cleared via the gut (Oberdörster, 1988; ICRP, 1994). Poorly soluble particles that deposit in the alveolar region are associated with a slow clearance phase (retention half-times of months to years in humans) (Bailey et al., 1985; Freedman & Robinson, 1988; ICRP, 1994). Translocation of particles to the interstitial region (interstitium) further increases the retention time of particles in the lungs (Oberdörster, 1988; Freedman & Robinson, 1988; ICRP, 1994). Some fractions of particles that deposit in the alveolar region may also be translocated to the lung-associated lymph nodes. Translocation may occur by transepithelial migration of alveolar macrophages after phagocytosis of the particle, or by translocation of free particles to the interstitium, where they may be phagocytosed by interstitial macrophages. Inflammation may alter mucociliary clearance, phagocytosis by alveolar macrophages, and the uptake and transport of particles to and through the respiratory epithelium (Oberdörster, 1988; ICRP, 1994).

The deposition and clearance of particles vary among individuals for several reasons, including age, sex, tobacco smoking status, and health status. Pre-existing lung diseases or conditions such as asthma or chronic obstructive pulmonary disease (COPD) can influence the efficiency and pattern of deposition within the respiratory tract. Deposition also depends on the level of activity and breathing patterns. Deposition and retention determine the initial and retained dose of particles in each region and may therefore influence the risk of developing diseases specific to those respiratory tract regions (Oberdörster, 1988; ICRP, 1994). Particles that are retained in the respiratory tract can lead to inflammation and oxidative stress (see Section 4.3.1).

4.1.3 Organic molecules

A detailed overview of the toxicokinetics of selected organic compounds is available in earlier *Monographs*: PAHs (IARC, 2010c), formaldehyde (IARC, 1982, 2006, 2012b), nitroarenes (IARC, 1984, 1989, 2013), and benzene (IARC, 1982, 2012b).

4.1.4 Inorganic gases

(a) Ozone

Ozone is a highly reactive gas, poorly soluble in water. The uptake and fate of ozone in the respiratory tract of humans and animals has been modelled by Miller (1995), Miller et al. (1985), Mercer & Crapo (1989), Pinkerton et al. (1992), and Pinkerton et al. (1995). Inhaled ozone can reach the major regions of the respiratory tract (extra-thoracic, tracheobronchial, and alveolar) and be absorbed there. Modelling based on the reactivity of ozone and its low solubility predicts that tissue doses will be low in the trachea, increase to a maximum in the terminal bronchioles, and decrease with further digital progression. Ozone can produce oxidative stress (see Section 4.3.1).

(b) Sulfur dioxide

Sulfur dioxide (SO_2) is a highly reactive, water-soluble gas and therefore is almost completely absorbed in the nasal passages of individuals at rest (IARC, 1992). With exercise, the pattern of SO_2 absorption shifts from the upper airways to the tracheobronchial airways in conjunction with a shift from nasal to oronasal breathing and increased ventilatory rates (EPA, 2006; Brain, 1970; Melville, 1970; Nodelman & Ultman, 1999). Similarly to ozone, the nasal passages remove SO_2 more efficiently than the oral pathway does.

(c) Nitrogen dioxide

Nitrogen dioxide (NO_2) is a reactive gas that is absorbed mainly in the upper respiratory tract, particularly the nasal passages, in individuals at rest. Exercise causes a shift from nasal to oronasal breathing and, because NO_2 is absorbed in the oral cavity less than in the nasal passages, more of the inhaled NO_2 reaches the pulmonary region, where the NO_2 is rapidly absorbed. Studies by Postlethwait and colleagues (Postlethwait et al., 1995, 1991; Postlethwait & Bidani, 1990) indicate that NO_2 absorption in the pulmonary region is due not to its solubility in the epithelial lining fluid of the lung but rather to interaction with constituents in this fluid, such as glutathione and ascorbic acid, in reactions mediated by free radicals. This may lead to oxidative stress (see Section 4.3.1).

4.1.5 Metals, inorganic dusts, and organic dusts

Outdoor air may contain different types of fibres and particles (e.g. asbestos and silica), dusts (e.g. wood dust), and various metals (e.g. beryllium, cadmium, chromium, nickel, and arsenic), including those reviewed in previous *Monographs* and classified as Group 1 human carcinogens (IARC, 2012a).

The presence of transition metals in outdoor air pollution may lead to the formation of reactive oxygen species (ROS), which can cause oxidative damage to DNA in the Fenton reaction. This comprises the reduction of hydrogen peroxide by a transition metal ion, resulting in the formation of the reactive hydroxyl radical and the oxidized metal ion. Transition-metal ions such as those of iron, copper, chromium, and nickel donate or accept free electrons via intracellular reactions and help in creating free radicals.

DNA is a target for metal ions due to its electron-rich structure, which offers ligands and complexation sites for positively charged metal ions. Ions such as copper(II) and iron(II) are able to interact with DNA in between the bases, and nickel(II) forms a complex with the phosphate backbone (Eichhorn & Shin, 1968), whereas chromium(III) ions are able to form stable adducts with DNA (Bridgewater et al., 1994). Cells treated with some metal ions under Fenton reaction conditions show enhanced levels of certain types of DNA damage (Imlay et al., 1988). Oxidized lesions in the form of DNA strand breaks and base modifications such as 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG) have been observed after exposure of DNA to the Fenton reaction involving copper (Toyokuni & Sagripanti, 1994), iron (Toyokuni & Sagripanti, 1992), nickel (Kawanishi et al., 1989), and chromium ions (Tsou et al., 1996).

4.2 Genetic and related effects

Outdoor air is a complex aerosol composed of gases (nitrogen, oxygen, carbon dioxide [CO_2], ozone, NO_2, SO_2, etc.), water vapour, PM (including both organic and inorganic PM), volatile organic compounds (VOCs), and semivolatile organic compounds (SVOCs). The complex physical–chemical characteristics of the outdoor air matrix, combined with its spatial and temporal heterogeneity, complicate assessment of genetic and related effects in human and experimental

systems. Experimental installations (e.g. exposure chambers) have been used to expose human subjects to components of outdoor air such as fine PM (Brook et al., 2002); however, there are only few such assessments of genotoxic effects in experimentally exposed humans (Vinzents et al., 2005; Bräuner et al., 2007). Importantly, human studies have monitored genetic and related effects in individuals exposed to outdoor air under specific circumstances (e.g. outdoor occupational exposures); the results obtained are generally compared with effectively matched controls. [The Working Group noted that although examinations of exposures to outdoor air pollution in selected occupations (e.g. filling station attendants, bus drivers, airport tarmac workers) are relevant for hazard identification, the exposures may not be representative, in terms of both compositions and level, of exposures in the general population.]

Similarly, a wide range of studies have used in situ exposures, including of rodents, birds, and plants (e.g. *Tradescantia* sp.), to assess the genetic and related effects of outdoor air. For in situ studies, exposure is quantified as the duration of time spent at the location of interest. Most published research on genetic and related effects induced by outdoor air used in vitro systems, primary human and animal cells, established human and animal cell lines, yeast, and bacteria, as well as naked DNA in solution. These in vitro assessments involved exposures of cultured cells, DNA, or 2′-deoxynucleotides to PM suspensions, extracts of PM, or concentrates of SVOCs.

4.2.1 Mutagenicity

(a) Humans – in vivo studies

In a cross-sectional study of 67 mothers and 64 newborns from the Cracow region of Poland, Perera et al. (2002) found that the frequency of aromatic DNA adducts measured by ^{32}P-postlabelling was positively associated with the hypoxanthine–guanine phosphoribosyltransferase (*HPRT*) mutant frequency in the cord blood of newborns (P = 0.03) after controlling for exposure to smoking, diet, and socioeconomic status. There was no significant association between mutation and DNA damage in the peripheral blood lymphocytes of the mothers. This study demonstrated a molecular linkage between somatic-cell mutation in the newborn and transplacental exposure to air pollutants.

In Denmark, a strategic environmental health programme, including studies of exposures and biomarkers related to traffic-generated air pollution, was carried out in the late 1990s. Mutagenic activity in urine was measured as biomarker of exposure in non-smoking bus drivers in city and rural areas on a work day and a day off and in non-smoking mail carriers working outdoors (on the streets) and indoors (in the office). Urinary mutagenic activity was assessed by the Ames assay with *Salmonella* tester strain YG1021 and with the addition of S9 mix (exogenous metabolic activation system). Bus drivers had higher mutagenic activity in urine than mail carriers did; the individual levels of urinary mutagenic activity were not correlated with excretion of the biomarker of exposure, 1-hydroxypyrene (1-OHP). Among bus drivers, *N*-acetyltransferase 2 (*NAT2*) fast acetylators had higher mutagenic activity in urine than *NAT2* slow acetylators did, and female bus drivers had higher mutagenic activity than male bus drivers did (Hansen et al., 2004).

(b) Experimental systems

(i) In vivo studies

Animals

The Working Group did not identify any publications that assessed the induction of mutations in experimental animals (e.g. rodents) experimentally exposed to outdoor air or samples derived from outdoor air. However, as summarized in Supplemental Table S24 (available online), Yauk & Quinn (1996) and Yauk

et al. (2000) used multilocus DNA fingerprinting and pedigree analyses to assess the frequency of heritable genetic minisatellite mutations in herring gulls (*Larus argentatus*) collected from several locations affected by urban and/or industrial activities. The results obtained showed a significant > 2-fold increase in mutation rate at industrial sites compared with rural controls and, moreover, decreasing mutation rates with increasing distance from the highlighted industrial sources.

The follow-up studies used modified animal enclosures to expose mice to outdoor air in situ at selected urban/industrial locations (Somers et al., 2002, 2004; Yauk et al., 2008). Results were compared with matched exposures at rural control sites. This strategy offers the distinct advantage of real outdoor air exposures under semi-controlled conditions (e.g. animal housing and food); however, it is generally not possible to reliably estimate the actual dose (i.e. milligrams of PM or cubic metres of air per kilogram body weight [bw] per day). These studies have shown an increase in induced heritable mutations at expanded simple tandem repeat (ESTR) loci. High-efficiency particulate air (HEPA) filtration of outdoor air reduced heritable mutation rates (Somers et al., 2004; Yauk et al., 2008) (see also Section 4.3.3b for genotoxic effects on germ cells).

Plants

Studies in plants (see Supplemental Table S1, available online) assessed the ability of outdoor air or samples derived from outdoor air to induce genetic mutations or chromosomal damage. For instance, studies by Ferreira et al. (2000, 2003, 2007) reported the mutagenic activity of outdoor air at selected locations in or near the São Paulo (Brazil) metropolitan area.

(ii) In vitro studies

Table 4.1 provides a summary of studies that have used in vitro assays to assess the ability of outdoor air or samples derived from outdoor air to induce genetic mutations or gene conversion.

Human cells

Eight studies used human h1A1v2 cells to assess the induction of mutations at the thymidine kinase $TK^{+/-}$ locus (Hannigan et al., 1997, 1998, 2005; Durant et al., 1998; Pedersen et al., 1999, 2004, 2005; Adonis & Gil, 2000).

The results showed that the mutagenic potency of PM extracts for urban sites expressed per unit of equivalent organic carbon (EOC) are generally less than 2-fold greater than values obtained for rural (control) sites (Hannigan et al., 1997, 2005; Pedersen et al., 1999, 2004, 2005). However, when expressed per equivalent cubic metre of outdoor air, the potency values for urban sites were 3–10-fold higher than those for rural sites.

Detailed source apportionment revealed that diesel and natural gas combustion emissions make a large contribution to the mutagenic activity of outdoor air PM (Hannigan et al., 1997, 2005). In addition, detailed extract fractionation revealed that polar, semipolar (e.g. nitro-PAHs, ketones, and quinones), and non-polar (e.g. PAHs) extract fractions can each account for a substantial portion of the observed mutagenic activity per unit of EOC. For example, in their analysis of organic extracts of standard reference mixture (SRM) 1649, Durant et al. (1998) noted that semipolar and non-polar extract fractions accounted for 70% of the mutagenic activity. In their analyses of samples collected in southern California, Hannigan et al. (1998) noted that aromatic substances can account for more than 50% of extract mutagenic activity. In their analyses of sites in the north-eastern USA, Pedersen et al. (2004) noted that moderate-molecular-weight PAHs can account for 4–38% of observed mutagenic activity and that polar compounds (e.g. organic acids and hydroxy-polycyclic aromatic

Table 4.1 Genetic mutations associated with outdoor air pollution in human or animal cells in vitro

Geographical location	Test article	Assay/exposure system	End-point(s) examined	Results	Reference
Human cells					
Southern California, USA (1993)	Airborne PM from central Los Angeles, Azusa, Rubidoux, Long Beach, and a control site (San Nicolas Island). Collected on quartz-fibre filters using a virtual impactor. DCM Soxhlet extraction	Human lymphoblastoid h1A1v2 cell line (expressing human CYP1A1), 72 h exposure to extract in DMSO	Point mutations at *TK* locus in h1A1v2 cells	PM extracts induced a significant increase in *TK* mutations. Urban samples showed similar mutagenic potency [IMF × 10^6/μg of EOC (0.137–0.176)], slightly higher than for control site (0.095). Urban sites an order of magnitude more potent when expressed as IMF × 10^6/m^3 (0.670–0.900 vs 0.077). Detailed source analyses revealed that natural gas and diesel combustion made the largest contributions to outdoor air mutagenicity. 2-Nitrofluoranthene accounted for ~1% of observed mutagenic activity	Hannigan et al. (1997, 2005)
Washington, DC, USA (1976–1977)	Time-integrated (baghouse) urban PM collected in 1976 and 1977 (SRM 1649). DCM Soxhlet extraction. Bioassay-directed fractionation	Human lymphoblastoid h1A1v2 cell line (expressing human CYP1A1), 72 h exposure to extract in DMSO	Point mutations at *TK* locus in h1A1v2 cells	PM extracts (> 180 μg equiv PM per mL) induced a significant increase in *TK* mutations. 70% of activity in non-polar and semipolar fraction (A), 30% in polar fraction (B). 4% of fraction A mass accounted for 70% of mutagenic activity. Total of 13 PAHs accounted for 15% of mutagenic activity	Durant et al. (1998)
Southern California, USA (1993)	Urban PM from central Los Angeles, Azusa, Rubidoux, Long Beach, and a control site (San Nicolas Island). Composite PM collected on quartz-fibre filters using a virtual impactor. DCM Soxhlet extraction. Fractionation by normal-phase HPLC	Human lymphoblastoid h1A1v2 cell line (expressing human CYP1A1), 72 h exposure to extract in DMSO	Point mutations at *TK* locus in h1A1v2 cells	Extract of composite PM induced a significant increase in *TK* mutations (mutagenic potency, ~150 IMF × 10^6/mg of EOC). 46% of mutagenicity in non-polar fractions (1 and 2), 41% in semipolar fraction, 13.4% in polar fraction. Subfractionation of fraction 1 indicated that aromatic substances accounted for > 50% of total mutagenicity. Putative mutagens included cyclopenta[*cd*]pyrene, an important contributor to the observed response	Hannigan et al. (1998)

Table 4.1 (continued)

Geographical location	Test article	Assay/exposure system	End-point(s) examined	Results	Reference
North-eastern USA, 5 sites (1995)	Outdoor PM from 5 urban, suburban, and rural locations. Annual composites of PM (> 3 μm) collected on quartz-fibre filters using a virtual impactor. DCM Soxhlet extraction. Detailed chemical analyses	Human lymphoblastoid h1A1v2 cell line (expressing human CYP1A1), 72 h exposure to extract in DMSO	Point mutations at $TK^{+/-}$ locus in h1A1v2 cells	27 of 30 PM extracts induced significant increases in $TK^{+/-}$ mutations. Annual averages for IMF × 10^6/μg of EOC similar for 3 Boston sites (0.08–0.1) and similar for downtown and rural sites in Rochester, New York (0.16–0.19). Mutagenic activity IMF × 10^6/m^3 in urban areas 1.5–2-fold higher than in rural areas (e.g. 0.42–0.63). Mutagenic activity ~2-fold higher in winter than in summer for all sites. Known mutagens accounted for 16–26% of total mutagenic activity. PAHs accounted for 1–16% of mutagenic activity. 6*H*-benzo[*cd*]pyrene-6-one accounted for 3–5% of mutagenic activity	Pedersen et al. (1999, 2005)
North-eastern USA, 5 sites (1995)	Outdoor PM from 5 urban, suburban, and rural locations. Annual composites of PM (> 3 μm) collected on quartz-fibre filters using a virtual impactor. DCM Soxhlet extraction. Fractionation by normal-phase HPLC into 4 fractions of increasing polarity	Human lymphoblastoid h1A1v2 cell line (expressing human CYP1A1), 72 h exposure to extract in DMSO	Point mutations at $TK^{+/-}$ locus in h1A1v2 cells	Extracts of PM from 5 sites induced significant increases in $TK^{+/-}$ mutations (IMF × 10^6/μg of EOC, 0.05–0.3). Activity per m^3 of air in urban Boston ~3-fold higher than in rural area (0.66 vs 0.22). Bioassay-directed fractionation indicated semipolar fraction (nitro-PAHs, ketones, quinones) accounted for 35–82% of total mutagenic activity (per mg of EOC). Non-polar fraction (moderate-molecular-weight PAHs) accounted for 4–38% of mutagenic activity. Polar fraction (carboxylic acids, hydroxy-PACs) accounted for 14–32% of mutagenic activity	Pedersen et al. (2004)
Santiago, Chile (1996)	TSP from an urban, heavy-traffic site, collected on GFFs using a high-volume sampler. DCM sonication extraction	Human lymphoblastoid h1A1v2 cell line (expressing human CYP1A1), 72 h exposure to extract in DMSO	Point mutations at *TK* locus in h1A1v2 cells	Significant elevation in $TK^{+/-}$ mutation frequency for all tested concentrations. Mutagenic potency ($400 \times 10^6/m^3$) 400-fold higher than reported for PM_{10} from Los Angeles in 1993. Mutation potency × 10^6/μg of EOC ~2-fold higher than for Los Angeles (0.300 vs 0.137)	Adonis & Gil (2000)
Animal cells					
Duisburg, Germany	Airborne PM from industrialized Rhine–Ruhr region. Draeger Box Micron filter. CX extraction	Chinese hamster V79 lung cells, 24 h exposure to extract in DMSO	*Hprt* mutations	Significant induction of *Hprt* mutations (i.e. 8-azaguanine-resistant colonies) for 4 m^3 and 8 m^3 equiv of air	Seemayer et al. (1987a, 1988)

Table 4.1 (continued)

Geographical location	Test article	Assay/exposure system	End-point(s) examined	Results	Reference
Paris, France (1983–1985)	Airborne PM from urban site, collected on GFFs using a high-volume sampler. DCM or Ac sonication extraction	Chinese hamster V79 lung cells, 1–3 h exposure to extract in DMSO, with and without Aroclor 1254-induced rat liver S9	*Hprt* mutations	Significant, dose-related (per µg of EOM) increase in *Hprt* mutations (i.e. 6-thioguanine-resistant colonies); increase with exogenous S9 activation. Maximum induction, ~1.25 mutants per 10^6 survivors per m^3	Courtois et al. (1988)
Athens, Greece	Monthly PM samples collected on cellulose filters using a high-volume sampler. Hx sonication extraction	BALB/c 3T3 mouse embryonic fibroblast cells, 48 h treatment with extract in DMSO	Ouabain-resistant colony assay	Weak, non-significant induction of ouabain-resistant colonies	Athanasiou et al. (1987)

Ac, acetone; CX, cyclohexane; DCM, dichloromethane; DMSO, dimethyl sulfoxide; EOC, equivalent organic carbon; EOM, extractable organic matter; equiv, equivalent; GFFs, glass-fibre filters; h, hour or hours; HPLC, high-performance liquid chromatography; Hprt, hypoxanthine–guanine phosphoribosyl transferase; Hx, hypoxanthine; IMF, induced mutant fraction; PACs, polycyclic aromatic compounds; PAHs, polycyclic aromatic hydrocarbons; PM, particulate matter; PM_{10}, particulate matter with particles of aerodynamic diameter < 10 µm; SRM, standard reference mixture; TK, thymidine kinase; TSP, total suspended particles.

compounds [hydroxy-PACs]) can account for 14–32% of the observed mutagenic activity. Pedersen et al. (1999, 2005) noted that mutagenic activity per cubic metre is approximately 2-fold higher in the winter relative to the summer across all sites investigated.

Adonis & Gil (2000) used the *TK*$^{+/-}$ locus mutation assay in h1A1v2 cells to assess the mutagenic activity of an organic extract of PM collected from an urban, heavy-traffic site in Santiago, Chile. The reported mutagenic potency (expressed per cubic metre equivalent per assay millilitre) is more than 400-fold greater than that observed in Los Angeles (i.e. Hannigan et al., 1997, 1998, 2005). Comparisons based on potency expressed per unit of EOC revealed that extracts of PM from Santiago are approximately 2-fold more potent than extracts of PM from Los Angeles.

Animal cells

Several studies have demonstrated that organic extracts of outdoor air PM can induce significant dose-dependent increases in mutant frequency in cultured non-human mammalian cells. For instance, studies by Seemayer et al. (1987a, 1988) revealed that extracts of PM collected from the industrialized Rhine–Ruhr region in Germany induced a significant increase in *Hprt* mutant frequency. Similarly, Courtois et al. (1988) noted that organic extracts of PM collected from an urban location in Paris, France, induced a significant dose-dependent increase in *Hprt* mutant frequency. Source apportionment revealed noteworthy contributions by natural gas and diesel combustion emissions, and extract fractionation revealed substantial contributions from each of several chemical classes, including non-polar compounds (e.g. PAHs), semipolar compounds (e.g. nitro-PAHs and quinones), and polar compounds (e.g. organic acids and hydroxy-PACs).

(c) Yeast

Some extracts of outdoor air PM can induce point mutations, gene conversion, and mitochondrial mutations in yeast (see Supplemental Table S2, available online). In autumn and winter samples from 1993–1994, point mutation frequencies were increased more than 10-fold compared with untreated controls. Rossi et al. (1995) noted high variability across season and year, with no evidence of temporal decline between 1990 and 1994. Buschini et al. (2001) noted that toluene extracts were more mutagenic than acetone extracts and that smaller-sized PM (i.e. PM with particles of aerodynamic diameter < 2.5 μm [$PM_{2.5}$]) was frequently more mutagenic per microgram of PM equivalent than PM with particles of aerodynamic diameter < 10 μm (PM_{10}). A similar study by Bronzetti et al. (1997) revealed that organic extracts of PM collected from a high-traffic site in Pisa, Italy, elicited significant increases in gene conversions and point mutations per cubic metre in the presence of exogenous metabolic activation.

(d) Bacteria

More than 250 scientific publications addressed bacterial mutagenicity assays of outdoor air or samples derived from outdoor air (in North America, South America, Europe, Asia, or Oceania) (see Supplemental Tables S3–S9; Supplemental Figures S1 and S2, available online). These studies analysed organic extracts of airborne PM and/or concentrates of SVOCs collected on adsorbents. Several studies have shown that a modification of the pre-incubation assay known as the microsuspension assay provides enhanced sensitivity to combustion emissions such as those present in urban air PM (Kado et al., 1983, 1986; Agurell & Stensman, 1992).

Identification of putative mutagens

Bagley et al. (1992) and Gundel et al. (1993) noted substantial declines in mutagenic activity in TA98 strains deficient in nitroreductase (NR) (TA98NR). The results indicated a strong involvement of nitro-PAHs, in particular compounds such as the dinitropyrenes.

Many studies of organic extracts of PM from urban areas compared mutagenic potencies in the absence of S9 between TA98 and TA98NR to infer the involvement of nitroarenes in the observed responses. For example, analyses of extracts of PM collected in France, Japan, the Netherlands, and Sweden recorded a marked reduction in mutagenic activity in TA98NR without S9 relative to TA98 (Festy et al., 1984; de Raat & de Meijere, 1988; Takagi et al., 1992; Strandell et al., 1994).

A wide range of studies used the NR-deficient and *O*-acetyltransferase (OAT)-deficient versions of TA98 to examine the influence of nitroarenes in determining the mutagenic activity of organic PM extracts. These studies collectively examined extracts of PM collected from a wide variety of urban and/or industrial locations in Chile, Germany, Italy, Japan, Mexico, Norway, Spain, Sweden, and the USA (Alfheim et al., 1983; Tokiwa et al., 1983; Löfroth et al., 1985; Moriske et al., 1985; Wolff et al., 1986; Crebelli, 1989; De Flora et al., 1989; Takagi et al., 1992; Adonis & Gil, 1993, Espinosa-Aguirre et al., 1993; Gundel et al., 1993; Strandell et al., 1994; Casellas et al., 1995; Sato et al., 1995). Some of these studies noted dramatic reductions in mutagenic activity in the NR-deficient strain TA98NR relative to TA98. Some studies have noted that the relative decline in mutagenic potency of air samples in strain TA98NR relative to TA98 is seasonally variable (Erdinger et al., 2005).

Similarly, numerous studies have used metabolically enhanced *Salmonella* strains such as YG1021 (NR-enhanced) and YG1024 (OAT-enhanced) for comparative assessment of PM extracts. For example, studies of extracts of PM collected from urban and/or industrial areas in Brazil, Italy, Japan, Mexico, and Poland noted substantial increases in mutagenic activity in strains YG1021 and/or YG1024 without S9 (Espinosa-Aguirre et al., 1993; Yamaguchi et al., 1994; Jadczyk & Kucharczyk, 2005; Pereira et al., 2010; Traversi et al., 2011; Lemos et al., 2012). These studies frequently found that OAT enhancement contributed to larger relative increases in potency (without S9) compared with NR enhancement. For example, Yamaguchi et al. (1994) observed 3–4-fold increases in potency in YG1021 and 5–10-fold increases in potency in YG1024 for extracts of PM collected from a high-traffic site in Kobe, Japan.

In addition, numerous studies have used the TA98-derived frameshift strain YG1041, which overexpresses both NR and OAT, for analyses of extracts of PM from diverse regions (e.g. Brazil, the Czech Republic, Denmark, and Poland) (Binková et al., 2003; Sharma et al., 2007; Umbuzeiro et al., 2008; Piekarska et al., 2009). For example, Umbuzeiro et al. (2008) reported dramatic (> 30-fold) increases in the mutagenic activity in YG1041 relative to TA98 without S9 of organic extracts of PM collected from urban locations in São Paulo, Brazil. Extract fractionation confirmed that the highest activity in YG1041 without S9 was associated with nitro-PAHs. This study also indicated more modest, but nevertheless substantial, increases in mutagenic activity in OAT-enhanced strains in the presence of S9. This pattern of activity is thought to be associated with aromatic amines, including *N*-heterocyclics, as well as polar mutagens that, to date, have not been well characterized (e.g. oxy-PAHs) (Umbuzeiro et al., 2008).

Mutagenic potential and particle size

Studies from several geographical regions reported that the mutagenic activity of $PM_{2.5}$ extracts was greater per unit of extractable

organic matter (EOM) or per milligram of PM than that of PM_{10}.

Several studies have documented a noteworthy increase in potency with decreasing particle size. For instance, Kawanaka et al. (2004) found that approximately 90% of the mutagenic activity associated with extracts of PM collected in the Tokyo, Japan, area was associated with fine particles. In addition, studies that examined extracts of PM from Germany (Massolo et al., 2002) and Italy (Pagano et al., 1996; Monarca et al., 1997) specifically reported enhanced potency for the fine (< 1.5 μm) and/or ultrafine (< 0.5 μm) PM fractions. Nonetheless, small PM size fractions make relatively small contributions to atmospheric mutagenic activity per cubic metre due to low atmospheric levels (i.e. mass concentration) of fine and ultrafine PM per cubic metre.

Mutagenic potential of semivolatile organic compounds

In addition to detailed analyses of PM extracts, several studies also evaluated extracted SVOCs. For example, the study by Ciganek et al. (2004), which examined both PM and extracts from urban sites in Brno, Czech Republic, noted that extracts accounted for 15–40% of the total mutagenic activity.

Several studies have indicated that the similarities and differences between SVOC concentrates and PM extracts are affected by season, ambient temperature, adsorbent type, and the presence of S9. For example, in their study of samples collected in the Flanders region of Belgium, Du Four et al. (2004) observed that polyurethane foam extracts were more potent per microgram of EOM in the summer, whereas PM extracts were more potent in the winter. In contrast, Tuominen et al. (1988) noted that XAD extracts from samples collected in Helsinki, Finland, during the winter were generally more potent than PM extracts, with no appreciable difference between XAD and PM extracts from samples collected during the summer.

Spatial and temporal patterns in atmospheric mutagenic activity

Many studies reported markedly higher mutagenic potencies per cubic metre of air for extracts of PM collected during the colder months (winter and autumn) compared with those from the warmer months (spring and summer). Numerous studies conducted in Asia compared extracts of PM samples collected during different seasons and observed that winter and/or autumn samples were markedly more mutagenic than samples collected in spring and/or summer (e.g. Goto et al., 1982; Shimizu et al., 1982; Takagi et al., 1992; Qian et al., 1997; Qian & Zhang, 1997; Vinitketkumnuen et al., 2002). Similarly, studies conducted in European countries found comparable elevations in potency during colder months (Møller & Alfheim, 1980; Wullenweber et al., 1982; Alfheim et al., 1983; Athanasiou et al., 1986; Morozzi et al., 1992; Crebelli et al., 1995; Černá et al., 1999; Binková et al., 2003; Du Four et al., 2004; Piekarska et al., 2009, 2011). Finally, several studies conducted in North America, South America, and New Zealand also indicated elevations in mutagenic potency during colder months (Crebelli, 1989; Daisey et al., 1980; Brown et al., 2005; Cavanagh et al., 2009; Müller et al., 2001; Török et al., 1989).

Nevertheless, some studies from diverse geographical regions failed to detect any appreciable seasonal trend in mutagenic potency or noted that the mutagenic potency levels of extracts of PM collected in the summer were higher relative to those of winter samples (Commoner et al., 1978; Ohtani et al., 1985; Athanasiou et al., 1987; Adonis & Gil, 1993; Greenberg et al., 1993; Kuo et al., 1998).

The trend towards an increased atmospheric burden of PM-associated mutagens during colder months is quite clear and well substantiated. Several studies have found that the root causes of the observed seasonal trends may not be evident. Although some authors have pointed

towards contributions from fuel oil combustion for residential heating during winter months (Daisey et al., 1980), others have reported that the presence of atmospheric oxidants and the atmospheric transformation of nitroarenes are important determinants of seasonal fluctuation in PM mutagenic activity (Arey et al., 1988). Villalobos-Pietrini et al. (2006) noted the importance of a ground-level temperature inversion. Finally, other studies (Festy, 1980; Festy et al., 1984) support the contention that mutagens associated with winter PM are chemically different from mutagens associated with PM emitted during warmer months.

Day-to-day and diurnal variability

Marked day-to-day variability in mutagenic potency has been reported. For instance, a study in Sagamihara, Japan (Takagi et al., 1992), found lower potency on Sundays and holidays and concluded that vehicular emissions were significant contributors to the mutagenic activity of atmospheric PM. Other studies noted differences in mutagenic activity during the day compared with evenings (Møller et al., 1982; Gupta et al., 1996). A study by Kameda et al. (2004) of PM extracts collected in Osaka, Japan, reported peaks in potency in the early morning and late evening; potency corresponded with peaks in atmospheric levels of nitrogen oxide (NO), carbon monoxide (CO), and 1-nitropyrene. Some studies indicated that diurnal patterns varied with the season. For example, Shimizu et al. (1982) observed that daytime PM potency per cubic metre for samples collected in the centre of Tokyo, Japan, exceeded night-time PM potency for winter samples only. Conversely, Sakitani & Hayashi (1986) found that daytime potency exceeded nighttime potency for summer and autumn samples only.

Temporal trends

Two studies investigated temporal trends in PM-associated mutagenicity across an extended period of time. Matsumoto et al. (1998) monitored PM-associated mutagenic activity in Sapporo, Japan, between 1974 and 1992 and indicated a modest 44–50% temporal decline in mutagenic activity with exogenous metabolic activation. This corresponded with a marked 75–80% temporal decline in benzo[*a*]pyrene (B[*a*]P) adsorbed to PM (nanograms per cubic metre). Mutagenic activity without exogenous metabolic activation did not change over time. Similarly, Poli et al. (1999) examined PM-associated mutagenic activity in Parma, Italy, between 1991 and 1998 and reported a marked decline in mutagenic activity between 1992 and 1998.

Spatial variability

Many studies examined the spatial variability in the atmospheric burden of PM-associated mutagenic activity. The most common comparisons concern site-specific conditions related to urbanization, industrial activities, and/or traffic density. For example, many studies conducted in a wide range of locations (Brazil, the Czech Republic, Germany, Greece, Italy, Japan, the Netherlands, Poland, Saudi Arabia, Taiwan [China], Thailand, and the USA) have observed that the mutagenic potency per cubic metre of extracts of PM collected from urban sites near roadways and/or sites described as high-traffic sites is markedly higher relative to more rural reference sites (Preidecker, 1980; Athanasiou et al., 1986; de Raat & de Meijere, 1988; Yu et al., 1989; Wei et al., 1991; Vellosi et al., 1994; Sato et al., 1995; Černá et al., 1999; Vinitketkumnuen et al., 2002; Erdinger et al., 2005; Elassouli et al., 2007; Piekarska et al., 2011).

Elevated mutagenic activity per cubic metre was reported at residential areas located downwind of urban/industrial locations (e.g. de Raat, 1983). Some studies, including those conducted in China (Kong et al., 1994; Zhao et al., 1996), the Netherlands, (van Houdt et al., 1987), and Chile (Gil et al., 1997), observed substantial levels of PM-associated mutagenic activity per cubic metre at control sites, such as a suburban park.

Few studies have compared the mutagenic activity per cubic metre of PM extracts collected from different elevations. Comparisons of extracts of PM collected from ground level with samples collected from the same location at an elevated site, such as a rooftop, reported reduced potency at the site with higher elevation (e.g. Alfheim et al., 1983).

Effect of combustion

Viau et al. (1982) found an increase in the PM-associated mutagenic activity with S9 activation during "smoky" conditions caused by a forest fire in Kentucky, USA. de Andrade et al. (2011) reported that increased levels of PM-associated mutagenic activity were associated with cane-burning activities near São Paulo, Brazil. Similarly, al-Khodairy et al. (1998) noted that increased levels of mutagenic activity were associated with oil well fires in Kuwait. Nevertheless, several studies that examined levels of PM-associated mutagenic activity close to a suspected source (e.g. a municipal waste incinerator or an aluminium smelting operation) were unable to detect any appreciable influence of the source (e.g. Alfheim et al., 1984; Watts et al., 1989).

Several studies conducted fairly rigorous source apportionment and found that a substantial portion of PM-associated atmospheric mutagenicity is from mobile-source emissions (e.g. Israël & Busing, 1983; Lee et al., 1994; Hannigan et al., 2005). Other studies highlighted emissions from wood smoke as more important than mobile-source emissions (e.g. Claxton et al., 2001). Daisey et al. (1980) indicated that in their study in New York City, 50% of PM-associated atmospheric mutagenic activity was from fuel oil combustion for residential heating.

Effect of atmospheric pollutants

Numerous studies from diverse geographical regions have reported positive associations with atmospheric pollutants. These include lead, CO, nitrogen oxides (NO_x, NO and NO_2), SO_2, PAHs, and non-methane hydrocarbons. Associations have been found between PM-associated mutagenic activities and atmospheric lead, a pollutant associated with metal refining and founding and municipal waste incineration, or, for studies conducted before the mid-1990s (UNEP, 1999), with gasoline engine emissions (Flessel et al., 1985; Pitts et al., 1985). Significant associations between PM-associated mutagenicity and NO_x, an indicator of mobile-source emissions, have also been reported (Morris et al., 1995). Several studies have also highlighted associations with SO_2, an atmospheric pollutant associated with combustion of coal, residential fuel oil, and heavy fuel oils, such as marine fuel oil (Israël & Busing, 1983; Wolff et al., 1986; Morris et al., 1995). Finally, numerous studies have documented associations between atmospheric mutagenic activity and levels of atmospheric PAHs, including several known mutagens and/or mutagenic carcinogens (Viras et al., 1990; Černá et al., 1999).

Effect of meteorological conditions

Several studies have observed that meteorological conditions, such as wind speed and direction, temperature, precipitation, humidity, and solar penetration, can influence the levels of PM-associated atmospheric mutagenicity.

Several studies reported that PM-associated atmospheric mutagenicity per cubic metre was negatively affected by precipitation (rain or snow).

Because moving air masses can contain urban/industrial combustion emissions, it is perhaps not surprising that several studies have highlighted the role of wind speed and direction in determining levels of PM-associated atmospheric mutagenicity per cubic metre (e.g. Commoner et al., 1978; Wang et al., 1980). Detailed analyses (e.g. as conducted by Alink et al., 1983; de Raat et al., 1985; de Raat & de Meijere, 1988, and Morris et al., 1995) specifically identified wind directions that were associated with increased

levels of atmospheric mutagenicity. For example, studies conducted in the Netherlands found increased levels of PM-associated mutagenicity for easterly or southerly winds, from Germany and Belgium.

Post-emission formation of potent mutagens: atmospheric reactions

Studies that investigated the effects of meteorological conditions on atmospheric mutagenic activity are congruent with those of Arey et al. (1988, 1992) regarding the post-emission formation of potent mutagens derived from combustion emissions. Arey et al. showed that atmospheric reactions can contribute to the formation of potent nitro-PAHs. Such observations are consistent with mutagen formation during airborne movement from an urban/industrial area to a less-congested area, and with some atmospheric transformation products being mutagenic.

Conclusions

In summary, several fundamental conclusions can be drawn from the more than 250 studies that used the *Salmonella* reverse mutation assay to examine samples derived from outdoor air (e.g. PM extracts) collected from locations on five continents over the past 30 years.

1. Outdoor air PM extracts, including samples of total suspended particles (TSP), PM_{10}, and $PM_{2.5}$, evaluated for mutagenicity yielded a significant positive response; however, the mutagenic potency values, expressed per cubic metre, ranged over 5 orders of magnitude. Thus, some atmospheric samples clearly contain very little mutagenic activity, whereas others carry a high burden of activity.
2. The mutagenic potency of outdoor air is positively associated with outdoor air PM levels, reflecting an overall correspondence between declines in air quality and increased levels of PM-associated mutagenic activity. Increased PM-associated mutagenic activity is positively associated with other measures of impaired air quality, such as increased NO_x, lead, PAHs, CO, nitro-PAHs, and SO_2.
3. Samples derived from outdoor air PM collected during colder seasons (winter) are generally more mutagenic (per cubic metre) than those from PM collected during warm seasons (summer). This is likely due to a combination of factors that include changes in source contributions, meteorological changes, and seasonal land-use changes. Concomitantly, studies find that the PM-associated mutagenic potency per cubic metre of outdoor air is inversely related with air temperature.
4. Bioassay-directed fractionation studies confirm that much of the mutagenic activity associated with the particulate portion of outdoor air is found in the moderately polar and/or polar organic fractions, and includes a wide range of acids, bases, and neutral compounds, confirming a significant role for numerous classes of organic compounds. Although several noteworthy mutagens associated with outdoor air PM have been identified (e.g. nitro-PAHs), in most cases the putative mutagens have not been well characterized.
5. Samples derived from outdoor air PM are generally more mutagenic (per cubic metre) during workdays relative to non-workdays (e.g. weekends) and are generally more mutagenic during daytime than at night. The higher mutagenic potencies during workdays and daytime are associated with higher outdoor concentrations of lead, CO, and NO_x, reflective of mobile-source emissions.
6. Studies conducted over 7 years in Parma, Italy, showed a decline (63–76%) in outdoor air mutagenic activity (per cubic metre), reflecting the potential benefits of increasingly stringent emission controls for mobile combustion sources (Poli et al., 1999). A similar study conducted over 18 years in

Sapporo, Japan, noted a modest (44–50%) decline only for mutagenic activity commonly associated with PAHs (i.e. not nitro-PAHs) (Matsumoto et al., 1998).

7. Samples derived from outdoor air PM are generally more mutagenic if sampled at ground level, relative to higher elevations. Mutagenic activity is also greatly affected by wind direction and other meteorological conditions. Precipitation events reduce the levels of PM-associated mutagenic activity (per cubic metre).
8. Smaller particles ($PM_{2.5}$) are generally more mutagenic per mass of particle than larger particles (PM_{10}); maximum mutagenic activity is associated with particles of 0.1–1.2 μm.
9. The main contributors to PM-associated outdoor air mutagenicity appear to be urbanization, industrial activity, and traffic density. In some cases, wood smoke and/or emissions associated with residential heating have been highlighted as important sources of PM-associated mutagens, and these latter sources can exceed contributions from mobile-source emissions. Many studies have associated outdoor air mutagenicity with SO_2, which is associated with the combustion of coal, residential fuel oil, and heavy fuel oils, including marine fuel oil.

4.2.2 Cytogenetic effects

(a) Humans

Cytogenetic studies have directly evaluated the frequencies of chromosomal aberrations (CAs), micronuclei (MN), or sister chromatid exchanges (SCEs) among workers exposed to polluted outdoor air or heavy-traffic roads, compared with subjects exposed primarily to indoor air. In addition, a few studies have evaluated cytogenetic end-points in populations living in urban/industrial areas versus rural areas. Most such studies compared cytogenetic end-points in peripheral blood lymphocytes.

(i) Chromosomal aberrations

Table 4.2 summarizes the studies in which CAs were evaluated as a biomarker of outdoor air exposure versus subjects who worked or spent the majority of their time indoors. The studies reviewed cover several categories of workers exposed to outdoor air, and nearly all showed an association between CAs and this exposure, although this was the case for only two exposure groups when the data were stratified by genotype/phenotype (Knudsen et al., 1999). Four studies included exposure assessments, and all of them found higher levels of exposure among the subjects exposed to outdoor air than among the controls (Burgaz et al., 2002; Cavallo et al., 2006; Srám et al., 2007; Zidzik et al., 2007).

Among the studies included in Table 4.2, three studies (Anwar & Kamal, 1988; Knudsen et al., 1999; Cavallo et al., 2006) cultured the lymphocytes for 48 hours; however, three studies (Burgaz et al., 2002; Beskid et al., 2007; Sree Devi et al., 2009) cultured the cells for 72 hours, and one study for 69 hours (Chandrasekaran et al., 1996). Culturing cells for more than 48 hours can result in increased frequencies of CAs formed during the extended period of growth in culture. However, only one study with long culturing times (Sree Devi et al., 2009) appears to have an elevated frequency of CAs among the controls. Nonetheless, all of the studies in Table 4.2 reported significantly higher frequencies of CAs among the exposed relative to control populations.

Ten studies found increased frequencies of CAs among traffic police compared with their respective control populations (Table 4.2). Thus, traffic police in Cairo, Egypt, had higher frequencies of CAs compared with police trainers (Anwar & Kamal, 1988), as did those in Ankara, Turkey, compared with office workers (Burgaz et al., 2002), as did traffic police in Hyderabad,

Table 4.2 Chromosomal aberrations in peripheral blood lymphocytes of humans exposed to outdoor air pollution

Country	Control		Exposed		*P* value	Finding	Reference
	Description (*n*)	Result[a]	Description (*n*)	Result[a]			
Egypt	Police trainers (15)	0 ± 0	Traffic police (28)	0.4 ± 0.7	< 0.05	+	Anwar & Kamal (1988)
Turkey	Office workers (23)	0.26 ± 0.14	Traffic police (15)	1.29 ± 0.30	< 0.05	+	Burgaz et al. (2002)
	Office workers (23)	0.26 ± 0.73	Taxi drivers (17)	1.82 ± 0.34	< 0.01	+	Burgaz et al. (2002)
India	Non-traffic workers (115)	3.35 ± 1.21	Traffic police (136)	6.48 ± 1.67	< 0.05	+	Sree Devi et al. (2009)
China	Police working in offices (30)	0.4%	Traffic police (45)	0.98%	< 0.01	+	Chen et al. (1999)
Czech Republic	Indoor workers (49)	0.24 ± 0.18	Traffic police (50)	0.33 ± 0.25	< 0.05	+	Beskid et al. (2007)
Slovakia	Indoor workers (45)	0.21 ± 0.20	Traffic police (46)	0.30 ± 0.19	< 0.05	+	Beskid et al. (2007)
Bulgaria	Indoor workers (25)	0.13 ± 0.13	Traffic police (26)	0.25 ± 0.14	< 0.01	+	Beskid et al. (2007)
	Indoor workers (25)	0.13 ± 0.13	Bus drivers (25)	0.25 ± 0.18	< 0.05	+	Beskid et al. (2007)
Czech Republic	Indoor workers (50)	1.94 ± 1.28	Traffic police (52)	2.33 ± 1.53	> 0.05	–	Zidzik et al. (2007)
Slovakia	Indoor workers (55)	2.14 ± 1.61	Traffic police (51)	2.60 ± 2.64	> 0.05	–	Zidzik et al. (2007)
Bulgaria	Indoor workers (45)	1.79 ± 0.77	Traffic police (50)	3.04 ± 1.64	< 0.05	+	Zidzik et al. (2007)
	Indoor workers (45)	1.79 ± 0.77	Bus drivers (50)	3.60 ± 1.63	< 0.05	+	Zidzik et al. (2007)
Italy	Indoor airport workers (31)	0	Outdoor airport workers (41)	0.37	0.005	+	Cavallo et al. (2006)
Denmark	Low-exposure bus drivers (19)	Stratified by genotype	High-exposure bus drivers (55)	Stratified by genotype		+	Knudsen et al. (1999)
	Office workers (41)	Stratified by genotype	Postal workers (60) (mail carriers)	Stratified by genotype		+	Knudsen et al. (1999)
China	Chorionic villi in women in Dalian (827)	0.11	Chorionic villi in women in Shenyang (811)	1.66	< 0.0001	+	Cui et al. (1991)
			Chorionic villi in women in Zhengzhou (1060)	0.52	< 0.0001	+	
Czech Republic	Traffic police sampled in March (low pollution) (61)	0.16 ± 0.17 by FISH	Traffic police sampled in January (high pollution) (61)	0.27 ± 0.18 by FISH	< 0.001	+	Srám et al. (2007)
		1.84 ± 1.28		2.07 ± 1.48	> 0.05	–	

[a] Results are expressed as the percentage of lymphocytes with aberrations; all studies examined 100 metaphases per subject, except for Sree Devi et al. (2009), which studied 150 metaphases per subject. All studies used conventional staining, except for Beskid et al. (2007) and, where noted, Srám et al. (2007), which used fluorescence in situ hybridization (FISH) of chromosomes 1 and 4.

+, positive; –, negative.

India, compared with subjects who did not work in traffic (Sree Devi et al., 2009), as did traffic police in Hebei City, Henan, China, compared with police who worked in offices (Chen et al., 1999). The study in Turkey included an exposure assessment, which found higher concentrations of urinary 1-OHP among the traffic police relative to the control population (Burgaz et al., 2002). The study by Beskid et al. (2007) showed that police officers who worked outdoors in Prague (Czech Republic), Košice (Slovakia), or Sofia (Bulgaria) had higher frequencies of CAs as determined by fluorescence in situ hybridization (FISH) compared with subjects who were indoors at least 90% of the time. However, when traditional cytogenetic analyses were used, only the Sofia, Bulgaria, traffic police had elevated CA frequencies (Zidzik et al., 2007). An exposure assessment of these three sets of populations showed that the police who worked outdoors had higher exposures to carcinogenic PAHs compared with the controls (Zidzik et al., 2007). Using FISH, Srám et al. (2007) showed that traffic police in Prague, Czech Republic, had higher CA frequencies in January, when air pollution (PM_{10}) was high, than in March, when the PM_{10} concentration was significantly lower. However, no differences in CA frequencies were found when traditional cytogenetic methods were used.

One study performed in the Czech Republic (Rubes et al., 2005) evaluated the association between exposure of men to polluted outdoor air and CAs in their sperm, and found no association between aneuploidy in the sperm and outdoor air pollution. A study in traffic police in Prague, Czech Republic, showed that the police had higher frequencies of CAs in sperm when sampled in January, when the PM_{10} concentrations were high, than in March, when the PM_{10} concentrations were low (Srám et al., 1999) (see Section 4.3.3a).

The frequencies of CAs were higher in taxi drivers in Ankara, Turkey, compared with office workers (Burgaz et al., 2002; Table 4.2), and the taxi drivers had higher concentrations of urinary 1-OHP compared with the control subjects.

An investigation of outdoor airport workers at the international airport in Rome, Italy, found higher frequencies of CAs in this population compared with the frequencies found among airport office workers (Cavallo et al., 2006; Table 4.2). Exposure assessments found higher concentrations of PAHs in the air outdoors compared with in the offices, but there was no difference in the concentrations of urinary 1-OHP among the exposed and control groups.

In Denmark, a strategic environmental health programme, including studies of exposures and biomarkers related to traffic-generated air pollution, was carried out with bus drivers, letters carriers, and post office workers. A study of bus drivers categorized the exposure groups as high for drivers within the city of Copenhagen, medium for drivers in the suburbs, and low for drivers in the countryside (Knudsen et al., 1999; Table 4.2). When stratified by genotype/phenotype, those bus drivers who were glutathione *S*-transferase M1 (*GSTM1*) null and had the *NAT2* slow acetylator genotype exhibited an exposure-related increase in CAs compared with those with the *NAT2* fast acetylator and *GSTM1*-positive genotypes (Knudsen et al., 1999). [The role of genotype/phenotype is discussed later in this *Monograph* (see Section 4.4).] A separate study of bus drivers in Sofia, Bulgaria, found increased frequencies of CAs in that population relative to office workers when analysed either by traditional cytogenetic methods (Zidzik et al., 2007) or by FISH (Beskid et al., 2007).

A comparison of mail carriers in Copenhagen, Denmark, with office workers found that the mail carriers who were *NAT2* slow acetylators had higher frequencies of CAs compared with those who were *NAT2* fast acetylators (Knudsen et al., 1999; Table 4.2). This result suggested that the *NAT2* genotype may influence responses to other common exposures or may influence the

baseline frequencies of CAs (Knudsen et al., 1999).

Using white blood cells from 55 children attending a school in a rural area of Thailand and from 91 children attending an urban school in Bangkok, Thailand, Tuntawiroon et al. (2007) and Ruchirawat et al. (2007) exposed the cells to 100 cGy of ionizing radiation from a ^{137}Cs source at a dose rate of 5 Gy/minute and then determined the frequency of CAs. The authors found significantly higher frequencies of deletions/metaphase among the urban schoolchildren (0.45 ± 0.01) than among the rural schoolchildren (0.26 ± 0.01). Exposure analyses showed that the urban schoolchildren had higher concentrations of urinary 1-OHP and blood benzene compared with the rural schoolchildren. In addition, the air in the urban area had higher concentrations of PAHs and benzene than that from the rural area. Together, these studies indicated that the global DNA repair system of the urban schoolchildren was less effective at repairing the DNA damage after a challenge by ionizing radiation compared with that of the rural schoolchildren.

Cui et al. (1991) determined the frequency of CAs in the chorionic villi of 2698 women (aged 25–35 years) having abortions for non-medical reasons at less than 10 weeks of pregnancy from three cities with different levels of air pollution. The three cities were Shenyang, which had heavy pollution due to industry and coal combustion (811 women), Zhengzhou, which had moderate air pollution (1060 women), and Dalian, which was the least polluted, with light industry (827 women). The incidences of polyploidy, trisomy, and chromosome structural abnormalities in the women in Shenyang were 2.3, 3.4, and 16 times, respectively, those in the women in Dalian. Similarly, the cytogenetic frequencies of polyploidy, trisomy, and chromosome structural abnormalities in the women in Zhengzhou were 3.9, 1.3, and 4.9 times, respectively, those in the women in Dalian. The data for structural abnormalities are shown in Table 4.2. The results suggested that there was a positive correlation between the incidence of numerical and/or structural CAs and the severity of air pollution, especially SO_2 concentrations (Cui et al., 1991).

(ii) Micronuclei

The studies reviewed here cover a variety of exposure situations (Table 4.3), and of those that included exposure assessments, all found higher levels of exposure to air pollutants among the group exposed to outdoor air compared with the unexposed controls. Three studies evaluated MN in buccal cells (Karahalil et al., 1999; Hallare et al., 2009; Sellappa et al., 2010), and the rest evaluated MN in lymphocytes; however, one evaluated MN in both cell types (Cavallo et al., 2006), and one evaluated MN in maternal lymphocytes and cord blood (Pedersen et al., 2009). Most studies found increased frequencies of MN in the outdoor versus indoor exposure settings, or in populations living in urban/industrial areas versus rural areas. All lymphocyte studies except that of Zhao et al. (1998) used the cytokinesis-block version of the MN assay; those studies that used buccal cells did not (Karahalil et al., 1999; Cavallo et al., 2006; Hallare et al., 2009; Sellappa et al., 2010).

Six studies investigated the induction of MN in traffic police relative to controls not exposed chronically to traffic (Table 4.3). Traffic police in Ankara, Turkey, had higher frequencies of buccal cell MN compared with the controls (details of controls not specified) (Karahalil et al., 1999; Table 4.3). Likewise, higher frequencies of buccal cell MN were found in traffic police in Manila, Philippines, compared with other residents of Manila (Hallare et al., 2009; Table 4.3). Increased frequencies of MN were found in buccal cells of traffic police in Lanzhou, China, compared with the frequencies found in police who worked in offices (Zhao et al., 1998; Table 4.3).

A study of MN in lymphocytes in traffic police in Genoa, Italy, found increased frequencies in this group relative to a group of indoor workers

Table 4.3 Micronuclei in humans exposed to outdoor air pollution

Country	Tissues	No. of cells[a]	Control		Exposed		*P* value	Finding	Reference
			Description (*n*)	Result[b]	Description (*n*)	Result[b]			
Turkey	BC	3000	Workers (20)	0.03 ± 0.03	Taxi drivers (17)	0.12 ± 0.05	< 0.0001	+	Karahalil et al. (1999)
			Workers (20)	0.03 ± 0.03	Traffic police (15)	0.10 ± 0.05	< 0.05	+	Karahalil et al. (1999)
Philippines	BC	2000	City residents (18)	6.5	Filling station attendants (18)	18.9	< 0.05	+	Hallare et al. (2009)
					Traffic police (18)	17.07	< 0.05	+	Hallare et al. (2009)
China	PBL	2000	Police working in offices (49)	1.97 ± 0.21	Traffic police (65)	4.27 ± 0.68	< 0.05	+	Bai et al. (2005)
India	BC	3000	City residents (100)	2.79 ± 0.16	Filling station attendants (110)	12.61 ± 0.39	< 0.001	+	Sellappa et al. (2010)
China		1000	Police working in offices (34)	3.22 ± 1.31	Traffic police (67)	5.72 ± 2.57	< 0.05	+	Zhao et al. (1998)
Italy	PBL	2000	Indoor workers (54)	4.49 ± 2.0	Traffic police (94)	3.75 ± 1.65	0.02	+	Merlo et al. (1997)
Czech Republic	PBL	1000	Traffic police, in May (49)	4.37 ± 2.56	Traffic police, in February (49)	7.16 ± 3.50	< 0.001	+	Rossnerova et al. (2009)
Italy	BC	2000	Indoor airport workers (31)	Buccal: 0.064 ± 0.054	Outdoor airport workers (41)	Buccal: 0.064 ± 0.098	0.251	–	Cavallo et al. (2006)
	PBL	1000		Blood: 0.710 ± 0.421		Blood: 0.815 ± 0.37	0.129	–	
Italy	PBL	2000	Laboratory workers (34)	4.03	Traffic police (82)	3.73	> 0.05	–	Bolognesi et al. (1997a)
Denmark	CBL	2000	Low traffic density (23)	0.291 ± 0.178	High traffic density (23)	0.429 ± 0.206	< 0.01	+	Pedersen et al. (2009)
China	PBL	1000	Rural residents (63)	1.02	Urban residents (66)	1.56	< 0.05	+	Ishikawa et al. (2006)
Czech Republic	PBL	500	Rural children (12)	0.49 ± 0.20	Urban children (12)	0.70 ± 0.23	0.039	+	Pedersen et al. (2006)
China	PBL	1000	Shanghai Botanical Garden officers (36)	0.69 ± 0.60	Bus drivers or bus ticket officers on route through the Dapu tunnel in Shanghai (40)	1.28 ± 1.01	< 0.01	+	Peng & Ye (1995)

[a] Number of cells analysed per sample.

[b] Results are expressed as percentage of cells with micronuclei; in the Pedersen et al. (2006, 2009) studies, the results were expressed as ‰ cells.

+, positive; –, negative; BC, buccal cells; CBL, cord blood lymphocytes; PBL, peripheral blood lymphocytes.

(Merlo et al., 1997; Table 4.3). Exposure assessments found a 30-fold higher concentration of PAHs in the air outdoors compared with that in the office space. Another study in lymphocytes of traffic police in Genoa found no increase in MN frequencies in traffic police compared with a group of laboratory workers (Bolognesi et al., 1997a; Table 4.3). Nonetheless, exposure assessments showed higher levels of B[*a*]P in the air outdoors compared with that in the laboratories. Higher frequencies of MN were found among traffic police in Hebei, China, compared with police who worked in offices (Bai et al., 2005; Table 4.3), and exposure assessments found increased concentrations of inhaled particles in the air breathed by the exposed compared with the control subjects. Increased concentrations of NO_x, CO, hydrocarbons, and lead were also found among the exposed versus the control populations.

Unlike the previous studies of traffic police, the study by Rossnerova et al. (2009) evaluated traffic police in Prague, Czech Republic, but compared the MN frequencies among the police as measured in a more-polluted month (February) versus a less-polluted month (May). Exposure assessments had shown that the air in February had higher concentrations of carcinogenic PAHs, B[*a*]P, and various VOCs (benzene, ethylbenzene, and *o*-xylene). Traffic police had frequencies of MN that were higher in the more-polluted month (February) compared with those in the less-polluted month (May) (Table 4.3).

Filling station attendants in Manila, Philippines, had higher frequencies of buccal cell MN compared with residents of Manila (Hallare et al., 2009; Table 4.3). The frequencies of buccal cell MN were higher in filling station attendants in Coimbatore City, India, compared with other residents of Coimbatore City (Sellappa et al., 2010; Table 4.3). The frequencies of buccal cell MN were higher in taxi drivers in Ankara, Turkey, compared with control subjects (Karahalil et al., 1999; Table 4.3). [The Working Group noted that this human study addressed an occupational situation and might not be broadly applicable.]

No increases in either buccal or lymphocyte MN frequencies were found among outdoor airport workers at the international airport in Rome, Italy, compared with airport office workers (Cavallo et al., 2006; Table 4.3). Exposure assessments found that the concentration of PAHs was higher outdoors than in the offices, but concentrations of urinary 1-OHP were not different between the two groups of workers.

One study found higher frequencies of MN in lymphocytes of mothers and umbilical cord blood from those mothers who lived in high- versus low-traffic areas of Denmark (Pedersen et al., 2009; Table 4.3).

Several studies evaluated subjects living in urban/industrial areas versus rural areas. For example, Ishikawa et al. (2006) showed that residents of an industrial district of Shenyang, China, had higher frequencies of MN compared with residents of a rural district of the same city (Table 4.3). Likewise, Pedersen et al. (2006) found that young children living in an urban area (Teplice, Czech Republic) had higher frequencies of MN compared with young children living in a rural area (Prachatice, Czech Republic) (Table 4.3).

Another comparison of subjects working in two different environments was performed by Peng & Ye (1995), who measured the frequency of MN in bus drivers or on-site bus ticket officers a route that runs through a tunnel in Shanghai, China, and compared the results with those obtained in officers who worked in the Shanghai Botanical Garden. Daily average TSP concentrations in the tunnel were extremely high (1.86 mg/m^3) compared with the established standard of 0.15 mg/m^3. The bus drivers and on-site bus ticket officers had higher MN frequencies compared with the officers in the botanical garden (Table 4.3).

(iii) Sister chromatid exchanges

SCEs have been used extensively as a biomarker of genotoxicity; however, unlike CAs and MN, SCEs have not turned out to be predictive of cancer risk (Norppa et al., 2006). Nonetheless, SCEs are a sensitive indicator of exposure to a variety of genotoxic agents; as reviewed below, this includes exposure to outdoor air pollution.

There were 11 studies in which SCEs in lymphocytes were investigated as a biomarker associated with exposure to outdoor air pollution (Table 4.4). Of these 11 reports, all but two found increased frequencies of SCEs in the exposed population compared with the control subjects. Among the 11 reports, four exposure groups were studied; three of the 10 studies included exposure assessments, all of which found a difference between the exposure levels of the exposed and control populations. All of the studies cultured the lymphocytes for 72 hours, except for Sree Devi et al. (2009), where the cells were cultured for 70 hours, and Cavallo et al. (2006), where the cells were cultured for 48 hours.

There were eight studies of SCEs in traffic police, all but one of which found higher frequencies of SCEs in the traffic police relative to the control populations (Table 4.4); the one negative study included an exposure assessment. Traffic police in Cairo, Egypt, had higher frequencies of SCEs compared with police trainers (Anwar & Kamal, 1988); the same was true for traffic police in Madras, India, compared with subjects not working in traffic (Chandrasekaran et al., 1996). Traffic police in Lanzhou, China, had higher frequencies of SCEs compared with police who worked in offices (Zhao et al., 1998); the same was true for traffic police in Hyderabad, India (Sreedevi et al., 2006), or Chennai City, India (Anbazhagan et al., 2010), compared with office workers. Traffic police in Bangkok, Thailand, had higher frequencies of SCEs compared with university students, who were used as the control population (Soogarun et al., 2006). Although traffic police in Genoa, Italy, did not have elevated frequencies of SCEs compared with laboratory workers, used as controls (Bolognesi et al., 1997b), an exposure assessment found that the concentration of B[*a*]P and other PAHs in the outdoor air was higher than that in the laboratory spaces. Traffic police in Hebei, China, had higher frequencies of SCEs compared with police who worked in offices (Bai et al., 2005; Table 4.4), and exposure assessments showed that there were higher concentrations of particles, NO_x, CO, hydrocarbons, and lead in the air for the exposed populations compared with the controls.

Outdoor workers at the international airport in Rome, Italy, had higher frequencies of SCEs compared with indoor workers at the airport (Cavallo et al., 2006; Table 4.4), and exposure assessments found that the outdoor air had higher concentrations of PAHs than the indoor air. Nonetheless, there was no difference in the urinary concentration of 1-OHP between the outdoor and indoor workers. The frequencies of SCEs were not higher among tunnel workers in the Umbrian Apennine Mountains, Italy, compared with outdoor workers away from traffic (Villarini et al., 2008; Table 4.4).

A comparison of subjects working in two different environments was performed by Peng & Ye (1995), who measured the frequency of SCEs in bus drivers or on-site bus ticket officers on a route that runs through a tunnel in Shanghai, China, versus that of officers who worked in the Shanghai Botanical Garden. Daily average TSP concentrations in the tunnel were extremely high (1.86 mg/m^3) compared with the established standard of 0.15 mg/m^3. The bus drivers and on-site bus ticket officers had higher SCE frequencies compared with the officers in the botanical garden (Table 4.4).

In summary, two types of studies were performed to evaluate CAs, MN, and SCEs in humans exposed to outdoor air pollution. One type studied subjects whose work involved being outside (frequently in or near traffic) for

Table 4.4 Sister chromatid exchanges in lymphocytes of humans exposed to outdoor air pollution

Country	No. of metaphases[a]	Control		Exposed				
		Description (*n*)	Result[b]	Description (*n*)	Result[b]	*P* value	Finding	References
Egypt	40	Police trainers (10)	4.8	Traffic police (21)	7.5	< 0.10	+	Anwar & Kamal (1988)
India	25	Unexposed (23)	5.67 ± 0.37	Traffic police (23)	12.78 ± 0.68	< 0.001	+	Chandrasekaran et al. (1996)
Italy	50	Laboratory workers (35)	7.36 ± 1.35	Traffic police (54)	7.47 ± 1.28	> 0.05	–	Bolognesi et al. (1997b)
China	100	Police working in offices (34)	3.73 ± 1.51	Traffic police (67)	8.81 ± 1.83	< 0.05	+	Zhao et al. (1998)
Italy	50	Indoor airport workers (31)	3.84 ± 0.58	Outdoor airport workers (41)	4.61 ± 0.80	< 0.001	+	Cavallo et al. (2006)
India	50	Office workers (60)	4.18 ± 1.85	Traffic police (85)	9.31 ± 5.29	< 0.05	+	Sreedevi et al. (2006)
Thailand	NR	University students (20)	0.24 ± 0.12	Traffic police (30)	4.40 ± 0.93	< 0.05	+	Soogarun et al. (2006)
China	NR	Police working in offices (49)	2.69 ± 0.35	Traffic police (65)	4.32 ± 0.58	< 0.05	+	Bai et al. (2005)
Italy	30	Outdoor workers away from traffic (34)	4.88 ± 0.08	Tunnel workers (39)	5.07 ± 0.11	> 0.05	–	Villarini et al. (2008)
India	25	Office workers (25)	6.49 ± 0.31	Traffic police (56)	10.62 ± 0.57	< 0.001	+	Anbazhagan et al. (2010)
China	25	Shanghai Botanical Garden officers (36)	4.50 ± 0.99	Bus drivers or bus ticket officers on route through the Dapu tunnel in Shanghai (40)	5.94 ± 1.23	< 0.001	+	Peng & Ye (1995)

[a] Number of metaphases analysed per sample.
[b] Results are from blood cells and are expressed as sister chromatid exchanges per cell.
+, positive; –, negative; NR, not reported.

most of the workday (e.g. traffic police, street vendors, and toll booth operators) compared with subjects who worked primarily indoors (e.g. office workers). Another type of study compared subjects who lived or worked in more- versus less-polluted airsheds. Nearly all studies showed that polluted outdoor air induced significantly higher cytogenetic effects relative to either indoor air or less-polluted outdoor air. These studies covered 10 countries for CAs, seven for MN, and five for SCEs. Two of these end-points (CAs and MN) are associated with increased risk of cancer, highlighting the importance of these genotoxicity biomarker studies.

(b) Experimental systems

(i) In vivo

Animals

See Table 4.5.

Chromosomal aberrations

Several studies have examined the effect of outdoor air pollution or samples derived from it on cytogenetic abnormalities in experimental animals in vivo. Only one study examined the frequency of cytogenetic abnormalities in animals exposed in situ at locations highlighted for poor air quality. Rubeš et al. (1997) investigated cytogenetic effects in peripheral blood lymphocytes of dairy cattle in the Teplice district of the Czech Republic, an industrialized area with severe air pollution, and the Prachatice district, an agricultural area with lower levels of air pollution. The results revealed a significantly higher percentage of aberrant cells (chromatid aberrations or CAs) in animals in Teplice relative to Prachatice. The CAs included chromatid breaks, isochromatid breaks, acentric fragments, and translocations (Rubeš et al., 1997).

Four studies conducted in China examined the ability of extracts of airborne PM to induce various cytogenetic abnormalities in murine bone marrow. The study by Wang & Zhang (1984) was conducted in the northern Chinese city of Harbin, which experiences a marked reduction in air quality in colder months due to residential heating by coal. The authors reported that mice exposed orally by gavage to methanol extracts of TSP collected from a residential site in the winter showed a dose-dependent increase in aneuploidy and CAs. The CAs included chromosome breaks, fragments, dicentric chromosomes, and ring chromosomes (Wang & Zhang, 1984).

The other three studies were conducted in Taiyuan, an industrialized city in north-western China that contains chemical production facilities and coal-fired electricity generation facilities. Yang & Wu (1984) found that mice (strain not specified) treated with a single intraperitoneal injection of methanol extracts of TSP collected from several locations had dose-dependent increases in CAs in bone marrow cells. Marked increases were noted for samples from industrial, commercial, and residential sites, and the CAs included chromatid or chromosome breaks for the industrial or high-traffic sites and ring chromosomes for the commercial or residential sites. The authors observed that the frequency of induced CAs was positively associated with PM level (Yang & Wu, 1984).

A similar study in Taiyuan involved intraperitoneal exposures of mice to inorganic (i.e. nitric acid) PM extracts, or PM extracts prepared using simulated lung fluid. The results showed significant dose-dependent increases in CA frequency and increased responses for particles smaller than 2.5 μm. For the inorganic extract, the authors reported that the observed CA frequency was correlated with concentrations of lead, manganese, chromium, nickel, and cadmium (Lei et al., 1993). The study by Sun et al. (1995) investigated CAs in male germ cells of Kunming mice treated intraperitoneally with dichloromethane (DCM) extracts of TSP collected downwind of a coal-fired electricity generation facility. The results revealed dose-dependent increases in sperm abnormalities, CAs

Table 4.5 Cytogenetic damage associated with outdoor air pollution in experimental animals in vivo

Geographical location	Assay/exposure system	End-point(s) examined	Results	Reference
Bohemia, Czech Republic (1992, 1993)	Cytogenetic damage in bovine lymphocytes from cow herds on 5 farms in the industrialized Teplice district and 5 farms in the agricultural Prachatice district	Chromatid and chromosomal aberrations in lymphocytes, excluding gaps	Significant elevation in frequency of aberrant cells for 2 of the 3 time periods investigated	Rubeš et al. (1997)
Harbin, China (1981)	TSP, MeOH Soxhlet extraction. Five consecutive daily gavage doses in sunflower oil	Polyploidy and CAs in bone marrow cells (details not provided)	Dose-dependent increase in aneuploidy and CAs (e.g. breaks, fragments, dicentrics, rings)	Wang & Zhang (1984)
Taiyuan, China (1984)	TSP from 5 locations, MeOH extraction. Single i.p. injection in corn oil	Polyploidy and CAs in bone marrow cells (details not provided)	Dose-dependent increase in CAs; mainly breaks and rings for industrial, commercial, or residential sites. Control-site TSP extract also elicited a significant positive response. Significant correlation between CA frequency and PM level	Yang & Wu (1984)
Taiyuan, China (1990)	Size-fractionated airborne PM, extraction with nitric acid and SLF. Single i.p. injection	Polyploidy and CAs in bone marrow cells in Kunming mice 24 h after dose	Nitric acid and SLF extract induced dose-dependent increases in CAs. Greater responses for smaller size fractions. Significant induction for particles < 2 μm in 2.5 m^3	Lei et al. (1993)
Taiyuan, China (1994)	TSP from site downwind from a coal-fired power plant, DCM extraction. Five consecutive daily i.p. doses in corn oil	CAs in spermatogonia and primary spermatocytes, and MN in early spermatids in Kunming mice 24 h after final dose for CAs; 14 d for MN	Significant increase in CAs in spermatogonia and primary spermatocytes. Dose-dependent increase in MN in early spermatids. Dose-dependent increase in abnormal sperm morphology	Sun et al. (1995)
Upper Silesia, Poland (1984–1985)	Airborne PM collected on GFFs, BZ Soxhlet extraction. Two sequential daily i.p. doses	MN in bone marrow of Balb/c mice, examined 30, 48, and 72 h after final injection	Significant increase in frequency of micronucleated PCEs	Motykiewicz et al. (1996)
Sicily, Italy (1993)	Airborne PM from urban and rural locations collected on GFFs using a high-volume sampler, CX Soxhlet extraction. Daily i.t. instillations of PM extracts for 5 consecutive days	MN in Sprague-Dawley rat PAMs and epithelial cells 72 h after final instillation of extract representing 400 m^3	Significant increase in frequency of MN in PAMs and epithelial cells, relative to sham control, for PM extract from urban location only	Izzotti et al. (1996)
Rome, Italy (1986)	Airborne PM_{10} from urban locations collected on GFFs using a high-volume sampler, DCM Soxhlet extraction. Two consecutive daily i.p. injections of PM extracts	MN in bone marrow of Swiss mice 24 h and 72 h after final injection	No significant increase in MN frequency in PCEs. Significant decline in % PCE at highest dose 48 h after exposure	Crebelli et al. (1988); Crebelli (1989)

Table 4.5 (continued)

Geographical location	Assay/exposure system	End-point(s) examined	Results	Reference
Beijing, China (1990)	TSP from 4 locations, NM sonication extraction. Two consecutive daily i.p. injections of extracts in DMSO	MN in bone marrow of Kunming mice 6 h after final injection	Significant, dose-related increase in MN frequency for all sites except control (park). Greater response for samples from industrial or commercial sites, compared with residential	Wang et al. (1991)
Shanghai, China	TSP from 13 locations, DCM sonication extraction. Two consecutive daily i.p. injections in DMSO	MN in bone marrow of Kunming mice 6 h after final injection	Significant, dose-related increase in MN frequency for samples from 10 of 13 locations	Yao et al. (1993)
Shanghai, China (1992–1993)	Airborne PM from 13 urban sites, collected on GFFs using a high-volume sampler, DCM sonication extraction, 2 daily i.p. injections (3 doses)	MN in bone marrow of Kunming mice; cells examined 6 h after final treatment	Significant, dose-related increase in frequency of micronucleated PCEs. Maximum response ~5-fold increase above control	Zhao et al. (2002)
Taiyuan, China	TSP samples from residential area, DCM sonication extraction, separated into 5 fractions, 2 consecutive daily i.p. injections	MN in bone marrow of Kunming mice; cells examined 6 h after final treatment	Significant, dose-related increase in MN frequency for all fractions except aliphatic hydrocarbons. Highest response for acidic fraction, followed by polar aromatics, basic fraction, and PAH fraction	Bai et al. (1999)
Taiyuan, China	TSP samples from foundry site and control site, DCM sonication extraction, single i.p. injection in DMSO	MN in bone marrow of Kunming mice (details not provided)	Significant, dose-related increase in MN frequency for both samples; greater response for extract of TSP from foundry site relative to control site	Zhang et al. (2002)
Lanzhou, China (1997)	TSP samples from heavy–traffic site and control site, DCM sonication extraction, 4 consecutive daily gavage doses in DMSO	MN in bone marrow of Kunming mice; cells examined 24 h after final treatment	Significant, dose-related increase in MN frequency	Zhao et al. (2001)
São Paulo state, Brazil	In situ 120 d exposures of caged Balb/c mice at a high-traffic urban location and a rural reference site	MN in peripheral blood on days 15, 30, 60, 90, and 120	ANOVA showed significant effect of treatment site and treatment time, with highest MN frequency observed at urban site after 90 d. Significant rank correlation of MN frequency and CO, NO_2, and PM_{10} for urban site	Soares et al. (2003)
Tokyo, Japan (1983)	Airborne PM_{10} collected on GFFs using a high-volume sampler, MeOH extract and MeOH:water, CX and nitromethane extract fractions. Four consecutive i.p. doses	MN in PCEs of Balb/c mice, 48 h after a single injection	Significant, dose-related increase in MN frequency for crude extract. Highest activity in nitromethane fraction	Sakitani & Suzuki (1986)

Table 4.5 (continued)

Geographical location	Assay/exposure system	End-point(s) examined	Results	Reference
West Virginia, USA (1984)	Airborne PM collected on GFFs using a high-volume sampler, Ac extraction. Single i.p. or p.o. doses of PM extracts in DMSO (5 dose levels)	SCEs in bone marrow and spleen cells of CD_1 mice	No significant increase in SCE frequency in either tissue	Krishna et al. (1986)

Ac, acetone; ANOVA, analysis of variance; BZ, benzene; CAs, chromosomal aberrations; CO, carbon monoxide; CX, cyclohexane; d, day or days; DCM, dichloromethane; DMSO, dimethyl sulfoxide; GFFs, glass-fibre filters; h, hour or hours; i.p., intraperitoneal; i.t., intratracheal; MeOH, methanol; MN, micronuclei; NM, nanomaterial; NO_2, nitrogen dioxide; PAHs, polycyclic aromatic hydrocarbons; PAMs, pulmonary alveolar macrophages; PCEs, polychromatic erythrocytes; PM, particulate matter; PM_{10}, particulate matter with particles of aerodynamic diameter < 10 µm; p.o., oral gavage; SCEs, sister chromatid exchanges; SLF, simulated lung fluid; TSP, total suspended particles.

in spermatogonia and primary spermatocytes, and frequencies of meiotic MN in early spermatids (Sun et al., 1995) (see also Section 4.3.3).

Micronuclei

Eleven published studies examined the ability of outdoor air or samples derived from outdoor air to induce MN in vivo. The majority of these studies (8 of 11) investigated the frequency of MN in haematopoietic tissues (bone marrow or peripheral blood) in mice exposed intraperitoneally to a single acute dose or to repeated (2–5) consecutive daily doses. One study examined the frequency of MN in peripheral blood of Balb/c mice exposed in situ for up to 120 days to urban air in São Paulo (Soares et al., 2003). The results revealed a significant increase in MN frequency relative to a rural control location, and MN frequency was positively correlated with atmospheric levels of CO, NO_2, and PM_{10} (Soares et al., 2003).

The study by Izzotti et al. (1996) examined the ability of cyclohexane extracts of TSP collected in Sicily, Italy, from urban and rural locations to induce MN in rat alveolar macrophages and pulmonary epithelial cells after five consecutive daily intratracheal instillations. The results showed significant 3.4-fold and 4.5-fold increases in MN frequency in pulmonary alveolar macrophages and epithelial cells, respectively, of rats treated with extracts from urban locations relative to the control (Izzotti et al., 1996). Zhao et al. (2001) noted that four consecutive gavage doses of DCM extracts of TSP collected at a heavy-traffic location in Lanzhou, an industrialized city in north-western China, induced a significant dose-dependent increase in MN frequency in bone marrow of Kunming mice (Zhao et al., 2001).

Two studies in Europe investigated the ability of PM extracts to induce increases in MN frequency in mouse bone marrow after intraperitoneal injection. Motykiewicz et al. (1990, 1996) showed that benzene extracts of PM collected from the heavily industrialized region of Upper Silesia, Poland (which has coke production, metal refining, steel foundries, etc.), induced a significant increase in micronucleated polychromatic erythrocytes (PCEs) in Balb/c mice after two consecutive intraperitoneal injections. Crebelli (1989) reported that two consecutive intraperitoneal doses of DCM extract from PM collected in Rome, Italy, failed to elicit significant increases in micronucleated PCEs in Swiss mice (Crebelli et al., 1988).

Six studies investigated the ability of organic extracts of PM collected in urban centres in China (Beijing, Shanghai, and Taiyuan) to induce significant increases in MN frequency in bone marrow of Kunming mice exposed via intraperitoneal injection. For example, Wang et al. (1991) noted that nanomaterial extracts of TSP from several sites in Beijing induced dose-dependent increases in MN frequencies and, moreover, that MN frequencies were markedly higher for samples from industrial or commercial areas relative to those from residential areas (Wang et al., 1991). Similarly, studies by Yao et al. (1993) and Zhao et al. (2002) revealed that DCM extracts of PM collected from a variety of locations in Shanghai induced significant dose-dependent increases in MN frequency for 10 of the 13 locations examined, with a maximum response approximately 5-fold above the control (Yao et al., 1993).

Studies by Bai et al. (1999) and Zhang et al. (2002) investigated the ability of DCM extracts of TSP collected in Taiyuan to induce a significant increase in MN frequency. Bai et al. (1999) found dose-dependent increases in MN frequency, and extract fractionation showed no induction of MN by the aliphatic hydrocarbon fraction but induction of high MN frequencies by fractions containing organic acids, polar aromatics, basic organics, and PAHs (Bai et al., 1999).

Zhang et al. (2002) studied a site near the Taiyuan steel foundry and compared results with those obtained from samples from a less-contaminated site at Yangqu. They found a significant

induction of MN by air sample extracts from both sites, but there was a marked increase for extracts of TSP from the foundry area. The authors observed that the results correspond to a higher incidence of lung cancer in the Taiyuan foundry area relative to the control site (Zhang et al., 2002).

A single study in Japan reported a significant dose-related increase in micronucleated PCEs in Balb/c mice exposed to a methanol extract of PM_{10} collected in Tokyo (Sakitani & Suzuki, 1986).

Sister chromatid exchanges

A single study that investigated the ability of organic extracts of PM collected in West Virginia, USA, to induce SCEs in bone marrow and spleen cells of CD1 mice exposed via single intraperitoneal or oral administration failed to show a significant increase relative to control (Krishna et al., 1986).

In summary, polluted outdoor air, outdoor air PM, or samples derived from outdoor air PM are capable of inducing significant increases in cytogenetic damage in animals exposed in situ or exposed experimentally via a variety of routes of administration. Exposures of experimental animals via oral, intraperitoneal, or intratracheal administration show a clear dose-dependent induction of cytogenetic damage recorded as CAs or MN. [The Working Group expressed concerns about intraperitoneal injections and their relevance to human cancer risk.]

Plants

Plant assays (see Supplemental Table S10, available online) have also been used to assess the ability of outdoor air pollution or samples derived from it to induce cytogenetic damage (Ma et al., 1994). In particular, many studies have examined the induction of MN in meiotic pollen mother cells (i.e. tetrads formed after the second meiotic division) of the sterile *Tradescantia* clone 4430 or isolates of *T. paludosa* or *T. pallida* exposed to outdoor air in situ for extended periods (e.g. several months) or in the laboratory to extracts of airborne PM.

In their review of the mutagenicity and carcinogenicity of outdoor air pollution, Claxton & Woodall (2007) observed that although the dynamic range of plant genotoxicity assays varies across plants and end-points, the dynamic range of the induced responses, relative to the control, for the popular *Tradescantia* assays ranges between 2-fold for the stamen-hair mutation assay and 20-fold for the MN assay. In their review of mutagens in contaminated soils, White & Claxton (2004) also critically examined the utility of the *Tradescantia* genotoxicity assays and noted the limited dynamic range and lack of sensitivity, particularly for short-term exposures.

(ii) In vitro

Cytogenetic effects induced by extracts of airborne particulates were assessed in cultured human lymphocytes, human cell lines, cultured animal primary cells, and animal cell lines. The cytogenetic effects included CAs, aneuploidy, MN, and SCEs. The results of these in vitro cytogenetic studies are summarized in Table 4.6.

Chromosomal aberrations

Human cells

A series of studies showed significant dose-related increases in the frequency of chromosome and chromatid breaks in cultured human lymphocytes exposed to organic extracts of airborne PM from the Rhine–Ruhr region of Germany (Hadnagy et al., 1986, 1989; Hadnagy & Seemayer, 1987; Seemayer et al., 1989). Acetone extracts of outdoor air PM collected in West Virginia, USA, also induced CAs in human lymphocytes in a dose-dependent manner (Krishna et al., 1984). Three studies in China also showed that extracts of outdoor air particles induced CAs in human lymphocytes. Organic extracts of airborne TSP samples collected at five sites in Lanzhou, a city heavily contaminated by

Table 4.6 Cytogenetic damage associated with outdoor air pollution in human and animal cells in vitro

Geographical location	Test article	Assay/exposure system	End-point(s) examined	Results	Reference
Human cells					
Rhine–Ruhr region, Germany	Airborne PM from Düsseldorf, collected on GFFs using a high-volume sampler. DCM extraction	Cultured human lymphocytes, 48 h or 72 h exposure to extract in DMSO	CAs with and without gaps	Significant, dose-related (equiv m^3/mL) increase in frequency of chromosome breaks. Chromatid breaks observed at low concentration only	Hadnagy et al. (1986), Hadnagy & Seemayer (1987)
West Virginia, USA	Airborne PM collected on GFFs using a high-volume sampler. Ac extraction	Cultured human lymphocytes, 10 h exposure to extract in DMSO	CAs with and without gaps	Significant, dose-related (mg of PM equiv/mL) increase in CA frequency (both with and without gaps)	Krishna et al. (1984)
Lanzhou, China	Airborne TSP from 5 sites with varying levels of air pollution. DCM sonication extraction	Cultured human lymphocytes, 50 h exposure to extract in DMSO	CAs with and without gaps	Significant, dose-related increase in CA frequencies for all TSP extracts. Highest response for suburban locations downwind from urban site and industrial site	Ding et al. (1999)
Shanghai, China	Airborne TSP from the Dapu tunnel. NaCl (saline) shaker extraction	Cultured human lymphocytes, exposure to saline extract	CAs	Significant, exposure-related increase in CA frequency. Effect similar to Japanese vehicle exhaust PM standard (NIES-8)	Tan et al. (2002)
Baotou and Wuwei, China (Mongolia)	$PM_{2.5}$ samples collected during sandstorm and control (non-storm) days. $PM_{2.5}$ suspension in saline	Cultured human lymphocytes, exposure to saline PM suspension	CAs with and without gaps	Significant, dose-related increase in CA frequency for samples from both cities during storm and non-storm conditions. For non-storm conditions, suspensions of $PM_{2.5}$ from industrial Baotou elicited higher CA frequencies	Wei & Meng (2006a)
Suwon, Republic of Korea	$PM_{2.5}$ collected in high-traffic area on Teflon-coated filter using a cascade impactor. DCM sonication extraction. Acid–base–neutral fractionation and subfractionation on silica	BEAS-2B human lung bronchial epithelial cells, 24 h treatment with extract in DMSO	Cytokinesis-block MN assay	Significant, dose-related (μg of EOM/mL) increase in MN frequency for crude extract. Significant increases in MN frequency for aliphatic, aromatic (i.e. PAHs and alkyl-PAHs), and semipolar (nitro-PAHs, ketones, quinones) fractions	Oh et al. (2011)
Mexico City metropolitan area, Mexico	PM_{10} from industrial and residential locations, collected on GFFs using a high-volume sampler. Water and DCM Soxhlet extraction	A549 human alveolar adenocarcinoma cells, 48 h exposure to extract in DMSO	Cytokinesis-block MN assay	Significant, dose-related (μg of PM_{10} equiv/mL) increases in MN frequency for water and DCM extracts for PM from both residential and industrial areas	Roubicek et al. (2007)

Table 4.6 (continued)

Geographical location	Test article	Assay/exposure system	End-point(s) examined	Results	Reference
L'Aquila, Italy	Airborne PM of 2.5–10 µm and 0.4–2.5 µm, collected using an 8-stage cascade impactor	Hs27 human skin fibroblasts, 44 h exposure to suspended PM	Cytokinesis-block MN assay	Significant, dose-related (m^3/mL) increases in MN frequency for samples collected in 6 sequential months. MN frequency values for fine PM slightly greater than for coarse PM	Poma et al. (2002)
Lanzhou, China	Airborne TSP from 5 sites with varying levels of air pollution. DCM sonication extraction	Cultured human lymphocytes, 52 h exposure to extract in DMSO	MN in harvested cells	Dose-dependent increase in MN frequency for all particle extracts. Highest response for suburban locations downwind from urban site and industrial site	Ding et al. (1999)
Taiyuan, China	Airborne particulates from a residential area, 6 size classes. Acid Soxhlet extraction, and sequential Soxhlet extraction with MeOH, Ac, and DCM	Cultured human lymphocytes, exposure to acid extract or pooled organic extract	Cytokinesis-block MN assay	For both types of extracts, dose-dependent increase in MN frequency for all samples, with enhanced responses for extracts of smaller particles. MN frequency elicited by acid extract positively correlated with metal (e.g. nickel, cadmium, chromium) concentrations	Yuan et al. (1999a, b)
Shanghai, China	Airborne PM from industrial Taopu area. NaCl (saline) shaker extraction	Cultured human lymphocytes, exposure to saline extracts	MN in harvested cells	Dose-dependent increase in MN frequency	Tan et al. (2004)
Baotou and Wuwei, China (Mongolia)	$PM_{2.5}$ samples collected during sandstorm and control (non-storm) days. NaCl (saline) PM suspension, NaCl shaker extraction, DCM Soxhlet extraction	Cultured human lymphocytes, exposures to PM suspensions, saline extracts, organic extracts	Cytokinesis-block MN assay	Dose-dependent increase in MN frequency elicited by PM suspensions and organic extracts. Higher MN frequency elicited by samples collected on non-storm days. For storm conditions, no significant difference between industrial Baotou and agricultural Wuwei	Wei & Meng (2006a), Wei et al. (2006)
Guangzhou, China	TSP and PM_{10} from a residential area. DCM sonication extraction. Fractionation by chromatography	Cultured human lymphocytes, exposure to extract in DMSO	Cytokinesis-block MN assay	TSP extracts elicited significant increase in MN frequency. No dose–response. Aromatic hydrocarbon fraction of PM_{10} extract elicited significant increase in MN frequency	Xu & Wang (2008)
Flanders, Belgium (2000)	PM_{10} from urban, rural, and industrial sites, collected on GFFs with a low-volume sampler. ASE extraction with THF:Hx (20:80)	Cultured human lymphocytes, 72 h exposure to extract in DMSO	Cytokinesis-block MN assay	Significant, dose-related (equiv m^3/mL) increase in MN frequency for urban location only. Urban PAH concentration (ng/m^3) higher than that for rural and industrial sites	Brits et al. (2004)

Table 4.6 (continued)

Geographical location	Test article	Assay/exposure system	End-point(s) examined	Results	Reference
Silesia, Poland (1984–1985)	Airborne PM, collected on GFFs. BZ Soxhlet extraction	Cultured human lymphocytes, 72 h exposure to extract in DMSO	SCE assay	Small, dose-related increase in SCE frequency	Motykiewicz et al. (1990)
Lexington, Kentucky, USA (1980)	Airborne PM before and during forest fires, collected on GFFs using a high-volume sampler. Sonication extraction with BZ and Ac	Cultured human lymphocytes, exposure to extract in DMSO	SCE assay	Strong, dose-related (m^3 or mg of PM equiv) increase in SCE frequency for "smoky" conditions. Weak, significant response for "non-smoky" conditions	Viau et al. (1982)
Lanzhou, China	Airborne PM from a district with high incidence of lung cancer. DCM sonication extraction	Cultured human lymphocytes, 72 h exposure to extract in DMSO	SCE assay	Significant, dose-related increase in SCE frequency	Zhang & Li (1994)
Lanzhou, China	Airborne TSP from 5 sites with varying levels of air pollution. DCM sonication extraction	Cultured human lymphocytes, 72 h exposure to extract in DMSO	SCE assay	Significant, dose-related increase in SCE frequency for all PM extracts. Higher responses for suburban locations downwind from urban site and industrial site	Wang & Ding (1998)
Duisburg, Germany	Airborne PM from industrialized Rhine–Ruhr region. Draeger Box Micron filter. CX extraction	Cultured human lymphocytes, 72 h exposure to extract in DMSO	SCE assay	Significant, dose-related (m^3 equiv/mL) increase in SCE frequency per metaphase in both cell types	Seemayer et al. (1987a, 1988)
Rhine–Ruhr region, Germany	Airborne PM from Duisburg and Düsseldorf, collected on GFFs using a high-volume sampler. DCM extraction	Cultured human lymphocytes, 72 h exposure to extract in DMSO	SCE assay	Significant, dose-related (equiv m^3/mL) increase in SCE frequency for samples from both Düsseldorf and Duisburg. Higher response for heavily industrialized area (Duisburg), relative to urban. As little as 0.3 m^3 equiv of Duisburg extract required to elicit a significant increase in SCE frequency	Hadnagy et al. (1989), Seemayer et al. (1989, 1990a)
Rhine–Ruhr region, Germany	Airborne PM from Düsseldorf, collected on GFFs using a high-volume sampler. DCM extraction	Cultured human lymphocytes, 48 h or 72 h exposure to extract in DMSO	SCE assay	Significant, dose-related (equiv m^3/mL) increase in SCE frequency	Hadnagy et al. (1986), Hadnagy & Seemayer (1987)

Table 4.6 (continued)

Geographical location	Test article	Assay/exposure system	End-point(s) examined	Results	Reference
Rhine–Ruhr and North Rhine-Westphalia regions, Germany	Airborne PM from Duisburg, Düsseldorf, and Borken, collected by GFFs using a low-volume sampler. DCM extraction	BEAS-2B human lung bronchial epithelial cells, 72 h exposure to extract in DMSO	SCE assay	Significant, dose-related (equiv m^3/assay) increase in SCE frequency per metaphase for samples from all locations. Highest responses for fine fraction ($PM_{2.5}$) relative to coarse (PM_{10}). Responses for industrial sites exceeded that of less-polluted area (Borken). Significant induction of SCE in response to < 0.5 m^3 equiv	Hornberg et al. (1998)
Rhine–Ruhr region, Germany	"City smog" for heavily industrialized site, collected on GFFs using a low-volume sampler. MeOH extraction	Cultured human lymphocytes, 72 h exposure to extract in DMSO	SCE assay	Significant, dose-related (equiv m^3/mL) increase in SCE frequency per metaphase	Seemayer et al. (1984)
Rhine–Ruhr region, Germany	41 samples of "city smog" collected in 1975–1990 at highly industrialized locations, collected on GFFs. Organic extraction	A549 human alveolar adenocarcinoma cells (24 h and 120 h) and cultured human lymphocytes (72 h) exposed to extract in DMSO	SCE assay	Site 54 (Düsseldorf) shown as an example. Significant, dose-related (equiv m^3/mL) increase in SCE frequency per metaphase	Seemayer et al. (1988, 1989, 1990b), Hadnagy et al. (1989)
Rhine–Ruhr region, Germany	20 samples of "city smog" collected in 1975–1986 at highly industrialized locations, collected on GFFs. MeOH extraction	Cultured human lymphocytes, exposure to extract in DMSO	SCE assay	Düsseldorf provided as an example. Significant, dose-related (equiv m^3/mL) increase in SCE frequency per metaphase	Seemayer et al. (1987b)
Mexico City metropolitan area, Mexico	Seasonal PM_{10} samples collected on GFFs using a high-volume sampler. DCM sonication extraction	Cultured human lymphocytes, 4 h exposure to extract in DMSO, with and without Aroclor-induced rat liver S9	SCE assay	Significant, dose-related (μg of EOM/assay) increase in SCE frequency both with and without S9. Higher responses with S9 in April and August. In November, similar responses with and without S9. November sample had highest concentrations of PAHs and nitro-PAHs	Calderón-Segura et al. (2004)
L'Aquila, Italy	Airborne PM of 2.5–10 μm and 0.4–2.5 μm, collected using an 8-stage cascade impactor	Hs27 human skin fibroblasts, 24 h exposure to suspended PM	SCE assay	Significant increases in SCE frequency for all fine PM samples collected in 6 sequential months; 3 of 6 monthly coarse PM samples induced significant increases in SCE frequency	Poma et al. (2002)
West Virginia, USA (1982)	Airborne PM collected on GFFs using a high-volume sampler. Ac extraction	Cultured human lymphocytes, 48 h exposure to extract in DMSO	SCE assay	Significant, dose-related (mg of PM equiv/mL) increase in SCE frequency	Krishna et al. (1984)

Table 4.6 (continued)

Geographical location	Test article	Assay/exposure system	End-point(s) examined	Results	Reference
Animal cells					
Sicily, Italy	Airborne PM from 2 locations in the centre of Catania, collected on GFFs using a high-volume sampler. DCM Soxhlet extraction	CHEL Chinese hamster epithelial liver cells and CHO cells, 24 h exposure to extract in DMSO	CAs (excluding gaps)	Significant, dose-related increase in frequency of CHEL cells with CAs for both sites. No significant increase for CHO cells without exogenous activation	Motta et al. (2004)
Baja California, Mexico	Atmospheric dust from the city of Mexicali	Balb 3T3 mouse embryonic fibroblast cells, 12 h exposure to dust suspension	Anaphase aberrations (lagging chromosomes, bridges)	Dose-related increase in anaphase aberrations, including multipolar anaphases, lagging chromosomes, and bridges	Alfaro Moreno et al. (1997)
Patagonia, Argentina	Airborne PM from two towns, inspirable dust collected on GFFs. DCM extraction	Primary F344 rat hepatocytes, 3 h exposure to extract in DMSO	CAs	No significant increase in CA frequency	Ares et al. (2000)
Basel, Switzerland	PM collected on GFFs in air conditioner units. Samples from several sites during and after a large industrial fire (Schweizerhalle). MeOH Soxhlet extraction	Chinese hamster V79 lung cells, 3 h treatment with and without Aroclor-induced rat liver S9	CAs with and without gaps	Significant induction of CAs in the presence of S9. Some urban PM collected 4–5 months after the fire also elicited positive responses, but highly variable. No evidence to support hypothesis that industrial fire released clastogenic material adsorbed to airborne PM	Zwanenburg (1988)
Silesia, Poland (1984–1985)	Airborne PM collected on GFFs at 8 "high-pollution" locations. BZ Soxhlet extraction. Extract fractionation on silica	Chinese hamster V79 lung cells, 5 h, 14 h, and 24 h treatments with each of 8 fractions	CAs with and without gaps	Significant increases in CA frequency for fractions containing polar aromatics (e.g. N-, S-, O-heterocyclics), monophenols, and basic N-heterocyclics. Higher responses for longer exposures. In some instances, dose-related increases (μg of EOM/mL)	Motykiewicz et al. (1988)
Silesia, Poland	Airborne PM collected on GFFs at 18 "high-pollution" locations in Katowice district, collected on GFFs using a high-volume sampler. BZ Soxhlet extraction. Extract fractionation on silica	Chinese hamster V79 lung cells, 16 h and 24 h treatments with each of 7 fractions	Aneuploidy, hyperdiploidy, and polyploidy	Significant increases in hyperdiploidy and polyploidy for crude extract and fraction containing monophenols	Motykiewicz et al. (1991)

Table 4.6 (continued)

Geographical location	Test article	Assay/exposure system	End-point(s) examined	Results	Reference
Rhine–Ruhr region, Germany	Airborne PM from Duisburg and Düsseldorf, collected on GFFs using a high-volume sampler. DCM extraction	Chinese hamster V79 lung cells, 16 h treatment with extract in DMSO	Aneuploidy and C-metaphases	Dose-related (equiv air m^3/mL) increases in aberrant metaphases, polyploidy, and hyperdiploidy	Hadnagy & Seemayer, (1991)
L'Aquila, Italy	Airborne PM of 0.43–2.1 µm, collected using an 8-stage cascade impactor	RAW 264.7 mouse macrophages, 48 h exposure to suspended PM	Cytokinesis-block MN assay	Significant, dose-related (µg/cm^2) increases in MN frequency for 3 samples collected in sequential months	Poma et al. (2006)
Beijing, China (2001)	$PM_{2.5}$ collected at Beijing University. Organic and inorganic extractions (details not provided)	Balb/c 3T3 mouse embryonic fibroblast cells, 8 h exposure	Cytokinesis-block MN assay	Organic PM extract induced significant, dose-related increase in MN frequency. Inorganic extract failed to induce a significant response	Zhang et al. (2003)
Taiyuan, China	Size-fractionated airborne PM from urban, residential, and suburban locations. Soxhlet extraction with MeOH, DCM, and Ac	CHL Chinese hamster lung cells, 2 h exposure to combined extract in DMSO, with and without exogenous S9	SCE assay	All extracts elicited significant, dose-related increase in SCE frequency. Greater response for extracts of smaller PM fractions. Positive association with PAH concentrations	Yang et al. (1994)
Silesia, Poland (1984–1985)	Airborne PM collected on GFFs. BZ Soxhlet extraction	Chinese hamster V79 lung cells, 26 h exposure to extract in DMSO	SCE assay	Significant, dose-related (m^3 equiv) increase in SCE frequency	Motykiewicz et al. (1990)
Paris, France (1983–1985)	Airborne PM from urban site, collected on GFFs using a high-volume sampler. DCM or Ac sonication extraction	Chinese hamster V79 lung cells, 1–3 h exposure to extract in DMSO, with and without Aroclor 1254-induced rat liver S9	SCE assay	Significant, dose-related (per µg of EOM) increase in SCE frequency; higher with exogenous metabolic activation system	Courtois et al. (1988)
Duisburg, Germany	Airborne PM from industrialized Rhine–Ruhr region. Draeger Box Micron filter. CX extraction	Chinese hamster V79 lung cells, 24 h exposure to extract in DMSO	SCE assay	Significant, dose-related (m^3 equiv/mL) increase in SCE frequency per metaphase	Seemayer et al. (1987a, 1988)

Table 4.6 (continued)

Geographical location	Test article	Assay/exposure system	End-point(s) examined	Results	Reference
Rhine–Ruhr region, Germany	Airborne PM from Duisburg, collected on GFFs using a high-volume sampler. DCM extraction	Primary tracheal epithelial cells from Syrian golden hamsters, 48 h exposure to extract in DMSO	SCE assay	Significant, dose-related (equiv m^3/mL) increase in SCE frequency per metaphase for both cell types	Seemayer et al. (1994)
Rhine–Ruhr region, Germany	Airborne PM from Duisburg and Düsseldorf, collected on GFFs using a high-volume sampler. DCM extraction	Primary tracheal epithelial cells from Wistar rats, 48 h exposure to extract in DMSO	SCE assay	Significant, dose-related (equiv m^3/assay) increase in SCE frequency per metaphase for samples from both locations	Hornberg & Seemayer, (1995)
Rhine–Ruhr region, Germany	Airborne PM from Duisburg and Düsseldorf, industrial and urban area with high traffic density, respectively, collected on GFFs using a high-volume sampler. DCM extraction	Primary tracheal epithelial cells from rat and Syrian golden hamster, 48 h exposure to extract in DMSO	SCE assay	Significant, dose-related (equiv m^3/assay) increase in SCE frequency per metaphase for both samples in both cell types. Significant induction of SCE in response to as little as 1 m^3 equiv	Hornberg et al. (1996)
Rhine–Ruhr region, Germany	Airborne PM from Duisburg, collected on GFFs using a high-volume sampler. DCM extraction	Primary tracheal epithelial cells from rat and Syrian golden hamster, 48 h exposure to extract in DMSO	SCE assay	Significant, dose-related (equiv m^3/assay) increase in SCE frequency per metaphase for both cell types. Significant induction of SCE in response to as little as 0.5 m^3 equiv	Hornberg et al. (1997)
Rijnmond area, Netherlands	Airborne PM collected on GFFs using a high-volume sampler. Soxhlet extractions with MeOH, CX, BZ, or Ac. Liquid–liquid fractionation	CHO cells, 1 h treatment with extract in DMSO, with and without Aroclor-induced rat liver S9	SCE assay	Significant, dose-related (m^3/assay) increase in SCE frequency both with and without S9. Potency (SCE/m^3/assay) highest for aromatic fraction with S9, followed by oxygenated compound fraction with and without S9. Aerosol gradient downwind from urban/industrial area	de Raat, (1983)
Coastal area in central Finland (1985)	Airborne PM and semivolatiles, collected in Kokkola using a high-volume sampler. PM collected on filter, semivolatiles on XAD-2 resin. Ac extraction. Fractionation on silica	CHO cells, 4 h treatment with extract in DMSO, with and without Clophen A50-induced rat liver S9	SCE assay	4 of the 5 tested PM extracts induced significant increases in SCE frequency; slight increase with S9. Winter PM extracts more genotoxic relative to spring samples. XAD-2 extracts consistently more genotoxic. Consistent activity in PAH fraction with S9, as well as in most polar fraction with and without S9	Pyysalo et al. (1987)

Table 4.6 (continued)

Geographical location	Test article	Assay/exposure system	End-point(s) examined	Results	Reference
Athens, Greece	Monthly PM samples, collected on cellulose filters using a high-volume sampler. Hx sonication extraction	CHO cells, 26 h treatment with extract in DMSO	SCE assay	All tested samples induced significant, dose-related (μg of EOM/mL) increases in SCE frequency	Athanasiou et al. (1987)
Wageningen and Terschelling, Netherlands (1979–1980)	Airborne PM from 2 rural sites, collected on GFFs using a high-volume sampler. MeOH Soxhlet extraction	Chinese hamster V79 lung cells, 2 h treatment with extract in DMSO	SCE assay	Significant, dose-related (per m^3) increases in SCE frequency when winds from east (i.e. Germany). Negligible response when winds from north	Alink et al. (1983)
West Virginia, USA	Airborne PM, collected on GFFs using a high-volume sampler. Ac extraction.	Mice primary bone marrow and spleen cells, 34 h and 44 h exposures, respectively, to extract in DMSO	SCE assay	Significant, dose-related (mg of PM equiv/mL) increase in SCE frequency in both cell types	Krishna et al. (1986)

Ac, acetone; ASE, accelerated solvent extraction; BZ, benzene; CAs, chromosomal aberrations; CHO, Chinese hamster ovary; CX, cyclohexane; DCM, dichloromethane; DMSO, dimethyl sulfoxide; EOM, extractable organic matter; equiv, equivalent; GFFs, glass-fibre filters; h, hour or hours; Hx, hexane; MeOH, methanol; MN, micronuclei; PAHs, polycyclic aromatic hydrocarbons; PM, particulate matter; PM_{10}, particulate matter with particles of aerodynamic diameter < 10 μm; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 μm; SCEs, sister chromatid exchanges; THF, tetrahydrofuran; TSP; total suspended particles.

coal combustion and automobile exhausts, all induced CAs in cultured human lymphocytes obtained from umbilical cord blood. The major CAs included chromatid gaps, chromosome gaps, chromatid breaks, chromosome breaks, and fragments. Potency was correlated with the degree of air pollution (Ding et al., 1999). Tan et al. (2002) examined water extracts of airborne TSP collected in a tunnel in Shanghai and noted significant induction of CAs, including fragments and dicentric chromosomes, in cultured human lymphocytes compared with controls. The authors reported that metals such as lead, zinc, manganese, and iron likely contribute to the observed increase in the frequency of CAs. Wei & Meng (2006a) examined water extracts of $PM_{2.5}$ samples collected from Baotou (an industrial city in Inner Mongolia) and Wuwei (an agricultural city in Gansu province) and noted dose-dependent increases in the frequencies of CAs in cultured human lymphocytes. Samples were collected during sandstorms as well as on non-storm control days, and CA frequencies were higher in Baotou compared with Wuwei, for non-storm conditions only. CAs included chromatid breaks, chromosome breaks, acentric fragments, dicentric chromosomes, and gaps (Wei & Meng, 2006b).

Animal cells

A study by Motta et al. (2004) showed significant increases in CA frequencies in Chinese hamster epithelial liver cells, which maintained metabolic competence, exposed to extracts of airborne PM from Catania, Italy. However, negative results were seen in Chinese hamster ovary cells that required exogenous metabolic activation (Motta et al., 2004). Alfaro Moreno et al. (1997) reported a dose-related increase in anaphase aberrations in murine Balb/c 3T3 cells exposed to a suspension of atmospheric dust collected in Mexico. A study by Zwanenburg (1988) reported significant induction of CAs in Chinese hamster V79 lung cells exposed to extracts of particles collected from several sites after a large industrial fire in Switzerland in the presence of S9 (Zwanenburg, 1988). Extracts of PM from some urban sites elicited positive responses 4–5 months after the fire, and the authors could not provide convincing evidence that the fire resulted in the release of clastogenic substances. A study conducted in Poland, which examined fractions of organic extracts of airborne PM from high-pollution locations, showed significant increases in CA frequencies in Chinese hamster V79 lung cells by fractions containing polar aromatics, monophenols, and basic *N*-heterocyclics (Motykiewicz et al., 1988). A study by Ares et al. (2000) failed to show significant increases in CA frequency in primary F344 rat hepatocytes treated with extracts of airborne PM from Patagonia (Ares et al., 2000). Two studies reported significant increases in aneuploidy in Chinese hamster V79 lung cells exposed to extracts of airborne PM from Poland (Motykiewicz et al., 1991) and Germany (Hadnagy & Seemayer, 1991).

Micronuclei

Human cells

Water or organic solvent extracts of airborne PM from five cities in China were tested for induction of MN in cultured human lymphocytes. In Lanzhou, DCM extracts of TSP from five sites with varying degrees of air pollution all caused dose-dependent increases in MN frequency in cultured human lymphocytes. The samples from sites with heavy traffic or close to petroleum industries showed more potent induction of MN compared with samples from moderately contaminated sites or relatively clean sites (Ding et al., 1999). In Shanghai, saline extracts of airborne PM from Taopu, an industrial region, caused a dose-dependent increase in MN in cultured human lymphocytes (Tan et al., 2004). Wei & Meng (2006a) and Wei et al. (2006) compared MN induction by organic and inorganic extracts of $PM_{2.5}$ collected during a sandstorm or in

non-storm conditions from the industrial city of Baotou (in Inner Mongolia) and the agricultural city of Wuwei (in Gansu province). The results indicated that organic and saline PM suspensions, collected during storm and non-storm conditions, showed dose-dependent increases in MN frequency in cultured human lymphocytes (Wei et al., 2006). DCM extracts of TSP and PM_{10} samples from Guangzhou also significantly increased MN frequency in cultured human lymphocytes, and extract fractionation showed significant MN induction by the aromatic hydrocarbon fraction of PM_{10} (Xu & Wang, 2008). A study by Yuan et al. (1999a) examined acid and organic solvent extracts of airborne PM of different sizes (< 1.1 μm, 1.1–2.0 μm, 2.0–3.3 μm, 3.3–7.0 μm, and > 7.0 μm) that were collected from a residential area in Taiyuan, and they observed dose-dependent increases in frequencies of MN in cultured human lymphocytes (Yuan et al., 1999a). Acid extract studies showed that the smaller the particulate size, the higher the MN frequency; the MN frequencies were also positively correlated with the concentrations of metals in the PM extracts (Yuan et al., 1999b). In addition, a study conducted in Flanders, Belgium, also reported a significant dose-related (i.e. equivalent cubic metres per millilitre) increase in MN frequency in cultured human lymphocytes exposed to organic extracts of urban air PM (Brits et al., 2004).

In addition to studies in cultured human lymphocytes, the induction of MN by suspended PM or extracts of PM was also investigated in human cell lines. Oh et al. (2011) found significant induction of MN in BEAS-2B human lung bronchial epithelial cells exposed to organic PM extracts and extract fractions from a high-traffic area in the Republic of Korea (Oh et al., 2011). Fractionation showed significant increases in MN for aliphatic, aromatic (i.e. PAHs), and slightly polar (i.e. nitro-PAHs and quinones) fractions. Significant increases in MN frequency were also induced in A549 human alveolar adenocarcinoma cells by water and organic extracts of industrial and residential particles from Mexico City (Roubicek et al., 2007), and in HS 27 human skin fibroblasts (Poma et al., 2002).

Animal cells

Significant increase in MN frequency were also observed in RAW 264.7 mouse macrophages exposed to suspensions of airborne PM from L'Aquila, Italy (Poma et al., 2006). Moreover, an organic extract of PM from Beijing, China, induced a significant dose-related increase in MN frequency in Balb/c 3T3 cells (Zhang et al., 2003).

Sister chromatid exchanges

Human cells

Twenty-five studies investigated the induction of SCEs in cultured human lymphocytes and a variety of cultured animal cells exposed to organic PM extracts, and most of the studies showed significant increases in SCE frequency. Organic PM extracts assessed in cultured human lymphocytes include samples derived from PM collected in Lexington, Kentucky, USA (Viau et al., 1982), Silesia, Poland (Motykiewicz et al., 1990), Lanzhou, China (Zhang & Li 1994; Wang & Ding 1998), West Virginia, USA (Krishna et al., 1984), and many sites in the Rhine–Ruhr region of Germany (Seemayer et al., 1984, 1987a, b, 1988, 1989, 1990a, 1990b; Hadnagy et al., 1986, 1989; Hadnagy & Seemayer, 1987). Seasonal PM samples from Mexico City induced significant dose-related increases in SCE frequency, with the highest frequencies produced by samples taken in November and the lowest by samples taken in April (Calderón-Segura et al., 2004). Significant increases in SCE frequencies were induced in HS 27 human skin fibroblasts exposed to suspensions of PM from L'Aquila, Italy (Poma et al., 2002), and in A549 human alveolar adenocarcinoma cells and human BEAS-2B cells exposed to organic extracts of PM collected from the

Rhine–Ruhr region of Germany (Seemayer et al., 1989; Hornberg et al., 1998).

Animal cells

A series of in vitro cytogenetic studies of organic extracts of PM from several locations within the Rhine–Ruhr region of Germany showed significant dose-dependent increases in SCE frequencies in primary tracheal epithelial cells from Syrian golden hamsters or Wistar rats (Seemayer et al., 1994; Hornberg & Seemayer, 1995; Hornberg et al., 1996, 1997). Significant dose-related increases in SCE frequencies were also induced in primary bone marrow and spleen cells exposed to extracts of PM from West Virginia, USA (Krishna et al., 1986). Three independent studies showed significant increases in SCE frequencies in Chinese hamster ovary cells exposed to extracts of PM from the Netherlands (de Raat, 1983), a coastal area in Finland (Pyysalo et al., 1987), and Athens, Greece (Athanasiou et al., 1987). Two independent studies showed significant increases in SCE frequency in Chinese hamster V79 cells exposed to organic extracts of PM from the Netherlands (Alink et al., 1983) and Paris, France (Courtois et al., 1988). The study in Finland noted that concentrates of SVOCs collected on XAD-2 resin consistently elicited stronger responses compared with PM extracts (Pyysalo et al., 1987).

A study by Yang et al. (1994) showed that extracts of airborne PM of various sizes (< 1.1 μm, 1.1–2.0 μm, 2.0–3.3 μm, 3.3–7.0 μm, and > 7.0 μm) collected from industrial, residential, and suburban districts in Taiyuan, China, induced significant dose-related increases in SCEs in Chinese hamster lung cells (Yang et al., 1994). The authors also observed that a greater response was produced by extracts of smaller-sized PM and that SCE induction was positively correlated with PAH concentrations.

In summary, substantial evidence consistently shows that organic extracts, water extracts, or suspensions of outdoor air PM from urban or industrial areas induce significant dose-related cytogenetic effects (CAs, aneuploidy, MN, and SCEs) in cultured human lymphocytes, human cell lines, cultured animal primary cells, or animal cell lines in vitro.

4.2.3 DNA damage and protein adducts

(a) DNA adducts

(i) Humans

Studies on DNA adducts in humans after exposure to polluted outdoor air are summarized in Table 4.7.

A systematic review (Demetriou et al., 2012) evaluated DNA adducts as one of several biomarkers with the potential to contribute an intermediate end-point in the association between air pollution and lung cancer and graded DNA adducts in leukocytes as A for evidence, A for replication, and B for bias.

In an early study of the effects of outdoor air pollution, male residents of an industrial and highly polluted city in Poland (Gliwice) were compared with men from a rural part of the country (Biała Podlaska) (Perera et al., 1992). Both summer and winter samples were analysed by enzyme-linked immunosorbent assay (ELISA) and by ^{32}P-postlabelling for PAH–DNA adducts and aromatic DNA adducts. The exposed residents of Gliwice had significantly increased PAH–DNA and aromatic adducts compared with rural residents. For the winter samples, the Gliwice values were significantly greater than the rural values by ELISA only, and the same was found for the summer samples. The Gliwice winter values were also significantly greater than the Gliwice summer values by both methods of analysis. Other comparisons that were statistically significant were by ^{32}P-postlabelling: control winter values were greater than exposed summer values, and exposed winter values were greater than control summer values (see Table 4.7).

Table 4.7 DNA adducts in humans exposed to outdoor air pollution

Location	Study populations	Method of analysis; source of DNA	Results	Reference
Poland	39 men in Gliwice (high pollution, exposed); 49 men in Biała Podlaska (low pollution, control)	^{32}P-postlabelling and immunoassay (ELISA) for PAH–DNA adducts; white blood cells	Exposed winter levels significantly greater than exposed summer levels; exposed winter levels significantly greater than control winter levels (ELISA only); exposed summer levels significantly greater than control summer levels (ELISA only)	Perera et al. (1992)
Poland	70 mothers and newborns in Cracow	Immunoassay (ELISA) for PAH–DNA adducts; maternal and umbilical white blood cells	Significant correlation between maternal and newborn adduct levels and outdoor air pollution levels close to place of residence	Whyatt et al. (1998)
Poland	70 mothers and newborns in Cracow (urban); 90 mothers and newborns in Limanowa (rural)	Immunoassay (ELISA) for PAH–DNA adducts; maternal and umbilical white blood cells	Intra-individual differences in Cracow cohort previously noted (Whyatt et al., 1998), but differences in adduct levels between urban and rural groups not significant. Rural district had lower outdoor pollution but heavier use of coal for residential heating. Among non-coal users, adduct levels in maternal Cracow samples 2-fold higher than those in maternal Limanowa samples ($P = 0.03$)	Perera et al. (1999)
Poland	319 non-smoking mothers and newborns in Cracow	HPLC/fluorescence for B[*a*]P–DNA adducts; white blood cells from maternal and cord blood	Significant interaction between prenatal exposure to PAHs and cord blood DNA adduct levels, especially for subjects with low levels of micronutrients (carotenoids, α-tocopherol, and retinol) in maternal blood compared with those with higher levels of the micronutrients	Kelvin et al. (2009)
Sweden	Taxi drivers (19), urban bus drivers (26), suburban bus drivers (23), and controls (22)	^{32}P-postlabelling; lymphocytes	Significantly higher adduct levels in taxi drivers ($P < 0.01$) and suburban bus drivers ($P < 0.001$) than in controls. Levels in urban bus drivers not significantly different	Hemminki et al. (1994)
Denmark	Bus drivers (90) and rural controls (60)	^{32}P-postlabelling; lymphocytes	Adduct levels were highest in drivers in central Copenhagen and intermediate in drivers in suburban Copenhagen and dormitory towns. Adduct levels in all 3 groups were significantly higher than in controls ($P < 0.001$)	Nielsen et al. (1996a)
Bangladesh	Dhaka City rickshaw drivers (46) and controls (48)	Immunoassay (ELISA) for PAH–DNA adducts; white blood cells	Adducts detectable in 19/46 rickshaw drivers vs 11/48 controls ($P = 0.06$). Mean adduct levels significantly higher in drivers than in controls ($P = 0.04$ overall; $P = 0.01$ for those with detectable adducts)	Rahman et al. (2003)
Czech Republic	30 women in Teplice (high pollution, exposed); 30 women in Prachatice (low pollution, control)	^{32}P-postlabelling; white blood cells	Significant correlation between individual personal exposures to PAHs and DNA adducts	Binková et al. (1996)

Table 4.7 (continued)

Location	Study populations	Method of analysis; source of DNA	Results	Reference
Czech Republic	51 women in Teplice (polluted area)	^{32}P-postlabelling and IHC-ACIS for PAH–DNA adducts; placenta	Bulky DNA adducts detected by ^{32}P-postlabelling in fresh frozen tissue (n = 37), with no differences between smokers, non-smokers, and ETS-exposed non-smokers. Adducts detected by IHC-ACIS in fixed (n = 14) placenta samples but not in frozen (n = 37) placenta (before fixation) samples	Pratt et al. (2011)
Czech Republic	Male police officers working outdoors in downtown Prague (n = 109)	^{32}P-postlabelling; lymphocytes	Correlation between adduct levels and levels of PAH exposure at different sampling times	Topinka et al. (2007)
Czech Republic	Male police officers (exposed; n = 53) and residents (unexposed; n = 52) in Prague	^{32}P-postlabelling; lymphocytes	No significant difference in adduct levels between exposed and control groups, but the level of a B[*a*]P-like adduct was significantly higher in the exposed group ($P < 0.01$)	Binková et al. (2007)
Czech Republic	Residents of Ostrava (polluted industrial region; n = 149) and Prague (relatively unpolluted city; n = 65)	^{32}P-postlabelling; lymphocytes	Levels of B[*a*]P-like adducts significantly higher in Prague than in Ostrava region, but B[*a*]P concentrations higher in Ostrava than in Prague. Levels of B[*a*]P-like adducts in Ostrava region positively affected by exposure to B[*a*]P (not found for Prague). Levels of bulky adducts negatively associated with B[*a*]P/pollution levels in both cohorts	Rossner et al. (2013a)
Czech Republic, Slovakia, and Bulgaria	Residents of Prague, Košice, and Sofia, including city police officers and bus drivers (exposed; n = 204) and controls (n = 152)	^{32}P-postlabelling; lymphocytes	Negative correlation between 8-oxodG levels and B[*a*]P-like DNA adducts (P = 0.002) and between 8-oxodG levels and bulky adducts (P = 0.04)	Singh et al. (2007a)
Denmark, Greece	Non-smoking men in Athens (n = 17) and in rural (n = 29) and urban (n = 73) areas of Denmark	^{32}P-postlabelling; white blood cells (Athens) or lymphocytes (Denmark)	Median adduct levels significantly different in the 3 groups; Athens > urban Denmark > rural Denmark	Nielsen et al. (1996b)
Denmark	50 students living in Copenhagen	^{32}P-postlabelling; lymphocytes	No significant association between DNA adduct levels and exposure markers ($PM_{2.5}$ and black smoke) measured by personal exposure monitors	Sørensen et al. (2003a)
Denmark	75 pregnant women living in Greater Copenhagen	^{32}P-postlabelling; maternal blood and cord blood cells	Adduct levels in maternal and cord blood were similar and positively correlated. Adduct levels significantly elevated in mother–newborn pairs living in medium traffic-density areas ($P < 0.01$) but not in high traffic-density areas	Pedersen et al. (2009)
Italy	Traffic police (n = 94) and urban residents (n = 52)	^{32}P-postlabelling; white blood cells	DNA adduct levels in police significantly higher than in controls, correlating with increased exposure to PAHs	Merlo et al. (1997)
Italy	Non-smoking police officers in Genoa (exposed; n = 34) and office workers (control)	^{32}P-postlabelling; white blood cells	Median DNA adduct level of exposed group significantly higher than median of controls	Peluso et al. (1998)

Table 4.7 (continued)

Location	Study populations	Method of analysis; source of DNA	Results	Reference
Italy	114 workers in Florence exposed to traffic pollution; 100 resident controls	^{32}P-postlabelling; white blood cells	DNA adduct levels significantly higher for traffic workers. Urban residents tended to have higher level than suburban residents (not significant), with higher levels in summer than in winter	Palli et al. (2001)
Italy	320 residents of Florence (114 traffic-exposed workers; 206 randomly sampled volunteers)	^{32}P-postlabelling; white blood cells	Significant correlation between DNA adduct levels and O_3 cumulative exposure	Palli et al. (2004)
Italy	Traffic-exposed workers (n = 62) and urban residents (n = 152) in Florence	^{32}P-postlabelling; white blood cells	DNA adduct levels in traffic-exposed workers correlated with average levels of exposure to PM_{10} over a prior time period of 1–2 weeks; levels in residents did not	Palli et al. (2008)
Italy	Residents of Pisa (urban; n = 520) and Cascina (suburban; n = 825)	ELISA for antibodies to BPDE–DNA adducts in serum	26.0% of urban subjects were positive for antibodies, compared with 17.9% of suburban residents; excess prevalence of antibody positivity for urban residents (OR, 1.49; 95% CI, 1.16–1.92)	Petruzzelli et al. (1998)
Italy	194 police officers in Rome (134 in traffic control; 60 in administrative division)	ELISA for antibodies to BPDE–DNA adducts in serum	10/134 traffic police were positive for antibodies; 1/60 office workers were positive. Difference is not significant (P = 0.095, χ^2 test)	Galati et al. (2001)
Italy	Newspaper vendors in high-traffic (n = 31) and low-traffic (n = 22) areas of Milan	^{32}P-postlabelling; lymphocytes	No difference in adduct levels between the high- and low-exposure groups	Yang et al. (1996)
Thailand	Male children aged 9–13 yr in Bangkok (high exposure; n = 107) and Chonburi (low exposure; n = 69)	^{32}P-postlabelling; lymphocytes	Mean DNA adduct level 5-fold higher in Bangkok children than in Chonburi children (P < 0.001)	Ruchirawat et al. (2007), Tuntawiroon et al. (2007)
Thailand	Police officers in Bangkok; traffic police (high exposure; n = 44) and office-based police (low exposure; n = 45)	^{32}P-postlabelling; lymphocytes	Mean DNA adduct levels significantly higher in high-exposure group than in low-exposure group (P = 0.029)	Ruchirawat et al. (2002)
Thailand	Adults living near Map Ta Phut Industrial Estate (exposed; n = 72) and residents of a control district (unexposed; n = 50)	^{32}P-postlabelling; white blood cells	Adduct levels in exposed residents, 0.85 ± 0.07 (SE) DNA adducts/10^8 nucleotides, significantly higher than in controls, 0.53 ± 0.05 (SE) (P < 0.05)	Peluso et al. (2008)
Thailand	Adults living near Map Ta Phut Industrial Estate (exposed; n = 65) and residents of a control district (unexposed; n = 45)	^{32}P-postlabelling; white blood cells	Higher levels in exposed group than in unexposed, as previously reported (Peluso et al., 2008). Increased levels of DNA adducts were correlated with marginally lower LINE-1 methylation (P = 0.06) and lower *p53* methylation (P = 0.01)	Peluso et al. (2012)

Table 4.7 (continued)

Location	Study populations	Method of analysis; source of DNA	Results	Reference
Ukraine	62 pregnant women in Kiev and Zaporizhia, Ukraine (exposed); 20 pregnant women from rural Eastern Carpathian area, Poland (unexposed)	CIA for PAH–DNA adducts; placenta	38/62 samples from exposed groups had detectable DNA adducts vs 10/20 samples from controls. Newborns with the most compromised health status had highest levels of DNA adducts	Obolenskaya et al. (2010)
Mexico	92 residents of the Mexico City metropolitan area	CIA for PAH–DNA adducts; white blood cells	Mean adduct level was significantly higher in the dry season than in the rainy season, correlating with higher airborne concentrations of PM_{10}, and $PM_{2.5}$ in the dry season	García-Suástegui et al. (2011)
Benin	Residents of Cotonou (urban, high exposure; $n = 57$), Godomey (suburban; $n = 20$), and Sohon (village; $n = 17$)	^{32}P-postlabelling; lymphocytes	DNA adduct levels in urban residents were significantly higher than those in suburban and village residents ($P < 0.001$)	Ayi-Fanou et al. (2011)
China	150 children born to non-smoking mothers in Tongliang (exposed to local coal-fired power plant)	HPLC/fluorescence for B[*a*]P–DNA adducts; white blood cells from maternal and cord blood	High cord blood adduct levels (> median) associated with decreased head circumference at birth ($P = 0.057$) and decreased weight at age 18, 24, and 30 months ($P < 0.05$). Maternal blood DNA adduct levels not associated with cord blood levels or birth outcomes	Tang et al. (2006)
China	110 non-smoking mother–infant pairs in Tongliang (exposed to local coal-fired power plant)	HPLC/fluorescence for B[*a*]P–DNA adducts; white blood cells from maternal and cord blood	Increased adduct levels in cord blood associated with DQs at age 2 yr: decreased motor area DQ, language area DQ, and average DQ	Tang et al. (2008)
China	Non-smoking mother–infant pairs in Tongliang. One cohort from 2002 ($n = 110$), before the shutdown of the local coal-fired power plant; second cohort from 2005 ($n = 107$), after shutdown of plant	HPLC/fluorescence for B[*a*]P–DNA adducts; white blood cells from maternal and cord blood	Associations between elevated adduct levels and decreased DQs at age 2 yr seen in the 2002 cohort were not observed in the 2005 cohort	Perera et al. (2008)

B[*a*]P, benzo[*a*]pyrene; BPDE, benzo[*a*]pyrene diol epoxide; CI, confidence interval; CIA, chemiluminescence immunoassay; DQ, development quotient; ETS, environmental tobacco smoke; HPLC, high-performance liquid chromatography; IHC-ACIS, immunohistochemistry with automated cellular imaging system; LINE-1, long interspersed nuclear element-1; 8-oxodG, 8-oxo-7,8-dihydro-2′-deoxyguanosine; O_3, ozone; OR, odds ratio; PM_{10}, particulate matter with particles of aerodynamic diameter < 10 µm; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 µm; SE, standard error; yr, year or years.

Other studies in Poland have focused on mother–newborn pairs. Analysis by immunoassay (ELISA) for PAH–DNA adducts of maternal and cord white blood cells of mothers and newborns from Cracow found significant correlations between adduct levels and outdoor air pollution levels (PM_{10}) close to their places of residence (Whyatt et al., 1998). In a subsequent study, the Cracow cohort was compared with a rural cohort from Limanowa, and differences in adduct levels between the urban and rural groups were not significant (Perera et al., 1999); however, it was noted that there was heavier use of coal for home heating in the rural district than in the city. Among non-coal users only, adduct levels in Cracow maternal samples were significantly higher than those in Limanowa maternal samples.

In a subsequent study of a larger group of Cracow women, PAH exposure was estimated from personal air monitors worn during pregnancy (Kelvin et al., 2009). There was a significant interaction between prenatal exposure to PAHs and the levels of cord blood B[*a*]P–DNA adducts, determined by high-performance liquid chromatography (HPLC)/fluorescence analysis. This association was stronger in babies with low blood levels of α-tocopherol and carotenoids.

An early study measured DNA adducts by ^{32}P-postlabelling in the lymphocytes of taxi drivers, urban bus drivers, suburban bus drivers, and controls (hospital workshop workers) in Stockholm, Sweden (Hemminki et al., 1994). The adduct levels in the taxi drivers and the suburban bus drivers were significantly higher than those in the controls ($P < 0.01$ and $P < 0.001$, respectively), but the adduct levels in urban bus drivers were not significantly different from those in the controls.

Another study investigated DNA adducts in bus drivers in Copenhagen, Denmark (Nielsen et al., 1996a). Significantly higher DNA adduct levels were found in the drivers in central Copenhagen compared with those driving in outer areas, and all driver groups had significantly higher levels than controls consisting of rural dwellers or the general population.

A study on rickshaw drivers in Dhaka City, Bangladesh, used ELISA to detect PAH–DNA adducts in white blood cells (Rahman et al., 2003). A higher proportion of the drivers, who were not shielded or protected from exposure to traffic pollution, had detectable DNA adducts than a control group of unexposed people (19/46 vs 11/48; $P = 0.06$), and the mean adduct level was significantly higher in the rickshaw drivers than in the controls (overall, $P = 0.04$; for those with detectable adducts, $P = 0.01$).

Studies in the Czech Republic have focused on comparisons of residents of a highly industrialized and polluted region, Northern Bohemia, with those of a relatively unpolluted rural part of the country. When women in Teplice (in the industrialized region) were compared with women in Prachatice (rural control), significant associations between bulky DNA adducts in white blood cells and individual levels of exposure to PAHs (measured by personal air monitors) were found (Binková et al., 1996). A study of the placentas of mothers in Teplice detected bulky DNA adducts by ^{32}P-postlabelling and PAH–DNA adducts by immunohistochemistry that were unrelated to the smoking status of the women (Pratt et al., 2011).

One study of male police officers working outdoors in the downtown area of Prague found a correlation between bulky DNA adducts in their lymphocytes and air levels of PAHs at the various sampling times (Topinka et al., 2007), but another study that compared male police officers in Prague with residents of the city did not find a difference in overall adduct levels between the two groups, although the level of a B[*a*]P-like adduct was significantly higher in the exposed group (Binková et al., 2007).

Comparisons of Prague residents with those of an area of higher pollution, the industrialized region of Ostrava, revealed that levels of B[*a*]P-like

adducts in lymphocytes were positively affected by B[*a*]P exposure levels for the Ostrava residents but not for Prague residents (Rossner et al., 2013a). Although B[*a*]P concentrations were higher in Ostrava, levels of B[*a*]P-like adducts were higher in Prague. For total bulky adducts, levels in both cohorts were negatively associated with B[*a*]P and pollution levels.

A study that monitored residents of Prague (Czech Republic), Košice (Slovakia), and Sofia (Bulgaria) compared several biomarkers of exposure, including DNA adducts detected by ^{32}P-postlabelling (Singh et al., 2007a). Levels of total bulky DNA adducts, and also of B[*a*]P-like adducts, negatively correlated with levels of the oxidatively generated lesion 8-oxodG in DNA.

In a study that compared non-smoking men in Athens, Greece, with men in urban and rural areas of Denmark, the median adduct levels in white blood cells (Athens) or lymphocytes (Denmark) were significantly different in the three groups; levels in Athens were higher than those in urban Denmark, and levels in urban Denmark were higher than those in rural Denmark (Nielsen et al., 1996b). However, in another study of students living in Copenhagen, Denmark, there was no significant association between levels of bulky DNA adducts in lymphocytes and two exposure markers – levels of $PM_{2.5}$ and black smoke – measured by personal exposure monitors (Sørensen et al., 2003a). Also, among mother–newborn pairs living in Copenhagen, adduct levels were significantly elevated in maternal and cord blood of those living in medium-traffic-density areas, but not of those living in high-traffic-density areas, relative to those living in low-traffic-density areas (Pedersen et al., 2009)

Several studies in Italy have shown a positive association between exposure to outdoor air pollution and DNA adduct levels. Traffic police had significantly higher levels of bulky DNA adducts in white blood cells than age-matched urban residents (Merlo et al., 1997). Police officers in Genoa had a significantly higher median DNA adduct level than office workers (Peluso et al., 1998). Traffic-exposed workers in Florence had significantly higher DNA adduct levels than urban residents (Palli et al., 2001), with a significant correlation between adduct levels and ozone concentrations (cumulative exposure) (Palli et al., 2004). DNA adduct levels in white blood cells in traffic-exposed workers in Florence correlated with average levels of exposure to PM_{10} (Palli et al., 2008). When urban (Pisa) and suburban (Cascina) residents were compared for antibodies to B[*a*]P diol epoxide (BPDE)–DNA adducts in serum, there was a significant excess prevalence of antibody positivity among the urban residents (Petruzzelli et al., 1998). However, the same measurement carried out among police officers in Rome found only a non-significant increase (P = 0.095) among traffic police (10/134 positive for antibodies) compared with those with office duties (1/60 positive) (Galati et al., 2001). An earlier study of newspaper vendors, in whom bulky DNA adducts were measured in lymphocytes, did not find a difference between those working in high-traffic areas and those working in low-traffic areas of Milan (Yang et al., 1996).

In Thailand, schoolchildren in Bangkok were found to be exposed to levels of airborne PAHs 3.5-fold higher than those in a rural area (Ruchirawat et al., 2007, Tuntawiroon et al., 2007); in the same study, mean levels of bulky DNA adducts in blood lymphocytes in the Bangkok schoolchildren were 5 times those in the rural schoolchildren. Bangkok traffic police had significantly higher levels of bulky DNA adducts than office-based police (Ruchirawat et al., 2002). Another Thai study, of residents near an industrial estate, found higher bulky adduct levels in white blood cells (Peluso et al., 2008) and also lower methylation of the *p53* gene, an epigenetic effect, associated with increased levels of DNA adducts (Peluso et al., 2012).

A study of placental DNA samples from Ukraine (exposed group) compared them with

samples from a rural area of Poland (control group) for DNA adducts measured by immunoassay (Obolenskaya et al., 2010). A higher proportion of the Ukrainian group had detectable levels of PAH–DNA adducts compared with the Polish group, and those newborns with the most compromised health status also had the highest adduct levels. Among residents of Mexico City, whose white blood cell DNA was monitored by the same immunoassay technique as for the Ukrainian and Polish placental samples, it was found that the seasonal variation in the mean adduct level correlated with airborne concentrations of PM_{10} and $PM_{2.5}$; all parameters were higher in the dry season than in the rainy season (García-Suástegui et al., 2011).

A single study in Africa found similar results to those of the studies in Europe and Asia; in Benin, levels of bulky DNA adducts in lymphocytes were significantly higher among urban residents than among people living in suburban or village environments (Ayi-Fanou et al., 2011).

Studies of non-smoking mother–newborn pairs in Tongliang, China, a city whose principal source of air pollution was a coal-fired power plant, have also measured the effect on birth outcomes and subsequent child development. When measured by HPLC/fluorescence, B[*a*]P–DNA adduct levels in cord blood, but not in maternal blood, were associated with decreased weight at up to 30 months and decreased head circumference at birth (Tang et al., 2006). Increased adduct levels in cord blood were also associated with several physical and cognitive scores measured at age 2 years (Tang et al., 2008). The subsequent closure of the power plant yielded the opportunity to make comparisons between infants born before the closure and those born after the closure. The associations between elevated adduct levels in cord blood and deficiencies in development seen in the earlier cohort were not seen in the post-closure cohort of infants, suggesting the benefit of reduced exposure to air pollution of children prenatally and/or postnatally (Perera et al., 2008).

Collectively, the majority of these studies demonstrate the presence of elevated levels of DNA adducts in adults occupationally exposed to outdoor air pollution, relative to comparable groups in environments with lower levels of pollution. Seasonal differences were also observed. Studies in children and newborns have found similar differences.

(ii) Experimental studies – in vivo systems

See Table 4.8.

When cyclohexane extracts of air particles from rural and urban areas of Sicily, Italy, were instilled intratracheally in rats for 5 consecutive days, they were found to lead to the formation of lung DNA adducts, detected by ^{32}P-postlabelling and synchronous fluorescence spectroscopy (Izzotti et al., 1996). Higher levels of adducts were found in the animals treated with the urban extract than in those treated with the rural sample.

Feral pigeons were caught at four different locations in the Netherlands and analysed for their DNA adduct levels in kidney, lung, and liver (Schilderman et al., 1997). Although the levels of PAHs in the particulate samples reflected the density of traffic at each location, no differences were found in the tissue adduct levels (measured by ^{32}P-postlabelling) in pigeons from the different sites.

Extracts of airborne particles from Shanghai, China, when tested on mouse skin, gave rise to DNA adducts, detected by ^{32}P-postlabelling, in the skin, liver, and kidney, but not in the lung, of the animals (Zhao et al., 2003). Most of the genotoxic activity of the fractions was attributed to the PAH component of the extracts.

When mice were exposed to diesel exhaust particles by inhalation, increased levels of bulky DNA adducts (detected by ^{32}P-postlabelling) were formed in their lungs (Dybdahl et al., 2004). In another study, oral exposure of pregnant mice

Table 4.8 DNA adducts in animals in vivo exposed to outdoor air pollution or extracts of air particles

Material or exposure	Species; route of exposure	Method of analysis	Results	Reference
Extracts of diesel exhaust	Mice; applied topically to skin	^{32}P-postlabelling	DNA adducts detected in lung > skin > liver	Gallagher et al. (1990)
Extracts of air particles from rural and urban sites in Sicily, Italy	Rats; intratracheal instillation	^{32}P-postlabelling; synchronous fluorescence spectroscopy	DNA adducts detected in lung. Urban > rural	Izzotti et al. (1996)
Feral pigeons caught at 4 locations in the Netherlands	Pigeons; environmental exposure	^{32}P-postlabelling	DNA adducts detected in kidney, liver, and lung. No association with PAH levels at each city site	Schilderman et al. (1997)
Extracts of airborne particles from Shanghai, China	Mice; applied topically to skin	^{32}P-postlabelling	DNA adducts detected in skin, liver, and kidney; not detected in lung	Zhao et al. (2003)
Diesel exhaust particles	Mice; inhalation	^{32}P-postlabelling	DNA adducts detected in lung	Dybdahl et al. (2004)
Diesel exhaust particles	Pregnant mice; oral exposure	^{32}P-postlabelling	DNA adducts detected in embryos	Reliene et al. (2005)
Vicinity of steel mills and major highway	Mice; environmental exposure	^{32}P-postlabelling	DNA adducts detected in lung (somatic tissue) but not in testis (germline tissue)	Yauk et al. (2008)

PAHs, polycyclic aromatic hydrocarbons.

to diesel exhaust particles resulted in detectable levels of bulky DNA adducts in the embryos (Reliene et al., 2005).

In a study investigating the germline mutagenicity of outdoor air pollution, a group of mice was exposed in situ in the vicinity of steel mills and a major highway (Yauk et al., 2008). When mouse samples were analysed by ^{32}P-postlabelling, bulky DNA adducts were detected in lung tissue but were below the limit of detection in testis tissue.

(iii) Experimental studies – in vitro systems

See Supplemental Table S11 (available online).

Human cells

Air samples from Prague (Czech Republic), Košice (Slovakia), and Sofia (Bulgaria) were compared in metabolically competent human hepatoma HepG2 cells, human diploid lung fibroblasts (HEL), and the human monocytic leukaemia cell line THP-1 (Sevastyanova et al., 2007). DNA adduct formation was highest in HepG2 cells, followed by HEL and then THP-1 cells. Winter samples were more active than summer samples; for the winter samples, the activity was highest for Prague, followed by Sofia and then Košice, but for the summer samples, the order was reversed, with the highest activity for Košice, followed by Sofia and then Prague. However, when the activities were related to the extractable content per cubic metre of air, the Sofia samples had the highest genotoxic activity regardless of the sampling period.

Animal cells

SRM 1649a was extracted with DCM and fractionated before testing for DNA adduct-forming activity in rat liver epithelial WB-F344 cells (Andrysík et al., 2011). When analysed by ^{32}P-postlabelling and HPLC, the crude extract formed only one major adduct peak, which corresponded with the (+)-*anti*-BPDE–dG

adduct. When analysed by ^{32}P-postlabelling and thin-layer chromatography, the crude extract and the non-polar fraction (containing PAHs, methylated PAHs, polychlorinated biphenyls, and polychlorinated dibenzodioxins/furans) gave rise to detectable adducts, but the polar fraction (containing oxygenated derivatives of PAHs) did not.

Air samples from the Czech Republic have also been tested in cellular assays for DNA adducts. Crude and fractionated DCM extracts of air samples from Teplice (industrialized area) and Prachatice (rural area) were incubated with cultured rat hepatocytes and Chinese hamster V79NH lung cells expressing nitroreductase activity (Topinka et al., 2000). In hepatocytes, the highest DNA adduct-forming activity was found in the fractions containing most of the PAHs and nitro-PAHs, and in V79NH cells, the highest levels were caused by the fraction containing only nitro-PAHs. Winter samples had 3–4-fold higher binding potential than summer samples.

Acellular systems

Several studies have investigated the effect of extracts of air samples from areas of the Czech Republic with different levels of air pollution on calf thymus DNA in the presence of S9. The extent of DNA adduct formation, detected by ^{32}P-postlabelling, was determined.

Overall, these studies demonstrated the potential of organic extracts of air sample particulates to form DNA adducts when incubated with DNA in the presence of an acellular metabolizing system, and when incubated with mammalian cells. Samples collected in the winter were generally more active than samples collected in the summer.

(b) Protein adducts

Several studies (see Supplemental Table S12, available online) have investigated the value of protein adducts in monitoring human exposure to environmental carcinogens, by comparing residents of cities with those living in rural environments, or by comparing occupations resulting in exposure to outdoor air pollution, such as bus and taxi drivers, with occupations with bystander exposure to air pollution, such as traffic police or street newspaper vendors, and with workers with indoor occupations. Most of these studies have used B[*a*]P as the standard pollutant and have measured adducts of its activated form, BPDE, with either haemoglobin in red blood cells or albumin in blood serum, mainly by ELISA or HPLC and GC-MS. The potential for such adducts to result from tobacco smoking or diet has generally been recognized, and most studies have attempted to control for these exposures.

In a study that also measured DNA adducts (see Section 4.2.3a(i)), Hemminki et al. (1994) measured PAH–plasma protein adduct levels in taxi drivers (n = 19), urban bus drivers (n = 26), suburban bus drivers (n = 21), and controls (n = 21) in Stockholm, Sweden. The levels were significantly elevated, relative to controls, in the taxi drivers ($P < 0.001$) but not in either group of bus drivers.

Studies comparing residents of industrialized, polluted regions of countries with residents of rural, unpolluted regions of the same countries have shown mixed results. Such a study in Denmark found that the rural residents (n = 29) had non-significantly higher levels of albumin adducts compared with urban residents (n = 73) (Nielsen et al., 1996b). A study of mothers and newborns in Denmark found that among non-smoking women resident in a rural area, adduct levels were significantly lower in a suburban group (n = 37) than in city dwellers (n = 40), but levels in rural dwellers were not significantly different from those in city dwellers (Autrup & Vestergaard, 1996). Levels of albumin adducts in cord blood were lower than those in maternal blood, and adduct levels in maternal blood were slightly higher in smokers and rural

residents than in non-smokers and suburban and city dwellers.

A study in the Czech Republic found no significant difference in serum albumin adduct levels between women in a polluted region (Teplice, n = 30) and those in a rural region (Prachatice, n = 30) (Binková et al., 1996). A study in Poland found that plasma albumin adduct levels in rural controls (n = 45) were significantly lower than those in exposed residents (n = 36) (summer samples) but were not correlated with air levels of B[*a*]P (stationary sampling) (Kure et al., 1997).

In a study of residents of Munich, Germany, that also considered diet and smoking as possible sources of B[*a*]P–protein adducts, adduct levels did not correlate with estimated dietary intake of B[*a*]P. Levels of albumin and haemoglobin adducts of B[*a*]P tended to be higher in suburban residents than in city dwellers; this was of borderline significance for B[*a*]P–albumin (Scherer et al., 2000).

A study in Germany analysed aromatic amine–haemoglobin adducts in children aged 7 years and found the highest levels of several aromatic amine adducts in children from Munich (population, 1.3 million); children from Augsburg (population, 250 000) had intermediate levels, and children from Eichstätt (population 13 000) had the lowest levels (Richter et al., 2001).

A study of traffic police (n = 44) in Bangkok, Thailand, found that they had significantly higher levels of BPDE–serum albumin adducts than police working in offices (n = 45) (Ruchirawat et al., 2002). A study of street newspaper vendors in Milan, Italy, found that those working at sites with high traffic flow (n = 30) had significantly higher levels of BPDE–haemoglobin adducts than those working at low-traffic sites (n = 23) (Pastorelli et al., 1996).

Thus, in most, but not all, of these studies of protein adducts, levels in urban dwellers were higher than those in suburban and rural dwellers, with elevated levels found in workers occupationally exposed to traffic pollution, similar to findings in studies that measured DNA adducts (see Section 4.2.3a).

(c) DNA strand breaks

(i) Humans – in vivo studies

Associations between air pollution and biomarkers of oxidative stress, including DNA strand breaks, have been assessed in a variety of biomonitoring studies, including controlled exposure, panel, and cross-sectional studies. The controlled exposure studies have typically been better than panel and cross-sectional studies because of better control for possible confounders. Table 4.9 provides an overview of studies that have assessed the association between air pollution exposure and DNA strand breaks in cells from humans.

In Belgium, a cross-sectional study showed that subjects in locations with heavy industry had increased levels of DNA strand breaks in leukocytes compared with subjects in low-pollution areas (Staessen et al., 2001). The levels of DNA strand breaks in leukocytes correlated with ozone levels as well as urinary excretion of 1-OHP and benzene metabolites (*trans*,*trans*-muconic acid [*t*,*t*-MA] and *o*-cresol) in univariate models (Koppen et al., 2007; Staessen et al., 2001). A later cross-sectional study in Belgium of subjects in areas with different types of air pollution showed that the highest levels of DNA strand breaks in leukocytes were observed in subjects living closest to air pollution sites, whereas there was no correlation between exposure markers (*t*,*t*-MA and 1-OHP) and levels of DNA strand breaks (De Coster et al., 2008; Ketelslegers et al., 2008).

A study in Benin investigated the association between four groups of exposed subjects, encompassing taxi-moto drivers in the city of Cotonou, subjects living near roads with heavy traffic or in the suburbs, and village controls. Exposure to air pollution was determined by urinary excretion of benzene metabolites and the number

Table 4.9 DNA strand breaks in blood cells from humans exposed to outdoor air pollution

Exposure	Exposure assessment	Reference
Subjects living in a rural village and 2 suburbs of Antwerp, Belgium	O_3: 15–58 μg/m³ 1-OHP (urine) *t,t*-MA (urine) *o*-Cresol (urine)	Koppen et al. (2007); Staessen et al. (2001)
Subjects living in Flanders, Belgium	1-OHP (urine) *t,t*-MA (urine)	De Coster et al. (2008); Ketelslegers et al. (2008)
Taxi-moto drivers, people living or working near busy roads, and rural controls in Benin	Outdoor (stationary) sampling of UFP (midday 1 h concentration at a busy street intersection and a town square in a rural village, 265 145 and 6961 UFP/cm³, respectively) and urinary excretion of *S*-PMA	Avogbe et al. (2005)
People living near or working at an oil refinery plant and controls from another location in Brazil	PM_{10}: 9–62 μg/m³ (in the location of the oil refinery plant)	Coronas et al. (2009)
Subjects living in towns with or without industrial areas in Brazil	TSP: higher in the towns with industry (84–154 μg/m³) than in non-industrial towns (28–104 μg/m³)	Pereira et al. (2013)
Male police officers working in traffic or indoors in Shanghai, China	Level of exposure was obtained by personal monitoring of $PM_{2.5}$ in traffic police (115.4 ± 46.2 μg/m³) and officers working indoors (74.9 ± 40.1 μg/m³)	Li et al. (2010)
Traffic police working in traffic or indoors in 8 districts in Guangzhou, China	NR	Zhu et al. (2003)
Mothers and newborn children in Teplice and Prachatice, Czech Republic	Air pollution levels were not specified, but levels of PM were typically higher in Teplice than in Prachatice	Srám et al. (1998)
Panel study of subjects in Teplice, Czech Republic	Personal PAH concentration in $PM_{2.5}$ (6.2–10 ng/m³)	Binková et al. (1996)
Police officers and controls in Prague, Czech Republic	Outdoor and personal PAH concentration (6.5 and 12.4 ng/m³ in February; 3.7 and 16.7 ng/m³ in June)	Cebulska-Wasilewska et al. (2005)
Police officers and a control group of subjects who were matched for age, sex, and length of employment in Prague, Czech Republic	$PM_{2.5}$ (stationary monitoring data: 33 ± 40 μg/m³ and 15 ± 9 μg/m³) PAHs (personal exposure: 8.5 ± 9 ng/m³ and 3.0 ± 3.4 ng/m³)	Novotna et al. (2007)
Bus drivers, garage workers, and controls in Prague, Czech Republic	Personal PAH concentration (3.9–5.7 ng/m³)	Bagryantseva et al. (2010)
Subjects living in Copenhagen, Denmark	Benzene (personal exposure and urinary excretion of *S*-PMA)	Sørensen et al. (2003c)
Panel study of students living in Copenhagen, Denmark	Personal $PM_{2.5}$: 16.1 (10–24.5) μg/m³ $PM_{2.5}$: 9.2 (5.3–14.8) μg/m³ (stationary monitoring stations)	Sørensen et al. (2005)
Subjects exposed to outdoor air while bicycling in Copenhagen, Denmark	Personal UFP: 32 400 and 13 400 UFP/cm³ PM_{10}: 23.5 μg/m³ (street) and 16.9 μg/m³ (background) NO_2: 32.1 and 24.2 μg/m³ (street) and 11.3 μg/m³ (background)	Vinzents et al. (2005)

concentration of ultrafine particles (UFP) at specific sites in Cotonou or in the village (midday 1-hour average, 6961–265 145 UFP/cm³). In addition, the personal exposure level of benzene was assessed as *S*-phenyl mercapturic acid (*S*-PMA) excretion in urine. The authors showed

Table 4.9 (continued)

Exposure	Exposure assessment	Reference
Controlled exposure to outdoor air in a chamber for 24 h in Copenhagen, Denmark	Personal UFP: 6169–15 362 UFP/cm³ (unfiltered air) and 91–542 UFP/cm³ (filtered air) NO_x: 25.3 ppb (unfiltered air), 28.3 ppb (filtered air), 11.6 ppb (background), and 59.5 ppb (busy street) O_3: 12.1 ppb (unfiltered air), 4.3 ppb (filtered air), 30.1 ppb (background), and 19.5 ppb (busy street)	Bräuner et al. (2007)
Subjects living within Athens (urban) or outside Athens (rural), Greece	None	Piperakis et al. (2000)
Subjects living in Florence (polluted area) and Sassari (non-polluted area), Italy	PM_{10}: 31–67 µg/m³ NO_x: 17–100 µg/m³ SO_2: 2.9–6.5 µg/m³ O_3: 17–75 µg/m³	Pacini et al. (2003)
Subjects in Florence, Italy	O_3 (stationary monitoring data): 15–75 µg/m³	Giovannelli et al. (2006)
Traffic police and controls in Rome, Italy	Benzene: 3.8–9.5 µg/m³	Carere et al. (2002)
Children and adults living in a low-pollution area and in Mexico City, Mexico	O_3: 269 ppb (average maximum) NO_2: usually < 53 ppb SO_2: usually < 30 ppb	Calderón-Garcidueñas et al. (1996, 1997)
Panel study of subjects in Mexico City, Mexico	NR	Fortoul et al. (2010)
Students in Mexico City, Mexico	O_3: 115–172 ppb	Rojas et al. (2000)
Children living in a low-pollution area and in Mexico City, Mexico	PM_{10}: < 14 to 53–61 µg/m³ O_3: < 10 to 261 ppb (max)	Calderón-Garcidueñas et al. (1999)
Police officers working in traffic or indoors in Bangkok, Thailand	Personal benzene (8–50 µg/m³), *t,t*-MA, *S*-PMA, and 1,3-butadiene (0.3–4.1 µg/m³) exposure	Arayasiri et al. (2010)
Children living in a rural area (Chonburi) and an urban area (Bangkok) in Thailand	Benzene (outdoor monitoring and personal exposure)	Buthbumrung et al. (2008); Ruchirawat et al. (2006, 2007)
Schoolchildren in Bangkok and a low-pollution area in Thailand	PAH: 2–26 ng/m³ 1-OHP excretion	Tuntawiroon et al. (2007)

h, hour or hours; NO_2, nitrogen oxide; NO_x, nitrogen oxides; NR, not reported; 1-OHP, 1-hydroxypyrene; O_3, ozone; PAHs, polycyclic aromatic hydrocarbons; PM, particulate matter; PM_{10}, particulate matter with particles of aerodynamic diameter < 10 µm; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 µm; SO_2, sulfur dioxide; *S*-PMA, *S*-phenyl mercapturic acid; TSP, total suspended particles; *t,t*-MA, *trans,trans*-muconic acid; UFP, ultrafine particles.

a positive relationship between the levels of DNA strand breaks in peripheral blood mononuclear cells (PBMCs) and air pollution levels in terms of either the outdoor air concentration of UFP or the *S*-PMA concentrations in urine (Avogbe et al., 2005).

In a study in Brazil, subjects living at a location near an oil refinery plant had higher levels of DNA strand breaks in lymphocytes compared with subjects from a city that was characterized as having little traffic and industry (Coronas et al., 2009). Another study in Brazil, with the same type of study design, showed no difference in the level of DNA strand breaks between subjects from urban industrialized and non-industrialized areas (Pereira et al., 2013). It should be noted that the results might be biased because it is difficult to separate the effect of air pollution exposure from the other variables that differ between subjects from different locations.

A study of traffic police and a matched group of reference subjects (officers working mainly indoors) in Shanghai, China, assessed exposure by personal monitoring of $PM_{2.5}$ and measured levels of DNA strand breaks in lymphocytes by the comet assay. The subjects were smokers or had stopped smoking for more than 6 months (including family members) before the study. The

personal monitoring data indicated that traffic police were exposed to higher levels of $PM_{2.5}$ (115.4 ± 46.2 μg/m³) compared with officers working indoors (74.9 ± 40.1 μg/m³). Traffic police had a higher percentage of lymphocytes with a comet tail compared with officers working indoors. In addition, the levels of DNA strand breaks, assessed as the average tail moment, were reported to be higher in lymphocytes from the group of traffic police compared with the group of officers working indoors (Li et al., 2010). [The Working Group noted that the statistical analysis of the reported results was based on the total number of cells from all the subjects, 100 scored nuclei per subject times the number of subjects, giving rise to group sizes of more than 10 000 data points for approximately 100 subjects per group. This is at odds with the standard procedure of statistical analysis for the comet assay.] Another study of police officers from eight districts in Guangzhou, China, showed that traffic police had significantly higher frequencies of DNA strand breaks in lymphocytes, measured as the comet tail length (4.2 μm; 95% confidence interval [CI], 3.98–4.42 μm), compared with officers working indoors (3.23 μm; 95% CI, 2.82–3.70 μm) ($P < 0.001$, $F = 9.23$, *t*-test). Smoking was identified as a confounding factor, although the results showed that traffic exhaust exposure was the main factor for the level of DNA strand breaks in lymphocytes (Zhu et al., 2003).

Several studies in the Czech Republic have assessed DNA strand breaks in people with different occupations or living in areas characterized by high or low air pollution levels. The early studies focused on differences in air pollution exposures between the regions of Teplice (industrial site) and Prachatice (low-pollution area). The Teplice area has higher air pollution levels than the Prachatice area. For instance, the $PM_{2.5}$ levels were 122 μg/m³ in Teplice and 44 μg/m³ in Prachatice during the winter of 1993 (Srám et al., 1996). During the summer of 1993, the levels were 29 μg/m³ in Teplice and 18 μg/m³ in Prachatice (Srám et al., 1996). In the subsequent years, the levels of air pollution were higher in Teplice than in Prachatice, although the differences were less dramatic than during the winter of 1993. During the summer of 1993 and the winter of 1998, the typical PM_{10} levels were 40–60 μg/m³ in Teplice and 20–40 μg/m³ in Prachatice (Srám et al., 1999). These early studies showed that personal exposures to PAHs in respirable particles correlated with levels of DNA strand breaks in lymphocytes (Binková et al., 1996). Mothers and children from the Teplice area and the Prachatice area had the same levels of DNA strand breaks in leukocytes (Srám et al., 1998). In Prague, police officers with personal exposure to PAHs had the same level of DNA strand breaks in lymphocytes as controls, although there was a difference in exposure. The personal PAH levels for the police officers and the controls were 6.5 ng/m³ and 12.4 ng/m³, respectively, in February and 3.7 ng/m³ and 16.7 ng/m³, respectively, in June (Cebulska-Wasilewska et al., 2005). Another study of police officers showed higher levels of DNA strand breaks in lymphocytes in the season with a high level of air pollution exposure (January; $PM_{2.5}$ = 33 μg/m³), whereas there was no effect in the season with a low level of air pollution exposure (September; $PM_{2.5}$ = 15 μg/m³) (Novotna et al., 2007). A study of bus drivers, garage workers, and office workers (controls) showed increased levels of DNA strand breaks in lymphocytes of workers exposed to air pollution (Bagryantseva et al., 2010).

A panel study of students who were living in the centre of Copenhagen, Denmark, showed no association between levels of DNA strand breaks in lymphocytes and personal exposure to $PM_{2.5}$ in the range of 10–24.5 μg/m³ (Sørensen et al., 2003a, b). Another study of residents of Copenhagen used benzene as marker of urban air pollution exposure and also showed no association between urinary excretion of *S*-PMA and levels of DNA strand breaks in lymphocytes (Sørensen et al., 2003c). The effect of personal exposure to UFP in air pollution was investigated

in people bicycling for approximately 90 minutes in the laboratory or on traffic-heavy streets in Copenhagen. This study showed no association between personal exposure to UFP and levels of DNA strand breaks in PBMCs (Vinzents et al., 2005). A later study on controlled exposure to air from a busy street in Copenhagen showed a correlation between particles in the size mode with a median diameter of 57 nm (representing carbonaceous soot) and levels of DNA strand breaks in PBMCs, whereas the size mode with a median diameter of 23 nm (representing SVOCs of diesel exhaust) was not associated with elevated levels of DNA strand breaks (Bräuner et al., 2007).

Non-smoking subjects in Athens, Greece, had elevated levels of DNA strand breaks in lymphocytes compared with subjects in a rural area; there was no difference in levels of DNA strand breaks in lymphocytes between smokers in Athens and those in the rural area (Piperakis et al., 2000).

A study in Florence, Italy, showed a positive association between urban ozone concentrations (~75 μg/m^3 in June and ~17 μg/m^3 in January) and levels of DNA strand breaks in nasal epithelial cells, and the residents of Florence had higher levels of DNA strand breaks and ozone exposure compared with people living in a city with a low air pollution level (45 μg/m^3 in June) in Sardinia (Pacini et al., 2003). Another study of subjects in Florence showed a positive association between ozone concentrations and levels of DNA strand breaks in lymphocytes (Giovannelli et al., 2006). Police officers from Rome, Italy, had unaltered levels of DNA strand breaks in leukocytes compared with a control group of office workers, despite a large difference in benzene exposure (9.5 μg/m^3 vs 3.8 μg/m^3 as measured by personal air sampling during a work shift) between the groups (Carere et al., 2002).

A study among subjects in Mexico City showed an association between levels of ozone and numbers of nasal epithelial cells with DNA strand breaks among adults from different locations in the city and in a low-pollution Pacific coastal town (Calderón-Garcidueñas et al., 1996). Embedded in the same study was also an assessment of the effect in young adults who moved to Mexico City from low-pollution small towns; the number of nasal cells with DNA strand breaks in this group of subjects increased during the first 2 weeks after arrival (Calderón-Garcidueñas et al., 1996). The same group of authors also showed that children in Mexico City had more nasal cells with DNA strand breaks compared with children in a low-pollution Pacific coastal town (Calderón-Garcidueñas et al., 1996, 1997). A seasonal variation was observed; samples of nasal epithelial cells that were collected during the autumn (with high air pollution levels) from a population chronically exposed to this atmospheric pollution had higher levels of DNA strand breaks compared with samples collected during the summer (with low air pollution levels) (Fortoul et al., 2010). A study of students in Mexico City showed that subjects living at a location with high outdoor air concentrations of ozone had elevated levels of DNA strand breaks in exfoliated tear duct cells compared with subjects from a location with lower ozone concentrations (Rojas et al., 2000). [This study had some limitations as judged by the standards that are used for comet assay analysis today. These include that the samples from exposed subjects and controls might have been collected and analysed at different times, without control for period effects, and that the results were reported as percentages of cells with DNA strand breaks rather than as numbers of lesions in the cells.] A later study by the same group investigated genotoxicity in nasal biopsies from children living in areas with different levels of exposure (a Pacific coastal town vs Mexico City) and showed positive associations between ozone exposure and elevated levels of DNA strand breaks in nasal cells (Calderón-Garcidueñas et al., 1999).

Table 4.10 DNA strand breaks in lungs of animals in vivo

Particles	Animal	Extraction	Dose and duration	Effect	Reference
Endotracheal instillation of $PM_{2.5}$ from an unspecified location in China	Wistar rats	Water (sonication)	1.5 or 7.5 mg/kg bw	Increased levels of DNA strand breaks (comet) in lung tissue	Lin et al. (2009)
Intratracheal instillation of $PM_{2.5}$ collected during normal weather and dust storm in China	Wistar rats	Water (sonication)	1.5–37 mg/kg bw for 24 h	Dose-dependent increases in levels of DNA strand breaks (comet) in lung for samples from both normal weather and dust storms	Meng & Zhang (2006b, 2007)
Intratracheal instillation of $PM_{2.5}$ or PM_{10} from locations near to or far away from traffic in Beijing, China	Wistar rats	Water (sonication)	7.5 mg/kg bw once/d for 14 d, and killed at 24 h after the last instillation	Increased level of DNA strand breaks (comet) in lung tissue. $PM_{2.5}$ generated higher levels of DNA strand breaks than PM_{10}. Particles collected closest to traffic generated the highest levels of DNA strand breaks	Zhang et al. (2011)
Intratracheal instillation of TSP samples from Minqin county, Gansu province, China, where sandstorms occurred frequently	Wistar rats	Water (sonication)	1.5, 7.5, or 37.5 mg/kg bw, and killed at 12, 24, or 48 h after the instillation	Dose-dependent increase in level of DNA strand breaks (comet) in lung tissue. Highest levels of DNA strand breaks observed at 12 h, and effects reduced at 24 h after treatment	Xu et al. (2008b)
Intratracheal instillation of SRM 1649 (urban dust)	*ApoE*$^{-/-}$ mice	NA	0.5 mg/kg bw at 26 h and 2 h before being killed	Unaltered levels of DNA strand breaks (comet) in lung tissue	Vesterdal et al. (2014)

bw, body weight; d, day or days; h, hour or hours; NA, not applicable; PM_{10}, particulate matter with particles of aerodynamic diameter < 10 μm; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 μm; SRM, standard reference mixture; TSP, total suspended particles.

A study in Thailand with a relatively large benzene exposure gradient (8–50 μg/m^3) among traffic police and office-based police showed no association with levels of DNA strand breaks in leukocytes, whereas there was a correlation between the levels of 1,3-butadiene and levels of DNA strand breaks (Arayasiri et al., 2010). A series of publications from studies of schoolchildren in Bangkok, compared with children in a provincial area (Chonburi), showed that the children exposed to air pollution had higher levels of DNA strand breaks in leukocytes (Buthbumrung et al., 2008; Ruchirawat et al., 2006, 2007). Schoolchildren in Bangkok had higher levels of DNA strand breaks in lymphocytes compared with children from a low-pollution area in Thailand (Tuntawiroon et al., 2007).

(ii) DNA strand breaks in the respiratory system of animals in vivo

Several studies have assessed the level of DNA strand breaks in the lungs of animals after pulmonary exposure to air pollution particles (Table 4.10). Three studies in China have observed increased levels of DNA strand breaks in lung tissue after intratracheal instillation of relatively high doses of air pollution particles (7.5 mg/kg bw and 37 mg/kg bw) (Lin et al., 2009; Meng & Zhang, 2006b, 2007; Zhang et al., 2011). Another study in China collected TSP from a residential area in Minqin county, Gansu province, where sandstorms occurred frequently. Wistar rats were exposed to these sandstorm particles in suspension by intratracheal instillation at doses of 0, 1.5, 7.5, 37.5 mg/kg bw. The TSP exposure caused a dose-dependent increase in the level of

DNA strand breaks; the highest levels of DNA strand breaks were observed at 12 hours, and the effects were reduced at 24 hours after the exposure. The lowest dose that caused significantly increased levels of DNA strand breaks was 1.5 mg/kg bw (Xu et al., 2008b). However, another study on intratracheal instillation of SRM 1649 (i.e. urban dust from Washington, DC, USA) showed that 0.5 mg/kg bw administered twice during 24 hours did not increase levels of DNA strand breaks in lung tissue in mice (Vesterdal et al., 2014). Researchers in Brazil studied native rodents (*Ctenomys minutus*) and showed a correlation between environmental exposure to automobile emission and levels of DNA strand breaks in blood leukocytes (Heuser et al., 2002). Another study showed that dogs from different locations in São Paulo, Brazil, which had similar levels of PM_{10}, also had the same levels of DNA strand breaks in cells from the olfactory or respiratory epithelium (Kimura et al., 2010).

(iii) Human and mammalian cells in vitro

Table 4.11 lists studies that have assessed levels of DNA strand breaks in cultured cells. Several studies have shown that suspensions of PM samples or EOM of PM samples generate the same levels of DNA strand breaks in cultured cells (Brits et al., 2004; Carreras et al., 2013; Gutiérrez-Castillo et al., 2006; Healey et al., 2005; Jayasekher, 2009; Perrone et al., 2013). In addition, SRM 1649 particles retained the ability to generate DNA strand breaks in human fibroblasts after extraction in different solvents, including hexane, acetone, DCM, dimethyl sulfoxide (DMSO), and water (Karlsson et al., 2004). Another study on SRM 1648 (i.e. urban dust collected from St. Louis, Missouri, USA) showed that washed particles and the DCM extract generated lower levels of DNA strand breaks in THP-1 and A549 cells compared with the pristine particles (Don Porto Carero et al., 2001). [The concentration–response relationship was unclear.] Other studies have shown that suspensions of particles from cities in China generated DNA strand breaks in cells, as did the water and DCM extract of the particles (Meng & Zhang, 2007; Yi et al., 2014). Organic extracts of airborne particles with various sizes (< 1.1 μm, 1.1–2.0 μm, 2.0–3.3 μm, 3.3–7.0 μm, and > 7.0 μm) were also collected in a residential area in Taiyuan, China. Concentration-dependent responses of levels of DNA strand breaks in human lymphocytes were observed for airborne particles; small particles generated the highest levels of DNA strand breaks. The lowest effect level for particles smaller than 3.3 μm was 25 μg/mL (Zhang et al., 2004). The air pollution in Taiyuan consisted mainly of emissions from coal combustion, whereas the air pollution in Beijing was a mixture of coal combustion emissions and automobile exhausts. In Guangzhou, China, TSP and PM_{10} samples were collected in a residential area in spring; organic extracts were separated into three fractions by chromatography and used to study the generation of DNA strand breaks. TSP or PM_{10} extracts induced DNA strand breaks in human lymphocytes in a concentration-dependent manner. The aromatic hydrocarbon fraction of the TSP or PM_{10} extract also induced a concentration-dependent increase in DNA strand breaks in human lymphocytes (Xu & Wang, 2008). In addition, the water extracts of $PM_{2.5}$ from Guangzhou on days with haze during summer and winter generated a concentration-dependent increase in DNA strand breaks (Qin et al., 2012).

Suspension solutions of $PM_{2.5}$ collected in Taiyuan, China, during the heating season caused a concentration-dependent increase in levels of DNA strand breaks in rat alveolar macrophage cells (Meng & Zhang, 2005). In another study, organic extracts and water extracts of $PM_{2.5}$ samples collected in Wuwei and Baotou, China, during normal weather or sandstorms caused a concentration-dependent increase in levels of DNA strand breaks in rat alveolar macrophage cells (Meng et al., 2006a). Zhang et al. (2003) reported that organic extracts of $PM_{2.5}$ collected

Table 4.11 DNA strand breaks in mammalian cells in vitro

Particles	Cells	Extraction	Concentration and time	Effect	Reference
PM_{10} (and EOM) from rural, industrial, and urban sites in Flanders, Belgium	Human leukocytes	Water (shaking) or THF:Hx (20:80) at 140 bar and 100 °C	5–20 m^3 air equiv/mL for 24 h	Increased DNA strand breaks for both particles and EOM, although without concentration dependency	Brits et al. (2004)
TSP from Córdoba, Argentina	Human lymphocytes	Methylene chloride (ultrasound)	20–80 µL of extract for 24 h	Concentration-dependent increase in DNA strand breaks	Carreras et al. (2013)
PM, or EOM thereof, from Mexico City, Mexico, or SRM 1649	A549 cells	Water (ultrasound) or DCM	0.05–1.6 m^3/mL equiv for 48 h	Water-soluble and EOM had similar DNA strand break generation potential. Little difference between samples obtained at different locations. $PM_{2.5}$, PM_{10}, and SRM 1649 had the same potency	Gutiérrez-Castillo et al. (2006)
Different size fractions and EOM of PM_{10} from Leeds, United Kingdom	A549 cells	Water (vortexing or brushing off particles from the filter) or DCM (vortexing)	25 µg/mL for 24 h	Increased levels of DNA strand breaks. Organic extract generated a similar level of DNA strand breaks as pristine particles, whereas washed particles generated low levels of DNA strand breaks	Healey et al. (2005)
PM_{10} sampled near a coal power plant in Tuticorin, India	Human lymphocytes	Acid (sonication)	5 µg of aerosol extract per 50 µL for 24 h	Increased levels of DNA strand breaks	Jayasekher (2009)
$PM_{2.5}$ and PM_1 from rural, urban, and remote sites in northern Italy	A549 cells	Water (ultrasound) or MeOH	6 µg/cm^2 for 24 h	Samples from urban areas, collected during spring, were the most potent inducer of DNA strand breaks. $PM_{2.5}$ had higher potency than PM_1	Perrone et al. (2013)
SRM 1649 or its particles after extraction with organic solvents	Human fibroblasts	DCM, Hx, Ac, or DMSO	0.1–100 µg/cm^2 for 24 h	Concentration-dependent increase in DNA strand breaks (comet). Particles generated DNA strand breaks after extraction of organic material	Karlsson et al. (2004)
SRM 1648 or organic extracts thereof	A549 or THP-1 cells	Water or DCM (shaking by hand)	16–1600 ng/mL for 48 h	Inconsistently increased levels of DNA strand breaks in A549 cells. Increased levels of DNA strand breaks in THP-1 cells by particles, but unaltered levels by extracts and washed particles	Don Porto Carero et al. (2001)
$PM_{2.5}$ (or EOM) collected during normal weather and dust storm in China	Human alveolar macrophages	Water or DCM (sonication)	33–300 µg/mL for 4 h	Concentration-dependent increased levels of DNA strand breaks by particles and EOM. Samples from normal weather and dust storms generated the same levels of DNA strand breaks	Meng & Zhang (2007)

Table 4.11 (continued)

Particles	Cells	Extraction	Concentration and time	Effect	Reference
PM_{10} from Beijing, China	A549 cells	Water (sonication)	10 µg/mL for 24 h	Increased DNA strand breaks by particles as well as soluble and insoluble fractions thereof	Yi et al. (2014)
Airborne particulates with various sizes (< 1.1 µm, 1.1–2.0 µm, 2.0–3.3 µm, 3.3–7.0 µm, > 7.0 µm) collected in a residential area in Taiyuan, China. TSP concentration, 0.481 mg/m³	Human peripheral blood from a healthy adult. Cultured human peripheral blood lymphocytes	Airborne particulates with various sizes extracted by Soxhlet method with MeOH, Ac, and DCM for 4 h, respectively. Combined extracts dried and dissolved in DMSO	25, 50, 100, 200 µg/mL particulate extracts (incubation time not reported)	Concentration-dependent increases in level of DNA strand breaks	Zhang et al. (2004)
TSP and PM_{10} samples collected in a residential area in Guangzhou, China, during spring in 2005	Human peripheral blood from a healthy adult	TSP and PM_{10} samples extracted by ultrasonication with DCM and then separated into 3 fractions by chromatography	4 m³/mL for 2 h	Increased generation of DNA strand breaks	Xu & Wang (2008)
PM_{10} samples collected at 4 sites in Dalian, China, during summer and winter in 2006	HepG2 cells	PM_{10} samples extracted by ultrasonication with DCM, Ac, and MeOH for 20 min; subsequently, the 3 extracts were combined, dried, and dissolved in DMSO	0, 7.5, 15, 30 µg/mL for 1 h	Increased generation of DNA strand breaks	Jiang et al. (2011)
$PM_{2.5}$ samples collected at Beijing University, China, in March 2001	Balb/c 3T3 cells	Organic or inorganic extract	0.5, 1, 2, 4 m³/mL equiv for 12 h	Concentration-dependent increases in level of DNA strand breaks	Zhang et al. (2003)
PM_{10} from different locations in Mexico City, Mexico	Balb/c 3T3 cells	Dry sonication and brushing off particles from the filter	2.5–40 µg/cm² for 72 h	Concentration-dependent increases in DNA strand breaks, without clear difference in genotoxicity between locations. At 20 µg/cm² and 40 µg/cm², comet length did not increase beyond that obtained with 10 µg/cm²	Alfaro-Moreno et al. (2002)
PM from a town with many wood stoves and a rural area, Denmark	A549 and THP-1 cells	Mechanical collection from plates	2.5–100 µg/mL for 3 h	Concentration-dependent increase in DNA strand breaks in A549 and THP-1 cells (comet). No difference between particles from different areas	Danielsen et al. (2011)

Table 4.11 (continued)

Particles	Cells	Extraction	Concentration and time	Effect	Reference
$PM_{2.5}$ or PM_{10} from background site in Milan, Italy	BEAS-2B cells	Water (ultrasound)	25 µg/cm² for 24 h	$PM_{2.5}$ exposure increased level of DNA strand breaks. No effect of PM_{10}	Gualtieri et al. (2011)
$PM_{2.5}$ from 5 cities in the USA	IB3-1 and K543 cells	PBS (vortexing)	50 µL of extracts containing 33 µg of extracted $PM_{2.5}$ for 3 h	Increased level of DNA strand breaks, without a clear difference between particles from different cities (concern about number of repeated experiments)	Dellinger et al. (2001)
Coarse or fine particles from Mexico City, Mexico	THP-1 cells	Water	10 µg/mL for 24 h	Increased level of DNA strand breaks (comet), with some difference related to size, location, and time of sampling	De Vizcaya-Ruiz et al. (2006)
$PM_{2.5}$ collected from a busy street or urban background in Copenhagen, Denmark	A549 cells	Water	25 µg/mL for 24 h	Increased level of DNA strand breaks, although not a clear difference between street and background particles	Sharma et al. (2007)
Fine particles from various cities in Germany	A549 cells	Water (sonication)	20 µg/cm² for 3 h	Increased level of DNA strand breaks, although no difference between particles from different cities	Shi et al. (2006)
$PM_{2.5}$ from Beijing and Taiyuan, China	A549 cells	Water (ultrasonic shaking)	5–200 µg/mL for 12 h or 24 h	Concentration-dependent increase in DNA strand breaks (uncertainty about number of repeats and statistics). No difference between cities	Xu & Zhang (2004)
PM_{10} from a busy street in Stockholm, Sweden	A549 cells	Water (sonication)	40 µg/cm² (70 µg/mL) for 4 h	Increased levels of DNA strand breaks in cells after exposure to particles from a busy street (PM_{10}) as well as particles collected when running a road simulator with studded tyres ($PM_{2.5}$ or PM_{10})	Karlsson et al. (2006)
EOM or aqueous extract from $PM_{2.5}$ in Piedmont, Italy	A549 cells	DCM or water (ultrasound)	1–7 m³ equiv for 24 h	Highest levels of DNA strand breaks after exposure to EOM of PM from highway site, whereas urban and industrial sites had the same DNA strand break induction potential. Higher induction of DNA strand breaks by aqueous extracts from industrial site compared with urban and highway sites	Bonetta et al. (2009)

Table 4.11 (continued)

Particles	Cells	Extraction	Concentration and time	Effect	Reference
PM_{10},$PM_{2.5}$, PM_1, and $PM_{0.4}$ from Milan, Italy, collected during summer or winter	A549 cells	Water (sonication)	10 μg/cm² for 24 h	Increased level of strand breaks (γH2AX expression) by all samples collected during winter with a similar intensity	Longhin et al. (2013)
TSP from an urban street in Copenhagen, Denmark	A549 cells	Water (ultrasonication)	2.5–100 μg/mL for 48 h	Concentration-dependent increase in DNA strand breaks (comet assay). No difference between days of sampling	Danielsen et al. (2008)
Particles from a street tunnel in Oslo, Norway, during seasons with or without use of studded tyres	A549 and THP-1 cells	Scraping off the filter	2.5–200 μg/mL for 3 h	Increased DNA strand break sites in A549 and THP-1 cells (comet). No difference between seasons with or without use of studded tyres	Danielsen et al. (2009)
Coal fly ash from a dumping site of a thermal power plant in Aligarh, India	Mononuclear blood cells	DMSO (0.5%) or water (sonication)	3–2400 ppm for 3 h	Concentration-dependent increase for DMSO (0.5%) extract, and unaltered DNA strand break generation by aqueous extract	Dwivedi et al. (2012)
PM_{10} from a busy street in Stockholm, Sweden	A549 cells	Water (vortexing or sonication)	5–40 μg/cm² (9–70 μg/mL) for 4 h	Concentration-dependent increase in DNA strand breaks (comet)	Karlsson et al. (2005)
Airborne PM from Düsseldorf, Germany	A549 cells	Baghouse	1–100 μg/mL for 24 h	Concentration-dependent increase in DNA strand breaks (FADU assay)	Upadhyay et al. (2003)
Oil fly ash collected from a power plant in Sicily, Italy	A549 cells	Water	17.2–68.8 μM $VOSO_4$ equiv for 0.5–4 h	Concentration-dependent increase in levels of DNA strand breaks. Ameliorated by treatment with DFO (results not shown)	Di Pietro et al. (2009)
Fine particles from Düsseldorf, Germany	A549 cells	Water (sonication)	5–20 μg/cm² for 3 h	Increased level of DNA strand breaks by particles, which was diminished by treatment with DFO. Filtered suspensions less potent than suspensions with particles	Knaapen et al. (2002)
EOM of $PM_{2.5}$ and PM_{10} from Paris, Rouen, and Strasbourg, France	HeLa cells	Acetonitrile and ultrasound	200 μL of organic extract for 24 h	Extracts from $PM_{2.5}$, compared with PM_{10}, generated higher levels of DNA strand breaks (comet)	Abou Chakra et al. (2007)

Table 4.11 (continued)

Particles	Cells	Extraction	Concentration and time	Effect	Reference
EOM of PM_{10} from 4 different areas in China	HepG2 cells	Sequential extraction in DCM, Ac, and MeOH	7.5–30 µg/mL for 1 h	Concentration-dependent increase in DNA strand breaks by samples from Kaifaqu district, Dalian (industrial area). Lower levels of DNA strand breaks by samples from 3 other cities. Samples collected during winter more potent than summer samples	Jiang et al. (2011)
EOM of PM_{10} from Prague (Czech Republic), Košice (Slovakia), and Sofia (Bulgaria)	HepG2 cells	DCM	5–150 µg/mL for 2 h	Concentration-dependent increase in DNA strand breaks. No difference between samples with regard to season or location	Gábelová et al. (2004)
EOM of PM_{10} from Prague (Czech Republic), Košice (Slovakia), and Sofia (Bulgaria)	HepG2 cells	DCM	10–250 µg/mL for 2–48 h	Concentration-dependent increase in DNA strand breaks. Little spatial or temporal difference between samples on mass basis	Gábelová et al. (2007)
EOM of PM_{10} from urban sites in Saudi Arabia	Human leukocytes	Ac (Soxhlet tube)	250 µg/mL (incubation time not reported)	Increased levels of DNA strand breaks, with difference between sampling locations	Elassouli et al. (2007)
TSP and PM_{10} from an urban green park in downtown Rome, Italy	Human mononuclear blood cells	Hx and MeOH	4–144 m^3/mL for 2 h	Concentration-dependent increase in levels of DNA strand breaks. No difference in potency between EOM from TSP and PM_{10} samples	Fabiani et al. (2008)
EOM of TSP, PM_{10}, and $PM_{2.5}$ from Parma, Italy	Human leukocytes	Ac and Tl	1–3 m^3 equiv for 1 h	Extracts of $PM_{2.5}$ reported to generate higher levels of DNA strand breaks (comet) than those of TSP and PM_{10}. Number of independent experiments and statistics uncertain	Buschini et al. (2001)
EOM of $PM_{2.5}$ from a low-traffic area in Hong Kong Special Administrative Region, China	Rat fibroblasts	DCM (ultrasound)	570–2321 ng/mL for 72 h	Concentration-dependent increase in levels of DNA strand breaks. Samples collected during winter more potent than summer samples	Hsiao et al. (2000)
EOM of PM_{10} from Teplice, Czech Republic	HepG2 and Caco-2 cells	DCM	1–50 µg/mL for 24 h	Concentration-dependent increase in DNA strand breaks in HepG2 and Caco-2 cells. Winter samples more potent than summer samples	Lazarová & Slamenová (2004)

Table 4.11 (continued)

Particles	Cells	Extraction	Concentration and time	Effect	Reference
EOM of $PM_{2.5}$ from Guangzhou, China	Human lymphocytes	Sequentially, DCM (ultrasound) and Hx	5–20 m^3 air equiv/mL for 2 h	Higher DNA strand break generation of samples collected on days with haze conditions compared with non-haze. Higher generation of DNA strand breaks by samples collected from roadside compared with rooftop	Xu et al. (2008a)
EOM of PM from Taiwan, China	MCF-7 cells	Hx/Ac (ultrasound)	0.04–0.05 m^3 air equiv for 72 h	No clear difference between PM from urban and rural sites with regard to DNA strand break generation	Chen et al. (2013)
EOM of $PM_{2.5}$ from high-traffic area in Suwon, Republic of Korea	BEAS-2B cells	DCM (sonication)	1–50 µg/mL for 24 h	Concentration-dependent increase in DNA strand breaks	Oh et al. (2011)
EOM of road tunnel particles from Shanghai, China	A549 cells	DCM (sonication)	1–400 µg/mL for 24 h	Concentration-dependent increase	Shang et al. (2013)
EOM of PM_{10} from an industrial site in France	HepG2 cells	DCM (Soxhlet extractor)	0.16 µM B[*a*]P and atmospheric samples for 24 h	Increased levels of DNA strand breaks (comet)	Tarantini et al. (2009)

Ac, acetone; B[*a*]P, benzo[*a*]pyrene; DCM, dichloromethane; DFO, deferoxamine; DMSO, dimethyl sulfoxide; EOM, extractable organic matter; equiv, equivalent; h, hour or hours; Hx, hexane; PM, particulate matter; PM_{10}, particulate matter with particles of aerodynamic diameter < 10 µm; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 µm; MeOH, methanol; min, minute or minutes; PBS, phosphate-buffered saline; SRM, standard reference mixture; THF, tetrahydrofuran; Tl, toluene; TSP, total suspended particles.

at Beijing University caused a concentration-dependent increase in levels of DNA strand breaks in Balb/c 3T3 cells. The lowest concentration of the organic extract that caused a significantly increased level of DNA strand breaks was 1 m^3 equiv/mL, whereas an aqueous extract of $PM_{2.5}$ had no significant effect on generation of DNA strand breaks (Zhang et al., 2003).

Several studies have found no clear difference in the potency to generate DNA strand breaks of particles collected at different locations (Alfaro-Moreno et al., 2002; Danielsen et al., 2011; Dellinger et al., 2001; De Vizcaya-Ruiz et al., 2006; Sharma et al., 2007; Shi et al., 2006; Xu & Zhang, 2004). Similarly, PM_{10} collected from a busy street in the centre of Stockholm, Sweden, had the same potency on a mass basis as particles collected when running a road simulator (Karlsson et al., 2006). In contrast, aqueous extracts of $PM_{2.5}$ samples from industrial sites showed a higher induction of DNA strand breaks in A549 cells (Bonetta et al., 2009). One study reported that samples of $PM_{0.4}$, PM_1, $PM_{2.5}$, and PM_{10} that were collected during the winter at a background site in Milan, Italy, were more potent than the same fractions collected during the summer (Longhin et al., 2013), whereas three studies reported no temporal variation in PM samples in regard to ability to generate DNA strand breaks (Danielsen et al., 2008; Danielsen et al., 2009, 2011). Studies on differences related to particle size indicated that the urban background $PM_{2.5}$ fraction was more potent than PM_{10} on a mass basis (Gualtieri et al., 2011; Perrone et al., 2013). In general, consistency has been observed in studies showing increased levels of DNA strand breaks by aqueous suspensions of particles from various locations, times of the year, and size fractions. Other studies that have assessed the effect of particles from only a single site also indicated increased levels of DNA strand breaks (Dwivedi et al., 2012; Karlsson et al., 2005; Upadhyay et al., 2003), which could be reduced only slightly by treatment with deferoxamine (DFO) (Di Pietro et al., 2009; Knaapen et al., 2002). This suggests that the content of soluble transition metals such as iron was not the most important constituent in particles for the formation of DNA strand breaks.

It has been shown that acetonitrile-extracted material from $PM_{2.5}$ that was collected from a location close to heavy traffic had higher potency in generating DNA strand breaks in fibroblasts compared with $PM_{2.5}$ samples from other urban zones (Abou Chakra et al., 2007). A comparative investigation of organic extract of $PM_{2.5}$ from samples collected at a highway site (with high traffic intensity) showed higher levels of DNA strand breaks in A549 cells compared with extracts from an urban site (with medium traffic intensity) and an industrial site near a foundry (Bonetta et al., 2009). Also, samples collected in the industrial area of Kaifaqu district, Dalian, China, showed higher potency in generating DNA strand breaks compared with samples from three other areas in China (Jiang et al., 2011). DCM extracts of PM_{10} samples from urban air in Prague (Czech Republic), Košice (Slovakia), and Sofia (Bulgaria) increased the generation of DNA strand breaks in HepG2 cells, whereas there were no clear spatial or temporal differences in potency (Gábelová et al., 2004, 2007). Another study found a difference between DCM extracts of PM_{10} from different locations in Saudi Arabia (Elassouli et al., 2007). EOM (hexane and methanol) of TSP and PM_{10} from an urban background site (a park) in Rome, Italy, had similar potency in generating DNA strand breaks in mononuclear blood cells (Fabiani et al., 2008). Another study in Parma, Italy, showed that EOM of $PM_{2.5}$ was more potent than TSP and PM_{10} in generating DNA strand breaks (Buschini et al. 2001).

Organic extracts of $PM_{2.5}$ or PM_{10} from samples that were collected in three French metropolitan areas in the winter had higher potential to generate DNA strand breaks than extracts collected in the summer (Abou Chakra

et al., 2007). Organic extracts of PM_{10} samples from an industrial area in China were more potent in generating DNA strand breaks in HepG2 cells when collected during the winter (Jiang et al., 2011). The same was shown for EOM of $PM_{2.5}$ collected in Hong Kong Special Administrative Region, China; the samples from the winter were more potent than those from the summer (Hsiao et al., 2000). EOM of PM_{10} particles collected in Teplice, Czech Republic, increased the levels of DNA strand breaks in HepG2 and Caco-2 cells, and the samples collected during the summer had a stronger effect than those collected during the winter (Lazarová & Slamenová, 2004). In addition, EOM of $PM_{2.5}$ collected on days with haze had higher potential to generate DNA strand breaks compared with extracts of samples collected on days without haze (Xu et al., 2008a). The association between EOM of PM from China, France, and the Republic of Korea has also been shown in other studies, albeit without assessment of temporal, spatial, or particle size differences (Chen et al., 2013; Oh et al., 2011; Shang et al., 2013; Tarantini et al., 2009).

(iv) Acellular test systems

Studies in acellular test systems are summarized in Supplemental Table S13 (available online). The studies on the ability of PM to generate strand breaks in DNA have typically used relaxation of plasmid or bacteriophage DNA, in which the supercoil structure is relaxed by introduction of DNA strand breaks. The literature on studies of air pollution particles generally shows that PM from air pollution is associated with relaxation of supercoiled DNA. Early studies showed that PM_{10} from Edinburgh, United Kingdom, increased the relaxation of supercoiled DNA and that this was reduced by treatment with an antioxidant (mannitol) or a metal chelating agent (DFO) (Donaldson et al., 1997; Gilmour et al., 1996). The strand-breaking potential of $PM_{2.5}$ samples from Baton Rouge, Louisiana, USA, was reduced in the presence of superoxide dismutase or catalase (Dellinger et al., 2001). The role of iron mobilization was demonstrated by studies showing that SRM 1648 and SRM 1649 were associated with strand breakage in DNA only in the presence of ascorbate, which functions as reductant (Smith & Aust, 1997). One study on coal fly ash also found increased generation of DNA strand breaks (Dwivedi et al., 2012). Particles collected in London, United Kingdom, in 1958 from an unknown site generated strand breaks in a concentration-dependent manner (Whittaker et al., 2004). Studies on different particle size fractions have produced mixed results, showing both higher potency in supercoil relaxation of small particles (Healey et al., 2005; Koshy et al., 2009; Lingard et al., 2005; Reche et al., 2012; Shao et al., 2006) and higher potency of coarse particles than fine particles (Greenwell et al., 2002). In addition, it has been shown that the potency of PM samples collected from a location near a busy motorway and steelworks depended on the wind direction, with the highest potency of strand scission activity observed for PM samples when the wind came from the motorway (Moreno et al., 2004). Another study showed that $PM_{2.5}$ from an urban site in Shanghai, China, was more potent in plasmid DNA supercoil relaxation compared with samples from a suburban site and that samples collected during the winter were more potent those collected during the summer (Senlin et al., 2008). Collectively, the studies indicate that aqueous suspensions of PM and water-soluble constituents have the ability to generate DNA strand breaks in naked DNA, which is driven mainly by production of ROS by transition metals.

Airborne particles from many cities in China have been reported to induce plasmid DNA relaxation in acellular conditions. Samples collected during sandstorms were less potent than non-sandstorm samples (Shi et al., 2004). Water extracts or particle suspensions of PM_{10} samples collected in four seasons in Lanzhou showed the ability to generate strand breaks in

plasmid DNA. Average values of TD20 (the level causing 20% of DNA damage) were 17, 625, 56, and 260 μg/mL in the winter, spring, summer, and autumn, respectively, for PM_{10} suspensions. Water extracts caused slightly lower induction of DNA strand breaks, with higher TD20. Suburban PM_{10} samples showed higher TD20 values than samples from Lanzhou. Similar to the study in Beijing, particles were collected during dust storm episodes or after days with rain. The results showed lower ability to generate DNA strand breaks (TD20 > 1000 μg/mL) compared with the PM that was collected in Lanzhou, although the TD20 values correlated negatively with metal concentration (Xiao et al., 2009). In Macao Special Administrative Region, China, PM_{10} samples from three sites (Sun Yat Sen Municipal Park, Avenida de Horta e Costa, and Macao University on Taipa Island) showed that whole PM_{10} suspension samples caused formation of DNA strand breaks with values of TD30 (the level causing 30% of DNA damage) of 3, 10, and 20 μg/mL, respectively, for the three sites. Water extracts showed slightly higher TD30 values (Shen et al., 2009).

In summary, the majority of human studies have shown positive associations between exposure to particulate air pollution and elevated levels of DNA strand breaks in leukocytes as well as nasal epithelial cells. In animal studies, elevated levels of DNA strand breaks in the lung have been noted in studies on doses of PM by instillation, whereas lower doses have not increased levels of DNA strand breaks. Studies in cultured cells and acellular conditions have provided supporting mechanistic evidence for the ability of outdoor air PM to generate DNA strand breaks.

(d) Chromatin damage in sperm

Four studies performed in the Czech Republic (Selevan et al., 2000; Rubes et al., 2005, 2007, 2010) evaluated the association between exposure of men to polluted outdoor air and chromatin damage in their sperm using the sperm chromatin structure assay (SCSA). Table 4.12 shows that all of these studies found an association between chromatin damage in sperm and exposure to elevated concentrations of various pollutants of outdoor air, including CO_2, PM_{10}, SO_2, NO_x, B[*a*]P, carcinogenic PAHs, benzene, and TSP.

(e) Oxidatively damaged nucleobases

(i) Humans

The associations between air pollution and biomarkers of oxidatively damaged nucleobases in human leukocytes have been assessed in a variety of biomonitoring studies, including controlled exposure, panel, and cross-sectional studies. A previous assessment of studies measuring oxidized nucleobases highlighted that approximately half of the published studies had either suboptimal study design or measurement of 8-oxodG by unspecific methods (Møller & Loft, 2010). The discussion of the biomonitoring studies adheres to this critical assessment of the studies. The studies on associations between exposure to air pollution particles and levels of oxidatively damaged DNA in cells from humans are listed in Table 4.13.

The first of two studies in Benin recruited taxi-moto drivers in the city of Cotonou, which has high levels of outdoor air pollution, as determined by assessments including total PAHs (35–103 ng/m^3) and urinary excretion of benzene metabolites (*S*-PMA, 6.8–9.3 μmol/mol creatinine), and a control group in a village with low air pollution (PAHs, 7.3 ng/m^3; *S*-PMA, 4.2 μmol/mol creatinine). This revealed that the taxi-moto drivers had higher levels of 8-oxodG in lymphocytes (21 lesions/10^6 dG) compared with controls in the village (11 lesions/10^6 dG) (Ayi-Fanou *et al.*, 2006). [The high background levels of 8-oxodG suggest spurious oxidation of the DNA during the HPLC-electrochemical detection (ECD) measurement, and the study design with comparison of subjects in the city and

Table 4.12 DNA fragmentation and abnormal chromatin in sperm in men exposed to outdoor air pollution

Subjects (number)	End-point	Associated air pollutant	Finding	Reference
Men (18 yr) in Teplice District, Czech Republic (272)	Abnormal chromatin (SCSA)	PM_{10}, TSP, CO_2	+	Selevan et al. (2000)
Young men in Teplice District, Czech Republic (36)	SCSA	PM_{10}, SO_2, NO_x	+	Rubes et al. (2005)
Young men in Teplice District, Czech Republic (35)	SCSA among *GSTM1* null	PM_{10}, SO_2, NO_x	+	Rubes et al. (2007)
Outdoor police in Prague, Czech Republic, sampled in winter (high pollution) and spring (low pollution) (47)	DNA damage (DFI by SCSA)	B[*a*]P, carcinogenic PAHs, benzene	+	Rubes et al. (2010)

+, positive; B[*a*]P, benzo[*a*]pyrene; CO_2, carbon dioxide; DFI, DNA fragmentation index; NO_x, nitrogen oxides; PAHs, polycyclic aromatic hydrocarbons; PM_{10}, particulate matter with particles of aerodynamic diameter < 10 μm; SCSA, sperm chromatin structure assay; SO_2, sulfur dioxide; TSP, total suspended particles; yr, year or years.

village is not optimal.] A subsequent study also used taxi-moto drivers in Cotonou and village controls, as well as groups of subjects with intermediate exposure to air pollution as determined by urinary excretion of benzene metabolites and the number concentration of UFP (midday 1-hour average, 6961–265 145 UFP/cm³). There were clear gradients in both air pollution levels (assessed as *S*-PMA) and levels of formamidopyrimidine DNA glycosylase (FPG)-sensitive sites in PBMCs between the subjects living in areas with different air pollution levels (Avogbe et al., 2005).

A panel study of students who were living in the centre of Copenhagen, Denmark, showed a positive association between personal exposure to $PM_{2.5}$ (10–24.5 μg/m³) and levels of 8-oxodG in lymphocytes, whereas the exposure did not correlate with levels of FPG-sensitive sites in lymphocytes (Sørensen et al., 2003a). In addition, there was a correlation between the levels of 8-oxodG in lymphocytes and the concentration of water-soluble transition metals in $PM_{2.5}$ that was collected over a 2-day period for each subject (Sørensen et al., 2005). The same study also showed that there was no correlation between background mass concentration of $PM_{2.5}$ measured at a stationary monitoring station or personal exposure to NO_2 and levels of 8-oxodG in lymphocytes. Another study of residents of Copenhagen used benzene as a marker of urban air pollution exposure and showed an association between urinary excretion of *S*-PMA and levels of 8-oxodG in lymphocytes, whereas the levels of endonuclease III (ENDOIII)/FPG sites were unaltered in lymphocytes (Sørensen et al., 2003c). The effect of personal exposure to UFP in air pollution was investigated in people bicycling for approximately 90 minutes in the laboratory or on traffic-heavy streets in Copenhagen. This study showed a positive association between personal exposure to UFP and levels of FPG-sensitive sites in PBMCs (Vinzents et al., 2005). The same group of researchers also studied controlled exposure to air from a busy street in Copenhagen and reported correlations between particles in the size mode with a median diameter of 23 nm (representing SVOCs of diesel exhaust) and the size mode with a median diameter of 57 nm (representing carbonaceous soot) and levels of FPG-sensitive sites in PBMCs (Bräuner et al., 2007).

A study in Florence, Italy, showed no correlation between outdoor ozone concentrations

Table 4.13 Exposure to air pollution and oxidatively damaged DNA in human leukocytes

Study population	Exposure assessment	Sex, age, smoking, number	Biomarker	Effect (notes)	Reference
Taxi-moto drivers (n = 35) and rural controls (n = 6) in Cotonou, Benin	Outdoor (stationary) concentrations of PAHs and benzene. Urinary excretion of *S*-PMA and 1-OHP	M 36 ± 5 yr NS n = 41	8-oxodG (HPLC-ECD)	Highest level in leukocytes of exposed subjects (high background level of 8-oxodG: 11 lesions/10^6 dG)	Ayi-Fanou et al. (2006)
Taxi-moto drivers, people living or working near busy roads, and rural controls in Benin	Outdoor (stationary) sampling of UFP (midday 1 h concentration at a busy street intersection and a town square in a rural village, 265 145 and 6 961 UFP/cm^3, respectively) and urinary excretion of *S*-PMA	M 34 ± 10 yr NS n = 135	FPG sites (comet)	Positive association between *S*-PMA excretion and FPG sites in PBMCs	Avogbe et al. (2005)
Panel study of students living in Copenhagen, Denmark	Personal $PM_{2.5}$: 16.1 (10–24.5) μg/m^3 $PM_{2.5}$: 9.2 (5.3–14.8) μg/m^3 (stationary monitoring stations)	M, F 20–33 yr NS n = 50	8-oxodG (HPLC-ECD) FPG sites (comet)	Correlation between personal exposure to $PM_{2.5}$ and 8-oxodG in lymphocytes, whereas no correlation between $PM_{2.5}$ and FPG sites. No correlation between biomarkers and stationary (urban background) measurements of $PM_{2.5}$	Sørensen et al. (2003a, 2005)
Subjects living in Copenhagen, Denmark	Benzene (personal exposure and urinary excretion of *S*-PMA)	M, F 27–46 yr S/NS n = 40	ENDOIII/FPG sites (comet) 8-oxodG (HPLC-ECD)	Positive association between urinary excretion of *S*-PMA and 8-oxodG in lymphocytes, whereas no association with ENDOIII/FPG sites	Sørensen et al. (2003c)
Subjects exposed to outdoor air while bicycling in Copenhagen, Denmark	Personal UFP: 32 400 and 13 400 UFP/cm^3 PM_{10}: 23.5 μg/m^3 (street) and 16.9 μg/m^3 (background) NO_2: 32.1 and 24.2 μg/m^3 (street) and 11.3 μg/m^3 (background)	M, F 25 ± 3 yr NS n = 15	FPG sites (comet)	Increased levels of FPG sites in PBMCs after bicycling in the traffic compared with bicycling in the laboratory	Vinzents et al. (2005)
Controlled exposure to outdoor air in a chamber for 24 h in Copenhagen, Denmark	Personal UFP: 6169–15 362 UFP/cm^3 (unfiltered air) and 91–542 UFP/cm^3 (filtered air) NO_x: 25.8 ppb (unfiltered air), 28.3 ppb (filtered air), 11.6 ppb (background), and 59.5 ppb (busy street) O_3: 12.1 ppb (unfiltered air), 4.3 ppb (filtered air), 30.1 ppb (background), and 19.5 ppb (busy street)	M, F 20–40 yr NS n = 29	FPG sites (comet)	Decreased levels of FPG sites in PBMCs after exposure to filtered air compared with unfiltered air	Bräuner et al. (2007)

Table 4.13 (continued)

Study population	Exposure assessment	Sex, age, smoking, number	Biomarker	Effect (notes)	Reference
Healthy subjects in Florence, Italy	O_3: 15–75 μg/m³ (stationary monitoring station)	M, F 24–80 yr S/NS *n* = 79	FPG sites (comet)	No association between O_3 exposure (days 3–30 before sampling) and levels of FPG sites in leukocytes	Giovannelli et al. (2006)
Subjects exposed to traffic (*n* = 44) and controls (*n* = 27) in Florence, Italy	O_3 (levels NR)	M, F 35–64 yr S/NS *n* = 71	FPG sites (comet)	Statistically non-significant higher level of FPG sites in leukocytes of exposed subjects. Correlation between O_3 exposure (days 60–90 before sampling) and levels of FPG sites in lymphocytes	Palli et al. (2009)
Police officers working in traffic (*n* = 24) or indoors (*n* = 24) in Bangkok, Thailand	Personal benzene (8–50 μg/m³), *t,t*-MA, *S*-PMA, and 1,3-butadiene (0.3–4.1 μg/m³) exposure	M 24–58 yr NS *n* = 48	8-oxodG (HPLC-ECD)	Increased levels of 8-oxodG in leukocytes of police officers working in traffic compared with those working indoors. Correlation between personal 1,3-butadiene exposure and levels of 8-oxodG in leukocytes	Arayasiri et al. (2010)
Subjects living near Map Ta Phut Industrial Estate, in a location with steel, oil refinery, and petrochemical factories (*n* = 58), factory workers (*n* = 67), and controls (*n* = 48) in Thailand	None	M, F 32 ± 7 yr S/NS *n* = 173	M_1dG adducts (^{32}P-postlabelling)	Increased M_1dG adducts in leukocytes of factory workers and residents of the polluted area compared with controls	Peluso et al. (2010, 2012)
Children living in a rural area (Chonburi) (*n* = 109) and an urban area (Bangkok) (*n* = 62) in Thailand	Benzene (outdoor monitoring and personal exposure)	M 9–13 yr NS *n* = 171	8-oxodG (HPLC-ECD)	Increased 8-oxodG in leukocytes. Positive correlation between individual benzene exposure and 8-oxodG in leukocytes	Buthbumrung et al. (2008)
Subjects living in a traffic-congested area in Bangkok, Thailand	$PM_{2.5}$: 183 ± 37 μg/m³	M, F 18–58 yr NS *n* = 50	8-oxodG (HPLC-MS/MS)	Association between $PM_{2.5}$ exposure and 8-oxodG in leukocytes	Vattanasit et al. (2014)

Table 4.13 (continued)

Study population	Exposure assessment	Sex, age, smoking, number	Biomarker	Effect (notes)	Reference
Police officers and controls in Prague, Czech Republic	$PM_{2.5}$ (stationary monitoring data: 33 ± 40 µg/m³ in January and 15 ± 9 µg/m³ in September) PAHs (personal exposure: 8.9 ± 1.4 µg/m³ in January and 3.1 ± 0.5 ng/m³ in September)	M 31 yr and 35 yr (median) NS *n* = 65	ENDOIII/FPG sites (comet)	Highest levels in lymphocytes of exposed subjects. Positive correlation between PAH exposure and oxidative DNA damage in samples collected in January	Novotna et al. (2007)
Bus drivers (*n* = 50), garage workers (*n* = 20), and controls (*n* = 50) in Prague, Czech Republic	Personal PAH concentration	M 24–66 yr NS *n* = 120	ENDOIII/FPG (comet)	No differences in the levels of ENDOIII/FPG sites in lymphocytes between exposed groups and control group	Bagryantseva et al. (2010)
Mothers living in Teplice (*n* = 594) or Prachatice (*n* = 297), Czech Republic	Air pollution levels not specified, but levels of PM typically higher in Teplice than in Prachatice	F 25 ± 5 yr S/NS *n* = 891	8-oxodG (ELISA)	No difference in placental levels of 8-oxodG between polluted city and control city. No association between air pollution markers and 8-oxodG in multivariable-adjusted models	Rossner et al. (2011a)
Police officers, bus drivers, and controls in Prague (Czech Republic), Košice (Slovakia), and Sofia (Bulgaria)	PAH concentration in personal $PM_{2.5}$ samples	M 34.1 ± 9 yr S/NS *n* = 356	8-oxodG (LC-MS/MS) M_1dG adducts (immunoslot blot)	Higher levels of 8-oxodG in lymphocytes of police officers in Košice compared with controls, whereas no effect seen in police officers in Prague. Significantly higher levels of M_1dG adducts in exposed subjects in Sofia	Singh et al. (2007b)
Children living in a low-pollution area (*n* = 12) and in Mexico City (*n* = 86), Mexico	PM_{10}: < 14 to 53–61 µg/m³ O_3: < 10 to 261 ppb (max)	M, F 6–13 yr NR *n* = 98	8-oxodG (immunohistochemistry)	Higher levels of 8-oxodG in nasal biopsies from children in Mexico City compared with children in the low-pollution area	Calderón-Garcidueñas et al. (1999)

dG, deoxyguanosine; ELISA, enzyme-linked immunosorbent assay; ENDOIII, endonuclease III; F, female; FPG, formamidopyrimidine DNA glycosylase; h, hour or hours; HPLC-ECD, high-performance liquid chromatography-electrochemical detection; LC-MS/MS, liquid chromatography-tandem mass spectrometry; M, male; M_1dG, malondialdehyde–deoxyguanosine; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; NR, not reported; NS, non-smokers; 1-OHP, 1-hydroxypyrene; 8-oxodG, 8-oxo-7,8-dihydro-2′-deoxyguanosine; O_3, ozone; PAHs, polycyclic aromatic hydrocarbons; PBMCs, peripheral blood mononuclear cells; PM, particulate matter; PM_{10}, particulate matter with particles of aerodynamic diameter < 10 µm; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 µm; S, smokers; *S*-PMA, *S*-phenyl mercapturic acid; *t,t*-MA, *trans,trans*-muconic acid; UFP, ultrafine particles; yr, year or years.

(days 3–30 before sampling) and levels of FPG-sensitive sites in lymphocytes from healthy subjects (Giovannelli et al., 2006). In a subsequent study, a positive correlation was shown between ozone levels (days 60–90 before sampling) and levels of FPG-sensitive sites in lymphocytes of traffic-exposed workers (Palli et al., 2009).

A study in Bangkok, Thailand, with a relatively large benzene exposure gradient (8–50 μg/m^3) between traffic police and office-based police showed no association with levels of 8-oxodG, whereas there was a correlation between personal 1,3-butadiene exposure and levels of 8-oxodG in leukocytes (Arayasiri et al., 2010). Another study in Thailand on malondialdehyde–deoxyguanosine (M_1dG) adducts, a biomarker of oxidative stress and lipid peroxidation, showed that residents living in a location near steel, oil refinery, and petrochemical factories had higher levels of DNA adducts in leukocytes (3.7 ± 0.4 lesions/10^8 nucleotides) than subjects in a location with a low air pollution level (2.9 ± 0.4 lesions/10^8 nucleotides) (Peluso et al., 2010; Peluso et al., 2012). One study on schoolchildren in Bangkok, compared with children in a provincial area (Chonburi), showed that the children exposed to air pollution had higher levels of 8-oxodG in leukocytes (Buthbumrung et al., 2008). In another study on healthy subjects living in traffic-congested areas in Bangkok, levels of 8-oxodG in leukocytes were significantly correlated with concentrations of individual exposure to $PM_{2.5}$ (Vattanasit et al., 2014).

Several studies in the Czech Republic have assessed biomarkers of oxidatively damaged DNA in people with different occupations or living in areas characterized by high or low air pollution levels. A study of police officers showed higher levels of ENDOIII/FPG sites in lymphocytes in the season with a high level of air pollution exposure ($PM_{2.5}$, 33 μg/m^3), whereas there was no effect in the season with a low level of air pollution exposure ($PM_{2.5}$, 15 μg/m^3) (Novotna et al., 2007). Studies of bus drivers, garage workers, and office workers (controls) indicated no associations between air pollution measures and levels of ENDOIII/FPG sites in lymphocytes from exposed subjects and controls (Bagryantseva et al., 2010). There was no difference in placental levels of 8-oxodG between mothers living in Teplice (urban area) and those living in Prachatice (rural area), and there was a lack of association between air pollution exposure levels and levels of 8-oxodG in multivariable-adjusted models (Rossner et al., 2011a). This research group also participated in the EXPAH project on associations between air pollution exposures in Prague (Czech Republic), Košice (Slovakia), and Sofia (Bulgaria) and biomarkers of genotoxicity in samples from male police officers, bus drivers, and office workers (Taioli et al., 2007). This study showed that police officers in Košice had higher levels of 8-oxodG in lymphocytes compared with controls, whereas there was no effect in police officers in Prague (Singh et al., 2007b). [The Working Group noted that there were very high levels of 8-oxodG in the reference group (i.e. 54 lesions/10^6 nucleotides, corresponding to 244 lesions/10^6 dG), indicating spurious oxidation during the measurement of 8-oxodG.] This study also showed that PAH-exposed subjects from Sofia had higher levels of lipid peroxidation-derived M_1dG adducts in lymphocytes, measured by immunoslot blot, compared with controls from the same city (Singh et al., 2007b).

One study showed that nasal biopsies from children living in areas with a low level of air pollution (a Pacific coastal town) had lower levels of immunostaining intensity for 8-oxodG compared with biopsies from children living in Mexico City, with a high level of air pollution (Calderón-Garcidueñas et al., 1999).

In summary, a substantial number of studies from humans (11 out of 13 studies) have reported positive associations between exposure to air pollution and levels of oxidatively damaged DNA in leukocytes.

(ii) Experimental systems

Few studies have assessed the level of oxidatively damaged DNA in lungs of animals after exposure to air pollution (see Supplemental Table S14, available online). Studies in rodents have reported no effect of intratracheal instillation of PM on levels of oxidatively damaged DNA in lung tissue. Studies in cultured cells (see Supplemental Table S15, available online) and in acellular test systems (see Supplemental Table S16, available online) have examined the induction of oxidatively damaged nucleobases by PM. Aqueous suspensions of PM from urban areas, mainly in Europe, have generated increased levels of oxidatively damaged DNA in cultured cells. There is also some evidence showing that organic extracts of PM are associated with generation of oxidatively damaged DNA in cultured cells. Aqueous suspensions of PM from urban areas, mainly in Europe, have generated increased levels of 8-oxodG in acellular conditions.

(f) Other damage

Several studies used a variety of other assays to assess the genotoxic activity of outdoor air or samples derived from outdoor air. Most used bacterial reporter assays that assess induction of error-prone DNA repair (the SOS response). The results of these studies are summarized in Supplemental Table S17 (available online). In summary, extracts, including inorganic, organic, and simulated lung fluid extracts of airborne PM from a variety of urban and industrial sites, induced significant dose-related increases in DNA damage in both bacteria and mammalian cells.

4.2.4 Gene expression

(a) Humans

See Table 4.14.

As noted in several reviews (e.g. Holloway et al., 2012), exposure of humans to air pollution can result in altered expression of a variety of genes, especially those in pathways associated with DNA damage and repair, oxidative stress, immune response, and so on.

Studies in the Czech Republic (van Leeuwen et al., 2006, 2008) evaluated gene expression in children and adults living in a rural area (Prachatice) versus those living in an urban area (Teplice). Genes that showed differential expression between the two groups of children (and two levels of outdoor air pollution) were largely in the nucleosome assembly. In the same study population, more differential gene expression between the two groups of children was observed compared with the differential gene expression between two groups of adults from the same populations. There was little overlap between the genes expressed differentially between the children and the adults; in children, the pathways most affected by the outdoor air pollution were the nucleosome and immune pathways.

A separate study in the Czech Republic found higher expression of the DNA repair gene *XRCC5* in the blood of residents of Ostrava (more polluted) than in the blood of residents of Prague (less polluted). The higher gene expression was associated with higher concentrations of carcinogenic PAHs in outdoor air (Rossner et al., 2011b).

Huang et al. (2010) exposed three subjects in a chamber in a cross-over design to filtered air or ultrafine particles (50 μg/m^3 for 2 hours) from Chapel Hill, North Carolina, USA, and identified differential expression for 10 genes in a variety of pathways, including inflammation and oxidative stress response, that could discriminate between types of PM exposure.

Hebels et al. (2011) studied nitrosamine exposure and gene expression in human lymphocytes from women participating in a mother–newborn study in Denmark. Participants were non-smoking pregnant women, with no

Table 4.14 Changes in gene expression in humans exposed to outdoor air pollution

Country	Subjects	Assay	Results		Reference
Czech Republic	Blood from 23 children from an urban area (Teplice) versus 24 children from a rural area (Prachatice)	Agilent Human 22K oligo microarray	Increased expression of genes in nucleosome response pathways	+	van Leeuwen et al. (2006)
Czech Republic	Blood from 12 adults from an urban area (Teplice) versus 12 adults from a rural area (Prachatice)	Agilent Human 22K oligo microarrays	More differential gene expression between the two sets of children than the two sets of adults, and little overlap between the children and adults; nucleosome and immune pathways most affected	+	van Leeuwen et al. (2008)
USA	Blood from 3 subjects exposed to ultrafines at 50 µg/m³ for 2 h	Affymetrix HU133 plus 2 microarray	Altered expression of genes in oxidative stress response and inflammation pathways	+	Huang et al. (2011)
Czech Republic	Blood from 64 subjects from Prague (less polluted) and 75 subjects from Ostrava (more polluted)	qPCR	Increased expression of *XRCC5* DNA repair gene among subjects from Ostrava; associated with increased concentration of c-PAHs	+	Rossner et al. (2011b)
Denmark	Blood and urine from 29 women participating in a mother–newborn biomarker study	Agilent 4x44K whole human genome microarrays NOC excretion by GC-MS	Differences in levels of NOC excretion are mainly associated with modifications in amino acid metabolism, apoptosis and survival, cell adhesion, and a few other signalling and metabolism pathways		Hebels et al. (2011)

+, positive; c-PAHs, carcinogenic polycyclic aromatic hydrocarbons; GC-MS, gas chromatography-mass spectrometry; h, hour or hours; NOC, *N*-nitroso compound; PCR, polymerase chain reaction.

residential environmental tobacco smoke and who spent the majority of their time at home. Modifications in cytoskeleton remodelling, cell cycle, apoptosis and survival, signal transduction, immune response, G-protein signalling, and development pathways were observed.

(b) Experimental systems

(i) In vivo

Several studies evaluated gene expression in lung, brain, or adipose tissue after inhalation exposure of rodents to outdoor air or to concentrated air particles (CAPs) (André et al., 2006; Heidenfelder et al., 2009; Bos et al., 2012; Soberanes et al., 2012; Tablin et al., 2012; Ljubimova et al., 2013; Mendez et al., 2013; Rowan-Carroll et al., 2013) (see Supplemental Table S18, available online). Other studies involved evaluation of gene expression in lung tissue of rats after intratracheal instillation of PM from urban air (Kooter et al., 2005; Wise et al., 2006).

(ii) In vitro

In vitro studies are summarized in Supplemental Table S19 (available online).

4.2.5 Epigenetic effects

(a) Humans

(i) DNA methylation

Collectively, the available studies generally show an association between DNA methylation and outdoor air pollution (see Table 4.15). Although air pollution enhances methylation of some genes, it reduces methylation of others. It is likely that this reflects different pathways and involves different components of air pollution (metals, PAHs, VOCs, PM, etc.). Nonetheless, the relatively consistent association between methylation of DNA and exposure to air pollution, resulting in altered gene expression, indicates that this is another mechanism by which air pollution may influence risk of cancer.

(ii) Leukocyte telomere length

Three studies have evaluated leukocyte telomere length relative to exposure to outdoor air pollution (see Table 4.16).

Truck drivers in Beijing, China, had longer telomeres than office workers (Hou et al., 2012). For both the truck drivers and the office workers, an increase in telomere length was associated with personal $PM_{2.5}$ concentration, personal elemental carbon concentration, and outdoor PM_{10} concentration on the day that blood was drawn from the subjects. However, shorter telomere length was associated with the PM_{10} concentration averaged over the 2 weeks before the blood draw. These results indicate that longer telomere length is associated with short-term exposure to outdoor air PM, consistent with an effect of PM on telomeres during acute inflammatory responses. In contrast, long exposures to PM may shorten telomeres due to extended exposures to pro-oxidants.

A population living in Massachusetts, USA, was evaluated for telomere length, which was compared with modelled exposure to carbon black as a marker for traffic-related particles (McCracken et al., 2010). This study found that telomere length shortened as carbon black exposure increased. This result is consistent with the study in China, showing that prolonged exposure to airborne particles is associated with shortened telomeres.

A third study of telomere length found shorter telomeres among traffic officers in Milan, Italy, compared with office workers (Hoxha et al., 2009). Among the traffic officers, the adjusted mean telomere length was shorter in subjects working in high traffic density compared with low traffic intensity. An additional exposure assessment found that telomere length decreased with increasing concentrations of personal exposure to benzene and toluene. Collectively, these studies show that leukocyte telomere length is shortened in subjects chronically exposed to air pollution.

(b) Experimental systems

In the study by Yauk et al. (2008), male C57BL/CBA mice were exposed for 6 weeks in situ to outdoor air near two integrated steel mills and a major highway in Hamilton, Canada; control mice breathed the same air but filtered through HEPA filters. Sperm DNA was hypermethylated in the mice breathing the unaltered outdoor air compared with those breathing the HEPA-filtered air, and this persisted after removal of the mice from the polluted air.

Soberanes et al. (2012) exposed male C57BL/6 mice to $PM_{2.5}$ CAPs from an unspecified urban area for 8 hours per day for 9 weeks. This exposure produced hypermethylation of the promoter region of the *p16* gene in the lung.

Table 4.15 Changes in DNA methylation in humans exposed to outdoor air pollution

Country	Subjects	End-points	Associated air pollutant	Reference
USA	718 residents of Greater Boston, Massachusetts	1097 blood samples assayed for LINE-1 methylation	Decreased LINE-1 methylation with increased black carbon ($P = 0.002$) Decreased LINE-1 methylation with increased $PM_{2.5}$ ($P < 0.001$)	Baccarelli et al. (2009)
USA	706 elderly residents of Greater Boston, Massachusetts	1406 blood samples assayed for LINE-1 and *Alu* methylation	Decreased LINE-1 methylation associated with increased SO_4, and decreased *Alu* methylation associated with increased black carbon	Madrigano et al. (2011)
Italy	63 male steel workers in Brescia	Methylation of *APC*, *P16*, *TP53*, and *RASSF1A* tumour suppressor genes	Increased methylation of *APC* ($P = 0.005$) and *P16* ($P = 0.006$) associated with increased metal-rich air particulate. Decreased methylation of *TP53* ($P = 0.015$), decreased methylation of *RASSF1A* ($P < 0.001$), and increased methylation of *APC* associated with increased PM_{10}	Hou et al. (2011)
USA	940 children in southern California	Methylation of *NOS2* promoter	Decreased methylation of *NOS2* promoter associated with increased $PM_{2.5}$ ($P = 0.01$)	Salam et al. (2012)
USA	699 elderly residents of Greater Boston, Massachusetts	1377 blood samples assayed for methylation of *NOS2* and *GCR* genes	Decreased methylation of *NOS2* promoter associated with increased black carbon and $PM_{2.5}$. No association between methylation of the *GCR* gene and pollutants	Madrigano et al. (2012)
Czech Republic	Children (average age, 11.6 yr); 100 in the more-polluted Ostrava region and 100 in the less-polluted Prachatice region	Methylation at 27 578 loci	Decreased methylation at 53 CpG sites in children from Ostrava, which had increased B[*a*]P, benzene, NO_2, metals, and $PM_{2.5}$ in outdoor air compared with Prachatice	Rossnerova et al. (2013)
USA	Cord blood from 164 non-smoking African-American and Dominican-American mothers in the New York City area	Global DNA methylation	Decreased global methylation in cord blood associated with increased maternal exposure to outdoor air PAH concentration	Herbstman et al. (2012)
Italy	20 male steel workers in Brescia with high exposure and 20 with low exposure to metal-rich air	Methylation of *MT-TF*, *MT-RNR1*, and D-loop of mtDNA	Increased methylation of *MT-TF* and *MT-RNR1* associated with increased metal-rich PM ($P = 0.025$) No association between D-loop methylation and pollutants	Byun et al. (2013)
Italy	20 male filling station attendants in Milan with high exposure and 20 with low exposure to benzene	Methylation of *MT-TF*, *MT-RNR1*, and D-loop of mtDNA	No association between methylation of any genes and pollutants	
China	20 truck drivers in Beijing with high exposure and 20 with low exposure to elemental carbon	Methylation of *MT-TF*, *MT-RNR1*, and D-loop of mtDNA	No association between methylation of any genes and pollutants	

Table 4.15 (continued)

Country	Subjects	End-points	Associated air pollutant	Reference
USA	704 elderly male residents of Greater Boston, Massachusetts	Methylation of *Alu*, LINE-1, *F3*, *TLR-2*, and *ICAM-1*	Decreased methylation of LINE-1 associated with increased black carbon and sulfates. Increased methylation of *Alu* and *TLR-2* associated with NO_2 and particle number	Bind et al. (2012)
Thailand	67 steel and petrochemical workers in Ma Ta Phut Industrial Estate, 65 residents of Ma Ta Phut Industrial Estate, and 45 rural residents	Methylation of LINE-1, *TP53*, *HIC1*, *P16*, and *IL-6*	Exposed population had decreased methylation of LINE-1 ($P < 0.001$), *TP53* ($P < 0.001$), and *IL-6* ($P = 0.027$) but increased methylation of *HIC1* ($P < 0.001$). Decreased methylation associated with increased DNA adducts	Peluso et al. (2012)
Belgium	Placental DNA from 240 newborns	Global methylation	Decreased global placental methylation associated with increased $PM_{2.5}$	Janssen et al. (2013)

B[*a*]P, benzo[*a*]pyrene; LINE-1, long interspersed nuclear element-1; NO_2, nitrogen dioxide; PAHs, polycyclic aromatic hydrocarbons; PM, particulate matter; PM_{10}, particulate matter with particles of aerodynamic diameter < 10 μm; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 μm; SO_4, sulfate; yr, year or years.

Table 4.16 Effects on leukocyte telomere length in humans exposed to outdoor air pollution

Country	Subjects	Results	Reference
China	120 office workers (controls) and 120 truck drivers (exposed) in Beijing	For both controls and exposed subjects, telomere length associated with personal $PM_{2.5}$ and elemental carbon, and outdoor PM_{10} on day of blood draw. However, decreased telomere length associated with PM_{10} averaged over 2 weeks before blood draw	Hou et al. (2012)
USA	165 subjects in Massachusetts	Decreased telomere length associated with carbon black in outdoor air	McCracken et al. (2010)
Italy	57 office workers (controls) and 77 traffic officers (exposed) in Milan	Decreased telomere length among traffic officers working in high vs low traffic intensity. Decreased telomere length associated with increasing concentrations of personal exposure to benzene and toluene	Hoxha et al. (2009)

PM_{10}, particulate matter with particles of aerodynamic diameter < 10 μm; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 μm.

4.3 Other data relevant to carcinogenicity

4.3.1 Oxidative stress and inflammation

(a) Pulmonary oxidative stress and inflammation in humans

See Table 4.17.

Studies on oxidative stress in humans who have been exposed to air pollution have mainly applied biomarkers of oxidatively damaged lipids or inflammation markers in exhaled breath or bronchoalveolar lavage fluid (BALF). The publications are grouped into controlled exposure, panel, and cross-sectional studies.

Among the controlled exposure studies are some that have obtained direct measurements of pulmonary inflammation by analysis of BALF cell counts. The Working Group has included studies on bronchial instillation of PM in humans for the purpose of bridging observations in animal models on the same exposure, although it recognizes that extrapolation to real-life human exposures is challenging. Ghio & Devlin (2001) reported results from a study in which young and healthy people were exposed by bronchial instillation to aqueous extracts of PM_{10} collected before, during, and after a steel mill strike in Utah Valley, Utah, USA (Ghio & Devlin, 2001). The particles that were collected before and after the strike were associated with higher levels of neutrophils, pro-inflammatory cytokines (interleukin-1 beta [IL-1β], tumour necrosis factor [TNF], and IL-8), and protein (a marker of epithelial damage) in the BALF at 24 hours after the instillation of 500 μg of particle extract into the lungs of non-smoking volunteers. Extracts from periods when the steel mill was operating had high concentrations of metals, and the extracts generated ROS in acellular conditions, which was diminished by addition of DFO (a metal chelator) or dimethylthiourea (an antioxidant) (Ghio & Devlin, 2001). Schaumann et al. (2004) instilled into the lungs of 12 healthy volunteers $PM_{2.5}$ (100 μg, corresponding to 24 hours of inhalation of 100 μg/m^3) from two locations in Germany, characterized as being an area with mining and smelter industry and a non-polluted area. The instillation increased the total number of cells in BALF, whereas there was no difference in differential cell counts of neutrophils, lymphocytes, and monocytes. Nevertheless, it was only instillation of particles from a polluted area that was associated with increased concentrations of some pro-inflammatory cytokines in BALF (IL-6 and TNF, but not IL-1 and IL-8) and increased ex vivo ROS production in zymosan-stimulated BAL cells. There

Table 4.17 Oxidative stress and inflammation biomarkers in exhaled breath condensate from humans exposed to air pollution

Exposure	Exposure assessment	Sex, age, smoking, number	Biomarker	Effect	Reference
Instillation of aqueous extracts of CAPs from Utah Valley, Utah, USA	500 µg and lavage 24 h later	M, F 26 ± 2 yr NS *n* = 24	Cell count, IL-1β, TNF, and IL-8 in BALF	Increased number of neutrophils and BALF content of IL-1β, TNF, and IL-8	Ghio & Devlin (2001)
Intratracheal instillation of PM from an industrialized area and a non-industrialized area in Germany	100 µg	M, F 27 ± 3 yr NS *n* = 12	Cell count, IL-1, IL-6, IL-8, and TNF	Increased number of cells, IL-6, and TNF in BALF. Unaltered levels of IL-1 and IL-8	Schaumann et al. (2004)
Exposure to CAPs from Chapel Hill, North Carolina, USA	23–311 µg/m³ for 2 h with intermittent, moderate exercise	M, F 26 ± 1 yr NS *n* = 38	Cell count, IL-6, IL-8, and PGE_2 in BALF	Increased number of neutrophils in BALF. Unaltered levels of IL-6, IL-8, and PGE_2	Ghio et al. (2000)
Controlled exposure to ultrafine CAPs from Chapel Hill, North Carolina, USA	PNC: 40 848–205 648/cm³ Mass: 1.2–50 µg/m³ for 2 h with intermittent, moderate exercise	M, F 18–35 yr NS *n* = 19	IL-6, IL-8, and PGE_2	Increased levels of IL-8 in BALF. Unaltered levels of IL-6 and PGE_2	Samet et al. (2009)
Controlled exposure to outdoor air while subjects exercising at locations with low and high traffic intensity in Pennsylvania, USA	7382–252 290 particles/cm³ NO_2: < 100 ppb O_3: 41 ppb	M 21 ± 2 yr NS *n* = 12	Exhaled NO (chemiluminescence) and MDA (HPLC)	Unaltered levels of exhaled NO. Increased MDA in EBC after exercise at location with high exposure	Rundell et al. (2008)
Controlled exposure to CAPs from Edinburgh, United Kingdom	UFP: 0 or 99 400 UFP/cm³ Mass: 190 µg/m³ for 2 h in subjects with stable coronary heart disease and controls NO_x: 7.2 and 6.3 ppb SO_2: 0.13 and 0.13 ppb O_3: 5.0 and 6.0 ppb	M 54 ± 2 yr (controls) and 59 ± 2 yr NS *n* = 12, *n* = 12	8-isoprostane and 3-nitrotyrosine (ELISA)	Increased EBC by CAPs exposure at 6 h and 24 h. No effect on 3-nitrotyrosine	Mills et al. (2008)
Controlled exposure of people with asthma to air in a road tunnel (Stockholm, Sweden) or a laboratory	PNC: 1.3 × 10⁵/mL $PM_{2.5}$: 80 µg/m³ PM_{10}: 183 µg/m³ NO_2: 265 µg/m³ for 2 h	M, F 18–55 yr NS *n* = 14	Exhaled NO, cytokines in nasal lavage	Unaltered exhaled NO. Increased IL-10, TNF, and IL-12p70 and unaltered IL-1β, IL-6, and IL-8 in nasal lavage	Larsson et al. (2010)

Table 4.17 (continued)

Exposure	Exposure assessment	Sex, age, smoking, number	Biomarker	Effect	Reference
Controlled exposure of subjects in Utrecht, Netherlands, for 5 h at 2 traffic sites and 1 urban site	PNC: 66 500/cm^3 PM_{10}: 13 or 252 μg/m^3	M, F 19–26 yr NS *n* = 31	FeNO (chemiluminescence)	Association between PNC and FeNO	Strak et al. (2012)
Subjects living in Beijing, China, before, during, and after the Olympics in 2008	$PM_{2.5}$: 98.9–71.9 μg/m^3 NO_2: 25.6–14.6 ppb SO_2: 7.5–3.0 ppb O_3: 31.8–39.6 ppb	M, F 19–33 yr NS *n* = 125	MDA (HPLC), 8-isoprostane (ELISA), FeNO, and nitrate/nitrite	Lower levels of oxidative stress biomarkers and inflammation during the Olympics compared with samples before and after the event	Gong et al. (2013), Huang et al. (2012)
Panel study of children with asthma in Seattle, Washington, USA	$PM_{2.5}$: 13 μg/m^3 personal	M, F 6–13 yr NS *n* = 19	Exhaled NO (chemiluminescence)	Positive association between $PM_{2.5}$ levels and exhaled NO in children who did not take corticosteroid medication	Koenig et al. (2003, 2005), Mar et al. (2005)
Panel study of people with asthma in Ontario, Canada	$PM_{2.5}$: 2.7–14.3 μg/m^3 SO_2: 1.3–13.8 ppb NO_2: 12.3–27.0 ppb O_3: 7.5–21.0 ppm for 4 wk	M, F 9–14 yr NS *n* = 182	TBARS (fluorescence detection), 8-isoprostanes (immunoassay), and FeNO	Positive association between TBARS in EBC and SO_2, NO_2, and $PM_{2.5}$, but not with O_3. Concentration of 8-isoprostanes in EBC was only associated with SO_2 concentration. No association between air pollution and FeNO	Liu et al. (2009a)
Panel study of children with asthma in Mexico City, Mexico	$PM_{2.5}$: 4.2–89.5 μg/m^3 NO_2: 13.9–73.5 ppb O_3: 9.8–60.7 ppb	M, F 10 ± 2 yr NS *n* = 107	MDA (fluorescence detection). IL-4, IL-10, and TNF were below limit of detection	Positive associations between outdoor air pollution ($PM_{2.5}$ and O_3) levels and MDA in EBC	Romieu et al. (2008)
Panel study of elderly subjects with asthma or COPD in Seattle, Washington, USA	$PM_{2.5}$: 10.5 μg/m^3	M, F 60–86 yr NS *n* = 16	FeNO (chemiluminescence)	Association between outdoor $PM_{2.5}$ and FeNO in subjects with asthma. No association with personal PM exposure	Jansen et al. (2005)
Panel study of subjects with coronary artery disease in retirement communities in Los Angeles basin, California, USA, in warm or cold season	$PM_{2.5}$: 24 μg/m^3 $PM_{0.25}$: 10.3 μg/m^3 NO_2: 26 ppb O_3: 33 ppb	M, F 84 ± 6 yr NS *n* = 60	FeNO (chemiluminescence)	Association between FeNO and exposure markers ($PM_{2.5}$ and O_3)	Delfino et al. (2010a)
Panel study of elderly subjects in Steubenville, Ohio, USA	$PM_{2.5}$: 20 μg/m^3 NO_2: 11 ppb O_3: 15 ppb SO_2: 13 ppb	M, F 54–91 yr NS *n* = 29	FeNO (chemiluminescence)	Association between FeNO and $PM_{2.5}$ concentration, but not NO_2, O_3, or SO_2	Adamkiewicz et al. (2004)

Table 4.17 (continued)

Exposure	Exposure assessment	Sex, age, smoking, number	Biomarker	Effect	Reference
Panel study of schoolchildren in Mexico City, Mexico	$PM_{2.5}$: 29 µg/m³ NO_2: 37 ppb O_3: 32 ppm	M, F 8–12 yr NS *n* = 208	FeNO (chemiluminescence) and IL-8	Generally positive associations between exposure markers ($PM_{2.5}$, NO_2, and O_3) and biomarkers (FeNO and IL-8) in asthmatics and non-asthmatics, albeit statistically non-significant in some analyses	Barraza-Villarreal et al. (2008)
Panel study of students in Christchurch, New Zealand	PM_{10}: typically < 40 µg/m³ $PM_{2.5}$: 22% lower than PM_{10} 1-OHP (urine)	M 12–18 yr NS *n* = 93	H_2O_2 (fluorescent probe)	No association between air pollution and H_2O_2 in EBC	Epton et al. (2008)
Cross-sectional study of subjects with lung diseases in 4 European cities	$PM_{2.5}$: 9–28 µg/m³. Also measurements in or near homes for 18 mo	M, F 36–85 yr S/NS *n* = 133	NO_x (Griess), glutathione	Association between coarse particle level at central monitoring station and NO_x. No association with personal exposures (near or inside homes). Assay for detection of glutathione was not sufficiently sensitive	Manney et al. (2012)
Children in a suburban area (Bilthoven) or an urban area (Utrecht), Netherlands	Black smoke: 16–29 µg/m³ NO_2: 41–53 µg/m³ SO_2: 5–7 µg/m³ O_3: 21–28 mg/m³	M, F 8–13 yr NS *n* = 82	IL-8 (protein), NO_x in nasal lavage and exhaled NO (chemiluminescence)	Positive association between PM_{10} and exhaled NO. IL-8 and NO_x highest in nasal lavage from children in urban area	Steerenberg et al. (2001)

BALF, bronchoalveolar lavage fluid; CAPs, concentrated ambient particles; COPD, chronic obstructive pulmonary disease; EBC, exhaled breath condensate; ELISA, enzyme-linked immunosorbent assay; F, female; FeNO, fractional exhaled nitrogen oxide; h, hour or hours; H_2O_2, hydrogen peroxide; HPLC, high-performance liquid chromatography; IL, interleukin; M, male; MDA, malondialdehyde; mo, month or months; n, number; NO, nitrogen oxide; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; NS, non-smokers; 1-OHP, 1-hydroxypyrene; O_3, ozone; PGE_2, prostaglandin E2; PM, particulate matter; PM_{10}, particulate matter with particles of aerodynamic diameter < 10 µm; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 µm; PNC, particle number concentration; S, smokers; SO_2, sulfur dioxide; TBARS, thiobarbituric acid reactive substances; TNF, tumour necrosis factor; UFP, ultrafine particles; wk, week or weeks; yr, year or years.

were unaltered levels of markers of cell damage in the BALF (protein, albumin, and lactate dehydrogenase activity), and the glutathione concentration was unaltered (Schaumann et al., 2004). A study on inhalation exposure to concentrated outdoor particles (23–311 μg/m^3) from Chapel Hill, North Carolina, USA, for 2 hours with moderate exercise (exercise 15 minutes; rest 15 minutes) and analysis of pulmonary inflammation 18 hours after cessation of the exposure showed a mild increase in neutrophils in BALF, whereas there were unaltered levels of IL-6, IL-8, and prostaglandin E2 (PGE_2) (Ghio et al., 2000). Another study in 19 healthy non-smoking volunteers from Chapel Hill on outdoor UFP (40 848–205 648 UFP/cm^3; 1–50 μg/m^3) showed a moderate increase in the concentration of IL-8 in BALF, whereas there were unaltered levels of IL-6 and PGE_2 (Samet et al., 2009).

A non-invasive way to study the effect of air pollution is by analysis of markers of inflammation and oxidative stress in exhaled air. As this is a relatively easy method, it has been used in epidemiological studies as well as studies on controlled exposures to air pollution. It was shown that healthy young subjects had elevated levels of malondialdehyde (MDA) in exhaled breath condensate (EBC) after exercise at a location with high traffic-generated UFP (252 290 UFP/cm^3) compared with the same type of exercise at a location with less traffic (7382 particles/cm^3) (Rundell et al., 2008). This study also showed lower concentrations of exhaled NO and nitrate, which was hypothesized to be due to the formation of peroxynitrite (Rundell et al., 2008). Another study of controlled exposure to elderly men with stable coronary heart disease showed that inhalation of CAPs (190 μg/m^3) increased the concentration of 8-isoprostanes in EBC at 6 hours and 24 hours, whereas there was no effect on 3-nitrotyrosine levels (Mills et al., 2008). Exposure to air in a road tunnel in Stockholm, Sweden (80 μg/m^3 of $PM_{2.5}$ for 2 hours), had no effect on exhaled NO in people with asthma, and there were inconsistent associations between exposure and levels of IL-10, IL-1β, IL-6, IL-8, and TNF in nasal lavage fluid (Larsson et al., 2010). Strak et al. (2012) studied subjects who were exposed to outdoor air at a traffic site or an urban site (5 hours, with intermittent exercise); they showed associations between the particle number concentration and fractional exhaled NO (FeNO).

The Beijing Olympics in 2008 has formed the basis for studies on the association between improvements in outdoor air quality and biomarkers of oxidative stress and inflammation. A study in 125 healthy adults showed that the EBC content of NO, nitrates, nitrites, MDA, and 8-isoprostanes (using an ELISA method) was lower in young and healthy subjects during the Olympics compared with periods before and after the Olympics (Gong et al., 2013; Huang et al., 2012).

Panel studies have typically focused on subjects with lung or cardiovascular diseases. It was shown that there was a positive association between personal $PM_{2.5}$ exposure and exhaled NO in children (aged 9–13 years) with asthma from Seattle, Washington, USA, who did not take corticosteroid medication (Koenig et al., 2003, 2005; Mar et al., 2005). Another panel study in Ontario, Canada, showed no association between air pollution exposure and FeNO; there was a positive association between levels of air pollution exposure components ($PM_{2.5}$, NO_2, and SO_2) and thiobarbituric acid reactive substances (TBARS; an oxidative stress marker) in EBC, which was not a particularly reliable assay for detection of lipid peroxidation products (Liu et al., 2009a). Positive associations between levels of $PM_{2.5}$ and ozone, based on stationary monitoring data, and MDA levels in EBC were observed in children with asthma in Mexico City (Romieu et al., 2008). A study in elderly subjects with asthma or COPD in Seattle, Washington, USA, showed an association between outdoor concentrations of $PM_{2.5}$ and FeNO, whereas there was no association

between FeNO and personal exposure to $PM_{2.5}$ (Jansen et al., 2005). In addition, elderly subjects with coronary artery disease in the Los Angeles basin, California, USA had a positive association between exposure markers ($PM_{2.5}$ and ozone) and FeNO (Delfino et al., 2010a). Studies of healthy children in Steubenville, Ohio, USA, or Mexico City also indicated positive associations between air pollution exposure and FeNO (Adamkiewicz et al., 2004; Barraza-Villarreal et al., 2008), whereas there was no association between levels of hydrogen peroxide (H_2O_2) in EBC and air pollution exposure among students in Christchurch, New Zealand (Epton et al., 2008).

A cross-sectional study of subjects with lung diseases (asthma or COPD) in four European cities showed an association between levels of coarse particles at a central monitoring station and levels of NO_x in EBC, whereas there was no association with personal exposure to $PM_{2.5}$, PM_{10}, or coarse fraction as measured either near or inside the homes (Manney et al., 2012). Another cross-sectional study on children in the Netherlands showed a positive association between PM_{10} exposure and exhaled NO; children from an urban area had higher nasal lavage levels of IL-8 and NO_x compared with children from a suburban area (Steerenberg et al., 2001).

(b) Systemic effects of inflammation in humans

The studies on systemic inflammation have mainly centred on markers of cardiovascular diseases, including acute-phase proteins (fibrinogen and C-reactive protein [CRP]), platelets, von Willebrand factor, haematocrit, whole blood viscosity, and leukocyte counts (Delfino et al., 2005). The measurement of CRP especially has been popular because it is used clinically, it can increase by more than 3 orders of magnitude during an acute-phase response, and it has a relatively short half-life in plasma (~19 hours). A recent review of the association between air pollution levels and CRP levels in humans encompassed a total of 44 publications, stratified into cross-sectional, panel, and randomized cross-over trials (Li et al., 2012). The most important conclusions from that survey were that there was an association between air pollution exposure and elevated levels of CRP in children in cross-sectional studies, whereas there were inconsistent results in adults, which might be related to the inclusion of subjects with prescribed statins or anti-inflammatory drugs. It was also noted that the randomized cross-over trials mainly showed no association between air pollution exposure and CRP levels in plasma, which could be because these studies had few subjects and relatively short exposure duration (Li et al., 2012). One of the studies on controlled exposure used relatively high concentrations of CAPs (190 μg/m^3 for 2 hours) and found no change in serum levels of CRP and total leukocyte counts, although there was a transient and marginal increase in the number of monocytes in blood (Mills et al., 2008). In addition, two studies on indoor air filtration for 24–48 hours with relatively low exposure gradients of traffic-generated emissions in Copenhagen, Denmark, showed no effect on levels of CRP, IL-6, TNF, and fibrinogen (Bräuner et al., 2008a, b). A 7-day intervention period with air filtration in homes of a wood smoke-affected area in British Columbia, Canada, found an association between the indoor concentration of fine particles and CRP levels, whereas there was no association with IL-6 levels (Allen et al., 2011).

The production of CRP is regulated in response to elevated levels of IL-6, IL-1, and TNF. A study indicated that children in Mexico City, compared with children in a low-pollution city, had a systemic pro-inflammatory state as determined by elevated plasma/serum levels of TNF, IL-1β, PGE_2, and CRP (Calderón-Garcidueñas et al., 2008). A very large study of subjects in Lausanne, Switzerland, with 6183 adult participants showed associations between short-term

exposures to PM_{10} and elevated levels of IL-1β, IL-6, and TNF, whereas there was no effect on CRP levels (Tsai et al., 2012). Other studies of people with coronary artery disease also found associations between exposure to small particles ($PM_{0.25}$) and levels of CRP, IL-6, and TNF in plasma (Delfino et al., 2008, 2009, 2010b). A study in Singapore showed that subjects had elevated serum levels of TNF, IL-1β, and IL-6 during a period with haze, with high outdoor air pollution concentrations (PM_{10}, 125 μg/m³), compared with a period afterwards with a low air pollution level (PM_{10}, 14 μg/m³) (van Eeden et al., 2001). However, there are also studies showing inconsistent associations between air pollution exposure and levels of CRP, IL-6, IL-8, serum amyloid A, and fibrinogen (Huttunen et al., 2012; Rückerl et al., 2006, 2007; Strak et al., 2013; Wu et al., 2012) or no association with levels of CRP, IL-6, IL-10, TNF, and fibrinogen (Liu et al., 2007, 2009b; Zuurbier et al., 2011).

Studies on oxidative stress biomarkers in biomonitoring include oxidation products of lipids, proteins, and DNA. Several studies of these products from areas in the Czech Republic have shown positive associations between air pollution exposure and oxidative stress markers (Bagryantseva et al., 2010; Rossner et al., 2007, 2011c, 2013b).

(c) Pulmonary inflammation and ROS production in experimental systems

(i) Pulmonary inflammation in experimental animals

Numerous studies have assessed pulmonary inflammation in animals after exposure to urban air particles (see Supplemental Table S20, available online). Notably, there is a clear effect on pulmonary inflammation after both inhalation and instillation exposure. This is observed by an increased number of leukocytes in BALF or elevated concentrations of pro-inflammatory cytokines. Increased inflammation has been observed after inhalation of CAPs from Bilthoven (Netherlands), Boston (Massachusetts, USA), Tuxedo (New York, USA), and Manhattan (New York, USA), with concentration ranges of approximately 100–1200 μg/m³ (Cassee et al., 2005; Clarke et al., 1999, 2000a, b; Gordon et al., 1998; Rhoden et al., 2004; Saldiva et al., 2002; Shukla et al., 2000).

Studies in mice intratracheally instilled with EHC93 (1 mg/mouse) have shown that the soluble fraction of the total dust sample was more inflammogenic than the insoluble fraction (Adamson et al., 1999a). Especially the content of zinc was found to be an important contributor to the inflammogenicity, although redox-active transition metals also had some effect on the inflammation response after intratracheal instillation of EHC93 (1 mg/mouse) (Adamson et al., 2000). The intratracheal instillation of SRM 1648 (1.6 mg/lung) in mice has also been associated with pulmonary inflammation in terms of increased concentrations of IL-6, TNF, and MIP2 in BALF (Becher et al., 2007).

Another study of PM from Duisburg (Germany), Prague (Czech Republic), Amsterdam (Netherlands), Helsinki (Finland), Barcelona (Spain), and Athens (Greece) showed that the coarse particles were more inflammogenic than the fine particles by intratracheal instillation (1–10 mg/kg for 4, 12, or 24 hours) in mice (Happo et al., 2007). Other studies also have indicated that coarse particles instilled intratracheally (100 μg/mouse) were more inflammogenic than fine particles (Farina et al., 2011). In addition to the potency of particles with different sizes, the studies in Europe have also revealed both temporal and spatial variation in the potency of PM (Farina et al., 2011; Happo et al., 2007).

Other studies on differences between particles have shown that desert dust from Arizona, USA, or Shapotou, China, was associated with pulmonary inflammation after instillation of 0.1 mg/mouse 4 times over 8 weeks (Ichinose et al., 2008). Instillation of 32–100 μg/mouse of

residual oil fly ash (ROFA) or SRM 1649 was associated with a higher degree of pulmonary inflammation than the same dose of World Trade Center fine particles (Gavett et al., 2003).

A few studies have used intranasal instillation, showing that $PM_{2.5}$ from the air in São Paulo (Brazil), PM from Buenos Aires (Argentina), or CAPs from Boston (Massachusetts, USA) increased the level of pulmonary inflammation (Martin et al., 2007; Martin et al., 2010; Riva et al., 2011; Sigaud et al., 2007).

Experimental studies also indicate that the pulmonary inflammation depends on oxidative stress, as indicated by a study where mice with overexpression of SOD compared with wild-type counterparts had lower levels of neutrophils, TNF, and MIP2 in BALF after an intratracheal instillation of 50 µg/mouse (Ghio et al., 2002). Similarly, pre-treatment with antioxidants decreased the level of particle-mediated pulmonary inflammation after the intratracheal instillation (10–100 µg/mouse) of urban air PM (Dick et al., 2003).

A study in Porto Alegre, Brazil, with relatively high outdoor particle concentrations (110–140 µg/m^3), showed increased pulmonary inflammation in rats (Pereira et al., 2007). However, it has also been reported that exposure to CAPs from Grand Rapids, Michigan, USA (493 µg/m^3, 8 hours/day for 13 days), Chapel Hill, North Carolina, USA (475–907 µg/m^3, 6 hours/day for 2–3 days), or Bilthoven, Netherlands (399–3612 µg/m^3, 6 hours/day for 2 days) was not associated with pulmonary inflammation in rats (Heidenfelder et al., 2009; Kodavanti et al., 2000; Kooter et al., 2006). The exposure concentrations do not appear to be different between the studies with null effect and studies that have shown pulmonary inflammation. A study on short-term inhalation exposure to EHC93 (57 µg/m^3 for 4 hours) was associated with an increased number of neutrophils in the air space and tissue of rats (Adamson et al., 1999b). Likewise, there was an increased level of pulmonary inflammation after inhalation (12 mg/m^3 for 6 hours) of ROFA or the corresponding dose administered by intratracheal instillation (110 µg/rat) (Costa et al., 2006). The effect on pulmonary inflammation was highest at 24 hours after the exposure, and it decreased gradually over the next 72 hours (Costa et al., 2006).

Relatively high bolus dose instillations of EHC93 (5–10 mg/kg) have indicated a bell-shaped response in regard to the number of cells in BALF, with the highest effect at 24–48 hours, whereas time points before (4 hours) and after (days 4–7) indicated lower effects on pulmonary inflammation (Bagate et al., 2004; Gerlofs-Nijland et al., 2005; Ulrich et al., 2002). Intratracheal instillation of the water-soluble fraction of TSP from Provo, Utah, USA, was associated with higher levels of neutrophils in BALF compared with instillation of the insoluble fraction of particles (Ghio et al., 1999).

A study of particles that were collected in Amsterdam (Netherlands), Lodz (Poland), Oslo (Norway), and Rome (Italy) showed that fine particles were more inflammogenic than coarse particles on a mass basis in rats by intratracheal instillation (Halatek et al., 2011). This study also revealed seasonal variability of particles for the influx of neutrophils in BALF, especially in Oslo, whereas the levels of TNF and MIP2 in BALF depended on both the season and the location (Halatek et al., 2011). However, another study of intratracheal instillation in spontaneously hypersensitive rats of particles (3 mg/kg or 10 mg/kg) collected in Munich (Germany), Hendrik-Ido-Ambacht (Netherlands), Dordrecht (Netherlands), Rome (Italy), and Lycksele (Sweden) showed that coarse particles were more inflammogenic than fine particles (Gerlofs-Nijland et al., 2007). Coarse particles were shown to be more inflammogenic than fine particles by intratracheal instillation in rats (Schins et al., 2004). Also, both temporal and spatial variation in the potency of PM has been shown (Gerlofs-Nijland et al., 2007; Halatek et al., 2011). A study

in Beijing, China, showed higher levels of TNF, IL-6, and IL-1 in lung homogenate after intratracheal instillation of $PM_{2.5}$ compared with the same dose of PM_{10} (7.5 mg/kg), and particles collected closest to traffic generated the highest level of inflammation (Zhang et al., 2011). Intratracheal instillation of ROFA (500 µg/rat) was associated with increased levels of neutrophils in BALF as well as elevated levels of IL-6, TNF, CCL2, and IL-1β (Roberts et al., 2003).

Collectively, there is compelling evidence for an association between exposure to air pollution particles and pulmonary inflammation in experimental animals.

(ii) ROS production in experimental animals

Relatively few studies have undertaken analysis of ROS production in vivo after pulmonary exposure. Inhalation of CAPs (300 µg/m³ for 5 hours) or ROFA (1.7 mg/m³ for 30 minutes) was associated with increased production of ROS in lung tissue, assessed by chemiluminescence (Gurgueira et al., 2002). Another study exposed rats to oil fly ash (500 µg/rat) by intratracheal instillation and subsequently injected 4-POBN (a spin trap) in the peritoneum at 1 hour before the rats were killed. Lung homogenates from exposed rats showed the presence of carbon-centred alkyl radicals, which were suspected to have been derived from peroxidation of lipids (Kadiiska et al., 2004).

(iii) Markers of inflammation in cultured cells

Studies on markers of inflammatory responses in cultured cells, summarized in Supplemental Table S21 (available online), evaluated a variety of cytokines. A substantial number of studies have documented increased levels of biomarkers of inflammation, in regard to cytokines, chemokines, and production of NO in various cell lines or primary cell cultures from rodents after exposure to authentic air pollution particles or model particles such as EHC93, SRM 1648, SRM 1649, or ROFA (Auger et al., 2006; Baulig et al., 2003; Becher et al., 2007; Brown et al., 2004, 2007; Fujii et al., 2001, 2002; Garçon et al., 2006; Jalava et al., 2005; Karlsson et al., 2006; Schneider et al., 2005; van Eeden et al., 2001; Watterson et al., 2007). Exposure of lung epithelial cells and alveolar macrophages in co-cultures to ROFA or SRM 1649 increased the secretion of MIP2 and TNF. This effect was not observed in lung epithelial cells or alveolar macrophages in mono-cultures (Tao & Kobzik, 2002). Higher levels of IL-6, IL-8, and IL-1β were also observed in A549/THP-1 in co-cultures compared with THP-1 mono-cultures after exposure to PM samples from Milan, Italy (Longhin et al., 2013).

Collectively, there is compelling evidence that exposure to PM in cultured cells is associated with inflammatory reactions, assessed mainly as secretion of cytokines and chemokines, which may be elicited secondary to oxidative stress in the cells. This association between exposure to PM and secretion of cytokines is observed especially in lung epithelial cells and macrophages. The inflammation potential seems to be higher for coarse particles compared with fine particles, which is likely to be related to the content of endotoxin in the coarse fraction. There is also some experimental evidence linking the inflammation reaction in cultured cells to oxidative stress and metal-catalysed ROS production, although it should be noted that the observations are mixed and the linkage between oxidative stress and inflammation might depend on both the physical–chemical properties of PM samples and their constituents.

(iv) ROS production in cultured cells

Studies on ROS production in cultured cells are summarized in Supplemental Table S22 (available online). It has been shown that exposure to air pollution particles was associated with intracellular ROS production, detected as oxidation products of 2′,7′-dichlorodihydrofluorescein (DCFH) or dihydroethidium, or chemiluminescence in different human cells (Auger

et al., 2006; Baulig et al., 2003; Becker et al., 1996, 2005; Goldsmith et al., 1997; Kamdar et al., 2008; Karlsson et al., 2008; Ohyama et al., 2007; Shukla et al., 2000; Yi et al., 2014; Zhang et al., 2008). Model particles such as SRM 1648, SRM 1649, EHC93, and various types of fly ashes have also been associated with intracellular ROS production (Baulig et al., 2003; Becher et al., 2007, Becker et al., 1996, 2005; Di Pietro et al., 2009; Dwivedi et al., 2012; Li et al., 2006; Schneider et al., 2005).

A few studies have assessed the ROS production potential of EOM in cultured cells. This revealed increased ROS production by extracts from both urban and rural sites in MCF-7 cells (Chen et al., 2013), PM_{10} from an industrial area in HepG2 cells (Jiang et al., 2011), and road tunnel particles in A549 cells (Shang et al., 2013).

Collectively, there is compelling evidence for intracellular ROS production in cells exposed to PM.

(v) Acellular ROS production

Studies on acellular ROS production are summarized in Supplemental Table S23 (available online). ROS can be detected by electron spin resonance (ESR) signals, which are typically obtained in experimental conditions with H_2O_2 as co-oxidant and 5,5-dimethyl-1-pyrroline-*N*-oxide (DMPO) as spin trap, indicating that the assay depends mainly on the presence of transition metals in the samples (Knaapen et al., 2002; Valavanidis et al., 2000, 2005). This is supported by observations that coal fly ash produced ROS, which correlated with the release of iron (Dwivedi et al., 2012; van Maanen et al., 1999). Nevertheless, other transition metals can be the dominant source of ROS production, which has been observed for $PM_{2.5}$ samples that were collected in the San Joaquin Valley, California, USA (Shen et al., 2011; Shen & Anastasio 2011, 2012). In addition, treatment with DFO, catalase, or antioxidants (DMSO or dimethylthiourea) diminished the ROS production of air pollution particles measured by ESR or other assays, such as oxidation products of DCFH or deoxyribose (Ball et al., 2000; Frampton et al., 1999; Ghio & Devlin, 2001; Imrich et al., 2007; Knaapen et al., 2002; Lindbom et al., 2007).

Collectively, there is strong evidence that PM generates ROS in suspensions by at least two mechanisms, encompassing transition metal catalysis or redox cycling by quinones.

In summary, controlled short-term inhalation exposures to CAPs or instillation of PM from especially urban areas in Europe and the USA have been associated with increased levels of pulmonary inflammation and oxidative stress. These observations are supported by results from cross-sectional and panel studies that show signs of pulmonary inflammation, whereas there are only few studies on oxidative stress end-points. There is strong evidence for pulmonary inflammation in animals after either inhalation or intratracheal instillation (or similar ways of exposure) of PM from urban air in Argentina, Brazil, China, Europe, and the USA. Aqueous suspensions of PM from urban areas in China, Europe, Japan, and the USA have been associated with increased ROS production in cultured cells. Organic extracts of PM from cities in China have likewise increased the intracellular ROS production. Aqueous suspensions of PM from urban areas, mainly in Europe and the USA, have promoted inflammation reactions in cultured macrophages or airway epithelial cells. A few studies on PM from China, Mexico, and Senegal also indicate inflammation in cultured cells. In comparison, very few studies have assessed the effect of organic extracts of PM on inflammation, and the results have been mixed. Aqueous suspensions of PM from urban areas, mainly in Europe and the USA, have been shown to generate ROS production in acellular conditions.

4.3.2 Non-cancer effects

Exposure to current-day concentrations of outdoor air pollution has been linked with a variety of non-cancer health effects ranging in severity from subclinical physiological changes to mortality, particularly involving cardiovascular and respiratory diseases, with evidence of additional effects on immunological, reproductive, and other systems (American Thoracic Society, 2000; WHO, 2006; Samet & Krewski, 2007) (see Supplemental Figure S3, available online) Exposure to outdoor particulate air pollution has been estimated to have contributed 3.2 million premature deaths and 74.4 million lost years of healthy life worldwide in 2010, due to cardiovascular disease, COPD, and acute lower respiratory infections, in addition to lung cancer (Lim et al., 2012). Although mortality and hospitalization have been the most studied effects of air pollution and have important public health impacts, the number of people affected by less-severe effects is larger (WHO, 2006).

(a) Cardiorespiratory effects

The cardiovascular and respiratory effects of outdoor air pollution have been examined in many studies worldwide using diverse research designs and are summarized in numerous reviews and regulatory documents (e.g. Brook, 2008; Brook et al., 2010; EPA, 2006; Hoek et al., 2013; Lai et al., 2013; WHO, 2006). The effects of airborne PM have been most extensively studied. Exposure to PM is linked with increases in all-cause, cardiovascular, and respiratory mortality, as well as with other cardiovascular and respiratory effects, including hospitalization for acute respiratory events, decreased lung function, ischaemic events, stroke, arrhythmia, and reduced heart rate variability (Brook, 2008; Hoek et al., 2013; Pieters et al., 2012; Samet & Krewski, 2007; WHO, 2006). Positive associations have also been observed between exposure to NO_x and mortality from all causes and ischaemic health disease (Hoek et al., 2013; Mustafic et al., 2012). However, because NO_2 is closely correlated with other air pollutants from traffic-related sources, it is difficult to determine whether the effects are due specifically to NO_2, to other air pollutants, or to the complex mixture of pollutants (WHO, 2006).

(b) Reproductive effects

Prenatal exposure to air pollution has been hypothesized to affect the unborn child through several mechanisms, including oxidative stress, inflammatory processes, endocrine disruption, and germ-cell changes (Schwartz, 2004; Slama et al., 2008). Research on this topic is still inconclusive, but there is some evidence that prenatal exposure to outdoor air pollution increases the risk of preterm delivery, fetal growth deficit, and cardiac birth deficit (Wigle et al., 2008). A meta-analysis based on 62 studies estimated that exposure to PM, NO_2, and CO during pregnancy was associated with low birth weight and that exposure to PM and CO was associated with preterm birth (Stieb et al., 2012). Another systematic review of air pollution exposures and birth outcomes reported similar conclusions regarding low birth weight and preterm birth, as well as associations of small-for-gestational-age births with prenatal exposure to PM and of preterm birth with exposure to SO_2 (Shah & Balkhair, 2011). Transcriptomics allows for more mechanistic and holistic studies by analysing several genes that are upregulated or downregulated in exposed populations, for example as performed in the well-characterized Czech populations, including gene profiling of newborns (Šrám et al., 2013). These studies are explorative.

(c) Immunotoxic effects

Associations between exposures to outdoor air pollution and biomarkers of immunotoxicity associated with inflammatory responses, for example cytokines, have been reported in several studies.

(d) Endocrine effects

Statistically significant associations between long-term exposure to traffic-related air pollution at the residence and diabetes mortality were reported in a Danish follow-up study of 52 061 cohort participants (Raaschou-Nielsen et al., 2013a). An association of type 2 diabetes in women with traffic-related air pollution measured by NO_2 has also been reported (Brook et al., 2008). Urinary excretion of 17-ketosteroids and 17-hydroxycorticosteroids, markers of adrenal cortex functions, was reported to be significantly lower in male children living in polluted areas compared with children living in clean areas (Watanabe, 2000), but the paper lacks important details about the study population.

4.3.3 Genotoxic and other deleterious effects on germ cells

Several lines of evidence have suggested that air pollution may cause deleterious effects to germ cells in wildlife, experimental animals, and humans (reviewed in Samet et al., 2004; Somers & Cooper, 2009; Somers, 2011). The studies of outdoor air pollution-induced genetic effects in germ cells are summarized in Table 4.18 and Supplemental Table S24 (available online).

(a) DNA damage and chromosomal aberrations in human sperm

See Table 4.18.

Several studies in the Czech Republic have evaluated the association of outdoor air pollution exposure with chromatin damage in humans by SCSA. A preliminary study showed an increased percentage of sperm with abnormal chromatin structure (denatured DNA susceptibility) (expressed as $COMP\alpha_t$, cells outside the main population of cells) at periods of high air pollution in Teplice (Selevan et al., 2000). High $COMP\alpha_t$ (> 30) has been associated with infertility and spontaneous abortion (Evenson et al., 1999). A subsequent 2-year follow-up study confirmed that there was a significant association between exposure to periods of air pollution and the increased DNA damage in human sperm; however, there was no association between aneuploidy in sperm and outdoor air pollution (Rubes et al., 2005). Rubes et al. also showed that men with the *GSTM1* null genotype exhibited increased susceptibility to sperm DNA damage associated with exposure (Rubes et al., 2007). Furthermore, significantly higher sperm DNA fragmentation index (DFI) values were observed in the winter compared with in the spring for police officers working outdoors in Prague (Rubes et al., 2010). A study in male traffic police in Prague showed that they had higher frequencies of aneuploidy in their sperm when sampled in January, when the PM_{10} concentrations were high, compared with in March, when the PM_{10} concentrations were low (Rubes et al., 1996; Srám et al., 1999).

(b) Mutations in male germ cells and the germline in animals

Studies of sentinel wildlife and laboratory rodents exposed to outdoor air (summarized in Supplemental Table S24, available online) have provided evidence for elevated germline mutation induced by air pollution (Somers & Cooper, 2009; Somers, 2011). Increased rates of germline mutations at minisatellite loci (tandem repetitive DNA loci) were seen in herring gulls (*Larus argentatus*) collected from industrial areas with high levels of air pollution, and minisatellite mutation rates decreased with increasing distance from the industrial coking oven and urbanization site (Yauk & Quinn, 1996; Yauk et al., 2000). When laboratory mice were exposed to outdoor air in a polluted industrial area near steel mills, a significant 1.5–2.0-fold elevation in heritable mutation frequency in the offspring was observed, primarily through ESTR mutation events in the paternal germline (Somers et al., 2002). This heritable mutation frequency was significantly reduced when mice were exposed in situ to air from a polluted area treated by a HEPA filtration

Table 4.18 Genotoxic effects in germ cells of humans exposed to outdoor air pollution

Location	Subjects	Experimental design/exposure	End-point	Results		Reference
Teplice, Czech Republic	Young men (18 yr)	Semen samples were collected from 272 men recruited from Teplice (industrialized area) or Prachatice (rural area)	Abnormal chromatin in sperm (SCSA)	Increased percentage of sperm with abnormal chromatin was associated with seasonally elevated levels of air pollution	+	Selevan et al. (2000)
Teplice, Czech Republic	Young men (19–21 yr)	228 semen samples were collected from 36 men in different seasons over 2 years	Sperm DFI by SCSA Aneuploidy	Increased DFI in sperm was associated with high levels of air pollution. No effect was observed for aneuploidy	+	Rubes et al. (2005)
Teplice, Czech Republic	Young men (19–21 yr)	Semen samples were collected from 35 men in different seasons	Sperm DFI by SCSA among *GSTM1* null	Statistically significant association between *GSTM1* null genotype and increased SCSA-defined DFI.	+	Rubes et al. (2007)
Prague, Czech Republic	Male outdoor police officers (33 ± 5 yr)	Semen samples were collected from 47 police officers in winter (high pollution) and spring (low pollution)	DNA damage in sperm (DFI by SCSA)	Sperm DFI was significantly higher in winter samples than in spring samples for all police and for non-smokers	+	Rubes et al. (2010)
Prague, Czech Republic	Male outdoor police officers	Outdoor police officers in Prague were sampled in winter (high pollution) and spring (low pollution)	Aneuploidy for YY8 (FISH)	YY8 aneuploidy was significantly associated with the season of heaviest air pollution	+	Rubes et al. (1996); Srám et al. (1999)

+, positive; DFI, DNA fragmentation index; FISH, fluorescence in situ hybridization; SCSA, sperm chromatin structure assay; yr, year or years.

system that removed 99.97% of particles 0.3 μm in diameter (Somers et al., 2004). [The Working Group noted that airborne PM was an important factor in induction of germline ESTR mutations.] Taken together, the series of studies indicate that exposure to outdoor air pollution could cause damage to male gametes, as shown in observed germline mutations and DNA damage in sperm of mice, although their contributions to fertility and reproduction are still unknown.

(c) Sperm abnormality in animals

In a sperm morphology study of mice treated with extracts of air samples collected in Shanghai, China, an increased frequency of germ-cell deformations was observed for most sites in the winter (Mao et al., 1993). A subsequent animal experimental study in Taiyuan, China, showed that intraperitoneal treatment of male Kunming mice with particle extracts from the residential area downwind of a coal combustion power plant induced sperm abnormality, CAs of spermatogonia and primary spermatocytes, and MN in spermatids (Sun et al., 1995). Elevated frequencies of head and tail deformities in the sperm were observed in feral mice living in an area with air highly polluted by automobile traffic in Rome, Italy (Ieradi et al., 1996).

In summary, a series of studies in humans, wildlife, and experimental animals indicate that outdoor air pollution might cause heritable mutations, sperm abnormalities, and germ-cell DNA damage. The evidence for heritable mutation derives from studies examining gulls as well as inbred and outbred mice.

4.3.4 Oncogenic cell transformation

Studies that used cultured animal cells to assess the ability of outdoor air to induce malignant cell transformation are summarized in Supplemental Table S25 (available online).

Several such studies have demonstrated that organic extracts of urban air PM can induce oncogenic transformation of cultured animal cells. Moreover, some studies have demonstrated that the resultant transformed cells can form malignant tumours in vivo.

4.4 Susceptible populations

4.4.1 Polymorphisms in carcinogen-metabolizing genes

Studies on the influence of genotype and lung cancer risk, and of genotype and biomarkers, are summarized in Supplemental Tables S26 and S27 (available online), respectively.

Data on the roles of genotypes/phenotypes related to outdoor air exposure are sparse. Hosgood et al. (2007) carried out a meta-analysis of six studies evaluating the associations of *GSTM1* null, *GSTT1* null, and *GSTP1* (105 Val polymorphism) genotypes and their association with risk of lung cancer in regions where exposure to indoor burning of coal, wood, and biomass fuels is common. The risk of lung cancer was elevated for carriers of the *GSTM1* null and *GSTT1* null genotypes, with the strongest association observed for *GSTM1* null carriers in four Asian regions where coal smoke is used for heating and cooking. However, individual data on exposure to air pollution were not available.

4.4.2 Age and sex

The potentially different effects of exposure early in life and greater life expectancy from childhood could influence the risk of cancer associated with air pollution. Indeed, children have different susceptibilities owing to their dynamic growth and developmental processes as well as physiological, metabolic, and behavioural differences. From conception through adolescence, rapid growth and developmental processes occur that can be disrupted by exposures to environmental chemicals. These include anatomical, physiological, metabolic, functional, toxicokinetic, and toxicodynamic processes (IPCS, 2008). Exposure pathways and exposure patterns may also be different in different stages of childhood. Children have a higher inhalation rate and a higher ratio of body surface area to body weight, which may lead to increased exposures. Children's metabolic pathways may differ from those of adults. Children have more years of future life and thus more time to develop chronic diseases that take decades to appear and that may be triggered by early environmental exposures (IPCS, 2008). However, aside from the studies of childhood cancer reviewed in Section 2.5, the Working Group found no specific studies of susceptibility in relation to age at exposure.

Men and women differ in body size, conductive airway size, and ventilatory parameters; therefore, sex differences in deposition might be expected. Since women are generally smaller than men, the increased minute ventilation of women compared with their normal ventilation could affect deposition patterns. This may help explain why sex-related effects on deposition have been observed in some studies.

Kim & Hu (1998) assessed the regional deposition patterns of particles of 1 μm, 3 μm, and 5 μm mass median aerodynamic diameter in healthy adult men and women using controlled breathing. The total fractional deposition in the lungs was similar in men and women for the 1 μm particles but was greater in women for the 3 μm and 5 μm particles. Deposition also appeared to be more localized in the lungs of women compared with those of men. Jaques & Kim (2000) measured deposition in healthy adults using sizes in the ultrafine mode (0.04–0.1 μm). Total fractional lung deposition was greater in women than in men for 0.04 μm and 0.06 μm particles. The region of peak fractional deposition was shifted closer to the mouth, and the peak height was slightly greater for women than for men for all exposure conditions. These

differences were generally attributed to the smaller size of the upper airways, particularly of the laryngeal structure, in women. In another study (Bennett et al., 1996), the total respiratory tract deposition of 2 µm particles was examined in adult men and women aged 18–80 years who breathed with a normal resting pattern. There was a tendency for greater deposition fractions in women than in men. However, since men had greater minute ventilation, the deposition rate (i.e. deposition per unit time) was greater in men than in women. More recently, Bennett & Zeman (2004) found no difference in the deposition of 2 µm particles in boys versus girls aged 6–13 years (n = 36) (EPA, 2009).

4.4.3 Socioeconomic status

Social inequalities in risk factors may account for more than half of the inequalities in outcomes of major noncommunicable diseases, including lung cancer (Di Cesare et al., 2013). Social inequalities in exposure to air pollution have been documented and are discussed in Section 1.4.3. Research into whether the effects of air pollution also differ by socioeconomic status has been focused largely on general mortality and cardiorespiratory diseases (O'Neill et al. 2003). However, several studies of cancer and air pollution have considered socioeconomic status as a potential confounder or effect modifier.

A cohort study in Rome, Italy, reported increased relative risks for the association of NO_2 and $PM_{2.5}$ and lung cancer with lower levels of education and an area-based socioeconomic index, but the trends were not statistically significant (Cesaroni et al., 2013). Several other studies of air pollution and lung cancer in Europe and North America adjusted for individual or aggregate indicators of socioeconomic status in addition to other covariates, but did not report results according to the levels of socioeconomic indicators (e.g. Jerrett et al., 2013; Carey et al. 2013; Raaschou-Nielsen et al. 2013b; Krewski et al., 2009; Beelen et al., 2008a). In general, the study results were not notably changed by adjustment for socioeconomic indicators.

4.4.4 Increased risk in diseased populations

Several studies have shown that non-malignant respiratory disease, particularly COPD, increases the risk of developing lung cancer (e.g. Skillrud et al., 1986; Turner et al., 2007). Abnormal regulation of the immune system and chronic inflammation appear to be key events in this process. In addition, the possibility of a genetic basis for lung cancer susceptibility in the context of COPD is becoming clear (Rooney & Sethi, 2011). Although there is evidence that comorbid conditions increase the risk of acute mortality associated with exposure to air pollution, the role of comorbidity has not been investigated in studies of air pollution and cancer.

4.5 Mechanistic considerations

Outdoor air pollution consists of a mixture of complex components, including diesel and gasoline engine exhausts, biomass combustion emissions, geological dust, and industrial emissions. The complexity of this "mixture of mixtures" contributes to the complexity of the mechanisms underlying the genetic and related effects reported in humans and experimental systems. The compiled evidence supports the operation of multiple mechanisms that involve DNA damage (e.g. formation of bulky adducts, strand breaks, oxidatively damaged DNA, and induction or alteration of DNA repair pathways), cytogenetic damage (e.g. chromosome breaks and aneuploidy), somatic- and germ-cell mutation, oncogenic cell transformation, epigenetic changes, changes in gene expression, and induction of oxidative stress and inflammation.

Table 4.19 Summary of genetic effects reported in molecular epidemiology studies of outdoor air pollution

Exposure scenario	End-point reported			
	DNA adducts[a]	Cytogenetic damage[b]	DNA strand breaks[c]	Changes in gene expression[d]
Traffic police	+	+	+	NA
Taxi drivers	+	+	+	NA
Bus drivers	+	+	NA	NA
Mail carriers	+	+	NA	NA
Urban residents	+	+	+	+
Urban children	+	+	+	+

[a] Refer to Section 4.2.3.
[b] Refer to Section 4.2.2.
[c] Refer to Section 4.2.3.
[d] Refer to Section 4.2.4.
+, positive; NA, not available.

4.5.1 Outdoor air pollution

Molecular epidemiology studies have been conducted in occupationally exposed populations, the general population in different geographical areas, and susceptible populations of children. Occupational (e.g. traffic police, bus drivers, and mail carriers) or environmental (e.g. urban residents exposed to traffic and residents exposed to combustion sources) exposure studies have confirmed significantly increased levels of biomarkers of exposure of mutagenicity (e.g. urinary 1-OHP and 8-oxodG, urinary mutagenic activity, and protein adducts), biologically active internal exposures (e.g. DNA adducts and strand breaks in target tissues), cytogenetic damage (e.g. MN and CAs), mutations (in human newborns), and changes in gene expression. Table 4.19 provides an overview of the mechanistically important/relevant genetic effects in humans exposed to elevated levels of outdoor air pollution.

Increased susceptibility in humans to the effects of outdoor air pollution has been associated with genetic polymorphisms, for example *GSTM1* null, alone or in combination with selected *CYP1A1* genotypes (Hosgood et al. 2007).

A relatively small number of studies have shown that animals exposed to outdoor air pollution in situ have elevated levels of DNA damage, cytogenetic damage, and heritable mutations. Pedigree analyses of herring gulls collected from urban/industrial areas, as well as pedigree and male germ-cell analyses of both inbred and outbred mice housed in an area with elevated levels of outdoor air pollution (Yauk, 2004; Yauk et al., 2008), showed increased levels of germ-cell mutations associated with the polluted sites, and elimination of the effect via PM removal. The hypervariable repeat sequence loci examined are not associated with any known phenotype. Nevertheless, significant increases in paternal germline and germ-cell mutation rates in organisms exposed to outdoor air pollution confirm the ability of genetic damage induced by outdoor air pollution to be transmitted between generations. The phenotypic consequences of this transmission remain unknown. The most recent investigation of heritable germ-cell mutations in mice exposed to outdoor air pollution detected DNA damage in lung tissue, but not in gonadal tissue, suggesting a mechanism independent of bulky adduct formation. In situ exposures of cattle and mice to polluted outdoor air showed significant increases in cytogenetic damage in haematopoietic tissues. Numerous studies have also documented mutations and cytogenetic damage in plants exposed to elevated levels of outdoor air pollution.

In addition, there is relatively good evidence for the induction of genetic and related effects after controlled experimental exposures to components of outdoor air pollution (e.g. VOCs,

SVOCs, PM, and PM extracts). Some of these components have been previously evaluated for their carcinogenic risk to humans (IARC, 2010c, 2012c, 2013).

4.5.2 Gases

The gaseous portion of outdoor air pollution contains well-known pulmonary irritants such as ozone and NO_x. Although no studies have investigated genetic and related effects induced by exposures to the gaseous portion of outdoor air pollution specifically, reviews of the scientific literature indicate that these agents can induce genetic effects in vivo (Victorin, 1994, 1996). Recent literature suggests that abnormal immune system regulation and chronic inflammation are key mechanistic features of obstructive pulmonary disorders that enhance lung cancer risk (Turner et al., 2007).

4.5.3 Volatile organic compounds

The VOC portion of outdoor air pollution can contain a wide range of substances, and the occurrence of these substances in outdoor air is reviewed in Section 1 of this *Monograph*. The types and concentrations of these substances (e.g. benzene, formaldehyde, 1,3-butadiene, and styrene) vary with respect to the type of sample, the atmospheric conditions, the physical–chemical properties of the compound, and the proximity to known sources. The carcinogenicity of these substances and the mechanisms underlying their carcinogenic activity are addressed in detail in *IARC Monograph* Volume 100F (IARC, 2012b).

4.5.4 Semivolatile organic compounds

The SVOC fraction of outdoor air pollution also contains a wide range of substances, and the occurrence of these substances is also reviewed in Section 1 of this *Monograph*. The types and concentrations of these substances in outdoor air samples, which can include PAHs and nitroarenes that are known mutagenic carcinogens (IARC, 2010c, 2013), vary with respect to the sample collection method, the physical–chemical properties of the compounds, the PM concentration and composition, the atmospheric conditions, and the proximity to known sources. Some components of outdoor polluted air, such as PAHs and nitro-PAHs, whether in the vapour phase or adsorbed to suspended PM, can be metabolically converted to reactive species that will bind covalently to DNA in human tissues and experimental systems. These substances have been previously reviewed by IARC (see Table 1.2 in Section 1) and several have been classified as Group 1, 2A, or 2B agents. The carcinogenicity of PAHs and selected nitro-PAHs and the mechanisms underlying PAH- and nitro-PAH-induced carcinogenesis are extensively reviewed in *IARC Monographs* Volumes 92 and 105 (IARC, 2010c, 2013). Volume 105 also provides an evaluation of diesel and gasoline engine emissions, important components of outdoor air pollution (IARC, 2013).

A small number of studies provide evidence that the SVOC portion of filtered outdoor air contains substances that induce mutations in bacteria and plants, DNA damage in bacteria, and mitotic recombination in *Drosophila*. Although the identity of the implicated substances and their mechanisms of action remain unclear, some studies have documented the presence of PAHs and nitro-PAHs that are known or suspected mutagenic carcinogens (Pyysalo et al., 1987; Sera et al., 1994; Gupta et al., 1996; Du Four et al., 2004; Škarek et al., 2007).

4.5.5 Airborne particulate matter

The adsorption of substances with a range of physical–chemical properties will influence the biological properties of PM in polluted outdoor air. Studies on model particles such as carbon black and titanium dioxide have shown inverse

correlations between particle size and inflammogenicity (Duffin et al., 2007; Stoeger et al., 2006). Metals ions are involved in generating oxidative processes associated with particles deposited in the respiratory tract, and thus are a source of oxidative stress and inflammation (Tao et al., 2003; Li et al., 2008). Absorption onto carbonaceous particles of high-molecular-weight organic compounds, such as PAHs and nitro-PAHs, provides a mechanism whereby these semivolatile or non-volatile compounds can be delivered into the airways, where they can be absorbed and metabolically converted into reactive intermediates. For genotoxic organic compounds adsorbed to PM to manifest their genotoxic activity, they must be bioavailable. It is clear that organic solvents can effectively remove organic compounds from PM in outdoor air, and based on results obtained in vitro with bacteria and human cells, there is some evidence that biological fluids can effectively remove genotoxic compounds adsorbed to airborne PM. Ohsawa et al. (1983) and Takeda et al. (1983) showed that bovine serum extracts of airborne PM can induce mutations in *Salmonella*, but the potency of the extracts is low relative to organic solvent extracts. Yuan & Xun (1994) and Yuan et al. (1994) showed that PM extracts prepared using simulated lung fluid can cause DNA damage in cultured human amnion cells. Lei et al. (1993) showed that simulated lung fluid PM extracts can induce chromosomal damage in mouse haematopoietic cells.

Controlled short-term human exposures to concentrated airborne particles have been shown to be associated with pulmonary inflammation (Ghio et al. 2000; Samet et al., 2009). Nevertheless, the studies did not investigate the degree of sustained inflammation observed in rodents, most notably rats, at high lung PM burdens.

The information available indicates that inhalation exposure to PM promotes a pro-oxidant and pro-inflammatory milieu. Concomitant ROS production, together with exposure to mutagenic carcinogens such as PAHs, can be expected to give rise to a multitude of DNA lesions. If left unrepaired, these lesions can be expected to contribute to mutations and chromosomal damage that initiate and promote carcinogenesis.

Experimental exposures of rodents to organic PM extracts induced chromosomal damage. However, only a few studies used a route of exposure (inhalation) that is relevant to elevated human lung cancer risk attributable to PM exposures (Izzotti et al., 1996; Zhao et al., 2001). Intratracheal exposures of rats to PM suspensions induced DNA damage measured as strand breaks and oxidatively damaged DNA (Meng & Zhang, 2007; Lin et al., 2009; Danielsen et al., 2010; Zhang et al., 2011).

Exposure of *Drosophila* to PM extracts (larval exposure via feed) induced elevations in both somatic and germ mutation frequency. In addition, in vitro exposures to PM suspensions induced chromosomal damage in human lymphocytes and mutations in rat primary hepatocytes and *Salmonella* (Wei & Meng, 2006a, c; Alfaro-Moreno et al., 1997; Du Four et al., 2004). Collectively, these studies indicate that pulmonary exposure to PM or PM extracts causes genetic damage.

The bulk of published studies that assessed the induction of genetic and related effects in experimental systems were performed with organic solvent extracts of PM collected from polluted locations. Chemical analysis of extracts of PM collected from a wide range of locations clearly indicates that the matrix contains numerous PAHs and nitro-PAHs that are classified by IARC as known or probable human carcinogens (Yang et al., 1994; Durant et al., 1998; Pedersen et al., 1999, 2004, 2005; Brits et al., 2004; Calderón-Segura et al., 2004). Not surprisingly, organic solvent extracts of outdoor air can induce CAs, MN, SCEs, DNA strand breaks, unscheduled DNA synthesis, bulky adducts, and oxidative DNA lesions in cultured human cells. In addition, organic solvent extracts of PM can induce

Table 4.20 Summary by end-point of genetic and related effects induced in humans and experimental systems by exposure to outdoor air pollution or samples derived from outdoor air pollution

End-point	Humans	Experimental animals	Mammalian cells	Plants	Bacteria	Acellular
Mutations	(+)[a]	+	+	+	+	–[b]
Cytogenetic damage (CAs, MN, SCEs)	+	+	+	+	NA	NA
Stable DNA adducts	+	+	+	NE	NE	+
DNA strand breaks	+	+/–[c]	+	NE	NE	+
Oxidatively damaged DNA	+	+/–[d]	+	NE	NE	+
Oxidative stress and inflammation	+	+	+	NE	NE	+
Cell transformation	NA	NA	+	NA	NA	NA
Epigenetic changes	+	+	NE	NE	NE	NA

[a] Limited information available.
[b] Not applicable.
[c] Few studies, conflicting results. See Table 4.10, Section 4.2.3c.
[d] Few studies, conflicting results. See Supplemental Table S14 (available online), Section 4.2.3e.
+, positive; –, negative; CAs, chromosomal aberration; MN, micronuclei; NA, not available; NE, not evaluated; SCEs, sister chromatid exchanges.

mutations, CAs, aneuploidy, MN, SCEs, DNA strand breaks, bulky adducts, and oxidative DNA lesions in cultured mammalian cells, as well as nuclear and mitochondrial DNA mutations and gene conversion in yeast, and mutations and DNA damage in bacteria. Finally, organic PM extracts can induce bulky adducts, DNA strand breaks, and oxidative lesions in naked DNA in solution.

In addition, effects induced by water and/or acid extracts of PM are also well documented. For example, acid extracts of PM induce MN and DNA strand breaks in cultured human lymphocytes (Yuan et al., 1999a, b; Jayasekher, 2009). Acid extracts contained transition metals, including nickel and chromium, which are known to participate in Fenton reactions that generate reactive peroxide and hydroxyl radicals, which contribute to the formation of ROS. Indeed, aqueous extracts of airborne PM have been shown to induce DNA strand breaks in rat lung, oxidative lesions on naked DNA in solution, the formation of ROS in vitro, and the formation of ROS in cultured mammalian cells.

Genetic and related effects of outdoor air pollution and other mechanistic events

Tables 4.20 and 4.21 summarize the genetic and related effects in humans and experimental systems induced by exposures to outdoor air pollution and samples derived from outdoor air pollution. A large body of evidence clearly indicates that humans exposed to elevated levels of outdoor air pollution have increased levels of chromosomal damage, including chromosome breaks and aneuploidy. Similar effects in experimental systems, both in vivo and in vitro, are also well documented. In addition, a variety of other genotoxic effects in humans and experimental animals exposed to elevated levels of outdoor air pollution or samples derived from outdoor air pollution (e.g. PM and PM extracts) are also well documented (e.g. mutations, DNA strand breaks, stable DNA adducts, and oxidized nucleobases). Sustained inflammation is induced in humans and experimental animals exposed to elevated levels of outdoor air pollution or samples derived from outdoor air pollution.

Table 4.21 Summary by exposure of genetic and related effects in humans and experimental systems induced by exposure to outdoor air pollution or samples derived from outdoor air pollution

Agent	End-point induced	
	Human	Experimental systems[a]
Outdoor air pollution	Mutations[b], CAs, MN, SCEs, DNA strand breaks, oxidative DNA lesions, bulky DNA adducts	Somatic[c] and gametic[d] mutations, CAs in mice, MN in plants, bulky DNA adducts, DNA strand breaks, oxidized nucleobases
VOCs[e]	NE	
SVOCs[f]	NA	Somatic[b] and gametic[g] mutations, SCEs in murine cells, mutations in bacteria, DNA damage in bacteria
Airborne suspension of concentrated PM (CAPs)	DNA strand breaks, oxidative DNA lesions, oxidative stress, inflammation	NA
PM suspensions	Inflammation	Mutations in bacteria and mammalian cells, CAs in human cells, strand breaks in mammalian cells and naked DNA, ROS formation
Aqueous or acidic PM extracts	NA	DNA strand breaks in rat lung, MN and DNA strand breaks in human cells, oxidative DNA lesions, ROS formation in mammalian cells and in vitro
Organic solvent PM extracts	NA	CAs, MN, SCEs, DNA strand breaks, unscheduled DNA synthesis, bulky adducts, and oxidative DNA lesions in human cells. Mutations, CAs, aneuploidy, MN, SCEs, bulky adducts, oxidative DNA lesions, and ROS formation in mammalian cells. Nuclear and mitochondrial DNA mutations and mitotic recombination in yeast. Mutations and DNA damage in bacteria

[a] Includes experimental and in situ plant, animal, and insect exposures, exposures of human cells in vitro, exposures of mammalian cells in vitro, exposures of yeast and bacteria, and exposures of naked DNA.
[b] Single study of newborns in the Cracow region of Poland (see Section 4.2.1a).
[c] *Drosophila* and *Tradescantia* only.
[d] Mice and herring gulls exposed in situ.
[e] Operationally defined as substances that exist in vapour phase at ambient temperatures and pressures.
[f] Operationally defined as substances that exist partially in vapour phase at ambient temperatures and pressures. Balance adsorbed to PM.
[g] *Arabidopsis* only (seed exposure).
CAs, chromosomal aberrations; CAPs, concentrated ambient particles; MN, micronuclei; NA, not applicable; NE, not evaluated; PM, particulate matter; ROS, reactive oxygen species; SCEs, sister chromatid exchanges; SVOCs, semivolatile organic compounds; VOCs, volatile organic compounds.

Cross-sectional studies of humans lend support to the contention that alterations in the pattern of DNA methylation in circulating lymphocytes can be induced by exposure to high levels of outdoor air pollution (Hou et al., 2011).

Polluted outdoor air can contain a wide range of agents, and the PM fraction is known to contain several substances that can initiate tumour formation via genetic damage and mutation (e.g. PAHs and transition metals), as well as less-harmful constituents that induce responses that contribute to tumour promotion (e.g. inflammation). In sum, there is compelling evidence across species and experimental systems that exposure to air pollution PM is associated with increased levels of DNA damage, mutations, and chromosomal damage. Other mechanistic events include sustained proliferative signalling, evasion of growth suppression, resistance to cell death, stimulation of angiogenesis, replicative immortality, activation of invasion, and metastasis (see Supplemental Figure S4).

References

Abou Chakra OR, Joyeux M, Nerrière E, Strub MP, Zmirou-Navier D (2007). Genotoxicity of organic extracts of urban airborne particulate matter: an assessment within a personal exposure study. *Chemosphere*, 66(7):1375–81. doi:10.1016/j.chemosphere.2006.06.066 PMID:16901531

Adamkiewicz G, Ebelt S, Syring M, Slater J, Speizer FE, Schwartz J et al. (2004). Association between air pollution exposure and exhaled nitric oxide in an elderly population. *Thorax*, 59(3):204–9. doi:10.1136/thorax.2003.006445 PMID:14985553

Adamson IY, Prieditis H, Hedgecock C, Vincent R (2000). Zinc is the toxic factor in the lung response to an atmospheric particulate sample. *Toxicol Appl Pharmacol*, 166(2):111–9. doi:10.1006/taap.2000.8955 PMID:10896852

Adamson IY, Prieditis H, Vincent R (1999a). Pulmonary toxicity of an atmospheric particulate sample is due to the soluble fraction. *Toxicol Appl Pharmacol*, 157(1):43–50. doi:10.1006/taap.1999.8658 PMID:10329506

Adamson IY, Vincent R, Bjarnason SG (1999b). Cell injury and interstitial inflammation in rat lung after inhalation of ozone and urban particulates. *Am J Respir Cell Mol Biol*, 20(5):1067–72. doi:10.1165/ajrcmb.20.5.3468 PMID:10226078

Adonis M, Gil L (1993). Mutagenicity of organic extracts from Santiago (Chile) airborne particulate matter. *Mutat Res*, 292(1):51–61. doi:10.1016/0165-1161(93)90007-M PMID:7688097

Adonis M, Gil L (2000). Polycyclic aromatic hydrocarbon levels and mutagenicity of inhalable particulate matter in Santiago, Chile. *Inhal Toxicol*, 12(12):1173–83. doi:10.1080/08958370050198520 PMID:11114787

Agurell E, Stensman C (1992). *Salmonella* mutagenicity of three complex mixtures assayed with the microsuspension technique. A WHO/IPCS/CSCM study. *Mutat Res*, 276(1–2):87–91. doi:10.1016/0165-1110(92)90057-G PMID:1370111

al-Khodairy F, Al-Dakan A, Akel M, Hannan MA (1998). A comparative analysis of mutagenic activities of air samples collected from Riyadh before, during and after the Gulf War. *Int J Environ Health Res*, 8(1):15–22. doi:10.1080/09603129873615

Alfaro Moreno E, Flores Rojas G, Hartasanchez Frenk F, Orozco de la Huerta A, Quintana Belmares R, Osornio Vargas AR (1997). In vitro induction of abnormal anaphases by contaminating atmospheric dust from the City of Mexicali, Baja California, Mexico. *Arch Med Res*, 28(4):549–53. PMID:9428582

Alfaro-Moreno E, Martínez L, García-Cuellar C, Bonner JC, Murray JC, Rosas I et al. (2002). Biologic effects induced in vitro by PM_{10} from three different zones of Mexico City. *Environ Health Perspect*, 110(7):715–20. doi:10.1289/ehp.02110715 PMID:12117649

Alfheim I, Hongslo J, Moller M, Ramdahl T, Sortland B, Wikström L et al. (1984). Air pollution from aluminum smelting plants. II. The contribution from an aluminum smelting plant using the Söderberg process to polycyclic aromatic hydrocarbons and mutagens in ambient air. *Toxicol Environ Chem*, 8(2–3):195–212. doi:10.1080/02772248409357052

Alfheim I, Löfroth G, Møller M (1983). Bioassay of extracts of ambient particulate matter. *Environ Health Perspect*, 47:227–38. doi:10.1289/ehp.8347227 PMID:6186477

Alink GM, Smit HA, van Houdt JJ, Kolkman JR, Boleij JS (1983). Mutagenic activity of airborne particulates at non-industrial locations. *Mutat Res*, 116(1):21–34. doi:10.1016/0165-1218(83)90003-4 PMID:6828047

Allen RW, Carlsten C, Karlen B, Leckie S, van Eeden S, Vedal S et al. (2011). An air filter intervention study of endothelial function among healthy adults in a woodsmoke-impacted community. *Am J Respir Crit Care Med*, 183(9):1222–30. doi:10.1164/rccm.201010-1572OC PMID:21257787

American Thoracic Society (2000). American Thoracic Society. What constitutes an adverse health effect of air pollution? Official statement of the American Thoracic Society. *Am J Respir Crit Care Med*, 161(2 Pt 1):665–73. doi:10.1164/ajrccm.161.2.ats4-00 PMID:10673213

Anbazhagan M, Arumugam P, Ramesh A, Santhiya ST (2010). Genetic risk assessment in traffic policemen of Chennai City by sister chromatid exchange analysis. *Int J Hum Genet*, 10(4):251–5.

André E, Stoeger T, Takenaka S, Bahnweg M, Ritter B, Karg E et al. (2006). Inhalation of ultrafine carbon particles triggers biphasic pro-inflammatory response in the mouse lung. *Eur Respir J*, 28(2):275–85. doi:10.1183/09031936.06.00071205 PMID:16641123

Andrysík Z, Vondráček J, Marvanová S, Ciganek M, Neča J, Pěnčíková K et al. (2011). Activation of the aryl hydrocarbon receptor is the major toxic mode of action of an organic extract of a reference urban dust particulate matter mixture: the role of polycyclic aromatic hydrocarbons. *Mutat Res*, 714(1–2):53–62. doi:10.1016/j.mrfmmm.2011.06.011 PMID:21762708

Anwar WA, Kamal AAM (1988). Cytogenetic effects in a group of traffic policemen in Cairo. *Mutat Res*, 208(3–4):225–31. doi:10.1016/0165-7992(88)90065-6 PMID:2456461

Arayasiri M, Mahidol C, Navasumrit P, Autrup H, Ruchirawat M (2010). Biomonitoring of benzene and 1,3-butadiene exposure and early biological effects in traffic policemen. *Sci Total Environ*, 408(20):4855–62. doi:10.1016/j.scitotenv.2010.06.033 PMID:20627202

Ares J, Eckl PM, Raffelsberger I (2000). Genotoxicity at low level dose of inspirable urban ambient air particulate in a semiarid regime. *Environ Monit Assess*, 63(3):388–408. doi:10.1023/A:1006202307463

Arey J, Harger WP, Helmig D, Atkinson R (1992). Bioassay-directed fractionation of mutagenic PAH atmospheric photooxidation products and ambient particulate extracts. *Mutat Res*, 281(1):67–76. doi:10.1016/0165-7992(92)90038-J PMID:1371594

Arey J, Zielinska B, Harger WP, Atkinson R, Winer AM (1988). The contribution of nitrofluoranthenes and nitropyrenes to the mutagenic activity of ambient particulate organic matter collected in southern California. *Mutat Res*, 207(2):45–51. doi:10.1016/0165-7992(88)90040-1 PMID:3340093

Athanasiou K, Arzimanoglou I, Piccoli C, Yamasaki H, Arzimanoglou II (1987). Mutagenicity, sister chromatid exchange inducibility and in vitro cell transforming ability of particulates from Athens air. *Cell Biol Toxicol*, 3(3):251–61. doi:10.1007/BF00117863 PMID:3333731

Athanasiou K, Viras LG, Siskos PA (1986). Mutagenicity and polycyclic aromatic hydrocarbons analysis of ambient airborne particles collected in Athens, Greece. *Sci Total Environ*, 52(3):201–9. doi:10.1016/0048-9697(86)90120-8 PMID:3526551

Auger F, Gendron MC, Chamot C, Marano F, Dazy AC (2006). Responses of well-differentiated nasal epithelial cells exposed to particles: role of the epithelium in airway inflammation. *Toxicol Appl Pharmacol*, 215(3):285–94. doi:10.1016/j.taap.2006.03.002 PMID:16647095

Autrup H, Vestergaard AB (1996). Transplacental transfer of environmental genotoxins – polycyclic aromatic hydrocarbon-albumin in nonsmoking women. *Environ Health Perspect*, 104:Suppl 3: 625–7. PMID:8781394

Avogbe PH, Ayi-Fanou L, Autrup H, Loft S, Fayomi B, Sanni A et al. (2005). Ultrafine particulate matter and high-level benzene urban air pollution in relation to oxidative DNA damage. *Carcinogenesis*, 26(3):613–20. doi:10.1093/carcin/bgh353 PMID:15591089

Ayi-Fanou L, Avogbe PH, Fayomi B, Keith G, Hountondji C, Creppy EE et al. (2011). DNA-adducts in subjects exposed to urban air pollution by benzene and polycyclic aromatic hydrocarbons (PAHs) in Cotonou, Benin. *Environ Toxicol*, 26(1):93–102. doi:10.1002/tox.20533 PMID:20014405

Ayi Fanou L, Mobio TA, Creppy EE, Fayomi B, Fustoni S, Møller P et al. (2006). Survey of air pollution in Cotonou, Benin – air monitoring and biomarkers. *Sci Total Environ*, 358(1–3):85–96. doi:10.1016/j.scitotenv.2005.03.025 PMID:15916795

Baccarelli A, Wright RO, Bollati V, Tarantini L, Litonjua AA, Suh HH et al. (2009). Rapid DNA methylation changes after exposure to traffic particles. *Am J Respir Crit Care Med*, 179(7):572–8. doi:10.1164/rccm.200807-1097OC PMID:19136372

Bagate K, Meiring JJ, Gerlofs-Nijland ME, Vincent R, Cassee FR, Borm PJ (2004). Vascular effects of ambient particulate matter instillation in spontaneous hypertensive rats. *Toxicol Appl Pharmacol*, 197(1):29–39. doi:10.1016/j.taap.2004.02.005 PMID:15126072

Bagley ST, Stoltz SL, Becker DM, Keen RE (1992). Characterization of organic extracts from standard reference materials 1649, 'urban dust/organics,' and 1650, 'diesel particulate matter', using a microsuspension assay. A WHO/IPCS/CSCM study. *Mutat Res*, 276(1–2):81–6. doi:10.1016/0165-1110(92)90056-F PMID:1370110

Bagryantseva Y, Novotna B, Rossner P Jr, Chvatalova I, Milcova A, Svecova V et al. (2010). Oxidative damage to biological macromolecules in Prague bus drivers and garagemen: impact of air pollution and genetic polymorphisms. *Toxicol Lett*, 199(1):60–8. doi:10.1016/j.toxlet.2010.08.007 PMID:20723587

Bai JY, Zhang JD, Wang HB, Yang WM (1999). The genetic toxicity of the organic fractions of air particulates. *Chin J Publ Health*, 18:89–91.

Bai YP, Li J, Fan XY, Yao SQ, Jiang SF, Jin YL (2005). Effects of traffic air pollution on the rate of micronucleus and sister chromatid exchange of traffic police in a city. *Carcinog Teratog Mutagen*, 17(4):250–3. Available from: http://www.egh.net.cn/EN/Y2005/V17/I4/250.

Bailey MR, Fry FA, James AC (1985). Long-term retention of particles in the human respiratory tract. *J Aerosol Sci*, 16(4):295–305. doi:10.1016/0021-8502(85)90037-0

Ball JC, Straccia AM, Young WC, Aust AE (2000). The formation of reactive oxygen species catalyzed by neutral, aqueous extracts of NIST ambient particulate matter and diesel engine particles. *J Air Waste Manag Assoc*, 50(11):1897–903. doi:10.1080/10473289.2000.10464231 PMID:11111334

Barraza-Villarreal A, Sunyer J, Hernandez-Cadena L, Escamilla-Nuñez MC, Sienra-Monge JJ, Ramírez-Aguilar M et al. (2008). Air pollution, airway inflammation, and lung function in a cohort study of Mexico City schoolchildren. *Environ Health Perspect*, 116(6):832–8. doi:10.1289/ehp.10926 PMID:18560490

Baulig A, Sourdeval M, Meyer M, Marano F, Baeza-Squiban A (2003). Biological effects of atmospheric particles on human bronchial epithelial cells. Comparison with diesel exhaust particles. *Toxicol In Vitro*, 17(5–6):567–73. doi:10.1016/S0887-2333(03)00115-2 PMID:14599446

Becher R, Bucht A, Øvrevik J, Hongslo JK, Dahlman HJ, Samuelsen JT et al. (2007). Involvement of NADPH oxidase and iNOS in rodent pulmonary cytokine responses to urban air and mineral particles. *Inhal Toxicol*, 19(8):645–55. doi:10.1080/08958370701353528 PMID:17510837

Becker S, Dailey LA, Soukup JM, Grambow SC, Devlin RB, Huang YC (2005). Seasonal variations in air pollution particle-induced inflammatory mediator release and oxidative stress. *Environ Health Perspect*, 113(8):1032–8. doi:10.1289/ehp.7996 PMID:16079075

Becker S, Soukup JM, Gilmour MI, Devlin RB (1996). Stimulation of human and rat alveolar macrophages by urban air particulates: effects on oxidant radical generation and cytokine production. *Toxicol Appl*

Pharmacol, 141(2):637–48. doi:10.1006/taap.1996.0330 PMID:8975789

Beelen R, Hoek G, van den Brandt PA, Goldbohm RA, Fischer P, Schouten LJ et al. (2008a). Long-term exposure to traffic-related air pollution and lung cancer risk. *Epidemiology*, 19(5):702–10. doi:10.1097/EDE.0b013e318181b3ca PMID:18633326

Bennett WD, Zeman KL (2004). Effect of body size on breathing pattern and fine-particle deposition in children *J Appl Physiol (1985)*, 97(3):821–6.

Bennett WD, Zeman KL, Kim C (1996). Variability of fine particle deposition in healthy adults: effect of age and gender. *Am J Respir Crit Care Med*, 153(5):1641–7. doi:10.1164/ajrccm.153.5.8630615 PMID:8630615

Beskid O, Binkova B, Dusek Z, Rössner P, Solansky I, Kalina I et al. (2007). Chromosomal aberrations by fluorescence in situ hybridization (FISH) – biomarker of exposure to carcinogenic PAHs. *Mutat Res*, 620(1–2):62–70. doi:10.1016/j.mrfmmm.2007.02.023 PMID:17412370

Bind M-A, Baccarelli A, Zanobetti A, Tarantini L, Suh H, Vokonas P et al. (2012). Air pollution and markers of coagulation, inflammation, and endothelial function: associations and epigene-environment interactions in an elderly cohort. *Epidemiology*, 23(2):332–40. doi:10.1097/EDE.0b013e31824523f0 PMID:22237295

Binková B, Cerná M, Pastorková A, Jelínek R, Benes I, Novák J et al. (2003). Biological activities of organic compounds adsorbed onto ambient air particles: comparison between the cities of Teplice and Prague during the summer and winter seasons 2000–2001. *Mutat Res*, 525(1–2):43–59. doi:10.1016/S0027-5107(02)00312-3 PMID:12650904

Binková B, Chvatalova I, Lnenickova Z, Milcova A, Tulupova E, Farmer PB et al. (2007). PAH-DNA adducts in environmentally exposed population in relation to metabolic and DNA repair gene polymorphisms. *Mutat Res*, 620(1–2):49–61. doi:10.1016/j.mrfmmm.2007.02.022 PMID:17412371

Binková B, Lewtas J, Mísková I, Rössner P, Cerná M, Mrácková G et al. (1996). Biomarker studies in northern Bohemia. *Environ Health Perspect*, 104:Suppl 3: 591–7. doi:10.1289/ehp.96104s3591 PMID:8781388

Bolognesi C, Gallerani E, Bonatti S, De Ferrari M, Fontana V, Valerio F et al. (1997b). Sister chromatid exchange induction in peripheral blood lymphocytes of traffic police workers. *Mutat Res*, 394(1–3):37–44. doi:10.1016/S1383-5718(97)00121-6 PMID:9434841

Bolognesi C, Merlo F, Rabboni R, Valerio F, Abbondandolo A (1997a). Cytogenetic biomonitoring in traffic police workers: micronucleus test in peripheral blood lymphocytes. *Environ Mol Mutagen*, 30(4):396–402. doi:10.1002/(SICI)1098-2280(1997)30:4<396::AID-EM4>3.0.CO;2-H PMID:9435880

Bonetta S, Gianotti V, Bonetta S, Gosetti F, Oddone M, Gennaro MC et al. (2009). DNA damage in A549 cells exposed to different extracts of $PM_{2.5}$ from industrial, urban and highway sites. *Chemosphere*, 77(7):1030–4. doi:10.1016/j.chemosphere.2009.07.076 PMID:19729187

Bos I, De Boever P, Emmerechts J, Buekers J, Vanoirbeek J, Meeusen R et al. (2012). Changed gene expression in brains of mice exposed to traffic in a highway tunnel. *Inhal Toxicol*, 24(10):676–86. doi:10.3109/08958378.2012.714004 PMID:22906174

Brain JD (1970). Free cells in the lungs. Some aspects of their role, quantitation, and regulation. *Arch Intern Med*, 126(3):477–87. doi:10.1001/archinte.1970.00310090107013 PMID:4915938

Bräuner EV, Forchhammer L, Møller P, Barregard L, Gunnarsen L, Afshari A et al. (2008a). Indoor particles affect vascular function in the aged: an air filtration-based intervention study. *Am J Respir Crit Care Med*, 177(4):419–25. doi:10.1164/rccm.200704-632OC PMID:17932377

Bräuner EV, Forchhammer L, Møller P, Simonsen J, Glasius M, Wåhlin P et al. (2007). Exposure to ultrafine particles from ambient air and oxidative stress-induced DNA damage. *Environ Health Perspect*, 115(8):1177–82. doi:10.1289/ehp.9984 PMID:17687444

Bräuner EV, Møller P, Barregard L, Dragsted LO, Glasius M, Wåhlin P et al. (2008b). Exposure to ambient concentrations of particulate air pollution does not influence vascular function or inflammatory pathways in young healthy individuals. *Part Fibre Toxicol*, 5(1):13 doi:10.1186/1743-8977-5-13 PMID:18837984

Bridgewater LC, Manning FC, Patierno SR (1994). Base-specific arrest of *in vitro* DNA replication by carcinogenic chromium: relationship to DNA interstrand crosslinking. *Carcinogenesis*, 15(11):2421–7. doi:10.1093/carcin/15.11.2421 PMID:7955085

Brits E, Schoeters G, Verschaeve L (2004). Genotoxicity of PM_{10} and extracted organics collected in an industrial, urban and rural area in Flanders, Belgium. *Environ Res*, 96(2):109–18. doi:10.1016/j.envres.2004.03.006 PMID:15325871

Bronzetti G, Cini M, Paoli M, Ciacchini G, Giaconi V, Morichetti E (1997). Mutagenicity and chemical analysis of airborne particulate matter collected in Pisa. *J Environ Pathol Toxicol Oncol*, 16(2–3):147–56. PMID:9275995

Brook RD (2008). Cardiovascular effects of air pollution. *Clin Sci (Lond)*, 115(6):175–87. doi:10.1042/CS20070444 PMID:18691154

Brook RD, Brook JR, Urch B, Vincent R, Rajagopalan S, Silverman F (2002). Inhalation of fine particulate air pollution and ozone causes acute arterial vasoconstriction in healthy adults. *Circulation*, 105(13):1534–6. doi:10.1161/01.CIR.0000013838.94747.64 PMID:11927516

Brook RD, Jerrett M, Brook JR, Bard RL, Finkelstein MM (2008). The relationship between diabetes mellitus and traffic-related air pollution. *J Occup Environ*

Med, 50(1):32–8. doi:10.1097/JOM.0b013e31815dba70 PMID:18188079

Brook RD, Rajagopalan S, Pope CA 3rd, Brook JR, Bhatnagar A, Diez-Roux AV et al.; American Heart Association Council on Epidemiology and Prevention, Council on the Kidney in Cardiovascular Disease, and Council on Nutrition, Physical Activity and Metabolism (2010). Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. *Circulation*, 121(21):2331–78. doi:10.1161/CIR.0b013e3181dbece1 PMID:20458016

Brown DM, Donaldson K, Stone V (2004). Effects of PM_{10} in human peripheral blood monocytes and J774 macrophages. *Respir Res*, 5(1):29 doi:10.1186/1465-9921-5-29 PMID:15613243

Brown DM, Hutchison L, Donaldson K, Stone V (2007). The effects of PM_{10} particles and oxidative stress on macrophages and lung epithelial cells: modulating effects of calcium-signaling antagonists. *Am J Physiol Lung Cell Mol Physiol*, 292(6):L1444–51. doi:10.1152/ajplung.00162.2006 PMID:17369293

Brown LE, Trought KR, Bailey CI, Clemons JH (2005). 2,3,7,8-TCDD equivalence and mutagenic activity associated with PM_{10} from three urban locations in New Zealand. *Sci Total Environ*, 349(1–3):161–74. doi:10.1016/j.scitotenv.2005.01.008 PMID:16198678

Burgaz S, Demircigil GC, Karahalil B, Karakaya AE (2002). Chromosomal damage in peripheral blood lymphocytes of traffic policemen and taxi drivers exposed to urban air pollution. *Chemosphere*, 47(1):57–64. doi:10.1016/S0045-6535(01)00185-0 PMID:11996136

Buschini A, Cassoni F, Anceschi E, Pasini L, Poli P, Rossi C (2001). Urban airborne particulate: genotoxicity evaluation of different size fractions by mutagenesis tests on microorganisms and comet assay. *Chemosphere*, 44(8):1723–36. doi:10.1016/S0045-6535(00)00550-6 PMID:11534904

Buthbumrung N, Mahidol C, Navasumrit P, Promvijit J, Hunsonti P, Autrup H et al. (2008). Oxidative DNA damage and influence of genetic polymorphisms among urban and rural schoolchildren exposed to benzene. *Chem Biol Interact*, 172(3):185–94. doi:10.1016/j.cbi.2008.01.005 PMID:18282563

Byun H-M, Panni T, Motta V, Hou L, Nordio F, Apostoli P et al. (2013). Effects of airborne pollutants on mitochondrial DNA methylation. *Part Fibre Toxicol*, 10(1):18 doi:10.1186/1743-8977-10-18 PMID:23656717

Calderón-Garcidueñas L, Osnaya N, Rodríguez-Alcaraz A, Villarreal-Calderón A (1997). DNA damage in nasal respiratory epithelium from children exposed to urban pollution. *Environ Mol Mutagen*, 30(1):11–20. doi:10.1002/(SICI)1098-2280(1997)30:1<11::AID-EM3>3.0.CO;2-F PMID:9258325

Calderón-Garcidueñas L, Osnaya-Brizuela N, Ramirez-Martinez L, Villarreal-Calderon A (1996). DNA strand breaks in human nasal respiratory epithelium are induced upon exposure to urban pollution. *Environ Health Perspect*, 104(2):160–8. PMID:8820583

Calderón-Garcidueñas L, Villarreal-Calderon R, Valencia-Salazar G, Henríquez-Roldán C, Gutiérrez-Castrellón P, Torres-Jardón R et al. (2008). Systemic inflammation, endothelial dysfunction, and activation in clinically healthy children exposed to air pollutants. *Inhal Toxicol*, 20(5):499–506. doi:10.1080/08958370701864797 PMID:18368620

Calderón-Garcidueñas L, Wen-Wang L, Zhang YJ, Rodriguez-Alcaraz A, Osnaya N, Villarreal-Calderón A et al. (1999). 8-hydroxy-2′-deoxyguanosine, a major mutagenic oxidative DNA lesion, and DNA strand breaks in nasal respiratory epithelium of children exposed to urban pollution. *Environ Health Perspect*, 107(6):469–74. PMID:10339447

Calderón-Segura ME, Gómez-Arroyo S, Villalobos-Pietrini R, Butterworth FM, Amador-Muñoz O (2004). The effects of seasonal weather on the genotoxicity, cytokinetic properties, cytotoxicity and organochemical content of extracts of airborne particulates in Mexico City. *Mutat Res*, 558(1–2):7–17. doi:10.1016/j.mrgentox.2003.10.018 PMID:15036114

Carere A, Andreoli C, Galati R, Leopardi P, Marcon F, Rosati MV et al. (2002). Biomonitoring of exposure to urban air pollutants: analysis of sister chromatid exchanges and DNA lesions in peripheral lymphocytes of traffic policemen. *Mutat Res*, 518(2):215–24. doi:10.1016/S1383-5718(02)00108-0 PMID:12113772

Carey IM, Atkinson RW, Kent AJ, van Staa T, Cook DG, Anderson HR (2013). Mortality associations with long-term exposure to outdoor air pollution in a national English cohort. *Am J Respir Crit Care Med*, 187(11):1226–33. doi:10.1164/rccm.201210-1758OC PMID:23590261

Carreras HA, Calderón-Segura ME, Gómez-Arroyo S, Murillo-Tovar MA, Amador-Muñoz O (2013). Composition and mutagenicity of PAHs associated with urban airborne particles in Córdoba, Argentina. *Environ Pollut*, 178:403–10. doi:10.1016/j.envpol.2013.03.016 PMID:23624338

Casellas M, Fernandez P, Bayona JM, Solanas AM (1995). Bioassay-directed chemical analysis of genotoxic components in urban airborne particulate matter from Barcelona (Spain). *Chemosphere*, 30(4):725–40. doi:10.1016/0045-6535(94)00438-Z PMID:7889349

Cassee FR, Boere AJ, Fokkens PH, Leseman DL, Sioutas C, Kooter IM et al. (2005). Inhalation of concentrated particulate matter produces pulmonary inflammation and systemic biological effects in compromised rats. *J Toxicol Environ Health A*, 68(10):773–96. doi:10.1080/15287390590930171 PMID:16020176

Cavallo D, Ursini CL, Carelli G, Iavicoli I, Ciervo A, Perniconi B et al. (2006). Occupational exposure in airport personnel: characterization and evaluation

of genotoxic and oxidative effects. *Toxicology*, 223(1–2):26–35. doi:10.1016/j.tox.2006.03.003 PMID:16621217

Cavanagh JA, Trought K, Brown L, Duggan S (2009). Exploratory investigation of the chemical characteristics and relative toxicity of ambient air particulates from two New Zealand cities. *Sci Total Environ*, 407(18):5007–18. doi:10.1016/j.scitotenv.2009.05.020 PMID:19570565

Cebulska-Wasilewska A, Wiecheć A, Panek A, Binková B, Srám RJ, Farmer PB (2005). Influence of environmental exposure to PAHs on the susceptibility of lymphocytes to DNA-damage induction and on their repair capacity. *Mutat Res*, 588(2):73–81. doi:10.1016/j.mrgentox.2005.08.013 PMID:16311068

Černá M, Pastorková A, Vrbíková V, Smíd J, Rössner P (1999). Mutagenicity monitoring of airborne particulate matter (PM_{10}) in the Czech Republic. *Mutat Res*, 444(2):373–86. doi:10.1016/S1383-5718(99)00107-2 PMID:10521677

Cesaroni G, Badaloni C, Gariazzo C, Stafoggia M, Sozzi R, Davoli M et al. (2013). Long-term exposure to urban air pollution and mortality in a cohort of more than a million adults in Rome. *Environ Health Perspect*, 121(3):324–31. doi:10.1289/ehp.1205862 PMID:23308401

Chandrasekaran R, Samy PL, Murthy PB (1996). Increased sister chromatid exchange (SCE) frequencies in lymphocytes from traffic policemen exposed to automobile exhaust pollution. *Hum Exp Toxicol*, 15(4):301–4. doi:10.1177/096032719601500405 PMID:8845219

Chen CH, Lu YM, Zhang KJ (1999). Analysis of chromosome aberration in peripheral blood lymphocytes from traffic policemen. *J Hyg Res*, 6:324–5.

Chen ST, Lin CC, Liu YS, Lin C, Hung PT, Jao CW et al. (2013). Airborne particulate collected from central Taiwan induces DNA strand breaks, poly(ADP-ribose) polymerase-1 activation, and estrogen-disrupting activity in human breast carcinoma cell lines. *J Environ Sci Health A Tox Hazard Subst Environ Eng*, 48(2):173–81. doi:10.1080/10934529.2012.717809 PMID:23043339

Ciganek M, Neca J, Adamec V, Janosek J, Machala M (2004). A combined chemical and bioassay analysis of traffic-emitted polycyclic aromatic hydrocarbons. *Sci Total Environ*, 334–335:141–8. doi:10.1016/j.scitotenv.2004.04.034 PMID:15504500

Clarke RW, Catalano P, Coull B Koutrakis P, Krishna Murthy GG, Rice T et al. (2000a). Age-related responses in rats to concentrated urban air particles (CAPs). *Inhal Toxicol*, 12:73–84. doi:10.1080/089583700196400

Clarke RW, Catalano PJ, Koutrakis P, Murthy GG, Sioutas C, Paulauskis J et al. (1999). Urban air particulate inhalation alters pulmonary function and induces pulmonary inflammation in a rodent model of chronic bronchitis. *Inhal Toxicol*, 11(8):637–56. doi:10.1080/089583799196781 PMID:10477440

Clarke RW, Coull B, Reinisch U, Catalano P, Killingsworth CR, Koutrakis P et al. (2000b). Inhaled concentrated ambient particles are associated with hematologic and bronchoalveolar lavage changes in canines. *Environ Health Perspect*, 108(12):1179–87. doi:10.1289/ehp.001081179 PMID:11133399

Claxton LD, Warren S, Zweidinger R, Creason J (2001). A comparative assessment of Boise, Idaho, ambient air fine particle samples using the plate and microsuspension *Salmonella* mutagenicity assays. *Sci Total Environ*, 275(1–3):95–108. doi:10.1016/S0048-9697(00)00857-3 PMID:11482407

Claxton LD, Woodall GM Jr (2007). A review of the mutagenicity and rodent carcinogenicity of ambient air. *Mutat Res*, 636(1–3):36–94. doi:10.1016/j.mrrev.2007.01.001 PMID:17451995

Commoner B, Madyastha R, Bronsdon A, Vithayathil AJ (1978). Environmental mutagens in urban air particulates. *J Toxicol Environ Health*, 4(1):59–77. doi:10.1080/15287397809529645 PMID:633412

Coronas MV, Pereira TS, Rocha JA, Lemos AT, Fachel JM, Salvadori DM et al. (2009). Genetic biomonitoring of an urban population exposed to mutagenic airborne pollutants. *Environ Int*, 35(7):1023–9. doi:10.1016/j.envint.2009.05.001 PMID:19500845

Costa DL, Lehmann JR, Winsett D, Richards J, Ledbetter AD, Dreher KL (2006). Comparative pulmonary toxicological assessment of oil combustion particles following inhalation or instillation exposure. *Toxicol Sci*, 91(1):237–46. doi:10.1093/toxsci/kfj123 PMID:16449252

Courtois YA, Min S, Lachenal C, Jacquot-Deschamps JM, Callais F, Festy B (1988). Genotoxicity of organic extracts from atmospheric particles. *Ann N Y Acad Sci*, 534:724–40. doi:10.1111/j.1749-6632.1988.tb30162.x PMID:3389685

Crebelli R (1989). Monitoring of urban air pollution by mutagenicity assays. *Ann Ist Super Sanita*, 25(4):591–4. PMID:2631625

Crebelli R, Fuselli S, Baldassarri LT, Ziemacki G, Carere A, Benigni R (1995). Genotoxicity of urban air particulate matter: correlations between mutagenicity data, airborne micropollutants, and meteorological parameters. *Int J Environ Health Res*, 5(1):19–34. doi:10.1080/09603129509356830

Crebelli R, Fuselli S, Meneguz A, Aquilina G, Conti L, Leopardi P et al. (1988). In vitro and in vivo mutagenicity studies with airborne particulate extracts. *Mutat Res*, 204(4):565–75. doi:10.1016/0165-1218(88)90059-6 PMID:3280990

Cui YQ, Ji XY, Chen CM et al. (1991). Mutagenic effect of air pollution on human chorionic villi: an analysis of 2698 cases. *Carcinog Teratog Mutagen*, 13:6–10.

Daisey JM, Kneip TJ, Hawryluk I, Mukai F (1980). Seasonal variations in the bacterial mutagenicity of airborne particulate organic matter in New York City. *Environ*

Sci Technol, 14(12):1487–90. doi:10.1021/es60172a001 PMID:22279993

Danielsen PH, Loft S, Jacobsen NR, Jensen KA, Autrup H, Ravanat JL et al. (2010). Oxidative stress, inflammation, and DNA damage in rats after intratracheal instillation or oral exposure to ambient air and wood smoke particulate matter. *Toxicol Sci*, 118(2):574–85. doi:10.1093/toxsci/kfq290 PMID:20864625

Danielsen PH, Loft S, Kocbach A, Schwarze PE, Møller P (2009). Oxidative damage to DNA and repair induced by Norwegian wood smoke particles in human A549 and THP-1 cell lines. *Mutat Res*, 674(1–2):116–22. doi:10.1016/j.mrgentox.2008.10.014 PMID:19041418

Danielsen PH, Loft S, Møller P (2008). DNA damage and cytotoxicity in type II lung epithelial (A549) cell cultures after exposure to diesel exhaust and urban street particles. *Part Fibre Toxicol*, 5(1):6 doi:10.1186/1743-8977-5-6 PMID:18397523

Danielsen PH, Møller P, Jensen KA, Sharma AK, Wallin H, Bossi R et al. (2011). Oxidative stress, DNA damage, and inflammation induced by ambient air and wood smoke particulate matter in human A549 and THP-1 cell lines. *Chem Res Toxicol*, 24(2):168–84. doi:10.1021/tx100407m PMID:21235221

de Andrade SJ, Varella SD, Pereira GT, Zocolo GJ, de Marchi MR, Varanda EA (2011). Mutagenic activity of airborne particulate matter (PM_{10}) in a sugarcane farming area (Araraquara city, southeast Brazil). *Environ Res*, 111(4):545–50. doi:10.1016/j.envres.2011.03.004 PMID:21481367

De Coster S, Koppen G, Bracke M, Schroijen C, Den Hond E, Nelen V et al. (2008). Pollutant effects on genotoxic parameters and tumor-associated protein levels in adults: a cross sectional study. *Environ Health*, 7(1):26 doi:10.1186/1476-069X-7-26 PMID:18522717

De Flora S, Bagnasco M, Izzotti A, D'Agostini F, Pala M, Valerio F (1989). Mutagenicity of polycyclic aromatic hydrocarbon fractions extracted from urban air particulates. *Mutat Res*, 224(2):305–18. doi:10.1016/0165-1218(89)90169-9 PMID:2677712

de Raat WK (1983). Genotoxicity of aerosol extracts. Some methodological aspects and the contribution of urban and industrial locations. *Mutat Res*, 116(1):47–63. doi:10.1016/0165-1218(83)90005-8 PMID:6298617

de Raat WK, de Meijere FA (1988). The mutagenicity of ambient air particles from local traffic and distant sources during episodes with moderate photochemical air pollution. *Sci Total Environ*, 73(3):159–79. doi:10.1016/0048-9697(88)90426-3 PMID:2463671

de Raat WK, de Meijere FA, Kooijman SALM (1985). Mutagenicity of ambient aerosol collected in an urban and industrial area of The Netherlands. *Sci Total Environ*, 44(1):17–33. doi:10.1016/0048-9697(85)90048-8 PMID:3895434

De Vizcaya-Ruiz A, Gutierrez-Castillo ME, Uribe-Ramirez M, Cebrián ME, Mugica-Alvarez V, Sepúlveda J et al. (2006). Characterization and in vitro biological effects of concentrated particulate matter from Mexico City. *Atmos Environ*, 40:Suppl 2: 583–92. doi:10.1016/j.atmosenv.2005.12.073

Delfino RJ, Sioutas C, Malik S (2005). Potential role of ultrafine particles in associations between airborne particle mass and cardiovascular health. *Environ Health Perspect*, 113(8):934–46. doi:10.1289/ehp.7938 PMID:16079061

Delfino RJ, Staimer N, Tjoa T, Arhami M, Polidori A, Gillen DL et al. (2010a). Associations of primary and secondary organic aerosols with airway and systemic inflammation in an elderly panel cohort. *Epidemiology*, 21(6):892–902. doi:10.1097/EDE.0b013e3181f20e6c PMID:20811287

Delfino RJ, Staimer N, Tjoa T, Arhami M, Polidori A, Gillen DL et al. (2010b). Association of biomarkers of systemic inflammation with organic components and source tracers in quasi-ultrafine particles. *Environ Health Perspect*, 118(6):756–62. doi:10.1289/ehp.0901407 PMID:20123637

Delfino RJ, Staimer N, Tjoa T, Gillen DL, Polidori A, Arhami M et al. (2009). Air pollution exposures and circulating biomarkers of effect in a susceptible population: clues to potential causal component mixtures and mechanisms. *Environ Health Perspect*, 117(8):1232–8. doi:10.1289/ehp.0800194 PMID:19672402

Delfino RJ, Staimer N, Tjoa T, Polidori A, Arhami M, Gillen DL et al. (2008). Circulating biomarkers of inflammation, antioxidant activity, and platelet activation are associated with primary combustion aerosols in subjects with coronary artery disease. *Environ Health Perspect*, 116(7):898–906. doi:10.1289/ehp.11189 PMID:18629312

Dellinger B, Pryor WA, Cueto R, Squadrito GL, Hegde V, Deutsch WA (2001). Role of free radicals in the toxicity of airborne fine particulate matter. *Chem Res Toxicol*, 14(10):1371–7. doi:10.1021/tx010050x PMID:11599928

Demetriou CA, Raaschou-Nielsen O, Loft S, Møller P, Vermeulen R, Palli D et al. (2012). Biomarkers of ambient air pollution and lung cancer: a systematic review. *Occup Environ Med*, 69(9):619–27. doi:10.1136/oemed-2011-100566 PMID:22773658

Di Cesare M, Khang YH, Asaria P, Blakely T, Cowan MJ, Farzadfar F et al.; Lancet NCD Action Group (2013). Inequalities in non-communicable diseases and effective responses. *Lancet*, 381(9866):585–97. doi:10.1016/S0140-6736(12)61851-0 PMID:23410608

Di Pietro A, Visalli G, Munaò F, Baluce B, La Maestra S, Primerano P et al. (2009). Oxidative damage in human epithelial alveolar cells exposed in vitro to oil fly ash transition metals. *Int J Hyg Environ Health*, 212(2):196–208. doi:10.1016/j.ijheh.2008.05.005 PMID:18667355

Dick CA, Singh P, Daniels M, Evansky P, Becker S, Gilmour MI (2003). Murine pulmonary inflammatory responses following instillation of size-fractionated

ambient particulate matter. *J Toxicol Environ Health A*, 66(23):2193–207. doi:10.1080/716100636 PMID:14669776

Ding GW, Wang WJ, Wang XY (1999). Research on genotoxicity of TSP in various functional regions of Lanzhou city. *J Lanzhou Med Coll*, 25:17–20.

Don Porto Carero A, Hoet PHM, Verschaeve L, Schoeters G, Nemery B (2001). Genotoxic effects of carbon black particles, diesel exhaust particles, and urban air particulates and their extracts on a human alveolar epithelial cell line (A549) and a human monocytic cell line (THP-1). *Environ Mol Mutagen*, 37(2):155–63. doi:10.1002/em.1023 PMID:11246222

Donaldson K, Brown DM, Mitchell C, Dineva M, Beswick PH, Gilmour P et al. (1997). Free radical activity of PM_{10}: iron-mediated generation of hydroxyl radicals. *Environ Health Perspect*, 105:Suppl 5: 1285–9. PMID:9400739

Du Four VA, Van Larebeke N, Janssen CR (2004). Genotoxic and mutagenic activity of environmental air samples in Flanders, Belgium. *Mutat Res*, 558(1–2):155–67. doi:10.1016/j.mrgentox.2003.12.002 PMID:15036129

Duffin R, Tran L, Brown D, Stone V, Donaldson K (2007). Proinflammogenic effects of low-toxicity and metal nanoparticles in vivo and in vitro: highlighting the role of particle surface area and surface reactivity. *Inhal Toxicol*, 19(10):849–56. doi:10.1080/08958370701479323 PMID:17687716

Durant JL, Lafleur AL, Plummer EF, Taghizadeh K, Busby WF, Thilly WG (1998). Human lymphoblast mutagens in urban airborne particles. *Environ Sci Technol*, 32(13):1894–906. doi:10.1021/es9706965

Dwivedi S, Saquib Q, Al-Khedhairy AA, Ali AY, Musarrat J (2012). Characterization of coal fly ash nanoparticles and induced oxidative DNA damage in human peripheral blood mononuclear cells. *Sci Total Environ*, 437:331–8. doi:10.1016/j.scitotenv.2012.08.004 PMID:22960109

Dybdahl M, Risom L, Bornholdt J, Autrup H, Loft S, Wallin H (2004). Inflammatory and genotoxic effects of diesel particles in vitro and in vivo. *Mutat Res*, 562(1–2):119–31. doi:10.1016/j.mrgentox.2004.05.010 PMID:15279835

Eichhorn GL, Shin YA (1968). Interaction of metal ions with polynucleotides and related compounds. XII. The relative effect of various metal ions on DNA helicity. *J Am Chem Soc*, 90(26):7323–8. doi:10.1021/ja01028a024 PMID:5725551

Elassouli SM, Alqahtani MH, Milaat W (2007). Genotoxicity of air borne particulates assessed by comet and the *Salmonella* mutagenicity test in Jeddah, Saudi Arabia. *Int J Environ Res Public Health*, 4(3):216–33. doi:10.3390/ijerph2007030004 PMID:17911660

EPA (2006). Report on air quality in nonattainment areas for 2003–2005 covering ozone, particulate matter, carbon monoxide, sulfur dioxide, nitrogen dioxide, and lead. Research Triangle Park (NC): US Environmental Protection Agency.

EPA (2009). Integrated science assessment for particulate matter (Final Report). EPA/600/R-08/139F. Washington (DC): US Environmental Protection Agency. Available from: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=216546.

Epton MJ, Dawson RD, Brooks WM, Kingham S, Aberkane T, Cavanagh JA et al. (2008). The effect of ambient air pollution on respiratory health of school children: a panel study. *Environ Health*, 7(1):16 doi:10.1186/1476-069X-7-16 PMID:18479529

Erdinger L, Dürr M, Höpker KA (2005). Correlations between mutagenic activity of organic extracts of airborne particulate matter, NO_x and sulphur dioxide in southern Germany: results of a two-year study. *Environ Sci Pollut Res Int*, 12(1):10–20. doi:10.1065/espr2004.04.196 PMID:15768736

Espinosa-Aguirre JJ, Reyes RE, Rubio J, Ostrosky-Wegman P, Martinez G (1993). Mutagenic activity of urban air samples and its modulation by chili extracts. *Mutat Res*, 303(2):55–61. doi:10.1016/0165-7992(93)90095-D PMID:7692278

Evenson DP, Jost LK, Marshall D, Zinaman MJ, Clegg E, Purvis K et al. (1999). Utility of the sperm chromatin structure assay as a diagnostic and prognostic tool in the human fertility clinic. *Hum Reprod*, 14(4):1039–49. doi:10.1093/humrep/14.4.1039 PMID:10221239

Fabiani R, De Bartolomeo A, Rosignoli P, Morozzi G, Cecinato A, Balducci C (2008). Chemical and toxicological characterization of airborne total suspended particulate (TSP) and PM_{10} organic extracts. *Polycycl Aromat Compd*, 28(4–5):486–99. doi:10.1080/10406630802377948

Farina F, Sancini G, Mantecca P, Gallinotti D, Camatini M, Palestini P (2011). The acute toxic effects of particulate matter in mouse lung are related to size and season of collection. *Toxicol Lett*, 202(3):209–17. doi:10.1016/j.toxlet.2011.01.031 PMID:21371539

Ferreira MI, Domingos M, Gomes HA, Saldiva PH, de Assunção JV (2007). Evaluation of mutagenic potential of contaminated atmosphere at Ibirapuera Park, São Paulo - SP, Brazil, using the *Tradescantia* stamen-hair assay. *Environ Pollut*, 145(1):219–24. doi:10.1016/j.envpol.2006.03.013 PMID:16777295

Ferreira MI, Petrenko H, Lobo DJ, Rodrigues GS, Moreira A, Saldiva PH (2000). In situ monitoring of the mutagenic effects of the gaseous emissions of a solid waste incinerator in metropolitan São Paulo, Brazil, using the *Tradescantia* stamen-hair assay. *J Air Waste Manag Assoc*, 50(10):1852–6. doi:10.1080/10473289.2000.10464217 PMID:11288313

Ferreira MI, Rodrigues GS, Domingos M, Saldiva PHDN (2003). In situ monitoring of mutagenicity of air pollutants in São Paulo city using *Tradescantia*-SHM bioassay.

Braz Arch Biol Technol, 46(2):253–8. doi:10.1590/S1516-89132003000200017

Festy B, Coviaux F, Le Moullec Y, Juguet B, Person A, Courtois Y (1984). Potential toxicity of urban air contamination by inert particles [in French]. *Ann Pharm Fr*, 42(6):519–28. PMID:6535427

Festy LP (1980). Biological activity of organic extracts from atmospheric particles in urban air. *Pollut Atmos*, 22:50–7.

Flessel CP, Guirguis GN, Cheng JC, Chang K-I, Hahn ES, Twiss SA et al. (1985). Sources of mutagens in Contra Costa County community aerosols during pollution episodes: diurnal variations and relations to source emissions tracers. *Environ Int*, 11(2–4):293–301. doi:10.1016/0160-4120(85)90021-2

Fortoul TI, Rojas-Lemus M, Avila-Casado MC, Rodriguez-Lara V, Montaño LF, Muñoz-Comonfort A et al. (2010). Endogenous antioxidants and nasal human epithelium response to air pollutants: genotoxic and inmmuno-cytochemical evaluation. *J Appl Toxicol*, 30(7):661–5. doi:10.1002/jat.1538 PMID:20981858

Frampton MW, Ghio AJ, Samet JM, Carson JL, Carter JD, Devlin RB (1999). Effects of aqueous extracts of PM_{10} filters from the Utah Valley on human airway epithelial cells. *Am J Physiol*, 277(5 Pt 1):L960–7. PMID:10564181

Freedman AP, Robinson SE (1988). Noninvasive magnetopneumographic studies of lung dust retention and clearance in coal miners. In: Frantz RL, Ramani RV, editors. Respirable dust in the mineral industries: health effects, characterization and control. University Park (PA): Penn State University Press; pp. 181–6.

Fujii T, Hayashi S, Hogg JC, Mukae H, Suwa T, Goto Y et al. (2002). Interaction of alveolar macrophages and airway epithelial cells following exposure to particulate matter produces mediators that stimulate the bone marrow. *Am J Respir Cell Mol Biol*, 27(1):34–41. doi:10.1165/ajrcmb.27.1.4787 PMID:12091243

Fujii T, Hayashi S, Hogg JC, Vincent R, Van Eeden SF (2001). Particulate matter induces cytokine expression in human bronchial epithelial cells. *Am J Respir Cell Mol Biol*, 25(3):265–71. doi:10.1165/ajrcmb.25.3.4445 PMID:11588002

Gábelová A, Valovicová Z, Horváthová E, Slamenová D, Binková B, Srám RJ et al. (2004). Genotoxicity of environmental air pollution in three European cities: Prague, Kosice and Sofia. *Mutat Res*, 563(1):49–59. doi:10.1016/j.mrgentox.2004.05.014 PMID:15324748

Gábelová A, Valovicová Z, Lábaj J, Bacová G, Binková B, Farmer PB (2007). Assessment of oxidative DNA damage formation by organic complex mixtures from airborne particles PM_{10}. *Mutat Res*, 620(1–2):135–44. doi:10.1016/j.mrfmmm.2007.03.003 PMID:17403525

Galati R, Zijno A, Crebelli R, Falasca G, Tomei F, Iecher F et al. (2001). Detection of antibodies to the benzo(a) pyrene diol epoxide-DNA adducts in sera from individuals exposed to low doses of polycyclic aromatic hydrocarbons. *J Exp Clin Cancer Res*, 20(3):359–64. PMID:11718215

Gallagher JE, Jackson MA, George MH, Lewtas J (1990). Dose-related differences in DNA adduct levels in rodent tissues following skin application of complex mixtures from air pollution sources. *Carcinogenesis*, 11(1):63–8. doi:10.1093/carcin/11.1.63 PMID:2403860

García-Suástegui WA, Huerta-Chagoya A, Carrasco-Colín KL, Pratt MM, John K, Petrosyan P et al. (2011). Seasonal variations in the levels of PAH-DNA adducts in young adults living in Mexico City. *Mutagenesis*, 26(3):385–91. doi:10.1093/mutage/geq104 PMID:21193517

Garçon G, Dagher Z, Zerimech F, Ledoux F, Courcot D, Aboukais A et al. (2006). Dunkerque City air pollution particulate matter-induced cytotoxicity, oxidative stress and inflammation in human epithelial lung cells (L132) in culture. *Toxicol In Vitro*, 20(4):519–28. doi:10.1016/j.tiv.2005.09.012 PMID:16298102

Gavett SH, Haykal-Coates N, Highfill JW, Ledbetter AD, Chen LC, Cohen MD et al. (2003). World Trade Center fine particulate matter causes respiratory tract hyperresponsiveness in mice. *Environ Health Perspect*, 111(7):981–91. doi:10.1289/ehp.5931 PMID:12782502

Gerlofs-Nijland ME, Boere AJ, Leseman DL, Dormans JA, Sandström T, Salonen RO et al. (2005). Effects of particulate matter on the pulmonary and vascular system: time course in spontaneously hypertensive rats. *Part Fibre Toxicol*, 2(1):2 doi:10.1186/1743-8977-2-2 PMID:15813961

Gerlofs-Nijland ME, Dormans JA, Bloemen HJ, Leseman DL, John A, Boere F et al. (2007). Toxicity of coarse and fine particulate matter from sites with contrasting traffic profiles. *Inhal Toxicol*, 19(13):1055–69. doi:10.1080/08958370701626261 PMID:17957546

Ghio AJ, Devlin RB (2001). Inflammatory lung injury after bronchial instillation of air pollution particles. *Am J Respir Crit Care Med*, 164(4):704–8. doi:10.1164/ajrccm.164.4.2011089 PMID:11520740

Ghio AJ, Kim C, Devlin RB (2000). Concentrated ambient air particles induce mild pulmonary inflammation in healthy human volunteers. *Am J Respir Crit Care Med*, 162(3 Pt 1):981–8. doi:10.1164/ajrccm.162.3.9911115 PMID:10988117

Ghio AJ, Stonehuerner J, Dailey LA, Carter JD (1999). Metals associated with both the water-soluble and insoluble fractions of an ambient air pollution particle catalyze an oxidative stress. *Inhal Toxicol*, 11(1):37–49. doi:10.1080/089583799197258 PMID:10380158

Ghio AJ, Suliman HB, Carter JD, Abushamaa AM, Folz RJ (2002). Overexpression of extracellular superoxide dismutase decreases lung injury after exposure to oil fly ash. *Am J Physiol Lung Cell Mol Physiol*, 283(1):L211–8. doi:10.1152/ajplung.00409.2001 PMID:12060579

Gil L, Cáceres D, Adonis M (1997). Influence of atmospheric air pollution on indoor air quality: comparison

of chemical pollutants and mutagenicity levels in Santiago (Chile). *Indoor Built Environ*, 6(6):320–30. doi:10.1177/1420326X9700600602

Gilmour PS, Brown DM, Lindsay TG, Beswick PH, MacNee W, Donaldson K (1996). Adverse health effects of PM_{10} particles: involvement of iron in generation of hydroxyl radical. *Occup Environ Med*, 53(12):817–22. doi:10.1136/oem.53.12.817 PMID:8994401

Giovannelli L, Pitozzi V, Moretti S, Boddi V, Dolara P (2006). Seasonal variations of DNA damage in human lymphocytes: correlation with different environmental variables. *Mutat Res*, 593(1–2):143–52. doi:10.1016/j.mrfmmm.2005.07.002 PMID:16095632

Goldsmith CA, Frevert C, Imrich A, Sioutas C, Kobzik L (1997). Alveolar macrophage interaction with air pollution particulates. *Environ Health Perspect*, 105:Suppl 5: 1191–5. doi:10.1289/ehp.97105s51191 PMID:9400722

Gong J, Zhu T, Kipen H, Wang G, Hu M, Ohman-Strickland P et al. (2013). Malondialdehyde in exhaled breath condensate and urine as a biomarker of air pollution induced oxidative stress. *J Expo Sci Environ Epidemiol*, 23(3):322–7. doi:10.1038/jes.2012.127 PMID:23321859

Gordon T, Nadziejko C, Schlesinger R, Chen LC (1998). Pulmonary and cardiovascular effects of acute exposure to concentrated ambient particulate matter in rats. *Toxicol Lett*, 96–97(1–2):285–8. doi:10.1016/S0378-4274(98)00084-8 PMID:9820679

Goto S, Kato Y, Orii A (1982). Daily variation of mutagenicities of airborne particulates. *J Jpn Soc Air Pollut*, 17:295–303.

Greenberg A, Lwo J, Antherholt TB, Rosen R, Hartman T, Butler J et al. (1993). Bioassay-directed fractionation of organic compounds associated with airborne particulate matter: an interseasonal study. *Atmos Environ Part A Gen Top*, 27(10):1609–26. doi:10.1016/0960-1686(93)90160-Z

Greenwell LL, Moreno T, Jones TP, Richards RJ (2002). Particle-induced oxidative damage is ameliorated by pulmonary antioxidants. *Free Radic Biol Med*, 32(9):898–905. doi:10.1016/S0891-5849(02)00782-7 PMID:11978491

Gualtieri M, Ovrevik J, Mollerup S, Asare N, Longhin E, Dahlman HJ et al. (2011). Airborne urban particles (Milan winter-$PM_{2.5}$) cause mitotic arrest and cell death: effects on DNA, mitochondria, AhR binding and spindle organization. *Mutat Res*, 713(1–2):18–31. doi:10.1016/j.mrfmmm.2011.05.011 PMID:21645525

Gundel LA, Dalsey JM, De Carvalho LRF, Kado NY, Schuetzle D (1993). Polar organic matter in airborne particles: chemical characterization and mutagenic activity. *Environ Sci Technol*, 27(10):2112–9. doi:10.1021/es00047a017

Gupta P, Harger WP, Arey J (1996). The contribution of nitro- and methylnitronaphthalenes to the vapor-phase mutagenicity of ambient air samples. *Atmos Environ*, 30(18):3157–66. doi:10.1016/1352-2310(96)00024-6

Gurgueira SA, Lawrence J, Coull B, Murthy GG, González-Flecha B (2002). Rapid increases in the steady-state concentration of reactive oxygen species in the lungs and heart after particulate air pollution inhalation. *Environ Health Perspect*, 110(8):749–55. doi:10.1289/ehp.02110749 PMID:12153754

Gutiérrez-Castillo ME, Roubicek DA, Cebrián-García ME, De Vizcaya-Ruíz A, Sordo-Cedeño M, Ostrosky-Wegman P (2006). Effect of chemical composition on the induction of DNA damage by urban airborne particulate matter. *Environ Mol Mutagen*, 47(3):199–211. doi:10.1002/em.20186 PMID:16355389

Hadnagy W, Seemayer NH (1987). Comparative investigation on the genotoxicity of city smog and automobile exhaust particulates. *J Aerosol Sci*, 18(6):697–9. doi:10.1016/0021-8502(87)90100-5

Hadnagy W, Seemayer NH (1991). In vitro cytogenetic assays for the detection of mitotic aneuploidy by particulate pollutants. *Toxicol In Vitro*, 5(5–6):507–10. doi:10.1016/0887-2333(91)90082-O PMID:20732066

Hadnagy W, Seemayer NH, Tomingas R (1986). Cytogenetic effects of airborne particulate matter in human lymphocytes in vitro. *Mutat Res*, 175(2):97–101. doi:10.1016/0165-7992(86)90131-4 PMID:3762578

Hadnagy W, Seemayer NH, Tomingas R, Ivanfy K (1989). Comparative study of sister-chromatid exchanges and chromosomal aberrations induced by airborne particulates from an urban and a highly industrialized location in human lymphocyte cultures. *Mutat Res*, 225(1–2):27–32. doi:10.1016/0165-7992(89)90028-6 PMID:2913489

Halatek T, Stepnik M, Stetkiewicz J, Krajnow A, Kur B, Szymczak W et al. (2011). The inflammatory response in lungs of rats exposed on the airborne particles collected during different seasons in four European cities. *J Environ Sci Health A Tox Hazard Subst Environ Eng*, 46(13):1469–81. doi:10.1080/10978526.2011.609064 PMID:21961642

Hallare AV, Gervasio MKR, Gervasio PLG, Acacio-Claro PJB (2009). Monitoring genotoxicity among gasoline station attendants and traffic enforcers in the City of Manila using the micronucleus assay with exfoliated epithelial cells. *Environ Monit Assess*, 156(1–4):331–41. doi:10.1007/s10661-008-0488-y PMID:18712612

Hannigan MP, Busby WF Jr, Cass GR (2005). Source contributions to the mutagenicity of urban particulate air pollution. *J Air Waste Manag Assoc*, 55(4):399–410. doi:10.1080/10473289.2005.10464633 PMID:15887882

Hannigan MP, Cass GR, Penman BW, Crespi CL, Lafleur AL, Busby WF et al. (1997). Human cell mutagens in Los Angeles air. *Environ Sci Technol*, 31(2):438–47. doi:10.1021/es960266z

Hannigan MP, Cass GR, Penman BW, Crespi CL, Lafleur AL, Busby WF et al. (1998). Bioassay-directed chemical

analysis of Los Angeles airborne particulate matter using a human cell mutagenicity assay. *Environ Sci Technol*, 32(22):3502–14. doi:10.1021/es9706561

Hansen AM, Wallin H, Binderup ML, Dybdahl M, Autrup H, Loft S et al. (2004). Urinary 1-hydroxypyrene and mutagenicity in bus drivers and mail carriers exposed to urban air pollution in Denmark. *Mutat Res*, 557(1):7–17. doi:10.1016/j.mrgentox.2003.09.007 PMID:14706514

Happo MS, Salonen RO, Hälinen AI, Jalava PI, Pennanen AS, Kosma VM et al. (2007). Dose and time dependency of inflammatory responses in the mouse lung to urban air coarse, fine, and ultrafine particles from six European cities. *Inhal Toxicol*, 19(3):227–46. doi:10.1080/08958370601067897 PMID:17365027

Healey K, Lingard JJ, Tomlin AS, Hughes A, White KL, Wild CP et al. (2005). Genotoxicity of size-fractionated samples of urban particulate matter. *Environ Mol Mutagen*, 45(4):380–7. doi:10.1002/em.20105 PMID:15662658

Hebels DG, Jennen DG, van Herwijnen MH, Moonen EJ, Pedersen M, Knudsen LE et al. (2011). Whole-genome gene expression modifications associated with nitrosamine exposure and micronucleus frequency in human blood cells. *Mutagenesis*, 26(6):753–61. doi:10.1093/mutage/ger043 PMID:21724973

Heidenfelder BL, Reif DM, Harkema JR, Cohen Hubal EA, Hudgens EE, Bramble LA et al. (2009). Comparative microarray analysis and pulmonary changes in Brown Norway rats exposed to ovalbumin and concentrated air particulates. *Toxicol Sci*, 108(1):207–21. doi:10.1093/toxsci/kfp005 PMID:19176365

Hemminki K, Zhang LF, Krüger J, Autrup H, Törnqvist M, Norbeck HE (1994). Exposure of bus and taxi drivers to urban air pollutants as measured by DNA and protein adducts. *Toxicol Lett*, 72(1–3):171–4. doi:10.1016/0378-4274(94)90025-6 PMID:7515516

Herbstman JB, Tang D, Zhu D, Qu L, Sjödin A, Li Z et al. (2012). Prenatal exposure to polycyclic aromatic hydrocarbons, benzo[*a*]pyrene-DNA adducts, and genomic DNA methylation in cord blood. *Environ Health Perspect*, 120(5):733–8. doi:10.1289/ehp.1104056 PMID:22256332

Heuser VD, da Silva J, Moriske HJ, Dias JF, Yoneama ML, de Freitas TR (2002). Genotoxicity biomonitoring in regions exposed to vehicle emissions using the comet assay and the micronucleus test in native rodent *Ctenomys minutus*. *Environ Mol Mutagen*, 40(4):227–35. doi:10.1002/em.10115 PMID:12489112

Hoek G, Krishnan RM, Beelen R, Peters A, Ostro B, Brunekreef B et al. (2013). Long-term air pollution exposure and cardio-respiratory mortality: a review. *Environ Health*, 12(1):43 doi:10.1186/1476-069X-12-43 PMID:23714370

Holloway JW, Savarimuthu Francis S, Fong KM, Yang IA (2012). Genomics and the respiratory effects of air pollution exposure. *Respirology*, 17(4):590–600. doi:10.1111/j.1440-1843.2012.02164.x PMID:22404320

Hornberg C, Maciuleviciute L, Seemayer NH (1996). Sister chromatid exchanges in rodent tracheal epithelium exposed in vitro to environmental pollutants. *Toxicol Lett*, 88(1–3):45–53. doi:10.1016/0378-4274(96)03717-4 PMID:8920716

Hornberg C, Maciuleviciute L, Seemayer NH (1997). Comparative analysis of cyto- and genotoxic effects of airborne particulates on human and rodent respiratory cells in vitro. *Toxicol In Vitro*, 11(5):711–5. doi:10.1016/S0887-2333(97)00065-9 PMID:20654375

Hornberg C, Maciuleviciute L, Seemayer NH, Kainka E (1998). Induction of sister chromatid exchanges (SCE) in human tracheal epithelial cells by the fractions PM_{10} and $PM_{2.5}$ of airborne particulates. *Toxicol Lett*, 96–97(1–2):215–20. doi:10.1016/S0378-4274(98)00075-7 PMID:9820670

Hornberg C, Seemayer NH (1995). Induction of sister chromatid exchanges in rodent tracheal epithelial cells as a sensitive bioassay for detection of genotoxic activity of airborne particulates. *Exp Toxicol Pathol*, 47(4):241–3. doi:10.1016/S0940-2993(11)80257-5 PMID:8855119

Hosgood HD 3rd, Berndt SI, Lan Q (2007). GST genotypes and lung cancer susceptibility in Asian populations with indoor air pollution exposures: a meta-analysis. *Mutat Res*, 636(1–3):134–43. doi:10.1016/j.mrrev.2007.02.002 PMID:17428724

Hou L, Wang S, Dou C, Zhang X, Yu Y, Zheng Y et al. (2012). Air pollution exposure and telomere length in highly exposed subjects in Beijing, China: a repeated-measure study. *Environ Int*, 48:71–7. doi:10.1016/j.envint.2012.06.020 PMID:22871507

Hou L, Zhang X, Tarantini L, Nordio F, Bonzini M, Angelici L et al. (2011). Ambient PM exposure and DNA methylation in tumor suppressor genes: a cross-sectional study. *Part Fibre Toxicol*, 8(1):25 doi:10.1186/1743-8977-8-25 PMID:21878113

Hoxha M, Dioni L, Bonzini M, Pesatori AC, Fustinoni S, Cavallo D et al. (2009). Association between leukocyte telomere shortening and exposure to traffic pollution: a cross-sectional study on traffic officers and indoor office workers. *Environ Health*, 8(1):41 doi:10.1186/1476-069X-8-41 PMID:19772576

Hsiao WL, Mo ZY, Fang M, Shi XM, Wang F (2000). Cytotoxicity of $PM_{2.5}$ and $PM_{2.5-10}$ ambient air pollutants assessed by the MTT and the Comet assays. *Mutat Res*, 471(1–2):45–55. doi:10.1016/S1383-5718(00)00116-9 PMID:11080660

Huang YC, Schmitt M, Yang Z, Que LG, Stewart JC, Frampton MW et al. (2010). Gene expression profile in circulating mononuclear cells after exposure to ultrafine carbon particles. *Inhal Toxicol*, 22(10):835–46. doi:10.3109/08958378.2010.486419 PMID:20507211

Huang W, Wang G, Lu SE, Kipen H, Wang Y, Hu M et al. (2012). Inflammatory and oxidative stress responses of

healthy young adults to changes in air quality during the Beijing Olympics. *Am J Respir Crit Care Med*, 186(11):1150–9. doi:10.1164/rccm.201205-0850OC PMID:22936356

Huang YC, Karoly ED, Dailey LA, Schmitt MT, Silbajoris R, Graff DW et al. (2011). Comparison of gene expression profiles induced by coarse, fine, and ultrafine particulate matter. *J Toxicol Environ Health A*, 74(5):296–312. doi:10.1080/15287394.2010.516238 PMID:21240730

Huttunen K, Siponen T, Salonen I, Yli-Tuomi T, Aurela M, Dufva H et al. (2012). Low-level exposure to ambient particulate matter is associated with systemic inflammation in ischemic heart disease patients. *Environ Res*, 116:44–51. doi:10.1016/j.envres.2012.04.004 PMID:22541720

IARC (1982). Some industrial chemicals and dyestuffs. *IARC Monogr Eval Carcinog Risk Chem Hum*. 29:1–398. Available from: http://monographs.iarc.fr/ENG/Monographs/vol1-42/mono29.pdf. PMID:6957379

IARC (1984). Polynuclear aromatic hydrocarbons, Part 2, carbon blacks, mineral oils (lubricant base oils and derived products) and some nitroarenes. *IARC Monogr Eval Carcinog Risk Chem Hum*. 33:1–222. Available from: http://monographs.iarc.fr/ENG/Monographs/vol1-42/mono33.pdf. PMID:6590450

IARC (1989). Diesel and gasoline engine exhausts and some nitroarenes. *IARC Monogr Eval Carcinog Risks Hum*, 46:1–458. Available from: http://monographs.iarc.fr/ENG/Monographs/vol46/index.php. PMID:2483415

IARC (1992). Occupational exposures to mists and vapours from strong inorganic acids and other industrial chemicals. *IARC Monogr Eval Carcinog Risks Hum*, 54:1–310. Available from: http://monographs.iarc.fr/ENG/Monographs/vol54/index.php. PMID:1345371

IARC (2006). Formaldehyde, 2-butoxyethanol and 1-tert-butoxypropan-2-ol. *IARC Monogr Eval Carcinog Risks Hum*, 88:1–478. Available from: http://monographs.iarc.fr/ENG/Monographs/vol88/index.php. PMID:17366697

IARC (2010a). Carbon black, titanium dioxide, and talc. *IARC Monogr Eval Carcinog Risks Hum*, 93:1–413. Available from: http://monographs.iarc.fr/ENG/Monographs/vol93/index.php. PMID:21449489

IARC (2010b). Household use of solid fuels and high-temperature frying. *IARC Monogr Eval Carcinog Risks Hum*, 95:1–430. Available from: http://monographs.iarc.fr/ENG/Monographs/vol95/index.php. PMID:20701241

IARC (2010c). Some non-heterocyclic polycyclic aromatic hydrocarbons and some related exposures. *IARC Monogr Eval Carcinog Risks Hum*, 92:1–853. Available from: http://monographs.iarc.fr/ENG/Monographs/vol92/index.php. PMID:21141735

IARC (2012a). Arsenic, metals, fibres, and dusts. *IARC Monogr Eval Carcinog Risks Hum*, 100C:1–499. Available from: http://monographs.iarc.fr/ENG/Monographs/vol100C/index.php. PMID:23189751

IARC (2012b). Chemical agents and related occupations. *IARC Monogr Eval Carcinog Risks Hum*, 100F:1–599. Available from: http://monographs.iarc.fr/ENG/Monographs/vol100F/index.php. PMID:23189753

IARC (2012c). Personal habits and indoor combustions. *IARC Monogr Eval Carcinog Risks Hum*, 100E:1–575. Available from: http://monographs.iarc.fr/ENG/Monographs/vol100E/index.php. PMID:23193840

IARC (2013). Diesel and gasoline engine exhausts and some nitroarenes. *IARC Monogr Eval Carcinog Risks Hum*, 105:1–704. Available from: http://monographs.iarc.fr/ENG/Monographs/vol105/index.php.

Ichinose T, Yoshida S, Sadakane K, Takano H, Yanagisawa R, Inoue K et al. (2008). Effects of Asian sand dust, Arizona sand dust, amorphous silica and aluminum oxide on allergic inflammation in the murine lung. *Inhal Toxicol*, 20(7):685–94. doi:10.1080/08958370801935133 PMID:18464056

ICRP (1994). Human respiratory tract model for radiological protection. A report of a task group of the International Commission on Radiological Protection (ICRP Publication 66). *Ann ICRP*, 24(1–3).

Ieradi LA, Cristaldi M, Mascanzoni D, Cardarelli E, Grossi R, Campanella L (1996). Genetic damage in urban mice exposed to traffic pollution. *Environ Pollut*, 92(3):323–8. doi:10.1016/0269-7491(95)00109-3 PMID:15091385

Imlay JA, Chin SM, Linn S (1988). Toxic DNA damage by hydrogen peroxide through the Fenton reaction in vivo and in vitro. *Science*, 240(4852):640–2. doi:10.1126/science.2834821 PMID:2834821

Imrich A, Ning Y, Lawrence J, Coull B, Gitin E, Knutson M et al. (2007). Alveolar macrophage cytokine response to air pollution particles: oxidant mechanisms. *Toxicol Appl Pharmacol*, 218(3):256–64. doi:10.1016/j.taap.2006.11.033 PMID:17222881

IPCS (2008). Principles for evaluating health risks in children associated with exposure to chemicals. *Environ Health Criteria*, No. 237. Geneva, Switzerland: International Programme on Chemical Safety. Available from: http://www.inchem.org/documents/ehc/ehc/ehc237.pdf.

Ishikawa H, Tian Y, Piao F, Duan Z, Zhang Y, Ma M et al. (2006). Genotoxic damage in female residents exposed to environmental air pollution in Shenyang city, China. *Cancer Lett*, 240(1):29–35. doi:10.1016/j.canlet.2005.08.023 PMID:16246488

Israël GW, Busing JB (1983). Investigations on the mutagenic action of urban particulates. *J Aerosol Sci*, 14(3):192–4. doi:10.1016/0021-8502(83)90025-3

Izzotti A, Camoirano A, D'Agostini F, Sciacca S, De Naro Papa F, Cesarone CF et al. (1996). Biomarker alterations produced in rat lung by intratracheal instillations of air particulate extracts and chemoprevention

with oral *N*-acetylcysteine. *Cancer Res*, 56(7):1533–8. PMID:8603398

Jadczyk P, Kucharczyk J (2005). Mutagenicity of pollutants and their fractions adsorbed on airborne particulate in the centre of Wrocław (Poland). *Environ Prot Eng*, 31(2):77–92.

Jalava P, Salonen RO, Hälinen AI, Sillanpää M, Sandell E, Hirvonen MR (2005). Effects of sample preparation on chemistry, cytotoxicity, and inflammatory responses induced by air particulate matter. *Inhal Toxicol*, 17(2):107–17. doi:10.1080/08958370590899550 PMID:15764488

Jansen KL, Larson TV, Koenig JQ, Mar TF, Fields C, Stewart J et al. (2005). Associations between health effects and particulate matter and black carbon in subjects with respiratory disease. *Environ Health Perspect*, 113(12):1741–6. doi:10.1289/ehp.8153 PMID:16330357

Janssen BG, Godderis L, Pieters N, Poels K, Kiciński M, Cuypers A et al. (2013). Placental DNA hypomethylation in association with particulate air pollution in early life. *Part Fibre Toxicol*, 10(1):22 doi:10.1186/1743-8977-10-22 PMID:23742113

Jaques PA, Kim CS (2000). Measurement of total lung deposition of inhaled ultrafine particles in healthy men and women. *Inhal Toxicol*, 12(8):715–31. doi:10.1080/08958370050085156 PMID:10880153

Jayasekher T (2009). Aerosols near by a coal fired thermal power plant: chemical composition and toxic evaluation. *Chemosphere*, 75(11):1525–30. doi:10.1016/j.chemosphere.2009.02.001 PMID:19264341

Jerrett M, Burnett RT, Beckerman BS, Turner MC, Krewski D, Thurston G et al. (2013). Spatial analysis of air pollution and mortality in California. *Am J Respir Crit Care Med*, 188(5):593–9. doi:10.1164/rccm.201303-0609OC PMID:23805824

Jiang LP, Dai H, Sun Q, Geng CY, Yang Y, Wu T et al. (2011). Ambient particulate matter on DNA damage in HepG2 cells. *Toxicol Ind Health*, 27(1):87–95. doi:10.1177/0748233710387001 PMID:20947658

Kadiiska MB, Ghio AJ, Mason RP (2004). ESR investigation of the oxidative damage in lungs caused by asbestos and air pollution particles. *Spectrochim Acta A Mol Biomol Spectrosc*, 60(6):1371–7. doi:10.1016/j.saa.2003.10.035 PMID:15134737

Kado NY, Guirguis GN, Flessel CP, Chan RC, Chang KI, Wesolowski JJ (1986). Mutagenicity of fine (less than 2.5 microns) airborne particles: diurnal variation in community air determined by a *Salmonella* micro preincubation (microsuspension) procedure. *Environ Mutagen*, 8(1):53–66. doi:10.1002/em.2860080106 PMID:3510862

Kado NY, Langley D, Eisenstadt E (1983). A simple modification of the *Salmonella* liquid-incubation assay. Increased sensitivity for detecting mutagens in human urine. *Mutat Res*, 121(1):25–32. doi:10.1016/0165-7992(83)90082-9 PMID:6306458

Kamdar O, Le W, Zhang J, Ghio AJ, Rosen GD, Upadhyay D (2008). Air pollution induces enhanced mitochondrial oxidative stress in cystic fibrosis airway epithelium. *FEBS Lett*, 582(25–26):3601–6. doi:10.1016/j.febslet.2008.09.030 PMID:18817777

Kameda T, Inazu K, Bandow H Sanukida S, Maeda Y (2004). Diurnal change of direct-acting mutagenicity of soluble organic fraction of airborne particles collected at Southern Osaka: correlation between the mutagenicity, particles-associated nitroarenes, and gaseous emission. *Atmos Environ*, 38(13):1903–12. doi:10.1016/j.atmosenv.2004.01.007

Karahalil B, Karakaya AE, Burgaz S (1999). The micronucleus assay in exfoliated buccal cells: application to occupational exposure to polycyclic aromatic hydrocarbons. *Mutat Res*, 442(1):29–35. doi:10.1016/S1383-5718(99)00055-8 PMID:10366770

Karlsson HL, Holgersson A, Möller L (2008). Mechanisms related to the genotoxicity of particles in the subway and from other sources. *Chem Res Toxicol*, 21(3):726–31. doi:10.1021/tx7003568 PMID:18260651

Karlsson HL, Ljungman AG, Lindbom J, Möller L (2006). Comparison of genotoxic and inflammatory effects of particles generated by wood combustion, a road simulator and collected from street and subway. *Toxicol Lett*, 165(3):203–11. doi:10.1016/j.toxlet.2006.04.003 PMID:16716543

Karlsson HL, Nilsson L, Möller L (2005). Subway particles are more genotoxic than street particles and induce oxidative stress in cultured human lung cells. *Chem Res Toxicol*, 18(1):19–23. doi:10.1021/tx049723c PMID:15651844

Karlsson HL, Nygren J, Möller L (2004). Genotoxicity of airborne particulate matter: the role of cell-particle interaction and of substances with adduct-forming and oxidizing capacity. *Mutat Res*, 565(1):1–10. doi:10.1016/j.mrgentox.2004.07.015 PMID:15576234

Kawanaka Y, Matsumoto E, Sakamoto K, Wang N, Yun S-J (2004). Size distributions of mutagenic compounds and mutagenicity in atmospheric particulate matter collected with a low-pressure cascade impactor. *Atmos Environ*, 38(14):2125–32. doi:10.1016/j.atmosenv.2004.01.021

Kawanishi S, Inoue S, Yamamoto K (1989). Site-specific DNA damage induced by nickel(II) ion in the presence of hydrogen peroxide. *Carcinogenesis*, 10(12):2231–5. doi:10.1093/carcin/10.12.2231 PMID:2686851

Kelvin EA, Edwards S, Jedrychowski W, Schleicher RL, Camann D, Tang D et al. (2009). Modulation of the effect of prenatal PAH exposure on PAH-DNA adducts in cord blood by plasma antioxidants. *Cancer Epidemiol Biomarkers Prev*, 18(8):2262–8. doi:10.1158/1055-9965.EPI-09-0316 PMID:19661084

Ketelslegers HB, Gottschalk RW, Koppen G, Schoeters G, Baeyens WF, van Larebeke NA et al. (2008). Multiplex genotyping as a biomarker for susceptibility

to carcinogenic exposure in the FLEHS biomonitoring study. *Cancer Epidemiol Biomarkers Prev*, 17(8):1902–12. doi:10.1158/1055-9965.EPI-08-0045 PMID:18708379

Kim CS, Hu SC (1998). Regional deposition of inhaled particles in human lungs: comparison between men and women. *J Appl Physiol (1985)*, 84(6):1834–44. PMID:9609774

Kimura KC, Fukumasu H, Chaible LM, Lima CE, Horst MA, Matsuzaki P et al. (2010). Evaluation of DNA damage by the alkaline comet assay of the olfactory and respiratory epithelia of dogs from the city of São Paulo, Brazil. *Exp Toxicol Pathol*, 62(3):209–19. doi:10.1016/j.etp.2009.03.008 PMID:19447591

Knaapen AM, Shi T, Borm PJA, Schins RPF (2002). Soluble metals as well as the insoluble particle fraction are involved in cellular DNA damage induced by particulate matter. *Mol Cell Biochem*, 234(–):235(1–2):317–26. doi:10.1023/A:1015970023889 PMID:12162450

Knudsen LE, Norppa H, Gamborg MO, Nielsen PS, Okkels H, Soll-Johanning H et al. (1999). Chromosomal aberrations in humans induced by urban air pollution: influence of DNA repair and polymorphisms of glutathione *S*-transferase M1 and *N*-acetyltransferase 2. *Cancer Epidemiol Biomarkers Prev*, 8(4 Pt 1):303–10. PMID:10207633

Kodavanti UP, Mebane R, Ledbetter A, Krantz T, McGee J, Jackson MC et al. (2000). Variable pulmonary responses from exposure to concentrated ambient air particles in a rat model of bronchitis. *Toxicol Sci*, 54(2):441–51. doi:10.1093/toxsci/54.2.441 PMID:10774827

Koenig JQ, Jansen K, Mar TF, Lumley T, Kaufman J, Trenga CA et al. (2003). Measurement of offline exhaled nitric oxide in a study of community exposure to air pollution. *Environ Health Perspect*, 111(13):1625–9. doi:10.1289/ehp.6160 PMID:14527842

Koenig JQ, Mar TF, Allen RW, Jansen K, Lumley T, Sullivan JH et al. (2005). Pulmonary effects of indoor- and outdoor-generated particles in children with asthma. *Environ Health Perspect*, 113(4):499–503. doi:10.1289/ehp.7511 PMID:15811822

Kong XH, Yi XJ, Wang H (1994). **A** study on mutagenicity of NO_2-PAHs in airborne particulates in Shenyang. *J Health Toxicol*, 8:160–3.

Kooter I, Pennings J, Opperhuizen A, Cassee F (2005). Gene expression pattern in spontaneously hypertensive rats exposed to urban particulate matter (EHC-93). *Inhal Toxicol*, 17(1):53–65. doi:10.1080/08958370590885717 PMID:15764483

Kooter IM, Boere AJ, Fokkens PH, Leseman DL, Dormans JA, Cassee FR (2006). Response of spontaneously hypertensive rats to inhalation of fine and ultrafine particles from traffic: experimental controlled study. *Part Fibre Toxicol*, 3(1):7 doi:10.1186/1743-8977-3-7 PMID:16700918

Koppen G, Verheyen G, Maes A, Van Gorp U, Schoeters G, Hond ED et al. (2007). A battery of DNA effect biomarkers to evaluate environmental exposure of Flemish adolescents. *J Appl Toxicol*, 27(3):238–46. doi:10.1002/jat.1174 PMID:17226746

Koshy L, Jones T, BéruBé K (2009). Characterization and bioreactivity of respirable airborne particles from a municipal landfill. *Biomarkers*, 14:Suppl 1: 49–53. doi:10.1080/13547500902965351 PMID:19604059

Krewski D, Jerrett M, Burnett RT, Ma R, Hughes E, Shi Y et al. (2009). Extended follow-up and spatial analysis of the American Cancer Society study linking particulate air pollution and mortality. *Res Rep Health Eff Inst*, 140(140):5–114, discussion 115–36. PMID:19627030

Krishna G, Nath J, Ong T (1984). Correlative genotoxicity studies of airborne particles in *Salmonella typhimurium* and cultured human lymphocytes. *Environ Mutagen*, 6(4):585–92. doi:10.1002/em.2860060411 PMID:6381042

Krishna G, Nath J, Soler L, Ong T (1986). Comparative in vivo and in vitro genotoxicity studies of airborne particle extract in mice. *Mutat Res*, 171(2–3):157–63. doi:10.1016/0165-1218(86)90049-2 PMID:3528836

Kuo CY, Cheng YW, Chen CY, Lee H (1998). Correlation between the amounts of polycyclic aromatic hydrocarbons and mutagenicity of airborne particulate samples from Taichung City, Taiwan. *Environ Res*, 78(1):43–9. doi:10.1006/enrs.1998.3838 PMID:9630444

Kure EH, Andreassen A, Ovrebø S, Grzybowska E, Fiala Z, Strózyk M et al. (1997). Benzo(a)pyrene-albumin adducts in humans exposed to polycyclic aromatic hydrocarbons in an industrial area of Poland. *Occup Environ Med*, 54(9):662–6. doi:10.1136/oem.54.9.662 PMID:9423579

Lai HK, Tsang H, Wong CM (2013). Meta-analysis of adverse health effects due to air pollution in Chinese populations. *BMC Public Health*, 13(1):360 doi:10.1186/1471-2458-13-360 PMID:23594435

Larsson BM, Grunewald J, Sköld CM, Lundin A, Sandström T, Eklund A et al. (2010). Limited airway effects in mild asthmatics after exposure to air pollution in a road tunnel. *Respir Med*, 104(12):1912–8. doi:10.1016/j.rmed.2010.06.014 PMID:20621461

Lazarová M, Slamenová D (2004). Genotoxic effects of a complex mixture adsorbed onto ambient air particles on human cells in vitro; the effects of vitamins E and C. *Mutat Res*, 557(2):167–75. doi:10.1016/j.mrgentox.2003.10.011 PMID:14729371

Lee H, Su SY, Liu KS, Chou MC (1994). Correlation between meteorological conditions and mutagenicity of airborne particulate samples in a tropical monsoon climate area from Kaohsiung City, Taiwan. *Environ Mol Mutagen*, 23(3):200–7. doi:10.1002/em.2850230309 PMID:8162895

Lei XF, Wang L, Xun Z (1993). Study of the genotoxicity and concentration of five metals in airborne particles. *Chin J Environ Sci*, 14:30–3.

Lemos AT, Coronas MV, Rocha JAV, Vargas VMF (2012). Mutagenicity of particulate matter fractions in areas under the impact of urban and industrial activities. *Chemosphere*, 89(9):1126–34. doi:10.1016/j.chemosphere.2012.05.100 PMID:22795069

Li N, Xia T, Nel AE (2008). The role of oxidative stress in ambient particulate matter-induced lung diseases and its implications in the toxicity of engineered nanoparticles. *Free Radic Biol Med*, 44(9):1689–99. doi:10.1016/j.freeradbiomed.2008.01.028 PMID:18313407

Li PK, Gao ZY, Jiang RF, Gai BB, Qin YQ, Song WM (2010). DNA damage in population exposed to fine particulate [in Chinese]. *J Environ Occup Med*, 27:254–6. Available from: http://www.cnki.net/kcms/detail/detail.aspx?filename=LDYX201005004&dbcode=CJFQ&dbname=CJFD2010.

Li Y, Rittenhouse-Olson K, Scheider WL, Mu L (2012). Effect of particulate matter air pollution on C-reactive protein: a review of epidemiologic studies. *Rev Environ Health*, 27(2–3):133–49. doi:10.1515/reveh-2012-0012 PMID:23023922

Li Z, Hyseni X, Carter JD, Soukup JM, Dailey LA, Huang YC (2006). Pollutant particles enhanced H_2O_2 production from NAD(P)H oxidase and mitochondria in human pulmonary artery endothelial cells. *Am J Physiol Cell Physiol*, 291(2):C357–65. doi:10.1152/ajpcell.00365.2005 PMID:16571865

Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H et al. (2012). A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*, 380(9859):2224–60. doi:10.1016/S0140-6736(12)61766-8 PMID:23245609

Lin ZQ, Xi ZG, Yang DF, Chao FH, Zhang HS, Zhang W et al. (2009). Oxidative damage to lung tissue and peripheral blood in endotracheal $PM_{2.5}$-treated rats. *Biomed Environ Sci*, 22(3):223–8. doi:10.1016/S0895-3988(09)60049-0 PMID:19725465

Lindbom J, Gustafsson M, Blomqvist G, Dahl A, Gudmundsson A, Swietlicki E et al. (2007). Wear particles generated from studded tires and pavement induces inflammatory reactions in mouse macrophage cells. *Chem Res Toxicol*, 20(6):937–46. doi:10.1021/tx700018z PMID:17516662

Lingard JJN, Tomlin AS, Clarke AG, Healey K, Hay AWM, Wild CP et al. (2005). A study of trace metal concentration of urban airborne particulate matter and its role in free radical activity as measured by plasmid strand break assay. *Atmos Environ*, 39(13):2377–84. doi:10.1016/j.atmosenv.2004.05.063

Liu L, Poon R, Chen L, Frescura AM, Montuschi P, Ciabattoni G et al. (2009a). Acute effects of air pollution on pulmonary function, airway inflammation, and oxidative stress in asthmatic children. *Environ Health Perspect*, 117(4):668–74. doi:10.1289/ehp.11813 PMID:19440509

Liu L, Ruddy T, Dalipaj M, Poon R, Szyszkowicz M, You H et al. (2009b). Effects of indoor, outdoor, and personal exposure to particulate air pollution on cardiovascular physiology and systemic mediators in seniors. *J Occup Environ Med*, 51(9):1088–98. doi:10.1097/JOM.0b013e3181b35144 PMID:19701101

Liu L, Ruddy TD, Dalipaj M, Szyszkowicz M, You H, Poon R et al. (2007). Influence of personal exposure to particulate air pollution on cardiovascular physiology and biomarkers of inflammation and oxidative stress in subjects with diabetes. *J Occup Environ Med*, 49(3):258–65. doi:10.1097/JOM.0b013e31803220ef PMID:17351511

Ljubimova JY, Kleinman MT, Karabalin NM, Inoue S, Konda B, Gangalum P et al. (2013). Gene expression changes in rat brain after short and long exposures to particulate matter in Los Angeles basin air: comparison with human brain tumors. *Exp Toxicol Pathol*, 65(7–8):1063–71. doi:10.1016/j.etp.2013.04.002 PMID:23688656

Löfroth G, Lazaridis G, Agurell E (1985). The use of the *Salmonella*/microsome mutagenicity test for the characterization of organic extracts from ambient air particulate matter. *Environ Int*, 11(2–4):161–7. doi:10.1016/0160-4120(85)90009-1

Longhin E, Pezzolato E, Mantecca P, Holme JA, Franzetti A, Camatini M et al. (2013). Season linked responses to fine and quasi-ultrafine Milan PM in cultured cells. *Toxicol In Vitro*, 27(2):551–9. doi:10.1016/j.tiv.2012.10.018 PMID:23159502

Ma TH, Cabrera GL, Chen R, Gill BS, Sandhu SS, Vandenberg AL et al. (1994). *Tradescantia* micronucleus bioassay. *Mutat Res*, 310(2):221–30. doi:10.1016/0027-5107(94)90115-5 PMID:7523893

Madrigano J, Baccarelli A, Mittleman MA, Sparrow D, Spiro A 3rd, Vokonas PS et al. (2012). Air pollution and DNA methylation: interaction by psychological factors in the VA Normative Aging Study. *Am J Epidemiol*, 176(3):224–32. doi:10.1093/aje/kwr523 PMID:22798479

Madrigano J, Baccarelli A, Mittleman MA, Wright RO, Sparrow D, Vokonas PS et al. (2011). Prolonged exposure to particulate pollution, genes associated with glutathione pathways, and DNA methylation in a cohort of older men. *Environ Health Perspect*, 119(7):977–82. doi:10.1289/ehp.1002773 PMID:21385671

Manney S, Meddings CM, Harrison RM, Mansur AH, Karakatsani A, Analitis A et al. (2012). Association between exhaled breath condensate nitrate + nitrite levels with ambient coarse particle exposure in subjects with airways disease. *Occup Environ Med*, 69(9):663–9. doi:10.1136/oemed-2011-100255 PMID:22767867

Mao DJ, Shi YM, Zhou YF,, Ding DH, Ma YS, Peng LH et al. (1993). The study of sperm abnormality in mice exposed to organic extracts of total suspended particulates in Shanghai. *Carcinog Teratog Mutagen*, 5:9

Mar TF, Jansen K, Shepherd K, Lumley T, Larson TV, Koenig JQ (2005). Exhaled nitric oxide in children with asthma and short-term $PM_{2.5}$ exposure in Seattle. *Environ Health Perspect*, 113(12):1791–4. doi:10.1289/ehp.7883 PMID:16330366

Martin S, Dawidowski L, Mandalunis P, Cereceda-Balic F, Tasat DR (2007). Characterization and biological effect of Buenos Aires urban air particles on mice lungs. *Environ Res*, 105(3):340–9. doi:10.1016/j.envres.2007.04.009 PMID:17628521

Martin S, Fernandez-Alanis E, Delfosse V, Evelson P, Yakisich JS, Saldiva PH et al. (2010). Low doses of urban air particles from Buenos Aires promote oxidative stress and apoptosis in mice lungs. *Inhal Toxicol*, 22(13):1064–71. doi:10.3109/08958378.2010.523030 PMID:21047167

Massolo L, Müller A, Tueros M, Rehwagen M, Franck U, Ronco A et al. (2002). Assessment of mutagenicity and toxicity of different-size fractions of air particulates from La Plata, Argentina, and Leipzig, Germany. *Environ Toxicol*, 17(3):219–31. doi:10.1002/tox.10054 PMID:12112630

Matsumoto Y, Sakai S, Kato T, Nakajima T, Satoh H (1998). Long-term trends of particulate mutagenic activity in atmosphere of Sapporo. 1. Determination of mutagenic activity by the conventional tester strains TA98 and TA100 during an 18-year period (1974–1992). *Environ Sci Technol*, 32(18):2665–71. doi:10.1021/es9801036

Maynard AM, Kuempel ED (2005). Airborne nanostructured particles and occupational health. *J Nanopart Res*, 7(6):587–614. doi:10.1007/s11051-005-6770-9

McCracken J, Baccarelli A, Hoxha M, Dioni L, Melly S, Coull B et al. (2010). Annual ambient black carbon associated with shorter telomeres in elderly men: Veterans Affairs Normative Aging Study. *Environ Health Perspect*, 118(11):1564–70. doi:10.1289/ehp.0901831 PMID:21465749

Melville GN (1970). Changes in specific airway conductance in healthy volunteers following nasal and oral inhalation of SO_2. *West Indian Med J*, 19(4):231–5. PMID:5504408

Mendez R, Zheng Z, Fan Z, Rajagopalan S, Sun Q, Zhang K (2013). Exposure to fine airborne particulate matter induces macrophage infiltration, unfolded protein response, and lipid deposition in white adipose tissue. *Am J Transl Res*, 5(2):224–34. PMID:23573366

Meng Z, Zhang Q (2007). Damage effects of dust storm $PM_{2.5}$ on DNA in alveolar macrophages and lung cells of rats. *Food Chem Toxicol*, 45(8):1368–74. doi:10.1016/j.fct.2007.01.014 PMID:17336437

Meng ZQ, Zhang QX (2005). Damage of atmospheric fine particles on DNA in alveolar macrophages of rats *Chin Environ Sci*, 25(1):15–7.

Meng ZQ, Zhang QX (2006b). Damaging effects of dust storm fine particles instillation on DNA in lung cells of rats [in Chinese]. *Chin J Publ Health*, 22:1458–9. Available from: http://www.cnki.net/kcms/detail/detail.aspx?filename=ZGGW200612027&dbcode=CJFQ&dbname=cjfd2006.

Meng ZQ, Zhang QX, Geng H (2006a). DNA damage effects of fine particles from sandstorm in rat alveolar macrophages [in Chinese]. *J Environ Occup Med*, 23:185–8. Available from: http://www.cnki.net/.

Mercer RR, Crapo JD (1989). Anatomical modeling of microdosimetry of inhaled particles and gases in the lung. In: Crapo JD, Smolko ED, Miller FJ, Graham JA, Hayes AW, editors. Extrapolation of dosimetry relationships for inhaled particles and gases. San Diego (CA): Academic Press; pp. 69–78.

Merlo F, Bolognesi C, Peluso M, Valerio F, Abbondandolo A, Puntoni R (1997). Airborne levels of polycyclic aromatic hydrocarbons: ^{32}P-postlabeling DNA adducts and micronuclei in white blood cells from traffic police workers and urban residents. *J Environ Pathol Toxicol Oncol*, 16(2–3):157–62. PMID:9275996

Miller FJ (1995). Uptake and fate of ozone in the respiratory tract. *Toxicol Lett*, 82–83:277–85. doi:10.1016/0378-4274(95)03562-1 PMID:8597066

Miller FJ, Overton JH Jr, Jaskot RH, Menzel DB (1985). A model of the regional uptake of gaseous pollutants in the lung. I. The sensitivity of the uptake of ozone in the human lung to lower respiratory tract secretions and exercise. *Toxicol Appl Pharmacol*, 79(1):11–27. doi:10.1016/0041-008X(85)90364-3 PMID:3840292

Mills NL, Robinson SD, Fokkens PH, Leseman DL, Miller MR, Anderson D et al. (2008). Exposure to concentrated ambient particles does not affect vascular function in patients with coronary heart disease. *Environ Health Perspect*, 116(6):709–15. doi:10.1289/ehp.11016 PMID:18560524

Møller M, Alfheim I (1980). Mutagenicity and PAH-analysis of airborne particulate matter. *Atmos Environ*, 14(1):83–8. doi:10.1016/0004-6981(80)90111-0 PMID:6986880

Møller M, Alfheim I, Larssen S, Mikalsen A (1982). Mutagenicity of airborne particles in relation to traffic and air pollution parameters. *Environ Sci Technol*, 16(4):221–5. doi:10.1021/es00098a010

Møller P, Loft S (2010). Oxidative damage to DNA and lipids as biomarkers of exposure to air pollution. *Environ Health Perspect*, 118(8):1126–36. doi:10.1289/ehp.0901725 PMID:20423813

Monarca S, Crebelli R, Feretti D, Zanardini A, Fuselli S, Filini L et al. (1997). Mutagens and carcinogens in size-classified air particulates of a northern Italian

town. *Sci Total Environ*, 205(2–3):137–44. doi:10.1016/S0048-9697(97)00194-0 PMID:9372626

Moreno T, Merolla L, Gibbons W, Greenwell L, Jones T, Richards R (2004). Variations in the source, metal content and bioreactivity of technogenic aerosols: a case study from Port Talbot, Wales, UK. *Sci Total Environ*, 333(1–3):59–73. doi:10.1016/j.scitotenv.2004.04.019 PMID:15364519

Moriske HJ, Block I, Schleibinger H, Rüden H (1985). Polar neutral organic compounds in urban aerosols. 1. Chemical characterization and mutagenic effect in relation to various sources [in German]. *Zentralbl Bakteriol Mikrobiol Hyg B*, 181(3–5):240–71. PMID:4096145

Morozzi G, Mastrandrea V, Trotta F, Tonti A, Scardazza F, Cenci E (1992). Chemical characterization and biological properties of airborne particulate matter. *Aerobiologia*, 8(3):451–7. doi:10.1007/BF02272915

Morris WA, Versteeg JK, Bryant DW, Legzdins AE, McCarry BE, Marvin CH (1995). Preliminary comparisons between mutagenicity and magnetic susceptibility of respirable airborne particulate. *Atmos Environ*, 29(23):3441–50. doi:10.1016/1352-2310(95)00203-B

Motta S, Federico C, Saccone S, Librando V, Mosesso P (2004). Cytogenetic evaluation of extractable agents from airborne particulate matter generated in the city of Catania (Italy). *Mutat Res*, 561(1–2):45–52. doi:10.1016/j.mrgentox.2004.03.008 PMID:15238229

Motykiewicz G, Hadnagy W, Seemayer NH, Szeliga J, Tkocz A, Chorazy M (1991). Influence of airborne suspended matter on mitotic cell division. *Mutat Res*, 260(2):195–202. doi:10.1016/0165-1218(91)90008-A PMID:2046700

Motykiewicz G, Michalska J, Szeliga J, Cimander B (1988). Mutagenic and clastogenic activity of direct-acting components from air pollutants of the Silesian industrial region. *Mutat Res*, 204(2):289–96. doi:10.1016/0165-1218(88)90102-4 PMID:3278218

Motykiewicz G, Michalska J, Szeliga J, Konopacka M, Tkocz A, Hadnagy W et al. (1990). Genotoxicity of airborne suspended matter determined by in vitro and in vivo short-term assays. In: Seemayer NH, Hadnagy W, editors. Environmental hygiene II. Berlin: Springer-Verlag; pp. 17–21.

Motykiewicz G, Perera FP, Santella RM, Hemminki K, Seemayer NH, Chorazy M (1996). Assessment of cancer hazard from environmental pollution in Silesia. *Toxicol Lett*, 88(1–3):169–73. doi:10.1016/0378-4274(96)03734-4 PMID:8920733

Müller A, Alzuet P, Herbarth O, Ronco A (2001). Assessment of toxicity and mutagenicity in air particulate matter from an urban industrial area in the coast of the Rio de la Plata. *Environ Toxicol*, 16(2):151–7. doi:10.1002/tox.1019 PMID:11339715

Mustafic H, Jabre P, Caussin C, Murad MH, Escolano S, Tafflet M et al. (2012). Main air pollutants and myocardial infarction: a systematic review and meta-analysis. *JAMA*, 307(7):713–21. doi:10.1001/jama.2012.126 PMID:22337682

NCRP (1997). Deposition, retention, and dosimetry of inhaled radioactive substances (Report No. 125). Bethesda (MD): National Council on Radiation Protection and Measurements.

Nielsen PS, de Pater N, Okkels H, Autrup H (1996a). Environmental air pollution and DNA adducts in Copenhagen bus drivers – effect of *GSTM1* and *NAT2* genotypes on adduct levels. *Carcinogenesis*, 17(5):1021–7. doi:10.1093/carcin/17.5.1021 PMID:8640907

Nielsen PS, Okkels H, Sigsgaard T, Kyrtopoulos S, Autrup H (1996b). Exposure to urban and rural air pollution: DNA and protein adducts and effect of glutathione-*S*-transferase genotype on adduct levels. *Int Arch Occup Environ Health*, 68(3):170–6. doi:10.1007/BF00381627 PMID:8919845

Nodelman V, Ultman JS (1999). Longitudinal distribution of chlorine absorption in human airways: a comparison to ozone absorption. *J Appl Physiol (1985)*, 87(6):2073–80. PMID:10601152

Norppa H, Bonassi S, Hansteen IL, Hagmar L, Strömberg U, Rössner P et al. (2006). Chromosomal aberrations and SCEs as biomarkers of cancer risk. *Mutat Res*, 600(1–2):37–45. doi:10.1016/j.mrfmmm.2006.05.030 PMID:16814813

Novotna B, Topinka J, Solansky I, Chvatalova I, Lnenickova Z, Sram RJ (2007). Impact of air pollution and genotype variability on DNA damage in Prague policemen. *Toxicol Lett*, 172(1–2):37–47. doi:10.1016/j.toxlet.2007.05.013 PMID:17590289

O'Neill MS, Jerrett M, Kawachi I, Levy JI, Cohen AJ, Gouveia N et al.; Workshop on Air Pollution and Socioeconomic Conditions (2003). Health, wealth, and air pollution: advancing theory and methods. *Environ Health Perspect*, 111(16):1861–70. doi:10.1289/ehp.6334 PMID:14644658

Oberdörster G (1988). Lung clearance of inhaled insoluble and soluble particles. *J Aerosol Med*, 1(4):289–330. doi:10.1089/jam.1988.1.289

Obolenskaya MY, Teplyuk NM, Divi RL, Poirier MC, Filimonova NB, Zadrozna M et al. (2010). Human placental glutathione *S*-transferase activity and polycyclic aromatic hydrocarbon DNA adducts as biomarkers for environmental oxidative stress in placentas from pregnant women living in radioactivity- and chemically-polluted regions. *Toxicol Lett*, 196(2):80–6. doi:10.1016/j.toxlet.2010.03.1115 PMID:20380873

Oh SM, Kim HR, Park YJ, Lee SY, Chung KH (2011). Organic extracts of urban air pollution particulate matter ($PM_{2.5}$)-induced genotoxicity and oxidative stress in human lung bronchial epithelial cells (BEAS-2B cells). *Mutat Res*, 723(2):142–51. doi:10.1016/j.mrgentox.2011.04.003 PMID:21524716

Ohsawa M, Ochi T, Hayashi H (1983). Mutagenicity in *Salmonella typhimurium* mutants of serum extracts

from airborne particulates. *Mutat Res*, 116(2):83–90. doi:10.1016/0165-1218(83)90099-X PMID:6338361

Ohtani Y, Shimada Y, Ujiiye A (1985). Comparison between mutagenic activities of airborne particulates in Maebashi and in Minato-ku Tokyo. *J Jpn Soc Air Pollut*, 20:463–9.

Ohyama M, Otake T, Adachi S, Kobayashi T, Morinaga K (2007). A comparison of the production of reactive oxygen species by suspended particulate matter and diesel exhaust particles with macrophages. *Inhal Toxicol*, 19:Suppl 1: 157–60. doi:10.1080/08958370701496103 PMID:17886063

Pacini S, Giovannelli L, Gulisano M, Peruzzi B, Polli G, Boddi V et al. (2003). Association between atmospheric ozone levels and damage to human nasal mucosa in Florence, Italy. *Environ Mol Mutagen*, 42(3):127–35. doi:10.1002/em.10188 PMID:14556220

Pagano P, De Zaiacomo T, Scarcella E, Bruni S, Calamosca M (1996). Mutagenic activity of total and particle-sized fractions of urban particulate matter. *Environ Sci Technol*, 30(12):3512–6. doi:10.1021/es960182q

Palli D, Russo A, Masala G, Saieva C, Guarrera S, Carturan S et al. (2001). DNA adduct levels and DNA repair polymorphisms in traffic-exposed workers and a general population sample. *Int J Cancer*, 94(1):121–7. doi:10.1002/ijc.1433 PMID:11668486

Palli D, Saieva C, Grechi D, Masala G, Zanna I, Barbaro A et al. (2004). DNA bulky adducts in a Mediterranean population correlate with environmental ozone concentration, an indicator of photochemical smog. *Int J Cancer*, 109(1):17–23. doi:10.1002/ijc.11687 PMID:14735463

Palli D, Saieva C, Munnia A, Peluso M, Grechi D, Zanna I et al. (2008). DNA adducts and PM_{10} exposure in traffic-exposed workers and urban residents from the EPIC-Florence City study. *Sci Total Environ*, 403(1–3):105–12. doi:10.1016/j.scitotenv.2008.05.041 PMID:18603281

Palli D, Sera F, Giovannelli L, Masala G, Grechi D, Bendinelli B et al. (2009). Environmental ozone exposure and oxidative DNA damage in adult residents of Florence, Italy. *Environ Pollut*, 157(5):1521–5. doi:10.1016/j.envpol.2008.09.011 PMID:18954923

Pastorelli R, Restano J, Guanci M, Maramonte M, Magagnotti C, Allevi R et al. (1996). Hemoglobin adducts of benzo[*a*]pyrene diolepoxide in newspaper vendors: association with traffic exhaust. *Carcinogenesis*, 17(11):2389–94. doi:10.1093/carcin/17.11.2389 PMID:8968053

Pedersen DU, Durant JL, Penman BW, Crespi CL, Hemond HF, Lafleur AL et al. (1999). Seasonal and spatial variations in human cell mutagenicity of respirable airborne particles in the northeastern United States. *Environ Sci Technol*, 33(24):4407–15. doi:10.1021/es9905997

Pedersen DU, Durant JL, Penman BW, Crespi CL, Hemond HF, Lafleur AL et al. (2004). Human-cell mutagens in respirable airborne particles in the northeastern United States. 1. Mutagenicity of fractionated samples. *Environ Sci Technol*, 38(3):682–9. doi:10.1021/es0347282 PMID:14968851

Pedersen DU, Durant JL, Taghizadeh K, Hemond HF, Lafleur AL, Cass GR (2005). Human cell mutagens in respirable airborne particles from the northeastern United States. 2. Quantification of mutagens and other organic compounds. *Environ Sci Technol*, 39(24):9547–60. doi:10.1021/es050886c PMID:16475335

Pedersen M, Vinzents P, Petersen JH, Kleinjans JC, Plas G, Kirsch-Volders M et al. (2006). Cytogenetic effects in children and mothers exposed to air pollution assessed by the frequency of micronuclei and fluorescence in situ hybridization (FISH): a family pilot study in the Czech Republic. *Mutat Res*, 608(2):112–20. doi:10.1016/j.mrgentox.2006.02.013 PMID:16829164

Pedersen M, Wichmann J, Autrup H, Dang DA, Decordier I, Hvidberg M et al. (2009). Increased micronuclei and bulky DNA adducts in cord blood after maternal exposures to traffic-related air pollution. *Environ Res*, 109(8):1012–20. doi:10.1016/j.envres.2009.08.011 PMID:19783246

Peluso M, Bollati V, Munnia A, Srivatanakul P, Jedpiyawongse A, Sangrajrang S et al. (2012). DNA methylation differences in exposed workers and nearby residents of the Ma Ta Phut industrial estate, Rayong, Thailand. *Int J Epidemiol*, 41(6):1753–60, discussion 1761–3. doi:10.1093/ije/dys129 PMID:23064502

Peluso M, Merlo F, Munnia A, Valerio F, Perrotta A, Puntoni R et al. (1998). ^{32}P-postlabeling detection of aromatic adducts in the white blood cell DNA of nonsmoking police officers. *Cancer Epidemiol Biomarkers Prev*, 7(1):3–11. PMID:9456236

Peluso M, Srivatanakul P, Munnia A, Jedpiyawongse A, Ceppi M, Sangrajrang S et al. (2010). Malondialdehyde-deoxyguanosine adducts among workers of a Thai industrial estate and nearby residents. *Environ Health Perspect*, 118(1):55–9. PMID:20056580

Peluso M, Srivatanakul P, Munnia A, Jedpiyawongse A, Meunier A, Sangrajrang S et al. (2008). DNA adduct formation among workers in a Thai industrial estate and nearby residents. *Sci Total Environ*, 389(2–3):283–8. doi:10.1016/j.scitotenv.2007.09.012 PMID:17935758

Peng BC, Ye SH (1995). Investigation on the cytogenetic effects in tunnel bus drivers and conductors. *Chinese J Indust Med*, 6:334–6.

Pereira CE, Heck TG, Saldiva PH, Rhoden CR (2007). Ambient particulate air pollution from vehicles promotes lipid peroxidation and inflammatory responses in rat lung. *Braz J Med Biol Res*, 40(10):1353–9. doi:10.1590/S0100-879X2006005000164 PMID:17713644

Pereira TS, Beltrami LS, Rocha JAV, Broto FP, Comellas LR, Salvadori DM et al. (2013). Toxicogenetic monitoring in urban cities exposed to different airborne

contaminants. *Ecotoxicol Environ Saf*, 90:174–82. doi:10.1016/j.ecoenv.2012.12.029 PMID:23395453

Pereira TS, Gotor GN, Beltrami LS, Nolla CG, Rocha JA, Broto FP et al. (2010). *Salmonella* mutagenicity assessment of airborne particulate matter collected from urban areas of Rio Grande do Sul State, Brazil, differing in anthropogenic influences and polycyclic aromatic hydrocarbon levels. *Mutat Res*, 702(1):78–85. doi:10.1016/j.mrgentox.2010.07.003 PMID:20643224

Perera F, Hemminki K, Jedrychowski W, Whyatt R, Campbell U, Hsu Y et al. (2002). In utero DNA damage from environmental pollution is associated with somatic gene mutation in newborns. *Cancer Epidemiol Biomarkers Prev*, 11(10 Pt 1):1134–7. PMID:12376523

Perera F, Li TY, Zhou ZJ, Yuan T, Chen YH, Qu L et al. (2008). Benefits of reducing prenatal exposure to coal-burning pollutants to children's neurodevelopment in China. *Environ Health Perspect*, 116(10):1396–400. doi:10.1289/ehp.11480 PMID:18941584

Perera FP, Hemminki K, Gryzbowska E, Motykiewicz G, Michalska J, Santella RM et al. (1992). Molecular and genetic damage in humans from environmental pollution in Poland. *Nature*, 360(6401):256–8. doi:10.1038/360256a0 PMID:1436106

Perera FP, Jedrychowski W, Rauh V, Whyatt RM (1999). Molecular epidemiologic research on the effects of environmental pollutants on the fetus. *Environ Health Perspect*, 107:Suppl 3: 451–60. doi:10.1289/ehp.99107s3451 PMID:10346993

Perrone MG, Gualtieri M, Consonni V, Ferrero L, Sangiorgi G, Longhin E et al. (2013). Particle size, chemical composition, seasons of the year and urban, rural or remote site origins as determinants of biological effects of particulate matter on pulmonary cells. *Environ Pollut*, 176:215–27. doi:10.1016/j.envpol.2013.01.012 PMID:23434772

Petruzzelli S, Celi A, Pulerà N, Baliva F, Viegi G, Carrozzi L et al. (1998). Serum antibodies to benzo(a)pyrene diol epoxide-DNA adducts in the general population: effects of air pollution, tobacco smoking, and family history of lung diseases. *Cancer Res*, 58(18):4122–6. PMID:9751623

Piekarska K, Zaciera M, Czarny A, Zaczyńska E (2009). Mutagenic and cytotoxic properties of extracts of suspended particulate matter collected in Wrocław city area. *Environ Prot Eng*, 35:37–48.

Piekarska K, Zaciera M, Czarny A, Zaczyńska E (2011). Application of short-term tests in assessment of atmospheric air pollution. *Environ Prot Eng*, 37:85–98.

Pieters N, Plusquin M, Cox B, Kicinski M, Vangronsveld J, Nawrot TS (2012). An epidemiological appraisal of the association between heart rate variability and particulate air pollution: a meta-analysis. *Heart*, 98(15):1127–35. doi:10.1136/heartjnl-2011-301505 PMID:22628541

Pinkerton KE, Menache M, Plopper CG (1995). Changes in the tracheobronchial epithelium, pulmonary acinus, and lung antioxidant enzyme activity. In: Consequences of prolonged inhalation of ozone on F344 rats: collaborative studies. Research Report No. 65, Parts VIII and IX. Cambridge (MA): Health Effects Institute; pp. 41–98.

Pinkerton KE, Mercer RR, Plopper CG, Crapo JD (1992). Distribution of injury and microdosimetry of ozone in the ventilatory unit of the rat. *J Appl Physiol (1985)*, 73(3):817–24. PMID:1400043

Piperakis SM, Petrakou E, Tsilimigaki S (2000). Effects of air pollution and smoking on DNA damage of human lymphocytes. *Environ Mol Mutagen*, 36(3):243–9. doi:10.1002/1098-2280(2000)36:3<243::AID-EM8>3.0.CO;2-9 PMID:11044906

Pitts JN Jr, Sweetman JA Jr, Harger W, Fitz DR, Paur HR, Winer AM (1985). Diurnal mutagenicity of airborne particulate organic matter adjacent to a heavily traveled West Los Angeles freeway. *J Air Pollut Control Assoc*, 35(6):638–43. doi:10.1080/00022470.1985.10465939 PMID:2410469

Poli P, Buschini A, Restivo FM, Ficarelli A, Cassoni F, Ferrero I et al. (1999). Comet assay application in environmental monitoring: DNA damage in human leukocytes and plant cells in comparison with bacterial and yeast tests. *Mutagenesis*, 14(6):547–56. doi:10.1093/mutage/14.6.547 PMID:10567029

Poma A, Arrizza L, Picozzi P, Spanò L (2002). Monitoring urban air particulate matter (fractions $PM_{2.5}$ and PM_{10}) genotoxicity by plant systems and human cells in vitro: a comparative analysis. *Teratog Carcinog Mutagen*, 22(4):271–84. doi:10.1002/tcm.10020 PMID:12111711

Poma A, Limongi T, Pisani C, Granato V, Picozzi P (2006). Genotoxicity induced by fine urban air particulate matter in the macrophages cell line RAW 264.7. *Toxicol In Vitro*, 20(6):1023–9. doi:10.1016/j.tiv.2006.01.014 PMID:16504459

Postlethwait EM, Bidani A (1990). Reactive uptake governs the pulmonary air space removal of inhaled nitrogen dioxide. *J Appl Physiol (1985)*, 68(2):594–603. PMID:2318771

Postlethwait EM, Langford SD, Bidani A (1991). Transfer of NO_2 through pulmonary epithelial lining fluid. *Toxicol Appl Pharmacol*, 109(3):464–71. doi:10.1016/0041-008X(91)90009-4 PMID:1853345

Postlethwait EM, Langford SD, Jacobson LM, Bidani A (1995). NO_2 reactive absorption substrates in rat pulmonary surface lining fluids. *Free Radic Biol Med*, 19(5):553–63. doi:10.1016/0891-5849(95)00058-6 PMID:8529914

Pratt MM, King LC, Adams LD, John K, Sirajuddin P, Olivero OA et al. (2011). Assessment of multiple types of DNA damage in human placentas from smoking and nonsmoking women in the Czech Republic. *Environ Mol Mutagen*, 52(1):58–68. doi:10.1002/em.20581 PMID:20839217

Preidecker BLB (1980). I. Bacterial mutagenicity of particulates from Houston air. *Environ Mutagen*, 2(1):75–83. doi:10.1002/em.2860020111 PMID:7035159

Pyysalo H, Tuominen J, Wickstrom K, Skyttä E, Tikkanen L, Salomaa S et al. (1987). Polycyclic organic material (POM) in urban air. Fractionation, chemical analysis and genotoxicity of particulate and vapour phases in an industrial town in Finland. *Atmos Environ*, 21(5):1167–80. doi:10.1016/0004-6981(87)90244-7

Qian LM, Zhang BQ (1997). Breakpoint regression in research of airborne particulate genotoxicity. *J Biomath*, 12:93–6.

Qian LM, Zhang BQ, Wang WX (1997). Correlation between genotoxicity of airborne particulates and meteorological condition in Guangzhou city. *Chin J Publ Health*, 16:160–2.

Qin HY, Peng XW, Meng ZJ,, Huang JL, Li Q, Yang XB et al. (2012). $PM_{2.5}$ induced DNA damage in human bronchial epithelial cells [in Chinese]. *J Environ Health*, 29:391–3. Available from: http://www.cnki.net/.

Raaschou-Nielsen O, Andersen ZJ, Beelen R, Samoli E, Stafoggia M, Weinmayr G et al. (2013b). Air pollution and lung cancer incidence in 17 European cohorts: prospective analyses from the European Study of Cohorts for Air Pollution Effects (ESCAPE). *Lancet Oncol*, 14(9):813–22. doi:10.1016/S1470-2045(13)70279-1 PMID:23849838

Raaschou-Nielsen O, Sørensen M, Ketzel M, Hertel O, Loft S, Tjønneland A et al. (2013a). Long-term exposure to traffic-related air pollution and diabetes-associated mortality: a cohort study. *Diabetologia*, 56(1):36–46. PMID:22918192

Rahman MH, Arslan MI, Chen Y, Ali S, Parvin T, Wang LW et al. (2003). Polycyclic aromatic hydrocarbon-DNA adducts among rickshaw drivers in Dhaka City, Bangladesh. *Int Arch Occup Environ Health*, 76(7):533–8. doi:10.1007/s00420-003-0431-z PMID:12827370

Reche C, Moreno T, Amato F, Viana M, van Drooge BL, Chuang HC et al. (2012). A multidisciplinary approach to characterise exposure risk and toxicological effects of PM_{10} and $PM_{2.5}$ samples in urban environments. *Ecotoxicol Environ Saf*, 78:327–35. doi:10.1016/j.ecoenv.2011.11.043 PMID:22177483

Reliene R, Hlavacova A, Mahadevan B, Baird WM, Schiestl RH (2005). Diesel exhaust particles cause increased levels of DNA deletions after transplacental exposure in mice. *Mutat Res*, 570(2):245–52. doi:10.1016/j.mrfmmm.2004.11.010 PMID:15708583

Rhoden CR, Lawrence J, Godleski JJ, González-Flecha B (2004). *N*-acetylcysteine prevents lung inflammation after short-term inhalation exposure to concentrated ambient particles. *Toxicol Sci*, 79(2):296–303. doi:10.1093/toxsci/kfh122 PMID:15056806

Richter E, Rösler S, Scherer G, Gostomzyk JG, Grübl A, Krämer U et al. (2001). Haemoglobin adducts from aromatic amines in children in relation to area of residence and exposure to environmental tobacco smoke. *Int Arch Occup Environ Health*, 74(6):421–8. doi:10.1007/s004200100243 PMID:11563605

Riva DR, Magalhães CB, Lopes AA, Lanças T, Mauad T, Malm O et al. (2011). Low dose of fine particulate matter ($PM_{2.5}$) can induce acute oxidative stress, inflammation and pulmonary impairment in healthy mice. *Inhal Toxicol*, 23(5):257–67. doi:10.3109/08958378.2011.566290 PMID:21506876

Roberts ES, Richards JH, Jaskot R, Dreher KL (2003). Oxidative stress mediates air pollution particle-induced acute lung injury and molecular pathology. *Inhal Toxicol*, 15(13):1327–46. doi:10.1080/08958370390241795 PMID:14569496

Rojas E, Valverde M, Lopez MC, Naufal I, Sanchez I, Bizarro P et al. (2000). Evaluation of DNA damage in exfoliated tear duct epithelial cells from individuals exposed to air pollution assessed by single cell gel electrophoresis assay. *Mutat Res*, 468(1):11–7. doi:10.1016/S1383-5718(00)00035-8 PMID:10863153

Romieu I, Barraza-Villarreal A, Escamilla-Nuñez C, Almstrand AC, Diaz-Sanchez D, Sly PD et al. (2008). Exhaled breath malondialdehyde as a marker of effect of exposure to air pollution in children with asthma. *J Allergy Clin Immunol*, 121(4):903–9.e6. doi:10.1016/j.jaci.2007.12.004 PMID:18234317

Rooney C, Sethi T (2011). The epithelial cell and lung cancer: the link between chronic obstructive pulmonary disease and lung cancer. *Respiration*, 81(2):89–104. doi:10.1159/000323946 PMID:21311210

Rossi C, Poli P, Buschini A, Cassoni F, Cattani S, DeMunari E (1995). Comparative investigations among meteorological conditions, air chemical-physical pollutants and airborne particulate mutagenicity: a long-term study (1990–1994) from a northern Italian town. *Chemosphere*, 30(10):1829–45. doi:10.1016/0045-6535(95)00065-G PMID:7780721

Rossner P Jr, Rossnerova A, Spatova M, Beskid O, Uhlirova K, Libalova H et al. (2013b). Analysis of biomarkers in a Czech population exposed to heavy air pollution. Part II: chromosomal aberrations and oxidative stress. *Mutagenesis*, 28(1):97–106. doi:10.1093/mutage/ges058 PMID:23053823

Rossner P Jr, Rossnerova A, Sram RJ (2011c). Oxidative stress and chromosomal aberrations in an environmentally exposed population. *Mutat Res*, 707(1–2):34–41. doi:10.1016/j.mrfmmm.2010.12.005 PMID:21167186

Rossner P Jr, Svecova V, Milcova A, Lnenickova Z, Solansky I, Santella RM et al. (2007). Oxidative and nitrosative stress markers in bus drivers. *Mutat Res*, 617(1–2):23–32. doi:10.1016/j.mrfmmm.2006.11.033 PMID:17328930

Rossner P Jr, Svecova V, Schmuczerova J, Milcova A, Tabashidze N, Topinka J et al. (2013a). Analysis of biomarkers in a Czech population exposed to

heavy air pollution. Part I: bulky DNA adducts. *Mutagenesis*, 28(1):89–95. doi:10.1093/mutage/ges057 PMID:23047913

Rossner P Jr, Tabashidze N, Dostal M, Novakova Z, Chvatalova I, Spatova M et al. (2011a). Genetic, biochemical, and environmental factors associated with pregnancy outcomes in newborns from the Czech Republic. *Environ Health Perspect*, 119(2):265–71. doi:10.1289/ehp.1002470 PMID:20923744

Rossner P Jr, Uhlirova K, Beskid O, Rossnerova A, Svecova V, Sram RJ (2011b). Expression of *XRCC5* in peripheral blood lymphocytes is upregulated in subjects from a heavily polluted region in the Czech Republic. *Mutat Res*, 713(1–2):76–82. doi:10.1016/j.mrfmmm.2011.06.001 PMID:21684294

Rossnerova A, Spatova M, Rossner P, Solansky I, Sram RJ (2009). The impact of air pollution on the levels of micronuclei measured by automated image analysis. *Mutat Res*, 669(1–2):42–7. doi:10.1016/j.mrfmmm.2009.04.008 PMID:19409399

Rossnerova A, Tulupova E, Tabashidze N, Schmuczerova J, Dostal M, Rossner P Jr et al. (2013). Factors affecting the 27K DNA methylation pattern in asthmatic and healthy children from locations with various environments. *Mutat Res*, 741–742:18–26. doi:10.1016/j.mrfmmm.2013.02.003 PMID:23458556

Roubicek DA, Gutiérrez-Castillo ME, Sordo M, Cebrián-García ME, Ostrosky-Wegman P (2007). Micronuclei induced by airborne particulate matter from Mexico City. *Mutat Res*, 631(1):9–15. doi:10.1016/j.mrgentox.2007.04.001 PMID:17500027

Rowan-Carroll A, Halappanavar S, Williams A, Somers CM, Yauk CL (2013). Mice exposed in situ to urban air pollution exhibit pulmonary alterations in gene expression in the lipid droplet synthesis pathways. *Environ Mol Mutagen*, 54(4):240–9. doi:10.1002/em.21768 PMID:23536514

Rubes J, Lower X, Cassel M, Moore D, Perreault SD, Slott VL et al. (1996). Aneuploidy detection in sperm nuclei using fluorescence in situ hybridization. *Arch Zootec.*, 45(170–171):323–7.

Rubeš J, Pokorná Z, Borkovec L, Urbanová J, Strnadová V (1997). Dairy cattle as a bioindicator of exposure to genotoxic substances in a heavily polluted area in Northern Bohemia. *Mutat Res*, 391(1–2):57–70. doi:10.1016/S0165-1218(97)00032-3 PMID:9219549

Rubes J, Rybar R, Prinosilova P, Veznik Z, Chvatalova I, Solansky I et al. (2010). Genetic polymorphisms influence the susceptibility of men to sperm DNA damage associated with exposure to air pollution. *Mutat Res*, 683(1–2):9–15. doi:10.1016/j.mrfmmm.2009.09.010 PMID:19800896

Rubes J, Selevan SG, Evenson DP, Zudova D, Vozdova M, Zudova Z et al. (2005). Episodic air pollution is associated with increased DNA fragmentation in human sperm without other changes in semen quality. *Hum Reprod*, 20(10):2776–83. doi:10.1093/humrep/dei122 PMID:15980006

Rubes J, Selevan SG, Sram RJ, Evenson DP, Perreault SD (2007). *GSTM1* genotype influences the susceptibility of men to sperm DNA damage associated with exposure to air pollution. *Mutat Res*, 625(1–2):20–8. doi:10.1016/j.mrfmmm.2007.05.012 PMID:17714740

Ruchirawat M, Mahidol C, Tangjarukij C, Pui-ock S, Jensen O, Kampeerawipakorn O et al. (2002). Exposure to genotoxins present in ambient air in Bangkok, Thailand – particle associated polycyclic aromatic hydrocarbons and biomarkers. *Sci Total Environ*, 287(1–2):121–32. doi:10.1016/S0048-9697(01)01008-7 PMID:11883753

Ruchirawat M, Navasumrit P, Settachan D, Autrup H (2006). Environmental impacts on children's health in Southeast Asia: genotoxic compounds in urban air. *Ann N Y Acad Sci*, 1076(1):678–90. doi:10.1196/annals.1371.037 PMID:17119245

Ruchirawat M, Settachan D, Navasumrit P, Tuntawiroon J, Autrup H (2007). Assessment of potential cancer risk in children exposed to urban air pollution in Bangkok, Thailand. *Toxicol Lett*, 168(3):200–9. doi:10.1016/j.toxlet.2006.09.013 PMID:17157453

Rückerl R, Greven S, Ljungman P, Aalto P, Antoniades C, Bellander T et al.; AIRGENE Study Group (2007). Air pollution and inflammation (interleukin-6, C-reactive protein, fibrinogen) in myocardial infarction survivors. *Environ Health Perspect*, 115(7):1072–80. doi:10.1289/ehp.10021 PMID:17637925

Rückerl R, Ibald-Mulli A, Koenig W, Schneider A, Woelke G, Cyrys J et al. (2006). Air pollution and markers of inflammation and coagulation in patients with coronary heart disease. *Am J Respir Crit Care Med*, 173(4):432–41. doi:10.1164/rccm.200507-1123OC PMID:16293802

Rundell KW, Slee JB, Caviston R, Hollenbach AM (2008). Decreased lung function after inhalation of ultrafine and fine particulate matter during exercise is related to decreased total nitrate in exhaled breath condensate. *Inhal Toxicol*, 20(1):1–9. doi:10.1080/08958370701758593 PMID:18236215

Sakitani T, Hayashi K (1986). Mutagenic activities of air pollutants. Part 1. Diurnal and seasonal variations in the concentrations of six polycyclic aromatic hydrocarbons in the urban air and the relationship between their concentrations and mutagenic activities. *Tokyo Jikeikai Med J*, 101:247–57.

Sakitani T, Suzuki Y (1986). Mutagenic activities of air pollutants. Part 2. Mutagenic activities of air pollutants observed by micronucleus test. *Tokyo Jikeikai Med J*, 101:259–66.

Salam MT, Byun H-M, Lurmann F, Breton CV, Wang X, Eckel SP et al. (2012). Genetic and epigenetic variations in inducible nitric oxide synthase promoter, particulate pollution, and exhaled nitric oxide levels in children. *J*

Allergy Clin Immunol, 129(1):232–9.e1–7. doi:10.1016/j.jaci.2011.09.037 PMID:22055874

Saldiva PH, Clarke RW, Coull BA, Stearns RC, Lawrence J, Murthy GG et al. (2002). Lung inflammation induced by concentrated ambient air particles is related to particle composition. *Am J Respir Crit Care Med*, 165(12):1610–7. doi:10.1164/rccm.2106102 PMID:12070061

Samet J, Krewski D (2007). Health effects associated with exposure to ambient air pollution. *J Toxicol Environ Health A*, 70(3–4):227–42. doi:10.1080/15287390600884644 PMID:17365585

Samet JM, DeMarini DM, Malling HV (2004). Biomedicine. Do airborne particles induce heritable mutations? *Science*, 304(5673):971–2. doi:10.1126/science.1097441 PMID:15143266

Samet JM, Rappold A, Graff D, Cascio WE, Berntsen JH, Huang YC et al. (2009). Concentrated ambient ultrafine particle exposure induces cardiac changes in young healthy volunteers. *Am J Respir Crit Care Med*, 179(11):1034–42. doi:10.1164/rccm.200807-1043OC PMID:19234105

Sato MIZ, Valent GU, Coimbrão CA, Coelho MC, Sanchez Sanchez P, Alonso CD et al. (1995). Mutagenicity of airborne particulate organic material from urban and industrial areas of São Paulo, Brazil. *Mutat Res*, 335(3):317–30. doi:10.1016/0165-1161(95)00035-6 PMID:8524347

Schaumann F, Borm PJ, Herbrich A, Knoch J, Pitz M, Schins RP et al. (2004). Metal-rich ambient particles (particulate matter$_{2.5}$) cause airway inflammation in healthy subjects. *Am J Respir Crit Care Med*, 170(8):898–903. doi:10.1164/rccm.200403-423OC PMID:15229099

Scherer G, Frank S, Riedel K, Meger-Kossien I, Renner T (2000). Biomonitoring of exposure to polycyclic aromatic hydrocarbons of nonoccupationally exposed persons. *Cancer Epidemiol Biomarkers Prev*, 9(4):373–80. PMID:10794481

Schilderman PA, Hoogewerff JA, van Schooten FJ, Maas LM, Moonen EJ, van Os BJ et al. (1997). Possible relevance of pigeons as an indicator species for monitoring air pollution. *Environ Health Perspect*, 105(3):322–30. doi:10.1289/ehp.97105322 PMID:9171994

Schins RP, Lightbody JH, Borm PJ, Shi T, Donaldson K, Stone V (2004). Inflammatory effects of coarse and fine particulate matter in relation to chemical and biological constituents. *Toxicol Appl Pharmacol*, 195(1):1–11. doi:10.1016/j.taap.2003.10.002 PMID:14962500

Schneider JC, Card GL, Pfau JC, Holian A (2005). Air pollution particulate SRM 1648 causes oxidative stress in RAW 264.7 macrophages leading to production of prostaglandin E2, a potential Th2 mediator. *Inhal Toxicol*, 17(14):871–7. doi:10.1080/08958370500244498 PMID:16282164

Schwartz J (2004). Air pollution and children's health. *Pediatrics*, 113(4):Suppl): 1037–43. PMID:15060197

Seemayer NH, Hadnagy W, Behrendt H, Tomingas R (1989). Inhalation hazards from airborne particulates evaluated by in vitro cyto- and genotoxicity testing: a long-term study over a period of 14 years (1975–1988) from a highly industrialized area. *Exp Pathol*, 37(1–4):228–30. doi:10.1016/S0232-1513(89)80054-4 PMID:2637158

Seemayer NH, Hadnagy W, Tomingas R (1987a). Mutagenic and carcinogenic effects of airborne particulate matter from polluted areas on human and rodent tissue cultures. *Experientia Suppl*, 51:231–4. doi:10.1007/978-3-0348-7491-5_39 PMID:2958327

Seemayer NH, Hadnagy W, Tomingas R (1990a). Enhancement of cell transformation and induction of sister chromatid exchanges as test systems for detection of seasonal and local differences in genotoxicity of airborne particulates. In: Seemayer NH, Hadnagy W, editors. Environmental hygiene II. Berlin, Germany: Springer-Verlag; pp. 50–3. Available from: doi:10.1007/978-3-642-46712-7_12.

Seemayer NH, Hadnagy W, Tomingas R (1990b). Evaluation of health risks by airborne particulates from in vitro cyto- and genotoxicity testing on human and rodent tissue culture cells: a longitudinal study from 1975 until now. *J Aerosol Sci*, 21:S501–4. doi:10.1016/0021-8502(90)90290-E

Seemayer NH, Hadnagy W, Tomingas R, Manojlovic N (1987b). Cell- and genotoxic activities of airborne particulates from a highly industrialized region: a survey over a period of 11 years (1975–1986). *J Aerosp Sci*, 18(6):721–4. doi:10.1016/0021-8502(87)90106-6

Seemayer NH, Hornberg C, Hadnagy W (1994). Comparative genotoxicity testing of airborne particulates using rodent tracheal epithelial cells and human lymphocytes in vitro. *Toxicol Lett*, 72(1–3):95–103. doi:10.1016/0378-4274(94)90015-9 PMID:8202962

Seemayer NH, Manojlovic N, Konig H, Tomingas R (1988). Comparative investigation of carcinogenic and mutagenic activity of airborne particulate matter from polluted areas using human and rodent tissue culture cells. *Ann Occup Hyg*, 32:247–56. doi:10.1093/annhyg/32.inhaled_particles_VI.247

Seemayer NH, Manojlovic N, Schurer CC, Tomingas R (1984). Cell cultures as a tool for detection of cytotoxic, mutagenic and carcinogenic activity of airborne particulate matter. *J Aerosol Sci*, 15(3):426–30. doi:10.1016/0021-8502(84)90135-6

Selevan SG, Borkovec L, Slott VL, Zudová Z, Rubes J, Evenson DP et al. (2000). Semen quality and reproductive health of young Czech men exposed to seasonal air pollution. *Environ Health Perspect*, 108(9):887–94. doi:10.1289/ehp.00108887 PMID:11017895

Sellappa S, Sadhanandhan B, Francis A, Vasudevan SG (2010). Evaluation of genotoxicity in petrol station workers in South India using micronucleus assay. *Ind*

Health, 48(6):852–6. doi:10.2486/indhealth.MS1055 PMID:20616461

Senlin L, Zhenkun Y, Xiaohui C, Minghong W, Guoying S, Jiamo F et al. (2008). The relationship between physicochemical characterization and the potential toxicity of fine particulates ($PM_{2.5}$) in Shanghai atmosphere. *Atmos Environ*, 42(31):7205–14. doi:10.1016/j.atmosenv.2008.07.030

Sera N, Fukuhara K, Miyata N, Tokiwa H (1994). Detection of nitro-azabenzo[*a*]pyrene derivatives in the semivolatile phase originating from airborne particulate matter, diesel and gasoline vehicles. *Mutagenesis*, 9(1):47–52. doi:10.1093/mutage/9.1.47 PMID:8208130

Sevastyanova O, Binkova B, Topinka J, Sram RJ, Kalina I, Popov T et al. (2007). In vitro genotoxicity of PAH mixtures and organic extract from urban air particles: part II: human cell lines. *Mutat Res*, 620(1–2):123–34. doi:10.1016/j.mrfmmm.2007.03.002 PMID:17420030

Shah PS, Balkhair T; Knowledge Synthesis Group on Determinants of Preterm/LBW Births (2011). Air pollution and birth outcomes: a systematic review. *Environ Int*, 37(2):498–516. doi:10.1016/j.envint.2010.10.009 PMID:21112090

Shang Y, Fan L, Feng J, Lv S, Wu M, Li B et al. (2013). Genotoxic and inflammatory effects of organic extracts from traffic-related particulate matter in human lung epithelial A549 cells: the role of quinones. *Toxicol In Vitro*, 27(2):922–31. doi:10.1016/j.tiv.2013.01.008 PMID:23333790

Shao L, Shi Z, Jones TP, Li J, Whittaker AG, Bérubé KA (2006). Bioreactivity of particulate matter in Beijing air: results from plasmid DNA assay. *Sci Total Environ*, 367(1):261–72. doi:10.1016/j.scitotenv.2005.10.009 PMID:16313948

Sharma AK, Jensen KA, Rank J, White PA, Lundstedt S, Gagne R et al. (2007). Genotoxicity, inflammation and physico-chemical properties of fine particle samples from an incineration energy plant and urban air. *Mutat Res*, 633(2):95–111. doi:10.1016/j.mrgentox.2007.05.013 PMID:17683978

Shen H, Anastasio C (2011). Formation of hydroxyl radical from San Joaquin Valley particles extracted in a cell-free surrogate lung fluid. *Atmos Chem Phys*, 11(18):9671–82. doi:10.5194/acp-11-9671-2011 PMID:22121357

Shen H, Anastasio C (2012). A comparison of hydroxyl radical and hydrogen peroxide generation in ambient particle extracts and laboratory metal solutions. *Atmos Environ (1994)*, 46:665–8. doi:10.1016/j.atmosenv.2011.10.006 PMID:22267949

Shen H, Barakat AI, Anastasio C (2011). Generation of hydrogen peroxide from San Joaquin Valley particles in a cell-free solution. *Atmos Chem Phys*, 11(2):753–65. doi:10.5194/acp-11-753-2011

Shen RR, Sha LY, Wang ZS,, Deng YH, Yang SS (2009). A toxicological study based on DNA damage of inhalable particulates collected in Macao during winter. *China Environ Sci*, 29:991–6.

Shi T, Duffin R, Borm PJ, Li H, Weishaupt C, Schins RP (2006). Hydroxyl-radical-dependent DNA damage by ambient particulate matter from contrasting sampling locations. *Environ Res*, 101(1):18–24. doi:10.1016/j.envres.2005.09.005 PMID:16298360

Shi ZB, Shao LY, Jones TP (2004). Oxidative DNA damage of urban airborne particulates in plasmid DNA assay. *Chin Sci Bull*, 49:673–8.

Shimizu H, Suzuki Y, Hayashi K (1982). Mutagenic activities of urban air pollutants: (part 1) diurnal and seasonal variations of mutagenicity of nitromethane extracts. *Tokyo Jikeikai Med J*, 97:785–95.

Shukla A, Timblin C, BeruBe K, Gordon T, McKinney W, Driscoll K et al. (2000). Inhaled particulate matter causes expression of nuclear factor (NF)-kappaB-related genes and oxidant-dependent NF-kappaB activation in vitro. *Am J Respir Cell Mol Biol*, 23(2):182–7. doi:10.1165/ajrcmb.23.2.4035 PMID:10919984

Sigaud S, Goldsmith CA, Zhou H, Yang Z, Fedulov A, Imrich A et al. (2007). Air pollution particles diminish bacterial clearance in the primed lungs of mice. *Toxicol Appl Pharmacol*, 223(1):1–9. doi:10.1016/j.taap.2007.04.014 PMID:17561223

Singh R, Kaur B, Kalina I, Popov TA, Georgieva T, Garte S et al. (2007b). Effects of environmental air pollution on endogenous oxidative DNA damage in humans. *Mutat Res*, 620(1–2):71–82. doi:10.1016/j.mrfmmm.2007.02.024 PMID:17434188

Singh R, Sram RJ, Binkova B, Kalina I, Popov TA, Georgieva T et al. (2007a). The relationship between biomarkers of oxidative DNA damage, polycyclic aromatic hydrocarbon DNA adducts, antioxidant status and genetic susceptibility following exposure to environmental air pollution in humans. *Mutat Res*, 620(1–2):83–92. doi:10.1016/j.mrfmmm.2007.02.025 PMID:17445838

Škarek M, Cupr P, Bartos T, Kohoutek J, Klánová J, Holoubek I (2007). A combined approach to the evaluation of organic air pollution – a case study of urban air in Sarajevo and Tuzla (Bosnia and Herzegovina). *Sci Total Environ*, 384(1–3):182–93. doi:10.1016/j.scitotenv.2007.06.040 PMID:17675217

Skillrud DM, Offord KP, Miller RD (1986). Higher risk of lung cancer in chronic obstructive pulmonary disease. A prospective, matched, controlled study. *Ann Intern Med*, 105(4):503–7. doi:10.7326/0003-4819-105-4-503 PMID:3752756

Slama R, Darrow L, Parker J, Woodruff TJ, Strickland M, Nieuwenhuijsen M et al. (2008). Meeting report: atmospheric pollution and human reproduction. *Environ Health Perspect*, 116(6):791–8. doi:10.1289/ehp.11074 PMID:18560536

Smith KR, Aust AE (1997). Mobilization of iron from urban particulates leads to generation of reactive oxygen species in vitro and induction of ferritin synthesis

in human lung epithelial cells. *Chem Res Toxicol*, 10(7):828–34. doi:10.1021/tx960164m PMID:9250418

Soares SRC, Bueno-Guimarães HM, Ferreira CM, Rivero DH, De Castro I, Garcia ML et al. (2003). Urban air pollution induces micronuclei in peripheral erythrocytes of mice in vivo. *Environ Res*, 92(3):191–6. doi:10.1016/S0013-9351(02)00061-0 PMID:12804515

Soberanes S, Gonzalez A, Urich D, Chiarella SE, Radigan KA, Osornio-Vargas A et al. (2012). Particulate matter air pollution induces hypermethylation of the p16 promoter via a mitochondrial ROS-JNK-DNMT1 pathway. *Sci Rep*, 2:275 doi:10.1038/srep00275 PMID:22355787

Somers CM (2011). Ambient air pollution exposure and damage to male gametes: human studies and in situ 'sentinel' animal experiments. *Syst Biol Reprod Med*, 57(1–2):63–71. doi:10.3109/19396368.2010.500440 PMID:21208146

Somers CM, Cooper DN (2009). Air pollution and mutations in the germline: are humans at risk? *Hum Genet*, 125(2):119–30. doi:10.1007/s00439-008-0613-6 PMID:19112582

Somers CM, McCarry BE, Malek F, Quinn JS (2004). Reduction of particulate air pollution lowers the risk of heritable mutations in mice. *Science*, 304(5673):1008–10. doi:10.1126/science.1095815 PMID:15143280

Somers CM, Yauk CL, White PA, Parfett CL, Quinn JS (2002). Air pollution induces heritable DNA mutations. *Proc Natl Acad Sci U S A*, 99(25):15904–7. doi:10.1073/pnas.252499499 PMID:12473746

Soogarun S, Suwansaksri J, Wiwanitkit V (2006). High sister chromatid exchange among a sample of traffic policemen in Bangkok, Thailand. *Southeast Asian J Trop Med Public Health*, 37(3):578–80. PMID:17120983

Sørensen M, Autrup H, Hertel O, Wallin H, Knudsen LE, Loft S (2003a). Personal exposure to $PM_{2.5}$ and biomarkers of DNA damage. *Cancer Epidemiol Biomarkers Prev*, 12(3):191–6. PMID:12646506

Sørensen M, Daneshvar B, Hansen M, Dragsted LO, Hertel O, Knudsen L et al. (2003b). Personal $PM_{2.5}$ exposure and markers of oxidative stress in blood. *Environ Health Perspect*, 111(2):161–6. doi:10.1289/ehp.5646 PMID:12573899

Sørensen M, Schins RP, Hertel O, Loft S (2005). Transition metals in personal samples of $PM_{2.5}$ and oxidative stress in human volunteers. *Cancer Epidemiol Biomarkers Prev*, 14(5):1340–3. doi:10.1158/1055-9965.EPI-04-0899 PMID:15894700

Sørensen M, Skov H, Autrup H, Hertel O, Loft S (2003c). Urban benzene exposure and oxidative DNA damage: influence of genetic polymorphisms in metabolism genes. *Sci Total Environ*, 309(1–3):69–80. doi:10.1016/S0048-9697(03)00054-8 PMID:12798093

Srám RJ, Benes I, Binková B, Dejmek J, Horstman D, Kotěsovec F et al. (1996). Teplice program – the impact of air pollution on human health. *Environ Health Perspect*, 104:Suppl 4: 699–714. PMID:8879999

Srám RJ, Beskid O, Rössnerova A, Rössner P, Lnenickova Z, Milcova A et al. (2007). Environmental exposure to carcinogenic polycyclic aromatic hydrocarbons – the interpretation of cytogenetic analysis by FISH. *Toxicol Lett*, 172(1–2):12–20. doi:10.1016/j.toxlet.2007.05.019 PMID:17604575

Šrám RJ, Binkova B, Dostal M, Merkerova-Dostalova M, Libalova H, Milcova A et al. (2013). Health impact of air pollution to children. *Int J Hyg Environ Health*, 216(5):533–40. doi:10.1016/j.ijheh.2012.12.001 PMID:23312845

Srám RJ, Binková B, Rössner P, Rubes J, Topinka J, Dejmek J (1999). Adverse reproductive outcomes from exposure to environmental mutagens. *Mutat Res*, 428(1–2):203–15. doi:10.1016/S1383-5742(99)00048-4 PMID:10517994

Srám RJ, Podrazilová K, Dejmek J, Mracková G, Pilcík T (1998). Single cell gel electrophoresis assay: sensitivity of peripheral white blood cells in human population studies. *Mutagenesis*, 13(1):99–103. doi:10.1093/mutage/13.1.99 PMID:9491403

Sree Devi V, Durga Rao V, Hara Gopal VV, Siva Prasad B, Sandhya Devi G, Jyothy A et al. (2009). Cytogenetic evaluation of traffic policemen occupationally exposed to vehicular exhaust. *Indian J Med Res*, 130(5):520–5. PMID:20090099

Sreedevi V, Hemaprasad M, Sandhyadevi G, Reddy PP (2006). Induction of sister chromatid exchanges in traffic policemen exposed to vehicular exhaust. *Mutat Res*, 606(1–2):80–4. doi:10.1016/j.mrgentox.2006.03.004 PMID:16697248

Staessen JA, Nawrot T, Hond ED, Thijs L, Fagard R, Hoppenbrouwers K et al. (2001). Renal function, cytogenetic measurements, and sexual development in adolescents in relation to environmental pollutants: a feasibility study of biomarkers. *Lancet*, 357(9269):1660–9. doi:10.1016/S0140-6736(00)04822-4 PMID:11425371

Stahlhofen W, Scheuch G, Bailey MR (1995). Investigations of retention of inhaled particles in the human bronchial tree. *Radiat Prot Dosimetry*, 60:311–9.

Steerenberg PA, Nierkens S, Fischer PH, van Loveren H, Opperhuizen A, Vos JG et al. (2001). Traffic-related air pollution affects peak expiratory flow, exhaled nitric oxide, and inflammatory nasal markers. *Arch Environ Health*, 56(2):167–74. doi:10.1080/00039890109604069 PMID:11339681

Stieb DM, Chen L, Eshoul M, Judek S (2012). Ambient air pollution, birth weight and preterm birth: a systematic review and meta-analysis. *Environ Res*, 117:100–11. doi:10.1016/j.envres.2012.05.007 PMID:22726801

Stoeger T, Reinhard C, Takenaka S, Schroeppel A, Karg E, Ritter B et al. (2006). Instillation of six different ultrafine carbon particles indicates a surface area

threshold dose for acute lung inflammation in mice. *Environ Health Perspect*, 114(3):328–33. doi:10.1289/ehp.8266 PMID:16507453

Strak M, Hoek G, Godri KJ, Gosens I, Mudway IS, van Oerle R et al. (2013). Composition of PM affects acute vascular inflammatory and coagulative markers – the RAPTES project. *PLoS ONE*, 8(3):e58944 doi:10.1371/journal.pone.0058944 PMID:23516583

Strak M, Janssen NA, Godri KJ, Gosens I, Mudway IS, Cassee FR et al. (2012). Respiratory health effects of airborne particulate matter: the role of particle size, composition, and oxidative potential – the RAPTES project. *Environ Health Perspect*, 120(8):1183–9. doi:10.1289/ehp.1104389 PMID:22552951

Strandell M, Zakrisson S, Alsberg T, Westerholm R, Winquist L, Rannug U (1994). Chemical analysis and biological testing of a polar fraction of ambient air, diesel engine, and gasoline engine particulate extracts. *Environ Health Perspect*, 102:Suppl 4: 85–92. doi:10.1289/ehp.94102s485 PMID:7529708

Sun TY, Li YF, Gao HN, Yang SL (1995). Mutagenic effect of extracts of ambient air fallout particulates on germ cells of male mice. *Carcinog Teratog Mutagen*, 7:180–4.

Tablin F, den Hartigh LJ, Aung HH, Lame MW, Kleeman MJ, Ham W et al. (2012). Seasonal influences on CAPs exposures: differential responses in platelet activation, serum cytokines and xenobiotic gene expression. *Inhal Toxicol*, 24(8):506–17. doi:10.3109/08958378.2012.695815 PMID:22746400

Taioli E, Sram RJ, Garte S, Kalina I, Popov TA, Farmer PB (2007). Effects of polycyclic aromatic hydrocarbons (PAHs) in environmental pollution on exogenous and oxidative DNA damage (EXPAH project): description of the population under study. *Mutat Res*, 620(1–2):1–6. doi:10.1016/j.mrfmmm.2007.02.016 PMID:17420032

Takagi Y, Sakiya K, Endoh O, Goto S, Kohzaki K, Murata M et al. (1992). Mutagenicity of airborne particulates in Sagamihara City. *J Vet Med Sci*, 54(2):193–9. doi:10.1292/jvms.54.193 PMID:1606249

Takeda N, Teranishi K, Hamada K (1983). Mutagenicity in *Salmonella typhimurium* TA98 of the serum extract of the organic matter derived from airborne particulates. *Mutat Res*, 117(1–2):41–6. doi:10.1016/0165-1218(83)90151-9 PMID:6339909

Tan MG, Wu YF, Li HY, Li Y, Zhang G, Shao S et al. (2004). Cytotoxicities of PM_{10} airborne particulates on human blood lymphocytes [in Chinese]. *Stud Trace Elem Health*, 21:1–4.

Tan MG, Wu YF, Shao SS, Li HY, Zou MJ, Dong M et al. (2002). Determination of TSP in the Da Pu tunnel of Shanghai and study of its chromosome aberration effect for human peripheral blood lymphocytes [in Chinese]. *Stud Trace Elem Health*, 19:51–4.

Tang D, Li TY, Liu JJ, Chen YH, Qu L, Perera F (2006). PAH-DNA adducts in cord blood and fetal and child development in a Chinese cohort. *Environ Health Perspect*, 114(8):1297–300. doi:10.1289/ehp.8939 PMID:16882543

Tang D, Li TY, Liu JJ, Zhou ZJ, Yuan T, Chen YH et al. (2008). Effects of prenatal exposure to coal-burning pollutants on children's development in China. *Environ Health Perspect*, 116(5):674–9. doi:10.1289/ehp.10471 PMID:18470301

Tao F, Gonzalez-Flecha B, Kobzik L (2003). Reactive oxygen species in pulmonary inflammation by ambient particulates. *Free Radic Biol Med*, 35(4):327–40. doi:10.1016/S0891-5849(03)00280-6 PMID:12899936

Tao F, Kobzik L (2002). Lung macrophage-epithelial cell interactions amplify particle-mediated cytokine release. *Am J Respir Cell Mol Biol*, 26(4):499–505. doi:10.1165/ajrcmb.26.4.4749 PMID:11919087

Tarantini A, Maitre A, Lefebvre E, Marques M, Marie C, Ravanat JL et al. (2009). Relative contribution of DNA strand breaks and DNA adducts to the genotoxicity of benzo[*a*]pyrene as a pure compound and in complex mixtures. *Mutat Res*, 671(1–2):67–75. doi:10.1016/j.mrfmmm.2009.08.014 PMID:19733579

Tokiwa H, Kitamori S, Nakagawa R, Horikawa K, Matamala L (1983). Demonstration of a powerful mutagenic dinitropyrene in airborne particulate matter. *Mutat Res*, 121(2):107–16. doi:10.1016/0165-7992(83)90108-2 PMID:6348530

Topinka J, Schwarz LR, Wiebel FJ, Cerná M, Wolff T (2000). Genotoxicity of urban air pollutants in the Czech Republic. Part II. DNA adduct formation in mammalian cells by extractable organic matter. *Mutat Res*, 469(1):83–93. doi:10.1016/S1383-5718(00)00061-9 PMID:10946245

Topinka J, Sevastyanova O, Binkova B, Chvatalova I, Milcova A, Lnenickova Z et al. (2007). Biomarkers of air pollution exposure – a study of policemen in Prague. *Mutat Res*, 624(1–2):9–17. doi:10.1016/j.mrfmmm.2007.02.032 PMID:17493640

Török G, Csik M, Kertesz M, Fay E, Somorjay T, Börzsönyi M et al. (1989). Mutagenicity and PAH content of airborn particulates and of fallen dusts from two Hungarian towns and emission samples from aluminum reduction and power plants. *Ann Ist Super Sanita*, 25(4):595–9. PMID:2631626

Toyokuni S, Sagripanti JL (1992). Iron-mediated DNA damage: sensitive detection of DNA strand breakage catalyzed by iron. *J Inorg Biochem*, 47(3–4):241–8. doi:10.1016/0162-0134(92)84069-Y PMID:1431883

Toyokuni S, Sagripanti JL (1994). Increased 8-hydroxydeoxyguanosine in kidney and liver of rats continuously exposed to copper. *Toxicol Appl Pharmacol*, 126(1):91–7. doi:10.1006/taap.1994.1094 PMID:8184438

Traversi D, Schilirò T, Degan R, Pignata C, Alessandria L, Gilli G (2011). Involvement of nitro-compounds in the mutagenicity of urban $PM_{2.5}$ and PM_{10} in Turin. *Mutat Res*, 726(1):54–9. doi:10.1016/j.mrgentox.2011.09.002 PMID:21920459

Tsai DH, Amyai N, Marques-Vidal P, Wang JL, Riediker M, Mooser V et al. (2012). Effects of particulate matter on inflammatory markers in the general adult population. *Part Fibre Toxicol*, 9(1):24 doi:10.1186/1743-8977-9-24 PMID:22769230

Tsou TC, Chen CL, Liu TY, Yang JL (1996). Induction of 8-hydroxydeoxyguanosine in DNA by chromium(III) plus hydrogen peroxide and its prevention by scavengers. *Carcinogenesis*, 17(1):103–8. doi:10.1093/carcin/17.1.103 PMID:8565117

Tuntawiroon J, Mahidol C, Navasumrit P, Autrup H, Ruchirawat M (2007). Increased health risk in Bangkok children exposed to polycyclic aromatic hydrocarbons from traffic-related sources. *Carcinogenesis*, 28(4):816–22. doi:10.1093/carcin/bgl175 PMID:17071945

Tuominen J, Salomaa S, Pyysalo H, Skytta E, Tikkanen L, Nurmela T et al. (1988). Polynuclear aromatic compounds and genotoxicity in particulate and vapor phases of ambient air: effect of traffic, season, and meteorological conditions. *Environ Sci Technol*, 22(10):1228–34. doi:10.1021/es00175a017 PMID:22148620

Turner MC, Chen Y, Krewski D, Calle EE, Thun MJ (2007). Chronic obstructive pulmonary disease is associated with lung cancer mortality in a prospective study of never smokers. *Am J Respir Crit Care Med*, 176(3):285–90. doi:10.1164/rccm.200612-1792OC PMID:17478615

Ulrich MM, Alink GM, Kumarathasan P, Vincent R, Boere AJ, Cassee FR (2002). Health effects and time course of particulate matter on the cardiopulmonary system in rats with lung inflammation. *J Toxicol Environ Health A*, 65(20):1571–95. doi:10.1080/00984100290071676 PMID:12396869

Umbuzeiro GA, Franco A, Martins MH, Kummrow F, Carvalho L, Schmeiser HH et al. (2008). Mutagenicity and DNA adduct formation of PAH, nitro-PAH, and oxy-PAH fractions of atmospheric particulate matter from São Paulo, Brazil. *Mutat Res*, 652(1):72–80. doi:10.1016/j.mrgentox.2007.12.007 PMID:18294902

UNEP (1999). Phasing lead out of gasoline: an analysis of policy approaches in different countries. Paris, France: United Nations Environment Programme. Available from: www.un.org/esa/gite/iandm/unep-lead.pdf.

Upadhyay D, Panduri V, Ghio A, Kamp DW (2003). Particulate matter induces alveolar epithelial cell DNA damage and apoptosis: role of free radicals and the mitochondria. *Am J Respir Cell Mol Biol*, 29(2):180–7. doi:10.1165/rcmb.2002-0269OC PMID:12600817

Valavanidis A, Fiotakis K, Bakeas E, Vlahogianni T (2005). Electron paramagnetic resonance study of the generation of reactive oxygen species catalysed by transition metals and quinoid redox cycling by inhalable ambient particulate matter. *Redox Rep*, 10(1):37–51. doi:10.1179/135100005X21606 PMID:15829110

Valavanidis A, Salika A, Theodoropoulou A (2000). Generation of hydroxyl radicals by urban suspended particulate air matter. The role of iron ions. *Atmos Environ*, 34(15):2379–86. doi:10.1016/S1352-2310(99)00435-5

van Eeden SF, Tan WC, Suwa T, Mukae H, Terashima T, Fujii T et al. (2001). Cytokines involved in the systemic inflammatory response induced by exposure to particulate matter air pollutants (PM_{10}). *Am J Respir Crit Care Med*, 164(5):826–30. doi:10.1164/ajrccm.164.5.2010160 PMID:11549540

van Houdt JJ, Alink GM, Boleij JSM (1987). Mutagenicity of airborne particles related to meteorological and air pollution parameters. *Sci Total Environ*, 61:23–36. doi:10.1016/0048-9697(87)90353-6

van Leeuwen DM, Pedersen M, Hendriksen PJ, Boorsma A, van Herwijnen MH, Gottschalk RW et al. (2008). Genomic analysis suggests higher susceptibility of children to air pollution. *Carcinogenesis*, 29(5):977–83. doi:10.1093/carcin/bgn065 PMID:18332047

van Leeuwen DM, van Herwijnen MH, Pedersen M, Knudsen LE, Kirsch-Volders M, Sram RJ et al. (2006). Genome-wide differential gene expression in children exposed to air pollution in the Czech Republic. *Mutat Res*, 600(1-2):12–22. doi:10.1016/j.mrfmmm.2006.05.032 PMID:16814814

van Maanen JMS, Borm PJA, Knaapen A, van Herwijnen M, Schilderman PA, Smith KR et al. (1999). In vitro effects of coal fly ashes: hydroxyl radical generation, iron release, and DNA damage and toxicity in rat lung epithelial cells. *Inhal Toxicol*, 11(12):1123–41. doi:10.1080/089583799196628 PMID:10562700

Vattanasit U, Navasumrit P, Khadka MB, Kanitwithayanun J, Promvijit J, Autrup H et al. (2014). Oxidative DNA damage and inflammatory responses in cultured human cells and in humans exposed to traffic-related particles. *Int J Hyg Environ Health*, 217(1):23–33. doi:10.1016/j.ijheh.2013.03.002 PMID:23567252

Vellosi R, Vannucchi C, Bianchi F, Fiorio R, Rosellini D, Ciacchini G et al. (1994). Mutagenic activity and chemical analysis of airborne particulates collected in Pisa (Italy). *Bull Environ Contam Toxicol*, 52(3):465–73. doi:10.1007/BF00197838 PMID:7511445

Vesterdal LK, Jantzen K, Sheykhzade M, Roursgaard M, Folkmann JK, Loft S et al. (2014). Pulmonary exposure to particles from diesel exhaust, urban dust or single-walled carbon nanotubes and oxidatively damaged DNA and vascular function in *apoE*$^{-/-}$ mice. *Nanotoxicology*, 8(1):61–71. doi:10.3109/17435390.2012.750385 PMID:23148895

Viau CJ, Lockard JM, Enoch HG, Sabharwal PS (1982). Comparison of the genotoxic activities of extracts from ambient and forest fire polluted air. *Environ Mutagen*, 4(1):37–43. doi:10.1002/em.2860040106 PMID:7040069

Victorin K (1994). Review of the genotoxicity of nitrogen oxides. *Mutat Res*, 317(1):43–55. doi:10.1016/0165-1110(94)90011-6 PMID:7507572

Victorin K (1996). Genotoxicity and carcinogenicity of ozone. *Scand J Work Environ Health*, 22:Suppl 3: 42–51. PMID:9122655

Villalobos-Pietrini R, Amador-Muñoz O, Waliszewski S, Hernández-Mena L, Munive-Colín Z, Gómez-Arroyo S et al. (2006). Mutagenicity and polycyclic aromatic hydrocarbons associated with extractable organic matter from airborne particles ≤10 µm in south-west Mexico City. *Atmos Environ*, 40(30):5845–57. doi:10.1016/j.atmosenv.2006.05.009

Villarini M, Moretti M, Fatigoni C, Agea E, Dominici L, Mattioli A et al. (2008). Evaluation of primary DNA damage, cytogenetic biomarkers and genetic polymorphisms for *CYP1A1* and *GSTM1* in road tunnel construction workers. *J Toxicol Environ Health A*, 71(21):1430–9. doi:10.1080/15287390802328580 PMID:18800292

Vinitketkumnuen U, Kalayanamitra K, Chewonarin T, Kamens R (2002). Particulate matter, PM_{10} & $PM_{2.5}$ levels, and airborne mutagenicity in Chiang Mai, Thailand. *Mutat Res*, 519(1–2):121–31. doi:10.1016/S1383-5718(02)00130-4 PMID:12160897

Vinzents PS, Møller P, Sørensen M, Knudsen LE, Hertel O, Jensen FP et al. (2005). Personal exposure to ultrafine particles and oxidative DNA damage. *Environ Health Perspect*, 113(11):1485–90. doi:10.1289/ehp.7562 PMID:16263500

Viras LG, Athanasiou K, Siskos PA (1990). Determination of mutagenic activity of airborne particulates and of the benzo[α]pyrene concentrations in Athens atmosphere. *Atmos Environ Part B Urban Atmos*, 24(2):267–74. doi:10.1016/0957-1272(90)90032-P

Wang CY, Lee MS, King CM, Warner PO (1980). Evidence for nitroaromatics as direct-acting mutagens of airborne particulates. *Chemosphere*, 9(2):83–7. doi:10.1016/0045-6535(80)90093-4

Wang XY, Ding GW (1998). Induction of SCE in human peripheral blood lymphocytes by TSP in Lanzhou region. *China Pub Health*, 14:417–8.

Wang XZ, Zhang YE (1984). The mutation test research on the indoor air pollutants and the outdoor ones. *J Harbin Med Univ*, 1:56–61.

Wang Y, Long DH, Zhu HG, Zhou DH (1991). Mutagenicity of total suspended particulate in the air of Beijing detected by micronucleus test in mice. *China Environ Sci*, 11:401–4.

Watanabe N (2000). Urinary 17-KS and 17-OHCS as markers of endocrine disruption by air pollution in primary school children. *Environ Health Prev Med*, 4(4):221–3. doi:10.1007/BF02931262 PMID:21432489

Watterson TL, Sorensen J, Martin R, Coulombe RA Jr (2007). Effects of $PM_{2.5}$ collected from Cache Valley Utah on genes associated with the inflammatory response in human lung cells. *J Toxicol Environ Health A*, 70(20):1731–44. doi:10.1080/15287390701457746 PMID:17885930

Watts R, Fitzgerald B, Heil G, Garabedian H, Williams R, Warren S et al. (1989). Use of bioassay methods to evaluate mutagenicity of ambient air collected near a municipal waste combustor. *JAPCA*, 39(11):1436–9. doi:10.1080/08940630.1989.10466636 PMID:2607359

Wei A, Meng Z (2006a). Evaluation of micronucleus induction of sand dust storm fine particles ($PM_{2.5}$) in human blood lymphocytes. *Environ Toxicol Pharmacol*, 22(3):292–7. doi:10.1016/j.etap.2006.04.003 PMID:21783723

Wei A, Meng Z (2006b). Induction of chromosome aberrations in cultured human lymphocytes treated with sand dust storm fine particles ($PM_{2.5}$). *Toxicol Lett*, 166(1):37–43. doi:10.1016/j.toxlet.2006.05.010 PMID:16814966

Wei AL, Meng ZQ (2006c). Genetic damage of dust storm fine particles on human blood lymphocytes. *J Environ Health*, 23:291–3.

Wei AL, Meng ZQ, Niu RF (2006). Effects of dust storm fine particles ($PM_{2.5}$) on micronuclei formation in human blood lymphocytes. *Acta Scientiae Circumstaniae*, 26:509–14.

Wei YH, Chang KT, Chiang PC, Chang SC (1991). Analysis and tracing of polycyclic aromatic hydrocarbons and mutagenicity of airborne particulates from the Taipei area. *Proc Natl Sci Counc Repub China B*, 15(1):53–62. PMID:1946812

White PA, Claxton LD (2004). Mutagens in contaminated soil: a review. *Mutat Res*, 567(2–3):227–345. doi:10.1016/j.mrrev.2004.09.003 PMID:15572286

Whittaker A, BéruBé K, Jones T, Maynard R, Richards R (2004). Killer smog of London, 50 years on: particle properties and oxidative capacity. *Sci Total Environ*, 334–335:435–45. doi:10.1016/j.scitotenv.2004.04.047 PMID:15504529

WHO (2006). Air quality guidelines, global update 2005. Copenhagen: World Health Organization Regional Office for Europe. Available from: http://www.who.int/phe/health_topics/outdoorair/outdoorair_aqg/en/.

Whyatt RM, Santella RM, Jedrychowski W, Garte SJ, Bell DA, Ottman R et al. (1998). Relationship between ambient air pollution and DNA damage in Polish mothers and newborns. *Environ Health Perspect*, 106:Suppl 3: 821–6. doi:10.1289/ehp.98106821 PMID:9646044

Wigle DT, Arbuckle TE, Turner MC, Bérubé A, Yang Q, Liu S et al. (2008). Epidemiologic evidence of relationships between reproductive and child health outcomes and environmental chemical contaminants. *J Toxicol Environ Health B Crit Rev*, 11(5–6):373–517. doi:10.1080/10937400801921320 PMID:18470797

Wise H, Balharry D, Reynolds LJ, Sexton K, Richards RJ (2006). Conventional and toxicogenomic assessment of the acute pulmonary damage induced by the instillation of Cardiff PM_{10} into the rat lung. *Sci Total Environ*,

360(1–3):60–7. doi:10.1016/j.scitotenv.2005.08.056 PMID:16597461

Wolff GT, Siak JS, Chan TL, Korsog PE (1986). Multivariate statistical analyses of air quality data and bacterial mutagenicity data from ambient aerosols. *Atmos Environ Part A Gen Top*, 20(11):2231–41. doi:10.1016/0004-6981(86)90314-8

Wu S, Deng F, Wei H, Huang J, Wang H, Shima M et al. (2012). Chemical constituents of ambient particulate air pollution and biomarkers of inflammation, coagulation and homocysteine in healthy adults: a prospective panel study. *Part Fibre Toxicol*, 9(1):49 doi:10.1186/1743-8977-9-49 PMID:23231781

Wullenweber M, Ketseridis G, Xander L, Ruden H (1982). Seasonal variations in the mutagenicity of urban aerosols, sampled in Berlin (West), with *Salmonella typhimurium* TA 98 (Ames test). *Staub Reinhalt Luft*, 42:411–5.

Xiao ZH, Shao LY, Zhang N (2009). A toxicological assessment of PM_{10} in Lanzhou: results from plasmid DNA assay. *China Environ Sci*, 29:561–6.

Xu DQ, Niu JP, Wan XZ, Wang YX, Chen XY, Xu J (2008b). DNA damages of fine particles from sandstorm in rat alveolar macrophages. *J Environ Health*, 25:67–8.

Xu DQ, Zhang WL (2004). Monitoring of pollution of air fine particles ($PM_{2.5}$) and study on their genetic toxicity. *Biomed Environ Sci*, 17(4):452–8. PMID:15745250

Xu H, Wang X, Pöschl U, Feng S, Wu D, Yang L et al. (2008a). Genotoxicity of total and fractionated extractable organic matter in fine air particulate matter from urban Guangzhou: comparison between haze and nonhaze episodes. *Environ Toxicol Chem*, 27(1):206–12. doi:10.1897/07-095.1 PMID:18092867

Xu HJ, Wang XM (2008). A comparison of comet assay and cell-blocked micronucleus for studying the genotoxicity of organic components in air particulate matters from urban area of Guangzhou. *China Trop Med*, 8:1321–3.

Yamaguchi T, Yamazaki H, Yamauchi A, Kakiuchi Y (1994). Mutagenicity of airborne particulates in a roadside atmosphere. *Jpn J Toxicol Environ Health*, 40(6):542–9. doi:10.1248/jhs1956.40.542

Yang K, Airoldi L, Pastorelli R, Restano J, Guanci M, Hemminki K (1996). Aromatic DNA adducts in lymphocytes of humans working at high and low traffic density areas. *Chem Biol Interact*, 101(2):127–36. doi:10.1016/0009-2797(96)03720-9 PMID:8760394

Yang WM, Wu BY (1984). Mutagenic study of airborne particulates: chromosomal aberrations in bone marrow cells in mice. *J Environ Health*, 1:11–4.

Yang WM, Wu BY, Ma YP (1994). Content of PAHs in different diameter airborne particles and relationship with their mutagenicity. *J Environ Health*, 11:10–3.

Yao JQ, Zhao XS, Zhu HG (1993). Mutagenicity of total suspended particulate in air by micronucleus test in mice. *Shanghai Environ Sci*, 12:18–20.

Yauk C, Polyzos A, Rowan-Carroll A, Somers CM, Godschalk RW, Van Schooten FJ et al. (2008). Germline mutations, DNA damage, and global hypermethylation in mice exposed to particulate air pollution in an urban/industrial location. *Proc Natl Acad Sci U S A*, 105(2):605–10. doi:10.1073/pnas.0705896105 PMID:18195365

Yauk CL (2004). Advances in the application of germline tandem repeat instability for in situ monitoring. *Mutat Res*, 566(2):169–82. doi:10.1016/j.mrrev.2003.08.001 PMID:15164979

Yauk CL, Fox GA, McCarry BE, Quinn JS (2000). Induced minisatellite germline mutations in herring gulls (*Larus argentatus*) living near steel mills. *Mutat Res*, 452(2):211–8. doi:10.1016/S0027-5107(00)00093-2 PMID:11024480

Yauk CL, Quinn JS (1996). Multilocus DNA fingerprinting reveals high rate of heritable genetic mutation in herring gulls nesting in an industrialized urban site. *Proc Natl Acad Sci U S A*, 93(22):12137–41. doi:10.1073/pnas.93.22.12137 PMID:8901546

Yi S, Zhang F, Qu F, Ding W (2014). Water-insoluble fraction of airborne particulate matter (PM_{10}) induces oxidative stress in human lung epithelial A549 cells. *Environ Toxicol*, 29(2):226–33. doi:10.1002/tox.21750 PMID:22331617

Yu ZY, Zhu HG, Jiang SH (1989). An investigation of mutagenicity of airborne particles in a gaswork in Shanghai. *J Health Toxicol*, 3:239–41.

Yuan FS, Ma YP, Wu ZC (1999a). Content of metals in different diameter airborne particles and effect on micronuclei formation in human lymphocytes [in Chinese]. *Wei Sheng Yan Jiu*, 28:21–2.

Yuan FS, Ma YP, Zhai WH (1999b). Effects of airborne particle sizes on micronuclei frequency in human binucleate lymphocytes. *J Health Toxicol*, 13:132–3.

Yuan FS, Xun Q (1994). Study of unscheduled DNA synthesis in human amnion cell FL induced atmospheric particles. *J Prev Med Chin People's Liberation Army*, 12:274–6.

Yuan FS, Xun Q, Ma YP (1994). Unscheduled DNA synthesis induced in human amnion cell FL by various-size atmospheric particles. *J Environ Health*, 11:49–51.

Zhang JH, Yang WM, Xu YW (2004). DNA damages in peripheral blood lymphocytes induced by organic extracts from ambient air particulates with various diameters [in Chinese]. *J Environ Health*, 21(2):88–90. Available from: http://www.cnki.net/kcms/detail/detail.aspx?filename=HJYJ200402012&dbcode=CJFQ&dbname=CJFD2004

Zhang M, Fu JL, He LY Wang Y, Hu M, Zhu T et al. (2003). Studies on the genetic and epigenetic toxicity of airborne fine particulate matter in Beijing. *China Environ Sci*, 23:337–40. Available from: http://en.cnki.

com.cn/Article_en/CJFDTOTAL-ZGHJ200304000.htm.

Zhang W, Lei TA, Lin ZQ, Zhang H-S, Yang D-F, Xi Z-G et al. (2011). Pulmonary toxicity study in rats with PM_{10} and $PM_{2.5}$: differential responses related to scale and composition. *Atmos Environ*, 45(4):1034–41. doi:10.1016/j.atmosenv.2010.10.043

Zhang XW, Li JW (1994). Effect of airborne particulate on sister chromatid exchange of lymphocytes of human peripheral blood. *J Lanzhou Med Coll*, 22:218–9.

Zhang XW, Zhang Z, Zhang XY, Yang WM (2002). Study on chromosomal damage induced by organic extracts of air particulates. *J Environ Health*, 19:200–1.

Zhang Y, Schauer JJ, Shafer MM, Hannigan MP, Dutton SJ (2008). Source apportionment of in vitro reactive oxygen species bioassay activity from atmospheric particulate matter. *Environ Sci Technol*, 42(19):7502–9. doi:10.1021/es800126y PMID:18939593

Zhao X, Niu J, Wang Y, Yan C, Wang X, Wang J (1998). Genotoxicity and chronic health effects of automobile exhaust: a study on the traffic policemen in the city of Lanzhou. *Mutat Res*, 415(3):185–90. doi:10.1016/S1383-5718(98)00066-7 PMID:9714799

Zhao X, Wan Z, Chen G, Zhu H, Jiang S, Yao J (2002). Genotoxic activity of extractable organic matter from urban airborne particles in Shanghai, China. *Mutat Res*, 514(1–2):177–92. doi:10.1016/S1383-5718(01)00338-2 PMID:11815256

Zhao X, Wan Z, Zhu H, Chen R (2003). The carcinogenic potential of extractable organic matter from urban airborne particles in Shanghai, China. *Mutat Res*, 540(1):107–17. doi:10.1016/S1383-5718(03)00178-5 PMID:12972063

Zhao XH, Wang XL, Niu JP, Wang J (2001). Pollution status and mutagenicity of particles in heavy traffic road of Lanzhou. *Acta Scientiae Circumstantiae*, 21:444–7.

Zhao XS, Zhu HG, Jiang SH, Yao JQ (1996). The mutagenic study of organic extract of suspended particulates in Shanghai. *Carcinog Teratog Mutagen*, 8:78–84.

Zhu CQ, Lam T, Jiang CQ, Wei BX, Chen YH, Xu QR (2003). A study on lymphocyte DNA damage in traffic policemen in Guangzhou [in Chinese]. *Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi*, 21(1):41–4. PMID:14761571

Zidzik J, Kalina I, Salagovic J, Sram RJ, Rössner P, Popov T et al. (2007). Influence of PAHs in ambient air on chromosomal aberrations in exposed subjects: international study – EXPAH. *Mutat Res*, 620(1–2):41–8. doi:10.1016/j.mrfmmm.2007.02.021 PMID:17391715

Zuurbier M, Hoek G, Oldenwening M, Meliefste K, Krop E, van den Hazel P et al. (2011). In-traffic air pollution exposure and CC16, blood coagulation, and inflammation markers in healthy adults. *Environ Health Perspect*, 119(10):1384–9. doi:10.1289/ehp.1003151 PMID:21665568

Zwanenburg TS (1988). Comparative analysis of the clastogenicity and cytotoxicity of airborne particulate matter generated during the fire at Schweizerhalle on November 1, 1986. *Mutat Res*, 206(3):395–409. doi:10.1016/0165-1218(88)90126-7 PMID:3200259

5. SUMMARY OF DATA REPORTED

5.1 Exposure data

5.1.1 The agent and its components

Air pollutants are ubiquitous – from anthropogenic activities and natural processes – and global, and cross international boundaries. Levels of individual contaminants can vary dramatically between locations, due to the contributing sources and atmospheric processing, which mixes and transforms pollutants and transports them across great distances. Several important species are formed in the atmosphere and are not directly emitted. Air pollution is a mixture of mixtures, which can be viewed from source-oriented or component-oriented perspectives. Any outdoor air pollution mixture includes gases and suspended particles that are constantly interacting. Gaseous pollutants include photochemical oxidants, numerous organic compounds, carbon monoxide (CO), volatile metals, and nitrogenous and sulfurous species. Suspended particles (a heterogeneous mixture of liquids and solids referred to as particulate matter [PM]) are also a very complex mixture, with variable and dynamic chemical composition and physical characteristics. Many of the individual species and mixtures present in air have been classified by IARC as Group 1 (e.g. benzene, benzo[*a*]pyrene, chromium (VI), and dioxin) and Group 2A carcinogens.

5.1.2 Sources

Although there are many sources of outdoor air pollution, the largest contributors of air pollutants in many locations are: mobile sources; stationary power generation; other industrial and agricultural emissions; residential heating and cooking; re-emission from terrestrial and aquatic surfaces; the manufacturing, distribution, and use of chemicals; and natural sources. The distribution of these sources, the implementation of emissions control technologies, and the resulting emissions vary considerably between and within regions. Many of these sources have diurnal, weekly, and seasonal patterns in emissions. Some important regional trends in source contributions to air pollution include: (1) substantial contributions from residential burning of solid fuels in developing countries in Asia, Africa, and parts of South America; (2) substantial contributions from coal-fired power plants in China; (3) substantial contributions from stationary sources in heavily industrialized cities where advanced emissions controls are not present; (4) large episodic dust storms in Asia, Africa, and the Middle East; and (5) mobile sources, which contribute to varying degrees in urban areas.

5.1.3 Measurement methods

A wide variety of measurement methods are applied to measure concentrations of air pollutants. Therefore, comparisons of measurements across space or time need to consider

these differences. Most methods for regulated gaseous pollutants, such as CO, nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and ozone, use in situ continuous monitors for hourly averaged (or shorter-duration) concentrations, whereas PM is most often measured using integrated sampling systems on filter substrates for air passed through size-selective inlets to determine mass concentration and major components such as multi-elements, ions, and carbon. Passive sampling is increasingly used to assess spatial variation, particularly for gases. With specified standard operating procedures and quality assurance/quality control, within- and between-network consistency may be achieved.

5.1.4 Environmental occurrence

In some countries outdoor air quality is monitored routinely in networks. Measurement methods and site selection differ between networks, partially limiting comparisons between countries. Satellite-based approaches provide global estimates, filling the gaps for a limited number of pollutants (e.g. PM with particles of aerodynamic diameter < 2.5 μm [$PM_{2.5}$], NO_2, SO_2, and formaldehyde). Network and satellite data have shown large variability across countries of concentrations of PM with particles of aerodynamic diameter < 10 μm (PM_{10}), $PM_{2.5}$, NO_2, and other pollutants. Annual average $PM_{2.5}$ concentrations range from below 10 μg/m^3 to well above 100 μg/m^3. In many areas, World Health Organization (WHO) air quality guidelines for $PM_{2.5}$ are substantially exceeded. High $PM_{2.5}$ concentrations are observed in South and East Asia and North Africa. High NO_2 concentrations are observed in areas with high population density and traffic density. Within countries, high concentrations are observed in urban areas and around traffic sites and industrial locations. Significant spatial variability is present, related to urban–rural differences and proximity to sources or source areas.

Trends differ by pollutant and region of the world. In North America and Europe, concentrations of major pollutants such as PM, SO_2, and NO_2 have decreased substantially in the past 30 years. In many developing countries, concentrations have increased with rapid economic development.

5.1.5 Exposure assessment in epidemiological studies

Epidemiological studies of relationships between air pollution exposure and cancer require long periods of observation and large populations. Therefore, it is almost impossible with currently available approaches to assess exposure via personal monitoring. Rather, epidemiological studies use measured or modelled concentrations of outdoor air pollution as the primary basis for exposure estimation. Air quality monitoring is usually limited to measurements of a relatively small number of indicator pollutants collected at discrete locations. Epidemiological studies have typically used centrally located outdoor monitors or geostatistical averaging of multiple measurements within a single study area in analyses of between-area variation in exposure, and various modelling techniques (e.g. atmospheric transport and land-use regression models), sometimes in combination with detailed spatial and temporal measurements, to assign individual estimates of exposure. Evaluation of these models indicates that they can accurately estimate outdoor concentrations at residential locations. More recently, satellite-based estimates, sometimes in combination with land-use information, have been used to produce relatively high resolution and compatible estimates of concentrations at national (and even global) scales, including rural areas, where in situ measurements are generally not available. Since it is important to estimate exposures over long time periods, assessments can be improved by using both estimates of air pollution concentrations for extended time

periods and residential histories for the study population of interest.

5.1.6 Personal exposure

Personal exposure is typically not used to assess exposure in epidemiological studies of air pollution and cancer but can be used to assess the agreement with outdoor exposure estimates. Human biomarkers of exposure provide information about individual exposures that may be used in evaluation studies.

There is strong evidence that temporal variation of outdoor concentration is correlated with temporal variation of personal exposure to fine particles. The few studies that have evaluated the agreement between average outdoor concentration estimated at a fine scale and personal exposure have generally found a moderate agreement, which differed between pollutants and studies. A few studies comparing personal exposure of subjects in cities with different outdoor air pollution concentrations have shown a strong correlation between average personal exposure and city-average outdoor concentration.

Personal exposure to air pollution is determined by the pollutant concentration in the microenvironment and by the time–activity patterns and location of individuals, including outdoors, indoors, and in transit. Personal exposures differ from those estimated based solely on outdoor concentrations because of time–activity patterns, variable infiltration of outdoor air pollution into indoor environments, and indoor sources. Thus, for studies of health effects of outdoor air pollution, the contributions from indoor and outdoor sources to total personal exposure should be considered separately.

People generally spend a large fraction of their time indoors (typically about 80–90%). A substantial fraction of the time spent indoors is spent in the home, supporting the assessment of exposure based upon the residential address. Because of the high fraction of time spent indoors, infiltration of outdoor pollution indoors is an important factor that modifies exposure. Infiltration varies substantially between pollutants and homes/buildings and by season. Relatively high infiltration factors (≥ 0.5) have generally been found for fine particles (particularly sulfate and elemental carbon) and CO. Lower infiltration factors have been found for ultrafine and especially coarse particles, NO_2, and ozone. For pollutants with lower infiltration factors, the potential for misclassification of exposure based on outdoor concentrations is higher. Infiltration factors are affected strongly by air exchange rates, which differ between homes and by season. Despite the typically small fraction of their time (< 10%) that people spend in traffic, the contribution to average personal exposure may be substantial because of the high concentrations found in traffic areas. Outdoor workers such as street vendors, traffic police, and toll booth operators experience long exposure durations and elevated exposure levels.

5.1.7 Guidelines and regulations

Given the chemical complexity of outdoor air pollution and the large number of anthropogenic sources, air pollution is managed with a combination of air quality standards for selected pollutants, regulation of sources, emissions permitting, and indirect control of sources, such as land-use regulation. Although the regulatory framework for outdoor air pollution control differs considerably across countries and across local government agencies within countries, most regions of the world have air quality standards for key air pollutants (ozone, SO_2, NO_2, CO, and PM, although there is limited specification on the components of PM). The control of these pollutants has beneficial consequences for the control of other pollutants. Useful air quality regulations include an indicator, a specified averaging time, and a statistical form, which is effectively the number of exceedances that are allowed. In

some locations where air quality standards have not been developed, WHO guidelines are used as a reference for air quality management. In many locations around the world, compliance with air quality standards and WHO guidelines is not achieved.

5.2 Human carcinogenicity data

5.2.1 Cancer of the lung

The association of exposure to outdoor air pollution with lung cancer risk has been examined in cohort and case–control studies conducted in countries in Europe, North America, Asia, and Oceania. Several of these are large studies of general population cohorts with individual-level information on cancer risk factors, including tobacco smoking, and with quantitative estimates of exposure to outdoor air pollution. Some relevant information is also available from studies of workers exposed to outdoor air pollution in their jobs. Other studies have evaluated the occurrence of lung cancer in populations potentially exposed to emissions from various specific sources and industries.

In evaluating the evidence from these epidemiological studies, the Working Group placed the greatest weight on cohort studies with quantitative exposure data within the general population. The most commonly examined pollutant in these studies was $PM_{2.5}$. The studies provided information on other indicators of atmospheric PM, including PM_{10}, total suspended particles, and black smoke, and other common components of air pollution, including nitrogen oxides (NO_x), NO_2, SO_2, and ozone. Several studies included indicators of exposure to traffic based on proximity to roads or traffic volume. The spatial and temporal scale at which the exposures were assessed in these studies varied widely, and few studies specifically considered exposure-time–response relationships.

Large cohort studies have been conducted almost exclusively in high-income countries, mostly in North America and Europe, and results of some studies have been reported in numerous publications. The follow-up of these studies extends from as early as the 1970s through 2010. During that period, outdoor air pollution levels generally declined in North America and Europe. The Working Group judged that among the North American studies, the Harvard Six Cities Study, the analyses of the American Cancer Society (ACS) cohort (especially the results for never-smokers), and the California Teachers Study (particularly its analysis for never-smokers) were the most informative for the evaluation of carcinogenicity. Among the European cohort studies, those judged to be most informative were studies conducted in Oslo (Norway), the Netherlands, Denmark, and Rome (Italy), and a Europe-wide study of 17 cohorts from the ESCAPE study. Of studies in other areas of the world, one study from New Zealand and two studies from Japan were considered to be the most informative because of the detailed exposure assessment or adjustment for potential confounders, including indoor air pollution.

Two large cohort studies – the European ESCAPE study and the ACS study in the USA – are particularly informative for their large scale, exposure assessment based on actual measurements, the broad range of exposures considered, very detailed information about potential confounders (e.g. duration and intensity of smoking), and standardization of methods. In addition, the ESCAPE study had incidence data and histological classification of lung cancer cases.

The Working Group also considered case–control studies in Europe and North America. Considering study design, availability of quantitative exposure estimates, sample size, and ability to control for confounders, the Working Group judged that population-based studies conducted since 1990 in Canada, Poland, and Sweden were informative.

Earlier case–control studies (before 1990) had several limitations: some were based on

deceased subjects, had a low response rate among controls, had a small sample size, used rather crude exposure assessment methods, and lacked adjustment for smoking as a possible confounder. Consequently, the Working Group gave these studies little weight.

Other case–control studies of populations potentially exposed to local sources of industrial emissions were reviewed but were considered to be less informative of a relationship between the general air pollution mixture and lung cancer risk because of the unique nature of the exposure sources and methodological limitations similar to those of the group of studies mentioned previously.

Overall, studies with quantitative measures of outdoor air pollution showed positive associations with lung cancer in both sexes and in cohort and case–control studies from all regions, with the potential confounding and effect modification by tobacco smoking accounted for by adjustment or stratification. A large number of potential individual- and area-level confounders were considered in the most informative studies, and overall there was no evidence of a substantial impact of these factors on the estimated associations. Some studies provided analyses stratified by smoking or restricted to never-smokers, and associations of lung cancer with outdoor air pollution were similarly observed in these studies.

Most cohort and case–control studies estimated relative risks using multiplicative models with a continuous variable for exposure, which assumes a linear exposure–response relationship. Evaluation of alternatives to a linear exposure–response model (i.e. smoothed terms or categorical modelling) was reported in the Harvard Six Cities Study, the ACS study, the Canadian case–control study, the Rome study, and the ESCAPE study. All studies that assessed smoothed exposure–response relationships found no statistically significant deviation from linearity. The results obtained with these approaches were consistent with those described previously, generally indicating increasing risk of lung cancer with increasing levels of exposure.

The available studies used a range of quantitative or qualitative estimates of exposure. Quantitative estimates were mainly for PM ($PM_{2.5}$ or PM_{10}) and NO_2 or NO_x. Qualitative or semi-quantitative estimates included traffic density or distance from heavy-traffic roads. The relative risk estimates for $PM_{2.5}$ and PM_{10} were indicative of positive associations in almost all the studies. When exposure–response relationships were examined, these generally indicated increasing risk of lung cancer with increasing levels of exposure to PM. There also was a suggestion of increasing risk with increasing levels of exposure to NO_2 and/or NO_x, but results were inconsistent.

In summary, both cohort and case–control studies with exposures assessed in the population setting, involving millions of subjects and many thousands of lung cancer cases in different parts of the world, consistently showed an association between exposure to **outdoor air pollution** and the risk of lung cancer, in both sexes and after adjustment for the main potential confounders. The association was present in almost all studies that specifically investigated the association of lung cancer and outdoor air pollution among never-smokers. Positive exposure–response relationships were reported in several studies. Although all of the studies are subject to error in estimating exposure, the most likely effect of such error is attenuation of the risk estimates. While not definitive in themselves because of the limitations noted previously, the findings of occupational cohort studies suggesting an association between professional driving and risk of lung cancer are supportive.

In addition to considering **particulate matter in outdoor air** as an indicator of the overall air pollution mixture, the Working Group also evaluated PM as a causal agent using the same body of epidemiological evidence. Because most evidence for an association between outdoor air

pollution and cancer comes from results for PM, the evidence for PM and lung cancer is generally similar to that for outdoor air pollution as a whole. Positive exposure–response relationships have been observed, and confounding and other forms of bias can be excluded with reasonable confidence for the reasons described previously. A challenge in interpreting the observed associations for PM lies in determining whether they are an effect of PM as a causal agent or of PM as a surrogate for the outdoor air pollution mixture or other components of it. One hypothetical alternative to PM as a causal agent is the existence of gas-phase carcinogens, highly correlated with PM concentration, that are the actual cause of lung cancer attributed to PM. However, this alternative is unrealistic and is contradicted by the known presence of multiple carcinogens in airborne PM. Furthermore, associations have been observed in multiple locations with different pollution mixtures, and lung cancer risk increases with increasing concentrations of mass-based PM indicators.

The Working Group also considered the evidence on traffic in relation to the risk of lung cancer. These studies used diverse approaches to estimate exposure to traffic. Six studies used measures of traffic intensity or distance from heavy-traffic roads as surrogate measures of exposure to traffic-related air pollution, and the reported associations with lung cancer were inconsistent. Four studies, including one that also reported associations for qualitative indicators of traffic exposure, explicitly modelled NO_2 or NO_x from traffic using dispersion models. Three other studies labelled NO_2 estimates as indicators of exposure to traffic, but the Working Group did not consider them exclusively as such because the estimates also included other sources of NO_2. The Working Group considered the evidence on pollution from traffic sources as supportive of an overall relationship between lung cancer and outdoor air pollution.

5.2.2 Cancer of the urinary bladder

Seven studies with cohort or case–control designs directly evaluated the association of cancer of the bladder with metrics of exposure to outdoor air pollution, traffic, or traffic fumes. In several studies, some of which adjusted for tobacco smoking, an increased risk of bladder cancer was associated with these exposure metrics.

Several studies also demonstrated a higher risk among people who were occupationally exposed to potentially high levels of outdoor air pollution after accounting for tobacco smoking. Since these studies involved occupations (specifically taxi, bus, and truck drivers) as surrogate indicators of exposure to outdoor air pollution, and specific air pollutants were not measured, the Working Group did not place as much weight on these studies in its evaluation.

5.2.3 Other cancer sites

The Working Group also reviewed in detail studies of breast cancer, leukaemia and lymphoma, and several other cancers in addition to those of the lung and bladder. The evidence of carcinogenicity for these sites was based on a relatively small number of informative studies, and the observed associations were inconsistent.

However, the Working Group noted that weak associations with childhood leukaemia (especially acute lymphoblastic leukaemia) could not be ruled out. Some of these were reported in studies that were informative because they were large, were population-based, used incidence as the end-point, used validated exposure assessment methods, had no potential for recall bias, and had no or limited potential for selection bias. Although the associations with childhood leukaemia were suggestive, they were inconsistent. There was also a tendency for stronger associations to be published in the smaller studies, indicating evidence for potential publication bias.

5.3 Animal carcinogenicity data

5.3.1 Studies of air pollutants evaluated in previous IARC Monographs

The Working Group reviewed and updated studies in experimental animals of the carcinogenicity of several components of air pollution that were evaluated in previous *IARC Monographs*. Inhalation exposure to emissions from combustion of coal caused high incidence of malignant lung tumours in two studies in mice and one study in rats. Emissions from combustion of wood caused an increased incidence of lung tumours (mainly adenocarcinomas) in one study in mice but not in another study in rats. Four skin application or subcutaneous injection studies using coal-derived soot extracts in mice and two subcutaneous injection studies using wood smoke extracts in mice showed increased incidences of lung cancers or skin tumours. Only one new skin application study using wood smoke extract in mice (judged inadequate for the evaluation) and no new studies on emissions from combustion of coal were available to the Working Group since the previous *IARC Monographs* evaluation.

It has been shown in 11 studies in rats that whole diesel engine exhaust from engines produced before 2000 caused an increased incidence of benign and/or malignant lung tumours after long-term inhalation exposure. All studies in mice exposed to whole diesel engine exhaust were negative except one, which showed inconsistent results. No increase in the incidence of lung tumours was observed in hamsters exposed to whole diesel engine exhaust. The gas phase of diesel engine exhaust (i.e. without particles) did not cause an increase in lung tumours in mice, rats, or hamsters. Diesel engine exhaust particles caused malignant lung tumours in rats after intratracheal instillation in one study. Extracts of diesel engine exhaust particles caused malignant lung tumours in rats after intrapulmonary implantation in one study and malignant fibrous histiocytomas in mice after subcutaneous injection in another study. Only one new skin application study using diesel engine exhaust particle extract in mice (a negative study) was available to the Working Group since the previous *IARC Monographs* evaluation.

In previous studies, no lung tumours were observed in rats, hamsters, or dogs after inhalation exposure to whole gasoline engine exhaust. However, gasoline engine exhaust condensates induced malignant tumours of the skin in three skin application studies in mice, malignant lung tumours in one intrapulmonary implantation study in rats, and pulmonary adenomas in one intratracheal instillation study in hamsters. No new studies on gasoline engine exhaust were available to the Working Group since the previous *IARC Monographs* evaluation.

5.3.2 Inhalation studies of exposure to outdoor air

In one study in male and female mice, in a first experiment, traffic-related outdoor air pollution in São Paulo, Brazil, caused an increase in the incidence of lung adenoma and increased the incidence and multiplicity of urethane-induced lung adenoma. In a second experiment, traffic-related outdoor air pollution promoted urethane-induced lung adenoma incidence in a dose-dependent manner. In another study in female mice, exposure to traffic-related outdoor air pollution in São Paulo increased the average number of lung adenomas per urethane-exposed animal. In a third study in mice exposed to traffic-related outdoor air pollution in São Paulo, there was no increase in the multiplicity of urethane-induced lung adenomas.

A study in male and female mice exposed to outdoor air in Los Angeles, USA, which gave inconsistent results, was judged inadequate for the evaluation.

A study in male and female rats exposed to outdoor air in Los Angeles gave negative results.

5.3.3 Non-inhalation studies of exposure to outdoor air

In a subcutaneous injection study in male and female mice, the crude benzene extract of PM sampled from outdoor air increased the incidence of injection-site tumours (mainly sarcomas and fibrosarcomas). In a second study in mice, a benzene extract increased the incidence of local fibrosarcomas. In a third study in female mice, several benzene extracts increased the incidence of injection-site sarcomas. In a fourth study in pre-weaned mice, a benzene extract increased the incidence of pulmonary adenocarcinoma and of multiple pulmonary adenoma in male and female mice. In a fifth study in newborn mice, a benzene extract of PM sampled from outdoor air increased the incidence of hepatoma in male mice and of multiple pulmonary adenoma in male and female mice. In a sixth study in newborn mice, different fractions of a benzene extract increased the incidence of tumours in male and female mice. In a seventh study in newborn mice, a neutral fraction of outdoor air particulates increased the incidence of pulmonary adenoma in male and female mice. Two studies in mice were judged inadequate for the evaluation.

In a skin application study in male and female mice, the benzene extract of PM sampled from outdoor air increased the incidence of skin papilloma and squamous cell carcinoma. Another skin application study in male and female mice was judged inadequate for the evaluation. In two two-stage carcinogenesis studies in mice, skin application of dichloromethane extracts initiated skin papillomas promoted by 12-*O*-tetradecanoylphorbol-13-acetate (TPA). A study on the role of aryl hydrocarbon receptor (AhR) using $AhR^{+/+}$ and $AhR^{-/-}$ female mice was judged inadequate for the evaluation.

One intraperitoneal injection study of benzene extract of PM sampled from outdoor air in mice and one intravenous injection study of PM sampled from outdoor air in mice were negative.

One intratracheal instillation study in male rats exposed to an extract of PM sampled from outdoor air was judged inadequate for the evaluation.

5.4 Mechanistic and other relevant data

5.4.1 Toxicokinetic considerations, including inhalation, deposition, clearance, and metabolism

The toxicokinetics of several classes of compounds that contribute to outdoor air pollution have been described in earlier *IARC Monographs* (see Section 4.1).

Some PM present in outdoor air is poorly soluble in water and may thus persist in the respiratory tract, producing effects associated with particle toxicity, such as inflammation and oxidative stress. The deposition of particles in the respiratory tract depends primarily on the size of the inhaled particle, the route of breathing, and the breathing pattern. Particles that deposit in the tracheobronchial region are cleared by mucociliary clearance; for particles that deposit in the alveolar region, the primary mechanism of clearance is phagocytosis by alveolar macrophages, followed by migration of the macrophages to the terminal bronchioles and subsequent mucociliary clearance. Particles that are cleared via the mucociliary escalator, whether from the tracheobronchial region or the alveolar region, can then be swallowed or expectorated. If swallowed, they will pass through the gastrointestinal tract and will subsequently be eliminated via the gut.

The deposition and clearance of particles can vary across individuals, depending on age, sex, tobacco smoking status, and pre-existing diseases such as asthma or chronic obstructive pulmonary disease.

Inhaled lipophilic organic vapours and gases readily distribute throughout the respiratory tract and are absorbed into the blood. Organic

compounds in PM or adsorbed to atmospheric PM can be extracted by biological fluids.

Many studies in humans that investigated the exposure and metabolism of organic substances adsorbed to PM in outdoor air have used measurements such as urinary concentrations of hydroxylated polycyclic aromatic hydrocarbons (PAHs) as indicators of exposure and metabolism. These studies have demonstrated the ability of humans to be exposed to carcinogenic organic pollutants such as PAHs and, moreover, to adsorb, distribute, metabolize, and excrete the metabolites. Additional studies have described haemoglobin adducts of nitro-PAHs and low-molecular-weight alkenes. Collectively, the results showed that urinary 1-hydroxypyrene and haemoglobin adducts (hydroxyethyl-valine and hydroxypropyl-valine) were present in populations exposed to outdoor air pollution.

5.4.2 Genetic and related effects of outdoor air pollution

(a) In humans

Studies have investigated the ability of unaltered outdoor air to induce genetic and related effects in humans and experimental systems that are mechanistically linked to cancer. Studies of people exposed to outdoor air pollution in occupational settings (e.g. traffic police, mail carriers, and newspaper vendors) or by living in areas with elevated levels of outdoor air pollution have shown enhanced frequencies of genetic damage (chromosomal aberrations and micronuclei) in lymphocytes of exposed individuals compared with controls. In addition, studies have shown an association between selected genetic polymorphisms, such as glutathione *S*-transferase M1 (*GSTM1*) null, and an increased frequency of genotoxic damage. A single observational study of newborns in an area with elevated levels of outdoor air pollution showed an increased frequency of somatic mutations in lymphocytes. These studies, which cover several countries, collectively confirm the induction of end-points that are empirically and mechanistically linked to increased risk of cancer in humans.

Many studies have shown significant elevation in the levels of DNA adducts in lymphocytes of humans exposed to elevated levels of outdoor air pollution in occupational and urban settings. These findings are supported by a more limited number of studies detecting blood protein adducts.

Studies that examined humans exposed to elevated levels of outdoor air pollution have also documented epigenetic alterations such as changes in DNA methylation patterns and telomere shortening.

(b) In experimental systems

(i) Experimental animals

Experimental studies of rodents exposed to outdoor air in situ provided evidence that outdoor air pollution in urban/industrial areas, especially the particulate fraction, induces heritable germ-cell mutations and cytogenetic damage. Experimental studies of plants exposed to outdoor air pollution at a range of locations also showed induction of mutations and cytogenetic damage.

There is also strong evidence that outdoor air PM or samples derived from outdoor air PM can induce increases in cytogenetic damage in animals.

(ii) Human and animal cells

There is strong evidence that organic extracts, aqueous extracts, or suspensions of outdoor air PM collected from a range of locations induce mutations and cytogenetic effects (chromosomal aberrations, aneuploidy, micronuclei, and sister chromatid exchanges), bulky DNA adducts, DNA strand breaks, oxidatively generated DNA lesions, and formation of reactive oxygen species in cultured human lymphocytes, human cell lines, cultured animal primary cells, animal cell lines in vitro, and naked DNA. Evidence from

source apportionment studies indicates that contributions from mobile-source emissions and residential heating combustion emissions are significant; chemical fractionation of PM extracts revealed contributions from several chemical classes, including non-polar compounds (e.g. PAHs), semipolar compounds (e.g. nitro-PAHs and quinones), and polar compounds (e.g. organic acids and hydroxy-polycyclic aromatic compounds).

(c) In bacteria

There is strong evidence that organic solvent extracts of outdoor air PM representing a wide range of locations, source emissions, seasons, and meteorological conditions induce mutations in bacteria. Published results generally show less than 10-fold variation in the mutagenic potency of PM extracts, expressed per milligram of PM or per microgram of extractable organic matter, across a wide range of locations and site conditions (i.e. source contributions, weather, season, and land use). In contrast, atmospheric mutagenic activity expressed per cubic metre varies by more than 5 orders of magnitude across locations and site conditions (i.e. season, source contributions, and land use), and increased atmospheric mutagenic activity is empirically related to increased levels of atmospheric PM. A large portion of the observed spatial and temporal variations in atmospheric mutagenic activity expressed per cubic metre can be attributed to variations in measured levels of suspended PM.

The atmospheric mutagenic activity at locations described as urban and/or industrial is generally about 2-fold higher compared with locations described as rural and/or residential. Similarly, the atmospheric mutagenic activity measured during colder months is generally about 2-fold higher compared with warmer months. High atmospheric mutagenic activity has been associated with emissions from both mobile and stationary combustion sources, and has been shown to be positively associated with higher levels of NO_x, PAHs, nitro-PAHs, lead, and SO_2. Chemical fractionation studies have noted that a significant portion of the mutagenic activity of organic extracts of outdoor air PM is associated with the moderately polar and polar organic fractions, and includes a wide range of substances, many of which have not been well characterized. Analyses of the non-particulate semivolatile organic compounds (SVOCs) fraction of outdoor air indicate that a significant fraction of the mutagens associated with the solvent-extractable portion of PM from polluted outdoor air may occur as organic vapours.

5.4.3 Other data relevant to carcinogenicity

Some studies have documented increased levels of DNA fragmentation in sperm in young men exposed to polluted outdoor air in an urban location. In addition, human observational studies have shown that exposure to polluted outdoor air in urban/industrial areas or outdoor occupational settings altered the expression of genes involved in DNA damage repair, cell-cycle control, inflammation, and response to oxidative stress.

One experimental exposure of human subjects to concentrated PM from outdoor air showed significant induction of inflammation, a physiological change that has been linked to tumour progression.

Several studies have demonstrated that organic solvent extracts of PM collected from urban environments cause oncogenic transformation of cultured animal cells. Moreover, cells transformed by in vitro exposures to organic solvent extracts of urban PM formed malignant tumours when injected into immunocompromised mice. There is also evidence that exposure of animal cells to PM induces inflammatory reactions, assessed mainly as secretion of cytokines and chemokines, and experimental evidence has linked the inflammation reaction in cultured cells to oxidative stress and metal-catalysed

production of reactive oxygen species. This association between exposure to PM and secretion of cytokines is observed especially in lung epithelial cells and macrophages.

5.4.4 Susceptibility

The available scientific information indicates that certain groups of individuals, such as the elderly, children, and individuals with conditions such as emphysema, bronchitis, and cardiovascular illness, are especially sensitive to the health effects of toxicants in outdoor air. It is recognized that obstructive pulmonary disorders increase lung cancer risk via abnormal immune system regulation and chronic inflammation. The risk of human cancer is related to age and sex via differences in PM deposition patterns and in the capacity to metabolize organic compounds adsorbed to PM.

Polymorphisms in carcinogen-metabolizing genes have been studied as part of human biomonitoring studies investigating the frequency of cytogenetic damage in individuals exposed to polluted outdoor air, and polymorphisms such as the *GSTM1* null genotype, alone or in combination with *CYP1A1* polymorphisms, are associated with an increased risk of genetic and related effects linked to cancer.

5.4.5 Mechanistic considerations

In conclusion, there is *strong mechanistic evidence* for the ability of outdoor air pollution, as well as many of its components, to induce a myriad of genetic and related effects in humans and a wide range of experimental systems. Well-documented genotoxic effects include bulky DNA adducts, DNA strand breaks, oxidatively damaged DNA bases, genetic mutations and chromosomal damage in somatic cells, gametic mutations, and oncogenic transformation in vitro. Molecular epidemiology studies in humans have documented significant empirical associations between the frequencies of DNA damage (i.e. adducts in lymphocytes) and cytogenetic damage (e.g. chromosomal translocations and micronuclei) and exposures to PM in outdoor air and/or levels of carcinogenic PAHs in outdoor PM. In addition, several studies in humans provide evidence of an empirical association between the frequency of stable adducts in lymphocytes of individuals occupationally exposed to outdoor air and levels of outdoor PM or levels of PAHs associated with outdoor PM. Bulky adducts and cytogenetic damage have been shown to be predictive of cancer in humans. Documented changes in gene expression in response to exposures to PM or organic solvent extracts of PM include genes involved in metabolism and activation of mutagenic carcinogens, responses to DNA damage and oxidative stress, alterations of cell-cycle control, and inflammation. The multiplicity of substantiated effects documented in humans as well as in experimental systems in vivo and in vitro supports the assertion that outdoor air pollution, as well as many of its components, is capable of initiating the development of human pulmonary cancers via a genotoxic mechanism and, moreover, of promoting the progress of tumour development via oxidative stress, responses to oxidative stress, and sustained inflammation.

6. EVALUATION

6.1 Cancer in humans

There is *sufficient evidence* in humans for the carcinogenicity of outdoor air pollution. Outdoor air pollution causes cancer of the lung. A positive association has been observed between exposure to outdoor air pollution and cancer of the urinary bladder.

There is *sufficient evidence* in humans for the carcinogenicity of particulate matter in outdoor air pollution. Particulate matter in outdoor air pollution causes cancer of the lung.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of organic solvent-extracted material from particles collected from outdoor air.

There is *sufficient evidence* in experimental animals for the carcinogenicity of particulate matter in outdoor air pollution.

There is *sufficient evidence* in experimental animals for the carcinogenicity of outdoor air pollution.

For the second evaluation, the Working Group considered the data on solvent-extracted material from particles collected from outdoor air and the evidence on the carcinogenicity of diesel engine exhaust particles. The third evaluation was based on findings of studies in experimental animals exposed to polluted outdoor air (in São Paulo, Brazil) in conjunction with updating and confirming the following evaluations:

There is *sufficient evidence* in experimental animals for the carcinogenicity of whole diesel engine exhaust, *sufficient evidence* in experimental animals for the carcinogenicity of emissions from combustion of coal, and *limited evidence* in experimental animals for the carcinogenicity of emissions from combustion of wood; and there is *sufficient evidence* in experimental animals for the carcinogenicity of diesel engine exhaust particles and of extracts of diesel engine exhaust particles, *sufficient evidence* in experimental animals for the carcinogenicity of condensates of gasoline engine exhaust, *sufficient evidence* in experimental animals for the carcinogenicity of extracts from coal-derived soot, and *sufficient evidence* in experimental animals for the carcinogenicity of wood smoke extracts.

6.3 Overall evaluation

Outdoor air pollution is *carcinogenic to humans (Group 1)*.

Particulate matter in outdoor air pollution is *carcinogenic to humans (Group 1)*.

The sufficient evidence in humans and experimental animals was also strongly supported by the multiplicity of documented genetic and related effects in humans and experimental systems. This strong mechanistic evidence indicated that outdoor air pollution worldwide is mutagenic and is carcinogenic to humans via genotoxicity. Human exposures to outdoor air pollution or particulate matter in polluted outdoor air are

associated with increases in genetic damage that have been shown to be predictive of cancer in humans. Moreover, exposure to outdoor air pollution can promote cancer progression via oxidative stress, responses to oxidative stress, and sustained inflammation.

LIST OF ABBREVIATIONS

AAQS	ambient air quality standards
ACS	American Cancer Society
AhR	aryl hydrocarbon receptor
AHSMOG	Adventist Health Study on Smog
AMs	alveolar macrophages
AOD	aerosol optical depth
B[*a*]P	benzo[*a*]pyrene
BALF	bronchoalveolar lavage fluid
BC	black carbon
BMI	body mass index
BPDE	benzo[*a*]pyrene diol epoxide
bw	body weight
CA	chromosomal aberration
CAPs	concentrated ambient particles
CEPI	Comprehensive Environmental Pollution Index
CI	confidence interval
CNS	central nervous system
CO	carbon monoxide
CO_2	carbon dioxide
COPD	chronic obstructive pulmonary disease
CPCB	Central Pollution Control Board
CPS-II	Cancer Prevention Study II
CRP	C-reactive protein
DB[*a*,*h*]A	dibenz[*a*,*h*]anthracene
DCFH	2′,7′-dichlorodihydrofluorescein
DCM	dichloromethane
DFI	DNA fragmentation index
DFO	deferoxamine
dG	deoxyguanosine
DIPN	*N*-nitrosodiisopropanolamine
DMPO	5,5-dimethyl-1-pyrroline-*N*-oxide
DMSO	dimethyl sulfoxide
DMTU	dimethylthiourea
DTT	dithiothreitol

EBC	exhaled breath condensate
EC	elemental carbon
ECD	electrochemical detection
EDTA	ethylenediaminetetraacetic acid
EEA	European Environment Agency
ELISA	enzyme-linked immunosorbent assay
EMEP	European Monitoring and Evaluation Programme
ENDOIII	endonuclease III
EOC	equivalent organic carbon
EOM	extractable organic matter
EPIC	European Prospective Investigation into Cancer and Nutrition
ESR	electron spin resonance
ESTR	expanded simple tandem repeat
FeNO	fractional exhaled nitrogen oxide
FISH	fluorescence in situ hybridization
FPG	formamidopyrimidine DNA glycosylase
GEM	gaseous elemental mercury
GFFs	glass-fibre filters
GIS	geographic information system
GSTM1	glutathione *S*-transferase M1
HAPs	hazardous air pollutants
HEPA	high-efficiency particulate air
Hg-P	particulate mercury
HPLC	high-performance liquid chromatography
Hprt	hypoxanthine–guanine phosphoribosyl transferase
HR	hazard ratio
ICD	International Classification of Diseases
IL	interleukin
IMF	induced mutant fraction
IQR	interquartile range
IRR	incidence rate ratio
LC	liquid chromatography
LC_{50}	median lethal concentration
M_1dG	malondialdehyde–deoxyguanosine
MDA	malondialdehyde
MN	micronuclei
MS	mass spectrometry
MSA	Metropolitan Statistical Area
MSATs	mobile source air toxics
NAAQS	National Ambient Air Quality Standards
NAMP	National Air Quality Monitoring Programme
NAPS	National Air Pollution Surveillance
NAT2	*N*-acetyltransferase 2
NATA	National-Scale Air Toxics Assessment
NDEA	*N*-nitrosodiethylamine
NDPA	*N*-nitrosodipentylamine
NESHAPs	National Emissions Standards for Hazardous Air Pollutants
NHAPS	National Human Activity Pattern Survey
NMHC	non-methane hydrocarbons
NO	nitrogen oxide

NO_2	nitrogen dioxide
NO_x	nitrogen oxides
NR	nitroreductase
OAT	*O*-acetyltransferase
OC	organic carbon
1-OHP	1-hydroxypyrene
OR	odds ratio
8-oxodG	8-oxo-7,8-dihydro-2′-deoxyguanosine
PACs	polycyclic aromatic compounds
PAHs	polycyclic aromatic hydrocarbons
PBMCs	peripheral blood mononuclear cells
PBS	phosphate-buffered saline
PCBs	polychlorinated biphenyls
PCEs	polychromatic erythrocytes
PEC	pulmonary endocrine cell
PGE_2	prostaglandin E2
PM	particulate matter
PM_{10}	particulate matter with particles of aerodynamic diameter < 10 μm
PM_{15}	particulate matter with particles of aerodynamic diameter < 15 μm
$PM_{2.5}$	particulate matter with particles of aerodynamic diameter < 2.5 μm
PMNs	polymorphonuclear leukocytes
PNC	particle number concentration
POPs	persistent organic pollutants
PUF	polyurethane foam
RGM	reactive gaseous mercury
ROFA	residual oil fly ash
ROS	reactive oxygen species
RR	relative risk
SCEs	sister chromatid exchanges
SCSA	sperm chromatin structure assay
SEER	Surveillance, Epidemiology, and End Results
SIR	standardized incidence ratio
SLF	surrogate lung fluid
SMR	standardized mortality ratio
SO_2	sulfur dioxide
SO_x	sulfur oxides
SPM	suspended particulate matter
S-PMA	*S*-phenyl mercapturic acid
SRM	standard reference mixture
SVOCs	semivolatile organic compounds
t,*t*-MA	*trans*,*trans*-muconic acid
TA98NR	TA98 strains deficient in nitroreductase
TBARS	thiobarbituric acid reactive substances
TEQ	toxic equivalence quotient
TIS	traffic intensity score
TK	thymidine kinase
TLC	thin-layer chromatography
TNF	tumour necrosis factor
TPA	12-*O*-tetradecanoylphorbol-13-acetate
TSP	total suspended particles

UFP	ultrafine particles
US EPA	United States Environmental Protection Agency
VOCs	volatile organic compounds
WHO	World Health Organization

IARC MONOGRAPHS

This volume of the *IARC Monographs* provides an evaluation of the carcinogenicity of outdoor air pollution.

Outdoor air pollution is a complex mixture of pollutants originating from natural and anthropogenic sources, including transportation, power generation, industrial activity, biomass burning, and domestic heating and cooking. The mix of pollutants in outdoor air varies widely in space and time, reflecting the diversity of sources and the influence of atmospheric processes. Commonly measured air pollutants include particulate matter ($PM_{2.5}$, PM_{10}), nitrogen dioxide, and sulfur dioxide; the concentration of particulate matter is often used as an indicator of pollution levels. Millions of people worldwide are exposed to outdoor air pollution at levels that substantially exceed existing health-based guidelines.

This evaluation is the culmination of a series that has examined individual pollutants that are contained in the mixture of outdoor air. Related previous evaluations have been published in *IARC Monographs* Volumes 92, 93, 95, 100C, 100E, 103, and 105.

An *IARC Monographs* Working Group reviewed epidemiological studies, animal cancer bioassays, and mechanistic data to assess the carcinogenic hazards of exposure to outdoor air pollution and particulate air pollution.