Concise International Chemical Assessment Document 67

SELECTED 2-ALKOXYETHANOLS

First draft prepared by Mr Philip Copestake, Toxicology Advice & Consulting Ltd, Surrey, United Kingdom

Published under the joint sponsorship of the United Nations Environment Programme, the International Labour Organization, and the World Health Organization, and produced within the framework of the Inter-Organization Programme for the Sound Management of Chemicals.

The **International Programme on Chemical Safety (IPCS)**, established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organization (ILO), and the World Health Organization (WHO). The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

The **Inter-Organization Programme for the Sound Management of Chemicals (IOMC)** was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, the United Nations Institute for Training and Research, and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

WHO Library Cataloguing-in-Publication Data:

Selected 2-alkoxyethanols.

(Concise international chemical assessment document ; 67)
First draft prepared by Mr Philip Copestake, Toxicology Advice & Consulting Ltd, Surrey, United Kingdom

1.Ethylene glycols - adverse effects. 2.Ethylene glycols - toxicity. 3.Environmental exposure. 4.Risk assessment. I.World Health Organization. II.International Programme on Chemical Safety. III.Inter-Organization Programme for the Sound Management of Chemicals. IV.Series.

ISBN 978 92 4 153067 5 (NLM Classification: QV 82)
ISSN 1020-6167

Risk assessment activities of the International Programme on Chemical Safety, including the production of Concise International Chemical Assessment Documents, are supported financially by the Department of Health and Department for Environment, Food & Rural Affairs, United Kingdom; Environmental Protection Agency, Food and Drug Administration and National Institute of Environmental Health Sciences, United States of America (USA); European Commission; German Federal Ministry of Environment, Nature Conservation and Nuclear Safety; Health Canada; Japanese Ministry of Health, Labour and Welfare; and Swiss Agency for Environment, Forests and Landscape.

Technically and linguistically edited by Marla Sheffer, Ottawa, Canada, and printed by Wissenchaftliche Verlagsgesellschaft mbH, Stuttgart, Germany

TABLE OF CONTENTS

FOREWORD

Concise International Chemical Assessment Documents (CICADs) are published by the International Programme on Chemical Safety (IPCS)—a cooperative programme of the World Health Organization (WHO), the International Labour Organization (ILO), and the United Nations Environment Programme (UNEP). CICADs have been developed from the Environmental Health Criteria documents (EHCs), more than 200 of which have been published since 1976 as authoritative documents on the risk assessment of chemicals.

International Chemical Safety Cards on the relevant chemical(s) are attached at the end of the CICAD, to provide the reader with concise information on the protection of human health and on emergency action. They are produced in a separate peer-reviewed procedure at IPCS. They may be complemented by information from IPCS Poison Information Monographs (PIM), similarly produced separately from the CICAD process.

CICADs are concise documents that provide summaries of the relevant scientific information concerning the potential effects of chemicals upon human health and/or the environment. They are usually based on selected national or regional evaluation documents or on existing EHCs. Before acceptance for publication as CICADs by IPCS, these documents undergo extensive peer review by internationally selected experts to ensure their completeness, accuracy in the way in which the original data are represented, and the validity of the conclusions drawn.

The primary objective of CICADs is characterization of hazard and dose–response from exposure to a chemical. CICADs are not a summary of all available data on a particular chemical; rather, they include only that information considered critical for characterization of the risk posed by the chemical. The critical studies are, however, presented in sufficient detail to support the conclusions drawn. For additional information, the reader should consult the identified source documents upon which the CICAD has been based.

Risks to human health and the environment will vary considerably depending upon the type and extent of exposure. Responsible authorities are strongly encouraged to characterize risk on the basis of locally measured or predicted exposure scenarios. To assist the reader, examples of exposure estimation and risk characterization are provided in CICADs, whenever possible. These examples cannot be considered as representing all possible exposure situations, but are provided as guidance only. The reader is referred to EHC 170.[1]

While every effort is made to ensure that CICADs represent the current status of knowledge, new information is being developed constantly. Unless otherwise stated, CICADs are based on a search of the scientific literature to the date shown in the executive summary. In the event that a reader becomes aware of new information that would change the conclusions drawn in a CICAD, the reader is requested to contact IPCS to inform it of the new information.

Procedures

The flow chart on page 2 shows the procedures followed to produce a CICAD. These procedures are designed to take advantage of the expertise that exists around the world—expertise that is required to produce the high-quality evaluations of toxicological, exposure, and other data that are necessary for assessing risks to human health and/or the environment. The IPCS Risk Assessment Steering Group advises the Coordinator, IPCS, on the selection of chemicals for an IPCS risk assessment based on the following criteria:

- there is the probability of exposure; and/or
- there is significant toxicity/ecotoxicity.

Thus, it is typical of a priority chemical that:

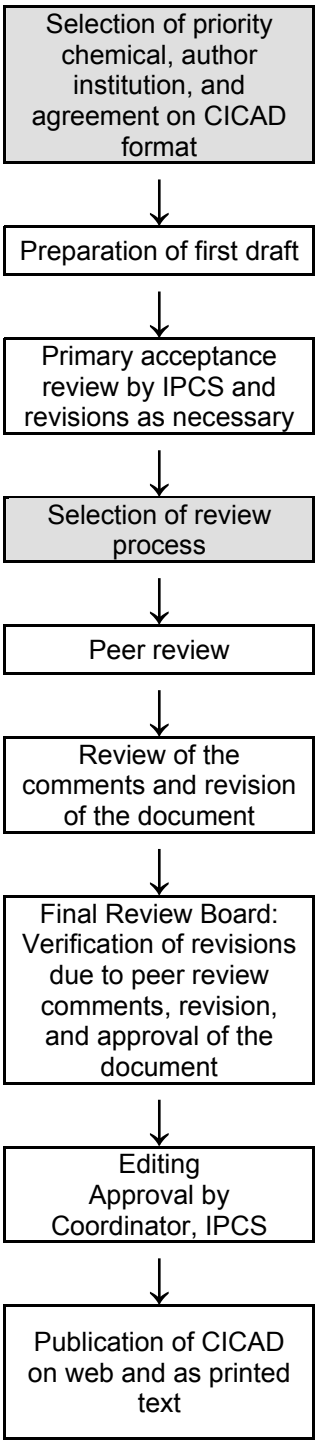
- it is of transboundary concern;
- it is of concern to a range of countries (developed, developing, and those with economies in transition) for possible risk management;
- there is significant international trade;
- it has high production volume;
- it has dispersive use.

The Steering Group will also advise IPCS on the appropriate form of the document (i.e. a standard CICAD or a *de novo* CICAD) and which institution bears the responsibility of the document production, as well as on the type and extent of the international peer review.

The first draft is usually based on an existing national, regional, or international review. When no appropriate source document is available, a CICAD may be produced *de novo.* Authors of the first draft are usually, but not necessarily, from the institution that developed the original review. A standard outline has been developed to encourage consistency in form. The

[1] International Programme on Chemical Safety (1994) *Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits.* Geneva, World Health Organization (Environmental Health Criteria 170) (also available at http://www.who.int/pcs/).

CICAD PREPARATION FLOW CHART



Advice from Risk Assessment Steering Group

Criteria of priority:

- there is the probability of exposure; and/or
- there is significant toxicity/ecotoxicity.

Thus, it is typical of a priority chemical that:

- it is of transboundary concern;
- it is of concern to a range of countries (developed, developing, and those with economies in transition) for possible risk management;
- there is significant international trade;
- the production volume is high;
- the use is dispersive.

Special emphasis is placed on avoiding duplication of effort by WHO and other international organizations.

A usual prerequisite of the production of a CICAD is the availability of a recent high-quality national/regional risk assessment document = source document. The source document and the CICAD may be produced in parallel. If the source document does not contain an environmental section, this may be produced *de novo*, provided it is not controversial. If no source document is available, IPCS may produce a *de novo* risk assessment document if the cost is justified.

Depending on the complexity and extent of controversy of the issues involved, the steering group may advise on different levels of peer review:

- standard IPCS Contact Points;
- above + specialized experts;
- above + consultative group.

first draft undergoes primary review by IPCS to ensure that it meets the specified criteria for CICADs.

The second stage involves international peer review by scientists known for their particular expertise and by scientists selected from an international roster compiled by IPCS through recommendations from IPCS national Contact Points and from IPCS Participating Institutions. Adequate time is allowed for the selected experts to undertake a thorough review. Authors are required to take reviewers' comments into account and revise their draft, if necessary. The resulting second draft is submitted to a Final Review Board together with the reviewers' comments. At any stage in the international review process, a consultative group may be necessary to address specific areas of the science. When a CICAD is prepared *de novo*, a consultative group is normally convened.

The CICAD Final Review Board has several important functions:

- to ensure that each CICAD has been subjected to an appropriate and thorough peer review;
- to verify that the peer reviewers' comments have been addressed appropriately;
- to provide guidance to those responsible for the preparation of CICADs on how to resolve any remaining issues if, in the opinion of the Board, the author has not adequately addressed all comments of the reviewers; and
- to approve CICADs as international assessments.

Board members serve in their personal capacity, not as representatives of any organization, government, or industry. They are selected because of their expertise in human and environmental toxicology or because of their experience in the regulation of chemicals. Boards are chosen according to the range of expertise required for a meeting and the need for balanced geographic representation.

Board members, authors, reviewers, consultants, and advisers who participate in the preparation of a CICAD are required to declare any real or potential conflict of interest in relation to the subjects under discussion at any stage of the process. Representatives of nongovernmental organizations may be invited to observe the proceedings of the Final Review Board. Observers may participate in Board discussions only at the invitation of the Chairperson, and they may not participate in the final decision-making process.

PART A

OVERALL SUMMARY OF 2-METHOXYETHANOL, 2-ETHOXYETHANOL, 2-PROPOXYETHANOL AND 2-BUTOXYETHANOL AND THEIR ACETATES

1. INTRODUCTION

This overall summary presents a comparison of the data relating to the ethylene series glycol ethers 2-methoxyethanol, 2-ethoxyethanol, 2-propoxyethanol and 2-butoxyethanol. It was prepared by Toxicology Advice & Consulting Ltd, United Kingdom, and the Agency for Toxic Substances and Disease Registry, United States of America (USA).[1] Detailed reviews of the available literature pertaining to the toxicological and ecotoxicological effects are presented for 2-methoxyethanol in Part B, for 2-ethoxyethanol and 2-propoxyethanol in Part C and for 2-butoxyethanol in Part D. In addition, an appendix is presented on computational toxicology and its application to the 2-alkoxyethanol series (see Appendix A at the end of the report). The information on 2-methoxyethanol, 2-ethoxyethanol and 2-butoxyethanol was obtained from documentation prepared as part of the Priority Substances Program under the *Canadian Environmental Protection Act* (CEPA). The summary of data on 2-propoxyethanol was based on documentation for a scientific basis for Swedish occupational exposure standards. Comprehensive literature searches of several on-line databases were conducted for each of the 2-alkoxyethanols to identify any references published subsequent to those incorporated in these source documents.

The database of biological literature relating to the 2-alkoxyethanols is generally fairly extensive, and comparisons of the key end-points across the group can be made and are discussed below. These should be considered in conjunction with the more detailed reviews for 2-methoxyethanol, 2-ethoxyethanol and 2-propoxyethanol, and 2-butoxyethanol in Parts B, C and D, respectively.

Computational toxicology (CT) methods, such as quantitative structure–activity relationship (QSAR) analysis, are tools that have been used to prioritize chemical substances for toxicity testing. They have also been used for estimating toxicity when experimental or epidemiological data are limited and it is desirable to estimate end-point toxicities. QSAR was used in this document as a predictive tool to fill data gaps on 2-alkoxyethanols, their acetates and oxidized metabolites. The use of these models has been for screening and prioritization but not directly for risk assessment.

[1] For a list of acronyms and abbreviations used in this report, please refer to Appendix 1.

2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES

2-Methoxyethanol (Chemical Abstracts Service [CAS] No. 109-86-4), 2-ethoxyethanol (CAS No. 110-80-5), 2-propoxyethanol (CAS No. 2807-30-9) and 2-butoxyethanol (CAS No. 111-76-2) are closely related in molecular structure and have similar physicochemical properties that differ in a regular and expected way as a result of increasing molecular weight and consistent functionality. A summary of their physical and chemical properties is presented in Table 1.

The compounds can be represented by the following generic molecular structure:

$$H(CH_2)_nOC_2H_4OH$$

where n = 1, 2, 3 or 4 for 2-methoxyethanol, 2-ethoxyethanol, 2-propoxyethanol and 2-butoxyethanol, respectively.

All concentrations of gaseous 2-alkoxyethanols in air are given in Système international d'unités (SI) units. For conversion factors for individual 2-alkoxyethanols, the reader should refer to the respective part of this Concise International Chemical Assessment Document (CICAD).

3. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

2-Alkoxyethanols are produced in a closed, continuous process by reacting ethylene oxide with the requisite anhydrous alcohol in the presence of a suitable catalyst. Depending on the molar ratios of the reactants and other process parameters, the product mixtures obtained contain varying amounts of the monoethylene, diethylene, triethylene and higher glycol ethers; typically, the products in these mixtures are separated and purified by fractional distillation.

2-Butoxyethanol is the 2-alkoxyethanol with the largest production; approximately 200 000–400 000 tonnes were produced annually in the USA and Europe in 2002–2003. The production and usage of both 2-methoxyethanol and 2-ethoxyethanol have sharply declined in recent years.

Table 1: Physicochemical characteristics of 2-alkoxyethanols.

Alkoxyethanol	Boiling point (°C)	Melting point (°C)	Relative density (water = 1)	Solubility in water	Vapour pressure (Pa)	Relative vapour density (air = 1)	Octanol–water partition coefficient (log K_{ow})
2-Methoxyethanol	125	−85	0.96	Miscible	1300 at 25 °C	2.6	−0.77
2-Ethoxyethanol	135	−70	0.93	Miscible	710 at 25 °C	3.1	−0.32
2-Propoxyethanol	149–152	−90	0.91	Miscible	130 at 25 °C	3.6	0.08
2-Butoxyethanol	171	−75	0.90	Miscible	100 at 20 °C	4.1	0.83

Human exposures to the 2-alkoxyethanols occur primarily via inhalation and dermal contact. Occupational exposures are possible during the application or use of surface coatings, printing inks, adhesives and cleaners that contain category members as components in various formulations. Worker exposures are essentially limited during the manufacture by the enclosed, continuous nature of the manufacturing process. Although most uses of the 2-alkoxyethanols are industrial or workplace, some consumer exposure may occur via the use of these chemicals in consumer products. Although consumer and general population exposures to environmental concentrations of 2-alkoxyethanols may also occur, these are considered to be very low to negligible due to the general lack of persistence of these agents in the environment.

4. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Although specific information for 2-propoxyethanol is limited, the 2-alkoxyethanols appear to be absorbed readily by the oral, inhalation and dermal routes and distributed extensively throughout the body. Penetration through the skin can occur following exposure to the liquid or vapour, and this can be a significant route of exposure. There is evidence from comparative in vitro studies using human skin that the ability to pass through the skin decreases as molecular weight increases.

Metabolism of these 2-alkoxyethanols is principally via a pathway involving oxidation by alcohol dehydrogenase enzymes to an intermediate 2-alkoxyacetaldehyde, followed by rapid conversion by aldehyde dehydrogenases to the corresponding 2-alkoxyacetic acid. This latter metabolite is considered in each case to be the major cause of observed toxicity. The 2-alkoxyacetic acid subsequently may be conjugated with glycine or *O*-dealkylated and further metabolized to yield carbon dioxide. A secondary pathway for metabolism of the 2-alkoxyethanols involves microsomal cytochrome P-450 mixed-function oxidases, with dealkylation to produce ethylene glycol. Direct conjugation with sulfate or glucuronic acid may also occur. The principal route of elimination for the 2-alkoxyethanols is via the urine as the 2-alkoxyacetic acid metabolite. In humans, there is evidence that 2-butoxyethanol is eliminated to a large extent as a glutamine conjugate. This has an influence on the kinetics of 2-butoxyethanol and may explain, for example, the shorter half-life for this compound.

There is some indication for 2-methoxyethanol and 2-ethoxyethanol that the 2-methoxyacetic acid (MAA) and 2-ethoxyacetic acid (EAA) metabolites, respectively, are eliminated from the blood much more slowly in humans than they are in laboratory rats.

A number of oral, intravenous, inhalation and percutaneous physiologically based pharmacokinetic (PBPK) models were developed for 2-methoxyethanol, 2-ethoxyethanol and 2-butoxyethanol to describe and predict the time course of these glycol ethers and their metabolites in the body or developing conceptus. The models were used to extrapolate data from one route of administration to another and from one animal species to another. The pharmacodynamic properties of these glycol ethers (effects on red blood cells, effects on reproduction and development) depend in part on the maximum concentrations of the acids (MAA, EAA and 2-butoxyacetic acid [BAA]) in target tissues (e.g. testes, embryo, fetus and blood).

The acetate derivatives of the 2-alkoxyethanols are hydrolysed readily by esterases present in blood or other tissues to their respective parent compound, and thus data on the 2-alkoxyethyl acetates can also provide useful insights into systemic biological effects of the group members.

5. EFFECTS ON LABORATORY MAMMALS AND IN VITRO TEST SYSTEMS

5.1 Single exposure

A summary of acute toxicity data for the four 2-alkoxyethanols is given in Table 2.

Table 2: Acute toxicity of 2-alkoxyethanols.

Alkoxyethanol	Rat acute oral LD_{50} (mg/kg body weight)	Rat acute inhalation LC_{50} (mg/m^3)	Rabbit acute dermal LD_{50} (mg/kg body weight)
2-Methoxyethanol	2460–3400	>6000 (4 h)	1300
2-Ethoxyethanol	2125–5490	16 000 (4 h) 5500–7400 (7–8 h)	3314–3920
2-Propoxyethanol	3100–4400	8500 (4 h) – >9100 (6 h)	900–1300
2-Butoxyethanol	2500	2200–2400 (4 h)	404–502

LC_{50}, median lethal concentration; LD_{50}, median lethal dose

2-Methoxyethanol, 2-ethoxyethanol, 2-propoxyethanol and 2-butoxyethanol were of low to moderate acute toxicity in laboratory animals. 2-Butoxyethanol appears to be somewhat more toxic than the other three members of the group by the inhalation and dermal routes. Clinical signs of acute toxicity seen in laboratory animals include narcosis, inactivity, sluggishness and death, indicative of a nonspecific depression of the central nervous system typical of many solvents.

For 2-methoxyethanol and 2-ethoxyethanol, the target site for acute toxicity following exposure to high doses was the haematopoietic system, whereas for 2-propoxyethanol and 2-butoxyethanol, increased fragility of red blood cells and haemolysis were the principal effects. The liver, kidneys, spleen, thymus and stomach have also all been cited as targets of toxicity following single high exposures to particular members. Effects on the male reproductive system have been consistently observed following single exposures to 2-methoxyethanol (≥50 mg/kg body weight). No effects on reproductive parameters were reported in experiments involving acute exposure to the other 2-alkoxyethanols, although it is not always clear whether they were looked for specifically.

5.2 Irritation and sensitization

A summary of the irritation and sensitization data for the four 2-alkoxyethanols is given in Table 3.

Table 3: Irritation and sensitization.

Alkoxyethanol	Skin irritation	Eye irritation	Skin sensitization
2-Methoxyethanol	No to slight	Not an eye irritant	Not a skin sensitizer
2-Ethoxyethanol	Slight	Slight	Not a skin sensitizer
2-Propoxyethanol	Slight	Moderate to severe	Not a skin sensitizer
2-Butoxyethanol	Severe	Moderate to severe	Not a skin sensitizer

The lower molecular weight 2-alkoxyethanols, 2-methoxyethanol and 2-ethoxyethanol, appear to have little potential to irritate the skin or eyes, causing at most only slight irritation in experiments using laboratory animals. 2-Propoxyethanol, although only a slight irritant when applied as a covered patch for 24 h to the skin of guinea-pigs, caused moderate to severe irritation when instilled into the eyes of rabbits. 2-Butoxyethanol is reported to be a severe irritant to the skin of rabbits on prolonged contact and is moderately to severely irritating to the eyes of rabbits.

None of the 2-alkoxyethanols appears to be a significant skin sensitizer when tested in guinea-pigs using adjuvant-type methods, such as the maximization test.

Structure–activity relationship (SAR) analysis has also been used to assess the skin sensitization potential of the 2-alkoxyethanols, 2-alkoxyethyl acetates and their oxidized metabolites. The model predicted a negative result for the four 2-alkoxyethanols, 2-alkoxyethyl acetates and their 2-alkoxyacetic acid metabolites. The 2-alkoxyacetaldehyde metabolites, however, were predicted to be sensitizers; the relevance of the dermal sensitization capacity of a metabolite apparently is limited in the hazard profile of the parent compound. The negative result for skin sensitization was in the input data for 2-methoxyethanol, 2-ethoxyethanol and 2-butoxyethanol. For more information, see Appendix A.

5.3 Repeated exposure

A consistent toxic sign observed across these 2-alkoxyethanols is changes to haematological parameters, although, again, there appears to be a fundamental difference in the effects induced by the lower molecular weight compounds compared with those induced by the longer-chain 2-alkoxyethanols. The principal effect on the blood associated with exposure to 2-propoxyethanol or 2-butoxyethanol involves red blood cell haemolysis, whereas for the short-chain 2-alkoxyethanols, 2-methoxyethanol and 2-ethoxyethanol, the evidence suggests that an effect on haematopoiesis is the predominant feature.

Effects on the blood have been most extensively investigated for 2-butoxyethanol—possibly a reflection of the declining or limited recent use of the other 2-alkoxyethanols being considered here. In long-term inhalation studies in rats and mice with 2-butoxyethanol, effects on the blood were the most sensitive indicators of toxicity, with haemolytic anaemia reported in female rats at the lowest exposure level of 153 mg/m^3 (whole body; 6 h/day, 5 days/week, for up to 2 years) and in mice at 614 mg/m^3 (with some indication of an effect in female mice at 308 mg/m^3). The severity of the effects in both species increased with increasing exposure. In 13- to 14-week inhalation studies, the lowest reported lowest-observed-effect concentration (LOEC) seen in female rats was 150 mg/m^3, with a no-observed-adverse-effect concentration (NOAEC) identified at 120 mg/m^3. A lowest-observed-adverse-effect level (LOAEL) of 70 mg/kg body weight per day, the lowest dose tested, was reported in a subchronic oral study in rats.

Results from investigations using in vitro systems suggest that it is the acetic acid metabolite BAA that may be primarily responsible for the haemolytic activity and also that rats and other laboratory animal species are more susceptible than humans to the haemolytic effects of 2-butoxyethanol or its acetic acid metabolite.

For 2-propoxyethanol, the data are more limited, but there are clear indications that haemolysis of red blood cells follows exposure. In an unpublished study in which rats were exposed by inhalation for 14 weeks, effects on the blood were observed in animals exposed 6 h/day, 5 days/week, to atmospheres containing 850 mg/m^3 or more. A NOAEC was said to be 425 mg/m^3. Blood effects were also reported when pregnant rats were exposed 6 h/day for 10 days to 425–1700 mg/m^3. Evidence of haemolytic activity was also seen in short-term studies in which rats were exposed (for 6 weeks) by gavage to 200 mg/kg body weight per day, the lowest tested dose.

In vitro investigations suggest that 2-propoxyethanol, in particular the acetic acid metabolite, 2-propoxyacetic acid, is less haematotoxic than 2-butoxyethanol, and, as for 2-butoxyethanol and BAA, humans may be less susceptible than rats to the haemolytic activity.

In medium-term oral studies in rats with 2-ethoxyethanol, anaemia was reported in females at doses of 247 mg/kg body weight per day via the drinking-water, with effects observed as soon as 1 week following start of the exposure. Reduced haemoglobin and haematocrit were also reported in a different strain of rat exposed to 93 mg/kg body weight per day by gavage for 59 days followed by exposure to 372 mg/kg body weight per day for 30 days. Haemosiderin pigmentation was observed in the spleen of both strains of rats, with the lowest effect level being 186 mg/kg body weight per day in Wistar rats. A no-observed-adverse-effect level (NOAEL) was said to be 93 mg/kg body weight per day.

Slight dose-related decreases in haemoglobin and haematocrit levels have also been reported in dogs administered 2-ethoxyethanol at 46–186 mg/kg body weight per day for 13 weeks using gelatine capsules.

By the inhalation route, significant data for 2-ethoxyethanol haematotoxicity are limited to those from studies designed primarily to investigate developmental toxicity. Changes in red blood cell parameters were reported in pregnant rats exposed to 940 mg/m^3 for 10 days, with no effects in the blood being observed at 190 mg/m^3. Alterations in haematological parameters were also observed in another study in which pregnant rats were exposed to 370 mg/m^3 or more.

For 2-methoxyethanol, blood effects were seen in rats given approximately 70 mg/kg body weight per day or more by the oral route or 950 mg/m^3 or more by inhalation in short-term studies lasting 5 days or longer. In a 13-week study in which rats were exposed via the drinking-water, anaemia and reduced white blood cell and platelet counts were observed at the lowest concentration, equivalent to a dose of 71 mg/kg body weight per day, or more, whereas alterations in haematological parameters were also observed in an inhalation study of similar length in which rats were exposed to 2-methoxyethanol at 950 mg/m^3 and above. No effects on the blood were reported at 320 mg/m^3.

For the three 2-alkoxyethanols (2-methoxyethanol, 2-ethoxyethanol and 2-butoxyethanol) for which data are adequate, mice seem to be less sensitive than rats to their toxic effects. It is also clear (in the case of 2-ethoxyethanol, 2-propoxyethanol and 2-butoxyethanol, where data are available) that females are more sensitive than their male counterparts.

The reproductive system, in particular that of the male, is also a sensitive target of toxicity for the lower molecular weight members of the group, 2-methoxyethanol and 2-ethoxyethanol, in experiments involving laboratory animals.

In the case of 2-methoxyethanol, effects on the testes have been reported in rats exposed for 9–10 days by the oral route to about 88 mg/kg body weight per day or more or by inhalation to at least 950 mg/m^3. In subchronic studies, histopathological changes in the testes were observed in rats receiving drinking-water providing a dose of 71 mg/kg body weight per day or more or exposed to atmospheres containing 950 mg/m^3. Rabbits appeared to be more sensitive to the testicular toxicity, with degeneration (although minimal) being reported at concentrations as low as 95 mg/m^3 following

exposure by inhalation for 13 weeks, whereas mice were less sensitive than rats in 13-week oral studies.

For 2-ethoxyethanol, effects on the prostate gland and sperm parameters were observed in rats exposed to a dose of 205 mg/kg body weight per day via the drinking-water for 13 weeks, with testicular degeneration observed from 400 mg/kg body weight per day. A NOAEL was 109 mg/kg body weight per day. In another strain of rat, effects were reported at 186 mg/kg body weight per day and above for 13 weeks, although not at 93 mg/kg body weight per day, suggesting that 2-ethoxyethanol is less toxic than 2-methoxyethanol with respect to this end-point. As in the case of 2-methoxyethanol, mice appeared to be less sensitive than rats to testicular toxicity, with effects being observed only at much higher doses in a subchronic oral study. In the dog, testicular effects were reported in short-term studies at 186 mg/kg body weight per day when the material was administered in capsules. The testes were also apparently the principal target for toxicity in long-term studies in rats and mice, although full results from these studies are not readily available.

Although effects have not been as well studied, the female reproductive system was also the target of toxicity by 2-methoxyethanol and 2-ethoxyethanol.

Changes in estrous cyclicity and hormone levels were observed in rats given 2-methoxyethanol at 100 mg/kg body weight per day or more for several days, with histopathological changes in the ovaries from 300 mg/kg body weight per day. A NOAEL was 10 mg/kg body weight per day. Mice again appeared to be less sensitive.

For 2-ethoxyethanol, effects on the estrous cycle were observed in rats and mice exposed via the drinking-water to 804 or 1304 mg/kg body weight per day or more, respectively, for 13 weeks.

There is little indication of the toxicity of 2-propoxyethanol or 2-butoxyethanol to the reproductive system.

There was no evidence of effects on the male or female reproductive organs in an unpublished study in which rats were exposed by inhalation to atmospheres containing 2-propoxyethanol at 1700 mg/m^3 for 14 weeks and in a study in which mice were exposed by gavage at up to 2000 mg/kg body weight per day for up to 5 weeks.

There was no clear evidence that the reproductive organs were affected following repeated exposure of laboratory animals to 2-butoxyethanol.

Other key targets of non-neoplastic toxicity for the 2-alkoxyethanols include the thymus (principally in the cases of 2-methoxyethanol and 2-ethoxyethanol) and the forestomach (for 2-butoxyethanol).

Reduced relative weight of the thymus was observed in rats orally exposed to repeated 2-methoxyethanol doses of 50 mg/kg body weight per day or more or airborne concentrations of 950 mg/m^3, with histopathological changes evident at higher exposures. Mice appeared to be less sensitive to the effects on the thymus, whereas there are indications that the rabbit may be more sensitive, with a report of thymus damage occurring in this species at an exposure level of 320 mg/m^3 and above for 13 weeks.

For 2-ethoxyethanol, relative thymus weights were reduced in rats administered 357 mg/kg body weight per day or more in the drinking-water following short-term exposure, whereas in a subchronic oral study, a LOAEL was 205 mg/kg body weight per day in male rats, with 109 mg/kg body weight per day being the NOAEL. Again, mice appeared to be less sensitive to the toxic activity.

The forestomach was a critical target of toxicity in mice exposed to 2-butoxyethanol in long-term inhalation studies. Increased incidences of inflammation, epithelial hyperplasia and ulceration were observed in mice exposed to airborne concentrations of 308 mg/m^3 (the lowest concentration tested) or more for up to 2 years. In subchronic studies, similar damage was seen in both rats and mice exposed by inhalation to higher concentrations. The forestomach effects are in concordance with neoplastic lesions that were observed at this site in mice (see section 5.4 below).

5.4 Carcinogenicity

A summary of the carcinogenicity data for the four 2-alkoxyethanols is given in Table 4.

Only 2-butoxyethanol has been tested adequately for carcinogenic potential in long-term studies in rats and mice. Although 2-ethoxyethanol did undergo some (early) testing, no final results are available because of problems within the laboratory conducting the studies. No data on carcinogenicity were identified for 2-methoxyethanol or 2-propoxyethanol.

In the long-term studies with 2-butoxyethanol, which involved exposure of rats and mice by inhalation, there was some evidence of carcinogenicity in mice (based on increased incidences of haemangiosarcomas of the liver in males and squamous cell papillomas of the forestomach in females) and equivocal evidence in female rats (based on a marginal increase in the

Table 4: Carcinogenicity and key genotoxicity results.

End-point	2-Methoxyethanol	2-Ethoxyethanol	2-Propoxyethanol	2-Butoxyethanol
Carcinogenicity	No data	No data	No data	Some evidence in mice (haemangiosarcomas of the liver in males and squamous cell papilloma or carcinomas of the forestomach in females) and equivocal evidence in female rats (phaeochromocytomas of the adrenal gland)
Genotoxicity				
In vivo				
Micronucleus assay	No data; 2-methoxyethyl acetate was negative (hamsters, single dose, intraperitoneal)	Negative (mice, single dose, intraperitoneal) 2-Ethoxyethyl acetate and EAA were also negative (mice, single doses, intraperitoneal)	No data	Negative (several tests in rats or mice, intraperitoneal); BAA also negative (mice, intraperitoneal)
Bone marrow clastogenicity	Negative (rats and mice; single or repeated exposure; oral, inhalation, intravenous)	No data	No data	No data
Other in vivo tests	Positive in comet assay (bone marrow; haploid testicular cells); mixed results in dominant lethal assays	No data	No data	Negative in range of tests including ^{32}P post-labelling assay for DNA adducts (brain, kidney, liver, spleen, testes); DNA methylation assay (brain, kidney, liver, spleen, testes); tumour formation in transgenic mice
In vitro				
Mammalian cell clastogenicity	Positive (chromosomal aberrations and micronuclei); the acetate was also positive for chromosomal aberrations MALD was also positive in assays for chromosomal aberrations, although MAA was negative; both MALD and MAA were positive in micronucleus tests	Mixed or equivocal results (chromosomal aberrations and micronuclei) for both 2-ethoxyethanol and its acetate; EALD gave positive results, although EAA was negative or equivocal	No data	Negative (chromosomal aberrations); a micronucleus test in Chinese hamster cells was equivocal BALD was positive (chromosomal aberration and micronuclei)
Mammalian cell mutagenicity	Negative; MALD was positive (*HPRT* and *GPT* mutations in Chinese hamster cells)	Negative; 2-ethoxyethyl acetate also negative	No data	Negative for *HPRT* in Chinese hamster ovary cells, but positive for *HPRT* in Chinese hamster lung cells
Salmonella typhimurium	Negative; MAA was also negative, although MALD was positive in one strain	Negative: 2-ethoxyethyl acetate, EALD and EAA also negative	No data	Negative (although inconsistent results with TA97a); BAA was also negative

BALD, 2-butoxyacetaldehyde; DNA, deoxyribonucleic acid; EALD, 2-ethoxyacetaldehyde; MALD, 2-methoxyacetaldehyde

incidence of benign or malignant phaeochromocytomas of the adrenal gland).

The lack of significant genotoxic activity for 2-butoxyethanol (see below and Part D of this CICAD) suggests that the routes to tumour induction may primarily involve non-genotoxic mechanisms. Data support the hypothesis that tumour formation in the forestomach of mice may result essentially from prolonged contact irritation caused by metabolites, followed by hyperplasia and response. In the liver, a mechanism for induction of tumours involving iron-induced oxidative stress has been proposed.

For the forestomach, the first stage in the proposed sequence of steps is the deposition of 2-butoxyethanol or BAA in the stomach and forestomach via consumption or reingestion of 2-butoxyethanol-laden mucus, salivary excretions or fur material. 2-Butoxyethanol or BAA may be retained in food particles in the forestomach long after being cleared from other organs. 2-Butoxyethanol is metabolized to 2-butoxyacetaldehyde (BALD), which

is then rapidly converted to BAA systemically and in the forestomach. Irritation of the target cells leads to hyperplasia and ulceration, with continued injury and degeneration resulting in high cell proliferation and turnover. The final stage on the path to tumour formation is the high cell proliferation and turnover leading to clonal growth of spontaneously initiated forestomach cells.

For the liver, the proposed mode of action suggests that excess iron from haemolysis caused by 2-butoxyethanol can result in sufficient iron-induced oxidative stress to cause the observed marginal increase in the incidence of liver haemangiosarcomas in the laboratory animals. Humans appear to be very much less sensitive to the haemolytic effects of 2-butoxyethanol and have higher levels of hepatic antioxidant capacity compared with rodents; thus, they are not considered likely to be at risk for development of haemolysis-associated tumours.

The role of direct interaction of a 2-butoxyethanol metabolite with deoxyribonucleic acid (DNA) in the development of tumours cannot be completely ruled out, however, given the weak positive effects induced by 2-butoxyethanol at high concentrations in some in vitro genotoxicity assays and the reported clastogenicity of the short-lived 2-butoxyethanol metabolite BALD. PBPK modelling suggests that the conditions in the in vitro genotoxicity assays (no metabolic activation; high cytotoxic concentration of BALD) are of little relevance to the expected target organ environment (high metabolic activity; low concentrations of BALD). Additional research to verify the PBPK modelling and further explore the relevance of genotoxic activity would enable a more definitive determination regarding the possible role of BALD in the formation of forestomach tumours in female mice and in the formation of tumours of the liver in male mice.

Given the similar genotoxic profiles across the group of 2-alkoxyethanols (see section 5.5 below) and the common pathways for metabolism for the various members, it is unlikely that significant carcinogenic potential would be a key feature of the toxic profile of those yet to be the subject of good-quality long-term investigations of carcinogenicity in laboratory animals.

The rodent carcinogenicity of the four 2-alkoxyethanols and 2-alkoxyethyl acetates and their oxidized metabolites (2-alkoxyacetaldehydes and 2-alkoxyacetic acids) has been evaluated using SAR analysis. Four United States National Toxicology Program (NTP) rodent carcinogenicity models specific for rat and mouse (male and female) carcinogenicity were used. The results predict that 2-methoxyethanol, 2-methoxyethyl acetate and the oxidized metabolites (2-methoxyacetaldehyde [MALD], MAA) are carcinogenic in the rat (both sexes). Furthermore, the other 2-alkoxyacetaldehydes and 2-alkoxyethyl acetates were predicted to be carcinogenic to male rats, with the exception of 2-ethoxyacetaldehyde (EALD), which was indeterminate. 2-Alkoxyacetic acids were predicted to be carcinogenic to female rats. For more details, see Appendix A.

5.5 Genotoxicity and related end-points

A summary of the key genotoxicity data for the four 2-alkoxyethanols is given in Table 4. Additional details are given in Parts B, C and D of this CICAD.

Publicly available data on in vivo and in vitro genotoxicity were found for three of the 2-alkoxyethanols, covering gene mutation and clastogenicity end-points. No data for 2-propoxyethanol were identified in the literature.

Data from in vivo studies for 2-methoxyethanol, 2-ethoxyethanol and 2-butoxyethanol suggest a lack of significant genotoxic activity. Tests for the induction of chromosomal aberrations or micronuclei in somatic cells of treated rats or mice have been consistently negative.

In the case of 2-methoxyethanol, however, there was evidence of induction of genetic effects in male germ cells, with indication of DNA damage in bone marrow and haploid testicular cells of rats following high oral exposure in a comet assay. There were mixed results from dominant lethal assays in rodents, although these need to be considered in the light of the testicular toxicity and spermatotoxicity of 2-methoxyethanol, making results difficult to interpret. Tests for germ cell mutagenicity have not been carried out with the 2-alkoxyethanols other than 2-methoxyethanol.

Results from in vitro studies are less clear across the group. There is no evidence that the two lower molecular weight 2-alkoxyethanols, 2-methoxyethanol and 2-ethoxyethanol, can induce mutations in vitro, whereas some inconsistent data exist for 2-butoxyethanol. Most of the standard mutagenicity assays in bacteria with 2-butoxyethanol suggested lack of activity. However, for one strain of *Salmonella typhimurium* bacteria (TA97a), there have been reports of both mutagenicity (in the presence and absence of metabolic activation) and lack of mutagenicity in Ames tests; and, whereas 2-butoxyethanol was not mutagenic at the *HPRT* locus in Chinese hamster ovary cells (again, in both the presence and absence of metabolic activation), there was evidence of gene mutation at this locus when using Chinese hamster lung (V79) cells.

There is some indication of clastogenic activity for the 2-alkoxyethanols in vitro. Evidence of such chromosomal effects has been published for both 2-methoxyethanol and its acetate, whereas mixed or equivocal results are available for 2-ethoxyethanol. For 2-butoxyethanol, an in vitro micronucleus test was also equivocal,

although several assays for chromosome damage using human lymphocytes, Chinese hamster lung (V79) cells and Chinese hamster ovary cells were negative.

There is fairly consistent evidence that the acetaldehyde metabolites of the 2-alkoxyethanols possess genotoxic activity in vitro. MALD, EALD and BALD have all demonstrated clastogenicity in assays for chromosomal aberrations or micronuclei. MALD has also given evidence of mammalian cell mutagenicity and gave a positive result for mutagenicity in one strain of *Salmonella typhimurium* bacteria (both with and without metabolic activation) in Ames tests. The acid metabolites do not seem to possess significant genotoxic potential.

SAR analysis has also been used to assess the mutagenicity of the 2-alkoxyethanols. The model predicted that the 2-alkoxyethanol compounds, their ethyl acetates and their metabolites are not mutagenic; a negative result for mutagenicity was in the modelling input data for 2-ethoxyethanol and 2-butoxyethanol. See Appendix A for more information.

5.6 Reproductive toxicity

5.6.1 Effects on fertility

As noted above in section 5.3, the male reproductive system was a consistent target for toxic attack by 2-methoxyethanol and 2-ethoxyethanol; although not as well studied, the female reproductive system also seemed to be a target for these 2-alkoxyethanols.

Adverse effects on reproduction have been confirmed for these two members of the group in studies designed to investigate fertility.

For 2-methoxyethanol, reduced male fertility has been observed in rats and mice following acute or repeated exposure by the oral or inhalation routes. Similarly, effects on the testes or male reproductive ability were reported in short-term and subchronic oral studies in guinea-pigs, rabbits and hamsters, the lowest LOAEL recorded being 25 mg/kg body weight per day in the rabbit. In a subchronic inhalation study, minimal reproductive effects in male rabbits were reported at 95 mg/m^3, the lowest concentration tested.

Reproductive ability has been assessed in mice exposed by the oral route to 2-ethoxyethanol, its acetate or its acetic acid metabolite/derivative. All these substances adversely affected reproductive success. For 2-ethoxyethanol, the LOAEL was approximately 1650 mg/kg body weight per day, whereas there were no adverse effects at 850 mg/kg body weight per day. Cross-over mating trials indicated that exposure of either sex to 2-ethoxyethanol or its acetate adversely affected reproductive ability. However, in an inhalation study, no effects on mating behaviour or fertility were observed in female rats exposed to 2-ethoxyethanol at concentrations up to 2430 mg/m^3 for 3 weeks prior to mating with unexposed males.

No studies on the effects of 2-propoxyethanol on fertility were identified in the literature. In subchronic studies with exposure by both ingestion and inhalation, and in contrast to 2-methoxyethanol and 2-ethoxyethanol, no histological evidence of damage to testicular tissue has been noted.

Adverse effects on the reproductive system do not seem to be a key feature of the toxicity profile of 2-butoxyethanol. Reproductive toxicity was evident only at concentrations that elicited general toxicity in a continuous-breeding study in mice.

5.6.2 Developmental toxicity

2-Methoxyethanol and 2-ethoxyethanol are also significant developmental toxicants.

2-Methoxyethanol has consistently induced developmental effects in studies involving several laboratory animal species following exposure by a range of routes, including oral, inhalation and dermal, generally at doses or concentrations lower than those that are maternally toxic, and often at the lowest exposure level tested. For example, decreased fetal body weights were noted in rats exposed to 2-methoxyethanol at doses of 16 mg/kg body weight per day (the lowest dose tested) or more in the diet during gestation, with malformations being observed at 31 mg/kg body weight per day or more, whereas maternal toxicity was evident only at 140 mg/kg body weight per day. In inhalation studies in rats, developmental toxicity was observed following repeated maternal exposure to atmospheres containing 160 mg/m^3 and above. The cardiovascular system, kidney and skeletal system seemed to be the principal targets of developmental toxicity for 2-methoxyethanol.

For 2-ethoxyethanol, signs of developmental toxicity in the absence of significant maternal toxicity have also been observed in studies involving rats, mice and rabbits, with exposures involving the oral, inhalation and dermal routes. In rats, a NOAEL for developmental toxicity was identified as 47 mg/kg body weight per day, with a LOAEL of 94 mg/kg body weight per day, in a study involving oral exposure. In inhalation studies, the lowest concentration of 2-ethoxyethanol reported to induce developmental toxicity in the absence of maternal toxicity was 190 mg/m^3, with a NOAEC of 40 mg/m^3, in rats. The cardiovascular and skeletal systems were again major targets of developmental toxicity.

Developmental toxicity does not appear to be a significant feature of the toxicity profiles of the other

two 2-alkoxyethanols, 2-propoxyethanol and 2-butoxyethanol. Although a dose-related increase in some skeletal anomalies was seen in a study involving exposure of pregnant rats to 2-propoxyethanol by inhalation, there was also evidence of maternal toxicity, and studies with rabbits and mice were without adverse developmental effects. Adequate studies with 2-butoxyethanol involving exposure of rats and rabbits by inhalation also suggested lack of developmental toxicity; minor skeletal variations were observed generally only at doses that showed some evidence of also being maternally toxic.

SAR analysis has also been used to assess the developmental toxicity of the 2-alkoxyethanols. This model predicts that 2-methoxyethyl acetate, but not the other 2-alkoxyethyl acetates, is toxic to development. The model further predicts that the 2-alkoxyethanols, except 2-butoxyethanol, and the 2-alkoxyacetic acids, with the exception of BAA, are developmental toxicants. 2-Alkoxyethyl acetates (except 2-methoxyethyl acetate) and 2-alkoxyacetaldehydes are not predicted to produce developmental effects. The input data for the modelling for 2-ethoxyethanol and 2-methoxyethanol include developmental toxicity. For more information, see Appendix A.

5.7 Immunological effects

Specific tests for immunological effects have been conducted with 2-methoxyethanol, 2-ethoxyethanol and 2-butoxyethanol, but not with 2-propoxyethanol.

For 2-methoxyethanol, immunosuppression has been observed in several studies in rats given oral doses of 50 mg/kg body weight per day or more for 2–21 days, and thymus weight reductions have been seen at doses as low as 25 mg/kg body weight per day. Occasionally, there were also reductions in spleen weights or cellularity.

Mice appear to be much less sensitive than rats to the immune effects induced by 2-methoxyethanol exposure, with no consistent evidence of immunotoxicity at repeated doses of up to 1000 mg/kg body weight per day (or MAA at 1920 mg/kg body weight per day), although decreased thymus weights were observed, and there was evidence of enhancement or modulation of immune system response in some studies.

There is evidence from studies in rats that 2-methoxyethanol itself is not the immunotoxicant, but that the aldehyde and acid metabolites (MALD and MAA) are responsible for the suppression of immune system function.

There was no evidence that 2-ethoxyethanol (or its acetate) were immunotoxic in rats or mice, the highest level of exposure being up to 2400 mg/kg body weight per day for 10 days.

For 2-butoxyethanol, immune system effects have been observed in rats given (by gavage) 200 mg/kg body weight per day for 2 days (but not at 100 mg/kg body weight per day) and in mice given 50 mg/kg body weight per day or more for 10 days. Effects observed included an increase in the mixed lymphocyte reaction and concanavalin A mitogenic stimulation of splenocytes and, at higher dose levels, increased cytotoxic T lymphocyte activity and elevated lipopolysaccharide stimulation of splenocytes.

Effects on the immune system (reduced splenic T cell proliferative response to concanavalin A and mixed lymphocyte response to allogeneic antigen) were also observed in mice given dermal 2-butoxyethanol doses of 500 mg/kg body weight per day, with an increase in spleen cellularity and relative spleen weights at 1500 mg/kg body weight per day. No such effects were observed at 100 mg/kg body weight per day. Dermal application of 4 mg of 2-butoxyethanol (in an acetone/olive oil vehicle) also decreased the contact hypersensitivity response induced by oxazolone in female mice.

5.8 Neurological effects

Two of the 2-alkoxyethanols, 2-methoxyethanol and 2-propoxyethanol, have been subject to specific tests for neurotoxicity.

Exposure to 2-methoxyethanol caused inhibition of an avoidance-escape conditioned response, increased barbiturate-induced sleeping time or partial limb paralysis in rats or mice exposed by inhalation to concentrations of 395 mg/m^3 or greater in acute or short-term studies. Enzyme activities in the brain were altered at 160 mg/m^3 or more. Avoidance conditioning and neurochemical changes were also reported in the offspring of rats exposed repeatedly during pregnancy to 2-methoxyethanol at 79 mg/m^3.

For 2-propoxyethanol, no neurotoxic effects were evident in rats exposed (6 h/day, 5 days/week) for up to 14 weeks to atmospheres containing up to 1700 mg/m^3. Tests included a functional observational battery to assess activity, coordination, behaviour and changes in sensory function, and evaluation of forelimb and hindlimb grip strength. No damage to central or peripheral nervous system tissues was seen on microscopic examination.

Whereas specific tests for neurotoxicity have not been conducted for 2-butoxyethanol, central nervous system effects were observed in acute and short-term studies with high doses. Effects have included loss of

Table 5: Effects of 2-alkoxyethanols and their acetates reported in exposed human populations.[a]

End-point	2-Methoxyethanol[b]	2-Ethoxyethanol[b]	2-Propoxyethanol[b]	2-Butoxyethanol[b]
Reproductive effects	Reduced sperm production	Reduced sperm production	No data	No data
Haematological effects	Anaemia, granulocytopenia, thrombocytopenia	Anaemia, granulocytopenia	No data	Haemolysis, haematuria, metabolic acidosis and kidney damage after accidental exposure

[a] Most, if not all, populations studied were also exposed to other chemicals.
[b] Findings are related to the glycol ether and its acetate.

coordination, sluggishness, narcosis, muscular flaccidity and ataxia. Neurological changes were reported in the offspring of rats exposed during pregnancy to 2-ethoxyethanol.

6. EFFECTS ON HUMANS

Although limited in each case (and non-existent for 2-propoxyethanol), available human data tend to support the information on critical targets identified in studies with laboratory animals. Interpretation of data from humans can be difficult, however, as exposures often involve substances other than the 2-alkoxyethanol of interest, and study populations are generally small.

For 2-methoxyethanol, epidemiological data are suggestive of effects on the haematological and nervous systems and on reproduction in men and women employed in occupations involving exposure to the compound. A clear association between effects on the blood and exposure to 2-methoxyethanol was reported in a study of workers in Taiwan, China. The blood and male reproductive system also seemed to be targets for 2-ethoxyethanol-associated toxicity in humans. Reduced sperm production was observed in workers exposed to 2-ethoxyethanol (along with a number of other substances), and blood effects were observed in shipyard painters exposed to 2-ethoxyethyl acetate (Table 5).

Case reports (available for 2-methoxyethanol, 2-ethoxyethanol and 2-butoxyethanol) of adverse effects resulting from deliberate or accidental ingestion generally additionally involve the central nervous system.

7. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

7.1 Aquatic environment

Although data on the environmental effects of these 2-alkoxyethanols are available, it is difficult to make direct comparisons between the individual compounds. They are not considered to pose a significant hazard to the aquatic environment. Where direct comparisons can be made, however, the limited data available suggest that 2-butoxyethanol may be more toxic than 2-methoxyethanol, 2-ethoxyethanol or 2-propoxyethanol to aquatic organisms. For 2-methoxyethanol, a 24 h median lethal concentration (LC_{50}) for *Daphnia magna* is reported as greater than 10 g/l. Also for *Daphnia magna*, a 48 h median inhibitory concentration (IC_{50}) for 2-ethoxyethanol and a 48 h LC_{50} for 2-propoxyethanol are 7.7 g/l and >5 g/l, respectively. For 2-butoxyethanol, 24 h LC_{50}s are reported as between approximately 1.7 and 5 g/l.

7.2 Terrestrial environment

Very few useful data are available on the environmental effects of these 2-alkoxyethanols on terrestrial organisms.

APPENDIX 1—ACRONYMS AND ABBREVIATIONS

BAA	2-butoxyacetic acid
BALD	2-butoxyacetaldehyde
CAS	Chemical Abstracts Service
CEPA	*Canadian Environmental Protection Act*
CICAD	Concise International Chemical Assessment Document
CT	computational toxicology
DNA	deoxyribonucleic acid
EAA	2-ethoxyacetic acid
EALD	2-ethoxyacetaldehyde
IC_{50}	median inhibitory concentration
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEC	lowest-observed-adverse-effect concentration
LOAEL	lowest-observed-adverse-effect level
LOEC	lowest-observed-effect concentration
MAA	2-methoxyacetic acid
MALD	2-methoxyacetaldehyde
NOAEC	no-observed-adverse-effect concentration
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program (USA)
PBPK	physiologically based pharmacokinetic
QSAR	quantitative structure–activity relationship
SAR	structure–activity relationship
SI	Système international d'unités (International System of Units)
USA	United States of America

PART B

2-METHOXYETHANOL

1. EXECUTIVE SUMMARY

This Concise International Chemical Assessment Document (CICAD)[1] on 2-methoxyethanol was prepared by Toxicology Advice & Consulting Ltd, United Kingdom, based on documentation prepared as part of the Priority Substances Program under the *Canadian Environmental Protection Act, 1999* (CEPA) (Environment Canada & Health Canada, 2002). The objective of assessments on priority substances under CEPA is to assess potential effects of indirect exposure in the general environment on human health as well as environmental effects. Data identified as of October 1999 were considered in the source document. A comprehensive literature search of several online databases was conducted in January 2004 to identify any key references published subsequent to those incorporated in the source document. Information on the nature of the peer review and the availability of the source document is presented in Appendix 2. Information on the peer review of this CICAD is presented in Appendix 3. The draft document was considered at the 12th Final Review Board meeting in Hanoi, Viet Nam, on 30 September – 3 October 2004. Participants at the 12th Final Review Board meeting are listed in Appendix 4. As relevant information on human health assessment had been published after the closing date for the literature search of the source document, the Final Review Board recommended that this information be incorporated and the document be reconsidered at another Final Review Board meeting. The document was revised accordingly and sent to another peer review. The CICAD was considered and approved as an international assessment at the 13th Final Review Board meeting, held in Nagpur, India, on 31 October – 3 November 2005. Participants at the 13th Final Review Board meeting are presented in Appendix 5. The International Chemical Safety Cards for 2-methoxyethanol (ICSC 0061; IPCS, 2002) and 2-methoxyethyl acetate (ICSC 0476; IPCS, 2006) (which is readily metabolized to 2-methoxyethanol), produced by the International Programme on Chemical Safety (IPCS) in a separate, peer-reviewed process, have also been reproduced in this document.

2-Methoxyethanol (Chemical Abstracts Service [CAS] No. 109-86-4) is a colourless, volatile liquid, with high water solubility. It has not been reported to occur as a natural product. It is produced commercially by the reaction of ethylene oxide with anhydrous methanol.

2-Methoxyethanol has been reported to be used in paints, coatings, inks, cleaners, polishes, brake fluids and jet fuels and in the manufacture of printed circuit board laminates and to find wide application as a solvent, chemical intermediate and solvent coupler of mixtures and water-based formulations. Use has declined, however, in recent years as a result of its replacement in some countries by other substances. Use reduction programmes have led to widespread restriction in consumer products.

Monitoring data upon which to base estimates of exposure of the general population to 2-methoxyethanol are limited. Worst-case or bounding estimates of exposure from environmental media (essentially air and water) and consumer products have been developed.

Absorption through the skin can be a major route of exposure, particularly in the occupational setting. 2-Methoxyethanol is also readily absorbed via the inhalation and oral routes and, following absorption, is distributed extensively throughout the body.

The major metabolic pathways involve oxidation to 2-methoxyacetaldehyde (MALD) and 2-methoxyacetic acid (MAA), the likely active metabolites. Urinary MAA is a specific and suitable indicator of exposure. MAA is eliminated from the body much more slowly in humans than in rats.

2-Methoxyethanol is of low to moderate acute toxicity following oral, inhalation or dermal exposure. It has low potential for causing skin or eye irritation and has not been shown to be a skin sensitizer. Based on a relatively extensive database in laboratory animals, the key adverse health effects following repeated exposure to 2-methoxyethanol are haematological effects and reproductive and developmental toxicity, including both effects on fertility and teratogenicity. Some changes have been found to occur at relatively low levels of exposure, often the lowest dose or concentration tested. In a medium-term study, testicular degeneration and effects on the blood were observed following oral exposure of rats to the lowest dose tested. In a medium-term inhalation study with rabbits, testicular toxicity was also observed at the lowest tested concentration. A no-observed-adverse-effect concentration (NOAEC) for developmental toxicity in laboratory animals was established as 32 mg/m^3. The immune and nervous systems have also been identified as targets for toxicity in laboratory animals. There is some indication that 2-methoxyethanol may be weakly genotoxic in somatic cells, likely through activation to the intermediate acetaldehyde metabolite. Although there is some indication that 2-methoxyethanol causes genetic damage to male germ cells in rats at high doses or concentrations, results from these studies are inconclusive. In the absence of long-term investigations in animals, there is uncertainty with regard to the potential of 2-methoxyethanol to induce neoplastic effects.

[1] For a list of acronyms and abbreviations used in this report, please refer to Appendix 1.

Epidemiological data are limited but are suggestive of effects on the haematological system and on reproduction in men and women employed in occupations involving exposure to 2-methoxyethanol. A clear association between effects on the blood and exposure to 2-methoxyethanol has been reported in a study of a group of workers.

Effects on red blood cell counts in a population not exposed to other alkoxy alcohols or chemicals known to affect the bone marrow have been reported at levels of exposure at which effects on spermatogenesis were not observed. The studies contain reliable exposure data on both airborne levels and workplace urinary MAA (as a measure of actual uptake), which can be used as a basis for characterizing the risk from exposure to airborne 2-methoxyethanol.

A clear-cut haematotoxic effect was observed in workers at a time-weighted exposure to an average 2-methoxyethanol concentration of 113 mg/m^3, with recovery towards normal at an exposure level of 8.4 mg/m^3 and full recovery at 1.7 mg/m^3.

Taking 1.7 mg/m^3 as a NOAEC, adjusting for continuous exposure and applying an uncertainty factor of 10 for interindividual variation, a tolerable concentration of 0.04 mg/m^3 can be derived. As the effect is readily reversible and has been observed after a long-term exposure, no additional uncertainty factor to compensate for less than lifetime exposure is used.

Although relevant data are limited, exposure of the general population through environmental media is expected to be low, as a result of reported declining use of the compound in recent years as it is replaced with less hazardous compounds. Margins between worst-case estimates of exposure from environmental media and levels identified at which haematological parameters had returned to normal in exposed workers are considered adequate, as are those between exposure estimates and lowest effect levels for developmental toxicity obtained in toxicological investigations in laboratory animals. Whereas available data are insufficient to conclude that margins are adequate between estimates of exposure from consumer products and levels that have been associated with haematological effects in workers and between these exposure levels and lowest effect levels identified in laboratory animal studies, it should be emphasized that the estimates are extreme worst case and have not been validated.

Data on the effects of 2-methoxyethanol on aquatic organisms are limited. The most sensitive organism was reported to be the flagellate protozoan, *Chilomonas paramecium*. No data were identified on the effects of 2-methoxyethanol on terrestrial wildlife.

Environmental effects have been evaluated for terrestrial, soil and aquatic organisms. For a conservative risk characterization for terrestrial wildlife, the estimated exposure value (EEV) for 2-methoxyethanol in air was compared with a critical toxicity value (CTV) based on an inhalation study in rabbits. It was determined, on the basis of this evaluation, that concentrations of 2-methoxyethanol in air in Canada are unlikely to cause adverse effects on populations of wildlife.

The evaluation for soil organisms was based on a quantitative structure–activity relationship for effects on benthic organisms and an estimated concentration of 2-methoxyethanol in soil in Canada. Based on this assessment, it was considered that concentrations of 2-methoxyethanol in soil in Canada are unlikely to cause adverse effects on populations of soil organisms.

For a conservative risk characterization for aquatic organisms, the EEV was compared with the CTV based on studies with the flagellate protozoan, *Chilomonas paramecium*. On the basis of this evaluation, it was considered unlikely that there would be adverse effects on populations of aquatic organisms in Canada.

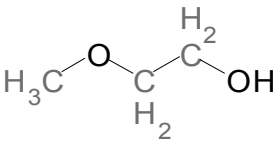
2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES

2-Methoxyethanol (Chemical Abstracts Service [CAS] No. 109-86-4; $C_3H_8O_2$; 2-methoxy-l-ethanol, ethylene glycol monomethyl ether [EGME], methyl cellosolve) is a colourless, viscous liquid of relative molecular mass 76.1 that is completely miscible in water (Budavari, 1996; DMER & AEL, 1996). 2-Methoxyethanol has a log octanol/water partition coefficient (K_{ow}) of −0.77 (Hansch & Leo, 1985), a vapour pressure of 1300 Pa at 25 °C (Riddick et al., 1986) and a Henry's law constant of 0.198 Pa·m^3/mol (calculated value) (DMER & AEL, 1996). The conversion factors for 2-methoxyethanol in air are 1 part per million (ppm) = 3.16 mg/m^3 and 1 mg/m^3 = 0.316 ppm[1]; those for 2-methoxyethyl acetate are 1 ppm = 4.91 mg/m^3 and 1 mg/m^3 = 0.204 ppm. 2-Methoxyethyl acetate is readily

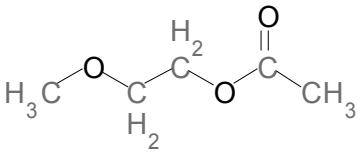
[1] In keeping with World Health Organization (WHO) policy, which is to provide measurements in Système international d'unités (SI) units, all concentrations of gaseous chemicals in air will be given in SI units in the CICAD series. Where the original study or source document has provided concentrations in SI units, these will be cited here. Where the original study or source document has provided concentrations in volumetric units, conversions will be done using the conversion factors given here, assuming a temperature of 20 °C and a pressure of 101.3 kPa. Conversions are to no more than two significant digits.

hydrolysed to 2-methoxyethanol, and thus relevant data on 2-methoxyethyl acetate are included in this Concise International Chemical Assessment Document (CICAD), where appropriate. Physical and chemical properties for both 2-methoxyethanol and 2-methoxyethyl acetate are presented in the International Chemical Safety Cards (ICSCs) reproduced in this document.

The structural formulae are shown below:



2-Methoxyethanol



2-Methoxyethyl acetate

3. ANALYTICAL METHODS

Several analytical procedures used for the determination of 2-methoxyethanol and 2-methoxyethyl acetate, and their major metabolite 2-methoxyacetic acid (MAA), in various environmental media are summarized in Table 1. In some reports, the useful range was indicated, but not the limit of detection. Gas chromatography with flame ionization detection is the method most commonly reported.

Metabolites of 2-methoxyethanol (2-methoxyacetaldehyde [MALD] and MAA) have been measured in urine using gas chromatography (Smallwood et al., 1984; Groeseneken et al., 1986, 1989b). MAA was determined by gas chromatography after extraction from urine and methylation, using 2-furoic acid as an internal standard. The mean (n = 30) recovery from urine was 31.4 ± 7.0%. The detection limit for MAA was 0.15 mg/l (Groeseneken et al., 1986). An improved method for the determination of alkoxyacetic acids in urine based on the gas chromatography of their pentafluorobenzyl esters, in which alkoxyacetic acid concentrations in the range of 0.1–200 mg/l could be determined with an average imprecision of ±3.5%, was described by Groeseneken et al. (1989b).

4. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

2-Methoxyethanol has not been reported to occur as a natural product (USEPA, 1986; IPCS, 1990). It is produced commercially by reacting ethylene oxide with anhydrous methanol (Kirk-Othmer, 1980). There are no known reactions that would lead to the in situ production of 2-methoxyethanol or other glycol ethers in the atmosphere (Rogozen et al., 1987).

Limited information on production and use, mostly from the source country of the national assessment on which this CICAD is based (Canada), is presented here.

2-Methoxyethanol was not produced in or exported from Canada in 1995 or 1996, according to data submitted to Environment Canada by 10 companies in a survey conducted under the 1988 *Canadian Environmental Protection Act* (Environment Canada, 1997b). According to data reported through this survey, importation of 2-methoxyethanol totalled less than 100 tonnes in 1995 and 80 tonnes in 1996.

2-Methoxyethanol has been reported to be used in paints, coatings, inks, cleaners, polishes, brake fluids and jet fuels and to find wide application as a solvent, chemical intermediate and solvent coupler of mixtures and water-based formulations (Stemmler et al., 1997). Data submitted to Environment Canada indicated that less than 200 and 75 tonnes of 2-methoxyethanol were used in Canada in 1995 and 1996, respectively, mainly as a chemical processing aid and as a component of formulated products (Environment Canada, 1997b). The total estimated use of 2-methoxyethanol in Canada in 2002 was 625 tonnes, distributed as follows: 80% (500 tonnes) as an anti-icing and decontamination agent; 15% (94 tonnes) as a chemical intermediate; approximately 2% (12 tonnes) as a process solvent in the production of printed circuit board laminates (e.g. electronics manufacturing) and in the electroplating, pharmaceutical and photographic industries; and 3% (19 tonnes) in coatings (as a solvent in pigment bases in specialty wood finishing products for wood furniture manufacturing and in specialty primer coatings for rubber manufacturing). There were no consumer uses for 2-methoxyethanol reported in this period (Environment Canada, 2003).

According to the 1993 Products Register in Sweden, 260–262 tonnes of 2-methoxyethanol were used in 23 products (Johanson & Rick, 1996). According to data from the Substances in Preparations in Nordic Countries (SPIN) database (http://195.215.251.229/DotNetNuke/default.aspx), total uses in Norway, Denmark, Finland and Sweden for 2002 were approximately 4177 tonnes (in 8 preparations), 11.6 tonnes (in 19 preparations), 0.4 tonne (in 14 preparations) and below 100 kg (in 22

Table 1. Analytical methods for 2-methoxyethanol, 2-methoxyethyl acetate and their metabolite, 2-methoxyacetic acid.

Matrix	Sampling method extraction/cleanup	Analytical method[a]	Limit of detection and/or useful range[a]	Reference
Air	Adsorption on charcoal, elution with methylene chloride, carbon disulfide or methylene chloride; methanol	GC-FID	Range: 2-ME 44–160 mg/m^3; 2-MEA 51–214 mg/m^3	NIOSH (1994)
Air (2-ME)	Diffusive sampling, adsorption on Tenax, thermal desorption	GC-FID	Range: 5–20 mg/m^3	Hamlin et al. (1982)
Air (2-ME)	Personal monitors with pump adsorption on Tenax, thermal desorption	GC-FID	NR	Health and Safety Executive (1993)
Blood (2-ME)	Methylene chloride extraction in presence of anhydrous sodium sulfate; average recovery 78%	GC-FID	8.8 mg/kg; range 8–946 mg/kg	Smallwood et al. (1984)
Blood (2-ME)	Headspace elution	GC-FID	NR	Denkhaus et al. (1986)
Urine (MAA)	Methylene chloride extraction followed by derivatization with pentafluorobenzyl bromide	GC-FID	11.4 mg/l; range 11.4–1140 mg/l	Smallwood et al. (1984)
Urine (MAA)	Lyophilization, methylene chloride extraction, methylation with diazomethane	GC-FID	0.15 mg/l	Groeseneken et al. (1986)
Urine (MAA)	Lyophilization followed by derivatization with pentafluorobenzyl bromide	GC-FID	0.03 mg/l; range 0.1–200 mg/l	Groeseneken et al. (1989b)
Urine (MAA)	Methylene chloride extraction	GC-MS	0.055 mg/l; range 0.3–200 mg/l	Shih et al. (1999a)

GC-FID, gas chromatography–flame ionization detector; GC-MS, gas chromatography–mass spectrometry; MAA, 2-methoxyacetic acid; 2-ME, 2-methoxyethanol; 2-MEA, 2-methoxyethyl acetate; NR, not reported.

[a] Only the range that has been confirmed as accurate is shown. These methods may be capable of measuring much lower levels of glycol ethers in air providing adequate sampling times are employed and desorption efficiencies are ascertained.

preparations, including those for consumer use), respectively.

Although the use of 2-methoxyethanol has declined in many parts of the world over recent years because of risk management procedures and its replacement by other substances, it is still in use in some areas. The annual consumption of 2-methoxyethanol in Taiwan, China, is reported to be over 3000 tonnes (Shih et al., 1999b). A voluntary programme to control the application and use of 2-methoxyethanol and 2-methoxyethyl acetate within the European Union has restricted their sale for use in consumer goods and household products, cosmetics, pesticide formulations, pharmaceutical preparations and medicines, and other applications where exposure is poorly controlled.

In 1994, total on-site environmental releases of 2-methoxyethanol reported to the Canadian National Pollutant Release Inventory (NPRI) amounted to 17 tonnes (NPRI, 1996). All of this was released into the atmosphere from one facility in southern Ontario. Total transfers of 2-methoxyethanol for off-site disposal amounted to 2.12 tonnes in 1994, with all going to incinerators. A reported total of 0.07 tonne of 2-methoxyethanol was sent for energy recovery in 1994 (NPRI, 1996).

In 1995, total on-site environmental releases of 2-methoxyethanol reported to the NPRI amounted to 6.3 tonnes (NPRI, 1998). All of this was released to the atmosphere from stack emissions at one facility in southern Ontario. Total transfers of 2-methoxyethanol for off-site disposal amounted to 33.9 tonnes in 1995 (NPRI, 1998).

No releases of 2-methoxyethanol were reported to the NPRI in 1996 (NPRI, 1998).

Based on preliminary 2002 NPRI data, two production facilities in Canada reported releases of 2-methoxyethanol. The largest emitter is furniture and furniture fixture manufacturers, which released 99% of the emissions of 2-methoxyethanol in Canada in 2002 (Environment Canada, 2003).

According to data submitted in a survey under the 1988 *Canadian Environmental Protection Act* (with different reporting requirements from the NPRI), environmental releases of 2-methoxyethanol in Canada totalled 8.7 tonnes in 1996, all to the air (Environment Canada, 1997b).

The Canadian Chemical Producers' Association (1997) reported total emissions of 2-methoxyethanol of 3.0, 0.036, 0.02 and 0.009 tonne from a single member company in 1992, 1993, 1994 and 1995, respectively, all of which were released to air. Reported releases totalled 0.006 tonne in 1996 and 0 tonnes in 1997 and 1998 (Canadian Chemical Producers' Association, 1999a,b).

In 2001, from various locations in the United States of America (USA), 392 tonnes of 2-methoxyethanol were emitted to the atmosphere, 14.5 tonnes were released to surface waters, 5.1 tonnes were released to land, 408 tonnes were released on site, 30 tonnes were released off site and 438 tonnes were released on and off site (USEPA, 2003).

5. ENVIRONMENTAL TRANSPORT, DISTRIBUTION AND TRANSFORMATION

Owing to its high volatility (vapour pressure 1300 Pa at 25 °C), 2-methoxyethanol is expected to be present principally in air. The half-life for 2-methoxyethanol in the atmosphere has been calculated to be in the range of 5.7–57 h, based on its reaction with hydroxyl radicals (USEPA, 1986; Howard et al., 1991).

2-Methoxyethanol volatilizes rapidly from the water surface, with an estimated half-life of 2.8 h (Lyman et al., 1982). Biodegradation would also be significant (USEPA, 1986); estimated half-lives in surface water and groundwater are 1–4 and 2–8 weeks, respectively, based on unacclimated aerobic biodegradation (Howard et al., 1991). Physical adsorption to suspended solids and sediments should not be significant (USEPA, 1986).

Its high water solubility and low K_{ow} (USEPA, 1986) would suggest that 2-methoxyethanol would be highly mobile in soil, although it would be expected that much of the substance would volatilize from the soil surface.

Howard et al. (1991) estimated half-lives in aerobic and anaerobic soils of 1–4 and 4–16 weeks, respectively, based on unacclimated aerobic biodegradation. 2-Methoxyethanol underwent bio-oxidation to MAA by the soil bacterium *Alcaligenes* MC11, which was able to use 2-methoxyethanol as a source of carbon (Harada & Nagashima, 1975). *Pseudomonas* sp. 4-5-3, *Xanthobacter autotrophicus* EC1-2-1 and a bacterium identified only as "strain MC2-2-1" could also use 2-methoxyethanol as a source of carbon for aerobic growth (Kawai, 1995).

A bioconcentration factor (BCF) of 0.15 was estimated for 2-methoxyethanol, based on its log K_{ow} of −0.77 and using the equation proposed by Lyman et al. (1982): log BCF = 0.76 log K_{ow} − 0.23 (USEPA, 1986). Bioaccumulation of 2-methoxyethanol in aquatic organisms would therefore not be significant.

The environmental partitioning of 2-methoxyethanol when released into air, water or soil was estimated by a Level III fugacity model (DMER & AEL, 1996). If 2-methoxyethanol is emitted into air, Equilibrium Criterion (EQC) Level III fugacity modelling (Mackay et al., 1996) predicts that about 50% would be present in air, whereas approximately 25% would be present in soil and about 25% in water. If 2-methoxyethanol is emitted into water, more than 99% would be present in water. If 2-methoxyethanol is released to soil, about 75% would be present in the soil, whereas approximately 25% would be present in water (DMER & AEL, 1996).

6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

Data on concentrations in the environment primarily from the source country of the national assessment on which this CICAD is based (i.e. Canada) are presented here, as a basis for the sample risk characterization for human health.

6.1 Environmental levels

Very few data on levels of 2-methoxyethanol in the environment have been identified (USEPA, 1986; IPCS, 1990). No data were identified on the concentration of 2-methoxyethanol in ambient air, surface water or soil, although one study was conducted to determine concentrations of 2-methoxyethanol in multiple Canadian media to which humans are exposed, including drinking-water and indoor and outdoor air. Thirty-five participants from the Greater Toronto area in Ontario, six participants from Queens Subdivision in Nova Scotia and nine from Edmonton, Alberta, were randomly selected. For each of the 50 participants, samples of drinking-water and indoor, outdoor and personal air were collected over a 24-h period. Samples of foods and beverages were not analysed for the determination of 2-methoxyethanol. The concentration of 2-methoxyethanol was below the method detection limit (0.6 µg/l) in all samples of drinking-water. Similarly, it was not detected (<5 $\mu g/m^3$) in any sample of indoor, outdoor or personal air (Conor Pacific Environmental Technologies Inc., 1998).

Environmental concentrations of 2-methoxyethanol were estimated by ChemCAN version 4 modelling (DMER & AEL, 1996). This is a Level III fugacity-based regional model developed to estimate the environmental fate of chemicals in Canada. Environmental concentrations of 2-methoxyethanol in southern Ontario predicted by ChemCAN modelling are as follows: 0.146 ng/m^3 in air; 4.8×10^{-5} µg/l in water; 9.4×10^{-4} ng/g dry weight in soil; and 2.34×10^{-5} ng/g dry weight in sediments. The ChemCAN model estimates average concentrations throughout the region; therefore, actual concentrations in the vicinity of releases will be higher than those estimated by the model.

Two studies providing data on concentrations of 2-methoxyethanol in indoor air have been identified. In a study conducted in Germany, indoor air samples were collected following the sealing of wooden parquet flooring in a school room with a product containing 2-methoxyethanol. The concentrations of 2-methoxyethanol in samples collected 10, 18, 25, 35, 52 and 90 days after sealing were 220, 150, 180, 160, 59 and 26 $\mu g/m^3$, respectively (Schriever & Marutzky, 1990). In northern Italy, six indoor air samples were collected from homes in 1983–1984 and analysed for several organic pollutants by gas chromatography with mass spectrometric detection. The concentration of 2-methoxyethanol in one of the samples was 70 $\mu g/m^3$; in the remaining five samples, however, the concentration was below the limit of detection (not specified) (De Bortoli et al., 1986).

2-Methoxyethanol was listed as a contaminant in drinking-water samples analysed between June 1977 and November 1980 in a survey of 12 cities in the USA (Lucas, 1984). Although no details on concentrations of the substance were provided, they were said to be less than 1 µg/l. No data on concentrations of 2-methoxyethanol in food were identified.

Glycol ethers, including 2-methoxyethanol, are used as solvents in a number of consumer products, including paints, paint thinners and cleaning products. In the USA, all-purpose cleaning products may contain 2-methoxyethanol concentrations up to 2%, and metal cleaners may contain up to 6% (Flick, 1986, 1989). Versar Inc. (1986) reported varnish to contain 1.1% 2-methoxyethanol. In the Clinical Toxicology of Commercial Products database, one consumer product in the category of "coatings/inks" (which includes paints, varnishes, sealants, other coatings, marking pens and other similar items) and two products in the category of "coating thinners/strippers" were reported to emit 2-methoxyethanol (Hodgson & Wooley, 1991). In a summary of the emissions of 2-methoxyethanol from materials listed in the National Aeronautics and Space Administration (NASA)/McDonnell Douglas Materials Testing Data Base, emissions of 2-methoxyethanol from five adhesives were in the range of 1.2–30 µg/g product (median 2.1 µg/g product), those from one fabric were 0.33 µg/g product and those from seven products in the category of "pens/inks" were in the range of 1.6–960 µg/g product (median 38 µg/g product) (Hodgson & Wooley, 1991).

In a study of the volatile organic compounds (VOCs) often found in household products, conducted in

Italy, 2-methoxyethanol was detected as a minor VOC component in one, a liquid wax for marble, ceramic and linoleum (Knöppel & Schauenburg, 1989).

2-Methoxyethanol was not detected in the emissions of 13 consumer products, including window cleaners, all-purpose cleaners, paints, nail polish removers and hair dye (classes of products reported to contain glycol ethers, based on available information), purchased in Ottawa, Canada (Zhu et al., 2001). Of the cosmetic products registered for use in Canada, one nail polish remover was reported to contain 2-methoxyethanol in the range of >30–100% (Health Canada, 1998c); 2-methoxyethanol has apparently also been said to be a component of an insecticidal formulation used on ornamental plants, although no information was available as to whether this was for professional or consumer use (Health Canada, 1998b).

Exposure to 2-methoxyethanol among 27 workers at a plant manufacturing semiconductor copper laminate circuit boards in Taiwan, China, has been evaluated (Shih et al., 1999b). In total, 149 8-h time-weighted average (TWA) personal breathing-zone samples were collected from Monday to Saturday from regular operation workers and special operation workers (involved in mixing, charging and discharging, or cleaning and maintenance operations). The average 8-h TWA exposure for the 18 regular operation workers ranged from 2.3 (standard deviation [SD] 2.3) to 31 (14) mg/m^3, with a weekly mean (SD) of 14 (8.1) mg/m^3. For the nine special operation workers, the weekly mean exposure (SD) was 260 (350) mg/m^3. Mean peak exposures (SD) during the mixing of raw materials and in the cleaning of coating machines were 2200 (590) mg/m^3 and 490 (49) mg/m^3, respectively. In another study, exposure monitoring over a period of 6 months, during which workplace control measures were introduced, found mean levels at baseline to be 110 mg/m^3 (range 2.4–1000 mg/m^3) for a group of 29 workers from the coating department. At the 6-month survey, airborne exposure for these workers had fallen to 1.7 mg/m^3 (range 0.3–11 mg/m^3) (Shih et al., 2003).

Sparer et al. (1988) conducted an industrial hygiene survey to characterize exposure of shipyard painters to 2-methoxyethanol in the USA. Samples (n = 102) were taken over six work shifts. Results showed that the airborne exposure (TWA) to 2-methoxyethanol ranged from 0 to 17.7 mg/m^3, with a mean of 2.6 mg/m^3 and a median of 1.6 mg/m^3. Limitations of the sampling and a few prior measurements suggested that these data may underestimate usual or previous exposure. Veulemans et al. (1987) reported the results of sampling 2-methoxyethanol from 78 different plants in Belgium. The mean exposure in painting operations was 31.3 mg/m^3, with a range from 5.6 to 136.9 mg/m^3.

6.2 Human exposure

The limitations of the available monitoring data for 2-methoxyethanol preclude the development of reliable estimates of typical exposure of the general population; instead, worst-case or bounding estimates of exposure to 2-methoxyethanol from environmental media and consumer products have been developed in order to characterize potential exposure from these pathways.

Because most of the consumer products for which suitable data are available are used primarily by adults, the estimated exposures have been derived for this age class only, although the limitations of the available data preclude confident estimation of intake for even one age group. (The differences among age classes in intake from a given medium, as a result of age-specific differences in intakes of environmental media and in body weight, would be small in relation to the variation in exposure from the various sources, in any case.) Extreme worst-case or bounding estimates of intake of 2-methoxyethanol by Canadian adults from various sources and the assumptions upon which they are based are summarized in Table 2.

The only environmental media for which available monitoring data allowed even crude estimation of exposure were air and water. These estimates are based on the limits of detection in air and tap water from the Canadian multimedia study in which concentrations of 2-methoxyethanol were below the limit of detection in all of the samples of air and tap water that were analysed for 50 participants (Conor Pacific Environmental Technologies Inc., 1998). However, although the limits of detection for this substance were relatively high, the lack of detection in these media is not surprising, in view of the decline in use and production of 2-methoxyethanol in Canada over the last several years.

Based on these values, the average adult in Canada would be exposed to airborne levels of 2-methoxyethanol no greater than 5 µg/m^3 and would not ingest more than 0.013 µg/kg body weight per day, although it is recognized that these values likely overestimate exposure. In addition, concentrations of 2-methoxyethanol in ambient air and surface water predicted by fugacity modelling, based on the highest reported release in recent years, were several orders of magnitude below these detection limits. Therefore, the estimated worst-case or bounding estimates of intake from air (0.0011 mg/kg body weight per day) and water (0.000 013 mg/kg body weight per day) are substantially less than the worst-case exposure estimates for consumer products.

Although no monitoring data are available, food is unlikely to be a principal source of exposure to 2-methoxyethanol in humans, as 2-methoxyethanol is

Table 2. Worst-case/bounding estimates of intake of 2-methoxyethanol by adult Canadians.

Exposure medium	Assumptions[a]	Estimated intake (mg/kg body weight per day)
Environmental media (indirect exposure)		
Air	• based on the limit of detection for 2-methoxyethanol in air in the Canadian multimedia study (5 µg/m^3) (Conor Pacific Environmental Technologies Inc., 1998) • an average Canadian adult is assumed to weigh 70.9 kg and to breathe 16.2 m^3 of air per day (Health Canada, 1998a) $\frac{(0.005\ mg/m^3)\ (16.2\ m^3)}{(70.9\ kg)}$	0.0011
Water	• based on the limit of detection for 2-methoxyethanol in water in the Canadian multimedia study (0.6 µg/l) (Conor Pacific Environmental Technologies Inc., 1998) • an average Canadian adult is assumed to weigh 70.9 kg and to consume 1.5 litres of tap water per day (Health Canada, 1998a) $\frac{(0.0006\ mg/l)\ (1.5\ litres)}{(70.9\ kg)}$	0.000 013
Consumer products (direct exposure)		
Nail polish remover	• based on the upper bound of the concentration range of >30–100% of 2-methoxyethanol in nail polish remover • assumes a typical quantity of product used per event for "nail polish & enamel remover" of 3.06 g and a maximum event frequency of 0.29 times per day for users only (USEPA, 1997) • a body weight of 70.9 kg is assumed for an average Canadian adult (Health Canada, 1998a) $\frac{(1.0)\ (0.29/day)\ (3060\ mg)}{(70.9\ kg)}$	12.5
All-purpose liquid cleaner	**Inhalation** • based on a maximum concentration of 2% 2-methoxyethanol in all-purpose liquid cleaner (Flick, 1986, 1989) • assumes a mass of 35 g is used per event, a 0.47-h duration of exposure, a room volume of 20 m^3, a breathing rate of 1.3 m^3/h for an average adult during light-level activity and a frequency of use of 360 days/year (Versar Inc., 1986) • a body weight of 70.9 kg is assumed for an average Canadian adult (Health Canada, 1998a) $\frac{(0.02)\ (35\ 000\ mg)\ (0.47\ h)\ (1.3\ m^3/h)\ (360/365\ days)}{(20\ m^3)\ (70.9\ kg)}$	0.30
	Dermal • based on a maximum concentration of 2% 2-methoxyethanol in all-purpose liquid cleaner (Flick, 1986, 1989) • assumes an event frequency of 360 days/year, an exposed surface area of 400 cm^2 (both palms), a product density of 1.19 g/cm^3 and a film thickness on the hands of 2.1×10^{-3} cm (Versar Inc., 1986) • a body weight of 70.9 kg is assumed for an average Canadian adult (Health Canada, 1998a) $\frac{(0.02)\ (360/365\ days)\ (400\ cm^2)\ (1.19\ g/cm^3)\ (2.1 \times 10^{-3}\ cm)\ (1000\ mg/g)}{(70.9\ kg)}$	0.28
All-purpose spray cleaner	**Inhalation** • based on a maximum concentration of 2% 2-methoxyethanol in all-purpose spray cleaner (Flick, 1986, 1989) • assumes a mass of 76 g is used per event, a 0.47-h duration of exposure, a room volume of 20 m^3, a breathing rate of 1.3 m^3/h for an average adult during light-level activity and a frequency of use of 360 days/year (Versar Inc., 1986) • a body weight of 70.9 kg is assumed for an average Canadian adult (Health Canada, 1998a) $\frac{(0.02)\ (76\ 000\ mg)\ (0.47\ h)\ (1.3\ m^3/h)\ (360/365\ days)}{(20\ m^3)\ (70.9\ kg)}$	0.65 [estimated indoor air concentration of 76 mg/m^3]

Table 2 (contd)

Exposure medium	Assumptions[a]	Estimated intake (mg/kg body weight per day)
	Dermal	0.21
	• based on a maximum concentration of 2% 2-methoxyethanol in all-purpose spray cleaner (Flick, 1986, 1989)	
	• assumes an event frequency of 360 days/year, an exposed surface area of 400 cm^2 (both palms), a product density of 0.88 g/cm^3 and a film thickness on the hands of 2.1×10^{-3} cm (Versar Inc., 1986)	
	• a body weight of 70.9 kg is assumed for an average Canadian adult (Health Canada, 1998a)	
	$\frac{(0.02)\ (360/365\ \text{days})\ (400\ cm^2)\ (0.88\ g/cm^3)\ (2.1 \times 10^{-3}\ cm)\ (1000\ mg/g)}{(70.9\ kg)}$	
Varnish	**Inhalation**	0.0075
	• based on a maximum concentration of 1.1% 2-methoxyethanol in varnish (Versar Inc., 1986)	[estimated indoor air concentration of 13 mg/m^3]
	• assumes a mass of 150 g is used per event, a 0.47-h duration of exposure, a room volume of 125 m^3, a breathing rate of 1.3 m^3/h for an average adult during light-level activity and a frequency of use of 24 days/year (Versar Inc., 1986)	
	• a body weight of 70.9 kg is assumed for an average Canadian adult (Health Canada, 1998a)	
	$\frac{(0.011)\ (150\ 000\ mg)\ (0.47\ h)\ (1.3\ m^3/h)\ (24/365\ \text{days})}{(125\ m^3)\ (70.9\ kg)}$	
	Dermal	0.027
	• based on a maximum concentration of 1.1% 2-methoxyethanol in varnish (Versar Inc., 1986)	
	• assumes an event frequency of 24 days/year, an exposed surface area of 190 cm^2 (10% of the hands and forearms), a product density of 0.88 g/cm^3 and a film thickness on the hands of 15.88×10^{-3} cm (Versar Inc., 1986)	
	• a body weight of 70.9 kg is assumed for an average Canadian adult (Health Canada, 1998a)	
	$\frac{(0.011)\ (24/365\ \text{days})\ (190\ cm^2)\ (0.88\ g/cm^3)\ (15.88 \times 10^{-3}\ cm)\ (1000\ mg/g)}{(70.9\ kg)}$	

[a] For all of the consumer products, it is assumed that 100% of the 2-methoxyethanol is absorbed.

released primarily to air from industrial activities and consumer products (no releases to other media have been reported). 2-Methoxyethanol is unlikely to partition to food from air owing to its high volatility and very low log K_{ow} of −0.77. (In fact, even if intake from food is estimated on the basis of extrapolation from the results of the fugacity modelling, this value would still be several orders of magnitude less than the worst-case scenarios calculated for air and drinking-water on the basis of the limit of detection in the multimedia study.)

Likewise, exposure to 2-methoxyethanol in soil is likely to be negligible in comparison with that in air, based on its release patterns and physical/chemical properties and the results of fugacity modelling.

Direct exposure to 2-methoxyethanol can result from the use of a variety of consumer products containing these substances. Both inhalation and dermal absorption are expected to be important routes of exposure for most consumer products, as many of those products expected to contain 2-methoxyethanol can contact the skin. Extreme worst-case estimated intakes from the few products for which quantitative data were identified are presented in Table 2. It should be emphasized, however, that as information on current compositions and use patterns of these products in Canada is extremely limited, these values likely considerably overestimate current exposures, particularly in view of the decline in use of this compound in many countries. The highest estimated worst-case intake of 2-methoxyethanol for consumer products was for nail polish remover (12.5 mg/kg body weight per day). This estimate was developed from product use scenarios (USEPA, 1997), assuming that 100% of the applied compound was absorbed, and refers to dermal absorption only. Upper-bounding estimates of intake of 2-methoxyethanol from exposure to household cleaning products and varnish were developed from product use scenarios (Versar Inc., 1986), assuming 100% absorption for the product contacting the skin and for the inhaled product (in view of lack of adequate data to support a more refined estimate). Worst-case estimates of indoor air concentrations

resulting from the use of products such as all-purpose spray cleaners were calculated to be up to 76 mg/m^3.

It should be noted that these estimates have been made for only a limited range of media and products for which at least some data were available. In addition, they do not represent typical exposures, as the limitations of the available data preclude development of such estimates; most are instead maximal or near-maximal estimates of potential exposure that have not been validated.

7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

2-Methoxyethanol is readily absorbed following oral, inhalation or dermal exposure and distributed extensively throughout the body, including the developing fetus, in which levels of metabolites may be greater than in the dams (Welsch & Sleet, 1987; Sleet et al., 1988; Scott et al., 1989; Kezic et al., 1997). The major metabolic pathways of 2-methoxyethanol involve oxidation. In the first pathway, 2-methoxyethanol is rapidly metabolized via alcohol and aldehyde dehydrogenases to MALD, then MAA (the likely active metabolites). MAA is subsequently conjugated with glycine or *O*-demethylated and then oxidized to produce carbon dioxide; some MAA may also undergo Krebs cycle transformation. Alternatively, 2-methoxyethanol may be oxidized via microsomal P450 mixed-function oxidases and *O*-demethylated to form formaldehyde and ethylene glycol. 2-Methoxyethanol may also be directly conjugated with sulfate or glucuronic acid. The various metabolic pathways are outlined in Figure 1.

In general, MAA (in free or conjugated form) was the principal metabolite detected in the urine of rats, mice and humans exposed by ingestion or inhalation; other urinary metabolites included ethylene glycol (particularly in rats following repeated exposure in drinking-water) (Medinsky et al., 1990) and products of Krebs cycle metabolism. The putatively toxic metabolite MAA is eliminated much more slowly in humans than in (pregnant) rats and (pregnant) monkeys, with half-lives in the blood of 77, 12 and 19 h, respectively (Groeseneken et al., 1989a).

After the single oral administration of radiolabelled 2-methoxyethanol at 76–660 mg/kg body weight to male rats, 50–65% of the radioactivity was excreted in the urine, 73% as MAA and ≤15% as 2-methoxyethanol; 10–12% was exhaled as carbon dioxide and another 3% as 2-methoxyethanol; only 1–2.7% was eliminated in the faeces over a collection period of 48 h. Of the administered radioactivity, 1.6% was detected in the liver, 0.2% in the kidney, 0.7% in the blood, 0.1% in the testes, 0.02% in the thymus, 0.03% in the spleen and 9.6% in the rest of the carcass (Miller et al., 1983b; Foster et al., 1984).

When male rats received radiolabelled 2-methoxyethanol in the drinking-water for 24 h (12–110 mg/kg body weight), 40–50% of the radioactivity was excreted in the urine during the 72-h collection period, 34–45% of which was as MAA, 42–60% as ethylene glycol and 6–8% as 2-methoxyethanol. The relative fraction of MAA in the urine increased with increasing dose, whereas the relative ethylene glycol content decreased. About 20–30% of the administered radioactivity was exhaled as carbon dioxide and <5% as unchanged 2-methoxyethanol (Medinsky et al., 1990).

After oral administration of radiolabelled 2-methoxyethanol to pregnant CD-1 mice on gestation day 11, 70–80% of the radioactivity was eliminated in the urine within 24 h, about 50% of which was as MAA and about 25% as 2-methoxyacetyl glycine; about 5–6% was exhaled as carbon dioxide over a 72-h period. At autopsy after 72 h, 0.025% of the radioactivity was detected in the embryos. It was shown using nuclear magnetic resonance spectroscopy that, besides the main metabolites (MAA and 2-methoxyacetyl glycine), ethylene glycol was also formed, which was degraded to glycine via glycolic acid. A conjugation of 2-methoxyethanol or MAA with glucuronic acid could have resulted in 2-methoxyethyl or 2-methoxyacetyl glucuronide, respectively, as well as the conjugation of 2-methoxyethanol with sulfate to form 2-methoxyethyl sulfate (Sleet et al., 1988; Mebus et al., 1992; Sumner et al., 1992).

After the daily oral administration of 12, 24 or 36 mg 2-methoxyethanol/kg body weight to pregnant monkeys (*Macaca fascicularis*) for 25 days, an increase in the MAA concentration in the blood serum was observed. Blood was taken from 3–6 animals at 2, 4, 7.5 and 24 h following dosing on the 1st, 8th, 15th and 22nd days and analysed. Significant amounts of MAA were detectable 24 h after the first treatment. The half-life for elimination of MAA was about 20 h, assuming that 2-methoxyethanol is rapidly converted to MAA. The MAA concentration in serum was 5–10 µg/ml 4 days after the end of the 25-day administration period and 0.1–1.0 µg/ml after 1 week. MAA was no longer detectable (detection limit 50 ng/ml) in blood serum thereafter (Scott et al., 1989).

The respiratory uptake following exposure of five volunteers (two men and three women) to an average 2-methoxyethanol concentration of 42 mg/m^3 during four 15-min exposure periods was measured by Kezic et al.

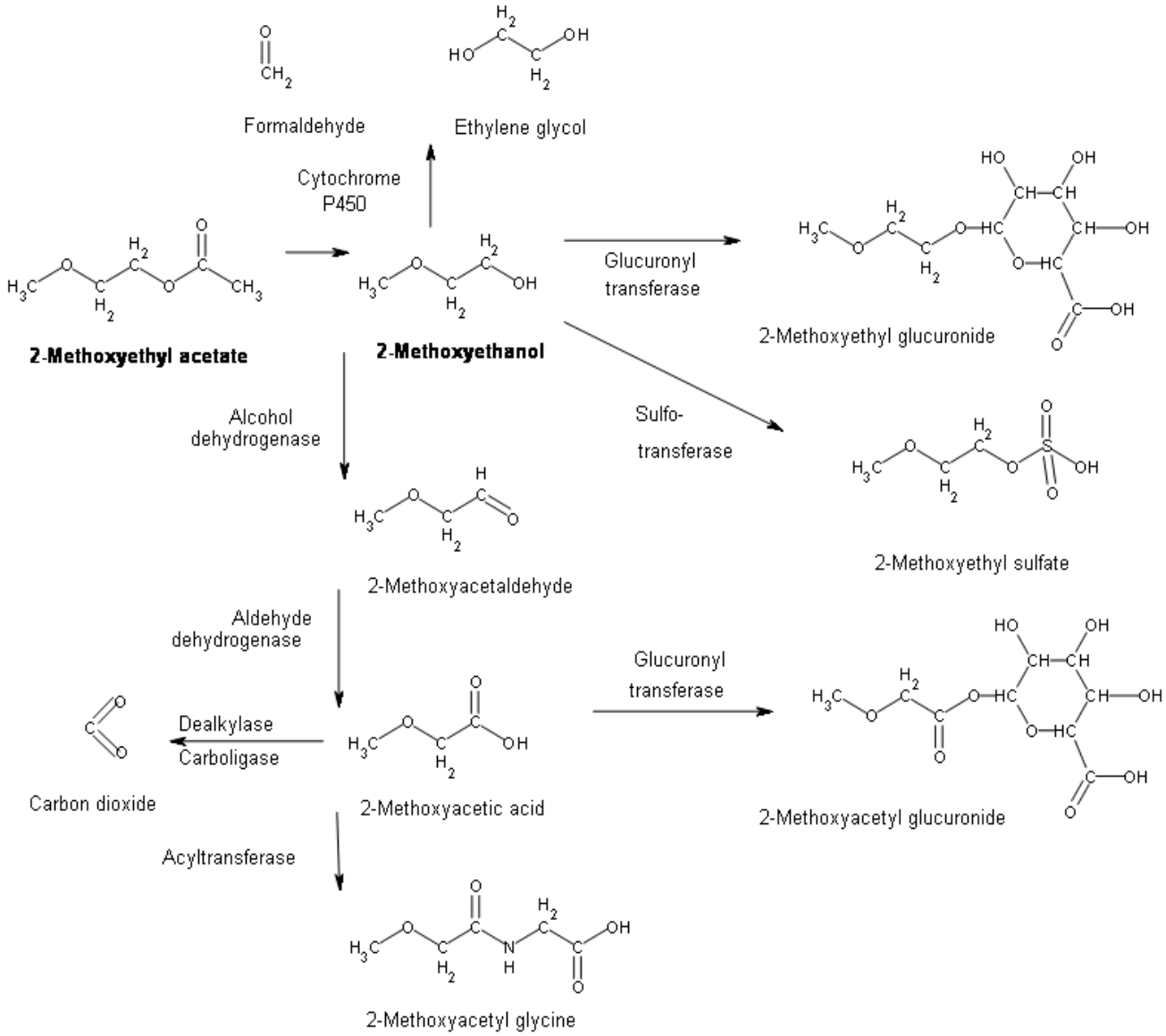


Figure 1. Metabolic pathways of methoxyethanol

(1997). The very high blood/air partition coefficient of 32 836 resulted in a respiratory retention of 80% of the inhaled 2-methoxyethanol and an inhalatory uptake of 19.0 mg of 2-methoxyethanol. Extrapolation to an 8-h inhalation exposure at a concentration of 16 mg/m^3 (the occupational exposure limit [OEL] in the Netherlands at the time of the study) resulted in an estimated uptake of 57 mg.

The dermal uptake of 2-methoxyethanol vapours or liquid was measured by Kezic et al. (1997) using five human volunteers (two men and three women). For the assessment of dermal absorption of vapour, one of the forearms and hands (an area of approximately 1000 cm^2) of each of these volunteers were exposed for 45 min to concentrations of 4000 mg 2-methoxyethanol/m^3. On another occasion, separated by at least 3 weeks, dermal exposure to liquid 2-methoxyethanol was for 15 min on areas of 27 cm^2 (forearm). Dermal uptake was assessed by measurement of the main urinary metabolite, MAA. For each volunteer, excretion of the metabolite was compared with a reference exposure by inhalation. The mean (SD) absorption rate of 2-methoxyethanol vapour was 36 (11) cm/h (permeability rate), and the mean (SD) absorption rate of the liquid 2-methoxyethanol amounted to 2.9 (2.0) mg/cm^2 per hour (flux rate). In the combined inhalation and dermal exposure, assuming the whole body surface was exposed to vapour, the uptake through

the skin was estimated to be 55% of the total uptake of 2-methoxyethanol. Dermal uptake resulting from skin contact of both hands and forearms (about 2000 cm^2) with liquid would exceed the inhalation uptake of the 8-h OEL (16 mg/m^3) by 100 times.

After dermal, semiocclusive application of 35, 109 or 321 mg radiolabelled 2-methoxyethanol/kg body weight in acetone to the shaved skin (area 9.4 cm^2) on the backs of four male F344 rats, 19–27% of the applied radioactivity was absorbed over 72 h, and 51–61% evaporated. During the 72-h collection period, independent of the dose, 67–72% of the absorbed radioactivity was excreted in the urine, 8.8–10% was excreted in the faeces and 14–16% remained in the animals. Of the radioactivity excreted in the urine (evaluated urine collection period 47 h), 62–63% was identified as MAA, 10–15% as ethylene glycol and 8.8–10% as 2-methoxyacetyl glycine; the remaining fraction of unidentified metabolites amounted to 1.2–2.1%. About 4.2–7.8% of the applied radioactivity was exhaled as carbon dioxide (Sabourin et al., 1992, 1993).

After a 2-h whole-body exposure of three female Sprague-Dawley rats to 4976 mg 2-methoxyethanol/m^3, an average concentration of 86 µg 2-methoxyethanol/ml was detected in the blood. After a single intraperitoneal 2-methoxyethanol injection of 761 mg/kg body weight (10 mmol/kg body weight) to four female Sprague-Dawley rats, the maximum mean 2-methoxyethanol blood concentration of about 685 µg/ml was measured after about 20 min, and 2-methoxyethanol at about 190 µg/ml was still detected in the blood after 2 h (Römer et al., 1985).

After a single intraperitoneal injection of 250 mg radiolabelled 2-methoxyethanol/kg body weight to male Sprague-Dawley rats, during a 24-h collection period, 40% of the administered radioactivity was excreted in the urine (a total of 55% over 48 h), 50–60% of which was identified as MAA and 18–25% as 2-methoxyacetyl glycine. The elimination half-life of 2-methoxyethanol in plasma was 0.6 h, and that for the total radioactivity in plasma, 20 h. If the alcohol dehydrogenase inhibitor pyrazole (400 mg) was administered intraperitoneally 1 h before the 2-methoxyethanol administration, only 18% of the administered radioactivity could be detected in the urine after the 48-h collection period. The plasma elimination half-life of 2-methoxyethanol was prolonged to 43 h, and that of the total radioactivity, to 51 h (Moss et al., 1985).

Römer et al. (1985) demonstrated that the degradation of 2-methoxyethanol is inhibited by the simultaneous presence of ethanol in the blood. This infers a mutually competitive degradation of ethanol and 2-methoxyethanol by alcohol dehydrogenase.

The oral administration of 300 mg 2-methoxyethanol/kg body weight per day for 20 days to eight male rats caused a significant increase in alcohol dehydrogenase activity in the liver (Kawamoto et al., 1990).

A lower relative affinity for 2-methoxyethanol than for ethanol was found for alcohol dehydrogenase isolated from the liver of pregnant CD-1 mice. In contrast to a Michaelis-Menten constant (K_m) value of 0.598 mmol/l and a maximum reaction rate (V_{max}) value of 391 nmol/mg protein per hour for ethanol, the K_m was 5.18 mmol/l and the V_{max} was 211 nmol/mg protein per hour for 2-methoxyethanol (Sleet et al., 1988).

Aasmoe & Aarbakke (1997) found sex differences in the elimination of 2-methoxyethanol and MAA by male and female rats. The rate of 2-methoxyethanol elimination was significantly faster in female than in male rats. No sex difference was seen in the elimination of MAA, and elimination was much slower than that for 2-methoxyethanol.

The acetate derivative of 2-methoxyethanol (2-methoxyethyl acetate), which is commonly encountered in the occupational environment, is rapidly hydrolysed to 2-methoxyethanol via esterases in several tissues in the body (IPCS, 1990). For this reason, data on the toxicity of 2-methoxyethyl acetate have been included in this CICAD.

Several physiologically based pharmacokinetic (PBPK) models of 2-methoxyethanol absorption, metabolism, disposition and excretion have been developed. Hays et al. (2000) modified an existing PBPK model of 2-methoxyethanol and MAA kinetics during mid-organogenesis in mice to simulate levels of these molecules in maternal plasma and total embryo tissues in rats on gestation days 13 and 15. The basic model included compartments representing the liver, fat, and slowly and richly perfused tissues. The original mouse model was modified to allow for PBPK description of MAA disposition, the embryos and placenta were included with the richly perfused tissues compartment and the mammary gland volume was grouped with the fat compartment. Model simulations closely reflected the biological measurements of 2-methoxyethanol and MAA concentrations in blood and embryo tissue following gavage or intravenous administration of 2-methoxyethanol or MAA. The model includes a description of the growth of the developing embryo and changes in the physiology of the dam during pregnancy.

The model was further extended to and validated for inhalation exposures by Gargas et al. (2000). Pregnant Sprague-Dawley rats were exposed for 5 days (gestation days 11–15), 6 h/day, to 2-methoxyethanol vapour at 32 and 160 mg/m^3. Validation consisted of comparing model output with maternal blood and fetal blood 2-

methoxyethanol and MAA concentrations during and following 5 days of exposure (gestation days 11–15). These concentrations corresponded to a known no-observed-adverse-effect concentration (NOAEC) and lowest-observed-adverse-effect concentration (LOAEC) for developmental effects in rats. The rat PBPK model for 2-methoxyethanol/MAA was scaled to humans and (without the pregnancy component) was used to predict data collected by other investigators on the kinetics of MAA excretion in urine following exposures to 2-methoxyethanol in human volunteers. The partially validated human model (with the pregnancy component) was used to predict equivalent human exposure concentrations based on MAA dose measures that corresponded to the concentrations measured at the rat NOAEC and LOAEC exposure concentrations. It was calculated that pregnant women exposed for 8 h/day, 5 days/week, for the duration of pregnancy would need to be exposed to 2-methoxyethanol at 38 or 190 mg/m^3 to produce maternal MAA blood concentrations (maximum concentration [C_{max}] or average daily area under the curve [AUC]) equivalent to those in rats exposed to the NOAEC (32 mg/m^3) or LOAEC (160 mg/m^3), respectively.

Because absorption via the dermal route can be a significant route of exposure, particularly in the occupational setting, inhalation exposure alone will not give sufficient indication of biological exposure. The level of the MAA metabolite in the urine can be used as a specific and suitable indicator of overall exposure (Veulemans et al., 1987; Groeseneken et al., 1989a,b).

8. EFFECTS ON LABORATORY MAMMALS AND IN VITRO TEST SYSTEMS

8.1 Single exposure

2-Methoxyethanol is of low to moderate acute toxicity in laboratory animals following oral, inhalation or dermal exposure, with oral median lethal doses (LD_{50}s) generally in the range of 2460–3400 mg/kg body weight, inhalation median lethal concentrations (LC_{50}s) greater than 6000 mg/m^3 and a dermal LD_{50} of approximately 1300 mg/kg body weight (Smyth et al., 1941; Carpenter et al., 1956; ECETOC, 1995). Sublethal effects following acute exposure to lower doses include toxicity to the reproductive system in males (≥50 mg/kg body weight), alterations in haematological parameters (≥200 mg/kg body weight) and effects in the liver, thymus and spleen (300 mg/kg body weight) (Chapin & Lamb, 1984; Anderson et al., 1987; Holloway et al., 1990; Kawamoto et al., 1990; Ku et al., 1994).

8.2 Irritation and sensitization

2-Methoxyethanol has low potential for causing skin or eye irritation (Carpenter & Smyth, 1946; Jacobs et al., 1987, 1989; Jacobs, 1992; Devillers & Chessel, 1995). It has not been shown to be a skin sensitizer in the guinea-pig by the maximized Magnusson and Kligman method (Zissu, 1995).

8.3 Short-term exposure

The thymus, testes and blood have consistently been the most sensitive targets for adverse effects in rats repeatedly exposed over the short term to 2-methoxyethanol or 2-methoxyethyl acetate via ingestion, inhalation or dermal application (Miller et al., 1981; Grant et al., 1985; Fairhurst et al., 1989; Feuston et al., 1989; Kawamoto et al., 1990; Exon et al., 1991; Smialowicz et al., 1991a; NTP, 1993; Butterworth et al., 1995; Williams et al., 1995). Reduced relative weight of the thymus was observed in rats orally administered 50 mg/kg body weight per day or more (4 days) or exposed to airborne concentrations of 950 mg/m^3 or higher (9 days), whereas histopathological changes were noted at higher exposure levels. Histopathological effects or reduced weights were also observed in the testes of rats exposed to around 88 mg/kg body weight per day or to 950 mg/m^3 or higher for 9 or 10 days, whereas alterations in haematological parameters were reported in rats administered 70 mg/kg body weight per day or 950 mg/m^3 or more for 5 days or longer.

Although the database in mice is more limited, mice appear to be less sensitive than rats to induction of effects on these organs, as effects on the thymus, blood and testes were noted only at oral doses of 1000, 500 and 250 mg/kg body weight per day (≥4 days) (Nagano et al., 1979, 1984; Miller et al., 1981; Hong et al., 1988) and airborne concentrations of 950, 950 and 3200 mg/m^3 (9 days), respectively (NTP, 1993). Available data on short-term toxicity in other laboratory species are too limited for meaningful comparison.

The nervous system has also been identified as a target for toxicity in rats and mice, although the database is somewhat limited (see section 8.8).

8.4 Medium-term exposure

The thymus, testes and blood were also the primary targets of 2-methoxyethanol-induced toxicity in rats exposed subchronically by gavage or in drinking-water. Atrophy or decreased weight of the thymus and testes and alterations in haematological parameters (including mean haemoglobin concentration, packed cell volume, and red and white blood cell counts) were observed in rats administered oral doses of 285 mg/kg body weight per day (the lowest dose tested) or more for 6 weeks

(USEPA, 1992). Testicular degeneration and decreased thymus weights, along with effects on the blood (including anaemia and reduced white blood cell and platelet counts), were also reported in F344/N rats exposed to 2-methoxyethanol in drinking-water for 13 weeks at concentrations equivalent to doses of 71 mg/kg body weight per day or more (NTP, 1993), which therefore constitutes a lowest-observed-adverse-effect level (LOAEL) for the oral route. A no-observed-adverse-effect level (NOAEL) was not identified in these studies.

Similar to the results in short-term studies, B6C3F1 mice were less sensitive than rats to effects induced by 2-methoxyethanol, as effects on the testes and thymus were noted only at doses of 530 and 990 mg/kg body weight per day and above, respectively, administered in drinking-water for 13 weeks (haematological parameters were not examined). Histopathological changes in the adrenal gland and splenic haematopoiesis were observed at doses as low as 492 mg/kg body weight per day (NTP, 1993).

Decreased thymus and testes weights, accompanied by histopathological changes in testes and alterations in several haematological (white blood cells, platelets and haemoglobin concentration) and clinical chemistry (total protein, albumin and globulin) parameters, were also observed in Sprague-Dawley rats exposed to 2-methoxyethanol at 950 mg/m^3 by inhalation for 13 weeks. The only effect noted at lower concentrations was a decrease in body weight in females at 320 mg/m^3 (Miller et al., 1983a; Rao et al., 1983; Hanley et al., 1984a). These investigators found New Zealand White rabbits to be more sensitive to the testicular toxicity of exposure to 2-methoxyethanol for 13 weeks, as degeneration was noted at concentrations as low as 95 mg/m^3, whereas lymphoid atrophy of the thymus occurred at 320 mg/m^3 and above. Effects on the blood (decreased counts of red and white blood cells and platelets and reduced haemoglobin concentration) were observed at 950 mg/m^3 (Miller et al., 1983a). The LOAEC identified for the inhalation route was, therefore, that for the rabbit (95 mg/m^3), with no NOAEC being identified.

Dermal exposure to 1000 mg/kg body weight per day for 13 weeks resulted in histopathological effects on the testes in guinea-pigs, along with reduced organ and body weights and changes in haematological (mild anaemia and reduced white blood cells) and clinical chemistry (blood enzymes and urinary calcium) parameters (Hobson et al., 1986).

8.5 Long-term exposure and carcinogenicity

No studies on the effects of chronic exposure to 2-methoxyethanol have been identified.

8.6 Genotoxicity and related end-points

Although 2-methoxyethanol does not induce gene mutations in in vitro investigations, there is some indication that it induces clastogenic damage, and there is consistent evidence that the initial metabolite, MALD, is genotoxic in several cell lines. Results of available in vivo studies suggest that 2-methoxyethanol is not genotoxic in somatic cells. Although there has been some suggestion of an induction of genetic effects in male germ cells, the results from these studies are inconclusive.

In in vivo studies, 2-methoxyethanol did not induce chromosomal aberrations in rats or mice following single or repeated exposure via inhalation, ingestion or intravenous injection (McGregor et al., 1983; Au et al., 1993), nor did 2-methoxyethyl acetate induce micronuclei in the bone marrow of hamsters administered a single dose via intraperitoneal injection (Basler, 1986). In the comet assay, a single gavage dose of 500 mg 2-methoxyethanol/kg body weight per day or more caused deoxyribonucleic acid (DNA) damage in bone marrow and haploid testicular cells of rats (Anderson et al., 1996). Results of dominant lethal assays in rodents have been mixed (McGregor et al., 1983; Rao et al., 1983; Anderson et al., 1987), although these need to be considered in the light of the testicular toxicity and spermatotoxicity of 2-methoxyethanol, making results difficult to interpret.

2-Methoxyethanol was not mutagenic in several strains of *Salmonella typhimurium* with or without S9 activation (McGregor et al., 1983; McGregor, 1984; Zeiger et al., 1992; Hoflack et al., 1995). Although its primary metabolite, MAA, was also not mutagenic (McGregor et al., 1983; Hoflack et al., 1995), the acetaldehyde intermediate (MALD) was active in one strain, both with and without exogenous metabolic activation (Hoflack et al., 1995). 2-Methoxyethyl acetate was not mutagenic in the yeast *Schizosaccharomyces pombe* when tested either in a host-mediated assay (Barale et al., 1979) or in culture (with and without S9 activation) (Abbondandolo et al., 1980), although it caused chromosome malsegregation and aneuploidy (Zimmermann et al., 1985; Whittaker et al., 1989). 2-Methoxyethanol did not induce point mutations in mammalian cells in vitro (McGregor, 1984; Ma et al., 1993; Chiewchanwit et al., 1995), although the acetaldehyde metabolite induced an increase in *hprt* and *gpt* mutations in Chinese hamster cells (Elias et al., 1996). MALD induced *gpt* gene mutations in Chinese hamster ovary (CHO)-AS52 cells, but not *hprt* gene mutations in the standard CHO-K1-PH.4 cells (Chiewchanwit et al., 1995). 2-Methoxyethanol, tested as a vapour, did not induce mutations in the *Drosophila* sex-linked recessive lethal assay (McGregor et al., 1983).

There is some evidence that 2-methoxyethanol and its acetate cause increases in chromosomal aberrations in cultured mammalian (including human) cells. Whereas the intermediate MALD was a potent inducer of chromosomal aberrations in various cell lines, MAA was inactive (Villalobos-Pietrini et al., 1989; Loveday et al., 1990; Chiewchanwit & Au, 1994; Elias et al., 1996). Positive results were obtained for induction of micronuclei in mammalian cells for the parent compound as well as for both metabolites, with the acetaldehyde being much more potent than either 2-methoxyethanol or MAA (Elias et al., 1996). There was no convincing evidence that 2-methoxyethanol induced sister chromatid exchanges in vitro, although both MALD and MAA were active in this assay (Villalobos-Pietrini et al., 1989; Loveday et al., 1990; Chiewchanwit & Au, 1994; Elias et al., 1996). 2-Methoxyethanol did not produce unscheduled DNA synthesis in cultured human embryo fibroblasts with or without S9 activation (McGregor et al., 1983). Both 2-methoxyethanol and MALD induced aneuploidy or other mitotic aberrations in vitro (Zimmermann et al., 1985; Whittaker et al., 1989; Elias et al., 1996).

8.7 Reproductive and developmental toxicity

8.7.1 Effects on fertility

In the large number of relevant studies identified, 2-methoxyethanol was consistently toxic to the male reproductive system in multiple species (mice, rats, guinea-pigs, rabbits and dogs) exposed by all routes of administration (subcutaneous, dermal, oral or inhalation). Effects on reproductive ability as well as reproductive organs have been observed, often at the lowest dose or concentration tested. Single or repeated oral administration of 2-methoxyethanol induced adverse effects on the testes (including weight and histopathological changes or biochemical indicators of testicular damage, such as urinary creatine) and/or various sperm parameters in every identified study in which these end-points were examined.

Testicular effects were reportedly induced at 30 mg/kg body weight per day, based on a secondary account of a multigeneration study in which rats were exposed to 2-methoxyethanol in drinking-water (Gulati et al., 1990a,b), although, generally, effects were reported at doses of about 50 mg/kg body weight per day or more (Foster et al., 1983, 1984; Chapin & Lamb, 1984; Chapin et al., 1985a,b; Creasy et al., 1985; Anderson et al., 1987; Ghanayem & Chapin, 1990; Holloway et al., 1990; Reader et al., 1991; Smialowicz et al., 1991a; Vachhrajani & Dutta, 1992; NTP, 1993; Ku et al., 1994; Butterworth et al., 1995; Aich & Manna, 1996; Timbrell et al., 1996; Watanabe et al., 2000). Alterations in sperm morphology were observed in mice or rats following acute oral administration of 500 mg/kg body weight or more (Anderson et al., 1987). Reduced male fertility was also observed in several acute and short-term studies (in one study at a dose lower than those that induced histopathological changes in the testes) (Chapin et al., 1985a; Anderson et al., 1987; Holloway et al., 1990).

In mice, effects on male fertility and reproductive organs were reported following short- and long-term administration of oral doses of 60 and 170 mg/kg body weight per day or more, respectively, although fewer studies in mice (compared with rats) were identified (Nagano et al., 1979, 1984; Anderson et al., 1987; Chapin et al., 1993; NTP, 1993). Similar effects on the testes or male reproductive ability were observed in short-term and subchronic studies in guinea-pigs, rabbits and hamsters, with the lowest LOAEL being 25 mg/kg body weight per day in rabbits (Nagano et al., 1984; Ku et al., 1994, 1995; Foote et al., 1995; Berndtson & Foote, 1997). A NOAEL was not identified.

Male reproductive toxicity (effects on organs, sperm parameters and/or fertility) was also induced in rats acutely or repeatedly exposed to 2-methoxyethanol by inhalation at 950 mg/m^3 or more (Doe et al., 1983; McGregor et al., 1983; Miller et al., 1983a; Rao et al., 1983; Hanley et al., 1984a; Samuels et al., 1984; Lee & Kinney, 1989; Lee et al., 1989). Reproductive effects were also observed in male mice exposed to 1600 mg 2-methoxyethanol/m^3 (the only concentration tested) for 5 days (McGregor et al., 1983) and in male rabbits at 95 mg/m^3 (the lowest concentration tested) or more for 13 weeks (Miller et al., 1983a). Although 95 mg/m^3 thus represents the lowest LOAEC identified, a NOAEC was again not identified.

Repeated dermal exposure (covered contact) to 2-methoxyethanol for 7 days also induced effects on the testes, sperm parameters and fertility in rats; effects were noted at all doses tested (i.e. ≥625 mg/kg body weight per day, representing the LOAEL for this route) (Feuston et al., 1989).

Although not as extensively investigated, effects on the female reproductive system have also been associated with exposure to 2-methoxyethanol. Changes in estrous cyclicity and hormone levels as well as histopathological changes in the ovaries were observed in rats administered 100 and 300 mg/kg body weight per day or more, respectively, for several days, with a NOAEL of 10 mg/kg body weight per day (Davis et al., 1997). Atrophy of female reproductive organs was also noted in rats exposed to oral doses of 297 mg/kg body weight per day or more for 13 weeks, although reduced body weight also occurred at these doses (NTP, 1993). Similarly, in mice, atrophy of the ovaries and altered estrous cycle were noted following subchronic oral administration of

2-methoxyethanol, but only at doses greater than those that induced these effects in rats (i.e. ≥1839 and ≥1194 mg/kg body weight per day, respectively; no effects were observed at lower exposure levels) (NTP, 1993). Conversely, however, Chapin et al. (1993) reported an increase in ovary weights in female mice at 636 mg/kg body weight per day in a multigeneration study.

No effects on female reproductive success or organs were observed in rats or rabbits exposed to 2-methoxyethanol by inhalation at concentrations of up to 950 mg/m^3 for 13 weeks (Miller et al., 1983a; Rao et al., 1983; Hanley et al., 1984a).

8.7.2 Developmental toxicity

2-Methoxyethanol and its principal metabolite, MAA, have consistently induced developmental toxicity in numerous oral studies in several species of laboratory animals (although data are insufficient to evaluate variations in sensitivity across species), generally at doses or concentrations lower than those that are maternally toxic, and often at the lowest exposure level tested. For example, decreased fetal body weights were noted in rats repeatedly exposed to 2-methoxyethanol doses of 16 mg/kg body weight per day (the lowest dose) or more in the diet during gestation, with malformations being observed at doses of 31 mg/kg body weight per day or greater, whereas maternal toxicity was present only at higher doses (i.e. ≥140 mg/kg body weight per day) (Nelson et al., 1989). Similar results were obtained in several other studies in rats exposed to 2-methoxyethanol in the diet or by gavage (single or repeated doses) (Ritter et al., 1985; Toraason et al., 1985, 1986a,b,c; Toraason & Breitenstein, 1988; Nelson et al., 1991; Sleet et al., 1996). In many of these studies, the cardiovascular system, kidney and skeletal system were the principal targets for 2-methoxyethanol-induced malformations; functional defects of the heart were also noted. Skeletal variations and delayed ossification were also reported in one study in mice repeatedly administered relatively low oral doses of 2-methoxyethanol (i.e. ≥31.25 mg/kg body weight per day), with more severe effects occurring at higher doses, which were also maternally toxic (Nagano et al., 1981, 1984). Although the heart appeared to be a sensitive target organ in rats, this was not observed in mice, although fewer studies in mice were identified. However, the developing immune system was a target in one study in mice, based on effects on thymic cellularity, thymocyte antigen expression and liver prolymphoid cells (Holladay et al., 1994). A NOAEL of 100 mg/kg body weight was established for pregnant CD-1 mice when 2-methoxyethanol was administered in a single dose on day 11 of gestation (Horton et al., 1985).

When groups of 6–14 cynomolgus monkeys (*Macaca fascicularis*) were given 0, 12, 24 or 36 mg 2-methoxyethanol/kg body weight per day by gavage on days 20–45 of pregnancy, dose-related maternal toxicity (weight loss, anorexia and a slight reduction in red blood cell numbers) was observed at all doses. Examination of fetuses on gestation day 100 revealed embryotoxicity (intrauterine deaths or resorptions) in all exposed animals (4/14, 4/11 and 8/8 at 12, 24 and 36 mg/kg body weight per day, respectively), which was attributed to 2-methoxyethanol exposure in all but two (one in each of the lower dose levels) cases. No live fetuses were found at the top dose. There were no intrauterine deaths or resorptions in six untreated control animals or in three ethanol-treated controls. However, there was no definitive evidence of malformations in surviving fetuses of the 2-methoxyethanol-treated monkeys, although a dead embryo from one of the high-dose females had digits missing from both forelimbs. The investigators reported that in a preliminary study involving the administration of 240 mg/kg body weight per day to a single pregnant female for 5 days, the offspring had a kinked tail. Neither of these deformities had been previously noted in unexposed cynomolgus monkey pregnancies in the laboratory (Scott et al., 1989). A dose of 12 mg/kg body weight per day thus represents the lowest reported LOAEL. A NOAEL for developmental toxicity by the oral route was not identified.

In inhalation studies in rats, developmental effects, including increased resorptions, decreased pup or fetal weights, and increased incidences of skeletal variations and malformations, were observed following repeated maternal exposure (on days 6–17, 6–15 or 7–15 of pregnancy) to 2-methoxyethanol concentrations of 160 mg/m^3 and above (Doe et al., 1983; Hanley et al., 1984a,b; Nelson et al., 1984a), whereas visceral malformations, such as heart defects, were noted at 320 mg/m^3 (Nelson et al., 1984a). No developmental effects were observed at 9 or 32 mg/m^3 (Hanley et al., 1984a,b). No overt maternal toxicity was evident in one study at 640 mg/m^3 (Nelson et al., 1984a). Doe et al. (1983) reported maternal toxicity at 320 mg/m^3, whereas Hanley et al. (1984a,b) described 160 mg/m^3 as slightly toxic to the dams. Dose-related, slight decreases in red blood cell count, blood haemoglobin concentration and packed cell volume were also observed in dams at exposure concentrations of 9 mg/m^3, the lowest exposure studied (Hanley et al., 1984a,b). Neurochemical changes and behavioural effects were observed in offspring of rats exposed to 79 mg/m^3 (Nelson et al., 1984b). In rabbits, an increased incidence of malformations and skeletal variations, as well as of resorptions and decreased fetal weight, was observed at 160 mg/m^3. At 32 mg/m^3, there was a statistically significant increase in the delay of ossification of sternebrae, whereas for the centra, there was statistically significantly less delayed ossification than in controls. For the other three ossification centrae, there were no differences. The investigators concluded that this represents the normal variation in the species and is not a sign of fetotoxicity or teratogenicity

at this dose level. In mice, unilateral hypoplasia of testis (at 160 mg/m^3) but no teratogenic effects were observed (highest exposure studied, 160 mg/m^3). The NOAEC for developmental effects in all three species was 32 mg/m^3.

Repeated dermal exposure of dams (on days 6–17, 10–14 or 6–15 of pregnancy) to doses of about 48 mg/kg body weight per day or more induced developmental toxicity (including malformations) in rats (Wickramaratne, 1986; Feuston et al., 1990; Hellwig, 1993). 2-Methoxyethanol was also teratogenic in rats and mice when administered by other routes of exposure (i.e. intravenous, subcutaneous or intraperitoneal injection) (Brown et al., 1984; Campbell et al., 1984; Clarke et al., 1990, 1992; Terry et al., 1994; Sleet et al., 1996).

Radiofrequency radiation (which also induces hyperthermia) is used in a variety of workplaces where workers are concurrently exposed to chemicals. Combined exposure to radiofrequency radiation (10 MHz) and 2-methoxyethanol produced enhanced teratogenicity in Sprague-Dawley rats (Nelson et al., 1991, 1994, 1997).

8.8 Haematological, immunological and neurological effects

Haematological effects have been observed after a single high dose of 2-methoxyethanol and after repeated administration by inhalation, ingestion or dermal application (see sections 8.1, 8.3 and 8.4). In a developmental toxicity study in rats, dose-related, slight decreases in blood haemoglobin and packed cell volume were observed in dams at an exposure concentration of 9 mg/m^3, the lowest exposure studied (Hanley et al., 1984a,b; see section 8.7.2).

Exposure to 2-methoxyethanol significantly altered immune function in rats exposed orally or dermally. Although fewer studies are available, mice appear to be much less sensitive than rats to the immunotoxicity of 2-methoxyethanol.

Immunosuppression was observed in several studies in male and/or female rats (several strains) repeatedly administered oral doses of 50 mg 2-methoxyethanol/kg body weight per day or more over periods of 2–21 days, based on alterations in lymphoproliferative response of splenic lymphocytes to various mitogens, antibody plaque-forming cell response to antigens and other immune function parameters (Exon et al., 1991; Smialowicz et al., 1991a,b, 1992a,b, 1993; Riddle et al., 1992, 1996; Williams et al., 1995). In addition, thymus weights were decreased in most studies (at doses as low as 25 mg/kg body weight per day); occasionally, reductions in spleen weights or cellularity were also observed. In mice, however, there was no consistent evidence of immunosuppression at repeated doses of up to 1000 mg 2-methoxyethanol/kg body weight per day or 1920 mg MAA/kg body weight per day, although decreased thymus weights were observed, and there was evidence of enhancement or modulation of immune system response in some studies (House et al., 1985; Kayama et al., 1991; Riddle et al., 1992, 1996; Smialowicz et al., 1992b, 1994). The results of studies in rats in which enzyme inhibitors were administered indicated that the parent compound was not in itself immunotoxic, but that both the aldehyde and acid metabolites (MALD and MAA) suppressed immune system function (Smialowicz et al., 1991a,b, 1993).

Although the database is limited to two studies in rats and a single study in mice, 2-methoxyethanol appears to induce neurological effects following acute or short-term inhalation exposure, including inhibition of conditioned avoidance response, increased barbiturate-induced sleeping time or partial hindlimb paralysis, at concentrations of 395 mg/m^3 or greater and altered enzyme activities in the brain at 160 mg/m^3 or more (Goldberg et al., 1962; Savolainen, 1980). In addition, as noted above (section 8.7.2), repeated exposure of pregnant rats to 79 mg/m^3 induced effects on avoidance conditioning and neurochemical changes in the offspring (Nelson et al., 1984b).

9. EFFECTS ON HUMANS

Several cases of adverse health effects following accidental or occupational exposure to 2-methoxyethanol have been identified in the literature. In general, effects on the nervous, respiratory and haematological systems (which appeared to be reversible after several months) have been associated with exposure in the work environment via inhalation and dermal contact. Although data on exposure levels were sparse, workplace concentrations in these case reports ranged from 25 to 12 316 mg/m^3 (Donley, 1936; Greenburg et al., 1938; Parsons & Parsons, 1938; Groetschel & Schuermann, 1959; Zavon, 1963; Ohi & Wegman, 1978; Cohen, 1984); however, these workers were also exposed to other substances in addition to 2-methoxyethanol.

Six cases of dysmorphic features and persistent cytogenetic damage (chromosomal aberrations, polyploid and endoreduplicated cells) have been reported in the offspring of women with occupational exposure, described by the investigators as extensive, to 2-methoxyethanol (El-Zein et al., 2002), although no quantitative exposure data were provided, and not all pregnancy outcomes of the exposed mothers were assessed. Bolt & Golka (1990) reported the case of abnormal development of male reproductive organs in two boys whose mother had been exposed via inhalation

and dermal contact to 2-methoxyethyl acetate during her pregnancies, but again, no quantitative detail on exposure was presented.

An accidental poisoning resulted in reversible renal toxicity in two men who ingested an estimated dose of 100 ml of pure 2-methoxyethanol (Nitter-Hauge, 1970). The first clinical symptoms occurred at 8–18 h. Marked acidosis was seen, and one patient developed oxaluria.

In the only relevant clinical study identified (which was primarily intended to investigate the toxicokinetics of 2-methoxyethanol in humans), there were no changes in pulmonary ventilation or heart rates in seven male volunteers exposed to 2-methoxyethanol at 16 mg/m^3 for 4 h (Groeseneken et al., 1989a).

Available data from cross-sectional surveys are indicative of an association between haematological abnormalities, as well as effects on the immune and nervous systems, and exposure to 2-methoxyethanol, along with other substances, via inhalation and dermal contact. Alterations in various blood parameters (including red blood cell, white blood cell [or specifically granulocyte or polymorphonuclear leukocyte] or platelet counts and haemoglobin levels) were observed in workers exposed to 2-methoxyethanol while treating collars in a shirt factory (78–236 mg/m^3; Greenburg et al., 1938), painting in a shipyard (up to 17.7 mg/m^3; Welch & Cullen, 1988) or laying parquet floors (up to 149 mg/m^3; Denkhaus et al., 1986) or in the manufacture and packaging of the compound (up to 62 mg/m^3; Cook et al., 1982). Significant differences in the distribution of lymphocyte subpopulations were also noted in the parquet floor workers compared with controls (Denkhaus et al., 1986).

In a study of male workers from two copper-clad laminate factories in Taiwan, China, mean haemoglobin, packed cell volume and red blood cell count were significantly lower in the 46 workers exposed to 2-methoxyethanol (geometric mean concentration 13 mg/m^3, range 2.1–95 mg/m^3, n = 66) as compared with 93 indirectly exposed (range non-detectable to 1.4 mg/m^3, n = 9) controls. The frequency of anaemia was significantly higher in the exposed group (26.1%) than in the control group (3.2%). No differences were found between the female workers exposed and those not exposed to 2-methoxyethanol (Shih et al., 2000).

In a follow-up study in one of the factories, Shih et al. (2003) examined the association between 2-methoxyethanol exposure and haematological effects among 29 workers (24 males and 5 females) from the coating department. Haematological parameters, 8-h full-shift exposure to 2-methoxyethanol and urinary MAA were repeatedly measured in three consecutive surveys over a 6-month period, during which exposure was substantially reduced as a result of implementation of workplace controls. At the start of the study, mean airborne exposure (SD) of 2-methoxyethanol was 113 (246) mg/m^3 (range 2.4–1010 mg/m^3), with "much higher" peak concentrations during certain daily operations. This dropped to 8.4 (4.8) mg/m^3 (range 0.6–32 mg/m^3) at 2.5 months and 1.7 (2.3) mg/m^3 (range 0.3–11 mg/m^3) at the 6-month survey. The average concentrations of MAA in the urine were 57.7, 24.6 and 13.5 mg/g creatinine, well in line with the values expected from the published relationship between time-weighted weekly airborne 2-methoxyethanol concentration and urinary MAA concentration (Shih et al., 1999b). Haemoglobin, packed cell volume and red blood cell count were significantly lower in the 24 male workers than in a comparison group of 90 personnel from the same facility when assessed at the start of the study. There was no detectable 2-methoxyethanol exposure for 58 people in the control group, whereas 32 had a low exposure (measurement for 9 indicated a mean concentration of 0.6 mg/m^3 and a maximum concentration of 2.5 mg/m^3). The frequency of anaemia was significantly higher in the exposed group (42%) than in the comparison group (3%). The haematological parameters of the exposed male workers were back within the normal range at 2.5 months and increased further at the 6-month survey. When compared with the control male workers (n = 67) with no or only minor exposure, haemoglobin levels in the exposed males from the coating department were 88% at the start of the study, but had risen to 98% at 2.5 months and 100% at 6 months; packed cell volume in the exposed workers was 87% of the value for the control group at the start of the study, but had risen to 94% at 2.5 months and 100% at 6 months; the corresponding figures for red blood cell count were 83% at the start, rising to 90% and 96% at 2.5 and 6 months, respectively.

Decreased sperm production together with increased prevalence of oligospermia and azoospermia were noted in a cross-sectional study of 73 shipyard painters exposed to 2-methoxyethanol along with 2-ethoxyethanol (Welch et al., 1988).

Forty men employed in the manufacture or packaging of 2-methoxyethanol claimed to have greater difficulty in fathering a child compared with 25 unexposed workers, although there were no significant differences in sperm count or hormone levels in small subgroups of these employees (Cook et al., 1982). With respect to the potential for reproductive effects in women exposed to 2-methoxyethanol, the results of a historical cohort study in 891 women indicated that there was an increase in spontaneous abortions in those engaged in the fabrication departments at 14 semiconductor plants compared with non-fabrication workers (relative risk [RR] = 1.45, 95% confidence interval [CI] = 1.02–2.06). The effect was particularly seen in women exposed to glycol ethers (RR = 1.56, 95% CI = 1.02–2.31; RR = 3.38, 95% CI =

1.61–5.73 for those with the highest qualitative exposure scores). It is not possible to discern the role of 2-methoxyethanol specifically, in view of the lack of data on exposure. In the prospective portion of this study, involving 481 women, there was again a significant association between occurrence of spontaneous abortions and exposure to glycol ethers (RR = 2.0, 95% CI = 1.46–2.75) and a non-significant reduction in fecundability (ability to become pregnant) ($P = 0.08$) (Beaumont et al., 1995; Schenker et al., 1995; Swan et al., 1995; Schenker, 1996; Swan & Forest, 1996).

Veulemans et al. (1993) reported a case–control study conducted among first-time patients at a Belgian clinic for reproductive disorders. The study groups consisted of 1019 cases (defined as patients diagnosed as infertile or subfertile on the basis of a spermiogram) and 475 controls (who were diagnosed as normally fertile by the same procedure). Possible exposure to ethylene glycol ethers was assessed by the presence of the urinary metabolite MAA, which was found in only 1 case and 2 controls, compared with 2-ethoxyacetic acid, which was detected in 39 cases and 6 controls.

Among impregnation workers in the coating department of a copper-clad laminate manufacturing plant, no difference was observed in the sperm count between the 14 exposed workers and 13 referents (Shih et al., 2000). The only volatile solvents used were 2-methoxyethanol and acetone (70/30), and the geometric mean airborne methoxyethanol concentration was 13 mg/m^3 (range 2.1–95 mg/m^3, $n = 66$).

There is some epidemiological evidence from studies of female workers that exposure to glycol ethers is associated with the development of congenital malformations in their offspring (Ha et al., 1996; Cordier et al., 1997; Saavedra et al., 1997), but data implicating specific glycol ethers are limited.

10. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

10.1 Aquatic environment

Data on chronic toxicity have been identified only for protozoans and algae. The most sensitive organism reported was the flagellate protozoan *Chilomonas paramecium*, with a 2-day toxicity threshold of 2.2 mg/l, based on inhibition of cell multiplication (Bringmann & Kühn, 1981). Data on acute toxicity have been reported for microorganisms, invertebrates and fish, although in many studies the LC_{50} for 2-methoxyethanol was above the highest concentration tested. For example, the 24-h LC_{50}s for *Daphnia magna* and goldfish (*Carassius auratus*) were >10 and >5 g/l, respectively (Bringmann & Kühn, 1977; Bridie et al., 1979). The 96-h LC_{50} for rainbow trout (*Oncorhynchus mykiss*) was 15.5 g/l (Benville, 1974).

10.2 Terrestrial environment

2-Methoxyethanol at a concentration of 16.7 (± 2.8) mmol/l caused a 50% inhibition of seed germination at 30 ºC in the lettuce *Lactuca sativa* cv. Great Lakes (Reynolds, 1977). No other information on the effects of 2-methoxyethanol on terrestrial organisms was identified.

11. EFFECTS EVALUATION

11.1 Evaluation of health effects

11.1.1 Hazard identification and dose–response assessment

2-Methoxyethanol is readily absorbed following oral, inhalation or dermal exposure and is distributed extensively throughout the body. Skin absorption can be an important route of exposure, particularly in the occupational setting. Inhalation exposure alone will not give sufficient indication of biological exposure, and thus the level of the MAA metabolite in the urine can be used as a specific and suitable indicator of overall exposure. Acute toxicity is low to moderate by the oral, inhalation and dermal routes. 2-Methoxyethanol has low potential for causing skin or eye irritation and has not been shown to be a skin sensitizer in the guinea-pig maximization test. Repeated exposure to 2-methoxyethanol has been associated with a range of adverse health effects in laboratory animals, including haematological, immunological and neurological effects, as well as reproductive and developmental toxicity, including teratogenicity. In many studies, effects were observed at the lowest dose or concentration tested. For example, the lowest reported LOAELs (oral exposure) for developmental toxicity were 12 and 16 mg/kg body weight per day in monkeys and rats (lower doses were not investigated), respectively, with increased malformations occurring in rats at 31 mg/kg body weight per day (in the absence of maternal toxicity) (Nelson et al., 1989; Scott et al., 1989). In inhalation studies in rats and rabbits, fetotoxicity and a high incidence of external, visceral and skeletal malformations were seen at 160 mg/m^3 (Doe et al., 1983; Hanley et al., 1984a,b; Nelson et al., 1984a). A NOAEC for developmental toxicity was established as 32 mg/m^3. In one developmental toxicity study in rats, a concentration-dependent decrease in circulating erythrocyte numbers, haemoglobin and packed cell volume was observed at all exposure levels studied (i.e. 9 mg/m^3 and

above). No carcinogenicity studies are available on 2-methoxyethanol. There is some indication that 2-methoxyethanol may be weakly genotoxic in somatic cells, likely through activation to the intermediate acetaldehyde metabolite, and that it causes genetic damage to male germ cells in rats at high doses or concentrations (i.e. >500 mg/kg body weight per day) (Anderson et al., 1987, 1996), which is in concordance with the observed effects on male reproduction.

Data from case reports or epidemiological studies are indicative of effects on the haematological system and sperm characteristics in men employed in occupations with exposure to 2-methoxyethanol and other substances. Shih et al. (2003) reported statistically significant changes in blood parameters in workers exposed to mean airborne 2-methoxyethanol levels of 113 mg/m^3 (SD 246, range 2.4–1010 mg/m^3), which had returned to normal over a period of several months, during which the exposure was reduced to 8.4 mg/m^3 (SD 4.8, range 0.6–32 mg/m^3) and subsequently to 1.7 mg/m^3 (SD 2.3, range 0.3–11 mg/m^3). No effect on sperm counts or morphology was observed in a small group of workers exposed to an average 2-methoxyethanol concentration of 13 mg/m^3, at which level of exposure anaemia was clearly demonstrated (Shih et al., 2000). Maternal exposure to glycol ether mixtures containing 2-methoxyethanol is weakly related to increased spontaneous abortions and, perhaps, ability to conceive. Such potential associations would be consistent with the observations in laboratory animals.

In available studies, therefore, 2-methoxyethanol has induced a wide range of adverse effects, including those considered to be severe and irreversible (e.g. teratogenicity), with some occurring at relatively low doses. The adverse effect documented at the lowest exposure level is the effect on erythropoiesis.

11.1.2 Criteria for setting tolerable intakes/ concentrations

The studies in Taiwan, China (Shih et al., 2000, 2003), demonstrate effects on red blood cell counts in a population not exposed to other alkoxy alcohols or chemicals known to affect the bone marrow, at levels of exposure at which effects on spermatogenesis were not observed. The studies contain reliable exposure data on both airborne levels and workplace urinary MAA (as a measure of actual uptake), which can be used as a basis for characterizing the risk from exposure to airborne 2-methoxyethanol.

A clear-cut haematotoxic effect was observed at a time-weighted exposure to an average 2-methoxyethanol concentration of 113 mg/m^3, with recovery to within the normal range at an exposure level of 8.4 mg/m^3, and further increases when exposure fell to 1.7 mg/m^3 (Shih et al., 2003).

Considering the significant increasing trend for haemoglobin, packed cell volume and red blood cell count over the 6-month monitoring period, the 1.7 mg/m^3 exposure is taken as the starting point for the derivation of the tolerable concentration. It should be recognized, however, that values were within the normal range once the exposure had fallen to 8.4 mg/m^3, and the increased values recorded at the 6-month survey may be temporal rather than exposure related. Adjusting the 1.7 mg/m^3 value for continuous exposure and applying an uncertainty factor of 10 for interindividual variation (IPCS, 1994), a tolerable concentration of 0.04 mg/m^3 can be derived. As the effect is readily reversible and has been observed after a long-term exposure, no additional uncertainty factor is used to compensate for less than lifetime exposure.

The most informative study on developmental toxicity in experimental animals by inhalation (Hanley et al., 1984a,b) gives 32 mg/m^3 as the NOAEC (although slight effects on the blood were seen at lower levels). Using the IPCS default uncertainty factors (IPCS, 1994) for interspecies (10) and intraspecies (10) extrapolation and correction to continuous exposure (6/24 h) would give a tolerable concentration of 0.08 mg/m^3. As the exposure in the study covered the relevant period in life with respect to the end-point, developmental toxicity, no adjustment for shorter than lifetime exposure need be applied. Using PBPK modelling rather than default values for uncertainty factors would lead to a still considerably higher tolerable concentration (Sweeney et al., 2001).

11.1.3 Sample risk characterization

The worst-case exposure level in air in Canada (5 µg/m^3) is 13% of the tolerable concentration derived from the studies in Taiwan, China. An even greater margin (6%) exists between this upper exposure level in Canadian air and the tolerable concentration derived from the developmental toxicity in rats, mice or rabbits (Hanley et al., 1984a,b). With respect to ingestion, no epidemiological investigations of the effects of ingested 2-methoxyethanol in humans were identified. However, the margin between the intake (14 µg/kg body weight) equivalent to inhalation of 2-methoxyethanol at a concentration of 40 µg/m^3 (assuming a daily inhalation volume of 22 m^3, a body weight of 64 kg [IPCS, 1994] and 100% absorption) and the worst-case exposure scenario for ingestion of 2-methoxyethanol in drinking-water (0.013 µg/kg body weight per day), assuming a 2-methoxyethanol concentration of 0.6 µg/l in drinking-water, daily water consumption of 1.4 litres and a body weight of 64 kg (IPCS, 1994), is about 3 orders of magnitude.

However, estimates of exposure to 2-methoxyethanol through use of some consumer products (based on the very limited information available) approach the level (113 mg/m^3) at which clear-cut haematological effects were seen in workers. For example, use of an all-purpose spray cleaner could result in exposure to concentrations in indoor air of up to 76 mg/m^3 (see Table 2 above). Estimated intake through use of a nail polish remover containing up to 100% 2-methoxyethanol could range up to 12.5 mg/kg body weight per day, exceeding by an order of magnitude the level at which adverse blood changes were no longer present in the exposed workers. It should be emphasized, however, that these estimates are extreme worst case and have not been validated. As information on current compositions and use patterns of products is extremely limited, these values likely considerably overestimate current exposures, particularly in view of the decline in use of this compound in many countries.

11.1.4 Uncertainties in the evaluation of health risks

The derivation of the tolerable concentration is based on haematological effects that were seen in exposed workers. In these workers, no effects on sperm count or morphology were observed, although the studied population was small; also, as it was limited to morphological spermatological end-points, it is uncertain whether functional disturbances, such as decreased fertility, might have been present. No quantitative estimation of developmental effects in humans can be made, as published studies all involve mixed exposures, and assessment of exposure is very weak. It is reassuring, however, that in laboratory animal studies, effects on haematological end-points were observed at exposure levels that did not induce effects on development.

No epidemiological or long-term experimental studies are available on the carcinogenicity of 2-methoxyethanol. 2-Methoxyethanol has been studied for genotoxicity in an extensive array of studies; although it does not induce gene mutations in vitro or chromosome damage in vivo, its initial metabolite, MALD, is a potent inducer of chromosomal aberrations in several cell lines in vitro and has also induced point mutations in some cell lines.

Although there is thus a moderate to high degree of confidence in the available data to serve as a basis for hazard characterization for the non-neoplastic effects associated with exposure to 2-methoxyethanol, in the absence of any long-term investigations in animals and in view of the limited evidence of weak genotoxicity (and stronger evidence of the genotoxicity of the initial metabolite), there is some uncertainty with regard to the potential of 2-methoxyethanol to induce neoplastic effects.

Owing to the paucity of data on levels of 2-methoxyethanol in environmental media in Canada, there is a high degree of uncertainty in the estimates of exposure to this substance. Although a worst-case exposure scenario was determined on the basis of the detection limits in a small number of samples in a multimedia study, it is not known if these values grossly overestimate environmental levels or if the general population is exposed to levels approaching these values, although predicted concentrations in ambient air and drinking-water (using fugacity modelling) were several orders of magnitude less than these detection limits. Although environmental levels are expected to decline in the wake of reduced use of 2-methoxyethanol by many countries, there is some uncertainty as to whether or not such a decline has occurred in environmental media in Canada, because of a lack of adequate monitoring data. In addition, the only media in which 2-methoxyethanol was measured in the multimedia study were drinking-water and air, although there is a moderate degree of certainty that food and soil do not represent important sources of exposure, based on the physical and chemical properties of this substance, the sources of release to the environment and the results of fugacity modelling.

There is an extremely low degree of confidence in the estimates of exposure to 2-methoxyethanol through the use of various consumer products, as a result of the large uncertainties concerning the presence and levels of the substance in products currently used. For example, it should be noted that 2-methoxyethanol was not detected in emissions from consumer products similar to those described in this CICAD when they were investigated more recently by Health Canada (Zhu et al., 2001). Therefore, it is likely that the values presented considerably overestimate potential current exposures and are not relevant in countries where the material is no longer used in consumer products. The estimates were also calculated assuming 100% absorption through the skin, in view of the lack of adequate data to support a lower per cent absorption. There is a high degree of confidence, however, that absorption through the skin can be significant.

11.2 Evaluation of environmental effects

In Canada, most environmental releases of 2-methoxyethanol are to the atmosphere. Based on its predicted environmental partitioning, assessment end-points for 2-methoxyethanol relate to terrestrial organisms, including terrestrial wildlife and soil organisms, and aquatic organisms.

For a conservative risk characterization for terrestrial wildlife, the estimated exposure value (EEV) is

0.146 ng/m^3, the estimated concentration of 2-methoxyethanol in air using ChemCAN modelling based on reported releases in 1994. This value is believed to be conservative, because releases of 2-methoxyethanol in Canada appear to have significantly decreased since 1994.

The critical toxicity value (CTV) is 3.2×10^7 ng/m^3, the NOAEC in inhalation studies in mice, rats and rabbits (Hanley et al., 1984a,b), based on fetal toxicity. Dividing this CTV by a factor of 10 (to account for the extrapolation from laboratory to field conditions and interspecies and intraspecies variations in sensitivity) gives an estimated no-effects value (ENEV) of 3.2×10^6 ng/m^3.

The conservative quotient (EEV/ENEV) is calculated as follows:

$$\frac{\text{EEV}}{\text{ENEV}} = \frac{0.146 \text{ ng/m}^3}{3.2 \times 10^6 \text{ ng/m}^3}$$

$$= 4.6 \times 10^{-8}$$

Therefore, concentrations of 2-methoxyethanol in air in Canada are unlikely to cause adverse effects on populations of wildlife. Concentrations of 2-methoxyethanol in Canadian indoor and outdoor air samples were all below the detection limit of 5 µg/m^3 (5×10^3 ng/m^3) (Conor Pacific Environmental Technologies Inc., 1998), a value that is well below the ENEV. Maximum reported concentrations of 2-methoxyethanol in indoor air samples from Italy (70 µg/m^3; De Bortoli et al., 1986) and Germany (220 µg/m^3; Schriever & Marutzky, 1990) were also below the ENEV.

For a conservative risk characterization for soil organisms, the EEV is 9.4×10^{-4} ng/g dry weight, the estimated concentration of 2-methoxyethanol in soil using ChemCAN modelling based on reported releases in 1994. This value is believed to be conservative, because releases of 2-methoxyethanol in Canada appear to have significantly decreased since 1994.

No information was identified regarding the toxicity of 2-methoxyethanol to soil organisms. Van Leeuwen et al. (1992) used quantitative structure–activity relationships to estimate that a sediment concentration of 1800 ng 2-methoxyethanol/g would be hazardous to 5% of benthic species (HC_5). Using this sediment HC_5 value as a CTV and an application factor of 100 (to account for the extrapolation from benthic to soil organisms) gives an ENEV of 18 ng/g for soil organisms.

The conservative quotient (EEV/ENEV) is calculated as follows:

$$\frac{\text{EEV}}{\text{ENEV}} = \frac{9.4 \times 10^{-4} \text{ ng/g}}{18 \text{ ng/g}}$$

$$= 5.2 \times 10^{-5}$$

Therefore, concentrations of 2-methoxyethanol in soil in Canada appear to be unlikely to cause adverse effects on populations of soil organisms.

For a conservative risk characterization for aquatic organisms, the EEV is 4.8×10^{-5} µg/l, the estimated concentration of 2-methoxyethanol in water using ChemCAN modelling based on reported releases in 1994. This value is believed to be conservative, because releases of 2-methoxyethanol in Canada appear to have decreased significantly since 1994.

The CTV for aquatic organisms is 2200 µg/l, the 2-day toxicity threshold for the flagellate protozoan *Chilomonas paramecium*, based on inhibition of cell multiplication. Dividing this CTV by a factor of 10 (to account for the extrapolation from laboratory to field conditions and interspecies and intraspecies variations in sensitivity) gives an ENEV of 220 µg/l.

The conservative quotient (EEV/ENEV) is calculated as follows:

$$\frac{\text{EEV}}{\text{ENEV}} = \frac{4.8 \times 10^{-5} \text{ µg/l}}{220 \text{ µg/l}}$$

$$= 2.2 \times 10^{-7}$$

Therefore, concentrations of 2-methoxyethanol in water in Canada appear to be unlikely to cause adverse effects on populations of aquatic organisms.

There are several sources of uncertainty in this environmental risk assessment. Very few data were identified on environmental concentrations of 2-methoxyethanol in Canada or elsewhere. The ChemCAN version 4.0 model was therefore used to estimate concentrations of 2-methoxyethanol in the various environmental compartments, based on the highest reported recent release of the substance in Canada, which occurred in 1994. These values are believed to be conservative, because releases of 2-methoxyethanol in Canada appear to have decreased significantly since then and because conservative estimates of persistence were used as inputs to the model. Kane (1993) compared measured environmental concentrations of five industrial chemicals and six pesticides with environmental concentrations estimated for the substances by the ChemCAN model. Sixty per cent of the measured environmental concentrations were within 1 order of magnitude of predicted values, and 75% were within 2 orders of magnitude. The few data that are available on the concentration of 2-methoxyethanol in the Canadian environment, including

indoor air and tap water, support the conclusion that levels are very low.

No information was identified regarding the toxicity of 2-methoxyethanol to soil organisms or to terrestrial wildlife through atmospheric exposure. An estimation of a hazardous concentration to benthic species was the basis for the assessment of risk to soil organisms. The results of an inhalation toxicity study using laboratory strains of rabbits and rodents were used for the assessment of risk to wildlife. To account for these uncertainties, application factors were used in the environmental risk assessment to derive ENEVs.

Usage and environmental releases of 2-methoxyethanol in Canada appear to be declining. Conservative risk quotients are very small for all environmental assessment end-points. Therefore, despite the data gaps regarding the environmental concentrations and effects of 2-methoxyethanol on soil organisms and terrestrial wildlife, the data available at this time are considered adequate for drawing a conclusion about the environmental risk of the substance in Canada.

12. PREVIOUS EVALUATIONS BY INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS (IOMC) BODIES

A World Health Organization (WHO) Environmental Health Criteria monograph (EHC) on 2-methoxyethanol, 2-ethoxyethanol and their acetates was published in 1990 (IPCS, 1990). No other evaluations published by IOMC organizations were identified.

REFERENCES

Aasmoe L, Aarbakke J (1997) Gender difference in the elimination of 2-methoxyethanol, methoxyacetic acid and ethoxyacetic acid in rat. *Xenobiotica,* 27(12):1237–1244.

Abbondandolo A, Bonatti S, Corsi C, Corti G, Fiorio R, Leporini C, Mazzaccaro A, Nieri R, Barale R, Loprieno N (1980) The use of organic solvents in mutagenicity testing. *Mutation Research*, 79(2):141–150.

Aich S, Manna CK (1996) Action of ethylene glycol monomethyl ether on male reproductive organs of Indian wild rat. *Endocrine Regulations*, 30(3):153–162.

Anderson D, Brinkworth MH, Jenkinson PC, Clode SA, Creasy DM, Gangolli SD (1987) Effect of ethylene glycol monomethyl ether on spermatogenesis, dominant lethality, and F_1 abnormalities in the rat and the mouse after treatment of F_0 males. *Teratogenesis, Carcinogenesis, and Mutagenesis*, 7(2):141–158.

Anderson D, Dhawan A, Yu TW, Plewa MJ (1996) An investigation of bone marrow and testicular cells in vivo using the comet assay. *Mutation Research*, 370(3–4):159–174.

Au WW, Morris DL, Legator MS (1993) Evaluation of the clastogenic effects of 2-methoxyethanol in mice. *Mutation Research*, 300(3–4):273–279.

Barale R, Presciuttini S, Rossi AM (1979) [*Schizosaccharomyces pombe*: forward mutation.] *Environmental Mutagenesis Method Analysis*, 1:105–121 (in Italian).

Basler A (1986) Aneuploidy-inducing chemicals in yeast evaluated by the micronucleus test. *Mutation Research*, 174(1):11–13.

Beaumont JJ, Swan SH, Hammond SK, Samuels SJ, Green RS, Hallock MF, Dominguez C, Boyd P, Schenker MB (1995) Historical cohort investigation of spontaneous abortion in the Semiconductor Health Study: epidemiologic methods and analyses of risk in fabrication overall and in fabrication work groups. *American Journal of Industrial Medicine*, 28(6):735–750.

Benville P (1974) *Acute toxicity of nine solvents to rainbow trout fingerlings*. Unpublished; transmitted from Tiburon Laboratory, National Oceanic and Atmospheric Administration (NOAA), 10 July 1974 [cited in Dawson et al., 1978].

Berndtson WE, Foote RH (1997) Disruption of spermatogenesis in rabbits consuming ethylene glycol monomethyl ether. *Reproductive Toxicology*, 11(1):29–36.

Bolt HM, Golka K (1990) Maternal exposure to ethylene glycol monomethyl ether acetate and hypospadia in offspring: a case report. *British Journal of Industrial Medicine*, 47(5):352–353.

Bridie AL, Wolff CJM, Winter M (1979) The acute toxicity of some petrochemicals to goldfish. *Water Research*, 13:623–626.

Bringmann G, Kühn R (1977) Results of the damaging effects of water pollutants on *Daphnia magna*. *Zeitschrift für Wasser- und Abwasser-Forschung*, 10:161–166.

Bringmann G, Kühn R (1981) Comparison of the effect of harmful substances on flagellates and ciliates as well as on bacteriovirous saprozoic protozoans. *Gas- und Wasserfach, Wasser - Abwasser,* 122:308–313.

Brown NA, Holt D, Webb M (1984) The teratogenicity of methoxyacetic acid in the rat. *Toxicology Letters*, 22(1):93–100.

Budavari S, ed. (1996) *The Merck index*, 12th ed. Whitehouse Station, NJ, Merck & Co., Inc.

Butterworth M, Creasy D, Timbrell JA (1995) The detection of subchronic testicular damage using urinary creatine: studies with 2-methoxyethanol. *Archives of Toxicology*, 69(3):209–211.

Campbell J, Holt D, Webb M (1984) Dimethylphthalate metabolism: teratogenicity of the diester and its metabolites in the pregnant rat. *Journal of Applied Toxicology*, 4(1):35–41.

Canadian Chemical Producers' Association (1997) *Reducing emissions 4. A Responsible Care initiative. 1995 emissions inventory and five year projections.* Ottawa, Ontario.

Canadian Chemical Producers' Association (1999a) *Reducing emissions 6. A Responsible Care initiative. 1997 emissions inventory and five year projections.* Ottawa, Ontario.

Canadian Chemical Producers' Association (1999b) *Reducing emissions 7. A Responsible Care initiative. 1998 emissions inventory and five year projections.* Ottawa, Ontario.

Carpenter CP, Smyth HF Jr (1946) Chemical burns of the rabbit cornea. *American Journal of Ophthalmology*, 29:1363–1372.

Carpenter CP, Pozzani UC, Weil CS, Nair JH 3rd, Keck GA, Smyth HF Jr (1956) The toxicity of butyl cellosolve solvent. *AMA Archives of Industrial Health*, 14(2):114–131.

Chapin RE, Lamb JC 4th (1984) Effects of ethylene glycol monomethyl ether on various parameters of testicular function in the F344 rat. *Environmental Health Perspectives*, 57:219–224.

Chapin RE, Dutton SL, Ross MD, Lamb JC 4th (1985a) Effects of ethylene glycol monomethyl ether (EGME) on mating performance and epididymal sperm parameters in F344 rats. *Fundamental and Applied Toxicology*, 5(1):182–189.

Chapin RE, Dutton SL, Ross MD, Swaisgood RR, Lamb JC (1985b) The recovery of the testis over 8 weeks after short-term dosing with ethylene glycol monomethyl ether: histology, cell-specific enzymes, and rete testis fluid protein. *Fundamental and Applied Toxicology*, 5(3):515–525.

Chapin RE, Morrissey RE, Gulati DK, Hope E, Barnes LH, Russell SA, Kennedy SR (1993) Are mouse strains differentially susceptible to the reproductive toxicity of ethylene glycol monomethyl ether? A study of three strains. *Fundamental and Applied Toxicology*, 21(1):8–14.

Chiewchanwit T, Au WW (1994) Cytogenetic effects of 2-methoxyethanol and its metabolite, methoxyacetaldehyde, in mammalian cells in vitro. *Mutation Research*, 320(1–2):125–132.

Chiewchanwit T, Ma H, El-Zein R, Hallberg L, Au WW (1995) Induction of deletion mutations by methoxyacetaldehyde in Chinese hamster ovary (CHO)-AS52 cells. *Mutation Research*, 335(2):121–128.

Clarke DO, Duignan JM, Welsch F (1990) Embryo dosimetry and incidence of malformations in CD-1 mice following subcutaneous infusion of 2-methoxyethanol (2-ME). *Teratology*, 41(5):544.

Clarke DO, Duignan JM, Welsch F (1992) 2-Methoxyacetic acid dosimetry–teratogenicity relationships in CD-1 mice exposed to 2-methoxyethanol. *Toxicology and Applied Pharmacology*, 114(1):77–87.

Cohen R (1984) Reversible subacute ethylene glycol monomethyl ether toxicity associated with microfilm production: a case report. *American Journal of Industrial Medicine*, 6(6):441–446.

Conor Pacific Environmental Technologies Inc. (1998) *A report on multimedia exposures to selected PSL2 substances.* Prepared on contract for Health Canada, Ottawa, Ontario (Project No. 741-6705).

Cook RR, Bodner KM, Kolesar RC, Uhlmann CS, VanPeenen PF, Dickson GS, Flanagan K (1982) A cross-sectional study of ethylene glycol monomethyl ether process employees. *Archives of Environmental Health*, 37(6):346–351.

Cordier S, Bergeret A, Goujard J, Ha MC, Aymé S, Bianchi F, Calzolari E, De Walle HE, Knill-Jones R, Candela S, Dale I, Dananché B, de Vigan C, Fevotte J, Kiel G, Mandereau L (1997) Congenital malformation and maternal occupational exposure to glycol ethers. Occupational Exposure and Congenital Malformations Working Group. *Epidemiology*, 8(4):355–363.

Creasy DM, Flynn JC, Gray TJ, Butler WH (1985) A quantitative study of stage-specific spermatocyte damage following administration of ethylene glycol monomethyl ether in the rat. *Experimental and Molecular Pathology*, 43(3):321–336.

Davis BJ, Almekinder JL, Flagler N, Travlos G, Wilson R, Maronpot RR (1997) Ovarian luteal cell toxicity of ethylene glycol monomethyl ether and methoxy acetic acid in vivo and in vitro. *Toxicology and Applied Pharmacology*, 142(2):328–337.

Dawson EB, Frey MJ, Moore TD, McGanity WJ (1978) Relationship of metal metabolism to vascular disease mortality rates in Texas. *American Journal of Clinical Nutrition*, 31(7):1188–1197.

De Bortoli M, Knoppel H, Pecchio E, Peil A, Rogora L, Schauenburg H, Schlitt H, Vissers H (1986) Concentrations of selected organic pollutants in indoor and outdoor air in northern Italy. *Environment International*, 12:343–350.

Denkhaus W, Von Steldern D, Botzenhardt U, Konietzko H (1986) Lymphocyte subpopulations in solvent-exposed workers. *International Archives of Occupational and Environmental Health*, 57(2):109–115.

Devillers J, Chessel D (1995) Can the enucleated rabbit eye test be a suitable alternative for the in vivo eye test? A chemometrical response. *Toxicology Modeling*, 1:21–34.

DMER, AEL (1996) *Pathways analysis using fugacity modelling of 2-methoxyethanol for the second Priority Substances List*. Report prepared for Chemicals Evaluation Division, Commercial Chemicals Evaluation Branch, Environment Canada, by Don Mackay Environmental Research, Peterborough, Ontario, and Angus Environmental Limited, Don Mills, Ontario, March.

Doe JE, Samuels DM, Tinston DJ, de Silva Wickramaratne GA (1983) Comparative aspects of the reproductive toxicology by inhalation in rats of ethylene glycol monomethyl ether and propylene glycol monomethyl ether. *Toxicology and Applied Pharmacology*, 69(1):43–47.

Donley DE (1936) Toxic encephalopathy and volatile solvents in industry. Report of two cases. *Journal of Industrial Hygiene and Toxicology*, 18:571–577.

ECETOC (1995) *The toxicology of glycol ethers and its relevance to man.* Brussels, European Centre for Ecotoxicology and Toxicology of Chemicals, 350 pp. (ECETOC Technical Report No. 64).

Elias Z, Daniere MC, Marande AM, Poirot O, Terzetti F, Schneider O (1996) Genotoxic and/or epigenetic effects of some glycol ethers: results of different short-term tests. *Occupational Hygiene*, 2:187–212.

El-Zein RA, Abdel-Rahman SZ, Morris DL, Legator MS (2002) Exposure to ethylene glycol monomethyl ether: clinical and cytogenetic findings. *Archives of Environmental Health*, 57(4):371–376.

Environment Canada (1997a) *Results of the CEPA section 16 notice respecting the second Priority Substances List and di(2-ethylhexyl) phthalate*. Hull, Quebec, Environment Canada, Commercial Chemicals Evaluation Branch, Use Patterns Section.

Environment Canada (1997b) Notice respecting the second Priority Substances List and di(2-ethylhexyl) phthalate. *Canada Gazette*, Part I, 15 February 1997, pp. 366–368.

Environment Canada (1999) *Canadian Environmental Protection Act—Priority Substances List supporting document for the environmental assessment of 2-methoxyethanol, 2-ethoxyethanol, 2-butoxyethanol.* Hull, Quebec, Environment Canada, Commercial Chemicals Evaluation Branch.

Environment Canada (2003) *Proposed risk management strategy for 2-methoxyethanol*. Hull, Quebec, Environment Canada (http:///www.ec.gc.ca/nopp/DOC/consult/2-methoxyethanol/en/rms2.cfm; accessed 17 March 2004).

Environment Canada, Health Canada (2002) *Canadian Environmental Protection Act Priority Substances List assessment report on 2-methoxyethanol*. Ottawa, Ontario, Government of Canada.

Exon JH, Mather GG, Bussiere JL, Olson DP, Talcott PA (1991) Effects of subchronic exposure of rats to 2-methoxyethanol or 2-butoxyethanol: thymic atrophy and immunotoxicity. *Fundamental and Applied Toxicology*, 16(4):830–840.

Fairhurst S, Knight R, Marrs TC, Scawin JW, Spurlock MS, Swanston DW (1989) Percutaneous toxicity of ethylene glycol monomethyl ether and of dipropylene glycol monomethyl ether in the rat. *Toxicology*, 57(2):209–215.

Feuston MH, Bodnar KR, Kerstetter SL, Grink CP, Belcak MJ, Singer EJ (1989) Reproductive toxicity of 2-methoxyethanol applied dermally to occluded and nonoccluded sites in male rats. *Toxicology and Applied Pharmacology*, 100(1):145–161.

Feuston MH, Kerstetter SL, Wilson PD (1990) Teratogenicity of 2-methoxyethanol applied as a single dermal dose to rats. *Fundamental and Applied Toxicology*, 15(3):448–456.

Flick EW (1986) *Household and automotive cleaners and polishes*, 3rd ed. Park Ridge, NJ, Noyes Publications.

Flick EW (1989) *Advanced cleaning product formulations: household, industrial, automotive. Vol. 1.* Park Ridge, NJ, Noyes Publications.

Foote RH, Farrell PB, Schlafer DH, McArdle MM, Trouern-Trend V, Simkin ME, Brockett CC, Giles JR, Li J (1995) Ethylene glycol monomethyl ether effects on health and reproduction in male rabbits. *Reproductive Toxicology*, 9(6):527–539.

Foster PM, Creasy DM, Foster JR, Thomas LV, Cook MW, Gangolli SD (1983) Testicular toxicity of ethylene glycol monomethyl and monoethyl ethers in the rat. *Toxicology and Applied Pharmacology*, 69(3):385–399.

Foster PM, Creasy DM, Foster JR, Gray TJ (1984) Testicular toxicity produced by ethylene glycol monomethyl and monoethyl ethers in the rat. *Environmental Health Perspectives*, 57:207–217.

Gargas ML, Tyler TR, Sweeney LM, Corley RA, Weitz KK, Mast TJ, Paustenbach DJ, Hays SM (2000) A toxicokinetic study of inhaled ethylene glycol monomethyl ether (2-ME) and validation of a physiologically based pharmacokinetic model for the pregnant rat and human. *Toxicology and Applied Pharmacology*, 165(1):53–62.

Ghanayem BI, Chapin RE (1990) Calcium channel blockers protect against ethylene glycol monomethyl ether (2-methoxyethanol)-induced testicular toxicity. *Experimental Molecular Pathology*, 52(3):279–290.

Goldberg ME, Haun C, Smyth HF Jr (1962) Toxicologic implication of altered behavior induced by an industrial vapor. *Toxicology and Applied Pharmacology*, 4:148–164.

Grant D, Sulsh S, Jones HB, Gangolli SD, Butler WH (1985) Acute toxicity and recovery in the hemopoietic system of rats after treatment with ethylene glycol monomethyl and monobutyl ethers. *Toxicology and Applied Pharmacology*, 77(2):187–200.

Greenburg L, Mayers MR, Goldwater LJ, Burke WJ, Moskowitz S (1938) Health hazards in the manufacture of “fused collars”. I. Exposure to ethylene glycol monomethyl ether. *Journal of Industrial Hygiene and Toxicology*, 20:134–147.

Groeseneken D, Van Vlem E, Veulemans H, Masschelein R (1986) Gas chromatographic determination of methoxyacetic and ethoxyacetic acid in urine. *British Journal of Industrial Medicine*, 43(1):62–65.

Groeseneken D, Veulemans H, Masschelein R, Van Vlem E (1989a) Experimental human exposure to ethylene glycol monomethyl ether. *International Archives of Occupational and Environmental Health*, 61(4):243–247.

Groeseneken D, Veulemans H, Masschelein R, Van Vlem E (1989b) An improved method for the determination in urine of alkoxyacetic acids. *International Archives of Occupational and Environmental Health*, 61(4):249–254.

Groetschel H, Schuermann D (1959) Mass toxic effects in printing workers where ethylene glycol monomethylether was used as a solvent. *Archives of Toxicology*, 17:243–251.

Gulati DK, Hope E, Barnes LH, Hommell L, Russell S, Poonacha KB (1990a) *Reproductive toxicity of ethylene glycol monomethyl ether (CAS No. 109-86-4) in Sprague-Dawley rats, litter two.* Lexington, KY, Environmental Health Research and Testing Inc., pp. 1–76 (NTIS PB90252313) [cited in ECETOC, 1995].

Gulati DK, Hope E, Christman KL, Barnes LH, Russell S (1990b) *Reproductive toxicity of ethylene glycol monomethyl ether (CAS No. 109-86-4) in Sprague-Dawley rats, litter five*. Lexington, KY, Environmental Health Research and Testing Inc., pp. 1–72 (NTIS PB90252321) [cited in ECETOC, 1995].

Ha MC, Cordier S, Dananche B, Bergeret A, Mandereau L, Bruno F (1996) Congenital malformations and occupational exposure to glycol ethers: a European collaborative case–control study. *Occupational Hygiene*, 2:417–421.

Hamlin JW, Hudson B, Sheen AD, Saunders KJ (1982) The measurement of glycol ether levels in the workplace. *Polymers Paint Colour Journal*, 772:61–63.

Hanley TR Jr, Young JT, John JA, Rao KS (1984a) Ethylene glycol monomethyl ether (EGME) and propylene glycol monomethyl ether (PGME): inhalation fertility and teratogenicity studies in rats, mice and rabbits. *Environmental Health Perspectives*, 57:7–12.

Hanley TR Jr, Yano BL, Nitschke KD, John JA (1984b) Comparison of the teratogenic potential of inhaled ethylene glycol monomethyl ether in rats, mice, and rabbits. *Toxicology and Applied Pharmacology*, 75(3):409–422.

Hansch C, Leo AJ (1985) *Medchem Project Issue No. 26*. Claremont, CA, Pomona College.

Harada T, Nagashima Y (1975) Utilization of alkyl ether compounds by soil bacteria. *Journal of Fermentation Technology*, 53:218–222.

Hays SM, Elswick BA, Blumenthal GM, Welsch F, Conolly RB, Gargas ML (2000) Development of a physiologically based pharmacokinetic model of 2-methoxyethanol and 2-methoxyacetic acid disposition in pregnant rats. *Toxicology and Applied Pharmacology*, 163(1):67–74.

Health and Safety Executive (1993) *Methods for the determination of hazardous substances: volatile organic compounds in air*. London, Health and Safety Executive, pp. 1–12 (MDHS-72).

Health Canada (1998a) *Exposure factors for assessing total daily intake of priority substances by the general population of Canada. Draft report.* Ottawa, Ontario, Health Canada, Environmental Health Directorate, March.

Health Canada (1998b) Personal communication on glycol ethers in pesticides from V. Bergeron, Pest Management Regulatory Agency, Health Canada, Ottawa, Ontario [cited in Environment Canada & Health Canada, 2002].

Health Canada (1998c) Personal communication on glycol ethers in cosmetic products from C. Denman, Health Protection Branch, Health Canada, Ottawa, Ontario [cited in Environment Canada & Health Canada, 2002].

Health Canada (1998d) *2-Methoxyethanol and its acetate*. Prepared by BIBRA International under contract to Health Canada, 29 March 1996; updated and modified by Priority Substances Section, Health Canada, Ottawa, Ontario, 1998.

Health Canada (1999) *Datasheets for recent studies on 2-methoxyethanol*. Ottawa, Ontario, Health Canada, Priority Substances Section.

Hellwig J (1993) *Study of the prenatal toxicity of 2-methoxyethanol in rats after dermal application*. Unpublished report. Ludwigshafen, BASF AG, Department of Toxicology (No. OR53/89002) [cited in ECETOC, 1995].

Hobson DW, D'Addario AP, Bruner RH, Uddin DE (1986) A subchronic dermal exposure study of diethylene glycol monomethyl ether and ethylene glycol monomethyl ether in the male guinea pig. *Fundamental and Applied Toxicology*, 6(2):339–348.

Hodgson AT, Wooley JD (1991) *Assessment of indoor concentrations, indoor sources and source emissions of selected volatile organic compounds. Final report.* Sacramento, CA, California Air Resources Board, Research Division, March 1991, 179 pp. (Contract No. A933-063; http://www.arb.ca.gov/research/abstracts/a933-063.htm#Pg).

Hoflack JC, Lambolez L, Elias Z, Vasseur P (1995) Mutagenicity of ethylene glycol ethers and of their metabolites in *Salmonella typhimurium* his−. *Mutation Research*, 341(4):281–287.

Holladay SD, Comment CE, Kwon J, Luster MI (1994) Fetal hematopoietic alterations after maternal exposure to ethylene glycol monomethyl ether: prolymphoid cell targeting. *Toxicology and Applied Pharmacology*, 129(1):53–60.

Holloway AJ, Moore HD, Foster PM (1990) The use of rat in vitro fertilization to detect reductions in the fertility of spermatozoa from males exposed to ethylene glycol monomethyl ether. *Reproductive Toxicology*, 4(1):21–27.

Hong HL, Canipe J, Jameson CW, Boorman GA (1988) Comparative effects of ethylene glycol and ethylene glycol monomethyl ether exposure on hematopoiesis and histopathology in B6C3F1 mice. *Journal of Environmental Pathology, Toxicology and Oncology*, 8(7):27–38.

Horton VL, Sleet RB, John-Greene JA, Welsch F (1985) Developmental phase-specific and dose-related teratogenic effects of ethylene glycol monomethyl ether in CD-1 mice. *Toxicology and Applied Pharmacology,* 80:108–118.

House RV, Lauer LD, Murray MJ, Ward EC, Dean JH (1985) Immunological studies in B6C3F1 mice following exposure to ethylene glycol monomethyl ether and its principal metabolite methoxyacetic acid. *Toxicology and Applied Pharmacology*, 77(2):358–362.

Howard PH, Boethling RS, Jarvis WF, Meylan WM, Michalenko EM (1991) *Handbook of environmental degradation rates*. Chelsea, MI, Lewis Publishers Inc.

IPCS (1990) *2-Methoxyethanol, 2-ethoxyethanol, and their acetates*. Geneva, World Health Organization, International Programme on Chemical Safety, 126 pp. (Environmental Health Criteria 115; http://www.inchem.org/documents/ehc/ehc/ehc115.htm).

IPCS (1994) *Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits.* Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 170; http://www.inchem.org/documents/ehc/ehc/ehc170.htm).

IPCS (2002) *International Chemical Safety Card—Ethylene glycol monomethyl ether*. Geneva, World Health Organization, International Programme on Chemical Safety (ICSC 0061; http://www.ilo.org/public/english/protection/safework/cis/products/icsc/dtasht/_icsc00/icsc0061.pdf).

IPCS (2006) *International Chemical Safety Card—2-Methoxyethyl acetate.* Geneva, World Health Organization, International Programme on Chemical Safety (ICSC 0476; http://www.ilo.org/public/english/protection/safework/cis/products/icsc/dtasht/_icsc04/icsc0476.pdf).

Jacobs GA (1992) Eye irritation tests on two ethylene glycol ethers. *Journal of the American College of Toxicology*, 11:738.

Jacobs G, Martens M, Mosselmans G (1987) Proposal of limit concentrations for skin irritation within the context of a new EEC directive on the classification and labelling of preparations. *Regulatory Toxicology and Pharmacology*, 7:370–378.

Jacobs GA, Castellazzi A, Dierickx PJ (1989) Evaluation of a non-invasive human and an in vitro cytotoxicity method as alternatives to the skin irritation test on rabbits. *Contact Dermatitis*, 21(4):239–244.

Johanson G, Rick U (1996) Use and use patterns of glycol ethers in Sweden. *Occupational Hygiene*, 2:105–110.

Kane DM (1993) *Evaluation of ChemCAN2—a fugacity-based multimedia exposure model used to predict the environmental fate of organic chemicals in Canada.* Draft report, 14 January 1993, 28 pp. [cited in Environment Canada & Health Canada, 2002].

Kawai F (1995) Bacterial degradation of glycol ethers. *Applied Microbiology and Biotechnology*, 44(3–4):532–538.

Kawamoto T, Matsuno K, Kayama F, Hirai M, Arashidani K, Yoshikawa M, Kodama Y (1990) Acute oral toxicity of ethylene glycol monomethyl ether and diethylene glycol monomethyl ether. *Bulletin of Environmental Contamination and Toxicology*, 44(4):602–608.

Kayama F, Yamashita U, Kawamoto T, Kodama Y (1991) Selective depletion of immature thymocytes by oral administration of ethylene glycol monomethyl ether. *International Journal of Immunopharmacology*, 13(5):531–540.

Kezic S, Mahieu K, Monster AC, de Wolff FA (1997) Dermal absorption of vaporous and liquid 2-methoxyethanol and 2-ethoxyethanol in volunteers. *Occupational and Environmental Medicine*, 54(1):38–43.

Kirk-Othmer (1980) *Kirk-Othmer encyclopedia of chemical technology*, 3rd ed. New York, NY, John Wiley & Sons.

Knöppel H, Schauenburg H (1989) Screening of household products for the emission of volatile organic compounds. *Environment International*, 15:413–418.

Ku WW, Ghanayem BI, Chapin RE, Wine RN (1994) Comparison of the testicular effects of 2-methoxyethanol (ME) in rats and guinea pigs. *Experimental and Molecular Pathology*, 61(2):119–133.

Ku WW, Wine RN, Chae BY, Ghanayem BI, Chapin RE (1995) Spermatocyte toxicity of 2-methoxyethanol (ME) in rats and guinea pigs: evidence for the induction of apoptosis. *Toxicology and Applied Pharmacology*, 134(1):100–110.

Lee KP, Kinney LA (1989) The ultrastructure and reversibility of testicular atrophy induced by ethylene glycol monomethyl ether (EGME) in the rat. *Toxicologic Pathology*, 17(4 Pt 2):759–773.

Lee KP, Kinney LA, Valentine R (1989) Comparative testicular toxicity of bis(2-methoxyethyl) ether and 2-methoxyethanol in rats. *Toxicology*, 59(3):239–258.

Loveday KS, Anderson BE, Resnick MA, Zeiger E (1990) Chromosome aberration and sister chromatid exchange tests in Chinese hamster ovary cells in vitro. V. Results with 46 chemicals. *Environmental and Molecular Mutagenesis*, 16(4):272–303.

Lucas SV (1984) *GC/MS analysis of organics in drinking water concentrates and advanced waste treatment concentrates. Vol. 2. Computer-printed tabulations of compound identification results for large-volume concentrates*. Research Triangle Park, NC, United States Environmental Protection Agency, Office of Research and Development, Health Effects Research Laboratory (EPA-600/l-84-020b).

Lyman WJ, Reehl WF, Rosenblatt DH (1982) *Handbook of chemical property estimation methods: environmental behavior of organic compounds.* New York, NY, McGraw-Hill.

Ma H, An J, Hsie AW, Au WW (1993) Mutagenicity and cytotoxicity of 2-methoxyethanol and its metabolites in Chinese hamster cells (the CHO/HPRT and AS52/GPT assays). *Mutation Research*, 298(3):219–225.

Mackay D, Paterson S, Di Guardo A, Cowan CE (1996) Evaluating the environmental fate of a variety of types of chemicals using the EQC model. *Environmental Toxicology and Chemistry*, 15(9):1627–1637.

McGregor DB (1984) Genotoxicity of glycol ethers. *Environmental Health Perspectives*, 57:97–103.

McGregor DB, Willins MJ, McDonald P, Holmstrom M, McDonald D, Niemeier RW (1983) Genetic effects of 2-methoxyethanol and bis(2-methoxyethyl)ether. *Toxicology and Applied Pharmacology*, 70(2):303–316.

Mebus CA, Clarke DO, Stedman DB, Welsch F (1992) 2-Methoxyethanol metabolism in pregnant CD-1 mice and embryos. *Toxicology and Applied Pharmacology*, 112(1):87–94.

Medinsky MA, Singh G, Bechtold WE, Bond JA, Sabourin PJ, Birnbaum LS, Henderson RF (1990) Disposition of three glycol ethers administered in drinking water to male F344/N rats. *Toxicology and Applied Pharmacology*, 102(3):443–455.

Miller RR, Ayres JA, Calhoun LL, Young JT, McKenna MJ (1981) Comparative short-term inhalation toxicity of ethylene glycol monomethyl ether and propylene glycol monomethyl ether in rats and mouse. *Toxicology and Applied Pharmacology*, 61(3):368–377.

Miller RR, Ayres JA, Young JT, McKenna MJ (1983a) Ethylene glycol monomethyl ether. I. Subchronic vapor inhalation study with rats and rabbits. *Fundamental and Applied Toxicology*, 3(1):49–54.

Miller RR, Hermann EA, Langvardt PW, McKenna MJ, Schwetz BA (1983b) Comparative metabolism and disposition of ethylene glycol monomethyl ether and propylene glycol monomethyl ether in male rats. *Toxicology and Applied Pharmacology*, 67(2):229–237.

Moss EJ, Thomas LV, Cook MW, Walters DG, Foster PMD, Creasy DM, Gray TJB (1985) The role of metabolism in 2-methoxyethanol-induced testicular toxicity. *Toxicology and Applied Pharmacology*, 79(3):480–489.

Nagano K, Nakayama E, Koyano M, Oobayashi H, Adachi H, Yamada T (1979) [Testicular atrophy of mice induced by ethylene glycol mono alkyl ethers.] *Sangyo Igaku*, 21(1):29–35 (in Japanese).

Nagano K, Nakayama E, Oobayashi H, Yamada T, Adachi H, Nishizawa T, Ozawa H, Nakaichi M, Okuda H, Minami K, Yamazaki K (1981) Embryotoxic effects of ethylene glycol monomethyl ether in mice. *Toxicology*, 20(4):335–343.

Nagano K, Nakayama E, Oobayashi H, Nishizawa T, Okuda H, Yamazaki K (1984) Experimental studies on toxicity of ethylene glycol alkyl ethers in Japan. *Environmental Health Perspectives*, 57:75–84.

Nelson BK, Setzer JV, Brightwell WS, Mathinos PR, Kuczuk MH, Weaver TE, Goad PT (1984a) Comparative inhalation teratogenicity of four glycol ether solvents and an amino derivative in rats. *Environmental Health Perspectives*, 57:261–271.

Nelson BK, Brightwell WS, Burg JR, Massari VJ (1984b) Behavioral and neurochemical alterations in the offspring of rats after maternal or paternal inhalation exposure to the industrial solvent 2-methoxyethanol. *Pharmacology, Biochemistry, and Behaviour*, 20:269–279.

Nelson BK, Vorhees CV, Scott WJ Jr, Hastings L (1989) Effects of 2-methoxyethanol on fetal development, postnatal behavior,

and embryonic intracellular pH of rats. *Neurotoxicology and Teratology*, 11(3):273–284.

Nelson BK, Conover DL, Brightwell WS, Shaw PB, Werren D, Edwards RM, Lary JM (1991) Marked increase in the teratogenicity of the combined administration of the industrial solvent 2-methoxyethanol and radiofrequency radiation in rats. *Teratology*, 43(6):621–634.

Nelson BK, Conover CL, Shaw PB, Werren DM, Edwards RM, Hoberman AM (1994) Interactive developmental toxicity of radiofrequency radiation and 2-methoxyethanol in rats. *Teratology*, 50(4):275–293.

Nelson BK, Conover DL, Krieg EF Jr, Snyder DL, Edwards RM (1997) Interactions of radiofrequency radiation-induced hyperthermia and 2-methoxyethanol teratogenicity in rats. *Bioelectromagnetics*, 18(5):349–359.

NIOSH (1994) *NIOSH manual of analytical methods (NMAM®)*, 4th ed. Cincinnati, OH, United States Department of Health and Human Services, National Institute of Occupational Safety and Health, August (DHHS (NIOSH) Publication 94-113).

Nitter-Hauge S (1970) Poisoning with ethylene glycol monomethyl ether. Report of two cases. *Acta Medica Scandinavica*, 188(4):277–280.

NPRI (1996) *Summary report 1994. Canadian Environmental Protection Act.* Ottawa, Ontario, Environment Canada, National Pollutant Release Inventory, 240 pp. (http://www.ec.gc.ca/inrp-npri/).

NPRI (1998) *Summary report 1996. Canadian Environmental Protection Act*. Ottawa, Ontario, Environment Canada, National Pollutant Release Inventory (http://www.ec.gc.ca/inrp-npri/).

NTP (1993) *NTP technical report on toxicity studies of ethylene glycol ethers 2-methoxyethanol, 2-ethoxyethanol, 2-butoxyethanol (CAS Nos.109-86-4, 110-80-5, 111-76-2) administered in drinking water to F344/N rats and B6C3F1 mice*. Research Triangle Park, NC, United States Department of Health and Human Services, National Institutes of Health, National Institute of Environmental Health Sciences, National Toxicology Program, 122 pp. + appendices (NTP Toxicity Report Series No. 26; NIH Publication No. 93-3349).

Ohi G, Wegman DH (1978) Transcutaneous ethylene glycol monomethyl ether poisoning in the work setting. *Journal of Occupational Medicine*, 20(10):675–676.

Parsons CE, Parsons ME (1938) Toxic encephalopathy and "granulopenic anemia" due to volatile solvents in industry: report of two cases. *Journal of Industrial Hygiene and Toxicology*, 20:124–133.

Rao KS, Cobel-Geard SR, Young JT, Hanley TR Jr, Hayes WC, John JA, Miller RR (1983) Ethylene glycol monomethyl ether II. Reproductive and dominant lethal studies in rats. *Fundamental and Applied Toxicology*, 3(2):80–85.

Reader SC, Shingles C, Stonard MD (1991) Acute testicular toxicity of 1,3-dinitrobenzene and ethylene glycol monomethyl ether in the rat: evaluation of biochemical effect markers and hormonal responses. *Fundamental and Applied Toxicology*, 16(1):61–70.

Reynolds T (1977) Comparative effects of aliphatic compounds on inhibition of lettuce fruit germination. *Annals of Botany*, 41:637–648.

Riddick J, Bunger WB, Sakano T (1986) *Organic solvents: physical properties and methods of purification*, 4th ed. New York, NY, John Wiley & Sons, 1325 pp.

Riddle M, Williams W, Andrews D, Copeland C, Luebke R, Smialowicz R (1992) Species and strain comparisons of immunosuppression by 2-methoxyethanol (ME) and 2-methoxyacetic acid (MAA). *Toxicologist*, 12:177 (Abstract 632).

Riddle MM, Williams WC, Smialowicz RJ (1996) Repeated high dose oral exposure or continuous subcutaneous infusion of 2-methoxyacetic acid does not suppress humoral immunity in the mouse. *Toxicology*, 109(1):67–74.

Ritter EJ, Scott WJ Jr, Randall JL, Ritter JM (1985) Teratogenicity of dimethoxyethyl phthalate and its metabolites methoxyethanol and methoxyacetic acid in the rat. *Teratology*, 32(1):25–31.

Rogozen MB, Rich HE, Gutman MA, Grosjean D (1987) *Evaluation of potential toxic air contaminants, Phase I.* Sacramento, CA, California Air Resources Board, 23 December 1987 (Final Report Contract A4-131-32).

Römer KG, Balge F, Freundt KJ (1985) Ethanol-induced accumulation of ethylene glycol monoalkyl ethers in rats. *Drug and Chemical Toxicology*, 8(4):255–264.

Saavedra D, Arteaga M, Tena M (1997) Industrial contamination with glycol ethers resulting in teratogenic damage. *Annals of the New York Academy of Sciences*, 837:126–137.

Sabourin PJ, Medinsky MA, Thurmond F, Birnbaum LS, Henderson RF (1992) Effect of dose on the disposition of methoxyethanol, ethoxyethanol, and butoxyethanol administered dermally to male F344/N rats. *Fundamental and Applied Toxicology*, 19(1):124–132.

Sabourin PJ, Medinsky MA, Thurmond F, Birnbaum LS, Henderson RF (1993) Erratum to "Effect of dose on the disposition of methoxyethanol, ethoxyethanol, and butoxyethanol administered dermally to male F344/N rats." *Fundamental and Applied Toxicology,* 20:508–510.

Samuels DM, Doe JE, Tinston DJ (1984) The effects on the rat testis of single inhalation exposures to ethylene glycol monoalkyl ethers, in particular ethylene glycol monomethyl ether. *Archives of Toxicology Supplement*, 7:167–170.

Savolainen H (1980) Glial cell toxicity of ethyleneglycol monomethylether vapor. *Environmental Research*, 22:423–430.

Schenker MB (1996) Reproductive health effects of glycol ether exposure in the semiconductor industry. *Occupational Hygiene*, 2:367–372.

Schenker MB, Gold EB, Beaumont JJ, Eskenazi B, Hammond SK, Lasley BL, McCurdy SA, Samuels SJ, Saiki CL, Swan SH (1995) Association of spontaneous abortion and other reproductive effects with work in the semiconductor industry. *American Journal of Industrial Medicine*, 28(6):639–659.

Schriever E, Marutzky R (1990) VOC emissions of coated parqueted floors. In: *Indoor Air '90. Proceedings of the 5th International Conference on Indoor Air Quality and Climate, 29 July – 3 August 1990, Toronto, Ontario. Vol. 3.* Ottawa, Ontario, Canada Mortgage and Housing Corporation, pp. 551–555.

Scott WJ, Fradkin R, Wittfoht W, Nau H (1989) Teratologic potential of 2-methoxyethanol and transplacental distribution of its metabolite, 2-methoxyacetic acid, in non-human primates. *Teratology*, 39(4):363–373.

Shih TS, Chou JS, Chen CY, Smith TJ (1999a) Improved method to measure urinary alkoxyacetic acids. *Occupational and Environmental Medicine*, 56(7):460–467.

Shih TS, Liou SH, Chen CY, Chou JS (1999b) Correlation between urinary 2-methoxy acetic acid and exposure of 2-methoxy ethanol. *Occupational and Environmental Medicine*, 56(10):674–678.

Shih TS, Hsieh AT, Liao GD, Chen YH, Liou SH (2000) Haematological and spermatotoxic effects of ethylene glycol monomethyl ether in copper clad laminate factories. *Occupational and Environmental Medicine*, 57(5):348–352.

Shih TS, Hsieh AT, Chen YH, Liao GD, Chen CY, Chou JS, Liou SH (2003) Follow up study of haematological effects in workers exposed to 2-methoxyethanol. *Occupational and Environmental Medicine*, 60(2):130–135.

Sleet RB, Greene JA, Welsch F (1988) The relationship of embryotoxicity to disposition of 2-methoxyethanol in mice. *Toxicology and Applied Pharmacology*, 93(2):195–207.

Sleet RB, Welsch F, Myers CB, Marr MC (1996) Developmental phase specificity and dose–response effects of 2-methoxyethanol in rats. *Fundamental and Applied Toxicology*, 29(1):131–139.

Smallwood AW, DeBord KE, Lowry LK (1984) Analyses of ethylene glycol monoalkyl ethers and their proposed metabolites in blood and urine. *Environmental Health Perspectives*, 57:249–253.

Smialowicz RJ, Riddle MM, Luebke RW, Copeland CB, Andrews D, Rogers RR, Gray LE, Laskey JW (1991a) Immunotoxicity of 2-methoxyethanol following oral administration in Fischer 344 rats. *Toxicology and Applied Pharmacology*, 109(3):494–506.

Smialowicz RJ, Riddle MM, Rogers RR, Copeland CB, Luebke RW, Andrews DL (1991b) Evaluation of the immunotoxicity of orally administered 2-methoxyacetic acid in Fischer 344 rats. *Fundamental and Applied Toxicology*, 17(4):771–781.

Smialowicz RJ, Williams WC, Riddle MM, Andrews DL, Luebke RW, Copeland CB (1992a) Comparative immunosuppression of various glycol ethers orally administered to Fischer 344 rats. *Fundamental and Applied Toxicology*, 18(4):621–627.

Smialowicz RJ, Riddle MM, Williams WC, Copeland CB, Luebke RW, Andrews DL (1992b) Differences between rats and mice in the immunosuppressive activity of 2-methoxyethanol and 2-methoxyacetic acid. *Toxicology*, 74(1):57–67.

Smialowicz RJ, Riddle MM, Williams WC (1993) Methoxyacetaldehyde, an intermediate metabolite of 2-methoxyethanol, is immunosuppressive in the rat. *Fundamental and Applied Toxicology*, 21(1):1–7.

Smialowicz RJ, Riddle MM, Williams WC (1994) Species and strain comparisons of immunosuppression by 2-methoxyethanol and 2-methoxyacetic acid. *International Journal of Immunopharmacology*, 16(8):695–702.

Smyth HF Jr, Seaton J, Fischer L (1941) The single dose toxicity of some glycols and derivatives. *Journal of Industrial Hygiene and Toxicology*, 23:259–268.

Sparer J, Welch LS, McManus K, Cullen MR (1988) Effects of exposure to ethylene glycol ethers on shipyard painters: I. Evaluation of exposure. *American Journal of Industrial Medicine*, 14(5):497–507.

Stemmler K, Mengon W, Kinnison DJ, Kerr JA (1997) OH radical-initiated oxidation of 2-butoxyethanol under laboratory conditions related to the troposphere: product studies and proposed mechanism. *Environmental Science and Technology*, 31:1496–1504.

Sumner SC, Stedman DB, Clarke DO, Welsch F, Fennell TR (1992) Characterization of urinary metabolites from [1,2,methoxy-^{13}C]-2-methoxyethanol in mice using ^{13}C nuclear magnetic resonance spectroscopy. *Chemical Research in Toxicology*, 5(4):553–560.

Swan SH, Forest W (1996) Reproductive risks of glycol ethers and other agents used in semiconductor manufacturing. *Occupational Hygiene*, 2:373–385.

Swan SH, Beaumont JJ, Hammond SK, VonBehren J, Green RS, Hallock MF, Woskie SR, Hines CJ, Schenker MB (1995) Historical cohort study of spontaneous abortion among fabrication workers in the Semiconductor Health Study: agent-level analysis. *American Journal of Industrial Medicine*, 28(6):751–769.

Sweeney LM, Tyler TR, Kirman CR, Corley RA, Reitz RH, Paustenbach DJ, Holson JF, Whorton MD, Thompson KM, Gargas ML (2001) Proposed occupational exposure limits for select ethylene glycol ethers using PBPK models and Monte Carlo simulations. *Toxicological Sciences*, 62(1):124–139.

Terry KK, Elswick BA, Stedman DB, Welsch F (1994) Developmental phase alters dosimetry–teratogenicity relationship for 2-methoxyethanol in CD-1 mice. *Teratology*, 49(3):218–227.

Timbrell JA, Draper RP, Butterworth M, Creasy DM (1996) Detection of testicular toxicity of 2-methoxyethanol using urinary creatine. *Occupational Hygiene*, 2:153–160.

Toraason M, Breitenstein M (1988) Prenatal ethylene glycol monomethyl ether (EGME) exposure produces electrocardiographic changes in the rat. *Toxicology and Applied Pharmacology*, 95(2):321–327.

Toraason M, Stringer B, Stober P, Hardin BD (1985) Electrocardiographic study of rat fetuses exposed to ethylene glycol monomethyl ether (EGME). *Teratology*, 32(1):33–39.

Toraason M, Breitenstein MJ, Smith RJ (1986a) Ethylene glycol monomethyl ether (EGME) inhibits rat embryo ornithine decarboxylase (ODC) activity. *Drug and Chemical Toxicology*, 9(3–4):191–203.

Toraason M, Niemeier RW, Hardin BD (1986b) Calcium homeostasis in pregnant rats treated with ethylene glycol monomethyl ether (EGME). *Toxicology and Applied Pharmacology*, 86(2):197–203.

Toraason M, Stringer B, Smith R (1986c) Ornithine decarboxylase activity in the neonatal rat heart following prenatal exposure to ethylene glycol monomethyl ether. *Drug and Chemical Toxicology*, 9(1):1–14.

USEPA (1986) *Health and environmental effects profile for 2-methoxyethanol.* Cincinnati, OH, United States Environmental Protection Agency, Environmental Criteria and Assessment Office (EPA/600/X-87/025; NTIS PB89119531).

USEPA (1992) *Initial submission: Letter from Eastman Kodak Co. to Office of Toxic Substances regarding toxicity studies of nine glycol ethers with attachments and cover letter dated 092892.* Washington, DC, United States Environmental Protection Agency (Document No. 88-920008915; NTIS/OTS0570960).

USEPA (1997) *Exposure factors handbook. Vol. III. Activity factors*. Washington, DC, United States Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, August (EPA/600/P-95/002Fc).

USEPA (2003) *Toxics Release Inventory chemical report (TRI Explorer report)*. Washington, DC, United States Environmental Protection Agency (http://www.epa.gov/tri/tridata; accessed 17 March 2004).

Vachhrajani KD, Dutta KK (1992) Stage specific effect during one seminiferous epithelial cycle following ethylene glycol monomethyl ether exposure in rats. *Indian Journal of Experimental Biology*, 30:892–896.

Van Leeuwen CJ, Van Der Zandt PTJ, Aldenberg T, Verhaar HJM, Hermens JLM (1992) Application of QSARs, extrapolation and equilibrium partitioning in aquatic effects assessment. I. Narcotic industrial pollutants. *Environmental Toxicology and Chemistry*, 11:267–282.

Versar Inc. (1986) *Standard scenarios for estimating exposure to chemical substances during use of consumer products. Vol. 1*. Prepared for Exposure Evaluation Division, Office of Toxic Substances, United States Environmental Protection Agency, Washington, DC, September (EPA Contract No. 68-02-3968).

Veulemans H, Groeseneken D, Masschelein R, Van Vlem E (1987) Survey of ethylene glycol ether exposures in Belgian industries and workshops. *American Industrial Hygiene Association Journal*, 48:671–676.

Veulemans H, Steeno O, Masschelein R, Groeseneken D (1993) Exposure to ethylene glycol ethers and spermatogenic disorders in man: a case–control study. *British Journal of Industrial Medicine*, 50:71–80.

Villalobos-Pietrini R, Gomez-Arroyo S, Altamirano-Lozano M, Orozco P, Rios P (1989) Cytogenetic effects of some cellosolves. *Revista Internacional de Contaminación Ambiental*, 5:41.

Watanabe A, Nakano Y, Endo T, Sato N, Kai K, Shiraiwa K (2000) Collaborative work to evaluate toxicity on male reproductive organs by repeated dose studies in rats. 27. Repeated toxicity study on ethylene glycol monomethyl ether for 2 and 4 weeks to detect effects on male reproductive organs in rats. *Journal of Toxicological Sciences*, 25(Special): 259–266.

Welch LS, Cullen MR (1988) Effect of exposure to ethylene glycol ethers on shipyard painters. III. Hematologic effects. *American Journal of Industrial Medicine*, 14(5):527–536.

Welch LS, Schrader SM, Turner TW, Cullen MR (1988) Effects of exposure to ethylene glycol ethers on shipyard painters. II. Male reproduction. *American Journal of Industrial Medicine*, 14(5):509–526.

Welsch F, Sleet RB (1987) Metabolism and disposition of a teratogenic dose of 2-methoxyethanol (ME) in pregnant CD-1 mice. *Teratology*, 36:16A.

Whittaker SG, Zimmermann FK, Dicus B, Piegorsch WW, Fogel S, Resnick MA (1989) Detection of induced mitotic chromosome loss in *Saccharomyces cerevisiae*—an interlaboratory study. *Mutation Research*, 224(1):31–78.

Wickramaratne GA (1986) The teratogenic potential and dose–response of dermally administered ethylene glycol monomethyl ether (EGME) estimated in rats with the Chernoff-Kavlock assay. *Journal of Applied Toxicology*, 6(3):165–166.

Williams WC, Riddle MM, Copeland CB, Andrews DL, Smialowicz RJ (1995) Immunological effects of 2-methoxyethanol administered dermally or orally to Fischer 344 rats. *Toxicology*, 98(1–3):215–223.

Zavon MR (1963) Methyl cellosolve intoxication. *American Industrial Hygiene Association Journal*, 24:36–41.

Zeiger E, Anderson B, Haworth S, Lawlor T, Mortelmans K (1992) *Salmonella* mutagenicity tests: V. Results from the testing of 311 chemicals. *Environmental and Molecular Mutagenesis*, 19(Suppl. 21):2–141.

Zhu J, Cao XL, Beauchamp R (2001) Determination of 2-butoxyethanol emissions from selected consumer products and its application in assessment of inhalation exposure associated with cleaning tasks. *Environment International*, 26(7–8):589–597.

Zimmermann FK, Mayer VW, Scheel I, Resnick MA (1985) Acetone, methyl ethyl ketone, ethyl acetate, acetonitrile and other polar aprotic solvents are strong inducers of aneuploidy in *Saccharomyces cerevisiae*. *Mutation Research*, 149(3):339–351.

Zissu D (1995) Experimental study of cutaneous tolerance to glycol ethers. *Contact Dermatitis*, 32(2):74–77.

APPENDIX 1—ACRONYMS AND ABBREVIATIONS

AUC	area under the curve
BCF	bioconcentration factor
CAS	Chemical Abstracts Service
CEPA	*Canadian Environmental Protection Act, 1999*
CHO	Chinese hamster ovary
CI	confidence interval
CICAD	Concise International Chemical Assessment Document
C_{max}	maximum concentration
CTV	critical toxicity value
DNA	deoxyribonucleic acid
EEV	estimated exposure value
EGME	ethylene glycol monomethyl ether
EHC	Environmental Health Criteria
ENEV	estimated no-effects value
EQC	Equilibrium Criterion
FID	flame ionization detection
GC	gas chromatography
HC_5	concentration hazardous to 5% of organisms
ICSC	International Chemical Safety Card
ILO	International Labour Organization
IOMC	Inter-Organization Programme for the Sound Management of Chemicals
IPCS	International Programme on Chemical Safety
K_m	Michaelis-Menten constant
K_{ow}	octanol/water partition coefficient
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEC	lowest-observed-adverse-effect concentration
LOAEL	lowest-observed-adverse-effect level
MAA	2-methoxyacetic acid
MALD	2-methoxyacetaldehyde
NASA	National Aeronautics and Space Administration
NOAEC	no-observed-adverse-effect concentration
NOAEL	no-observed-adverse-effect level
NPRI	National Pollutant Release Inventory (Canada)
OEL	occupational exposure limit
PBPK	physiologically based pharmacokinetic
PIM	Poison Information Monograph
ppm	part per million
RR	relative risk
SD	standard deviation
SI	Système international d'unités (International System of Units)
SPIN	Substances in Preparations in Nordic Countries
TWA	time-weighted average
UNEP	United Nations Environment Programme
USA	United States of America
V_{max}	maximum reaction rate
VOC	volatile organic compound
WHO	World Health Organization

APPENDIX 2—SOURCE DOCUMENT

Environment Canada & Health Canada (2002)

Copies of the *Canadian Environmental Protection Act* Priority Substances List assessment report on 2-methoxyethanol are available upon request from:

Inquiry Centre
Environment Canada
Main Floor, Place Vincent Massey
351 St. Joseph Boulevard
Gatineau, Quebec
Canada K1A OH3

or by e-mailing PSL.LSIP@ec.gc.ca.

Unpublished supporting documentation, which presents additional information, is available upon request from:

Commercial Chemicals Evaluation Branch
Environment Canada
14th Floor, Place Vincent Massey
351 St. Joseph Boulevard
Gatineau, Quebec
Canada K1A 0H3

or

Existing Substances Division
Health Canada
Environmental Health Centre
Tunney's Pasture
Address Locator 0801C2
Ottawa, Ontario
Canada K1A 0L2

Sections of the assessment report related to the environmental assessment of 2-methoxyethanol and the environmental supporting document (Environment Canada, 1999) were prepared or reviewed by the members of the Environmental Resource Group, established by Environment Canada to support the environmental assessment:

D. Boersma, Environment Canada
R. Breton, Environment Canada
P. Cureton, Environment Canada
N. Davidson, Environment Canada
R. Desjardins, Environment Canada
L. Hamel, Union Carbide Canada Inc.
B. Lee, Environment Canada
S. Lewis, Chemical Manufacturers' Association
B. Sebastien, Environment Canada
K. Taylor, Environment Canada (lead for the environmental assessment)

Sections of the assessment report relevant to the environmental assessment and the environmental supporting document (Environment Canada, 1999) were also reviewed by:

S. Dobson, Institute of Terrestrial Ecology
C. Staples, Assessment Technologies Inc.

Data on the health effects of 2-methoxyethanol were identified primarily from a review prepared in 1996 by BIBRA International, which was updated and modified by Health Canada in 1998 (Health Canada, 1998d). Relevant data identified subsequent to this update are summarized in Health Canada (1999). The search strategies used in the identification of relevant data on health effects from 1996 to October 1999 are outlined below.

The health-related sections of the assessment report were prepared and the background supporting document was updated by the following staff of Health Canada:

H. Hirtle
K. Hughes
M.E. Meek
L. Turner

Adequacy of data coverage and defensibility of the conclusions presented in the health assessment were considered in a written review by:

M. Dourson, Toxicology Excellence in Risk Assessment
J.B. Knaak, Oxychem (retired)
R.A. Rudel, Silent Spring Institute

The health-related sections of the assessment report were reviewed and approved by the Healthy Environments and Consumer Safety Branch Risk Management meeting of Health Canada.

The entire assessment report was reviewed and approved by the Environment Canada/Health Canada CEPA Management Committee.

Search strategies employed for identification of relevant data for the source document are as follows:

Environmental assessment

Data relevant to the assessment of whether 2-methoxyethanol is "toxic" to the environment under CEPA were identified from existing review documents, published reference texts and online searches, conducted between January and May 1996, of the following databases: ASFA (Aquatic Sciences and Fisheries Abstracts, Cambridge Scientific Abstracts; 1990–1996), BIOSIS (Biosciences Information Services; 1990–1996), CAB (Commonwealth Agriculture Bureaux; 1990–1996), CESARS (Chemical Evaluation Search and Retrieval System, Ontario Ministry of the Environment and Michigan Department of Natural Resources; 1996), CHRIS (Chemical Hazard Release Information System; 1964–1985), Current Contents (Institute for Scientific Information; 1993 – 15 January 1996), ELIAS (Environmental Library Integrated Automated System, Environment Canada library; January 1996), Enviroline (R.R. Bowker Publishing Co.; November 1995 – June 1996), Environmental Abstracts (1975 – February 1996), Environmental Bibliography (Environmental Studies Institute, International Academy at Santa Barbara; 1990–1996), GEOREF (Geo Reference Information System, American Geological Institute; 1990–1996), HSDB (Hazardous Substances Data Bank, United States National Library of Medicine; 1996), Life Sciences (Cambridge Scientific Abstracts; 1990–1996), NTIS (National Technical Information Service, United States Department of Commerce; 1990–1996), Pollution Abstracts (Cambridge Scientific Abstracts, United States National Library of Medicine; 1990–1996), POLTOX (Cambridge Scientific Abstracts, United States National Library of Medicine; 1990–1995), RTECS (Registry of Toxic Effects of Chemical Substances, United States National Institute for Occupational Safety and Health; 1996), Toxline (United States National Library of Medicine; 1990–1996), TRI93 (Toxic Chemical Release Inventory, United States Environmental Protection Agency, Office of Toxic Substances; 1993), USEPA-ASTER (Assessment Tools for the Evaluation of Risk, United States Environmental Protection Agency; up to 21 December 1994), WASTEINFO (Waste Management Information Bureau of the American Energy Agency; 1973 – September 1995) and Water Resources Abstracts (United States Geological Survey, United

States Department of the Interior; 1990–1996). Reveal Alert was used to maintain an ongoing record of the current scientific literature pertaining to the potential environmental effects of 2-methoxyethanol. Data obtained after 30 September 1999 were not considered for the source document unless they were critical data received during a public review period from 19 August to 18 October 2000.

In addition, a survey of Canadian industry was carried out under the authority of section 16 of CEPA (Environment Canada, 1997a,b). Targeted companies with commercial activities involving more than 1000 kg of 2-methoxyethanol were required to supply information on uses, releases, environmental concentrations, effects or other data that were available to them for 2-methoxyethanol.

Health assessment

In addition to studies included in the review prepared by BIBRA International, recent data have been identified through searching the following databases beginning in August 1996 using the chemical name or the CAS number for both 2-methoxyethanol and 2-methoxyethyl acetate: CAB Abstracts, Canadian Research Index, DIALOG (CANCERLIT, Environmental Bibliography, Waternet, Water Resources Abstracts, Enviroline, Pollution Abstracts and NTIS), Food Science and Technology Abstracts, Medline, Toxline Plus and TOXNET (CCRIS [Chemical Carcinogenesis Research Information System, United States National Cancer Institute], GENE-TOX [Genetic Toxicology, United States Environmental Protection Agency] and EMIC [Environmental Mutagen Information Center database, Oak Ridge National Laboratory]). Data acquired as of October 1999 were considered for inclusion in the source document.

As well as these databases, officials at the Product Safety Bureau and Drugs Directorate of Health Canada, along with the Pest Management Regulatory Agency, were contacted to obtain information relevant to this assessment.

A comprehensive literature search was conducted in January 2004 by Toxicology Advice & Consulting Ltd in order to identify critical data published since publication of the source document. Databases searched included:

- ChemID*plus* (The ChemID*plus* system searches and/or identifies literature from a wide range of online databases and databanks, including Agency for Toxic Substances and Disease Registry [ATSDR], CANCERLIT, CCRIS, Developmental and Reproductive Toxicology Database [DART]/ Environmental Teratology Information Center [ETIC], GENE-TOX, HSDB, Integrated Risk Information System [IRIS], Medline, Toxline Core, Toxline Special and Toxic Substances Control Act Chemical Substances Inventory [TSCA]).
- INCHEM (The INCHEM database consolidates information from a number of intergovernmental organizations, including the Joint FAO/WHO Expert Committee on Food Additives [JECFA] Evaluations and Monographs, the Joint FAO/WHO Meeting on Pesticide Residues [JMPR], the International Agency for Research on Cancer [IARC], Chemical Information System [CIS], EHCs and Screening Information Data Sets [SIDS]).
- RTECS

APPENDIX 3—CICAD PEER REVIEW

The draft CICAD on 2-methoxyethanol was sent for review to institutions and organizations identified by IPCS after contact with IPCS national Contact Points and Participating Institutions, as well as to identified experts. An open invitation to participate in the peer review process was also published on the IPCS web site. Comments were received from:

M. Baril, Institut de Recherche en Santé et en Sécurité du Travail du Québec, Montreal, Quebec, Canada
R. Benson, United States Environmental Protection Agency, Denver, CO, USA
R. Chhabra, National Institute of Environmental Health Sciences, Department of Health and Human Services, Research Triangle Park, NC, USA
I. Desi, Department of Public Health, Budapest, Hungary
Ethylene Glycol Ethyl Ether - Ethylene Glycol Methyl Ether Task Group of the American Chemistry Council Glycol Ether Panel
L. Fishbein, Fairfax, Virginia, USA
E. Frantik, National Institute of Public Health, Prague, Czech Republic
H. Gibb, Sciences International Inc., Alexandria, VA, USA
H. Greim, Technical University of Munich, Munich, Germany
R. Hertel, Federal Institute for Risk Assessment, Berlin, Germany
R. Jäckh, BASF AG, Ludwigshafen, Germany
J. Kielhorn, Fraunhofer Institute for Toxicology and Experimental Medicine, Hanover, Germany
H. Nagy, National Institute of Occupational Safety and Health, Cincinnati, OH, USA
P.I. Rabbani, Food and Drug Administration, College Park, MD, USA
H. Savolainen, Department of Occupational Safety & Health, Tampere, Finland
E. Soderlund, Norwegian Institute of Public Health, Oslo, Norway
J.L. Stauber, CSIRO Energy Technology, Bangor, Australia
V. Stransky, National Institute of Public Health, Prague, Czech Republic
M.H. Sweeney, Health Attaché – Viet Nam, United States Department of Health and Human Services, Hanoi, Viet Nam
D. Willcocks, National Industrial Chemicals Notification & Assessment Scheme, Sydney, Australia
K. Ziegler-Skylakakis, European Commission, Luxembourg

APPENDIX 4—CICAD 12TH FINAL REVIEW BOARD

Hanoi, Viet Nam
28 September – 1 October 2004

Members

Mr D.T. Bai, Centre of Environmental Protection & Chemical Safety, Institute of Industrial Chemistry, Hanoi, Viet Nam

Dr R. Chhabra, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA

Mr P. Copestake, Toxicology Advice & Consulting Ltd, Surrey, United Kingdom

Dr C. De Rosa, Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention, Atlanta, GA, USA

Dr S. Dobson, Centre for Ecology & Hydrology, Monks Wood, United Kingdom

Dr G. Dura, National Institute of Environmental Health of József Fodor Public Health Centre, Budapest, Hungary

Ms C.W. Fang, National Institute of Occupational Safety and Health Malaysia, Selangor, Malaysia

Dr L. Fishbein, Fairfax, VA, USA

Dr L. Fruchtengarten, Poison Control Center of São Paulo, São Paulo, Brazil

Dr C.L. Geraci, Document Development Branch, Centers for Disease Control and Prevention / National Institute for Occupational Safety and Health, Cincinnati, OH, USA

Dr H. Gibb, Sciences International Inc., Alexandria, VA, USA

Dr R.F. Hertel, Federal Institute for Risk Assessment, Berlin, Germany

Mr P. Howe, Centre for Ecology & Hydrology, Monks Wood, United Kingdom

Dr S. Ishimitsu, Division of Safety Information on Drug, Food and Chemicals, National Institute of Health Sciences, Tokyo, Japan

Dr J. Kielhorn, Fraunhofer Institute for Toxicology and Experimental Medicine, Hanover, Germany

Dr S. Kunarattanapruke, Food & Drug Administration, Ministry of Public Health, Nonthaburi, Thailand

Dr Y. Liang, Department of Occupational Health, Fudan University School of Public Health, Shanghai, China

Ms M.E. Meek, Existing Substances Division, Environmental Health Directorate, Health Canada, Ottawa, Ontario, Canada

Mr F.K. Muchiri, Directorate of Occupational Health and Safety Services, Nairobi, Kenya

Dr O. Sabzevari, Food and Drug Control Labs, Ministry of Health & Medical Education, Tehran, Islamic Republic of Iran

Dr J. Stauber, CSIRO Energy Technology, Menai, New South Wales, Australia

Dr M.H. Sweeney, United States Embassy, Hanoi, Viet Nam

Mr P. Watts, Toxicology Advice & Consulting Ltd, Surrey, United Kingdom

Ms D. Willcocks, National Industrial Chemicals Notification and Assessment Scheme, Sydney, New South Wales, Australia

Dr K. Ziegler-Skylakakis, European Commission, Luxembourg

Secretariat

Dr A. Aitio, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

APPENDIX 5—CICAD 13TH FINAL REVIEW BOARD

Nagpur, India
31 October – 3 November 2005

Members

Dr T. Chakrabarti, National Environmental Engineering Research Institute, Nagpur, India

Dr R. Chhabra, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA

Mr P. Copestake, Toxicology Advice & Consulting Ltd, Surrey, United Kingdom

Dr C. De Rosa, Agency for Toxic Substances and Disease Registry, Atlanta, GA, USA

Dr S. Dobson, Centre for Ecology & Hydrology, Monks Wood, United Kingdom

Dr L. Fishbein, Fairfax, VA, USA

Dr L. Fruchtengarten, Poison Control Center of São Paulo, São Paulo, Brazil

Dr H. Gibb, Sciences International Inc., Alexandria, VA, USA

Dr R.F. Hertel, Federal Institute for Risk Assessment, Berlin, Germany

Mr P. Howe, Centre for Ecology & Hydrology, Monks Wood, United Kingdom

Ms K. Hughes, Existing Substances Division, Environmental Health Directorate, Health Canada, Ottawa, Ontario, Canada

Dr D. Kanungo, Directorate General of Health Services, New Delhi, India

Dr J. Kielhorn, Fraunhofer Institute for Toxicology and Experimental Medicine, Hanover, Germany

Dr G. Kong, Hanyang University, Seoul, Republic of Korea

Dr J. Rischer, Agency for Toxic Substances and Disease Registry, Chamblee, GA, USA

Dr O. Sabzevari, Tehran University of Medical Sciences, Tehran, Islamic Republic of Iran

Dr R. Sonawane, National Center for Environmental Assessment, Environmental Protection Agency, Washington, DC, USA

Dr J. Stauber, CSIRO Energy Technology, Menai, New South Wales, Australia

Dr M.H. Sweeney, United States Embassy, Hanoi, Viet Nam

Ms D. Willcocks, National Industrial Chemicals Notification and Assessment Scheme, Sydney, New South Wales, Australia

Dr Y. Zheng, National Institute for Occupational Health & Poison Control, Beijing, People's Republic of China

Dr K. Ziegler-Skylakakis, Secretariat of the Commission for the Investigation of Health Hazards of Chemical Compounds in the Workplace Area (MAK Commission), Freising-Weihenstephan, Germany

Observer

Mr P. Ashford, Resorcinol Task Force, Wotton-under-edge, Gloucestershire, United Kingdom

Secretariat

Dr A. Aitio, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Ms L. Onyon, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Mr M. Shibatsuji, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

ETHYLENE GLYCOL MONOMETHYL ETHER

ICSC: 0061
May 2003

CAS #	**109-86-4**	**2-Methoxyethanol**
RTECS #	**KL5775000**	**Monomethyl glycol ether**
UN #	**1188**	**Methyl oxitol**
EC Annex 1 Index #	**603-011-00-4**	**EGME**
EC/EINECS #	**203-713-7**	**Methyl cellosolve**
		$C_3H_8O_2$ / $CH_3OCH_2CH_2OH$
		Molecular mass: 76.1

TYPES OF HAZARD / EXPOSURE	ACUTE HAZARDS / SYMPTOMS	PREVENTION	FIRST AID / FIRE FIGHTING
FIRE	Flammable.	NO open flames, NO sparks, and NO smoking.	Powder, alcohol-resistant foam, water spray, carbon dioxide.
EXPLOSION	Above 39°C explosive vapour/air mixtures may be formed.	Above 39°C use a closed system, ventilation, and explosion-proof electrical equipment.	In case of fire: keep drums, etc., cool by spraying with water.
EXPOSURE		**AVOID EXPOSURE OF (PREGNANT) WOMEN! STRICT HYGIENE!**	**IN ALL CASES CONSULT A DOCTOR!**
Inhalation	Confusion. Cough. Sore throat. Dizziness. Headache. Nausea. Unconsciousness. Vomiting. Weakness.	Ventilation, local exhaust, or breathing protection.	Fresh air, rest. Refer for medical attention.
Skin	MAY BE ABSORBED! (Further see Inhalation).	Protective gloves. Protective clothing.	Remove contaminated clothes. Rinse skin with plenty of water or shower. Refer for medical attention.
Eyes	Redness. Pain. Blurred vision.	Face shield, or eye protection in combination with breathing protection.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion	Abdominal pain. Diarrhoea. Nausea. Vomiting. (Further see Inhalation).	Do not eat, drink, or smoke during work.	Rinse mouth. Give one or two glasses of water to drink. Refer for medical attention.

SPILLAGE DISPOSAL

Ventilation. Remove all ignition sources. Collect leaking and spilled liquid in sealable containers as far as possible. Wash away remainder with plenty of water. (Extra personal protection: filter respirator for organic gases and vapours.)

PACKAGING & LABELLING

Airtight. Do not transport with food and feedstuffs.
EU Classification
Symbol: T
R: 60-61-10-20/21/22
S: 53-45
Note: E
UN Classification
UN Hazard Class: 3
UN Pack Group: III

EMERGENCY RESPONSE

Transport Emergency Card: TEC (R)-30GF1-III
NFPA Code: H 2; F 2; R 0;

STORAGE

Fireproof. Separated from strong oxidants, food and feedstuffs. Keep in the dark. Cool.

IPCS
International Programme on Chemical Safety
WHO ILO UNEP

SEE IMPORTANT INFORMATION ON BACK

ETHYLENE GLYCOL MONOMETHYL ETHER

ICSC: 0061

IMPORTANT DATA

PHYSICAL STATE; APPEARANCE
COLOURLESS LIQUID , WITH CHARACTERISTIC ODOUR.

CHEMICAL DANGERS
The substance can form explosive peroxides. Reacts with strong oxidants causing fire and explosion hazard. Attacks some forms of plastic, coatings.

OCCUPATIONAL EXPOSURE LIMITS
TLV: 0.1 ppm as TWA; (skin); (ACGIH 2008).
MAK: (sum of concentrations in air of ethylene glycol monomethyl ether and its acetate) 1 ppm, 3.2 mg/m³; H; Pregnancy risk group: B; Peak limitation category: II(8); (DFG 2008).

ROUTES OF EXPOSURE
The substance can be absorbed into the body by inhalation, through the skin and by ingestion.

INHALATION RISK
A harmful contamination of the air can be reached rather quickly on evaporation of this substance at 20°C.

EFFECTS OF SHORT-TERM EXPOSURE
The substance is mildly irritating to the eyes and the respiratory tract. The substance may cause effects on the central nervous system, blood, bone marrow, kidneys and liver. Exposure at high levels may result in unconsciousness. Medical observation is indicated.

EFFECTS OF LONG-TERM OR REPEATED EXPOSURE
The liquid defats the skin. The substance may have effects on the bloodand bone marrow , resulting in anaemiaand lesions of blood cells. May cause toxicity to human reproduction or development.

PHYSICAL PROPERTIES

Boiling point: 125°C
Melting point: -85°C
Relative density (water = 1): 0.96
Solubility in water: miscible
Vapour pressure, kPa at 20°C: 0.83
Relative vapour density (air = 1): 2.6

Relative density of the vapour/air-mixture at 20°C (air = 1): 1.01
Flash point: 39°C c.c.
Auto-ignition temperature: 285°C
Explosive limits, vol% in air: 2.3- 24.5
Octanol/water partition coefficient as log Pow: -0.503

ENVIRONMENTAL DATA

NOTES

Depending on the degree of exposure, periodic medical examination is indicated. The odour warning when the exposure limit value is exceeded is insufficient. Check for peroxides prior to distillation; eliminate if found. Card has been partially updated in July 2009: see Occupational Exposure Limits, Ingestion First Aid.

ADDITIONAL INFORMATION

2-METHOXYETHYL ACETATE

ICSC: 0476
November 2003

CAS #	**110-49-6**	**Ethylene glycol monomethyl ether acetate**
RTECS #	**KL5950000**	**2-Methoxyethanol acetate**
UN #	**1189**	**Acetic acid, 2-methoxyethyl ester**
EC Annex 1 Index #	**607-036-00-1**	**Methyl cellosolve acetate**
EC/EINECS #	**203-772-9**	**Methyl glycol acetate**
		$C_5H_{10}O_3$ / $CH_3COOCH_2CH_2OCH_3$
		Molecular mass: 118.1

TYPES OF HAZARD / EXPOSURE	ACUTE HAZARDS / SYMPTOMS	PREVENTION	FIRST AID / FIRE FIGHTING
FIRE	Flammable.	NO open flames, NO sparks, and NO smoking.	Powder, alcohol-resistant foam, water spray, carbon dioxide.
EXPLOSION	Above 45°C explosive vapour/air mixtures may be formed.	Above 45°C use a closed system, ventilation, and explosion-proof electrical equipment.	In case of fire: keep drums, etc., cool by spraying with water.
EXPOSURE		**AVOID ALL CONTACT!**	
Inhalation	Dizziness. Drowsiness. Headache.	Ventilation, local exhaust, or breathing protection.	Fresh air, rest. Refer for medical attention.
Skin	MAY BE ABSORBED! Dry skin. (Further see Inhalation).	Protective gloves. Protective clothing.	Remove contaminated clothes. Rinse skin with plenty of water or shower. Refer for medical attention.
Eyes	Redness.	Safety goggles, or eye protection in combination with breathing protection.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion	Abdominal pain. Nausea. Vomiting. Weakness. Unconsciousness. (Further see Inhalation).	Do not eat, drink, or smoke during work.	Rinse mouth. Do NOT induce vomiting. Refer for medical attention.

SPILLAGE DISPOSAL

Ventilation. Remove all ignition sources. Collect leaking and spilled liquid in sealable containers as far as possible. Absorb remaining liquid in sand or inert absorbent and remove to safe place. Do NOT let this chemical enter the environment. (Extra personal protection: filter respirator for organic gases and vapours.)

PACKAGING & LABELLING

EU Classification
Symbol: T
R: 60-61-20/21/22
S: 53-45
Note: E
UN Classification
UN Hazard Class: 3
UN Pack Group: III

EMERGENCY RESPONSE

Transport Emergency Card: TEC (R)-30GF1-III
NFPA Code: H1; F2; R

STORAGE

Fireproof. Separated from strong oxidants, strong bases, strong acids. Keep in the dark.

IPCS
International Programme on Chemical Safety

WHO UNEP

SEE IMPORTANT INFORMATION ON BACK

2-METHOXYETHYL ACETATE

ICSC: 0476

IMPORTANT DATA

PHYSICAL STATE; APPEARANCE
COLOURLESS LIQUID , WITH CHARACTERISTIC ODOUR.

CHEMICAL DANGERS
The substance can presumably form explosive peroxides. Reacts with strong oxidants, strong bases.

OCCUPATIONAL EXPOSURE LIMITS
TLV: 0.1 ppm as TWA; (skin); (ACGIH 2007).
MAK: (sum of concentrations in air of 2-methoxyethanol and its acetate) 1 ppm, 4.9 mg/m³; H; Peak limitation category: II(8); Pregnancy risk group: B; (DFG 2009).

ROUTES OF EXPOSURE
The substance can be absorbed into the body by inhalation of its vapour, through the skin and by ingestion.

INHALATION RISK
A harmful contamination of the air can be reached rather quickly on evaporation of this substance at 20°C.

EFFECTS OF SHORT-TERM EXPOSURE
The vapour is mildly irritating to the eyes. The substance may cause effects on the bone marrow and central nervous system. The substance may cause effects on the blood , resulting in lesions of blood cells and kidney impairment at high levels. Exposure far above the OEL may result in unconsciousness.

EFFECTS OF LONG-TERM OR REPEATED EXPOSURE
The liquid defats the skin. The substance may have effects on the bone marrow and blood , resulting in lesions of blood cells and kidney impairment. May cause toxicity to human reproduction or development.

PHYSICAL PROPERTIES

Boiling point: 145°C
Melting point: -65°C
Relative density (water = 1): 1.01
Solubility in water: miscible
Vapour pressure, kPa at 20°C: 0.27
Relative vapour density (air = 1): 4.1

Relative density of the vapour/air-mixture at 20°C (air = 1): 1.01
Flash point: 45°C c.c.
Auto-ignition temperature: 380°C
Explosive limits, vol% in air: 1.5 (93°C) - 12.3 (93°C)
Octanol/water partition coefficient as log Pow: 0.121

ENVIRONMENTAL DATA

The substance is harmful to aquatic organisms.

NOTES

Check for peroxides prior to distillation; eliminate if found. Health effects of exposure to the substance have not been investigated adequately. Its effects are deduced from those of similar substances. Card has been partially updated in July 2009: see Occupational Exposure Limits.

ADDITIONAL INFORMATION

RÉSUMÉ D'ORIENTATION

Le présent CICAD[1] (Concise International Chemical Assessment Document / Document concis d'évaluation chimique internationale) relatif au 2-méthoxyéthanol a été préparé par Toxicology Advice & Consulting Ltd (Royaume-Uni). Il repose sur une documentation préparée dans le cadre du Programme d'évaluation des substances prioritaires prévu par la *Loi canadienne sur la protection de l'environnement* (LCPE) de 1999 (Environnement Canada & Santé Canada, 2002). Les évaluations de substances prioritaires prescrites par la LCPE ont pour objectif de déterminer les effets potentiels sur la santé humaine d'une exposition indirecte à ces substances dans l'environnement général ainsi que leurs effets sur cet environnement. Le document de base prend en compte les données relevées jusqu'à d'octobre 1999. Une recherche bibliographique exhaustive portant sur plusieurs bases de données en ligne a été effectuée en janvier 2004 afin de retrouver toute référence intéressante postérieure à celles qui sont prises en compte dans le document de base. Des renseignements sur la disponibilité du document de base et son examen par des pairs sont donnés à l'appendice 2. L'appendice 3 donne des indications sur l'examen par des pairs du présent CICAD. La première version du document a été examinée lors de la 12ème réunion du Comité d'évaluation finale qui s'est tenue à Hanoi (Viet Nam) du 30 septembre au 3 octobre 2004. La liste des participants à cette réunion figure à l'appendice 4. Des informations utiles à l'évaluation des effets sur la santé humaine ayant été publiées après l'achèvement de la recherche bibliographique effectuée pour le document de base, le Comité d'évaluation finale a recommandé que ces informations soient incorporées dans le document et que celui-ci soit réexaminé lors d'une autre de ses réunions. En conséquence, le document a été révisé puis soumis à un second examen par des pairs. Le CICAD a été examiné et approuvé en tant qu'évaluation internationale lors de la 13ème réunion du Comité d'évaluation finale qui a eu lieu à Nagpur (Inde) du 31 octobre au 3 novembre 2005. La liste des participants à cette réunion figure à l'appendice 5. Les fiches internationales sur la sécurité chimique du 2-méthoxyéthanol (ICSC 0061; IPCS, 2002) et de l'acétate de 2-méthoxyéthyle (ICSC 0476; IPCS, 2006) (qui est facilement métabolisé en 2-méthoxyéthanol) établies par le Programme international sur la sécurité chimique (IPCS/PISC) dans le cadre d'un processus distinct d'examen par des pairs, sont également reproduites dans le présent CICAD.

Le 2-méthoxyéthanol (Chemical Abstracts Service [CAS] No 109-86-4), se présente sous la forme d'un liquide incolore et volatil, très soluble dans l'eau. Autant qu'on sache, il n'existe pas à l'état naturel. Il est produit à des fins commerciales par réaction de l'oxyde d'éthylène sur le méthanol anhydre.

Selon les informations disponibles, le 2-méthoxyéthanol entre dans la composition de peintures, d'enduits et revêtements, d'encres, de produits de nettoyage, de vernis et encaustiques, de liquides pour freins et de carburéacteurs. On l'utilise aussi dans la fabrication de laminés pour circuits imprimés et il trouve par ailleurs de nombreuses applications comme solvant, comme intermédiaire de synthèse et comme solvant de couplage (tiers solvant) pour les mélanges et les formulations à base d'eau. Son usage recule toutefois depuis quelques années dans certains pays en raison de son remplacement par d'autres substances. Les programmes visant à réduire son utilisation ont conduit à largement restreindre sa présence dans les produits de consommation.

Les données de surveillance sur lesquelles baser une estimation de l'exposition de la population générale au 2-méthoxyéthanol restent limitées. On a procédé à des estimations de l'exposition due au contact avec certains milieux de l'environnement (eau et air essentiellement) et produits de consommation en partant de la situation la pire ou de la limite supérieure constatée pour l'exposition.

L'absorption transcutanée du 2-méthoxyéthanol peut constituer une importante voie d'exposition, en particulier sur le lieu de travail. Le 2-méthoxyéthanol est également facilement absorbé par inhalation ou par la voie orale et une fois absorbé, il se répartit très largement dans l'organisme.

Les principales voies métaboliques consistent en une oxydation conduisant au 2-méthoxyacétaldéhyde (MALD) et à l'acide 2-méthoxyacétique (MAA), qui en sont vraisemblablement les métabolites actifs. La présence d'acide 2-méthoxyacétique dans les urines constitue un bon indicateur spécifique de l'exposition. L'acide 2-méthoxyacétique est éliminé beaucoup plus lentement par l'organisme humain que par celui du rat.

Le 2-méthoxyéthanol présente une toxicité aiguë faible à modérée après exposition par la voie orale, respiratoire ou cutanée. Ce composé n'est guère capable de provoquer une irritation cutanée ou oculaire et il ne s'est pas révélé avoir d'effet sensibilisateur sur la peau. D'après la base de données relativement abondante dont on dispose au sujet de l'expérimentation animale de ce composé, ses principaux effets indésirables après une exposition répétée portent sur le sang, la reproduction et le développement, avec notamment une action sur la fécondité et des effets tératogènes. On a observé certaines anomalies à des niveaux d'exposition relativement faibles, souvent à la dose ou à la concentration la

[1] La liste des acronymes et abréviations utilisés dans le présent rapport figure à l'appendice 1.

plus faible qui ait été étudiée. Une étude à moyen terme consistant à exposer des rats à ce composé par la voie orale a révélé une dégénérescence testiculaire et des effets hématologiques à la plus faible dose étudiée. Une autre étude à moyen terme, par inhalation cette fois et avec des lapins, a également mis en évidence des effets toxiques sur les testicules, à la dose la plus faible étudiée. On a fixé à 32 mg/m^3 la concentration sans effet indésirable observé (NOAEC), le critère retenu étant les effets toxiques sur le développement d'animaux de laboratoire. L'expérimentation animale a également montré que le système immunitaire et le système nerveux constituent des cibles de l'action toxique de ce composé. On possède quelques indices évoquant une faible génotoxicité du 2-méthoxyéthanol pour les cellules somatiques, vraisemblablement par activation de l'acétaldéhyde qui constitue son métabolite intermédiaire. Même si, selon certaines indications, le 2-méthoxyéthanol provoque des lésions génétiques dans les cellules germinales de rats mâles à forte dose ou concentration, ces résultats ne sont pas concluants. Faute d'études à long terme sur l'animal, on n'a aucune certitude quant à la possibilité d'effets néoplasiques dus au 2-méthoxyéthanol.

Les données épidémiologiques sont limitées mais elles donnent à penser que chez des hommes et des femmes exposés au 2-méthoxyéthanol de par leur activité professionnelle, ce composé provoque des effets sur le système sanguin et sur la reproduction. On a constaté qu'il y avait clairement un lien entre les effets hématologiques observés dans un groupe de travailleurs et leur exposition au 2-méthoxyéthanol.

Des effets sur la numération des érythrocytes dans une population non exposée à d'autres alkoxyalcools ou substances chimiques notoirement toxiques pour la moelle osseuse ont été signalés à un niveau d'exposition pour lequel aucun effet sur la spermatogénèse n'a été observé. Les études effectuées comportent des données d'exposition fiables concernant les concentrations dans l'air et la teneur des urines en acide 2-méthoxyacétique mesurée sur le lieu de travail (qui constitue la mesure de l'absorption effective); ces données peuvent être utilisées pour caractériser le risque résultant d'une exposition au 2-méthoxyéthanol présent dans l'air.

Un net effet hémotoxique a été observé chez des travailleurs exposés (avec pondération en fonction du temps) à une concentration moyenne de 2-méthoxyéthanol égale à 113 mg/m^3, une tendance au retour à la normale étant constatée à un niveau d'exposition de 8,4 mg/m^3 et la récupération étant totale à 1,7 mg/m^3.

En prenant 1,7 mg/m^3 comme valeur de la NOAEC, en se basant sur une exposition continue et en appliquant un facteur d'incertitude de 10 pour tenir compte des variations interindividuelles, on arrive à une concentration tolérable de 0,04 mg/m^3. Comme il s'agit d'un effet facilement réversible et qu'il a été observé au bout d'une longue période d'exposition, il n'y a pas lieu d'appliquer un facteur d'incertitude supplémentaire qui prendrait en compte le fait qu'il n'y a pas exposition pendant toute la vie.

En dépit du caractère limité des données significatives, on peut considérer comme faible l'exposition de la population générale par contact avec les divers milieux de l'environnement, conséquence du recul de l'utilisation de ce composé signalé depuis quelques années et de son remplacement par des produits moins dangereux. On estime suffisante la marge de sécurité qui existe entre les estimations les plus pessimistes de l'exposition par contact avec les divers milieux de l'environnement et les valeurs à partir desquelles les paramètres hématologiques sont revenus à la normale chez les travailleurs exposés. Il en va de même pour la marge de sécurité entre les valeurs estimatives de l'exposition et les concentrations les plus faibles qui, selon les résultats des investigations toxicologiques sur des animaux de laboratoire, sont capables de provoquer des effets sur le développement. Même si les données disponibles sont insuffisantes pour que l'on puisse conclure qu'il existe une marge de sécurité suffisante entre les estimations de l'exposition due à des produits de consommation et les niveaux d'exposition donnant lieu à des effets hématologiques chez les travailleurs, de même qu'entre ces niveaux d'exposition et les niveaux les plus faibles qui produisent des effets sur les animaux de laboratoire, il importe de souligner que ces estimations correspondent à des situations qui sont de loin les pires et qu'elles n'ont pas été validées.

Les données relatives aux effets du 2-méthoxyméthanol sur les organismes aquatiques sont limitées. L'organisme le plus sensible dont il ait été fait état est un protozoaire flagellé, *Chilomonas paramecium*. On n'a pas trouvé de données concernant les effets du 2-méthoxyméthanol sur la faune et la flore terrestres.

Les effets environnementaux ont été évalués dans le cas des organismes terrestres, terricoles et aquatiques. En vue de procéder à une caractérisation prudente du risque pour la faune et la flore terrestres, on a comparé le niveau estimatif de l'exposition au 2-méthoxyméthanol présent dans l'air à la valeur toxicologique critique obtenue à partir d'une étude d'inhalation chez le lapin. Sur la base de cette évaluation, il a été conclu qu'à la concentration où il est présent dans l'air au Canada, le 2-méthoxyméthanol ne provoque vraisemblablement pas d'effets indésirables chez les diverses populations de la faune et de la flore sauvages.

L'évaluation relative aux organismes terricoles est fondée sur une relation quantitative structure-activité concernant des effets sur les organismes benthiques et

sur la concentration estimative du 2-méthoxyméthanol dans le sol au Canada. En se fondant sur cette évaluation, on a estimé qu'à la concentration où il est présent dans le sol au Canada, le 2-méthoxyméthanol n'a vraisemblablement pas d'effets indésirables sur les populations d'organismes terricoles.

En vue de procéder à une caractérisation prudente du risque pour les organismes aquatiques, on a comparé le niveau estimatif de l'exposition à la valeur toxicologique critique fournie par des études sur un protozoaire flagellé, *Chilomonas paramecium.* Sur la base de cette évaluation, on estime peu probable que les organismes aquatiques du Canada puissent subir des effets indésirables.

RESUMEN DE ORIENTACIÓN

El presente Documento Internacional Conciso sobre Evaluación de Sustancias Químicas (CICAD)[1] relativo al 2-metoxietanol fue preparado por Toxicology Advice & Consulting Ltd (Reino Unido) y se basa en la documentación preparada como parte del Programa de Sustancias Prioritarias en el marco de la *Ley Canadiense de Protección del Medio Ambiente, 1999* (CEPA) (Ministerios de Medio Ambiente y de Salud del Canadá, 2002). La evaluación de las sustancias prioritarias en el marco de la CEPA tiene por objeto determinar los efectos potenciales sobre la salud de la exposición indirecta en el entorno general, así como las repercusiones para el medio ambiente. En el documento original se examinaron los datos identificados hasta octubre de 1999. En enero de 2004 se realizó una búsqueda bibliográfica amplia en varias bases de datos en línea para identificar cualquier referencia importante publicada después de las incorporadas al documento original. La información sobre el carácter del examen colegiado y la disponibilidad de los documentos originales se presenta en el apéndice 2. La información relativa al examen colegiado del presente CICAD figura en el apéndice 3. El proyecto de documento se examinó en la 12ª reunión de la Junta de Evaluación Final, celebrada en Hanoi (Viet Nam) del 30 de septiembre al 3 de octubre de 2004. La lista de participantes en esta reunión figura en el apéndice 4. Dado que se había publicado información de interés sobre la evaluación en relación con la salud humana después de la fecha de conclusión de la búsqueda bibliográfica para el documento original, la Junta de Evaluación Final recomendó que se incorporara dicha información y que el documento se volviera a examinar en otra reunión de la Junta. El documento se revisó en consecuencia y se presentó a otro examen colegiado. Este CICAD se examinó y aprobó como evaluación internacional en la 13ª reunión de la Junta de Evaluación Final, celebrada en Nagpur (India) del 31 de octubre al 3 de noviembre de 2005. Los participantes en esta reunión figuran en el apéndice 5. También se reproducen en este documento las Fichas internacionales de seguridad química para el 2-metoxietanol (ICSC 0061; IPCS, 2002) y el 2-metoxietilacetato (ICSC 0476; IPCS, 2006) (que se metaboliza con rapidez a 2-metoxietanol), preparadas por el Programa Internacional de Seguridad de las Sustancias Químicas (IPCS) en un proceso de examen colegiado independiente.

El 2-metoxietanol (Servicio de Resúmenes Químicos [CAS] Nº 109-86-4) es un líquido incoloro volátil con una solubilidad en agua elevada; no parece encontrarse como producto natural. Se produce

[1] La lista de siglas y abreviaturas utilizadas en el presente informe figuran en el apéndice 1.

comercialmente por reacción del óxido de etileno con metanol anhidro.

Se ha informado de la utilización del 2-metoxietanol en pinturas, revestimientos, tintas, limpiadores, abrillantadores, líquidos de frenos y combustibles para reactores y en la fabricación de láminas para placas de circuitos impresos, y tiene una aplicación amplia como disolvente, intermediario químico y acoplador de disolventes en mezclas, así como en formulaciones acuosas. Sin embargo, su uso ha disminuido en los últimos años debido a que en algunos países se ha sustituido por otras sustancias. Los programas de reducción de su utilización han llevado a una restricción generalizada en los productos de consumo.

Los datos de vigilancia en los que se basan las estimaciones de la exposición de la población general al 2-metoxietanol son limitados. Se han establecido estimaciones para el caso peor o límite de la exposición a partir del medio ambiente (sobre todo el aire y el agua) y de los productos de consumo.

La absorción a través de la piel puede ser una vía importante de exposición, sobre todo en el entorno profesional. El 2-metoxietanol también se absorbe con rapidez por inhalación y por vía oral y tras la absorción se distribuye ampliamente por todo el organismo.

Las principales rutas metabólicas son la oxidación a 2-metoxiacetaldehído (MALD) y ácido 2-metoxiacético (MAA), probables metabolitos activos. La presencia de MAA en la orina es un indicador específico y adecuado de la exposición y su eliminación del organismo es mucho más lenta en las personas que en las ratas.

La toxicidad aguda del 2-metoxietanol tras la exposición oral, por inhalación o cutánea es entre baja y moderada. Tiene un potencial reducido de irritación cutánea u ocular y no se ha demostrado su actividad como sensibilizador cutáneo. De acuerdo con una base de datos relativamente amplia en animales de laboratorio, los principales efectos adversos en la salud tras la exposición repetida al 2-metoxietanol son hematológicos y de toxicidad reproductiva y en el desarrollo, con efectos tanto en la fertilidad como en la teratogenicidad. Se han observado algunos cambios con niveles relativamente bajos de exposición, con frecuencia la dosis o la concentración más baja sometida a prueba. En un estudio de duración media se observó degeneración testicular y efectos hematológicos tras la exposición oral de ratas a la dosis más baja sometida a prueba. En un estudio de exposición por inhalación de duración media con conejos, se observó toxicidad testicular con la concentración más baja utilizada. Para la toxicidad en el desarrollo en animales de laboratorio se estableció una concentración sin efectos adversos observados (NOAEC) de 32 mg/m^3. También se han identificado los sistemas inmunitario y nervioso como destinatarios de la toxicidad en animales de laboratorio. Hay algunos indicios de que el 2-metoxietanol pueda tener un efecto débilmente genotóxico en las células somáticas, probablemente mediante su activación para convertirse en acetaldehido, metabolito intermedio. Aunque hay algunos indicios de que el 2-metoxietanol puede provocar daños genéticos en las células germinales masculinas de ratas en dosis o concentraciones elevadas, los resultados de estos estudios no son concluyentes. En ausencia de investigaciones prolongadas en animales, hay dudas acerca de la capacidad del 2-metoxietanol para inducir efectos neoplásicos.

Los datos epidemiológicos son limitados, pero parecen indicar efectos hematológicos y reproductivos en los hombres y mujeres que en su trabajo están expuestos al 2-metoxietanol. En un estudio realizado con un grupo de trabajadores se ha informado de una asociación clara entre los efectos hematológicos y la exposición al 2-metoxietanol.

Se han descrito efectos en el número de glóbulos rojos en una población no expuesta a otros alcoxi-alcoholes o sustancias químicas con efectos conocidos en la médula ósea a niveles de exposición sin efectos observados en la espermatogénesis. Los estudios contienen datos fidedignos de la exposición en el puesto de trabajo tanto sobre las concentraciones en el aire como sobre la presencia de MAA en la orina (como medida de la absorción efectiva), que pueden servir de base para caracterizar el riesgo de la exposición al 2-metoxietanol suspendido en el aire.

Se observaron efectos hematotóxicos claramente definidos en trabajadores expuestos a una concentración media de 2-metoxietanol ponderada por el tiempo de 113 mg/m^3, con la recuperación parcial de la normalidad a un nivel de exposición de 8,4 mg/m^3 y la recuperación completa a 1,7 mg/m^3.

Si se toma el valor de 1,7 mg/m^3 como NOAEC, se ajusta para una exposición continua, y se aplica un factor de incertidumbre de 10 para la variación intraespecífica se puede derivar una concentración tolerable 0,04 mg/m^3. Dado que el efecto es fácilmente reversible y se ha observado tras una exposición prolongada, no se utiliza un factor de incertidumbre adicional para compensar la exposición inferior a la duración de toda la vida.

Aunque los datos pertinentes son limitados, cabe prever una exposición baja de la población general a través de los compartimentos del medio ambiente, gracias a la menor utilización notificada del compuesto en los últimos años, ya que se ha sustituido con sustancias menos peligrosas. Se considera que los

márgenes entre las estimaciones del caso peor de exposición a partir de los distintos compartimentos del medio ambiente y los niveles identificados a los cuales los parámetros hematológicos de los trabajadores expuestos habían vuelto a la normalidad, son adecuados, al igual que los obtenidos en las estimaciones de la exposición y los niveles más bajos con efectos para la toxicidad en el desarrollo obtenidos en investigaciones toxicológicas en animales de laboratorio. Si bien los datos disponibles son insuficientes para llegar a la conclusión de que hay márgenes adecuados entre las estimaciones de la exposición a partir de los productos de consumo y los niveles asociados a los efectos hematológicos en los trabajadores y entre estos niveles de exposición y los niveles más bajos con efectos identificados en los estudios de laboratorio, hay que subrayar que las estimaciones del caso peor son extremas y no se han validado.

Los datos relativos a los efectos del 2-metoxietanol en los organismos acuáticos son limitados. Se ha notificado que el protozoo flagelado *Chilomonas paramecium* es el organismo más sensible. No hay datos sobre los efectos del 2-metoxietanol en la flora y fauna silvestres terrestres.

Se han evaluado los efectos en los organismos terrestres, del suelo y acuáticos a partir del medio ambiente. En una caracterización del riesgo prudente para la flora y fauna silvestres terrestres, se comparó el valor estimado de la exposición al 2-metoxietanol en el aire con un valor crítico de la toxicidad basado en un estudio de inhalación en conejos. Sobre la base de esta evaluación se determinó que es poco probable que las concentraciones de 2-metoxietanol en el aire en el Canadá provoquen efectos adversos en las poblaciones de flora y fauna silvestres.

La evaluación para los organismos del suelo se basó en una relación cuantitativa entre la estructura y la actividad para los efectos sobre los organismos bentónicos y una concentración estimada de 2-metoxietanol en el suelo en el Canadá. Tomando como base esta evaluación, se determinó que es poco probable que las concentraciones de 2-metoxietanol en el suelo en el Canadá provoquen efectos adversos en las poblaciones de organismos que se encuentran en él.

En una caracterización del riesgo prudente para los microorganismos acuáticos, se comparó el valor estimado de la exposición con el valor crítico de la toxicidad basado en los estudios con el protozoo flagelado *Chilomonas paramecium*. Sobre la base de esta evaluación se consideró que era poco probable que provocara efectos adversos en las poblaciones de organismos acuáticos en el Canadá.

PART C

2-ETHOXYETHANOL AND 2-PROPOXYETHANOL

1. EXECUTIVE SUMMARY

This Concise International Chemical Assessment Document (CICAD)[1] on 2-ethoxyethanol and 2-propoxyethanol was prepared by Toxicology Advice & Consulting Ltd, United Kingdom. For 2-ethoxyethanol, it is based on documentation prepared as part of the Priority Substances Program under the *Canadian Environmental Protection Act, 1999* (CEPA) (Environment Canada & Health Canada, 2002). The objective of assessments on priority substances under CEPA is to assess potential effects of indirect exposure in the general environment on human health as well as environmental effects. Data identified as of January 2000 were considered in the source document. The sections on 2-propoxyethanol are based on the consensus report prepared by the Criteria Group for Occupational Standards in Sweden (Lundberg, 1994). A comprehensive literature search of several online databases was conducted in January 2004 to identify any key references published subsequent to those incorporated in the source documents. Information on the nature of the peer review and the availability of the source documents is presented in Appendix 2. Information on the peer review of this CICAD is presented in Appendix 3. This CICAD was considered at the 12th Final Review Board meeting held in Hanoi, Viet Nam, on 28 September – 1 October 2004. Participants at the 12th Final Review Board meeting are given in Appendix 4. The draft was revised according to the views presented at that meeting, and the new draft was again peer reviewed. Finally, the CICAD was considered and approved as an international assessment at the 13th Final Review Board meeting, held in Nagpur, India, on 31 October – 3 November 2005. Participants at the 13th Final Review Board meeting are given in Appendix 5. The International Chemical Safety Cards for 2-ethoxyethanol (ICSC 0060; IPCS, 2002), 2-ethoxyethyl acetate (which is readily metabolized to 2-ethoxyethanol) (ICSC 0364; IPCS, 2006) and 2-propoxyethanol (ICSC 0607; IPCS, 2004), produced by the International Programme on Chemical Safety (IPCS) in a separate, peer-reviewed process, have also been reproduced in this document.

2-Ethoxyethanol (Chemical Abstracts Service [CAS] No. 110-80-5) and 2-propoxyethanol (CAS No. 2807-30-9) are colourless liquids that are completely miscible with water and have low octanol/water partition coefficients (K_{ow}). They have not been reported to occur as natural products. 2-Ethoxyethanol is produced commercially from ethylene oxide and excess anhydrous ethanol.

2-Ethoxyethanol has been reported to be used in paints, coatings, inks, cleaners, polishes, brake fluids and jet fuels and to find wide application as a solvent, chemical intermediate and solvent coupler of mixtures and water-based formulations. Its presence in consumer products is generally regarded as unacceptable, and use reduction programmes have led to widespread restriction in such uses. The production and use of 2-ethoxyethanol as a solvent in industry may result in its release to the environment through various waste streams.

2-Propoxyethanol is used in lubricants, paints, surface coatings and polishes. The production and use of 2-propoxyethanol in industry may result in its release to the environment through various waste streams.

Monitoring data on which to base estimates of exposure of the general population to 2-ethoxyethanol are limited. Estimates of exposure from environmental media (essentially air and water) and consumer products have been developed. Occupational exposure data are available for a number of production and product use scenarios.

Information on which to base estimates of exposure of the general population to 2-propoxyethanol was not identified.

Absorption of 2-ethoxyethanol through the skin can be a major route of exposure, particularly in the occupational setting. 2-Ethoxyethanol is also readily absorbed via the inhalation and oral routes and, following absorption, is distributed extensively throughout the body.

Based on in vitro studies, it is likely that 2-propoxyethanol is rapidly absorbed through the skin.

The major metabolic pathways of 2-ethoxyethanol involve oxidation to 2-ethoxyacetaldehyde (EALD) and 2-ethoxyacetic acid (EAA), the likely active metabolites. There is some indication that humans may absorb the inhaled substance to a greater extent than do rats and that it may be converted to EAA at a greater rate in humans than in rats, with subsequent elimination being slower in humans.

No data on the metabolism of 2-propoxyethanol were identified, but it is thought that alcohol dehydrogenase and aldehyde dehydrogenase will be involved.

2-Ethoxyethanol is of low to moderate acute toxicity following oral exposure, but is of low toxicity only following inhalation or dermal exposure. It has low potential for causing skin or eye irritation and has not been shown to be a skin sensitizer. 2-Ethoxyethanol has consistently induced haematological, reproductive (effects on testes and sperm parameters and estrous cyclicity) and developmental effects in multiple species

[1] For a list of acronyms and abbreviations used in this report, please refer to Appendix 1.

of laboratory animals exposed by various routes. Mice appear to be less sensitive than rats to the effects of 2-ethoxyethanol. EAA formed during the metabolism of 2-ethoxyethanol is presumed to be responsible for the significant reproductive, developmental and haematological effects observed in experimental animals. The available information on the genotoxicity of 2-ethoxyethanol suggests that it may have some potential to induce cytogenetic damage in vitro, although this was not reflected in in vivo studies in mice. There is no evidence that it induces mutations. Adequate long-term studies for carcinogenic potential are lacking.

2-Propoxyethanol is of low acute toxicity by the oral, inhalation and dermal routes of exposure. It does not appear to be a significant irritant to the skin or a skin sensitizer. It was an eye irritant to rabbits. The principal effect following repeated exposure to 2-propoxyethanol involves the blood. No data on genotoxicity or carcinogenicity were identified. In a limited study, no embryotoxicity, fetotoxicity or teratogenicity was noted, but a small number of skeletal aberrations were observed in the fetuses at dose levels that also induced toxicity to the dams.

Although epidemiological data are limited, there is a suggestion that the blood and male reproductive system are also targets of 2-ethoxyethanol toxicity in humans. Reduced sperm production was observed in workers exposed to mean 2-ethoxyethanol concentrations of 9.9 or 24 mg/m^3. Blood effects were observed in shipyard painters exposed to a mean 2-ethoxyethyl acetate concentration equivalent to 11 mg 2-ethoxyethanol/m^3. It should be recognized, however, that these studies also involved exposure to other substances.

The studies in humans are too limited for the development of a tolerable intake or concentration for 2-ethoxyethanol. From developmental toxicity studies in rats and rabbits, a no-observed-adverse-effect concentration (NOAEC) of 40 mg/m^3 may be derived. Adjusting for continuous exposure and using uncertainty factors for interspecies (10) and interindividual (10) variation, a tolerable concentration of 0.1 mg/m^3 can be derived.

The available information does not allow development of a tolerable intake or concentration for 2-propoxyethanol.

The limitations of the available monitoring data for 2-ethoxyethanol preclude the development of reliable estimates of typical exposure of the general population. Using a crude upper-bounding estimate of exposure to 2-ethoxyethanol in the general environment (based on the detection limit in a multimedia exposure study), the margin between this and the tolerable concentration is approximately 30. If the tolerable concentration is compared with the highest concentration of 2-ethoxyethanol actually detected in ambient air in Canada (detected outside of an automotive plant), this margin would be approximately 120. However, based on uncertain data on composition of sample consumer products that may contain the substance, worst-case estimates of exposure to 2-ethoxyethanol from the use of these may exceed the tolerable concentration. The degree of confidence in these estimates of exposure is, however, extremely low, and limited available data indicate that 2-ethoxyethanol is no longer commonly present in consumer products in Canada, the United States of America (USA) or the European Union (EU). Occupational settings may still present a possibility for exposure, however, and production and product use scenarios suggest that levels in the workplace may exceed effect levels in humans.

Only limited data were available on effects of 2-ethoxyethanol on aquatic organisms. Critical toxicity values (CTVs) from studies in mammalian laboratory animals have been used as surrogates for the terrestrial environment. Based on estimated exposure values (EEVs) for terrestrial biota, soil and the aquatic environment in Canada, conservative risk characterizations established that concentrations of 2-ethoxyethanol were unlikely to cause adverse effects on relevant populations of wildlife.

The very limited ecotoxicological data and absence of environmental concentration data do not permit environmental risk assessment of 2-propoxyethanol.

2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES

2-Ethoxyethanol (Chemical Abstracts Service [CAS] No. 110-80-5; $C_4H_{10}O_2$; 2-ethoxy-l-ethanol, ethylene glycol monoethyl ether, ethyl cellosolve) is a colourless liquid of relative molecular mass 90.1 and is completely miscible in water (Kirk-Othmer, 1980). 2-Ethoxyethanol has a log octanol/water partition coefficient (K_{ow}) of −0.32 (Hansch et al., 1995), a vapour pressure of 710 Pa at 25 °C (Riddick et al., 1986) and a calculated Henry's law constant of 0.213 Pa·m^3/mol (DMER & AEL, 1996). The conversion factors[1] for 2-

[1] In keeping with World Health Organization (WHO) policy, which is to provide measurements in Système international d'unités (SI) units, all concentrations of gaseous chemicals in air will be given in SI units in the CICAD series. Where the original study or source document has provided concentrations in SI units, these will be cited here. Where the original study or source document has provided concentrations in volumetric units, conversions will be done using the conversion factors

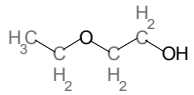
ethoxyethanol in air are 1 part per million (ppm) = 3.75 mg/m^3 and 1 mg/m^3 = 0.267 ppm. The conversion factors for ethoxyethyl acetate are 1 ppm = 5.45 mg/m^3 and 1 mg/m^3 = 0.183 ppm. 2-Ethoxyethyl acetate is readily hydrolysed to 2-ethoxyethanol, and data on this compound are therefore included where appropriate.

2-Propoxyethanol (CAS No. 2807-30-9; $C_5H_{12}O_2$; ethylene glycol propyl ether, EGPE, propyl glycol, propyl oxitol, propyl cellosolve) is a volatile, colourless liquid with a mild, ether-like aroma and a bitter taste. It is miscible with water and has a low octanol/water partition coefficient (estimated log K_{ow} 0.075), a vapour pressure of 130–387 Pa at 20–25 °C and a calculated Henry's law constant of 1.5–7.5 × 10^{-3} Pa·m^3/mol (HSDB, 2004; OECD, 2004). The conversion factors for 2-propoxyethanol in air are 1 ppm = 4.3 mg/m^3 and 1 mg/m^3 = 0.23 ppm. The conversion factors for 2-propoxyethyl acetate, the acetate ester of 2-propoxyethanol, in air are 1 ppm = 6.1 mg/m^3 and 1 mg/m^3 = 0.16 ppm.

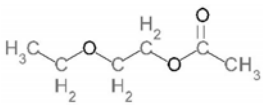
Additional physical and chemical properties are presented in the International Chemical Safety Cards reproduced in this document.

The structural formulae are shown below:

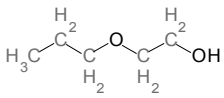
2-Ethoxyethanol



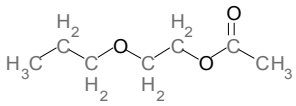
2-Ethoxyethyl acetate



2-Propoxyethanol



2-Propoxyethyl acetate



3. ANALYTICAL METHODS

Several analytical procedures used for the determination of 2-ethoxyethanol, 2-ethoxyethyl acetate and their major metabolite, ethoxyacetic acid (EAA), in various environmental media are summarized in Table 1. In some reports, the useful range was indicated, but not the limit of detection.

In reporting the methods validated by NIOSH (1994), only the range that has been confirmed as accurate is shown. However, these methods may be capable of measuring much lower levels of glycol ethers in air, providing adequate sampling times are employed and desorption efficiencies are ascertained. The limit of detection is given as 0.7 µg/sample.

Metabolites of 2-ethoxyethanol in urine have been measured using either gas chromatography (Smallwood et al., 1984, 1988; Groeseneken et al., 1986a, 1989) or high-performance liquid chromatographic analysis (Cheever et al., 1984). The detection limit for gas chromatography–flame ionization detection analysis was 5.0 mg/kg for EAA (Smallwood et al., 1984). Cheever et al. (1984) analysed urine samples directly at pH 3 by high-performance liquid chromatography for EAA after animals were dosed with 230 mg 2-ethoxyethanol/kg body weight, but no limit of detection or appropriate range for use was reported. However, this method may be useful for biological monitoring of exposed populations.

4. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

2-Ethoxyethanol has not been reported to occur as a natural product (USEPA, 1986; IPCS, 1990). There are no known reactions that would lead to the in situ production of 2-ethoxyethanol, 2-propoxyethanol or other glycol ethers in the atmosphere (Rogozen et al., 1987).

4.1 2-Ethoxyethanol

Limited information on production and use of 2-ethoxyethanol, mostly from the source country of the national assessment on which the text on 2-ethoxyethanol in this document is based (Canada), is presented here.

2-Ethoxyethanol is produced commercially by the reaction of ethylene oxide with anhydrous ethanol (Boatman & Knaak, 2001). 2-Ethoxyethanol was not produced in Canada in 1995 or 1996, according to data reported to Environment Canada by 14 companies in a survey carried out under the 1988 *Canadian Environmental Protection Act* (Environment Canada, 1997a). According to these data, importation of 2-ethoxyethanol totalled 4700 tonnes in 1995 and 3000 tonnes in 1996. There was no export of 2-ethoxyethanol in 1995, and 2.3 tonnes were exported in 1996. IPCS (1990) reported that the production of 2-ethoxyethanol in 1986 in the United States of America (USA), western Europe and Japan amounted to 79 000 tonnes, 116 000 tonnes and 9800 tonnes, respectively. In 1996, the production of 2-

given here, assuming a temperature of 20 °C and a pressure of 101.3 kPa. Conversions are to no more than two significant digits.

Table 1. Analytical methods for selected glycol ethers and their metabolites.

Matrix	Sampling method extraction/cleanup	Analytical method	Limit of detection and/or useful range[a]	Reference
Air (2-EE)	Adsorption on charcoal, elution with methylene chloride, carbon disulfide or methylene chloride; methanol	GC-FID	Range: 340–1460 mg/m^3	NIOSH (1994)
Air (2-EE)	Inhaled or expired air pumped through silica gel, desorbed with methanol (88% efficient)	GC-FID	NR	Groeseneken et al. (1986b)
Air (2-EE)	Diffusive sampling, adsorption on Tenax, thermal desorption	GC-FID	Range: 5–20 mg/m^3	Hamlin et al. (1982)
Air (2-EE)	Personal monitors with pump adsorption on Tenax, thermal desorption	GC-FID	Range: 0.5–250 mg/m^3	Health and Safety Executive (1988)
Water (2-EEA)	Direct analysis of aqueous solutions	HPLC-UV	5 mg/l; range: 5–1000 mg/l	Bailey et al. (1985)
Blood (2-EE)	Methylene chloride extraction in presence of anhydrous sodium sulfate; average recovery 84%	GC-FID	5.0 mg/kg; range 6–895 mg/kg	Smallwood et al. (1984)
Blood (2-EE)	Headspace elution	GC-FID	NR	Denkhaus et al. (1986)
Urine (EAA)	Methylene extraction followed by derivatization with pentafluorobenzyl bromide	GC-FID	5.0 mg/l; range 10–1000 mg/l	Smallwood et al. (1984)
Urine (EAA)	Lyophilization followed by derivatization with pentafluorobenzyl bromide	GC-FID	0.03 mg/l; range 0.1–200 mg/l	Groeseneken et al. (1989)

EAA = 2-ethoxyacetic acid; 2-EE = 2-ethoxyethanol; 2-EEA = 2-ethoxyethyl acetate; GC-FID = gas chromatography–flame ionization detector; HPLC-UV = high-performance liquid chromatography with ultraviolet light detection; NR = not reported.

[a] Only the range that has been confirmed as accurate is shown. These methods may be capable of measuring much lower levels of glycol ethers in air providing adequate sampling times are employed and desorption efficiencies are ascertained.

ethoxyethanol in the USA was reported to be 14 500 tonnes (Chinn et al., 1996). OSHA (2003) reported that the peak production of 2-ethoxyethanol in the USA occurred in 1980 and amounted to 79 000 tonnes; in 1999, production amounted to 24 000 tonnes.

2-Ethoxyethanol has been used in paints, coatings, inks, cleaners, polishes, brake fluids and jet fuels and has been widely used as a solvent, chemical intermediate and solvent coupler of mixtures and water-based formulations (Stemmler et al., 1997). Data reported to Environment Canada indicated that 68.2 and 42.8 tonnes of 2-ethoxyethanol were used in Canada in 1995 and 1996, respectively, mainly as a component of formulated products (Environment Canada, 1997a). It is unclear, however, why there is a large discrepancy between these figures and those for the corresponding imports. In 2002, the consumption of 2-ethoxyethanol was 10.4, 0.5, 2.9 and 13.8 kilotonnes for the USA, western Europe, Japan and total, respectively (Chinn, 2004). According to data from the Substances in Preparations in Nordic Countries (SPIN) database (http://195.215.251.229/DotNetNuke/default.aspx), total uses in Denmark, Finland, Sweden and Norway for 2002 were approximately 140 tonnes (in 94 preparations), 100 tonnes (in 12 preparations), 7 tonnes (in 29 preparations, including those for consumer use) and 1.6 tonnes (in 13 preparations), respectively. Use categories registered in these countries included solvents, paints, lacquers and varnishes, process regulators, cleaning/washing agents, adhesives, binding agents, fillers and surface treatment products.

In the European Union (EU), there is one production site, based on information current in 2000, and the compound is imported by another company from outside the EU. It has been estimated that approximately 5000 tonnes are used annually within the EU. Use patterns reported in 2000 were as follows: 45% processed to intermediates in the chemical industry; 35% as a solvent in paints, lacquers and varnishes; 13% for solvent use in the chemical industry; and 7% as a solvent in the printing industry. A voluntary programme to control the application and use of 2-ethoxyethanol and 2-ethoxyethyl acetate within the EU has restricted their sale for use in consumer goods and household products, cosmetics, pesticide formulations, pharmaceutical preparations and medicines, photo-resist mixtures for semiconductor fabrication and other applications where exposure is poorly controlled (BfR, 2003).

In 1994, total on-site environmental releases of 2-ethoxyethanol reported to the Canadian National Pollutant Release Inventory (NPRI) amounted to 2.36 tonnes. Most of this (at least 81%) was released into the atmosphere from four facilities (producing plastics and synthetic resins, paint and varnish, petroleum products and printing ink) in Quebec (NPRI, 2000).

In 1995, total on-site environmental releases of 2-ethoxyethanol reported to the NPRI amounted to 8.1 tonnes (NPRI, 2000), almost all of which was released into the atmosphere as emissions from storage from one facility (plastics manufacturing) in Ontario.

In 1996, total on-site environmental releases of 2-ethoxyethanol reported to the NPRI were 0.2 tonne, released about equally from two facilities (producing motor vehicle stampings and industrial and household chemicals) in Ontario and Quebec (NPRI, 2000). Preliminary releases reported for 1997 totalled 9.32 tonnes, from two printing ink industries in Ontario and Quebec (NPRI, 2000).

In 2001, 47 tonnes of 2-ethoxyethanol were emitted to the atmosphere from various locations in the USA, 0.02 tonne was released to surface waters, 0.25 tonne was released to land, 42 tonnes were released on site, 1.5 tonnes were released off site and 49 tonnes were released on and off site (USEPA, 2003).

According to data reported in a survey under the 1988 *Canadian Environmental Protection Act* (with different reporting requirements from the NPRI), 5.8 tonnes of 2-ethoxyethanol were released to landfills in 1996, whereas 3.9 tonnes were released as waste and 0.9 tonne was released to air from several facilities in Ontario and Quebec (Environment Canada, 1997a).

The Canadian Chemical Producers' Association (1999a) reported total environmental emissions of 2-ethoxyethanol of 0.3, 0.015, 0.015 and 0.013 tonne from a single member company in 1992, 1993, 1994 and 1995, respectively, all of which were released to air. Reported emissions fell to 0 tonnes in 1996 (Canadian Chemical Producers' Association, 1999a), totalled 0.003 tonne in 1997 and returned to 0 tonnes in 1998 (Canadian Chemical Producers' Association, 1999b).

4.2 2-Propoxyethanol

2-Propoxyethanol is produced commercially by the reaction of ethylene oxide with anhydrous *n*-propanol (OECD, 2004).

The production capacity of 2-propoxyethanol in the USA was in the category of 4540–27 200 tonnes in 2002; no production was known to take place in the EU (OECD, 2004).

Only very limited information on production and use of 2-propoxyethanol from the source country of the national assessment on which the text on 2-propoxyethanol in this document is based (Sweden) is available.

2-Propoxyethanol and its acetate ester, 2-propoxyethyl acetate, are not used to a great extent in Sweden. 2-

Propoxyethanol was identified in seven chemical products (lubricants, paints, surface coatings, polishes), with an estimated produced/imported amount of 1–2 tonnes in 1992. 2-Propoxyethyl acetate was registered in two products, but no importation or production occurred during 1992 (U. Rick, personal communication, Swedish National Chemicals Inspectorate, undated). According to the United States National Institutes of Health Household Products Database, 2-propoxyethanol is found in the USA in the following products: liquid adhesives at 1–3% concentration; varnish at 4–6% concentration; liquid sander at 5–10% concentration; stone sealer (concentration not given); liquid window cleaner at 0.1–1% concentration; and carpet spot and stain remover at 1–5% concentration (OECD, 2004).

5. ENVIRONMENTAL TRANSPORT, DISTRIBUTION AND TRANSFORMATION

5.1 2-Ethoxyethanol

2-Ethoxyethanol's production and use as a solvent in the coatings industry may result in its release to the environment through various waste streams (HSDB, 2004).

The half-life of 2-ethoxyethanol in air has been estimated at between about 5 h and 4 days, based on reaction with hydroxyl radicals (USEPA, 1985; Howard et al., 1991). An atmospheric half-life of 9.8 h was determined in a smog chamber with irradiation at a 2-ethoxyethanol to nitrogen oxides ratio of 2:1 (Joshi et al., 1982).

Howard et al. (1991) estimated half-lives of 2-ethoxyethanol of 7–28 days and 14–56 days in surface water and groundwater, respectively, based on unacclimated aerobic biodegradation. Because of the high water solubility of 2-ethoxyethanol and its low log K_{ow}, physical adsorption to suspended solids and sediments should not be significant (USEPA, 1985).

A soil sorption coefficient (K_{oc}) of 113 was calculated for 2-ethoxyethanol using the method of Sabljic (1984), indicating moderate mobility in soil (USEPA, 1985). Retention values for 2-ethoxyethanol in 21 New Zealand and Fijian soils ranged from 8 to 178 mg/g; these values were well correlated with the cation exchange capacity and a number of measures of moisture content of these soils (Churchman & Burke, 1991).

There is little information available on the biodegradation of 2-ethoxyethanol in soil. Howard et al. (1991) estimated a half-life for 2-ethoxythanol in soil of 7–28 days, based on unacclimated aerobic biodegradation. 2-Ethoxyethanol underwent bio-oxidation to EAA by the soil bacterium *Alcaligenes* MC11, for which 2-ethoxyethanol was a source of carbon (Harada & Nagashima, 1975). *Pseudomonas* sp. 4-5-3, *Xanthobacter autotrophicus* EC1-2-1 and a bacterium identified only as "strain MC2-2-1" could also use 2-ethoxyethanol as a source of carbon for aerobic growth (Kawai, 1995).

A bioconcentration factor (BCF) of 0.3 may be estimated for 2-ethoxyethanol, based on a log K_{ow} value of −0.32 using the equation proposed by Lyman et al. (1982) (i.e. log BCF = 0.76 log K_{ow} − 0.23). Bioaccumulation of 2-ethoxyethanol in aquatic organisms would therefore not be significant.

The environmental partitioning of 2-ethoxyethanol when released into air, water or soil was estimated by a Level III fugacity model (DMER & AEL, 1996). If 2-ethoxyethanol is emitted into air, Equilibrium Criterion (EQC) Level III fugacity modelling (Mackay et al., 1996) predicts that about 50% would be present in air, whereas approximately 25% would be present in soil and about 25% in water. If 2-ethoxyethanol is emitted into water, more than 99% would be present in water. If 2-ethoxyethanol is released to soil, about 75% would be present in the soil, whereas approximately 25% would be present in water (DMER & AEL, 1996).

5.2 2-Propoxyethanol

2-Propoxyethanol's production and use as a solvent in the coatings industry may result in its release to the environment through various waste streams (HSDB, 2004).

If released to soil, 2-propoxyethanol is expected to have very high mobility. Volatilization from moist soil surfaces is not expected to be important, given an estimated Henry's law constant of 1.5×10^{-3} Pa·m^3/mol, but volatilization from dry soil surfaces may occur, based on an experimental vapour pressure of 387 Pa. 2-Propoxyethanol may biodegrade quickly in soil and water (based on biodegradation studies with the related alkoxyethanol, 2-butoxyethanol) (HSDB, 2004).

If released to water, 2-propoxyethanol is not expected to adsorb to suspended solids and sediment, and it will be essentially non-volatile from water surfaces. An estimated BCF value of 0.7, calculated using the equation given above by Lyman et al. (1982) and an estimated log K_{ow} of 0.08, suggests that 2-propoxyethanol will not bioconcentrate in aquatic organisms.

If released to the atmosphere, 2-propoxyethanol will exist as a vapour. Vapour-phase 2-propoxyethanol is degraded in the atmosphere by reaction with photochemically produced hydroxyl radicals. The rate constant for this reaction has been estimated as 2.2×10^{-11}

cm^3/molecule per second at 25 ºC. This corresponds to an atmospheric half-life of about 18 h at an atmospheric concentration of 5×10^5 hydroxyl radicals/cm^3 (HSDB, 2004).

Output from the EPIWIN Level III fugacity model suggested that 2-propoxyethanol is likely to be distributed to water (52.9%), soil (45.4%), air (1.58%) and biota (0.0891%). Estimated half-lives in air, water, soil and sediment were 12 h, 15 days, 15 days and 60 days, respectively (OECD, 2004).

6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

6.1 Environmental levels

6.1.1 2-Ethoxyethanol

Few data on levels of 2-ethoxyethanol in the environment have been identified. One study was conducted in Canada to determine concentrations of 2-ethoxyethanol in multiple media to which humans are exposed, including drinking-water and indoor and outdoor air (Conor Pacific Environmental Technologies Inc., 1998). Thirty-five participants were randomly selected from the Greater Toronto area in Ontario, six from Queens Subdivision in Nova Scotia and nine from Edmonton, Alberta. For each participant, samples of drinking-water, beverages and indoor, outdoor and personal air were collected over a 24-h period; however, samples of food were not analysed for 2-ethoxyethanol. Although confidence in the results of this survey was low, the concentration of 2-ethoxyethanol was below the method detection limit (0.05 µg/l) in all samples of drinking-water. Similarly, it was not detected (detection limit 3.6 µg/m^3) in any samples of indoor, outdoor or personal air. 2-Ethoxyethanol was not detected in composite beverage samples (method detection limit 3.3 µg/l).

In an air quality study in Canada, the concentrations of 2-ethoxyethanol were measured in 24 samples of ambient air collected in the vicinity of an automotive plant and in 7 samples collected in downtown Windsor, Ontario (OMEE, 1994). Concentrations of 2-ethoxyethanol were less than the limit of detection (0.81 µg/m^3) in all the samples collected in downtown Windsor. Of the 24 samples collected at the automotive plant, concentrations of 2-ethoxyethanol were above the limits of detection (which ranged from 0.18 to 0.34 µg/m^3) in 16 (over 66%) samples; the mean value for these samples was 0.43 µg/m^3 when concentrations in samples where 2-ethoxyethanol was not detected were assumed to be equivalent to one half the limit of detection (maximum 0.86 µg/m^3). The authors stated that the probable sources of 2-ethoxyethanol in ambient air samples downwind of the plant were paints and lacquers in which 2-ethoxyethanol is used as a solvent. In all of the samples from downtown Windsor or in the vicinity of the automotive plant, concentrations of 2-ethoxyethyl acetate, the acetate derivative of 2-ethoxyethanol, were below the limits of detection (range 0.55–2.9 µg/m^3).

2-Ethoxyethanol was not detected in samples of ambient air collected at six public buildings from various locations in the USA in 1984–1985 (limit of detection 0.25 µg/m^3) (Sheldon et al., 1988).

In northern Italy, six indoor air samples collected from homes in 1983–1984 contained 2-ethoxyethanol at concentrations up to 60 µg/m^3 (De Bortoli et al., 1986). 2-Ethoxyethanol was detected at concentrations up to 18.3 µg/m^3 in indoor air samples collected in new buildings (hospital, office, nursing home) in the USA. In older buildings (office, nursing home, school), concentrations were lower (i.e. up to 4.15 µg/m^3) (Sheldon et al., 1988).

Samples of water from a polluted river in Japan contained 2-ethoxyethanol at concentrations of 250–1200 µg/l (Yasuhara et al., 1981).

Available data suggest that 2-ethoxyethanol and its acetate are not commonly present in consumer products in many parts of the world. 2-Ethoxyethanol was not detected in the emissions of 13 consumer products, including window cleaners, all-purpose cleaners, paints, nail polish removers and hair dye (classes of products reported to contain glycol ethers, based on available information), purchased in Ottawa, Canada (Cao, 1999). Of the cosmetic products registered for use in Canada, one nail polish contained 2-ethoxyethanol in the reporting category of >0.3–1%, whereas 2-ethoxyethyl acetate was present in an eye makeup product and a skin moisturizer in the >30 and >1–3% reporting categories, respectively (Health Canada, 2001). 2-Ethoxyethanol is a component in 26 wood preservatives registered for use in Canada (<1.25%) (Ballantine, 1997; Health Canada, 1998a).

Earlier information from the USA indicated that concentrations of 2-ethoxyethanol up to 5% could be found in various consumer products, including hard surface cleaners, floor polishes and windshield washing fluid (Flick, 1986). However, in a more recent listing of ingredients in “advanced” cleaning product formulations, none of the products contained 2-ethoxyethanol or 2-ethoxyethyl acetate (Flick, 1994). (It should be noted that these data were submitted voluntarily by numerous companies and other organizations and may not represent a comprehensive list of formulations of consumer products available in the USA.) Additional data on emissions of 2-ethoxyethanol and its acetate from

several consumer products tested in the USA are presented in Table 2 (although no information was provided in the secondary account regarding the number of products examined). Within the EU, a voluntary programme restricts the sale of 2-ethoxyethanol and 2-ethoxyethyl acetate in goods for consumer use and other applications where exposure is poorly controlled. According to the Products Register in Sweden, 2-ethoxyethanol and its acetate were listed as components of consumer products in 2001 and 2002 (SPIN; http://195.215.251.229/DotNetNuke/default.aspx).

Environmental concentrations of 2-ethoxyethanol have been estimated by ChemCAN4 modelling (DMER & AEL, 1996). This is a Level III fugacity-based regional model developed to estimate the environmental fate of chemicals in Canada. The highest reported recent (before 1997) release of 2-ethoxyethanol in Canada is 8 tonnes/year, released into the air by one facility in southern Ontario in 1995 (NPRI, 1998). "Ontario – Mixed Wood Plain" was selected as the geographical region for ChemCAN4 modelling. The input rate was 0.913 kg 2-ethoxyethanol/h, all to the atmosphere. Chemical input values were as follows: molecular weight, 90.1 g/mol; vapour pressure, 710 Pa; water solubility, 300 000 mg/l; log K_{ow}, −0.32; Henry's law constant, 0.213 Pa·m^3/mol; half-life in air, 55 h; half-life in water, 550 h; half-life in soil, 550 h; and half-life in sediment, 1700 h. Environmental characteristics were as follows: total surface area, 169 000 km^2; percentage covered by water, 43.8%; average air height, 2 km; average water depth, 20 m; average soil depth, 10 cm; residence time in air, 1.71 days; residence time in water, 618 days; environmental temperature, 7.4 ºC. Environmental concentrations of 2-ethoxyethanol in southern Ontario predicted by ChemCAN4 modelling are as follows: 6.9×10^{-2} ng/m^3 in air; 2.2×10^{-5} µg/l in water; 4.15×10^{-4} ng/g dry weight in soil; and 1.05×10^{-5} ng/g dry weight in sediments. The ChemCAN4 model estimates average concentrations throughout the region; therefore, actual concentrations in the vicinity of releases will be higher than those estimated by the model.

Industrial activities using 2-ethoxyethanol present opportunities for occupational exposure. Exposure ranges depend on the particular operation and the risk reduction measures in use. At a facility in the EU involved in the production of 2-ethoxyethanol, 8-h time-weighted average (TWA) concentrations (70 samples taken between 1998 and 2000) were <0.01–5.3 mg/m^3 (median 0.01 mg/m^3; 95th percentile 3.0 mg/m^3) (BfR, 2003).

Measurements from workplaces involved in the formulation of preparations and products such as paints have been performed by the German Workers' Compensation Funds (BGAA, 1999), Söhnlein et al. (1993) and Vincent et al. (1996) (see Table 3). The measurement data given in BGAA (1999) were collected during activities such as mixing, stirring, dissolving and decanting. Highest measurements were recorded for decanting and stirring. Measurements described by Söhnlein et al. (1993) were performed in a varnish production plant on 2 days after an exposure-free weekend, whereas Vincent et al. (1996) presented data on measurements carried out during the manufacturing of paints and varnishes. According to additional information provided by the Monitoring Authorities of the Federal States of Germany, workplace monitoring during the production of coating agents for printing plates reveals a concentration of 2-ethoxyethanol in workplace air between 1.8 and 14 mg/m^3 (n = 10, 8-h TWA). Other workplace measurements carried out by the Monitoring Authorities of the Federal States in Germany during the production of lacquers (roller coating, cleaning of formulation vessels, mixing, filling, drumming) reveal 2-ethoxyethanol concentrations between 3 and 10 mg/m^3 (n = 4).

Data are also available on exposure to 2-ethoxyethanol or 2-ethoxyethyl acetate at workplaces during the use of preparations containing these compounds. Products containing 2-ethoxyethanol may be used in a variety of industrial and skilled-trade operations. Applications can be subdivided into manual application (see Table 4), spray activities (see Table 5), automated processes, such as printing (see Table 6), and the manufacture of electronic components (see Table 7). Manual application comprises activities such as wiping, rolling, brushing, dipping or covering by pouring. Manual coating described by BGAA (1999) was observed in the construction industry and in metal processing/mechanical engineering. Highest measurements were taken during activities such as varnishing and soaking. Exposure data given by Vincent (1999) were obtained during cleaning activities in different areas.

Sparer et al. (1988) reported an industrial hygiene survey to characterize exposure of shipyard painters to 2-ethoxyethanol. Samples (102) taken over six workshifts showed that airborne exposure (TWA) to 2-ethoxyethanol (for 90 usable samples) ranged from 0 to 80.5 mg/m^3, with a mean of 9.9 mg/m^3 and a median of 4.4 mg/m^3. From all data collected by the United States National Institute for Occupational Safety and Health, the United States Occupational Safety and Health Administration and the United States Environmental Protection Agency on exposures at work to glycol ethers between approximately 1985 and 1990, OSHA (2003) estimated the geometric means of 8-h TWA exposures to 2-ethoxyethanol or 2-ethoxyethyl acetate to be 0.06–0.3 mg/m^3 (calculated as 2-ethoxyethanol) in the manufacture of glycol ethers and manufacture of chemical intermediates, 0.02–14 mg/m^3 in metal spray painting applications, 0.4–14 mg/m^3 in formulation and

Table 2. Emissions of 2-ethoxyethanol and its acetate from consumer products.[a]

Product category	Number of products with detectable emissions	Amount emitted (µg/g product)
Cleaning compounds	4 (as 2-ethoxyethanol)	na
Spot/stain remover	1 (as 2-ethoxyethanol)	na
Window/glass cleaner	2 (as 2-ethoxyethanol)	na
Rug/upholstery cleaner	3 (as 2-ethoxyethanol)	na
Coatings/inks	10 (as 2-ethoxyethanol)	na
	4 (as 2-ethoxyethyl acetate)	
Coating thinners/strippers	6 (as 2-ethoxyethanol)	na
	1 (as 2-ethoxyethyl acetate)	
Herbicide and fungicide	1 (as 2-ethoxyethanol)	na
Medical/personal hygiene	1 (as 2-ethoxyethanol)	na
Adhesives	3 (as 2-ethoxyethanol)	0.1–200
	5 (as 2-ethoxyethyl acetate)	0.1–900
Coatings	14 (as 2-ethoxyethanol)	0.09–450
	66 (as 2-ethoxyethyl acetate)	0.05–1578
Fabric	1 (as 2-ethoxyethanol)	0.23
	3 (as 2-ethoxyethyl acetate)	0.07–0.7
Pens/inks	6 (as 2-ethoxyethanol)	0.1–2800
	5 (as 2-ethoxyethyl acetate)	0.49–4.3
Foam/plastic products	2 (as 2-ethoxyethyl acetate)	0.095–0.7

na, no information available.

[a] Clinical Toxicology of Commercial Products Database. No information on the number of products tested was provided in the secondary account of these studies (Hodgson & Wooley, 1991).

Table 3. Exposure to 2-ethoxyethanol at workplaces during the formulation of paints.

Job category / activities	Years of measurement	Number of samples	Technical measures	8-h TWA concentration (mg/m^3)			
				Range	Mean	90th percentile	95th percentile
Production of paints (e.g. mixing, filling, weighing, stirring)[a]	1991–1995	18	With LEV	na	3[b]	14	22
		15	Without LEV	na	3[b]	18	25
Varnish production[c]	Published 1993	12	na	<2.2–56.8	10.8	na	na
	Published 1993	12	na	<0.4–23.2	7.9	na	na
Fabrication of paints[d]	1988–1993	na	na	<0.4–19.1	1.5	na	na

LEV, local exhaust ventilation; na, no information available; TWA, time-weighted average.

[a] BGAA (1999).
[b] 50th percentile.
[c] Söhnlein et al. (1993).
[d] Vincent et al. (1996) (sampling time = shift length).

application of inks, and 0.04–0.5 mg/m^3 in semiconductor manufacturing and printed circuit board manufacturing. Veulemans et al. (1987a), in sampling 78 different plants in Belgium, found a mean exposure to 2-ethoxyethanol in painting operations of 9.5 mg/m^3, with a range of 1.4–210.3 mg/m^3.

Spraying of paints is performed in many different industrial and skilled-trade sectors (e.g. vehicle production and repair, treatment and processing of metal and wood, and the furniture industry). Spray application of paints and coatings often results in a significant potential for inhalation and dermal exposure. In addition to inhalation exposure caused by the evaporation of the substance, droplet aerosols may be a source of exposure. Spray applications described in BGAA (1999) were observed in the construction and wood industries as well as in the electrical engineering and metal processing industries. In Vincent et al. (1994), a comprehensive description of the painting operations in the aeronautical

Table 4. Exposure to 2-ethoxyethanol at workplaces during the use of preparations: manual application.

Job category / activities	Years of measurement	Number of samples	Technical measures	8-h TWA concentration (mg/m^3)			
				Range	50th percentile	90th percentile	95th percentile
Manual coating (without spraying)[a]	1991–1995	35	Without LEV	na	[b]	11	44
Cleaning[a]	1991–1995	23	With LEV	na	[b]	5	6
	1991–1995	19	Without LEV	na	[b]	6	28
Use of paints (brushing, rolling)[c]	1987–1998	13	na	0.5–44	2 (AM)	na	44
Cleaning activities during silkscreen printing[c]	1987–1998	21	na	0.4–41	2	na	33
Cleaning activities in different areas[c]	1987–1998	16	na	0.1–2.1	0.1	na	2.1
Painting[c]	na	38	na	0.2–23	0.5	na	19

AM, arithmetic mean; LEV, local exhaust ventilation; na, no information available; TWA, time-weighted average.

[a] BGAA (1999).

[b] Value below the detection limit, 0.1 mg/m^3 (for 2 h of sampling).

[c] Vincent (1999) (sampling time 60–480 min).

Table 5. Exposure to 2-ethoxyethanol at workplaces during the use of preparations: spray application.

Job category / activities	Years of measurement	Number of samples	Technical measures	8-h TWA concentration (mg/m^3)			
				Range	50th percentile	90th percentile	95th percentile
Manual coating (spray application)[a]	1991–1995	91	With LEV	na	[b]	11	22
	1991–1995	25	Without LEV	na	[b]	8	17
New vehicle painting[c]	1987–1998	39	na	0.4–8.2	0.75	na	na
Powder coating – paint spraying[c]	1987–1998	76	na	0.1–495	2	na	90
Plastic material painting[c]	1987–1998	79	na	<0.4–3 .7	<0.4	na	na
Metal container painting[c]	1987–1998	168	na	<0.4–7.1	<0.4	na	na

LEV, local exhaust ventilation; na, no information available; TWA, time-weighted average.

[a] BGAA (1999).

[b] Value below detection limit, 0.1 mg/m^3 (for 2 h of sampling).

[c] Vincent (1999) (sampling time 60–480 min).

industry is given. Painting operations comprise different activities, including the cleaning of surfaces, preparing and thinning paints, spray painting and equipment cleaning. The duration of spraying operations ranged from 30 to 90 min per shift. Workers normally wore gloves, boots and aprons as well as respiratory equipment during spray operations. Measurement data were obtained only for 2-ethoxyethyl acetate. The measurement results are in the same order of magnitude as in the case of spray application of preparations containing 2-ethoxyethanol.

Automated applications take place mainly in the printing industry (e.g. silkscreen printing, offset printing and flexo printing). Machine coating described by BGAA (1999) takes place in different industrial areas. Highest measurement results were observed with silkscreen printing. Within the printing industry, Vincent (1999) performed measurements during different processes (silkscreen, offset, flexo printing), whereas Vincent et al. (1996) presented measurements carried out in the silkscreen printing industry. Additional measurement results presented by Ahrens & Jöckel (1996) are given in a report on exposure in the paper industry. In the field of finishing and packaging of paper, 24 measurements of 2-ethoxyethanol were performed (1974–1993). The 90th percentile was located at 39 mg/m^3, and the maximum value amounted to 78 mg/m^3. There is no information concerning the measurement method or sampling strategy. It is not clear during which activities

Table 6. Exposure to 2-ethoxyethanol at workplaces during the use of preparations: automated processes.

Job category / activities	Years of measurement	Number of samples	Technical measures	8-h TWA concentration (mg/m^3)			
				Range	50th percentile	90th percentile	95th percentile
Printing (machine coating)[a]	1991–1995	94	With LEV	na	[b]	14	29
	1991–1995	95	Without LEV	na	[b]	14	28
Silkscreen printing machine (manual or automatic)[c]	1987–1998	155	na	0.1–561	4 (AM)	na	108
Offset printing[c]	1987–1998	3	na	1.2–64	22.3 (M)	na	na
Flexo printing[c]	1987–1998	7	na	1.8–103	46.9 (M)	na	na
Silkscreen printing[d]	1988–1993	295	na	<0.4–37.8	0.7 (M)	na	na

AM, arithmetic mean; LEV, local exhaust ventilation; M, mean; na, no information available; TWA, time-weighted average.
[a] BGAA (1999).
[b] Value below detection limit, 0.1 mg/m^3 (for 2 h of sampling).
[c] Vincent (1999) (sampling time 60–480 min).
[d] Vincent et al. (1996) (sampling time = shift length).

Table 7. 2-Ethoxyethyl acetate exposure at workplaces during the manufacturing of electronic components.

Job category / activities	Years of measurement	Number of samples	Technical measures	Measurement data (mg/m^3)
8-h TWA				
Electronics (board marking)[a]	Published 1990	8	LEV	≤0.1 (limit of detection)
Electronics (board marking)[b]	1986–1988	2	LEV	2.3 and 0.4
Photolithography area clean room[c]	1990–1991	23	na	Maximum 4.1, mean 0.3
Semiconductor fabrication[d]	Published 2000	48	na	<0.002–4.0
Short-term values				
Electronics (board marking, 15 min)[e]	Published 1990	23	LEV	≤0.7 (limit of detection)
Electronics (board marking, 15 min)[b]	1986–1988	2	LEV	13 and 2.4
Photolithography area clean room[f]	1990–1991	4 / 2 / 3	na	0.2 / <0.01 / 0.6

LEV, local exhaust ventilation; na, no information available; TWA, time-weighted average.
[a] Piacitelli et al. (1990) (sampling time 5–8 h, result not time-weighted to 8 h).
[b] Sartori & Pahlmann (1990) (sampling time 140 and 200 min for long-term samples).
[c] Hammond et al. (1996).
[d] Woskie et al. (2000).
[e] Piacitelli et al. (1990).
[f] Hammond et al. (1996). Data are for unloading cassettes, loading cassettes and unloading the soft bake oven, respectively.

(cutting to size, printing, folding or packaging) the measurement results were obtained, and no information is available on whether or not the workplaces were equipped with local exhaust ventilation.

Surveys of workers in China indicated average 2-ethoxyethanol exposure levels at three photosensitizing plate manufacturers of between 18.7 and 203 mg/m^3 (Gao et al. 1997), whereas printing workers (n = 56) were exposed to 2-ethoxyethanol at levels between 3.1 and 159 mg/m^3 (Liu et al., 1999).

6.1.2 2-Propoxyethanol

No information was available on environmental levels of 2-propoxyethanol.

6.2 Human exposure

6.2.1 2-Ethoxyethanol

6.2.1.1 General population

The limitations of the available monitoring data for 2-ethoxyethanol preclude the development of reliable estimates of typical exposure of the general population; instead, crude upper-bounding estimates of exposure to 2-ethoxyethanol from environmental media and consumer products have been developed in order to characterize potential exposure from these pathways.

Table 8. Upper-bounding estimates of intake of 2-ethoxyethanol by various age groups.

Route of exposure	Upper-bounding estimates of intake of 2-ethoxyethanol by various age groups in the general population of Canada (µg/kg body weight per day)					
	0–6 months[a]	7 months–4 years[b]	5–11 years[c]	12–19 years[d]	20–59 years[e]	60+ years[f]
Ambient air[g]	0.13	0.27	0.21	0.12	0.10	0.09
Indoor air[h]	0.87	1.87	1.46	0.83	0.71	0.62
Drinking-water[i]	0.005[j]	0.002	0.002	0.001	0.001	0.001
Total[k]	1.0	2.1	1.7	0.9	0.8	0.7

[a] Assumed to weigh 7.5 kg, to drink 0.8 litres of water per day and to breathe 2.1 m^3 of air per day (Health Canada, 1998b).
[b] Assumed to weigh 15.5 kg, to drink 0.7 litres of water per day and to breathe 9.3 m^3 of air per day (Health Canada, 1998b).
[c] Assumed to weigh 31.0 kg, to drink 1.1 litres of water per day and to breathe 14.5 m^3 of air per day (Health Canada, 1998b).
[d] Assumed to weigh 59.4 kg, to drink 1.2 litres of water per day and to breathe 15.8 m^3 of air per day (Health Canada, 1998b).
[e] Assumed to weigh 70.9 kg, to drink 1.5 litres of water per day and to breathe 16.2 m^3 of air per day (Health Canada, 1998b).
[f] Assumed to weigh 72.0 kg, to drink 1.6 litres of water per day and to breathe 14.3 m^3 of air per day (Health Canada, 1998b).
[g] Based on the detection limit (3.6 µg/m^3) for 2-ethoxyethanol in 50 ambient air samples collected outside of Canadian residences (Conor Pacific Environmental Technologies Inc., 1998). The average Canadian is assumed to spend 3 h of every day outdoors (Health Canada, 1998b).
[h] Based on the detection limit (3.6 µg/m^3) for 2-ethoxyethanol in 50 indoor air samples collected in Canadian residences (Conor Pacific Environmental Technologies Inc., 1998). The average Canadian is assumed to spend 21 h of every day indoors (Health Canada, 1998b).
[i] Based on the detection limit (0.05 µg/l) for 2-ethoxyethanol in 50 drinking-water samples collected in Canadian residences (Conor Pacific Environmental Technologies Inc., 1998).
[j] Based on the assumption that infants were exclusively formula fed and consumed 800 ml of formula that was prepared with tap water.
[k] Insufficient data were available to estimate intake from soil or food.

The only environmental media for which available monitoring data allowed even crude estimation of exposure were air and water. Upper-bounding estimates of intake of 2-ethoxyethanol from these media by six age groups in the general population of Canada are presented in Table 8. These estimates are based on the limits of detection in air and tap water from the limited Canadian multimedia exposure study in which concentrations of 2-ethoxyethanol were below the limits of detection (3.6 µg/m^3 and 0.05 µg/l, respectively) in all samples analysed (Conor Pacific Environmental Technologies Inc., 1998). Although confidence in the results of this survey is low, comparison with estimates of intake in air and water on the basis of results of fugacity modelling and in ambient air based on the data from the Windsor, Ontario, study indicates that this approach is conservative in deriving upper-bounding estimates of intake in air. Based on these values, the intake of an average adult in Canada of 2-ethoxyethanol from ambient and indoor air would be no greater than 0.81 µg/kg body weight per day and from drinking-water would be no more than 0.001 µg/kg body weight per day, although it is recognized that these values likely overestimate exposure.

As no monitoring data are available, it is not possible to determine the contribution of food to the overall intake of 2-ethoxyethanol. However, 2-ethoxyethanol is released primarily to air from industrial activities and through volatilization from consumer products and is unlikely to partition to food from air as a result of its volatility and very low log K_{ow} value of −0.32. In addition, if intake from food is estimated on the basis of extrapolation from the results of fugacity modelling, this value would be several orders of magnitude less than the upper-bounding estimates calculated for air and drinking-water on the basis of the limits of detection in the multimedia study. Likewise, exposure to 2-ethoxyethanol in soil is likely to be negligible in comparison with that in air, based on its release patterns and the relatively small quantities ingested.

Although 2-ethoxyethanol and its acetate are not commonly present in consumer products in many parts of the world, it cannot be precluded that they are still used in some areas. Both inhalation and dermal absorption would be expected to be important routes of exposure for consumer products, as many of those products that might contain 2-ethoxyethanol or its acetate can contact the skin. Extreme worst-case estimates of intake of 2-ethoxyethanol (on a per event basis as well as average daily intakes based on annual event frequencies) from exposure to household cleaning products and nail polish were developed from product use scenarios as examples (Versar Inc., 1986). Assumptions of 100% absorption for the product contacting the skin and for the inhaled product and 100% transfer of 2-ethoxyethanol from the product into air were made in view of the lack of adequate data to support more refined estimates (see Table 9). The maximum estimate for exposure through use of a household cleaning product that is used on an almost daily basis (all-purpose spray cleaner, the only cleaning product for which composition data were available) was 1.6 or 0.5 mg/kg body weight per event or per

Table 9. Upper-bounding estimates of intake of 2-ethoxyethanol from consumer products by adult Canadians.

Consumer product	Assumptions	Estimated intake per event (mg/kg body weight)	Estimated average intake (mg/kg body weight per day)
Nail polish	**Dermal**[a] • based on the upper bound of the concentration range of 0.3–1% of 2-ethoxyethanol in nail polish (Health Canada, 2001) • assuming a typical quantity of product used per event for "nail polish & enamel" of 0.28 g and a maximum event frequency of 0.71 times per day for users only (USEPA, 1997) • a body weight of 70.9 kg is assumed for an average Canadian adult (Health Canada, 1998b) $\frac{(0.01)\ (280\ mg)\ (0.71/day)}{(70.9\ kg\ body\ weight)}$	0.04	0.03
All-purpose spray cleaner	**Inhalation**[b] • based on the upper bound of the concentration range of 3–5% of 2-ethoxyethanol in hard surface cleaner (Flick, 1986) • assuming a mass of 76 g is used per event, a 0.47-h duration of exposure, a room volume of 20 m^3, a breathing rate of 1.3 m^3/h for an average adult during light-level activity and a frequency of use of 360 days/year (Versar Inc., 1986) • a body weight of 70.9 kg is assumed for an average Canadian adult (Health Canada, 1998b) $\frac{0.05 \times 360/365\ days \times 76\ g \times 0.47\ h \times 1.3\ m^3/h \times 1000\ mg/g}{20\ m^3 \times 70.9\ kg\ body\ weight}$	1.6 [estimated indoor air concentration of 190 mg/m^3]	1.6
	Dermal[a] • based on the upper bound of the concentration range of 3–5% of 2-ethoxyethanol in hard surface cleaner (Flick, 1986) • assuming an event frequency of 360 days/year, an exposed surface area of 400 cm^2 (both palms), a product density of 0.88 g/cm^3 and a film thickness on the hands of 2.1×10^{-3} cm (Versar Inc., 1986) • a body weight of 70.9 kg is assumed for an average Canadian adult (Health Canada, 1998b) $\frac{0.05 \times 360/365\ days \times 400\ cm^2 \times 0.88\ g/cm^3 \times 2.1 \times 10^{-3}\ cm \times 1000\ mg/g}{70.9\ kg\ body\ weight}$	0.5	0.5

[a] Estimates of intake by dermal absorption of 2-ethoxyethanol in liquid consumer products are based on the assumptions that a portion of the skin contacts the liquid and the amount absorbed is directly proportional to the area of exposed skin. It is assumed that all of the ingredient present in the liquid is absorbed through the skin. Standard exposure scenarios for dermal absorption of ingredients of liquid consumer products (e.g. Versar Inc., 1986; USEPA, 1997) often include recommended skin surface areas and surface film thickness depending on the type of product and the manner in which it is used. For example, in Versar Inc. (1986), surface areas assumed are 400 cm^2 for both palms of adult hands for scenarios involving some liquid cleaning products. Experimental data for surface film thickness are often not available for some types of consumer products and are estimated by analogy with other liquid substances.

[b] Estimates of intake by inhalation are based on the assumptions that the ingredient is completely and instantaneously released from the applied product, the concentration is homogeneous throughout the assumed volume and no air exchange occurs between this volume and adjacent areas. Standard exposure scenarios for inhalation intakes of volatile ingredients of consumer products used in indoor spaces (e.g. Versar Inc., 1986; USEPA, 1997) often include recommended room volumes intended to be representative of the areas within a residence where the products are typically used. For example, in Versar Inc. (1986), a room volume of 20 m^3 is assumed for tasks involving all-purpose liquid spray cleaners.

day via inhalation and dermal absorption, respectively. Concentrations in indoor air resulting from use of such products could range up to 190 mg/m^3, assuming complete volatilization.

6.2.1.2 Occupational exposure

There is still considerable potential for occupational exposure to 2-ethoxyethanol or its acetate. Estimates of exposure via the inhalation and dermal routes are presented in Tables 10 and 11 (BfR, 2003).

6.2.2 2-Propoxyethanol

No information was available on human exposure to 2-propoxyethanol.

Table 10. Summary of inhalation exposure data (reasonable worst case) for 2-ethoxyethanol that are relevant for occupational risk assessment.

Scenario number, area of production and use	Form of exposure	Activity	Duration (h/day)	Frequency	Exposure metric	8-h TWA exposure concentration (mg/m^3)	Short-term concentration (mg/m^3)	Method
Production and further processing in the large-scale industry								
1. Production and further processing [Table 3]	Vapour (liquid)	Charging, repair, filling, cleaning, maintenance	Shift length (assumed)	Daily	95th percentile	25	–	–
Formulation								
2. Formulation of preparations and products [Table 3]	Vapour (liquid)	Charging, repair, filling, cleaning, maintenance	2	Daily	90th percentile	18	–	–
Use of preparations								
3. Use of preparations: manual application [Table 4]	Vapour (liquid)	Brushing, rolling, cleaning	Shift length (assumed)	Daily	90th percentile	11	–	–
4. Use of preparations: spray application [Table 5]	Vapour (liquid)	Spraying, coating	Shift length (assumed)	Daily	95th percentile	90	455	Analogous data
5. Use of preparations: automated processes [Table 6]	Vapour (liquid)	Printing, textile finishing	Shift length (assumed)	Daily	95th percentile	108		
6. Use of preparations in the manufacturing of electronic components [Table 7]	Vapour (liquid)	Charging, repair, cleaning, maintenance	Shift length (assumed)	Daily	Highest measurement data	4	13	Analogy/expert judgement

Table 11. Summary of dermal exposure data (reasonable worst case) for 2-ethoxyethanol that are relevant for occupational risk assessment.

Scenario number, area of production and use (maximal 2-ethoxyethanol content in the product)	Form of exposure	Activity	Frequency	Contact level[a]	Level of exposure (mg/cm^2 per day)	Exposed area (cm^2)	Shift average (mg/person per day)	Method (use of gloves)
Production and further processing in the large-scale industry								
1. Production and further processing	Liquid	Charging, repair, filling, cleaning, maintenance	Daily	Intermittent	0.1–1	420	42	EASE (90% protection, suitable gloves)
Formulation								
2. Formulation of preparations and products	Liquid	Charging, repair, filling, cleaning, maintenance	Daily	Intermittent	0.1–1	420	420	EASE[b]
Use of preparations								
3. Use of preparations: manual application (50%)	Liquid	Brushing, rolling cleaning	Daily	Intermittent	1–5	840	2100	EASE[b]
4. Use of preparations: spray application (50%)	Liquid	Spraying, coating	Daily	Intermittent	1–5	1300	3250	EASE[b]
5. Use of preparations: automated processes (50%)	Liquid	Printing, textile finishing	Daily	Intermittent	0.1–1	840	420	EASE[b]
6. Use of preparations in the manufacturing of electronic components (80%)	Liquid	Charging, repair, cleaning, maintenance	Daily	Incidental	0–0.1	420	34	EASE[b]

EASE, Estimation and Assessment of Substance Exposure.

[a] Contact level according to the EASE model.

[b] Gloves are not regularly worn; therefore, the EASE estimation is made for the unprotected worker (without gloves).

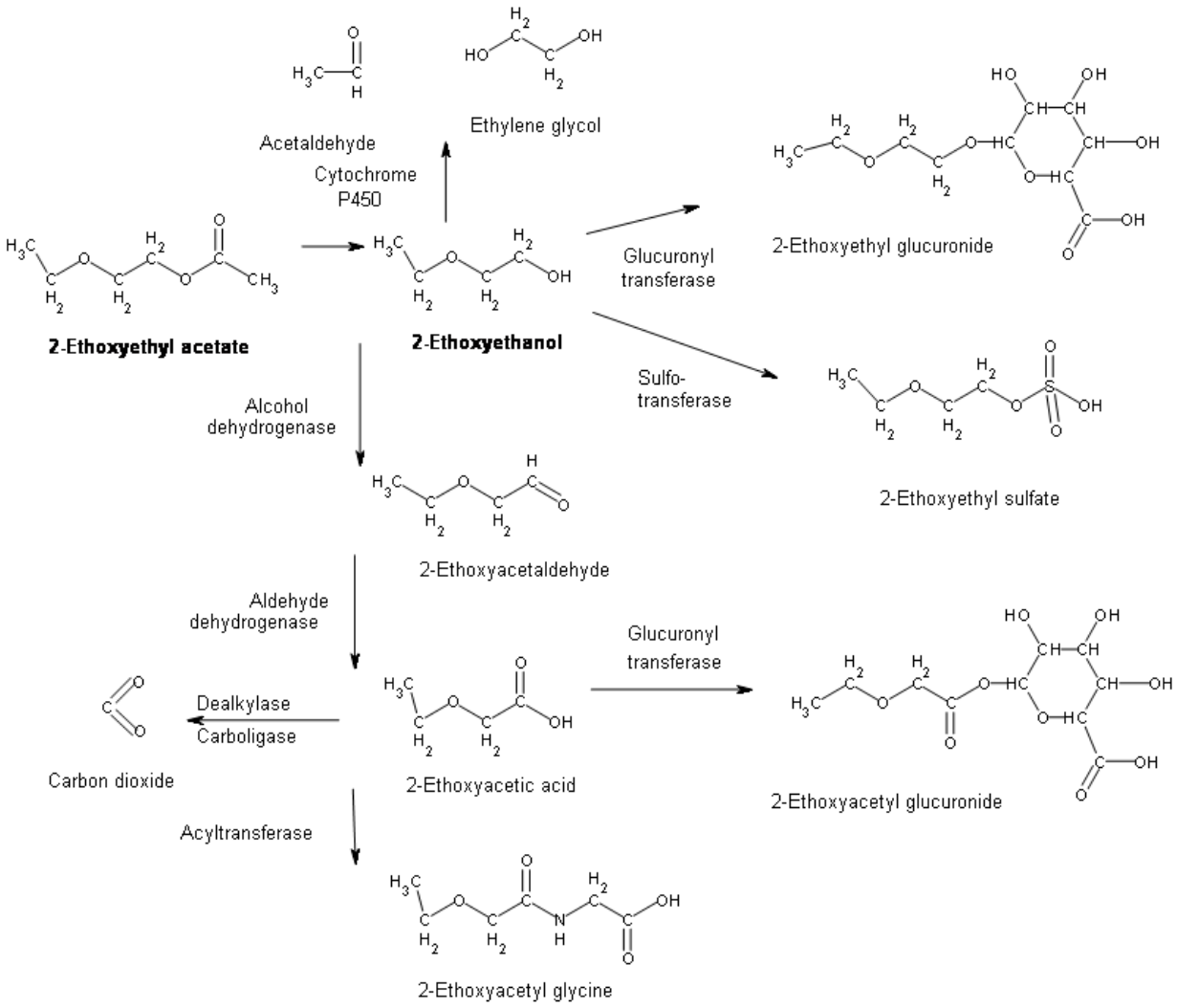


Figure 1. Metabolism of 2-ethoxyethanol.

7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

7.1 2-Ethoxyethanol

Available data from studies on kinetics, metabolism and systemic toxicity indicate that 2-ethoxyethanol is rapidly absorbed in humans and laboratory animals exposed via ingestion, inhalation or dermal contact and is distributed extensively throughout the body. In humans and laboratory animals, 2-ethoxyethanol is oxidized via alcohol dehydrogenases to the intermediate 2-ethoxyacetaldehyde (EALD) and then rapidly converted via aldehyde dehydrogenases to EAA, the principal and putatively active metabolite, which is eliminated primarily in the urine. In rats, EAA may be conjugated with glycine or may be *O*-deethylated and then further metabolized to carbon dioxide. A secondary pathway in rodents involves microsomal P450 mixed-function oxidases, with deethylation producing acetaldehyde and ethylene glycol. The various metabolic pathways are outlined in Figure 1.

Kezic et al. (1997) described the dermal absorption following exposure to 2-ethoxyethanol vapours and liquid in five Dutch volunteers (two men and three women). Dermal exposure (area of about 100 cm^2 involving the forearm and hand) to 3700 mg 2-ethoxyethanol/m^3 lasted for 45 min. The duration of exposure to liquid 2-ethoxyethanol (on a forearm area of 27 cm^2) was 15 min. Uptake was measured using urinary EAA. Mean (standard deviation [SD]) absorption rates of 2-ethoxyethanol vapour and liquid were 19 (6) cm/h (permeability rate) and 0.7 (0.3) mg/cm^2 per hour (flux

rate), respectively. In the combined inhalation and dermal exposure to vapour, uptake through the skin was estimated to be 42%.

It has been suggested from human studies that percutaneous absorption predominates whenever a direct skin contact occurs (Angerer et al., 1990). Twelve workers at a varnish factory were investigated during production of a particular varnish containing 2-ethoxyethanol and 2-ethoxyethyl acetate. There was no correlation found between individual workplace air concentrations for these compounds and the concentration of the metabolite EAA in the urine, a fact the investigators suggested might be due to significant skin absorption.

Topical application of undiluted [^{14}C]2-ethoxyethanol to occluded rat skin in vivo resulted in 25% of the dose being absorbed after 24 h. As a result of the rapid penetration of 2-ethoxyethanol through the skin, it is unlikely to be metabolized there, and systemic exposure after skin contact is likely to be to the parent compound. A comparison of rat and human skin in vitro indicated that 2-ethoxyethanol absorption in humans (8%) is about one third of that in the rat (20%) using split skin samples (Lockley et al., 2002).

In vitro studies using the skin of Beagle dogs determined that 2-ethoxyethanol was absorbed at a rate of 2.3 mg/cm^2 of skin per hour (Guest et al., 1984). In vitro studies of isolated human skin showed an absorption rate of 0.8 mg/cm^2 per hour (Dugard et al., 1984).

Following a 2-h whole-body exposure of three female Sprague-Dawley rats to 1596 mg/m^3, an average of 121 µg 2-ethoxyethanol/ml was detected in the blood (Römer et al., 1985).

An inhalation experiment in Beagle dogs showed that 2-ethoxyethyl acetate is taken up rapidly by the lungs. Four male dogs were exposed (whole body) for 5 h to 270 mg/m^3. Inhaled and exhaled air was collected at various times throughout the exposure. About 80% of the inhaled 2-ethoxyethyl acetate was absorbed 10 min after the start of the exposure. The 2-ethoxyethyl acetate concentration in the exhaled air subsequently increased and corresponded to 68% absorption during the 3rd to 5th exposure hours (Guest et al., 1984).

The routes of ^{14}C excretion following the administration of a single oral dose of 230 mg 2-ethoxyethanol/kg body weight to male Sprague-Dawley rats showed that elimination of the ^{14}C by the urinary route accounted for 76–80% of the dose within 96 h. The main pathway of biotransformation was oxidation to EAA, with some subsequent conjugation of the acid metabolite with glycine. The major metabolites, EAA and 2-ethoxyacetyl glycine, represented 73–76% of the administered dose and were eliminated in the urine (Cheever et al., 1984).

Although little information is available regarding interspecies differences in the toxicokinetics and metabolism of 2-ethoxyethanol, there is some indication that humans may absorb the inhaled substance to a greater extent than do rats. Inhaled 2-ethoxyethanol was rapidly and extensively absorbed in groups of 5–10 volunteers exposed at rest to 10, 20 or 40 mg/m^3 through a mask for 4 h. Based on measurements in exhaled air, about 64% of the inhaled amount was retained (determined to be approximately equivalent to doses of 0.25, 0.5 and 1.0 mg/kg body weight). Retention was not affected by exposure concentration, indicating that metabolic clearance capacity had not been saturated, although the rate of uptake increased with ambient concentration. A steady-state level was reached almost immediately upon initiation of exposure. During the exposure period and within 38 h after cessation of exposure, 21–26% of the absorbed dose was excreted in the urine. Urinary excretion increased rapidly from the 1st hour of exposure, reached a maximum rate 3–4 h after the end of exposure and followed a slow exponential decrease thereafter, with an estimated half-life of 42 h (Groeseneken et al., 1986b,c, 1988). In rats exposed (nose only) to radiolabelled 2-ethoxyethanol at 19 mg/m^3 for 5.7 h or 170 mg/m^3 for 6 h, measurement of radioactivity in the excreta and carcass at 66 h and as exhaled parent compound during exposure indicated that 28–29% of inhaled 2-ethoxyethanol was absorbed from the respiratory system. Of the absorbed amount, 37–38% was excreted over 72 h in the expired air as radiolabelled carbon dioxide, 46% was excreted in the urine, 1–2% appeared in the faeces and 10–11% remained in the carcass (Kennedy et al., 1993). In addition, although relevant data are very limited, 2-ethoxyethanol may be converted to EAA at a greater rate in humans than in rats, with subsequent renal clearance of the metabolite being slower in humans (Groeseneken et al., 1988); thus, the putatively active metabolite may be present in the blood of humans at higher levels and for longer durations than in rats. In humans, urinary excretion of EAA for equivalent low doses of 2-ethoxyethanol differed from that in the rat by a longer elimination half-life (mean 42 h), by the absence of EAA conjugates and by a higher recovery (Groeseneken et al., 1988).

When rats were exposed to unlabelled 2-ethoxyethanol, the combined urinary excretion of free EAA and 2-ethoxyacetyl glycine was only 30% of the absorbed dose, suggesting that the route of exposure can have a significant effect on the metabolic profile (Jönsson et al., 1982). Compared with rats and dogs (Guest et al., 1984), the biological half-life of EAA excretion was 2.5–3 times greater in humans. At any time after the exposure period, EAA excretion was found to be proportional to the absorbed dose of 2-ethoxyethanol (Guest et al., 1984; Groeseneken et al., 1987a).

The acetate derivative of 2-ethoxyethanol, 2-ethoxyethyl acetate, which is used in occupational and residential environments, is rapidly hydrolysed to 2-ethoxyethanol via esterases in several tissues in the body (Stott & McKenna, 1985). Urinary excretion of EAA during and after exposure to 2-ethoxyethyl acetate was followed in 10 healthy male volunteers (Groeseneken et al., 1987b). EAA levels appeared with a half-life of 2.2 ± 0.1 h. EAA continued to increase after exposure was discontinued, reaching maximal levels 3–4 h later. The decline afterwards could generally be described assuming a half-life of 3.6 ± 1.8 h. A second maximum excretion of EAA was noticed about 3 h after the first and could be explained as redistribution of 2-ethoxyethyl acetate or EAA, or both, from a peripheral compartment to the central compartment. On average, 22.2 ± 0.9% of the absorbed 2-ethoxyethyl acetate was recovered within 42 h.

Veulemans et al. (1987b) studied the urinary excretion of EAA in a group of five Belgian women exposed daily to 2-ethoxyethyl acetate and 2-ethoxyethanol during 5 days of normal production and 7 days after a 12-day production break. The mean combined exposure concentration expressed in equivalent weight of 2-ethoxyethanol was 14.0 mg/m^3, with occasional slight excursions above the current Belgian occupational exposure limit (OEL). The daily combined exposure profiles for the two materials were rather constant during the first observation. An EAA estimate of 150 ± 35 mg/g was found to correspond with repeated 5-day full-shift exposures to the respective OEL of 2-ethoxyethanol (19 mg/m^3) or 2-ethoxyethyl acetate (27 mg/m^3).

A physiologically based pharmacokinetic (PBPK) model of 2-ethoxyethanol (and 2-ethoxyethyl acetate) absorption, metabolism, disposition and excretion has been described for pregnant rats and humans (Gargas et al., 2000a). The objective of the study was to develop PBPK models that could be used to identify human exposure levels (mg/m^3 in air) equivalent to the rat no-observed-effect concentration (NOEC) and lowest-observed-effect concentration (LOEC) for developmental effects reported by Tyl et al. (1988). The model was based on that developed for 2-methoxyethanol (Gargas et al., 2000b; Hays et al., 2000). The model structure contained three submodels (one each for 2-ethoxyethyl acetate, 2-ethoxyethanol and EAA), each with discrete compartments for the lung, liver, fat, and richly and slowly perfused tissues. Fetuses were grouped into the richly perfused tissue compartment. Pregnant Sprague-Dawley rats were exposed to concentrations of 2-ethoxyethyl acetate corresponding to the reported NOEC and LOEC values. Maternal blood, urine and fetal tissue concentrations of 2-ethoxyethanol and EAA were used to validate the rat models, and data collected by other investigators were used to validate the capabilities of the rodent models to predict the kinetics in humans. The models for estimating circulating blood concentrations of EAA were considered valid based on the ability of the model to accurately predict EAA concentrations in rat blood, urine and fetal tissue. The human inhaled concentrations equivalent to the rat NOEC for 2-ethoxyethyl acetate (270 mg/m^3) were predicted to be 140 mg/m^3 using the maternal blood average daily area under the curve (AUC) and 220 mg/m^3 using the maximum concentration achieved in maternal blood (C_{max}). The human inhaled concentrations equivalent to the rat LOEC for 2-ethoxyethyl acetate (550 mg/m^3) were determined to be 300 mg/m^3 using the maternal blood average daily AUC and 440 mg/m^3 using the maternal blood C_{max}. The model has been used to develop proposed OELs (Sweeney et al., 2001), although the recommendations assumed that dermal exposure would be minimal or non-existent.

Because absorption via the dermal route can be a significant route of exposure, particularly in the occupational setting, the inhalation exposure alone will not give sufficient indication of biological exposure. The level of the EAA metabolite in the urine can be used as a specific and suitable indicator of overall exposure (Groeseneken et al., 1987a,b; Veulemans et al., 1987a,b, 1993; Lowry, 1996).

7.2 2-Propoxyethanol

No information was found on the uptake of 2-propoxyethanol via the respiratory tract. The uptake of 2-propoxyethyl acetate by inhalation has been measured at 74% in dogs (Guest et al., 1984).

Relatively high skin absorption of 2-propoxyethanol and 2-propoxyethyl acetate has been demonstrated in vitro. Measured skin uptakes were 2.3 mg/cm^2 per hour (intact skin from rats) and 0.58 mg/cm^2 per hour (stratum corneum from humans) for 2-propoxyethanol (Barber et al., 1992) and 1.02 mg/cm^2 per hour (116 nmol/cm^2 per minute, intact skin from dogs) for 2-propoxyethyl acetate (Guest et al., 1984). It is suggested that skin uptake may exceed intake via inhalation. However, results of a study in which rats were administered approximately 450 mg/kg by the dermal route indicated absorption of less than 27% of the material during a 6-h exposure period (Boatman et al., 1998).

No studies were found on the distribution of 2-propoxyethanol or 2-propoxyethyl acetate in the body. At 37 °C, the olive oil/water partition coefficients for the ethylene glycol ethers range from 0.015 to 0.77. For the structurally related compounds isopropoxyethanol and 2-ethoxyethyl acetate, values were 0.13 and 1.3, respectively (Johanson & Dynesius, 1988). The K_{ow} for isopropoxyethanol is 2.7 (log K_{ow} = 0.43) (Tanii et al., 1992). These values suggest that neither 2-propoxy-

ethanol nor 2-propoxyethyl acetate would accumulate in fatty tissues.

No information on the metabolism of 2-propoxyethanol or 2-propoxyethyl acetate was found in the literature. It is probable that the acetate, as for other glycol ether esters, is rapidly biotransformed in the body to the corresponding glycol ether, 2-propoxyethanol. For this reason, data on the acetate ester are included in this CICAD.

Alcohol dehydrogenase and aldehyde dehydrogenase are likely primarily involved in the metabolism. In experimental animals given high doses, glycol ethers are conjugated with sulfate and glucuronic acid, and splitting of the ether bond is followed by formation of ethanediol. All the metabolites are excreted in the urine.

8. EFFECTS ON LABORATORY MAMMALS AND IN VITRO TEST SYSTEMS

8.1 Single exposure

8.1.1 2-Ethoxyethanol

2-Ethoxyethanol is of low to moderate acute toxicity in laboratory animals following oral exposure, with reported median lethal doses (LD_{50}s) in rats ranging from 2125 to 5490 mg/kg body weight (Laug et al., 1939; Smyth et al., 1941; Carpenter, 1947; Carpenter et al., 1956; Stenger et al., 1971; Truhaut et al., 1979; Krasavage & Terhaar, 1981; Dow Chemical Company, unpublished data, cited in Clayton & Clayton, 1982; Cheever et al., 1984). It is of low toxicity following inhalation or dermal exposure, with median lethal concentrations (LC_{50}s) of 16 000 mg/m^3 (4 h) in rats and 5500–7400 mg/m^3 (7 or 8 h) in rats and mice (Werner et al., 1943a; Pozzani et al., 1959; Shell, unpublished data, cited in Tyl et al., 1988; ECETOC, 1995) and dermal LD_{50}s of 3314–3920 mg/kg body weight (covered application for 24 h) in rabbits (Carpenter et al., 1956; Krasavage & Terhaar, 1981; Daughtrey et al., 1984). Target sites of 2-ethoxyethanol-induced acute toxicity include the haematopoietic system, liver, kidneys and stomach.

8.1.2 2-Propoxyethanol

The acute toxicity of 2-propoxyethanol by the oral route is low. The LD_{50} for oral administration to rats was 3100 mg/kg body weight (Katz et al., 1984) and for mice was 1800 mg/kg body weight (Krasavage & Terhaar, 1981). Clinical signs of toxicity following high oral doses included inactivity, laboured breathing, weakness, tremors, prostration and death. An older publication reports an LD_{50} of 4400 mg/kg body weight for oral administration to rats and 900 mg/kg body weight for dermal application to rabbits (Smyth et al., 1969). An LD_{50} of 1300 mg/kg body weight following dermal application to rabbits has also been reported (Krasavage & Terhaar, 1981). In guinea-pigs, dermal application of 4500 mg/kg body weight under occlusion for 24 h resulted in the death of all animals, whereas all five treated similarly with 900 mg/kg body weight survived (Katz et al., 1984).

The acute toxicity of 2-propoxyethyl acetate is also low, with an LD_{50} of 9500 mg/kg body weight for oral administration to rats (Katz et al., 1984). All five guinea-pigs survived occluded 24-h dermal application of 18 000 mg 2-propoxyethyl acetate/kg body weight (Katz et al., 1984).

There were no deaths when rats were exposed for 6 h to 4800 or 9100 mg 2-propoxyethanol/m^3 or 5700 mg 2-propoxyethyl acetate/m^3. The only clinical observation at these exposures was haemoglobin in the urine (Katz et al., 1984). In an older experiment, about half the rats exposed to 8500 mg 2-propoxyethanol/m^3 died after 4 h (Carpenter et al., 1949). In another study, exposure to 260 mg/m^3 for 4 h was reported to cause significantly increased osmotic fragility of red blood cells in female rats; the effect was not observed at 140 mg/m^3 (Carpenter et al., 1956).

From an older 7-h inhalation study with mice (Werner et al., 1943a), the LC_{50} value for 2-propoxyethanol can be estimated to be 6400 mg/m^3. Dyspnoea, splenic stasis, pronounced haemoglobinuria and a few cases of interstitial nephritis were observed at exposures near the lethal concentration

8.2 Irritation and sensitization

8.2.1 2-Ethoxyethanol

2-Ethoxyethanol and its acetate have only low potential for irritation of skin and eyes (Werner et al., 1943b; Carpenter & Smyth, 1946; Truhaut et al., 1979; Krasavage & Terhaar, 1981; Barbee et al., 1984; Daughtrey et al., 1984; Kennah et al., 1989). 2-Ethoxyethanol has not been shown to be a skin sensitizer in the guinea-pig by the maximized Magnusson and Kligman method (Zissu, 1995).

8.2.2 2-Propoxyethanol

Neat 2-propoxyethanol applied under occlusion for 24 h to the skin of guinea-pigs resulted in slight irritation (erythema and oedema), which had healed within a week. Repeated application for 10 days yielded somewhat increased irritation (Katz et al., 1984).

When 0.1 ml 2-propoxyethanol was applied to the eyes of rabbits, there was moderate to severe irritation (redness, oedema, iritis, clouding of the cornea). The effects had resolved within 2 weeks, and immediately rinsing the eyes following instillation lessened the irritation (Katz et al., 1984).

No evidence of sensitization was reported following a (non-adjuvant) Buehler test in which 10 guinea-pigs were given repeated 6-h dermal applications of neat 2-propoxyethanol weekly for 3 weeks, followed 2 weeks later by a challenge patch, again with the neat material (Shepard, 1988a).

No evidence of sensitization was found in 10 guinea-pigs treated by dermal injection into the footpad with 1% 2-propoxyethanol (together with an adjuvant), followed 7 days later by dermal patch application of 10% (Shepard, 1988b). In a similar study using induction and challenge concentrations of 1% 2-propoxyethanol, one of five animals showed a weak positive response (Katz et al., 1984).

8.3 Short-term exposure

8.3.1 2-Ethoxyethanol

Based on the few short-term oral studies available, the testis appears to be a sensitive target organ, with histopathological effects (degeneration or atrophy) and/or decreased weights being observed in rats, mice and dogs following repeated doses of 2-ethoxyethanol at 919 mg/kg body weight per day (in drinking-water), 1000 mg/kg body weight per day (by gavage) and 186 mg/kg body weight per day (in capsules), respectively (Stenger et al., 1971; Nagano et al., 1979, 1984; NTP, 1993). 2-Ethoxyethyl acetate induced similar effects in the testes at gavage doses of 1000 mg/kg body weight per day or more in mice (Nagano et al., 1979, 1984). Reductions in relative thymus weights were also observed in rats administered 357 mg/kg body weight per day or more in drinking-water (i.e. doses lower than those that induced testicular effects); no effects on the thymus were observed in mice exposed to much higher doses (NTP, 1993). Haematological effects, consisting of reduced white blood cell counts and packed cell volume, were also observed in mice exposed to 2000 mg/kg body weight per day or more of 2-ethoxyethanol or the acetate by gavage (Nagano et al., 1979, 1984). In the only other short-term oral study in which haematological parameters were investigated, there were slight dose-related decreases in haemoglobin and haematocrit levels after 5 weeks in dogs administered 46–186 mg/kg body weight per day of 2-ethoxyethanol in gelatine capsules for 13 weeks (statistical significance not reported) (Stenger et al., 1971).

Available data on the toxicity of 2-ethoxyethanol or 2-ethoxyethyl acetate following short-term exposure via inhalation are limited to studies designed primarily to investigate developmental toxicity and two early limited studies in small groups of dogs. Doe (1984) reported changes in red blood cell parameters in pregnant rats exposed to 2-ethoxyethanol at 940 mg/m^3 for 10 days, whereas no effects on the blood were observed at 190 mg/m^3. Similarly, alterations in haematological parameters (red blood cells, white blood cells and platelets) were observed in pregnant rats exposed to 2-ethoxyethanol at 370 mg/m^3 or more (Tyl et al., 1988). In studies in rabbits, no effects on the blood were noted in pregnant females exposed to 2-ethoxyethanol at concentrations up to 660 mg/m^3, whereas a reduction in haemoglobin concentration was observed only following exposure to the highest concentration of 2-ethoxyethyl acetate tested, equivalent to 1500 mg 2-ethoxyethanol/m^3 (Doe, 1984).

Alterations in haematological parameters characteristic of anaemia (i.e. effects on red blood cells) and an increase in calcium oxalate crystals in the urine were observed in dogs exposed to 2-ethoxyethanol vapour at 3100 mg/m^3 for 12 weeks (Werner, 1943b), although no such effects were noted in dogs exposed to 2200 mg 2-ethoxyethyl acetate vapour/m^3 for 6 months (Carpenter, 1947). No histopathological changes were observed in the limited range of organs examined in either study.

8.3.2 2-Propoxyethanol

When 2-propoxyethanol was given to groups of 10 CR(COBS)CD:BR rats by gavage for 6 weeks at doses of 0, 200, 400, 800 and 1600 mg/kg body weight per day, there were deaths (1–3 rats of 10) at 400 mg/kg body weight per day and above, but none in the lowest dose group. Rats in the highest dose group also had reduced food intake and gained weight more slowly. Haemoglobin was observed in the urine of all animals at 400 mg/kg body weight per day and above and in 2 of 10 animals in the lowest dose group. Reduced haemoglobin values were observed in all treated animals, and red blood cell counts were also lower. Animals in the higher dose groups had increased absolute and relative spleen weights, whereas haematocrit values, average cell volumes (mean corpuscular volume [MCV]), haemoglobin per cell (mean corpuscular haemoglobin [MCH]) and average concentration of haemoglobin in cells (mean corpuscular haemoglobin concentration [MCHC]) were reduced (Katz et al., 1984).

In a similar experiment with 2-propoxyethyl acetate, all 10 rats in the highest dose group (4400 mg/kg body weight per day) died, whereas all animals in the lowest dose group (2200 mg/kg body weight per day) survived. The observed effects were otherwise similar to those reported for 2-propoxyethanol (Katz et al., 1984).

Increased numbers of reticulocytes (immature red blood cells) and slight polychromasia (variation in haemoglobin content) in red blood cells were observed when pregnant rats were exposed 6 h/day for 10 days to airborne concentrations of 425–1700 mg 2-propoxyethanol/m^3. One of the 30 rats exposed to 425 mg/m^3 had red urine on days 6 and 7. At 850 mg/m^3 and above, red blood cells were reduced in number and had higher average cell volume (MCV) and haemoglobin content (MCH); spleen weight was also increased. During the first days of exposure, food intake was reduced, and there was temporary red coloration of the urine. Histological changes, especially at 1275 and 1700 mg/m^3, were macrocytosis and anisocytosis (enlarged and irregular-sized red blood cells). Effects were also observed on the spleen (stasis and accumulation of haemosiderin), liver (pale cytoplasm) and thymus (necrotic changes in medulla), but not in kidneys, bone marrow or mesenteric lymph nodes (Krasavage & Katz, 1985).

Rats were exposed to 2-propoxyethanol (425–3400 mg/m^3, 6 h/day, 5 days/week; 11 exposure days) in a 2-week inhalation study. Haemoglobin was observed in the urine of both males and females at 3400 mg/m^3 and males at 1700 mg/m^3, but only after the 1st or 2nd day of exposure. At these exposure levels, there were also slight effects on peripheral blood (reduced red blood cell count, increased MCV and MCH), spleen (darkening and granulation, increased absolute and relative weights, stasis and extramedullary blood formation), liver (accumulation of haemosiderin) and kidneys (extramedullar blood formation). No effects were observed at 850 mg/m^3 (Katz et al., 1984).

In a similar experiment with 2-propoxyethyl acetate, haemoglobinuria was observed in both sexes at 4900 mg/m^3 and in female rats at 2400 mg/m^3 and 1200 mg/m^3. As with 2-propoxyethanol, there were slight effects on peripheral blood, spleen, liver and kidneys (extramedullary blood formation) at 2400 and 4900 mg/m^3. No effects were observed at 600 mg/m^3 (Katz et al., 1984). The above effects were also observed in pregnant rats exposed to 600–4900 mg 2-propoxyethyl acetate/m^3 (6 h/day, days 6–15 of gestation); in addition, a slight elevation of MCV was noted at 1200 mg/m^3 (Krasavage & Katz, 1984).

Rats exposed for 5 weeks to 1300 mg 2-propoxyethanol/m^3 (7 h/day, 5 days/week) showed a temporary reduction of haemoglobin values and number of red blood cells and an elevated proportion of immature granulocytes in the blood. Histological examination revealed, in some animals, fatty degeneration in the bone marrow and reduced cytoplasmic density in the liver. No effect on the number of reticulocytes was observed (Werner et al., 1943c).

Pregnant rabbits exposed for 2 weeks to airborne 2-propoxyethanol concentrations of 530–2100 mg/m^3 showed no adverse effects, except that 1 of 15 had red urine following the 2nd day of exposure (Krasavage et al., 1990).

8.4 Medium-term exposure

8.4.1 Oral

8.4.1.1 2-Ethoxyethanol

In the identified subchronic studies (Stenger et al., 1971; Krasavage & Vlaovic, 1982; NTP, 1993) in which rats were administered 2-ethoxyethanol by the oral route, the critical targets were the male reproductive organs and the blood.

Groups of 10 male and 10 female F344/N rats were administered 2-ethoxyethanol in drinking-water for 13 weeks at concentrations of 0, 1250, 2500, 5000, 10 000 or 20 000 mg/l (estimated to be equivalent to doses of 0, 109, 205, 400, 792 and 2240 mg/kg body weight per day in males and 0, 122, 247, 466, 804 and 2061 mg/kg body weight per day in females) (NTP, 1993). Microscopic examination was performed on an extensive range of tissues from all animals at the two higher dose levels and controls and on the major organs at the three lower dose levels. Haematological parameters, along with clinical chemistry and urine analyses, were investigated at 1, 3 and 13 weeks. Sperm morphology and vaginal cytology evaluations were performed on animals administered 205/247, 400/466 or 792/804 mg/kg body weight per day.

In males, atrophy of the prostate gland was observed at concentrations equivalent to doses of 205 mg/kg body weight per day or more, the severity of the lesions increasing with dose. Concentrations of spermatogonia and sperm were also significantly lower in rats administered 205 mg/kg body weight per day or more (although not clearly dose related), and dose-related testicular degeneration was observed at 400 mg/kg body weight per day or more.

In females, mild anaemia, which was characterized as macrocytic (increased MCV), hypochromic (decreased MCHC) and poorly regenerative, as well as moderate to marked thrombocytopenia and moderate leukopenia, were observed after 1 week of exposure to 2-ethoxyethanol. Several parameters were affected (although generally transiently) at doses as low as 247 mg/kg body weight per day, with an effect on platelet count being reported (at weeks 3 and 13) even at 122 mg/kg body weight per day. The severity of the anaemia was considered to have progressed to moderate after 3 and 13 weeks of exposure and was accompanied by moderate thrombocytopenia and marked leukopenia,

which progressed to marked leukocytosis. Increased haematopoiesis and haemosiderin pigmentation of the spleen and liver were also noted, but were considered secondary to haematological effects.

Male rats also exhibited mild anaemia (again characterized as macrocytic, hypochromic and poorly regenerative) at doses of 792 mg/kg body weight per day and above as early as 1 week after initiation of exposure. The severity of the anaemia increased with duration of exposure and was described as marked to moderate after 3 and 13 weeks. Mild thrombocytopenia and leukopenia were also present in males exposed to 400 mg/kg body weight per day or more after 1 week of exposure; however, the thrombocytopenia appeared to be reversible, based on the lack of significant reduction in platelet count, whereas leukopenia was judged to be moderate after 13 weeks.

Alterations in clinical chemistry parameters indicative of general toxicity or liver dysfunction were noted in males and females at ≥205 and ≥466 mg/kg body weight per day, respectively.

Based on effects on the thymus, testes, prostate gland and blood, the investigators (NTP, 1993) considered the lowest-observed-adverse-effect level (LOAEL) in male rats to be 205 mg/kg body weight per day (with a no-observed-adverse-effect level [NOAEL] of 109 mg/kg body weight per day). The investigators considered the NOAEL in female rats to be 466 mg/kg body weight per day, based on the haematological and associated histopathological changes (although some blood parameters were altered, generally transiently, at lower doses).

A similar profile of effects was observed in other subchronic oral studies in different strains of rats. When groups of 10 rats (strain CR,COBS,CD,BR) were administered 2-ethoxyethanol by gavage, 5 days/week for 6 weeks, at doses of 0, 450, 900 and 1800 mg/kg body weight per day, haematological effects consistent with anaemia as well as alterations in white blood cell parameters were observed in those administered at least 900 mg/kg body weight per day. Microscopic examination included a wide range of tissues, and haematological and clinical chemistry analyses were undertaken (Krasavage & Vlaovic, 1982). In another study, groups of five male and five female Wistar rats were exposed by gavage for 13 weeks at dose levels equivalent to 0, 46, 93 and 186 mg/kg body weight per day or were exposed to 93 or 186 mg/kg body weight per day for 59 days followed by 372 or 743 mg/kg body weight per day for a further 30 days. Microscopic examination of a wide range of tissues and haematological analysis (haemoglobin and haematocrit levels only) were performed on weeks 5, 9 and 13 (Stenger et al., 1971). Reduced haemoglobin and haematocrit were reported in those exposed to 93 mg/kg body weight per day by gavage for 59 days followed by exposure to 372 mg/kg body weight per day for 30 days. Haemosiderin pigmentation was also noted in the spleen of both these strains of rats, with the lowest effect level being 186 mg/kg body weight per day in the Wistar rat. Effects on male reproductive organs (including reduced testicular weights, atrophy and degeneration) and on sperm parameters (degenerated spermatozoa and hypospermia) were observed in these strains of rats at doses of 450 mg/kg body weight per day (the lowest dose tested) and above for 6 weeks (Krasavage & Vlaovic, 1982) or 186 mg/kg body weight per day and above for 13 weeks, but not at 93 mg/kg body weight per day (considered to be the NOAEL) (Stenger et al., 1971). Histopathological changes in the stomach and bone marrow were also noted at 450 mg/kg body weight per day or higher (Krasavage & Vlaovic, 1982).

Data on the effects in mice following subchronic oral exposure to 2-ethoxyethanol are limited to a single study in which groups of 10 male and 10 female B6C3F1 mice were exposed via drinking-water to 0, 2500, 5000, 10 000, 20 000 or 40 000 mg/l (equivalent to approximately 0, 587, 971, 2003, 5123 or 7284 mg/kg body weight per day in males and 0, 722, 1304, 2725, 7255 or 11 172 mg/kg body weight per day in females) for 13 weeks. Microscopic examination was performed on an extensive range of tissues in all high-dose and control animals and on the adrenal gland (female), spleen and testis in the lower dose groups. Sperm morphology and vaginal cytology evaluations were conducted in animals exposed to 0, 5000, 10 000 or 20 000 mg/l (NTP, 1993). Based on the results of this study, mice appear to be less sensitive than rats to 2-ethoxyethanol-induced toxic effects. As in rats, the male reproductive system was a target organ in mice, with effects on weight and histopathology of testes observed at 5123 mg/kg body weight per day and above and 7284 mg/kg body weight per day, respectively, whereas effects on sperm parameters were noted at 5123 mg/kg body weight per day or more. In addition, effects on the estrous cycle were observed in females exposed to 1304 mg/kg body weight per day and above. Although haematological parameters were not examined in mice, haematopoiesis of the spleen was noted at the highest dose in males and at 7255 mg/kg body weight per day and above in females. The incidence of a rather rare lesion, hypertrophy of the X-zone of the adrenal gland, resulting from marked lipid vacuolization, was significantly increased in female mice administered 2725 mg/kg body weight per day or more (and non-significantly increased at 1304 mg/kg body weight per day); this lesion was not observed in any of the subchronic oral studies in rats. Based on this study, the LOAELs in male and female mice are considered to be 5123 and 1304 mg/kg body weight per day, with NOAELs of 2003 and 722 mg/kg body weight per day, respectively.

8.4.1.2 2-Propoxyethanol

No data were identified on oral exposure to 2-propoxyethanol in medium-term studies.

8.4.2 Inhalation

8.4.2.1 2-Ethoxyethanol

Identified information on the subchronic toxicity of inhaled 2-ethoxyethanol and its acetate is limited to earlier studies in rats and rabbits. Exposure to 94 mg 2-ethoxyethanol/m^3 or more for 13 weeks was irritating to the eyes and nose of Sprague-Dawley rats. However, no exposure-related lesions were observed in the extensive range of tissues (including the testes) examined at the highest concentration of 1500 mg/m^3, and the only systemic effects noted were reductions in relative weights of the pituitary gland in males and the spleen in females exposed to 1500 mg/m^3 and alterations in leukocyte count and blood urea nitrogen in female rats at the highest concentration (Barbee et al., 1984). In male and female Wistar rats exposed to 2-ethoxyethyl acetate at a concentration corresponding to 750 mg 2-ethoxy-ethanol/m^3 for 10 months, no haematological effects were noted, and the only histopathological change observed was renal tubular nephritis in males, although only a limited range of tissues was examined (Truhaut et al., 1979).

Exposure to airborne 2-ethoxyethanol (≥94 mg/m^3) was also irritating to the eyes and nose of rabbits. Reduced weight and degeneration of the testes were observed at 1500 mg/m^3, whereas anaemia was present in both sexes at this concentration (Barbee et al., 1984). Histopathological examinations of target tissues, including the testes, were apparently conducted in animals exposed to lower concentrations, without significant findings. As in rats, exposure to 750 mg 2-ethoxyethanol/m^3 via inhalation resulted in renal tubular nephritis in male rabbits; no effects on reproductive organs or blood parameters were reported (Truhaut et al., 1979).

8.4.2.2 2-Propoxyethanol

The results of two unpublished studies (Katz, 1987; Bernard, 1989) in which rats were exposed by inhalation for 14 weeks are detailed in the Screening Information Dataset (SIDS) dossier for 2-propoxyethanol prepared under the Organisation for Economic Co-operation and Development (OECD) high production volume (HPV) programme (OECD, 2004).

There were apparently no deaths or clinical signs of toxicity when groups of 15 male and 15 female CRL:CD(SD)BR rats were exposed 6 h/day, 5 days/week, for 14 weeks to atmospheres containing 2-propoxyethanol at 0, 425, 850 or 1700 mg/m^3. Following the exposure, animals exhibited lacrimation, red or brown discoloration of facial hair and a nasal discharge. Red urine was observed in 1–6 males (at various times throughout the exposure) and all females exposed to 1700 mg/m^3. When the urine of 12 females from each exposure group was further analysed, it was found to be haemolysed in all those exposed to 1700 mg/m^3 and in half of those exposed to 850 mg/m^3 (Katz, 1987).

Blood changes were observed in animals exposed to 850 or 1700 mg/m^3. These included decreased red blood cell count and haemoglobin concentration. Haematocrit was also decreased in high-dose males and in females exposed at the mid and high doses. MCV and MCH were increased in high-dose males and females. Platelet counts were also increased in mid- and high-dose females. Reticulocyte counts in high-dose males and females were 2 and 5 times those of controls, respectively. There was an increase in polychromasia in the blood of high-dose males and mid- and high-dose females and an increased incidence of Howell-Jolly bodies in high-dose females.

Relative kidney weights were increased in males and females exposed to 1700 mg/m^3 and in males at 850 mg/m^3. Relative spleen weights were increased in males exposed to 1700 mg/m^3 and females exposed to 850 or 1700 mg/m^3. Relative heart weights of males exposed to 1700 mg/m^3 were also increased.

Pigment deposition (morphologically similar to haemosiderin) was observed in the spleen of all high-dose males and Kupffer cells of the liver and renal tubules of most high-dose males and females. Pigment deposition was also observed in the renal tubules (mid-dose males and females), spleen (mid-dose males) and liver (mid-dose females). Pigment deposition was also apparently seen in the livers of control rats. The NOAEL was stated to be 425 mg/m^3 (Katz, 1987).

Similar effects were also observed in a neurotoxicity study (see section 8.8) in which groups of rats were treated using the same regime (Bernard, 1989).

8.5 Long-term exposure and carcinogenicity

No adequate long-term or carcinogenicity studies on 2-ethoxyethanol or 2-propoxyethanol have been published in the literature.

8.6 Genotoxicity and related end-points

8.6.1 2-Ethoxyethanol

The available information on the genotoxicity of 2-ethoxyethanol suggests that 2-ethoxyethanol may have some potential to induce cytogenetic damage in vitro,

although this was not reflected in in vivo studies in mice. There is no evidence that it induces mutations.

In the limited in vivo database, there was no evidence of the induction of micronuclei in the bone marrow of Swiss Webster or CD-1 mice given single intraperitoneal injections of 2-ethoxyethanol (up to 2000 or 3000 mg/kg body weight) (Guzzie et al., 1986; Elias et al., 1996), 2-ethoxyethyl acetate (no details of dose levels given in the published abstract) (Slesinski et al., 1988) or EAA (up to 200 mg/kg body weight) (Elias et al., 1996).

Neither 2-ethoxyethanol nor its acetate was mutagenic in several in vitro assays in *Salmonella typhimurium* (eight different strains tested, in both the presence and absence of metabolic activation) (Ong, 1980; Shimizu et al., 1985; Zeiger et al., 1985; Guzzie et al., 1986; Slesinski et al., 1988; Hüls AG, 1989; Hoflack et al., 1995) or in a limited number of studies in cultured mammalian cells (Guzzie et al., 1986; Myhr et al., 1986; Slesinski et al., 1988). Mixed or equivocal results have been reported for the induction of chromosomal aberrations, micronuclei or sister chromatid exchange by 2-ethoxyethanol or 2-ethoxyethyl acetate in various mammalian cell lines: in Chinese hamster ovary cells, positive (for 2-ethoxyethanol) (Guzzie et al., 1986; Galloway et al., 1987) and equivocal (for 2-ethoxyethyl acetate) (Slesinski et al., 1988) results were reported for induction of chromosomal aberrations in the absence of metabolic activation, whereas in the presence of activation, 2-ethoxyethanol was positive (Slesinski et al., 1988) and 2-ethoxyethyl acetate was negative (Guzzie et al., 1986; Galloway et al., 1987). 2-Ethoxyethanol failed to induce chromosomal aberrations in Chinese hamster lung (V79) cells (Elias et al., 1996) and human lymphocytes (Villalobos-Pietrini et al., 1989; Elias et al., 1996) without activation. An equivocal response was reported for the induction of micronuclei in Chinese hamster V79 cells (Elias et al., 1996). 2-Ethoxyethanol induced sister chromatid exchange in Chinese hamster ovary cells in both the presence and absence of activation (Guzzie et al., 1986; Galloway et al., 1987), whereas the acetate was negative (Slesinski et al., 1988). Sister chromatid exchange was also induced in human lymphocytes treated with 2-ethoxyethanol in the absence of metabolic activation (Villalobos-Pietrini et al., 1989); in Chinese hamster V79 cells, an equivocal result was reported (Elias et al., 1996). 2-Ethoxyethanol did not induce morphological transformation or aneuploidy in vitro, although it did show weak potential to interfere with mitotic division (Elias et al., 1996). Although neither of the two principal metabolites of 2-ethoxyethanol, EALD and EAA, was mutagenic in *S. typhimurium* (Hoflack et al., 1995), the aldehyde consistently tested positive for numerous cytogenetic end-points in vitro, although results for the acid metabolite were negative or equivocal (Elias et al., 1996).

8.6.2 2-Propoxyethanol

No studies on the genotoxicity of 2-propoxyethanol or 2-propoxyethyl acetate have been identified.

8.7 Reproductive and developmental toxicity

8.7.1 Effects on fertility

8.7.1.1 2-Ethoxyethanol

The majority of the relevant studies identified have involved exposure of male rats or mice by the oral route. Ingested 2-ethoxyethanol, as well as the acetate derivative and the acetic acid metabolite, consistently induced effects on male reproductive organs or sperm parameters in multiple strains of both species. Testicular and epididymal weights were reduced in Long-Evans, Sprague-Dawley, F344/N and CR,COBS,CD,BR rats administered doses of 200 mg/kg body weight per day or more by gavage in water or olive oil or in the drinking-water for 4 weeks or longer (Krasavage & Vlaovic, 1982; Oudiz & Zenick, 1986; NTP, 1993; Chung et al., 1999). Histopathological effects on the testes and spermatocytes were noted following oral exposure to 450 mg/kg body weight per day (the lowest dose tested) or more for 6 weeks (Krasavage & Vlaovic, 1982). Reductions in testicular or epididymal sperm counts or alterations in sperm motility or morphology were noted at doses as low as 150 mg/kg body weight per day (the lowest dose tested) when administered for 6 weeks or longer, with regularly mated males being more sensitive to these effects than non-mated rats (Hurtt & Zenick, 1986). Sperm counts were not assessed in the only study in which lower doses were investigated (i.e. Chung et al., 1999) or in a shorter-term study (11 days) in rats administered 250 mg/kg body weight per day (Foster et al., 1983), although spermatocyte degeneration was observed in the latter study only at 500 mg/kg body weight per day or more. Effects on male reproductive organs and on sperm parameters were not observed at 93 mg/kg body weight per day for 13 weeks (Stenger et al., 1971), considered to be a NOAEL (see section 8.4.1.1). Repeated oral administration of EAA, the predominant metabolite of 2-ethoxyethanol, induced a similar profile of male reproductive effects in rats (Foster et al., 1983, 1987), suggesting that this metabolite may be, at least in part, responsible for these effects.

Reduction in testicular or epididymal weights or alterations in sperm parameters were also observed in mice orally exposed to 2-ethoxyethanol or 2-ethoxyethyl acetate for 5 weeks or longer (Nagano et al., 1979, 1984; Morrissey et al., 1989; NTP, 1993; Chapin & Sloane, 1997), although this species appears to be less sensitive than rats, as the lowest dose associated with male reproductive effects in mice was 1000 mg/kg body

weight per day (with a NOAEL of 500 mg/kg body weight per day).

Although not as extensively investigated as in males, exposure to 2-ethoxyethanol in the drinking-water for 13 weeks induced effects on the estrous cycle in female rats and mice at doses of 804 and 1304 mg/kg body weight per day or more, respectively, with uterine atrophy occurring in rats at higher doses (NTP, 1993).

Oral studies were identified in which the effects of exposure to 2-ethoxyethanol, 2-ethoxyethyl acetate or EAA on reproductive ability were assessed in mice (Gulati et al., 1985; Morrissey et al., 1989; Chapin & Sloane, 1997). In a continuous-breeding study, in which both sexes were exposed in the drinking-water, all three substances adversely affected reproductive success (in terms of decreased fertility and reductions in numbers and weights of pups), with the LOAEL for 2-ethoxy-ethanol being approximately 1650 mg/kg body weight per day, whereas no adverse effects were noted at 850 mg/kg body weight per day. Effects were observed at all doses of the EAA metabolite tested (i.e. ≥300 mg/kg body weight per day). The results of crossover mating trials indicated that exposure of either sex to 2-ethoxy-ethanol or its acetate adversely affected reproductive ability, whereas such effects were noted only when females were exposed to EAA. However, effects on reproductive organs and sperm or estrous cycle parameters were observed at similar doses for all compounds. Continuous exposure in utero and until mating to 1860 mg 2-ethoxyethyl acetate/kg body weight per day also induced effects on reproductive success and organs and sperm parameters in males of the second generation; however, the investigators indicated that it was unclear whether the second generation was more sensitive than the first (Morrissey et al., 1989; Chapin & Sloane, 1997). In a secondary account of a similar continuous-breeding study in mice (Gulati et al., 1985), similar effects on reproductive success were observed at 2-ethoxyethyl acetate doses of 1800 mg/kg body weight per day or more (which were attributed to exposure of females in a crossover study), as well as effects on sperm and testes in males; in addition, histopathological changes in the testes were observed in the second generation.

In 13-week inhalation studies, reduced testes weight and degeneration of the seminiferous tubules were noted in rabbits exposed to 1500 mg/m^3, considered to be a LOAEL; however, effects on the testes were not observed in similarly exposed rats (Barbee et al., 1984) or in rats or rabbits exposed to higher concentrations of the acetate (Truhaut et al., 1979).

In the only identified inhalation study on the effects of 2-ethoxyethanol on reproductive ability, no effects on mating behaviour or fertility were observed in female rats exposed to up to 2430 mg/m^3 for 3 weeks prior to mating with unexposed males (Andrew & Hardin, 1984). This represents a NOAEC for this end-point.

8.7.1.2 2-Propoxyethanol

No studies on the effects of 2-propoxyethanol on fertility have been identified.

When groups of 15 male and 15 female CRL:CD(SD)BR rats were exposed 6 h/day, 5 days/ week, for 14 weeks to atmospheres containing 0 or 1700 mg 2-propoxyethanol/m^3, no effects on the sex organs (testes, epididymides, male accessory sex glands, ovaries, vagina, uterus, fallopian tubes) were observed (Katz, 1987).

2-Propoxyethanol given by gavage to male JCL-ICR mice (500–2000 mg/kg body weight per day) for 5 weeks had no effect on either weight or morphology of the testes (Nagano et al., 1984).

8.7.2 Developmental toxicity

8.7.2.1 2-Ethoxyethanol

Although only limited information is available on the developmental effects of 2-ethoxyethanol following oral exposure, adverse effects, including increased implantation loss, resorptions and embryo mortality, decreased fetal body weight, and various skeletal and cardiovascular abnormalities, were observed in multiple strains of rats, often in the absence of maternal toxicity (Stenger et al., 1971; Goad & Cranmer, 1984; Chester et al., 1986). In only one of the three limited accounts could a NOAEL be determined (NOAEL = 47 mg/kg body weight per day; LOAEL = 94 mg/kg body weight per day) (Stenger et al., 1971). In this study, 2-ethoxyethanol was administered to groups of 20–39 Wistar rats at doses equivalent to 0, 12, 24, 47, 94, 188 or 376 mg/kg body weight per day on days 1–21 of pregnancy. There were 69 control females. Dams were killed on day 22, and the numbers of implantation sites, resorptions, and live and dead fetuses were assessed. Fetuses were weighed and examined for external and skeletal malformations. No information on maternal toxicity was provided. Increased numbers of absorbed and resorbed fetuses were found at the highest dose. A decrease in the number of live fetuses and an increase in the number of pre- and post-implantation losses were reported at 188 and 376 mg/kg body weight per day. There was a decrease in the number of implantation sites at 188 mg/kg body weight per day and a decrease in fetal body weight at 94 mg/kg body weight per day and above. The incidence of skeletal variations was increased at 94 mg/kg body weight per day and above.

Similar developmental effects were observed at doses lower than those that were maternally toxic in the only identified relevant study in mice. Wier et al. (1987) exposed female mice to 2-ethoxyethanol by oral gavage at concentrations that ranged from 0 to 4.2 g/kg body weight per day from days 8 to 14 of gestation. At dose levels that did not produce maternal toxicity (1.8 and 2.6 g/kg body weight per day), 2-ethoxyethanol produced a statistically significant increase in malformations (fused or missing digits and kinked tail). Fetotoxicity, present as a decrease in fetal body weights, was marginally apparent at the 1.0 g/kg body weight per day dose level and above. Embryolethality occurred at 1.8 g/kg body weight per day (NOAEL [maternal] = 1000 mg/kg body weight per day; LOAEL [developmental toxicity] = 1000 mg/kg body weight per day).

Although the doses investigated in mice were higher than those in rats, mice appear to be less sensitive than rats to the developmental toxicity of ingested 2-ethoxyethanol, as only reduced fetal body weight was observed at the lowest dose tested (i.e. 1000 mg/kg body weight per day), whereas increased abnormalities were noted in rats at much lower doses.

The developmental toxicity of inhaled 2-ethoxyethanol and its acetate has been investigated in rats and rabbits. In many of these studies, fetotoxic effects were observed in multiple strains at concentrations lower than those causing maternal toxicity.

Groups of 24 Wistar-derived Alderley Park rats were exposed 6 h/day to 0, 40, 190 or 940 mg 2-ethoxyethanol/m^3 on days 6–15 of gestation and examined on day 21 (Tinston et al., 1983a; Doe, 1984). Skeletal variations, minor skeletal defects and renal pelvic dilatation were observed at 940 mg/m^3, and delayed ossification was seen at 190 mg/m^3. Intrauterine deaths were increased at 940 mg/m^3. An increase in preimplantation loss was observed at 190 mg/m^3. A smaller, statistically borderline increase in preimplantation loss was also observed at 40 mg/m^3, but no such effect was seen at the top exposure level of 940 mg/m^3. Maternal toxicity, as evidenced by reduced haemoglobin, haematocrit and mean red blood cell volume, was observed in rats exposed to 940 mg/m^3 (NOAEC [maternal] = 190 mg/m^3; NOAEC [developmental] = 40 mg/m^3).

In Sprague-Dawley and Fischer 344 rats, exposure to 2-ethoxyethyl acetate during gestation resulted in increased incidences of skeletal variations at the lowest concentrations tested, equivalent to 490 mg 2-ethoxyethanol/m^3. No evidence of maternal toxicity was reported (Nelson et al., 1984). The incidence of external malformations was increased in Fischer 344 rats after exposure to 2-ethoxyethyl acetate corresponding to 750 mg 2-ethoxyethanol/m^3 or more, and the incidence of visceral malformations and skeletal variations was increased at 370 mg 2-ethoxyethanol/m^3 and above. At 370 mg 2-ethoxyethanol/m^3 and above, slight maternal toxicity, including effects on erythropoiesis, was observed. No evidence of maternal or developmental toxicity was seen at 190 mg 2-ethoxyethanol/m^3 (Tyl et al., 1988). Similarly, 2-ethoxyethanol exposure during gestation induced fetal growth inhibition and terata in rats at 750 mg/m^3 (lowest concentration studied) and 2870 mg/m^3. Embryo mortality was additionally seen at the high exposure. There was evidence of maternal toxicity (reduced weight gain) only at 2870 mg/m^3 (Hardin et al., 1981; Andrew & Hardin, 1984).

Exposure of Sprague-Dawley rats to 2-ethoxyethanol for 7 h/day on gestation days 7–13 or 14–20 also induced neurological effects in the developing young, based on behavioural differences, consistent with decreased neuromotor function, and alterations in levels of several neurochemicals (particularly in the cerebrum) observed when the mothers were exposed to 370 mg/m^3 (the lowest concentration tested) and above. Maternal weight gain was reported to be unaffected at this exposure level, although in those exposed on days 14–20, there was an increase in the length of pregnancy (Nelson et al., 1981, 1982a,b).

In a range-finding study in which groups of six female Dutch rabbits were exposed to 0, 190, 560 or 1500 mg 2-ethoxyethanol/m^3 on gestation days 6–18, with examination of fetuses on day 21, Tinston (1983b) observed reduced mean number of implantations and number of live fetuses at 190 mg 2-ethoxyethanol/m^3 or more, in the absence of maternal effects. In the subsequent full study with 24 rabbits per group (Tinston et al., 1983b; Doe, 1984), no effects on these end-points, when examined on day 29, were observed at concentrations of 40, 190 or 660 mg/m^3. Increased incidences of skeletal defects and variations were observed at the highest exposure level. Because of haemolysis, effects on maternal blood parameters could not be assessed in this study (NOAEC [maternal] = 190 mg/m^3; NOAEC [developmental toxicity] = 40 mg/m^3). Developmental effects (increased number of resorptions, malformations and skeletal variations) were observed in fetuses of New Zealand White rabbits exposed to 2-ethoxyethanol at 600 mg/m^3 (the lowest concentration tested) during gestation; slight maternal toxicity (reduced weight gain) was also present at this exposure level. Exposure to 2300 mg/m^3 induced 100% embryo mortality (Hardin et al., 1981; Andrew & Hardin, 1984).

The developmental toxicity of 2-ethoxyethyl acetate was studied by inhalation in a study with Dutch rabbits (24 rabbits per group, exposure to 2-ethoxyethyl acetate, 6 h/day, on days 6–18 of pregnancy, corresponding to 94, 370 and 1500 mg 2-ethoxyethanol/m^3) (Tinston et al., 1983c; Doe, 1984). 2-Ethoxyethyl acetate induced

skeletal malformations of the vertebral column, an increase in total resorptions and a reduction in the weights of the surviving fetuses at exposure concentrations corresponding to 1500 mg 2-ethoxyethanol/m^3—a concentration also inducing haematological toxicity in the dams. It also caused skeletal variations at 370 mg/m^3 in Dutch rabbits. The NOAEC was identified as 94 mg 2-ethoxyethanol/m^3.

In New Zealand White rabbits exposed to 2-ethoxyethyl acetate, increased incidence of resorptions, decrease in viable implants and increase in malformations were observed at concentrations corresponding to 750 and 1100 mg 2-ethoxyethanol/m^3, and an increase in skeletal variations was observed at 370 mg/m^3. No evidence of fetotoxicity or teratogenicity was observed at 190 mg/m^3 (Tyl et al., 1988). At exposures to 2-ethoxyethyl acetate corresponding to 370 mg 2-ethoxyethanol/m^3 or more, slight maternal toxicity, including haematological effects, was also observed (NOAEC [maternal] = 190 mg/m^3; LOAEC [developmental toxicity] = 370 mg/m^3).

Dermally applied 2-ethoxyethanol or its acetate induced developmental effects, including increased resorptions, reduced number of live fetuses per litter, decreased fetal body weights and increased incidence of visceral malformations (predominantly of the cardiovascular system) and skeletal variants, in Sprague-Dawley rats at all doses tested (i.e. ≥4000 mg/kg body weight per day, a dose that was not or only slightly maternally toxic, as evidenced by reduced body weight gain) (Hardin et al., 1982, 1984).

8.7.2.2 2-Propoxyethanol

No embryotoxic, fetotoxic or teratogenic effects were seen in the fetuses of pregnant COBS CD(SD)BR rats exposed 6 h/day to 2-propoxyethanol (0, 425, 850, 1275 or 1700 mg/m^3) during organogenesis (days 6–15 of gestation), with examination on day 20. There was, however, a dose-related increase in the number of skeletal anomalies (such as partial ossification, rudimentary ribs and extra ribs). The increase was small and not statistically significant at 425 mg/m^3. Maternal toxicity, expressed as reduced food intake, effects on blood profile and haemoglobinuria, was observed at 850 mg/m^3 and above. One mother exposed to 425 mg/m^3 had red urine after the sixth and seventh exposures only, but there was otherwise no sign of maternal toxicity at this level of exposure (Krasavage & Katz, 1985).

Exposure to 2-propoxyethyl acetate (0, 600, 1200, 2400 or 4900 mg/m^3) using the same regime gave similar results. No embryotoxic, fetotoxic or teratogenic effects were seen. Exposure to 600 mg/m^3 yielded a weak (although not statistically significant) increase in the number of common skeletal anomalies, which reached statistical significance at exposures of 1200 mg/m^3 or higher. Maternal toxicity was observed at 2400 or 4900 mg/m^3 (Krasavage & Katz, 1984).

Pregnant New Zealand White rabbits (groups of 15) exposed to 2-propoxyethanol (0, 530, 1060 or 2100 mg/m^3) for 6 h/day on days 6–18 of gestation showed no embryotoxic, fetotoxic or teratogenic effects, and there was no increase in skeletal anomalies among the fetuses examined on day 29 of pregnancy. There was some evidence of maternal toxicity (reduced body weight gain) at the top dose (Krasavage et al., 1990).

In a preliminary range-finding study, groups of 50 CD-1 mice were given 0 or 2000 mg/kg body weight per day on days 6–13 of pregnancy and allowed to deliver normally. There was no treatment-related effect on the number of live pups per litter at birth, pup postnatal survival, pup weight gain or pup birth weight. Offspring were not examined for defects. One of the treated mothers died, compared with none of the controls (Hardin et al., 1987).

The above observations, taken together, suggest that the effects of these glycol ethers on skeletal formation in the young may be a secondary effect of their toxic (haemolytic) effects on the mothers.

8.8 Immunological and neurological effects

8.8.1 2-Ethoxyethanol

In the two relevant studies identified, there was no evidence that exposure to 2-ethoxyethanol or its acetate induced adverse effects on the immune system in rats or mice (the highest dose tested was 2400 mg/kg body weight per day for 10 days) (Houchens et al., 1984; Smialowicz et al., 1992).

8.8.2 2-Propoxyethanol

The results of an unpublished neurotoxicity study in rats are detailed in the SIDS dossier prepared under the OECD HPV programme (OECD, 2004). Groups of 10 male and 10 female CD(SD)BR rats were exposed for 6 h/day, 5 days/week, to airborne concentrations of 0, 425, 850 or 1700 mg 2-propoxyethanol/m^3. A functional observational battery (FOB) to assess activity, coordination, behaviour and changes in sensory function was conducted 4 days prior to exposure and on days 4, 10, 32, 60 and 95 of treatment. Forelimb and hindlimb grip strength were also evaluated. Central nervous system and peripheral nervous system tissues were examined microscopically in five males and five females at the end of the experiment. No treatment-related effects indicative of neurotoxicity were observed in any of the exposure groups during the FOB or on microscopic examination of nervous system tissues (Bernard, 1989).

8.9 In vitro haemolytic effects

2-Propoxyacetic acid, the acid metabolite of 2-propoxyethanol, added to rat blood in concentrations of 1, 2 or 4 mmol/l resulted in increases of about 10%, 20% and 40% in haematocrit values and a weak, not statistically significant, increase in the amount of free haemoglobin in plasma (Ghanayem et al., 1989). Butoxyacetic acid added to rat blood caused more pronounced haemolysis and erythrocyte swelling than did 2-propoxyacetic acid (Ghanayem et al., 1989), and the effects were much more pronounced in rat blood than in human blood (Carpenter et al., 1956; Ghanayem, 1989).

9. EFFECTS ON HUMANS

9.1 2-Ethoxyethanol

Acute toxicity (including severe symptoms and death) has been observed after consumption of between 40 and 200 ml 2-ethoxyethanol (equivalent to approximately 600 and 3000 mg/kg body weight) (Fucik, 1969; Bonitenko et al., 1990). Two phases of poisoning have been described. A temporary mild state of stupor and nausea ensued in some cases immediately after the 2-ethoxyethanol consumption. Patients then remained symptomless for 3–18 h, followed by gastrointestinal disturbances, nausea, vomiting, pain in the epigastral region, diarrhoea and central nervous system disturbances (weakness, headache, ataxia, psychomotoric excitation and coma).

Several epidemiological studies, designed to investigate the potential effects on the lymphohaematopoietic system or on reproduction and development, have been conducted in populations exposed to 2-ethoxyethanol or its acetate in the occupational environment. However, in most of these studies, many of which involved small populations, workers were also exposed to various other substances in the workplace. Although these studies are limited, effects on the blood and, possibly, reproductive effects in men were observed.

In a well-conducted cross-sectional study (Kim et al., 1999), effects on white blood cells, suggestive of bone marrow depression, were observed in a group of 57 painters exposed to 2-ethoxyethyl acetate (along with several other substances, including toluene, ethylbenzene, xylene, butanol, isopropanol, ethanol, ethyl acetate, butyl acetate, methyl isobutyl ketone and nonane). White blood cell and granulocyte counts were reduced in both exposure groups (categorized as "high" [$n = 27$] and "low" [$n = 30$]), in an exposure-related manner. Those painters exposed to mean concentrations of 17 mg 2-ethoxyethyl acetate/m^3 (approximately equivalent to 11 mg 2-ethoxyethanol/m^3) (range from not detected to 68 mg 2-ethoxyethanol/m^3) had a statistically significantly lower white blood cell and granulocyte count ($P < 0.05$), although this was not considered by the authors to be clinically significant. A statistically significantly higher proportion of all exposed painters had leukopenia (6/57 or 11%, five of which were in the high exposure group) compared with controls (0/41) ($P < 0.05$), and bone marrow hypoplasia was noted in the three leukopenic men examined. The effects remained after controlling for several potentially confounding factors (smoking and alcohol consumption, age and duration of work).

The incidence of anaemia and granulocytopenia was significantly ($P = 0.04$) increased in a group of 94 United States shipyard painters (mean age 38 ± 12 years) exposed to low levels (8-h TWA 0–80.5 mg/m^3, mean 9.9 mg/m^3) of 2-ethoxyethanol (along with several other substances, including 2-methoxyethanol) for a mean of 8 (± 7) years, as compared with 55 controls (mean age 48 ± 10 years; duration of employment 22 ± 11 years) (Welch & Cullen, 1988). Haemoglobin levels in these workers had declined since first employment, but were not related to duration of exposure. Exposed workers also had a slightly higher prevalence of low polymorphonuclear leukocyte counts. Bone marrow hypoplasia was also observed in a survey of seven printers exposed to 2-ethoxyethanol and other substances (Cullen et al., 1983).

Low haemoglobin and haematocrit values were observed in women exposed to 2-ethoxyethyl acetate at a level corresponding to 35 mg 2-ethoxyethanol/m^3 (geometric mean) in silk screening; they were also exposed to "small amounts" of toluene and methyl isobutyl ketone. Haemoglobin, haematocrit and red blood cell count showed a statistically significant negative association with exposure to 2-ethoxyethyl acetate. There was no effect on the leukocyte, granulocyte or platelet counts, and no effect on erythropoiesis was observed in men exposed to a geometric mean concentration of 18 mg/m^3 (Loh et al., 2003).

In the three relevant epidemiological investigations identified, reduced sperm production was consistently observed in populations occupationally exposed to mean 2-ethoxyethanol concentrations of 9.9 or 24 mg/m^3 (with maximum levels up to 88 mg/m^3), along with other substances (Welch et al., 1988; Ratcliffe et al., 1989; Schrader et al., 1996). Welch et al. (1988) examined the semen of 73 painters (mean age 37.5 years, range 19–62 years), employed for an average of 7.9 years (range 0.5–33 years) in a United States shipyard and exposed to a TWA concentration of 0–80.5 mg/m^3, with a mean of 9.9 mg/m^3 (matched with 40 controls: mean age 47.9 years [range 28–64 years], employed for 22 years [range 7–42 years]). Painters had an increased prevalence of

oligospermia and azospermia (odds ratio [OR] = 1.85; 95% confidence interval [CI] = 0.6–5.6).

The cross-sectional study of Ratcliffe et al. (1989) involved 37 men exposed to 2-ethoxyethanol used as a binder slurry in a United States metal castings process and 39 non-exposed controls. Full-shift breathing-zone exposures ranged from non-detectable to 90 mg/m^3 (geometric mean concentration of 25 mg/m^3). Urine measurements of the metabolite EAA ranged from non-detectable to 163 mg/g creatinine. A marginal, but statistically significant (P = 0.05), reduction in the average sperm count per ejaculate was found among the exposed workers compared with controls, after adjustment for age, smoking, alcohol and caffeine consumption, urogenital disorders, fever and other illnesses.

In a case–control study of 1019 men in Belgium with a clinical diagnosis of infertility or reduced fertility, there was a significant association between this diagnosis and the detection of EAA in the urine (OR = 3.11, P = 0.004) (Veulemans et al., 1993). Strong associations were reported between detection of EAA and exposure to paint products (P < 0.0001), glues (P = 0.004), solvents (P = 0.017), degreasers and cleaning products (P = 0.02) and petroleum products and fuels (P = 0.027).

There was no consistent evidence of effects on male or female reproductive ability in other investigations of men or women exposed to 2-ethoxyethanol, although most of these studies are limited by the lack of analyses for associations with 2-ethoxyethanol specifically (Beaumont et al., 1995; Schenker et al., 1995; Swan et al., 1995; Correa et al., 1996; Gray et al., 1996; Ha et al., 1996; Schenker, 1996; Swan & Forest, 1996; Chia et al., 1997).

9.2 2-Propoxyethanol

No case-studies or other reports of health effects associated with exposure to 2-propoxyethanol or 2-propoxyethyl acetate were found in the literature.

10. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

10.1 Aquatic environment

10.1.1 2-Ethoxyethanol

Data on the chronic toxicity of 2-ethoxyethanol have been identified only for protozoans, algae and hydra. The most sensitive organisms were microbial populations in waste stabilization ponds, with an approximately 40% inhibition of respirometric activity (i.e. changes in total organic carbon, chemical oxygen demand and 2-ethoxyethanol concentration) at 1 g/l in a 5-day study (Davis et al., 1989).

Data on acute toxicity have been reported for invertebrates and fish, although in many studies the LC_{50} for 2-ethoxyethanol was above the highest concentration tested. For example, the 24-h LC_{50}s for brine shrimp (*Artemia salina*) and goldfish (*Carassius auratus*) were >10 and >5 g/l, respectively (Price et al., 1974; Bridie et al., 1979). Hermens et al. (1984) reported a 48-h median inhibitory concentration (IC_{50}) of 7.7 g/l for *Daphnia magna*. Rose et al. (1998) reported a 48-h median effective concentration (EC_{50}) for *Ceriodaphnia dubia* immobilization of 1.9 g/l.

10.1.2 2-Propoxyethanol

Data on the toxicity of 2-propoxyethanol to aquatic organisms are summarized in Table 12. The very limited data available indicate low toxicity.

10.2 Terrestrial environment

10.2.1 2-Ethoxyethanol

No information on the effects of 2-ethoxyethanol on terrestrial wildlife was identified. Laboratory animal data are summarized in section 8.

A no-effect level of >100 µl/l was reported for the germination, hypocotyl growth and root growth of ryegrass, radish and lettuce (Katz, 1978).

10.2.2 2-Propoxyethanol

No information on the effects of 2-propoxyethanol on terrestrial wildlife was identified. Laboratory animal data are summarized in section 8.

11. EFFECTS EVALUATION

11.1 Evaluation of health effects

11.1.1 Hazard identification and dose–response assessment

11.1.1.1 2-Ethoxyethanol

2-Ethoxyethanol is readily absorbed following oral, inhalation or dermal exposure and is distributed extensively throughout the body. Skin absorption can be an important route of exposure, particularly in the occupational setting. Inhalation exposure alone will not give sufficient indication of biological exposure, and

Table 12. Data on the toxicity of 2-propoxyethanol to aquatic organisms.

Organism	Exposure	Test end-point	Value	Reference
Microorganisms				
Sewer microorganisms (not further defined)	16 h	IC_{50} (growth) (no further details given)	>1000 mg/l	Waggy (1987)
Microtox bacteria (not further defined)	Not stated	EC_{50} (growth) (no further details given)	2000 mg/l	Waggy (1987)
Plants				
Green algae	96 h	EC_{50} (EPIWIN/ECOSAR modelling)	2600 mg/l	OECD (2004)
Invertebrates				
Daphnia magna	48 h	LC_{50} (no further details given)	>5000 mg/l	Waggy (1987)
Daphnia magna	96 h	No-effect level (no further details given)	>100 µl/l	Katz et al. (1984)
Flatworm (not further defined)	96 h	No-effect level (no further details given)	>100 µl/l	Katz (1978)
Snail (not further defined)	96 h	No-effect level (no further details given)	>100 µl/l	Katz (1978)
Fish				
Fathead minnow (*Pimephales promelas*)	96 h	LC_{50} (no further details given)	>5000 mg/l	Waggy (1987)

thus the level of the EAA metabolite in the urine can be used as a specific and suitable indicator of overall exposure. 2-Ethoxyethanol is of low to moderate acute toxicity in laboratory animals following oral exposure and of low acute toxicity by the inhalation and dermal routes.

Little information was identified on the effects of 2-ethoxyethanol in humans. However, although the epidemiological data are not conclusive, the results of available investigations in occupationally exposed populations are suggestive of effects on the blood and on sperm production in men (Cullen et al., 1983; Welch & Cullen, 1988; Welch et al., 1988; Ratcliffe et al., 1989; Veulemans et al., 1993; Kim et al., 1999). There is consistent evidence from toxicological studies that haematological, male and female reproductive, and developmental effects are associated with exposure to 2-ethoxyethanol or its acetate. The results of mechanistic studies suggest that metabolic activation to the acetic acid metabolite, EAA, is required for the induction of these effects. For example, co-exposure to substances that interfere with metabolism via alcohol or aldehyde dehydrogenases (e.g. toluene, xylene and ethanol) reduced the severity of testicular atrophy in male rats (Chung et al., 1999) and the effects on neurological development in rats exposed to 2-ethoxyethanol in utero (Nelson et al., 1982a,b, 1984). Metabolism to EAA via alcohol and aldehyde dehydrogenases is the principal metabolic pathway in both humans and laboratory animals; indeed, there is some evidence, although limited, that humans may have greater potential than rats for formation of EAA and slower clearance than in rats (Groeseneken et al., 1988). Therefore, although there is only limited evidence of effects on the blood and sperm production in occupationally exposed human populations, based on the consistent evidence in laboratory animals and the similarity in metabolism across species, haematopoietic effects, reproductive toxicity (in males) and developmental toxicity are considered critical effects for 2-ethoxyethanol.

11.1.1.2 2-Propoxyethanol

The toxicological database for 2-propoxyethanol is limited. No information was identified on the effects of 2-propoxyethanol in humans.

From acute and subchronic studies in rats, the most sensitive target for toxicity appears to be the blood. Increased osmotic fragility of red blood cells was observed in an older study after acute inhalation exposure to 260 mg 2-propoxyethanol/m^3, but not at 140 mg/m^3 (Carpenter et al., 1956). In a study in which pregnant rats were exposed 6 h/day for 10 days, increased numbers of reticulocytes were observed at the lowest exposure level of 425 mg/m^3 (Krasavage & Katz, 1985). Haematotoxicity was also the principal effect observed when rats were exposed for 14 weeks to atmospheres containing 850 mg/m^3 or more; 425 mg/m^3 was identified as a NOAEC (Katz, 1987).

In a developmental toxicity study, the young of rats exposed during pregnancy to 425–1700 mg/m^3 showed a dose-related increase in the number of skeletal

anomalies; there was also evidence of maternal toxicity (Krasavage & Katz, 1985).

No data on genotoxicity or carcinogenicity were identified.

11.1.2 Criteria for setting tolerable intakes/ concentrations

11.1.2.1 2-Ethoxyethanol

It is widely accepted that 2-ethoxyethanol or its acetate should not be present in consumer products, and programmes to restrict such use are in place in many parts of the world. Use in an industrial setting may still present the possibility for exposure, however.

Three studies in populations exposed at work to 2-ethoxyethanol indicate effects on spermatogenesis (Welch et al., 1988; Ratcliffe et al., 1989; Veulemans et al., 1993). In the Welch et al. (1988) study, a slight effect on sperm count was observed among painters exposed to 2-ethoxyethanol at a mean concentration of 9.9 mg/m^3; the effect reached statistical significance only among non-smokers. The workers were, however, also exposed to other chemicals, notably to 2-methoxyethanol, at approximately the same concentrations. A slight, statistically borderline decrease in the sperm count was observed in foundry workers potentially exposed to 2-ethoxyethanol at an estimated geometric mean concentration of 24 mg/m^3 (Ratcliffe et al., 1989). An association with the presence of EAA in urine and low sperm count was observed in a case–referent study among patients attending a fertility clinic, although there was no clear relationship between the concentration of EAA in urine and the sperm count (Veulemans et al., 1993).

At a geometric mean exposure of 51 mg/m^3, a slight deficiency in erythropoiesis was observed in female workers exposed to 2-ethoxyethanol in silk screening (Loh et al., 2003). When there was a more mixed exposure (Kim et al., 1999), a similar slight haematological effect was reported in exposure to 2-ethoxyethyl acetate,[1] corresponding to an average 2-ethoxyethanol concentration of 11 mg/m^3.

None of these studies provides information sufficient for the development of a tolerable concentration. However, for comparison with the tolerable concentration developed below from the animal experiments, an approximation can be performed from the study of Ratcliffe et al. (1989) (with less important confounding exposures than in the Welch et al. [1988] study). Using the estimated geometric mean concentration of 24 mg/m^3 (at which a slight decrease in sperm count was observed among workers), adjusting for continuous exposure, using the default uncertainty factor of 10 for inter-individual variation and, considering the small changes observed and uncertainty of the findings, using an uncertainty factor of $10^{0.5}$ for the extrapolation from a LOAEC to a NOAEC, this gives a value of 0.2 mg/m^3. It should be emphasized, however, that these studies also involved exposure to other substances.

In studies on experimental animals, effects on fetal development have been observed at lowest concentrations of 2-ethoxyethanol. Studies on the developmental effects of 2-ethoxyethanol and 2-ethoxyethyl acetate indicate 40 mg/m^3 as a NOAEC in rats and in rabbits (Tinston et al., 1983a,b,c; Doe, 1984; Tyl et al., 1988). Adjusting for continuous exposure and using uncertainty factors for interspecies (10) and interindividual (10) variation, a tolerable concentration of 0.1 mg/m^3 can be derived.

11.1.2.2 2-Propoxyethanol

The available information does not allow derivation of a tolerable concentration for 2-propoxyethanol.

11.1.3 Sample risk characterization

The upper-bounding estimate of concentration in air in Canada is 3.6 µg/m^3, based on the detection limit in the multimedia exposure study by Conor Pacific Environmental Technologies Inc. (1998). The margin between the tolerable concentration derived and exposure is therefore about 30. If the tolerable concentration is compared with the highest concentration of 2-ethoxyethanol detected outside of an automotive plant in Windsor, Ontario (i.e. the maximum level actually detected in ambient air in Canada, 0.86 µg/m^3), this margin would be approximately 120.

With respect to ingestion, the margin between the intake equivalent to inhalation of 2-ethoxyethanol at a concentration of 0.1 mg/m^3 and the upper-bounding estimate of intake in drinking-water is about 4 orders of magnitude. Although intake of 2-ethoxyethanol in food could not be estimated, it is considered unlikely to be greater than the upper-bounding estimate for air or drinking-water.

In contrast, worst-case estimates of exposure to 2-ethoxyethanol through use of a consumer product containing 2-ethoxyethanol could approach or exceed even the effect levels for health effects in humans. For example, the estimates of indoor air concentrations

[1] As the acetate derivative of 2-ethoxyethanol is rapidly converted to 2-ethoxyethanol in the body, with similar resulting health effects, it was considered appropriate to develop effect levels on the basis of studies in which the toxicity of 2-ethoxyethyl acetate was investigated, converting the exposure levels of the acetate to equivalent concentrations or doses of 2-ethoxyethanol on a relative molecular weight basis.

resulting from use of all-purpose spray cleaners containing the substance (the only household cleaning product for which information on composition was available) are more than an order of magnitude greater than the tolerable concentration (190 mg/m^3 for 0.47 h, corresponding to a 24-h TWA concentration of 3.7 mg/m^3). Under these circumstances, it has been estimated that 75% of the systemic dose is due to inhalation (see Table 9). It should be emphasized, however, that these estimates are extreme worst case and have not been validated. As information on current compositions and use patterns of products is extremely limited, these values likely considerably overestimate current exposures, particularly in view of the decline in use of this compound in many countries.

Measurements of the concentration of 2-ethoxyethanol and its acetate in workplace air do not allow reliable prediction of the resulting systemic dose, because of the possibility of additional dermal exposure and the fact that there may be significant absorption through the skin. However, recent exposure data from occupational scenarios indicate that levels in many workplaces may largely exceed the tolerable concentration.

11.1.4 Uncertainties in the evaluation of health risks

In humans, information on reproductive effects of 2-ethoxyethanol and its acetate is limited to possible effects on sperm counts and morphology. In animals, however, while effects on testis and sperm have been reported, effects on the fetus and embryo have been recorded at lower exposure levels, and the tolerable concentration is derived from experimental studies on developmental toxicity.

Reversible effects on erythropoiesis have been observed consistently in experimental animals at levels approximately similar to those for developmental effects; very limited information available would tend to indicate that in humans also, the sensitivities of bone marrow and reproductive function are rather similar.

There is a moderate to high degree of confidence in the characterization of the health hazards associated with exposure to 2-ethoxyethanol for the purposes of identifying critical effects for risk characterization as haematology and reproductive effects. There is some uncertainty concerning the effects of 2-ethoxyethanol following long-term exposure, as no adequate chronic or carcinogenicity studies in animals are available. Likewise, no epidemiological investigations of the potential effects in humans in which both magnitude and duration of exposure to 2-ethoxyethanol were considered have been identified.

Owing to the paucity of data on levels of 2-ethoxyethanol in environmental media, there is a high degree of uncertainty in the estimates of exposure. Conservative upper-bounding estimates of exposure were determined on the basis of the detection limits reported in the multimedia exposure study in Canada. However, predicted concentrations in ambient air and drinking-water based on fugacity modelling were several orders of magnitude below these detection limits, and levels in the small survey of ambient air in Windsor, Ontario, Canada (in which confidence is greater), were lower than the detection limit reported for the multimedia study. This approach is thus likely to be conservative. It should also be noted that uptake of 2-ethoxyethanol vapour via dermal absorption has not been considered in these estimates of exposure. As well, the contribution of food and soil to overall intake of 2-ethoxyethanol is unknown, as no relevant data were identified, although predictions based on fugacity modelling suggest that intake from these sources is likely to be much less than the upper-bounding estimates of intake from air and drinking-water upon which the conclusions presented here are based.

There is an extremely low degree of confidence in the estimates of exposure to 2-ethoxyethanol from consumer products, as a result of the large uncertainties regarding the presence and concentrations of the substance in products currently used. Therefore, it is likely that the values presented here considerably overestimate potential current exposures and are not relevant in countries where the material is no longer used in consumer products. The estimates were also calculated assuming 100% absorption through the skin, in view of the lack of adequate data to support a lower per cent absorption. There is a high degree of confidence, however, that absorption through the skin can be significant.

11.2 Evaluation of environmental effects

11.2.1 2-Ethoxyethanol

Most environmental releases of 2-ethoxyethanol are to the atmosphere. Based on its predicted environmental partitioning, assessment end-points for 2-ethoxyethanol relate to terrestrial organisms, including terrestrial wildlife and soil organisms, and aquatic organisms.

For a conservative risk characterization for terrestrial biota, the estimated exposure value (EEV) is 860 ng/m^3, the highest concentration of 2-ethoxyethanol reported in Canada (near an automotive plant in Windsor, Ontario) (OMEE, 1994). The critical toxicity value (CTV) is 1.9×10^8 ng/m^3, the concentration that had minimal fetotoxic effects on rats and rabbits in inhalation studies. Dividing this CTV by a factor of 100 (to account for the extrapolation from laboratory to field

conditions and interspecies and intraspecies variations in sensitivity) gives an estimated no-effects value (ENEV) of 1.9×10^6 ng/m^3.

The conservative quotient (EEV/ENEV) is calculated as follows:

$$\frac{\text{EEV}}{\text{ENEV}} = \frac{860 \text{ ng/m}^3}{1.9 \times 10^6 \text{ ng/m}^3}$$

$$= 4.53 \times 10^{-4}$$

Therefore, concentrations of 2-ethoxyethanol in air in Canada are unlikely to cause adverse effects on populations of wildlife.

For a conservative risk characterization for soil organisms, the EEV is 4.15×10^{-4} ng/g, the estimated concentration of 2-ethoxyethanol in soil using ChemCAN4 modelling based on reported releases in 1995. This value is believed to be conservative, because releases of 2-ethoxyethanol in Canada appear to have decreased significantly since 1995.

No information was identified regarding the toxicity of 2-ethoxyethanol to soil organisms. Van Leeuwen et al. (1992) used quantitative structure–activity relationships to estimate that a sediment concentration of 2800 ng 2-ethoxyethanol/g would be hazardous to 5% of benthic species (HC_5). Using this sediment HC_5 value as a CTV and an application factor of 100 (to account for the extrapolation from benthic to soil organisms) gives an ENEV of 28 ng/g for soil organisms.

The conservative quotient (EEV/ENEV) is calculated as follows:

$$\frac{\text{EEV}}{\text{ENEV}} = \frac{4.15 \times 10^{-4} \text{ ng/g}}{28 \text{ ng/g}}$$

$$= 1.48 \times 10^{-5}$$

Therefore, concentrations of 2-ethoxyethanol in soil in Canada are unlikely to cause adverse effects on populations of soil organisms.

For a conservative risk characterization for aquatic organisms, the EEV is 2.2×10^{-5} µg/l, the estimated concentration of 2-ethoxyethanol in water using ChemCAN4 modelling based on reported releases in 1995. This value is believed to be conservative, because releases of 2-ethoxyethanol in Canada appear to have decreased significantly since 1995.

The CTV for aquatic organisms was based on the 48-h EC_{50} for *Ceriodaphnia dubia* of 1.9×10^6 µg/l. Dividing this CTV by a factor of 100 (to account for the conversion of a short-term EC_{50} to a long-term no-effects value, extrapolation from laboratory to field conditions, and interspecies and intraspecies variations in sensitivity) gives an ENEV of 1.9×10^4 µg/l.

The conservative quotient (EEV/ENEV) is calculated as follows:

$$\frac{\text{EEV}}{\text{ENEV}} = \frac{2.2 \times 10^{-5} \text{ µg/l}}{1.9 \times 10^4 \text{ µg/l}}$$

$$= 1.2 \times 10^{-9}$$

Therefore, concentrations of 2-ethoxyethanol in water in Canada are unlikely to cause adverse effects on populations of aquatic organisms.

There are several sources of uncertainty in this environmental risk assessment. Few data on environmental concentrations of 2-ethoxyethanol in Canada or elsewhere were identified; limited monitoring data were identified for air only. The EEV for wildlife exposure is considered to be conservative, as it was based on the maximum concentration measured near an industrial facility in Windsor, Ontario. In addition, 2-ethoxyethanol was not detected in ambient air in the multimedia exposure study in Canada (Conor Pacific Environmental Technologies Inc., 1998) or in a survey of six locations in the USA (Sheldon et al., 1988).

In view of the lack of adequate monitoring data, the ChemCAN4 model was used to estimate concentrations of 2-ethoxyethanol in the other environmental compartments (i.e. soil and water), based on the highest reported recent (before 1997) release of the substance in Canada, which occurred in 1995. Kane (1993) compared measured environmental concentrations of five industrial chemicals and six pesticides with environmental concentrations estimated for the substances by the ChemCAN4 model. Sixty per cent of the measured environmental concentrations were within 1 order of magnitude of predicted values, and 75% were within 2 orders of magnitude. In the only relevant study identified from other countries, the concentration of 2-ethoxyethanol in a polluted river in Japan ranged up to 1200 µg/l (Yasuhara et al., 1981), a value that is an order of magnitude lower than the ENEV for aquatic organisms.

No information was identified regarding the toxicity of 2-ethoxyethanol to soil organisms or to terrestrial wildlife through atmospheric exposure. An estimation of a hazardous concentration to benthic species was the basis for the assessment of risk to soil organisms. The results of inhalation toxicity studies using laboratory strains of rats and rabbits were used for the assessment of risk to terrestrial biota. To account for these uncertainties, application factors were used in the environmental risk assessment to derive ENEVs.

Conservative risk quotients were very small for all environmental assessment end-points. Therefore, despite the data gaps regarding the effects of 2-ethoxyethanol on soil organisms and terrestrial wildlife, the data available at this time are considered adequate for drawing a conclusion about the environmental risk of the substance in Canada.

11.2.2 2-Propoxyethanol

The available data and incomplete reporting do not permit an environmental risk assessment of 2-propoxyethanol.

12. PREVIOUS EVALUATIONS BY BODIES OF THE INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS (IOMC)

A WHO Environmental Health Criteria monograph (EHC) on 2-methoxyethanol, 2-ethoxyethanol and their acetates was published in 1990 (IPCS, 1990). No other evaluations published by IOMC organizations were identified.

REFERENCES

Ahrens W, Jöckel KH (1996) *Stoffbelastung in der Papierindustrie*. Bremerhaven, Wirtschaftsverlag NW, Schriftenreihe der Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (GA 48).

Andrew FD, Hardin BD (1984) Developmental effects after inhalation exposure of gravid rabbits and rats to ethylene glycol monoethyl ether. *Environmental Health Perspectives*, 57:13–23.

Angerer J, Lichterbeck E, Begerow J, Jekel S, Lehnert G (1990) Occupational chronic exposure to organic solvents. XIII. Glycol-ether exposure during the production of varnishes. *International Archives of Occupational and Environmental Health*, 62(2):123–126.

Bailey H, Liu DHW, Javitz HA (1985) Time/toxicity relationships in short-term static, dynamic, and plug-flow bioassays. In: Bahner RC, Hansen DJ, eds. *Aquatic toxicology and hazard assessment: Eighth symposium*. Philadelphia, PA, American Society for Testing and Materials, pp. 193–212 (ASTM STP 891).

Ballantine J (1997) Personal communication. Letter from J. Ballantine, Pest Management Regulatory Agency, to K. Lloyd, Commercial Chemicals Evaluation Branch, Environment Canada, dated 12 September 1997 [cited in Environment Canada & Health Canada, 2002].

Barbee SJ, Terrill JB, DeSousa DJ, Conaway CC (1984) Subchronic inhalation toxicology of ethylene glycol monoethyl ether in the rat and rabbit. *Environmental Health Perspectives*, 57:157–163.

Barber ED, Teetsel NM, Kolberg KF, Guest D (1992) A comparative study of the rates of in vitro percutaneous absorption of eight chemicals using rat and human skin. *Fundamental and Applied Toxicology*, 19:493–497.

Beaumont JJ, Swan SH, Hammond SK, Samuels SJ, Green RS, Hallock MF, Dominguez C, Boyd P, Schenker MB (1995) Historical cohort investigation of spontaneous abortion in the Semiconductor Health Study: epidemiologic methods and analyses of risk in fabrication overall and in fabrication work groups. *American Journal of Industrial Medicine*, 28(6):735–750.

Bernard LG (1989) *A subchronic inhalation study of ethylene glycol monopropyl ether in rats using a functional observational battery and neuropathology to detect neurotoxicity*. Rochester, NY, Eastman Kodak Company, 5 July 1989 (HAEL No. 88-0017) [cited in OECD, 2004].

BfR (2003) *2-Ethoxyethanol*. Berlin, Bundesinstitut für Risikobewertung (Federal Institute for Risk Assessment).

BGAA (1999) *Altstoffe – Exposition am Arbeitsplatz – 3.20 2-Ethoxyethanol / 3.21 2-Ethoxyethylacetat.* Sankt Augustin, Hauptverband der gewerblichen Berufsgenossenschaften, Berufsgenossenschaftlicher Arbeitskreis Altstoffe (BGAA Report 1/99).

Boatman RJ, Knaak JB (2001) Ethers of ethylene glycol and derivatives. In: *Patty's industrial hygiene and toxicology*, 5th ed. New York, NY, John Wiley & Sons, pp. 73–270.

Boatman RJ, Perry LG, English JC (1998) *The disposition and pharmacokinetics of ethylene glycol mono propyl ether in male Sprague-Dawley rats after intravenous or oral administration, nose-only inhalation, or dermal exposure*. Rochester, NY, Eastman Kodak Co., 18 September 1998 (HAEL No. 88-0017) [cited in OECD, 2004].

Bonitenko I, Kutsenko SA, Koposov ES, Bonitenko E (1990) [Acute poisoning with ethylene glycol esters.] *Klinicheskaia meditsina*, 68(5):126–130 (in Russian).

Bridie AL, Wolff CJM, Winter M (1979) The acute toxicity of some petrochemicals to goldfish. *Water Research*, 13:623–626.

Canadian Chemical Producers' Association (1999a) *Reducing emissions 6. A Responsible Care initiative. 1997 emissions inventory and five year projections.* Ottawa, Ontario.

Canadian Chemical Producers' Association (1999b) *Reducing emissions 7. A Responsible Care initiative. 1998 emissions inventory and five year projections.* Ottawa, Ontario.

Cao XL (1999) *Emissions of glycol ethers from consumer products—a final report for 1998/1999 CEPA project.* Ottawa, Ontario, Health Canada, June.

Carpenter CP (1947) Cellosolve. *Journal of the American Medical Association*, 135:880.

Carpenter CP, Smyth HF Jr (1946) Chemical burns of the rabbit cornea. *American Journal of Ophthalmology*, 29:1363–1372.

Carpenter CP, Smyth HF Jr, Pozzani UC (1949) The assay of acute vapor toxicity, and the grading and interpretation of results on 96 chemical compounds. *Journal of Industrial Hygiene and Toxicology*, 31:343–346.

Carpenter CP, Pozzani UC, Weil CS, Nair JH 3rd, Keck GA, Smyth HF Jr (1956) The toxicity of butyl cellosolve solvent. *AMA Archives of Industrial Health*, 14(2):114–131.

Chapin RE, Sloane RA (1997) Reproductive assessment by continuous breeding: evolving study design and summaries of ninety studies. *Environmental Health Perspectives*, 105(Suppl. 1):199–205.

Cheever KL, Plotnick HB, Richards DE, Weigel WW (1984) Metabolism and excretion of 2-ethoxyethanol in the adult male rat. *Environmental Health Perspectives*, 57:241–248.

Chester A, Hull J, Andrew F (1986) Lack of teratogenic effect after ethylene glycol monoethyl ether (EGEE) in rats via drinking water. *Teratology*, 33:57C (Abstract P24).

Chia SE, Foo SC, Khoo NY, Jeyaratnam J (1997) Menstrual patterns of workers exposed to low levels of 2-ethoxyethyl-acetate (EGEEA). *American Journal of Industrial Medicine*, 31(2):148–152.

Chinn H (2004) CEH marketing report: Glycol ethers. In: *Chemical economics handbook*. Menlo Park, CA, SRI International, July, p. 6.

Chinn H, Anderson E, Tainiro M (1996) CEH marketing research reports: Glycol ethers. In: *Chemical economics handbook*. Menlo Park, CA, SRI International.

Chung WG, Yu IJ, Park CS, Lee KH, Roh HK, Cha YN (1999) Decreased formation of ethoxyacetic acid from ethylene glycol monoethyl ether and reduced atrophy of testes in male rats upon combined administration with toluene and xylene. *Toxicology Letters*, 104(1–2):143–150.

Churchman GJ, Burke CM (1991) Properties of subsoils in relation to various measures of surface area and water content. *Journal of Soil Science*, 42:463–478.

Clayton GD, Clayton FR, eds (1982) *Patty's industrial hygiene and toxicology*, 3rd rev. ed. New York, NY, Wiley-Interscience.

Conor Pacific Environmental Technologies Inc. (1998) *A report on multimedia exposures to selected PSL2 substances.* Prepared on contract for Health Canada, Ottawa, Ontario (Project No. 741-6705).

Correa A, Gray RH, Cohen R, Rothman N, Shah F, Seacat H, Corn M (1996) Ethylene glycol ethers and risks of spontaneous abortion and subfertility. *American Journal of Epidemiology*, 143(7):707–717.

Cullen MR, Rado T, Waldron JA, Sparer J, Welch LS (1983) Bone marrow injury in lithographers exposed to glycol ethers and organic solvents used in multicolor offset and ultraviolet curing printing processes. *Archives of Environmental Health*, 38(6):347–354.

Daughtrey WC, Ward DP, Lewis SC, Peterson DR (1984) Acute toxicity of dermally applied 2-ethoxyethanol. *Toxicologist*, 4:180 (Abstract 717).

Davis EM, Sullivan EC, Downs TD (1989) Determination of cellosolve and chlorex concentrations inhibitory to industrial waste stabilization pond treatment efficiencies. *Water Science and Technology*, 21:1833–1836.

De Bortoli M, Knoppel H, Pecchio E, Peil A, Rogora L, Schauenburg H, Schlitt H, Vissers H (1986) Concentrations of selected organic pollutants in indoor and outdoor air in northern Italy. *Environment International*, 12:343–350.

Denkhaus W, Von Steldern D, Botzenhardt U, Konietzko H (1986) Lymphocyte subpopulations in solvent-exposed workers. *International Archives of Occupational and Environmental Health*, 57(2):109–115.

DMER, AEL (1996) *Pathways analysis using fugacity modelling of 2-ethoxyethanol for the second Priority Substances List.* Report prepared for Chemicals Evaluation Division, Commercial Chemicals Evaluation Branch, Environment Canada, by Don Mackay Environmental Research, Peterborough, Ontario, and Angus Environmental Limited, Don Mills, Ontario, March.

Doe JE (1984) Ethylene glycol monoethyl ether and ethylene glycol monoethyl ether acetate teratology studies. *Environmental Health Perspectives*, 57:33–41.

Dugard PH, Walker M, Mawdsley SJ, Scott RC (1984) Absorption of some glycol ethers through human skin in vitro. *Environmental Health Perspectives*, 57:193–197.

ECETOC (1995) *The toxicology of glycol ethers and its relevance to man.* Brussels, European Centre for Ecotoxicology and Toxicology of Chemicals, 350 pp. (ECETOC Technical Report No. 64).

Elias Z, Daniere MC, Marande AM, Poirot O, Terzetti F, Schneider O (1996) Genotoxic and/or epigenetic effects of some glycol ethers: results of different short-term tests. *Occupational Hygiene*, 2:187–212.

Environment Canada (1997a) *Results of the CEPA section 16 notice respecting the second Priority Substances List and di(2-ethylhexyl) phthalate.* Hull, Quebec, Environment Canada, Commercial Chemicals Evaluation Branch, Use Patterns Section.

Environment Canada (1997b) Notice respecting the second Priority Substances List and di(2-ethylhexyl) phthalate. *Canada Gazette*, Part I, 15 February 1997, pp. 366–368.

Environment Canada (1999) *Canadian Environmental Protection Act—Priority Substances List supporting document for the*

environmental assessment of 2-methoxyethanol, 2-ethoxyethanol, 2-butoxyethanol. Hull, Quebec, Environment Canada, Commercial Chemicals Evaluation Branch.

Environment Canada, Health Canada (2002) *Canadian Environmental Protection Act, 1999. Priority Substances List assessment report: 2-Ethoxyethanol.* Ottawa, Ontario, Government of Canada, August (http://www.hc-sc.gc.ca/ewh-semt/alt_formats/hecs-sesc/pdf/pubs/contaminants/psl2-lsp2/2_ethoxyethanol/2_ethoxyethanol-eng.pdf).

Flick EW (1986) *Household and automotive cleaners and polishes*, 3rd ed. Park Ridge, NJ, Noyes Publications.

Flick EW (1994) *Advanced cleaning product formulations. Vol. 2.* Park Ridge, NJ, Noyes Publications.

Foster PM, Creasy DM, Foster JR, Thomas LV, Cook MW, Gangolli SD (1983) Testicular toxicity of ethylene glycol monomethyl and monoethyl ethers in the rat. *Toxicology and Applied Pharmacology*, 69(3):385–399.

Foster PM, Lloyd SC, Blackburn DM (1987) Comparison of the in vivo and in vitro testicular effects produced by methoxy-, ethoxy- and *N*-butoxy acetic acids in the rat. *Toxicology*, 43(1):17–30.

Fucik J (1969) Poisoning by ethylene glycol monoethyl ether. *Pracovní Lékařstvi*, 21:116–118.

Galloway SM, Armstrong MJ, Reuben C, Colman S, Brown B, Cannon C, Bloom AD, Nakamura F, Ahmed M, Duk S, Rimpo J, Margolin BH, Resnick MA, Anderson B, Zeiger E (1987) Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: evaluations of 108 chemicals. *Environmental and Molecular Mutagenesis*, 10(Suppl. 10):1–175.

Gao X, Chen BQ, Zhang P, Shen YY (1997) [Effects of 2-ethyloxyethanol [*sic*] on the activity of LDH-C_4 and the relationship between its exposure and sperm toxicity.] *Chinese Journal of Industrial Medicine*, 10(2):72–75 (in Chinese).

Gargas ML, Tyler TR, Sweeney LM, Corley RA, Weitz KK, Mast TJ, Paustenbach DJ, Hays SM (2000a) A toxicokinetic study of inhaled ethylene glycol ethyl ether acetate and validation of a physiologically based pharmacokinetic model for rat and human. *Toxicology and Applied Pharmacology*, 165(1):63–73.

Gargas ML, Tyler TR, Sweeney LM, Corley RA, Weitz KK, Mast TJ, Paustenbach DJ, Hays SM (2000b) A toxicokinetic study of inhaled ethylene glycol monomethyl ether (2-ME) and validation of a physiologically based pharmacokinetic model for the pregnant rat and human. *Toxicology and Applied Pharmacology*, 165(1):53–62.

Ghanayem BI (1989) Metabolic and cellular basis of 2-butoxyethanol-induced hemolytic anemia in rats and assessment of human risk in vitro. *Biochemical Pharmacology*, 38:1679–1684.

Ghanayem BI, Burka LT, Matthews HB (1989) Structure–activity relationships for the in vitro hematotoxicity of *N*-alkoxyacetic acids, the toxic metabolites of glycol ethers. *Chemico-Biological Interactions*, 70:339–352.

Goad PT, Cranmer JM (1984) Gestation period sensitivity of ethylene glycol monoethyl ether in rats. *Toxicologist*, 4:87 (Abstract 345).

Gray RH, Correa A, Hakim R, Cohen R, Corn M, Shah R, Rothman N, Hou W, Secat H (1996) Ethylene glycol ethers and reproductive health in semiconductor workers. *Occupational Hygiene*, 2:331–338.

Groeseneken D, Van Vlem E, Veulemans H, Masschelein R (1986a) Gas chromatographic determination of methoxyacetic and ethoxyacetic acid in urine. *British Journal of Industrial Medicine*, 43(1):62–65.

Groeseneken D, Veulemans H, Masschelein R (1986b) Respiratory uptake and elimination of ethylene glycol monoethyl ether after experimental human exposure. *British Journal of Industrial Medicine*, 43(8):544–549.

Groeseneken D, Veulemans H, Masschelein R (1986c) Urinary excretion of ethoxyacetic acid after experimental human exposure to ethylene glycol monoethyl ether. *British Journal of Industrial Medicine*, 43(9):615–619.

Groeseneken D, Veulemans H, Masschelein R, Van Vlem E (1987a) Pulmonary absorption and elimination of ethylene glycol monoethyl ether acetate in man. *British Journal of Industrial Medicine*, 44(5):309–316.

Groeseneken D, Veulemans H, Masschelein R, Van Vlem E (1987b) Ethoxyacetic acid: a metabolite of ethylene glycol monoethyl ether acetate in man. *British Journal of Industrial Medicine*, 44(7):488–493.

Groeseneken D, Veulemans H, Masschelein R, Van Vlem E (1988) Comparative urinary excretion of ethoxyacetic acid in man and rat after single low doses of ethylene glycol monoethyl ether. *Toxicology Letters*, 41(1):57–68.

Groeseneken D, Veulemans H, Masschelein R, Van Vlem E (1989) An improved method for the determination in urine of alkoxyacetic acids. *International Archives of Occupational and Environmental Health*, 61(4):249–254.

Guest D, Hamilton ML, Deisinger PJ, DiVincenzo GD (1984) Pulmonary and percutaneous absorption of 2-propoxyethyl acetate and 2-ethoxyethyl acetate in Beagle dogs. *Environmental Health Perspectives*, 57:177–183.

Gulati DK, Barnes LH, Russell S, Poonacha KB (1985) *Ethylene glycol monoethyl ether acetate: Reproduction and fertility assessment in CD-1 mice when administered in drinking water*. Research Triangle Park, NC, United States Department of Health and Human Services, National Institutes of Health, National Institute of Environmental Health Sciences, National Toxicology Program, pp. 1–51, 75–76, 80, 84, 89–101, 317–320, 327 [cited in ECETOC, 1995].

Guzzie PJ, Slesinski RS, Hengler WC, Tyler TR (1986) Assessment of 2-ethoxyethanol for genotoxicity using a battery of in vitro and in vivo test systems. *Environmental Mutagenesis*, 8(Suppl. 6):33 (Abstract 86).

Ha MC, Cordier S, Dananche B, Bergeret A, Mandereau L, Bruno F (1996) Congenital malformations and occupational exposure to glycol ethers: a European collaborative case–control study. *Occupational Hygiene*, 2:417–421.

Hamlin JW, Hudson B, Sheen AD, Saunders KJ (1982) The measurement of glycol ether levels in the workplace. *Polymers Paint Colour Journal*, 772:61–63.

Hammond SK, Hines CJ, Hallock MF, Woskie SR, Kenyon EM, Schenker MB (1996) Exposures to glycol ethers in the semiconductor industry. *Occupational Hygiene*, 2:355–366.

Hansch C, Leo A, Hoekman D (1995) *Exploring QSAR. Hydrophobic, electronic, and steric constants.* Washington, DC,

American Chemical Society (ACS Professional Reference Book).

Harada T, Nagashima Y (1975) Utilization of alkyl ether compounds by soil bacteria. *Journal of Fermentation Technology*, 53:218–222.

Hardin BD, Bond GP, Sikov MR, Andrew FD, Beliles RP, Niemeier RW (1981) Testing of selected workplace chemicals for teratogenic potential. *Scandinavian Journal of Work, Environment and Health*, 7(Suppl. 4):66–75.

Hardin BD, Niemeier RW, Smith RJ, Kuczuk MH, Mathinos PR, Weaver TF (1982) Teratogenicity of 2-ethoxyethanol by dermal application. *Drug and Chemical Toxicology*, 5(3):277–294.

Hardin BD, Goad PT, Burg JR (1984) Developmental toxicity of four glycol ethers applied cutaneously to rats. *Environmental Health Perspectives*, 57:69–74.

Hardin BD, Schuler RL, Burg JR, Booth GM, Hazelden KP, MacKenzie KM, Piccirillo VJ, Smith KN (1987) Evaluation of 60 chemicals in a preliminary developmental toxicity test. *Teratogenesis, Carcinogenesis, and Mutagenesis*, 7:29–48.

Hays SM, Elswick BA, Blumenthal GM, Welsch F, Conolly RB, Gargas ML (2000) Development of a physiologically based pharmacokinetic model of 2-methoxyethanol and 2-methoxyacetic acid disposition in pregnant rats. *Toxicology and Applied Pharmacology*, 163(1):67–74.

Health and Safety Executive (1988) *Methods for the determination of hazardous substances: Glycol ethers and glycol acetate vapors in air*. London, United Kingdom Health and Safety Executive, pp. 1–7 (MDHS-23).

Health Canada (1998a) Personal communication on glycol ethers in pesticides from V. Bergeron, Pest Management Regulatory Agency, Health Canada, Ottawa, Ontario [cited in Environment Canada & Health Canada, 2002].

Health Canada (1998b) *Exposure factors for assessing total daily intake of priority substances by the general population of Canada. Draft report.* Ottawa, Ontario, Health Canada, Environmental Health Directorate, March.

Health Canada (2001) *Cosmetic Notification System database*. Ottawa, Ontario, Health Canada, Product Safety Bureau (searched 20 March 2001).

Hermens J, Canton H, Janssen P, DeJong R (1984) Quantitative structure–activity relationships and toxicity studies of mixtures of chemicals with anaesthetic potency: acute lethal and sublethal toxicity to *Daphnia magna*. *Aquatic Toxicology*, 5:143–154.

Hodgson AT, Wooley JD (1991) *Assessment of indoor concentrations, indoor sources and source emissions of selected volatile organic compounds. Final report.* Sacramento, CA, California Air Resources Board, Research Division, March 1991, 179 pp. (Contract No. A933-063).

Hoflack JC, Lambolez L, Elias Z, Vasseur P (1995) Mutagenicity of ethylene glycol ethers and of their metabolites in *Salmonella typhimurium* his−. *Mutation Research*, 341(4):281–287.

Houchens DP, Ovejera AA, Niemeier RW (1984) Effects of ethylene glycol monomethyl (EGME) and monoethyl (EGEE) ethers on the immunocompetence of allogeneic and syngeneic mice bearing L1210 mouse leukemia. *Environmental Health Perspectives*, 57:113–118.

Howard PH, Boethling RS, Jarvis WF, Meylan WM, Michalenko EM (1991) *Handbook of environmental degradation rates*. Chelsea, MI, Lewis Publishers.

HSDB (2004) *Hazardous Substances Data Bank*. Bethesda, MD, United States Department of Health and Human Services, National Institutes of Health, National Library of Medicine (http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB).

Hüls AG (1989) *Report No. AM-89/22*. Marl, Hüls AG [cited in ECETOC, 1995].

Hurtt ME, Zenick H (1986) Decreasing epididymal sperm reserves enhances the detection of ethoxyethanol-induced spermatotoxicity. *Fundamental and Applied Toxicology*, 7(2):348–353.

IPCS (1990) *2-Methoxyethanol, 2-ethoxyethanol, and their acetates.* Geneva, World Health Organization, International Programme on Chemical Safety, 126 pp. (Environmental Health Criteria 115).

IPCS (2002) *International Chemical Safety Card—Ethylene glycol monoethyl ether.* Geneva, World Health Organization, International Programme on Chemical Safety (ICSC 0060; http://www.ilo.org/public/english/protection/safework/cis/products/icsc/dtasht/_icsc00/icsc0060.pdf).

IPCS (2004) *International Chemical Safety Card—Ethylene glycol monopropyl ether.* Geneva, World Health Organization, International Programme on Chemical Safety (ICSC 0607; http://www.ilo.org/public/english/protection/safework/cis/products/icsc/dtasht/_icsc06/icsc0607.pdf).

IPCS (2006) *International Chemical Safety Card—2-Ethoxyethyl acetate.* Geneva, World Health Organization, International Programme on Chemical Safety (ICSC 0364; http://www.ilo.org/public/english/protection/safework/cis/products/icsc/dtasht/_icsc03/icsc0364.pdf).

Johanson G, Dynesius B (1988) Liquid/air partition coefficients of six commonly used glycol ethers. *British Journal of Industrial Medicine*, 45:561–564.

Jönsson AK, Pedersen J, Steen G (1982) Ethoxyacetic acid and *N*-ethoxyacetylglycine: metabolites of ethoxyethanol (ethylcellosolve) in rats. *Acta Pharmacologica et Toxicologica*, 50(5):358–362.

Joshi SB, Dodge MC, Bufalini JJ (1982) Reactivities of selected organic compounds and contamination effects. *Atmospheric Environment*, 16:1301–1310.

Kane DM (1993) *Evaluation of ChemCAN2—a fugacity-based multimedia exposure model used to predict the environmental fate of organic chemicals in Canada.* Draft report, 14 January 1993, 28 pp. [cited in Environment Canada & Health Canada, 2002].

Katz GV (1978) *Basic toxicity of 2-propoxyethanol*. Rochester, NY, Eastman Kodak Co., 30 November 1978 (Report HS&HFL No. 78-144) [cited in OECD, 2004].

Katz GV (1987) *Subchronic inhalation toxicity study of ethylene glycol monopropyl ether in the rat.* Rochester, NY, Eastman Kodak Co., 9 June 1987 (HAEL No. 85-0105) [cited in OECD, 2004].

Katz GV, Krasavage WJ, Terhaar CJ (1984) Comparative acute and subchronic toxicity of ethylene glycol monopropyl ether and ethylene glycol monopropyl ether acetate. *Environmental Health Perspectives*, 57:165–175.

Kawai F (1995) Bacterial degradation of glycol ethers. *Applied Microbiology and Biotechnology*, 44(3–4):532–538.

Kennah HE 2nd, Hignet S, Laux PE, Dorko JD, Barrow CS (1989) An objective procedure for quantitating eye irritation based upon changes of corneal thickness. *Fundamental and Applied Toxicology*, 12(2):258–268.

Kennedy CH, Bechtold WE, Chang IY, Henderson RF (1993) Effect of dose on the disposition of 2-ethoxyethanol after inhalation by F344/N rats. *Fundamental and Applied Toxicology*, 21(4):486–491.

Kezic S, Mahieu K, Monster AC, de Wolff FA (1997) Dermal absorption of vaporous and liquid 2-methoxyethanol and 2-ethoxyethanol in volunteers. *Occupational and Environmental Medicine*, 54(1):38–43.

Kim Y, Lee N, Sakai T, Kim KS, Yang JS, Park S, Lee CR, Cheong HK, Moon Y (1999) Evaluation of exposure to ethylene glycol monoethyl ether acetates and their possible haematological effects on shipyard painters. *Occupational and Environmental Medicine*, 56(6):378–382.

Kirk-Othmer (1980) *Kirk-Othmer encyclopedia of chemical technology*, 3rd ed. *Vol. 11*. New York, NY, John Wiley & Sons.

Krasavage WJ, Katz GV (1984) Developmental toxicity of ethylene glycol monopropyl ether acetate (EGPEA) in the rat. *Environmental Health Perspectives*, 57:25–32.

Krasavage WJ, Katz GV (1985) Developmental toxicity of ethylene glycol monopropyl ether in the rat. *Teratology*, 32:93–102.

Krasavage WJ, Terhaar CJ (1981) *Comparative toxicity of nine glycol ethers: I. Acute oral LD_{50} and II. Acute dermal LD_{50}.* Initial submission: letter from Eastman Kodak Co. to United States Environmental Protection Agency regarding toxicity studies of nine glycol ethers with attachments and cover letter dated 09/28/92 (Document No. 88-920008915; NTIS/OTS0570960).

Krasavage WJ, Vlaovic MS (1982) *Comparative toxicity of nine glycol ethers: III. Six weeks repeated dose study.* Initial submission: letter from Eastman Kodak Co. to United States Environmental Protection Agency regarding toxicity studies of nine glycol ethers with attachments and cover letter dated 09/28/92 (Document No. 88-920008915; NTIS/OTS0570960).

Krasavage WJ, Hosenfeld RS, Katz GV (1990) Ethylene glycol monopropyl ether: a developmental toxicity study in rabbits. *Fundamental and Applied Toxicology*, 15:517–527.

Laug EP, Calvery HO, Morris HJ, Woodard G (1939) The toxicology of some glycols and derivatives. *Journal of Industrial Hygiene and Toxicology*, 21:173–201.

Liu YQ, Li CQ, Zhang ZG, Zhao J, Wang WL (1999) Changes in levels of serum β_2-microglobumine [*sic*] and creatine among workers exposed to 2-ethyloxyethanol [*sic*]. *Chinese Journal of Occupational Medicine*, 26(3):52–53.

Lockley DJ, Howes D, Williams FM (2002) Percutaneous penetration and metabolism of 2-ethoxyethanol. *Toxicology and Applied Pharmacology*, 180(2):74–82.

Loh CH, Shih TS, Lin YC, Hsieh AT, Chen CY, Liao GD (2003) Haematological effects among silk screening workers exposed to 2-ethoxy ethyl acetate. *Occupational and Environmental Medicine*, 60(9):E7.

Lowry LK (1996) 2-Ethoxyethanol (EGEE) and 2-ethoxyethyl acetate (EGEAA). In: *Biological monitoring of chemical exposure in the workplace. Vol. 1.* Geneva, World Health Organization, pp. 175–185.

Lundberg P, ed. (1994) *Scientific basis for Swedish occupational standards. XV. Consensus report for ethylene glycol monopropylether and its acetate.* Solna, National Institute for Working Life, Criteria Group for Occupational Standards (Arbete och Hälsa 30).

Lyman WJ, Reehl WF, Rosenblatt DH (1982) *Handbook of chemical property estimation methods: Environmental behavior of organic compounds.* New York, NY, McGraw-Hill.

Mackay D, Paterson S, Di Guardo A, Cowan CE (1996) Evaluating the environmental fate of a variety of types of chemicals using the EQC model. *Environmental Toxicology and Chemistry*, 15(9):1627–1637.

Morrissey RE, Lamb JC, Morris RW, Chapin RE, Gulati DK, Heindel JJ (1989) Results and evaluations of 48 continuous breeding reproduction studies conducted in mice. *Fundamental and Applied Toxicology*, 13(4):747–777.

Myhr BC, Bowers LR, Caspary WJ (1986) Results from the testing of coded chemicals in the L5178Y $TK^{+/-}$ mouse lymphoma mutagenesis assay. *Environmental Mutagenesis*, 8:58 (Abstract 154).

Nagano K, Nakayama E, Koyano M, Oobayashi H, Adachi H, Yamada T (1979) [Testicular atrophy of mice induced by ethylene glycol mono alkyl ethers.] *Sangyo Igaku*, 21(1):29–35 (in Japanese).

Nagano K, Nakayama E, Oobayashi H, Nishizawa T, Okuda H, Yamazaki K (1984) Experimental studies on toxicity of ethylene glycol alkyl ethers in Japan. *Environmental Health Perspectives*, 57:75–84.

Nelson BK, Brightwell WS, Setzer JV, Taylor BJ, Hornung RW, O'Donohue TL (1981) Ethoxyethanol behavioral teratology in rats. *Neurotoxicology*, 2(2):231–249.

Nelson BK, Brightwell WS, Setzer JV (1982a) Prenatal interactions between ethanol and the industrial solvent 2-ethoxyethanol in rats: maternal and behavioral teratogenic effects. *Neurobehavioral Toxicology and Teratology*, 4(3):387–394.

Nelson BK, Brightwell WS, Setzer JV, O'Donohue TL (1982b) Prenatal interactions between ethanol and the industrial solvent 2-ethoxyethanol in rats: neurochemical effects in the offspring. *Neurobehavioral Toxicology and Teratology*, 4(3):395–401.

Nelson BK, Setzer JV, Brightwell WS, Mathinos PR, Kuczuk MH, Weaver TE, Goad PT (1984) Comparative inhalation teratogenicity of four glycol ether solvents and an amino derivative in rats. *Environmental Health Perspectives*, 57:261–271.

NIOSH (1994) *NIOSH manual of analytical methods (NMAM®)*, 4th ed. Cincinnati, OH, United States Department of Health and Human Services, National Institute for Occupational Safety and Health, August (DHHS (NIOSH) Publication 94-113).

NPRI (1998) *National Pollutant Release Inventory*. Ottawa, Ontario, Environment Canada (http://www.ec.gc.ca/pdb/npri/).

NPRI (2000) *National Pollutant Release Inventory*. Ottawa, Ontario, Environment Canada (http://www.ec.gc.ca/pdb/npri/).

NTP (1993) *NTP technical report on toxicity studies of ethylene glycol ethers 2-methoxyethanol, 2-ethoxyethanol, 2-butoxy-*

ethanol (CAS Nos. 109-86-4, 110-80-5, 111-76-2) administered in drinking water to F344/N rats and B6C3F1 mice. Research Triangle Park, NC, United States Department of Health and Human Services, National Institutes of Health, National Institute of Environmental Health Sciences, National Toxicology Program, 122 pp. + appendices (NTP Toxicity Report Series No. 26; NIH Publication No. 93-3349).

OECD (2004) *Monoethylene glycol ethers category. SIDS initial assessment report for SIAM 19.* Paris, Organisation for Economic Co-operation and Development; Geneva, UNEP Publications, 251 pp. (http://www.chem.unep.ch/irptc/sids/oecdsids/MonoethyleneGlycolEthers.pdf).

OMEE (1994) *Windsor Air Quality Study: TAGA 6000 survey results.* Windsor, Ontario, Ontario Ministry of Environment and Energy, Air Quality Committee; Toronto, Ontario, Queen's Printer for Ontario (PIBS 3152E).

Ong T (1980) Internal NIOSH communication reported in NIOSH (1983) *Current Intelligence Bulletin No. 39.* Cincinnati, OH, National Institute for Occupational Safety and Health, pp. 1–22 (NMS/PB 80-155742) [cited in ECETOC, 1995].

OSHA (2003) *Occupational exposure to 2-methoxy ethanol, 2-ethoxyethanol and their acetates (glycol ethers). Proposed rule.* Washington, DC, United States Department of Labor, Occupational Safety and Health Administration (29 CFR Part 1960; Federal Register 68(250)).

Oudiz D, Zenick H (1986) In vivo and in vitro evaluations of spermatotoxicity induced by 2-ethoxyethanol treatment. *Toxicology and Applied Pharmacology*, 84(3):576–583.

Piacitelli GM, Votaw DM, Krishnan ER (1990) An exposure assessment of industries using ethylene glycol ethers. *Applied Occupational and Environmental Hygiene*, 5(2):107–114.

Pozzani UC, Weil CS, Carpenter CP (1959) The toxicological basis of threshold limit values. 5. The experimental inhalation of vapour mixtures by rats, with notes upon the relationship between single dose inhalation and single dose oral data. *American Industrial Hygiene Association Journal*, 20:364–369 [cited in ECETOC, 1995].

Price KS, Waggy GT, Conway RA (1974) Brine shrimp bioassay and seawater BOD of petrochemicals. *Journal of the Water Pollution Control Federation*, 46:63–77.

Ratcliffe JM, Schrader SM, Clapp DE, Halperin WE, Turner TW, Hornung RW (1989) Semen quality in workers exposed to 2-ethoxyethanol. *British Journal of Industrial Medicine*, 46(6):399–406.

Riddick J, Bunger WB, Sakano TK (1986) *Organic solvents: physical properties and methods of purification*, 4th ed. New York, NY, John Wiley & Sons, 1325 pp.

Rogozen MB, Rich HE, Gutman MA, Grosjean D (1987) *Evaluation of potential toxic air contaminants, Phase I.* Sacramento, CA, California Air Resources Board, 23 December 1987 (Final Report Contract A4-131-32).

Römer KG, Balge F, Freundt KJ (1985) Ethanol-induced accumulation of ethylene glycol monoalkyl ethers in rats. *Drug and Chemical Toxicology*, 8(4):255–264.

Rose RM, Warne MSJ, Lim RP (1998) Quantitative structure–activity relationships and volume fraction analysis for nonpolar narcotic chemicals to the Australian cladoceran *Ceriodaphnia* cf. *dubia*. *Archives of Environmental Contamination and Toxicology*, 34(3):248–252.

Sabljic A (1984) Prediction of the nature and strength of soil sorption of organic pollutants by molecular topology. *Journal of Agricultural and Food Chemistry*, 32:243–246.

Sartori P, Pahlmann W (1990) *Stoffbelastungen in der Mikroelektronik. Schriftenreihe der Bundesanstalt für Arbeitsschutz – Gefährliche Arbeitsstoffe.* Bremerhaven, Wirtschaftsverlag NW, 136 pp. (GA 36).

Schenker MB (1996) Reproductive health effects of glycol ether exposure in the semiconductor industry. *Occupational Hygiene*, 2:367–372.

Schenker MB, Gold EB, Beaumont JJ, Eskenazi B, Hammond SK, Lasley BL, McCurdy SA, Samuels SJ, Saiki CL, Swan SH (1995) Association of spontaneous abortion and other reproductive effects with work in the semiconductor industry. *American Journal of Industrial Medicine*, 28(6):639–659.

Schrader SM, Turner TW, Ratcliffe JM, Welch LS, Simon SD (1996) Combining reproductive studies of men exposed to 2-ethoxyethanol to increase statistical power. *Occupational Hygiene*, 2:411–415.

Sheldon L, Zeion H, Sickles J, Eaton C, Hartwell T (1988) *Indoor air quality in public buildings. Vol. II.* Washington, DC, United States Environmental Protection Agency (EPA/600/6-88/0096).

Shepard KP (1988a) *Skin sensitization study (Buehler method) of 2-propoxyethanol.* Rochester, NY, Eastman Kodak Co., Health and Environment Laboratories, Toxicological Sciences Laboratory, 3 May 1988 (HAEL No. 88-0017) [cited in OECD, 2004].

Shepard KP (1988b) *Skin sensitization study (footpad method) of 2-propoxyethanol.* Rochester, NY, Eastman Kodak Co., Health and Environment Laboratories, Toxicological Sciences Laboratory, 4 May 1988 (HAEL No. 88-0017) [cited in OECD, 2004].

Shimizu H, Suzuki Y, Takemura N, Goto S, Matsushita H (1985) The results of microbial mutation test for forty-three industrial chemicals. *Sangyo Igaku*, 27(6):400–419.

Slesinski RS, Guzzie PJ, Tyler TR (1988) Cytotoxicity and genotoxic potential of ethylene glycol monoethyl ether acetate (EGEEAc) in a battery of short term test systems. *Environmental and Molecular Mutagenesis*, 11(Suppl. II):97 (Abstract 236).

Smallwood AW, DeBord KE, Lowry LK (1984) Analyses of ethylene glycol monoalkyl ethers and their proposed metabolites in blood and urine. *Environmental Health Perspectives*, 57:249–253.

Smallwood AW, Debord K, Burg J, Moseley C, Lowry L (1988) Determination of urinary 2-ethoxyacetic acid as an indicator of occupational exposure to 2-ethoxyethanol. *Applied Industrial Hygiene*, 3(2):47–50.

Smialowicz RJ, Williams WC, Riddle MM, Andrews DL, Luebke RW, Copeland CB (1992) Comparative immunosuppression of various glycol ethers orally administered to Fischer 344 rats. *Fundamental and Applied Toxicology*, 18(4):621–627.

Smyth HF Jr, Seaton J, Fischer L (1941) The single dose toxicity of some glycols and derivatives. *Journal of Industrial Hygiene and Toxicology*, 23:259–268.

Smyth HF Jr, Carpenter CP, Weil CS, Pozzani UC, Striegel JA, Nycum JS (1969) Range-finding toxicity data: List VII. *American Industrial Hygiene Association Journal*, 30(5):470–476.

Söhnlein B, Letzel S, Weltle D, Rudiger HW, Angerer J (1993) Occupational chronic exposure to organic solvents. XIV. Examinations concerning the evaluation of a limit value for 2-ethoxyethanol and 2-ethoxyethyl acetate and the genotoxic effects of these glycol ethers. *International Archives of Occupational and Environmental Health*, 64(7):479–484.

Sparer J, Welch LS, McManus K, Cullen MR (1988) Effects of exposure to ethylene glycol ethers on shipyard painters: I. Evaluation of exposure. *American Journal of Industrial Medicine*, 14(5):497–507.

Stemmler K, Mengon W, Kinnison DJ, Kerr JA (1997) OH radical-initiated oxidation of 2-butoxyethanol under laboratory conditions related to the troposphere: product studies and proposed mechanism. *Environmental Science and Technology*, 31:1496–1504.

Stenger EG, Aeppli L, Muller D, Peheim E, Thomann P (1971) [Toxicology of ethyleneglycol-monoethyl ether.] *Arzneimittel-forschung*, 21(6):880–885.

Stott WT, McKenna MJ (1985) Hydrolysis of several glycol ether acetates and acrylate esters by nasal mucosal carboxylesterase in vitro. *Fundamental and Applied Toxicology*, 5(2):399–404.

Swan SH, Forest W (1996) Reproductive risks of glycol ethers and other agents used in semiconductor manufacturing. *Occupational Hygiene*, 2:373–385.

Swan SH, Beaumont JJ, Hammond SK, VonBehren J, Green RS, Hallock MF, Woskie SR, Hines CJ, Schenker MB (1995) Historical cohort study of spontaneous abortion among fabrication workers in the Semiconductor Health Study: agent-level analysis. *American Journal of Industrial Medicine*, 28(6):751–769.

Sweeney LM, Tyler TR, Kirman CR, Corley RA, Reitz RH, Paustenbach DJ, Holson JF, Whorton MD, Thompson KM, Gargas ML (2001) Proposed occupational exposure limits for select ethylene glycol ethers using PBPK models and Monte Carlo simulations. *Toxicological Sciences*, 62(1):124–139.

Tanii H, Saito S, Hashimoto K (1992) Structure–toxicity relationship of ethylene glycol ethers. *Archives of Toxicology*, 66:368–371.

Tinston DJ, Doe JE, Godley MJ, Head LK, Killick M, Litchfield MH, Wickramaratne GA (1983a) *Ethylene glycol monoethylether (EE): teratogenicity study in rats.* Imperial Chemical Industries PLC Report No. CTL/P/761 to Chemical Manufacturers' Association.

Tinston D, Doe JE, Thomas M, Wickramaratne GA (1983b) *Ethylene glycol monoethyl ether (EE): inhalation teratogenicity study in rabbits.* Imperial Chemical Industries PLC Report No. CTL/P/776 to Chemical Manufacturers' Association.

Tinston DJ, Doe JE, Killick M, Thomas M (1983c) *Ethylene glycol monoethyl ether acetate (EEAc). Inhalation teratogenicity study in rabbits.* Imperial Chemical Industries PLC Report No. CTL/P/840 to Chemical Manufacturers' Association.

Truhaut R, Dutertre-Catella H, Phu-Lich N, Huyen VN (1979) Comparative toxicological study of ethylglycol acetate and butylglycol acetate. *Toxicology and Applied Pharmacology*, 51(1):117–127.

Tyl RW, Pritts IM, France KA, Fisher LC, Tyler TR (1988) Developmental toxicity evaluation of inhaled 2-ethoxyethanol acetate in Fischer 344 rats and New Zealand White rabbits. *Fundamental and Applied Toxicology*, 10(1):20–39.

USEPA (1985) *Health and environmental effects profile for 2-ethoxyethanol*. Cincinnati, OH, United States Environmental Protection Agency, Environmental Criteria and Assessment Office (EPA/600/X-85/373; NTIS PB88-174586).

USEPA (1986) *Health and environmental effects profile for 2-methoxyethanol.* Cincinnati, OH, United States Environmental Protection Agency, Environmental Criteria and Assessment Office (EPA/600/X-87/025; NTIS PB89-119531).

USEPA (1997) *Exposure factors handbook. Vol. III. Activity factors.* Washington, DC, United States Environmental Protection Agency, National Center for Environmental Assessment, Office of Research and Development, August (EPA/600/P-95/002Fc).

USEPA (2003) *Toxics Release Inventory chemical report (TRI Explorer report).* Washington, DC, United States Environmental Protection Agency (http://www.epa.gov/tri/tridata; accessed 17 March 2004).

Van Leeuwen CJ, Van Der Zandt PTJ, Aldenberg T, Verhaar HJM, Hermens JLM (1992) Application of QSARs, extrapolation and equilibrium partitioning in aquatic effects assessment. I. Narcotic industrial pollutants. *Environmental Toxicology and Chemistry*, 11:267–282.

Versar Inc. (1986) *Standard scenarios for estimating exposure to chemical substances during use of consumer products. Vol. 1.* Prepared for Exposure Evaluation Division, Office of Toxic Substances, United States Environmental Protection Agency, Washington, DC, September (EPA Contract No. 68-02-3968).

Veulemans H, Groeseneken D, Masschelein R, Van Vlem E (1987a) Survey of ethylene glycol ether exposures in Belgian industries and workshops. *American Industrial Hygiene Association Journal*, 48(8):671–676.

Veulemans H, Groeseneken D, Masschelein R, Van Vlem E (1987b) Field study of the urinary excretion of ethoxyacetic acid during repeated daily exposure to the ethyl ether of ethylene glycol and the ethyl ether of ethylene glycol acetate. *Scandinavian Journal of Work, Environment and Health*, 13(3):239–242.

Veulemans H, Steeno O, Masschelein R, Groeseneken D (1993) Exposure to ethylene glycol ethers and spermatogenic disorders in man: a case–control study. *British Journal of Industrial Medicine*, 50(1):71–78.

Villalobos-Pietrini R, Gomez-Arroyo S, Altamirano-Lozano M, Orozco P, Rios P (1989) Cytogenetic effects of some cello-solves. *Revista Internacional de Contaminación Ambiental*, 5:41.

Vincent R (1999) [Occupational exposure.] In: *Ethers de glycol: Quels risques pour la santé?* Paris, Expertise Collective INSERM, Les éditions INSERM (in French).

Vincent R, Poirot P, Subra I, Rieger B, Cicolella A (1994) Occupational exposure to organic solvents during paint stripping and painting operations in the aeronautical industry. *International Archives of Occupational and Environmental Health*, 65(6):377–380.

Vincent R, Rieger B, Subra I, Poirot P (1996) Exposure assessment to glycol ethers by atmosphere and biological monitoring. *Occupational Hygiene*, 2:79–90.

Waggy GT (1987) *Glycol ethers: Summary of available ecological fate and effects data.* Union Carbide Corporation File No. 35931 [cited in OECD, 2004].

Welch LS, Cullen MR (1988) Effect of exposure to ethylene glycol ethers on shipyard painters: III. Hematologic effects. *American Journal of Industrial Medicine*, 14(5):527–536.

Welch LS, Schrader SM, Turner TW, Cullen MR (1988) Effects of exposure to ethylene glycol ethers on shipyard painters: II. Male reproduction. *American Journal of Industrial Medicine*, 14(5):509–526.

Werner HW, Mitchell JL, Miller JW, Von Oettingen WF (1943a) The acute toxicity of vapours of several monoalkyl ethers of ethylene glycol. *Journal of Industrial Hygiene and Toxicology*, 25:157–163.

Werner H, Mitchell JL, Miller JW, Von Oettingen WF (1943b) Effects of repeated exposure of dogs to monoalkyl ethylene glycol ether vapors. *Journal of Industrial Hygiene and Toxicology*, 25:409–414.

Werner HW, Nawrocki CZ, Mitchell JL, Miller JW, Von Oettingen WF (1943c) Effects of repeated exposure of rats to vapors of monoalkyl ethylene glycol ethers. *Journal of Industrial Hygiene and Toxicology*, 25:374–379.

Wier PJ, Lewis SC, Traul KA (1987) A comparison of developmental toxicity evident at term to postnatal growth and survival using ethylene glycol monoethyl ether, ethylene glycol monobutyl ether and ethanol. *Teratogenesis, Carcinogenesis, and Mutagenesis*, 7(1):55–64.

Woskie SR, Hammond SK, Hines, CJ, Hallock MF, Kenyon E, Schenker MB (2000) Personal fluoride and solvent exposures and their determinants in semiconductor manufacturing. *Applied Occupational and Environmental Hygiene*, 15(4):354–361.

Yasuhara A, Shiraishi H, Tsuji M, Okuno T (1981) Analysis of organic substances in highly polluted river water by mass spectrometry. *Environmental Science and Technology*, 15:570–573.

Zeiger E, Haworth S, Mortelmans K, Speck W (1985) Mutagenicity testing of di(2-ethylhexyl)phthalate and related chemicals in *Salmonella*. *Environmental Mutagenesis*, 7(2):213–232.

Zissu D (1995) Experimental study of cutaneous tolerance to glycol ethers. *Contact Dermatitis*, 32(2):74–77.

APPENDIX 1—ACRONYMS AND ABBREVIATIONS

AUC	area under the curve
BCF	bioconcentration factor
CAS	Chemical Abstracts Service
CEPA	*Canadian Environmental Protection Act, 1999*
CI	confidence interval
CICAD	Concise International Chemical Assessment Document
C_{max}	maximum concentration
CTV	critical toxicity value
EAA	2-ethoxyacetic acid
EALD	2-ethoxyacetaldehyde
EASE	Estimation and Assessment of Substance Exposure
EC_{50}	median effective concentration
EEV	estimated exposure value
EGPE	ethylene glycol propyl ether
EHC	Environmental Health Criteria
ENEV	estimated no-effects value
EQC	Equilibrium Criterion
EU	European Union
FID	flame ionization detection
FOB	functional observational battery
GC	gas chromatography
HC_5	concentration hazardous to 5% of organisms
HPLC	high-performance liquid chromatography
HPV	high production volume
IC_{50}	median inhibitory concentration
ILO	International Labour Organization
IOMC	Inter-Organization Programme for the Sound Management of Chemicals
IPCS	International Programme on Chemical Safety
K_{oc}	soil sorption coefficient
K_{ow}	octanol/water partition coefficient
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
LOEC	lowest-observed-effect concentration
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
NOAEC	no-observed-adverse-effect concentration
NOAEL	no-observed-adverse-effect level
NOEC	no-observed-effect concentration
NPRI	National Pollutant Release Inventory (Canada)
OECD	Organisation for Economic Co-operation and Development
OEL	occupational exposure limit
OR	odds ratio

PBPK	physiologically based pharmacokinetic
PIM	Poison Information Monograph
ppm	part per million
SD	standard deviation
SI	Système international d'unités (International System of Units)
SIDS	Screening Information Dataset
SPIN	Substances in Preparations in Nordic Countries
TWA	time-weighted average
UNEP	United Nations Environment Programme
USA	United States of America
UV	ultraviolet
WHO	World Health Organization

APPENDIX 2—SOURCE DOCUMENTS

2-Ethoxyethanol

Environment Canada & Health Canada (2002)

Copies of the CEPA Priority Substances List assessment report on 2-ethoxyethanol are available upon request from:

Inquiry Centre
Environment Canada
Main Floor, Place Vincent Massey
351 St. Joseph Boulevard
Gatineau, Quebec
Canada K1A OH3

or by e-mailing PSL.LSIP@ec.gc.ca. The document may also be downloaded online at http://www.hc-sc.gc.ca/ewh-semt/alt_formats/hecs-sesc/pdf/pubs/contaminants/psl2-lsp2/2_ethoxyethanol/2_ethoxyethanol-eng.pdf.

Unpublished supporting documentation, which presents additional information, is available upon request from:

Existing Substances Branch
Environment Canada
14th Floor, Place Vincent Massey
351 St. Joseph Boulevard
Gatineau, Quebec
Canada K1A 0H3

or

Existing Substances Division
Environmental Health Centre
Health Canada
Tunney's Pasture
Address Locator 080 1C2
Ottawa, Ontario
Canada K1A 0L2

Sections of the assessment report related to the environmental assessment of 2-ethoxyethanol and the environmental supporting document (Environment Canada, 1999) were prepared or reviewed by the members of the Environmental Resource Group, established by Environment Canada to support the environmental assessment:

D. Boersma, Environment Canada
R. Breton, Environment Canada
P. Cureton, Environment Canada
N. Davidson, Environment Canada
R. Desjardins, Environment Canada
L. Hamel, Union Carbide Canada Inc.
B. Lee, Environment Canada
S. Lewis, Chemical Manufacturers' Association
B. Sebastien, Environment Canada
K. Taylor, Environment Canada (lead for the environmental assessment)

Sections of the assessment report relevant to the environmental assessment and the environmental supporting document (Environment Canada, 1999) were also reviewed by C. Staples, Assessment Technologies Inc.

Data relevant to assessment of population exposure and potential effects on human health effects were identified on the basis of a review prepared in 1996 by BIBRA Toxicology International, as well as through literature searches (prior to January 2000), the strategies for which are described below.

The health-related sections of the assessment report and the background supporting documentation were prepared by the following staff of Health Canada:

K. Hughes
M.E. Meek
L. Turner

Comments on the adequacy of data coverage in the sections of the supporting documentation related to health effects were provided in a written review by J.B. Knaak, Oxychem (retired).

The health-related sections of the assessment report were reviewed and approved by the Healthy Environments and Consumer Safety Branch Risk Management meeting of Health Canada.

The entire assessment report was reviewed and approved by the Environment Canada/Health Canada CEPA Management Committee.

Search strategies employed for identification of relevant data are as follows:

Environmental assessment

Data relevant to the assessment of whether 2-ethoxyethanol is "toxic" to the environment under CEPA were identified from existing review documents, published reference texts and online searches, conducted between January and May 1996, of the following databases: ASFA (Aquatic Sciences and Fisheries Abstracts, Cambridge Scientific Abstracts; 1990–1996), BIOSIS (Biosciences Information Services; 1990–1996), CAB (Commonwealth Agriculture Bureaux; 1990–1996), CESARS (Chemical Evaluation Search and Retrieval System, Ontario Ministry of the Environment and Michigan Department of Natural Resources; 1996), CHRIS (Chemical Hazard Release Information System; 1964–1985), Current Contents (Institute for Scientific Information; 1993 – 15 January 1996), ELIAS (Environmental Library Integrated Automated System, Environment Canada library; January 1996), Enviroline (R.R. Bowker Publishing Co.; November 1995 – June 1996), Environmental Abstracts (1975 – February 1996), Environmental Bibliography (Environmental Studies Institute, International Academy at Santa Barbara; 1990–1996), GEOREF (Geo Reference Information System, American Geological Institute; 1990–1996), HSDB (Hazardous Substances Data Bank, United States National Library of Medicine; 1996), Life Sciences (Cambridge Scientific Abstracts; 1990–1996), NTIS (National Technical Information Service, United States Department of Commerce; 1990–1996), Pollution Abstracts (Cambridge Scientific Abstracts, United States National Library of Medicine; 1990–1996), POLTOX (Cambridge Scientific Abstracts, United States National Library of Medicine; 1990–1995), RTECS (Registry of Toxic Effects of Chemical Substances, United States National Institute for Occupational Safety and Health; 1996), Toxline (United States National Library of Medicine; 1990–1996), TRI93 (Toxic Chemical Release Inventory, United States Environmental Protection Agency, Office of Toxic Substances; 1993), USEPA-ASTER (Assessment Tools for the Evaluation of Risk, United States Environmental Protection Agency; up to 21 December 1994), WASTEINFO (Waste Management Information Bureau of the American Energy Agency; 1973 – September 1995) and Water Resources Abstracts (United States Geological Survey, United States Department of the Interior; 1990–1996). Reveal Alert was used to maintain an ongoing record of the current scientific literature pertaining to the potential environmental effects of 2-ethoxyethanol. Data obtained after 30 September 1999 were not considered in this assessment unless they were critical data received during a public review period 19 August – 18 October 2000.

In addition, a survey of Canadian industry was carried out under the authority of section 16 of CEPA (Environment Canada, 1997a,b). Targeted companies with commercial activities involving more than 1000 kg of 2-ethoxyethanol were required to supply information on uses, releases, environmental concentrations, effects or other data that were available to them for 2-ethoxyethanol.

Health assessment

In addition to studies included in the review prepared by BIBRA Toxicology International, recent data were identified through searching the following databases beginning in August 1996 using the chemical name or the CAS number for both 2-ethoxyethanol and 2-ethoxyethyl acetate: Canadian Research Index, DIALOG (CANCERLIT, Environmental Bibliography, Waternet, Water Resources Abstracts, Enviroline, CAB Abstracts, Food Science and Technology Abstracts, Pollution Abstracts and NTIS), Medline, Toxline Plus and TOXNET (CCRIS [Chemical Carcinogenesis Research Information System, United States National Cancer Institute], GENE-TOX [Genetic Toxicology, United States Environmental Protection Agency] and EMIC [Environmental Mutagen Information Center database, Oak Ridge National Laboratory]). Data acquired as of January 2000 were considered for inclusion in this draft.

As well as these databases, officials at the Product Safety Bureau and Drugs Directorate of Health Canada, along with the Pest Management Regulatory Agency, were contacted to obtain information relevant to this assessment.

2-Propoxyethanol

Lundberg (1994)

The document *Scientific basis for Swedish occupational standards. XV. Consensus report for ethylene glycol monopropylether and its acetate* was prepared by the Secretariat of the Criteria Group for Occupational Standards in Sweden, with P. Lundberg as the editor, and reviewed and approved by the Criteria Group (G. Agrup, University of Lund; O. Axelson, University of Linköping; S. Bergström, Swedish Trade Union Confederation; C. Edling, University of Uppsala; F. Gamberale, National Institute of Occupational Health; S. Grehn, Swedish Metal Workers' Union; B. Holmberg, Swedish Confederation of Professional Associations; J. Högberg, National Institute of Occupational Health; G. Johanson, National Institute of Occupational Health; B. Knave, National Institute of Occupational Health; U. Lavenius, Swedish Factory Workers' Union; B. Sjögren, National Institute of Occupational Health; S. Skerfving, University of Lund; J. Wahlberg, National Institute of Occupational Health; A. Wennberg, National Institute of Occupational Health; O. Vesterberg, National Institute of Occupational Health).

In searching the literature, several databases were used, such as RTECS, Toxline, Medline, CANCERLIT, NIOSHTIC and Riskline. Also, information in existing criteria documents was used, such as documents from WHO, the European Commission, United States National Institute for Occupational Safety and Health, the Dutch Expert Committee for Occupational Standards (DECOS) and the Nordic Expert Group.

***

A comprehensive literature search was conducted in January 2004 by Toxicology Advice & Consulting Ltd in order to identify critical data published since publication of the source documents. Databases searched included:

- ChemID*plus* (The ChemID*plus* system searches and/or identifies literature from a wide range of online databases and databanks, including Agency for Toxic Substances and Disease Registry [ATSDR], CANCERLIT, CCRIS, Developmental and Reproductive Toxicology Database [DART]/ Environmental Teratology Information Center [ETIC], GENE-TOX, HSDB, Integrated Risk Information System [IRIS], Medline, Toxline Core, Toxline Special and Toxic Substances Control Act Chemical Substances Inventory [TSCA]).
- INCHEM (The INCHEM database consolidates information from a number of intergovernmental organizations, including the Joint FAO/WHO Expert Committee on Food Additives [JECFA] Evaluations and Monographs, the Joint FAO/WHO Meeting on Pesticide Residues [JMPR], the International Agency for Research on Cancer [IARC], Chemical Information System [CIS], EHCs and Screening Information Datasets [SIDS]).
- RTECS

APPENDIX 3—CICAD PEER REVIEW

The draft CICADs on 2-ethoxyethanol and 2-propoxyethanol (later combined into one CICAD) were sent for review to institutions and organizations identified by IPCS after contact with IPCS national Contact Points and Participating Institutions, as well as to identified experts. An open invitation to participate in the peer review process was also published on the IPCS web site. Comments were received from:

S. Anderson Lewis, American Chemistry Council, Arlington, VA, USA
M. Baril, Institut de Recherche en Santé et en Sécurité du Travail du Québec, Montreal, Quebec, Canada
R. Benson, United States Environmental Protection Agency, Denver, CO, USA
R.S. Chhabra, National Institute for Environmental Health Sciences, Research Triangle Park, NC, USA
I. Desi, Department of Public Health, Budapest, Hungary
L. Fishbein, Fairfax, VA, USA
E. Frantik, National Institute of Public Health, Prague, Czech Republic
H. Gibb, Sciences International Inc., Alexandria, VA, USA
H. Greim, University of Munich, Munich, Germany
P. Harvey, National Industrial Chemicals Notification and Assessment Scheme, Sydney, Australia
R.F. Hertel, Federal Institute for Risk Assessment (BfR), Berlin, Germany
I. Mangelsdorf, Fraunhofer Institute for Toxicology and Experimental Medicine, Hanover, Germany
H. Nagy, National Institute for Occupational Safety and Health, Cincinnati, OH, USA
I. Rabbani, Food and Drug Administration, College Park, MD, USA
H. Savolainen, Ministry of Social Affairs & Health, Tampere, Finland
E. Soderlund, Department of Chemical Toxicology, Norwegian Institute of Public Health, Oslo, Norway
J. Stauber, CSIRO Energy Technology, Menai, New South Wales, Australia
M.H. Sweeney, United States Embassy, Hanoi, Viet Nam
K. Ziegler-Skylakakis, European Commission, Luxembourg

APPENDIX 4—CICAD 12TH FINAL REVIEW BOARD

Hanoi, Viet Nam
28 September – 1 October 2004

Members

Mr D.T. Bai, Centre of Environmental Protection & Chemical Safety, Institute of Industrial Chemistry, Hanoi, Viet Nam

Dr R. Chhabra, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA

Mr P. Copestake, Toxicology Advice & Consulting Ltd, Surrey, United Kingdom

Dr C. De Rosa, Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention, Atlanta, GA, USA

Dr S. Dobson, Centre for Ecology & Hydrology, Monks Wood, Abbots Ripton, Huntingdon, Cambridgeshire, United Kingdom

Dr G. Dura, National Institute of Environmental Health of József Fodor Public Health Centre, Budapest, Hungary

Ms C.W. Fang, National Institute of Occupational Safety and Health Malaysia, Selangor, Malaysia

Dr L. Fishbein, Fairfax, VA, USA

Dr L. Fruchtengarten, Poison Control Center of São Paulo, São Paulo, Brazil

Dr C.L. Geraci, Document Development Branch, Centers for Disease Control and Prevention / National Institute for Occupational Safety and Health, Cincinnati, OH, USA

Dr H. Gibb, Sciences International Inc., Alexandria, VA, USA

Dr R.F. Hertel, Federal Institute for Risk Assessment, Berlin, Germany

Mr P. Howe, Centre for Ecology & Hydrology, Monks Wood, Abbots Ripton, Huntingdon, Cambridgeshire, United Kingdom

Dr S. Ishimitsu, Division of Safety Information on Drug, Food and Chemicals, National Institute of Health Sciences, Tokyo, Japan

Dr J. Kielhorn, Fraunhofer Institute for Toxicology and Experimental Medicine, Hanover, Germany

Dr S. Kunarattanapruke, Food & Drug Administration, Ministry of Public Health, Nonthaburi, Thailand

Dr Y. Liang, Department of Occupational Health, Fudan University School of Public Health, Shanghai, China

Ms M.E. Meek, Existing Substances Division, Environmental Health Directorate, Health Canada, Ottawa, Ontario, Canada

Mr F.K. Muchiri, Directorate of Occupational Health and Safety Services, Nairobi, Kenya

Dr O. Sabzevari, Food and Drug Control Labs, Ministry of Health & Medical Education, Tehran, Islamic Republic of Iran

Dr J. Stauber, CSIRO Energy Technology, Menai, New South Wales, Australia

Dr M.H. Sweeney, United States Embassy, Hanoi, Viet Nam

Mr P. Watts, Toxicology Advice & Consulting Ltd, Surrey, United Kingdom

Ms D. Willcocks, National Industrial Chemicals Notification and Assessment Scheme, Sydney, New South Wales, Australia

Dr K. Ziegler-Skylakakis, European Commission, Luxembourg

Secretariat

Dr A. Aitio, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

APPENDIX 5—CICAD 13TH FINAL REVIEW BOARD

Nagpur, India
31 October – 3 November 2005

Members

Dr T. Chakrabarti, National Environmental Engineering Research Institute, Nagpur, India

Dr R. Chhabra, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA

Mr P. Copestake, Toxicology Advice & Consulting Ltd, Surrey, United Kingdom

Dr C. De Rosa, Agency for Toxic Substances and Disease Registry, Atlanta, GA, USA

Dr S. Dobson, Centre for Ecology and Hydrology, Monks Wood, Abbots Ripton, Huntingdon, Cambridgeshire, United Kingdom

Dr L. Fishbein, Fairfax, VA, USA

Dr L. Fruchtengarten, Poison Control Center of São Paulo, São Paulo, Brazil

Dr H. Gibb, Sciences International Inc., Alexandria, VA, USA

Dr R.F. Hertel, Federal Institute for Risk Assessment (BfR), Berlin, Germany

Mr P. Howe, Centre for Ecology and Hydrology, Monks Wood, United Kingdom

Ms K. Hughes, Health Canada, Ottawa, Ontario, Canada

Dr D. Kanungo, Directorate General of Health Services, New Delhi, India

Dr J. Kielhorn, Fraunhofer Institute for Toxicology and Experimental Medicine, Hanover, Germany

Dr G. Kong, Hanyang University, Seoul, Republic of Korea

Dr J. Rischer, Agency for Toxic Substances and Disease Registry, Chamblee, GA, USA

Dr O. Sabzevari, Tehran University of Medical Sciences, Tehran, Islamic Republic of Iran

Dr R. Sonawane, National Center for Environmental Assessment, Environmental Protection Agency, Washington, DC, USA

Dr J. Stauber, CSIRO Energy Technology, Menai, New South Wales, Australia

Dr M.H. Sweeney, United States Embassy, Hanoi, Viet Nam

Ms D. Willcocks, National Industrial Chemicals Notification and Assessment Scheme, Sydney, New South Wales, Australia

Dr Y. Zheng, National Institute for Occupational Health & Poison Control, Beijing, China

Dr K. Ziegler-Skylakakis, Secretariat of the Commission for the Investigation of Health Hazards of Chemical Compounds in the Workplace Area (MAK Commission), Freising-Weihenstephan, Germany

Observer

Mr P. Ashford, Resorcinol Task Force, Wotton-under-edge, Gloucestershire, United Kingdom

Secretariat

Dr A. Aitio, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Ms L. Onyon, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Mr M. Shibatsuji, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

ETHYLENE GLYCOL MONOETHYL ETHER

ICSC: 0060
May 2003

CAS #	**110-80-5**	**2-Ethoxyethanol**
RTECS #	**KK8050000**	**Monoethyl glycol ether**
UN #	**1171**	**Oxitol**
EC Annex 1 Index #	**603-012-00-X**	**EGEE**
EC/EINECS #	**203-804-1**	**Cellosolve**
		$C_4H_{10}O_2$ / $CH_3CH_2OCH_2CH_2OH$
		Molecular mass: 90.1

TYPES OF HAZARD / EXPOSURE	ACUTE HAZARDS / SYMPTOMS	PREVENTION	FIRST AID / FIRE FIGHTING
FIRE	Flammable.	NO open flames, NO sparks, and NO smoking.	Powder, alcohol-resistant foam, water spray, carbon dioxide.
EXPLOSION	Above 44°C explosive vapour/air mixtures may be formed.	Above 44°C use a closed system, ventilation, and explosion-proof electrical equipment.	In case of fire: keep drums, etc., cool by spraying with water.
EXPOSURE		**AVOID EXPOSURE OF (PREGNANT) WOMEN! STRICT HYGIENE!**	**IN ALL CASES CONSULT A DOCTOR!**
Inhalation	Cough. Drowsiness. Headache. Shortness of breath. Sore throat. Weakness. Unconsciousness.	Ventilation, local exhaust, or breathing protection.	Fresh air, rest. Refer for medical attention.
Skin	MAY BE ABSORBED! (Further see Inhalation).	Protective gloves. Protective clothing.	Remove contaminated clothes. Rinse skin with plenty of water or shower. Refer for medical attention.
Eyes	Blurred vision. Redness. Pain.	Face shield, or eye protection in combination with breathing protection.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion	Abdominal pain. Nausea. Vomiting. (Further see Inhalation).	Do not eat, drink, or smoke during work.	Rinse mouth. Do NOT induce vomiting. Give one or two glasses of water to drink. Refer for medical attention.

SPILLAGE DISPOSAL

Ventilation. Remove all ignition sources. Collect leaking and spilled liquid in sealable containers as far as possible. Wash away remainder with plenty of water. (Extra personal protection: filter respirator for organic gases and vapours.)

PACKAGING & LABELLING

Airtight. Do not transport with food and feedstuffs.
EU Classification
Symbol: T
R: 60-61-10-20/21/22
S: 53-45
Note: E
UN Classification
UN Hazard Class: 3
UN Pack Group: III

EMERGENCY RESPONSE

Transport Emergency Card: TEC (R)-30GF1-III
NFPA Code: H 2; F 2; R 0;

STORAGE

Fireproof. Separated from strong oxidants, food and feedstuffs. Keep in the dark. Cool.

IPCS
International Programme on Chemical Safety

WHO ILO UNEP

Prepared in the context of cooperation between the International Programme on Chemical Safety and the Commission of the European Communities

SEE IMPORTANT INFORMATION ON BACK

ETHYLENE GLYCOL MONOETHYL ETHER

ICSC: 0060

IMPORTANT DATA

PHYSICAL STATE; APPEARANCE
COLOURLESS, OILY LIQUID , WITH CHARACTERISTIC ODOUR.

CHEMICAL DANGERS
The substance can form explosive peroxides. Reacts with strong oxidants causing fire and explosion hazard. Attacks many plastics and rubber.

OCCUPATIONAL EXPOSURE LIMITS
TLV: 5 ppm (as TWA); (skin); BEIissued; (ACGIH 2008).
MAK: (sum of concentrations in air of ethylene glycol monoethyl ether and its acetate) 2 ppm, 7.5 mg/m³; Peak limitation category: II (8); H; Pregnancy risk group: B; (DFG 2009).

ROUTES OF EXPOSURE
The substance can be absorbed into the body by inhalation, through the skin and by ingestion.

INHALATION RISK
A harmful contamination of the air can be reached rather quickly on evaporation of this substance at 20°C.

EFFECTS OF SHORT-TERM EXPOSURE
The substance is mildly irritating to the eyes and the respiratory tract. The substance may cause effects on the central nervous system, blood, bone marrow, kidneys and liver. Exposure at high levels may result in unconsciousness. Medical observation is indicated.

EFFECTS OF LONG-TERM OR REPEATED EXPOSURE
The liquid defats the skin. The substance may have effects on the bloodand bone marrow , resulting in anaemiaand lesions of blood cells. May cause toxicity to human reproduction or development.

PHYSICAL PROPERTIES

Boiling point: 135°C
Melting point: -70°C
Relative density (water = 1): 0.93
Solubility in water: miscible
Vapour pressure, kPa at 20°C: 0.5
Relative vapour density (air = 1): 3.1

Relative density of the vapour/air-mixture at 20°C (air = 1): 1.00
Flash point: 44°C c.c.
Auto-ignition temperature: 235°C
Explosive limits, vol% in air: (at 93°C) 1.7-15.6
Octanol/water partition coefficient as log Pow: -0.540

ENVIRONMENTAL DATA

NOTES

Depending on the degree of exposure, periodic medical examination is indicated. The odour warning when the exposure limit value is exceeded is insufficient. Check for peroxides prior to distillation; eliminate if found. Card has been partially updated in July 2009: see Occupational Exposure Limits, Ingestion First Aid.

ADDITIONAL INFORMATION

ETHYLENE GLYCOL MONOPROPYL ETHER

ICSC: 0607
May 2003

CAS #	**2807-30-9**	**Propylglycol**
RTECS #	**KM2800000**	**2-Propoxyethanol**
UN #	**1993**	**Propyl cellosolve**
EC Annex 1 Index #	**603-095-00-2**	**$C_5H_{12}O_2$**
EC/EINECS #	**220-548-6**	**Molecular mass: 104.2**

TYPES OF HAZARD / EXPOSURE	ACUTE HAZARDS / SYMPTOMS	PREVENTION	FIRST AID / FIRE FIGHTING
FIRE	Flammable.	NO open flames, NO sparks, and NO smoking.	Powder, alcohol-resistant foam, water spray, carbon dioxide.
EXPLOSION	Above 57°C explosive vapour/air mixtures may be formed.	Above 57°C use a closed system, ventilation, and explosion-proof electrical equipment.	In case of fire: keep drums, etc., cool by spraying with water.
EXPOSURE		**PREVENT GENERATION OF MISTS!**	
Inhalation	Cough. Sore throat.	Ventilation, local exhaust, or breathing protection.	Fresh air, rest.
Skin	Redness. Dry skin.	Protective gloves.	Rinse skin with plenty of water or shower.
Eyes	Redness. Pain.	Safety goggles.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion		Do not eat, drink, or smoke during work.	Rinse mouth. Give one or two glasses of water to drink. Refer for medical attention.

SPILLAGE DISPOSAL

Ventilation. Collect leaking and spilled liquid in sealable containers as far as possible. Wash away remainder with plenty of water. Personal protection: filter respirator for organic gases and vapours.

PACKAGING & LABELLING

EU Classification
Symbol: Xn
R: 21-36
S: (2-)26-36/37-46
UN Classification
UN Hazard Class: 3
UN Pack Group: III

EMERGENCY RESPONSE

Transport Emergency Card: TEC (R)-30GF1-III.

STORAGE

Fireproof. Separated from strong oxidants.

IPCS
International Programme on Chemical Safety

WHO UNEP

Prepared in the context of cooperation between the International Programme on Chemical Safety and the Commission of the European Communities

SEE IMPORTANT INFORMATION ON BACK

ETHYLENE GLYCOL MONOPROPYL ETHER ICSC: 0607

IMPORTANT DATA

PHYSICAL STATE; APPEARANCE
COLOURLESS LIQUID , WITH CHARACTERISTIC ODOUR.

CHEMICAL DANGERS
Reacts with strong oxidants.

OCCUPATIONAL EXPOSURE LIMITS
TLV not established.
MAK: 20 ppm, 86 mg/m³; H; Peak limitation category: I(2); Pregnancy risk group: C; (DFG 2009).

ROUTES OF EXPOSURE
The substance can be absorbed into the body by inhalation of its vapour, through the skin and by ingestion.

INHALATION RISK
A harmful contamination of the air will be reached rather slowly on evaporation of this substance at 20°C.

EFFECTS OF SHORT-TERM EXPOSURE
The substance is severely irritating to the eyes, mildly to the skin, and is irritating to the respiratory tract. The substance may cause effects on the blood , resulting in lesions of blood cells.

EFFECTS OF LONG-TERM OR REPEATED EXPOSURE
The liquid defats the skin.

PHYSICAL PROPERTIES

Boiling point: 149-152°C
Melting point: -90°C
Relative density (water = 1): 0.91
Solubility in water: miscible
Vapour pressure, Pa at 25°C: 130
Relative vapour density (air = 1): 3.6

Flash point: 57°C c.c.
Explosive limits, vol% in air: 1.3-16
Octanol/water partition coefficient as log Pow: 0.08

ENVIRONMENTAL DATA

NOTES

EGnPE is also used as a name. The relation between odour and the occupational exposure limit cannot be indicated. Card has been partly updated in October 2004. See sections Occupational Exposure Limits, EU classification, Emergency Response. Card has been partially updated in July 2009: see Ingestion First Aid, Occupational Exposure Limits.

ADDITIONAL INFORMATION

2-ETHOXYETHYL ACETATE

ICSC: 0364
November 2003

CAS #	**111-15-9**	**Ethylene glycol monoethyl ether acetate**
RTECS #	**KK8225000**	**2-Ethoxyethanol acetate**
UN #	**1172**	**Acetic acid, 2-ethoxyethyl ester**
EC Annex 1 Index #	**607-037-00-7**	**Cellosolve acetate**
EC/EINECS #	**203-839-2**	**Ethyl glycol acetate**
		$C_6H_{12}O_3$ / $CH_3COOCH_2CH_2OCH_2CH_3$
		Molecular mass: 132.2

TYPES OF HAZARD / EXPOSURE	ACUTE HAZARDS / SYMPTOMS	PREVENTION	FIRST AID / FIRE FIGHTING
FIRE	Flammable.	NO open flames, NO sparks, and NO smoking.	Powder, alcohol-resistant foam, water spray, carbon dioxide.
EXPLOSION	Above 51.1°C explosive vapour/air mixtures may be formed.	Above 51.1°C use a closed system, ventilation, and explosion-proof electrical equipment.	In case of fire: keep drums, etc., cool by spraying with water.
EXPOSURE		**AVOID ALL CONTACT!**	
Inhalation	Dizziness. Drowsiness. Headache. Unconsciousness.	Ventilation, local exhaust, or breathing protection.	Fresh air, rest. Refer for medical attention.
Skin	MAY BE ABSORBED! Dry skin. (Further see Inhalation).	Protective gloves. Protective clothing.	Remove contaminated clothes. Rinse skin with plenty of water or shower. Refer for medical attention.
Eyes	Redness.	Safety goggles, or eye protection in combination with breathing protection.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion	Nausea. Vomiting. (Further see Inhalation).	Do not eat, drink, or smoke during work.	Rinse mouth. Do NOT induce vomiting. Refer for medical attention.

SPILLAGE DISPOSAL

Ventilation. Remove all ignition sources. Collect leaking and spilled liquid in sealable containers as far as possible. Absorb remaining liquid in sand or inert absorbent and remove to safe place. Do NOT let this chemical enter the environment. (Extra personal protection: filter respirator for organic gases and vapours.)

PACKAGING & LABELLING

EU Classification
Symbol: T
R: 60-61-20/21/22
S: 53-45
Note: E
UN Classification
UN Hazard Class: 3
UN Pack Group: III

EMERGENCY RESPONSE

Transport Emergency Card: TEC (R)-30S1172
NFPA Code: H1; F2; R

STORAGE

Fireproof. Separated from strong oxidants, strong bases, strong acids. Keep in the dark.

IPCS
International Programme on Chemical Safety

WHO UNEP

SEE IMPORTANT INFORMATION ON BACK

2-ETHOXYETHYL ACETATE

ICSC: 0364

IMPORTANT DATA

PHYSICAL STATE; APPEARANCE
COLOURLESS LIQUID , WITH CHARACTERISTIC ODOUR.

CHEMICAL DANGERS
The substance can presumably form explosive peroxides. Reacts with strong acids, strong bases, strong oxidants.

OCCUPATIONAL EXPOSURE LIMITS
TLV: 5 ppm, 27 mg/m³, as TWA; (skin); BEI issued (ACGIH 2005).
MAK: (Sum ethylene glycol monoethyl ether & its acetate): 2 ppm, 11 mg/m³; skin absorption (H); Peak limitation category: II(8); Pregnancy risk group: B; (DFG 2007).

ROUTES OF EXPOSURE
The substance can be absorbed into the body by inhalation of its vapour, through the skin and by ingestion.

INHALATION RISK
A harmful contamination of the air will be reached rather slowly on evaporation of this substance at 20°C.

EFFECTS OF SHORT-TERM EXPOSURE
The vapour is mildly irritating to the eyes. The substance may cause effects on the blood , resulting in lesions of blood cells and kidney impairment at high levels. The substance may cause effects on the central nervous system. Exposure far above the OEL may result in unconsciousness.

EFFECTS OF LONG-TERM OR REPEATED EXPOSURE
The liquid defats the skin. The substance may have effects on the blood , resulting in lesions of blood cells, anaemiaand kidney impairment. May cause toxicity to human reproduction or development.

PHYSICAL PROPERTIES

Boiling point: 156°C
Melting point: -62°C
Relative density (water = 1): 0.97 (at 20°C)
Solubility in water, g/100 ml at 20°C: 23
Vapour pressure, kPa at 20°C: 0.27
Relative vapour density (air = 1): 4.7

Relative density of the vapour/air-mixture at 20°C (air = 1): 1.01)
Flash point: 51.1°C c.c.
Auto-ignition temperature: 379°C
Explosive limits, vol% in air: 1.3-14
Octanol/water partition coefficient as log Pow: 0.24

ENVIRONMENTAL DATA

The substance is harmful to aquatic organisms.

NOTES

Check for peroxides prior to distillation; eliminate if found. Card has been partially updated in January 2008: see Occupational Exposure Limits.

ADDITIONAL INFORMATION

RÉSUMÉ D'ORIENTATION

Le présent CICAD[1] (Concise International Chemical Assessment Document / Document concis d'évaluation chimique internationale) relatif au 2-éthoxyéthanol et au 2-propoxyéthanol a été préparé par Toxicology Advice & Consulting Ltd (Royaume-Uni). En ce qui concerne le 2-éthoxyéthanol, il repose sur une documentation préparée dans le cadre du Programme d'évaluation des substances prioritaires prévu par la *Loi canadienne sur la protection de l'environnement* (LCPE) de 1999 (Environnement Canada & Santé Canada, 2002). Les évaluations de substances prioritaires prescrites par la LCPE ont pour objectif de déterminer les effets potentiels sur la santé humaine d'une exposition indirecte à ces substances dans l'environnement général ainsi que leurs effets sur cet environnement. Le document de base prend en compte les données relevées jusqu'à janvier 2000. Les paragraphes relatifs au 2-propoxyéthanol ont été rédigés sur la base d'un rapport de consensus établi par le Groupe suédois sur les critères applicables aux normes professionnelles (Swedish Criteria Group for Occupational Standards) (Lundberg, 1994). Une recherche bibliographique exhaustive portant sur plusieurs bases de données en ligne a été effectuée en janvier 2004 afin de retrouver toute référence intéressante postérieure à celles qui sont prises en compte dans les documents de base. Des renseignements sur la disponibilité des documents de base et leur examen par des pairs sont donnés à l'appendice 2. L'appendice 3 donne des indications sur l'examen par des pairs du présent CICAD. Ce CICAD a été examiné lors de la 12ème réunion du Comité d'évaluation finale qui s'est tenue à Hanoi (Viet Nam) du 28 septembre au 1er octobre 2004. La liste des participants à cette réunion figure à l'appendice 4. La première version du document a été révisée pour tenir compte des points de vue exprimés lors de cette réunion et une nouvelle version a été à nouveau soumise à un examen par des pairs. Finalement, le CICAD a été examiné et approuvé en tant qu'évaluation internationale lors de la 13ème réunion du Comité d'évaluation finale qui a eu lieu à Nagpur (Inde) du 31 octobre au 3 novembre 2005. La liste des participants à cette réunion figure à l'appendice 5. Les fiches internationales sur la sécurité chimique du 2-éthoxyéthanol (ICSC 0060; IPCS, 2002), de l'acétate de 2-éthoxyéthyle (qui est facilement métabolisé en 2-éthoxyéthanol) (ICSC 0364; IPCS ,2006) et du 2-propoxyéthanol (ICSC 0607; IPCS, 2004) établies par le Programme international sur la sécurité chimique (IPCS/PISC) dans le cadre d'un processus distinct d'examen par des pairs, sont également reproduites dans le présent CICAD.

[1] La liste des acronymes et abréviations utilisés dans le présent rapport figure à l'appendice 1.

Le 2-éthoxyéthanol (Chemical Abstracts Service [CAS] No 110-80-5) et le 2-propoxyéthanol (CAS No 2807-30-9) se présentent sous la forme de liquides incolores totalement miscibles à l'eau et dont le coefficient de partage octanol/eau (K_{ow}) est faible. Autant qu'on sache, ils n'existent pas à l'état naturel. Le 2-éthoxyéthanol est préparé à des fins commerciales avec de l'oxyde d'éthylène et de l'éthanol anhydre en excès.

Selon les informations disponibles, le 2-éthoxyéthanol entre dans la composition de peintures, d'enduits et revêtements, d'encres, de produits de nettoyage, de vernis et encaustiques, de liquides pour freins et de carburéacteurs. Il trouve également de nombreuses applications comme solvant, comme intermédiaire de synthèse et comme solvant de couplage (tiers solvant) pour les mélanges et les formulations à base d'eau. Sa présence dans des produits de consommation est, d'une façon générale, considérée comme inacceptable et les programmes visant à réduire son utilisation ont conduit à largement restreindre les usages de ce genre. Par suite de sa production et de son utilisation comme solvant dans l'industrie, le 2-éthoxyéthanol peut passer dans l'environnement mélangé à divers effluents liquides.

Le 2-propoxyéthanol entre dans la composition de lubrifiants, peintures, revêtements de surface, vernis et encaustiques. Par suite de sa production et de son utilisation comme solvant dans l'industrie, le 2-propoxyéthanol peut passer dans l'environnement mélangé à divers effluents liquides.

Les données de surveillance sur lesquelles baser une estimation de l'exposition de la population générale au 2-éthoyxéthanol restent limitées. On a obtenu des estimations de l'exposition due au contact avec certains milieux de l'environnement (air et eau essentiellement) ou avec des produits de consommation. Il existe des données sur l'exposition professionnelle pour un certain nombre de modalités de production et d'utilisation des produits.

On n'a pas trouvé d'informations sur lesquelles s'appuyer pour établir une estimation de l'exposition de la population générale au 2-propoxyéthanol.

L'absorption transcutanée du 2-éthoxyéthanol peut constituer une importante voie d'exposition, en particulier sur le lieu de travail. Le 2-éthoxyéthanol est également facilement absorbé par inhalation ou par la voie orale et une fois absorbé, il se répartit très largement dans l'organisme.

D'après des études in vitro, il est probable que le 2-éthoxyéthanol est rapidement résorbé par la voie transcutanée.

Les principales voies métaboliques du 2-éthoxyéthanol consistent en une oxydation en 2-éthoxyacétaldéhyde (EALD) et en acide 2-éthoxyacétique (EAA) qui en sont vraisemblablement les métabolites actifs. On a quelques raisons de penser que, chez les sujets humains, le composé, une fois inhalé, pourrait être plus largement absorbé que chez le rat et qu'il pourrait également être plus rapidement transformé en acide éthoxyacétique, l'élimination se faisant ensuite plus lentement chez l'Homme.

On n'a pas trouvé de données sur le métabolisme du 2-propoxyéthanol, mais on pense qu'il doit y avoir intervention de l'alcool- et de l'aldéhyde-déshydrogénase.

Le 2-éthoxyéthanol présente une toxicité aiguë faible à modérée après exposition par la voie orale, mais c'est seulement en cas d'exposition par la voie respiratoire ou cutanée qu'il se montre faiblement toxique. Ce composé n'est guère capable de provoquer une irritation cutanée ou oculaire et il ne s'est pas révélé avoir d'effet sensibilisateur sur la peau. Chez de nombreuses espèces d'animaux de laboratoire exposés à ce produit par diverses voies, le 2-éthoxyéthanol a constamment produit des effets hématologiques, des effets sur la reproduction (effets sur certains paramètres testiculaires ou spermazoïdiques et sur le cycle oestral) et également sur le développement. La souris se révèle moins sensible que le rat aux effets du 2-éthoxyéthanol. On suppose que l'acide éthoxyacétique qui se forme lors de la métabolisation du 2-éthoxyéthanol est responsable des effets importants sur le reproduction, le développement et le sang observés chez les animaux de laboratoire. Les données dont on dispose au sujet de la génotoxicité du 2-éthoxyéthanol incitent à penser qu'il pourrait avoir une certaine capacité à produire des lésions cytogénétiques in vitro, mais cela ne ressort toutefois pas des études in vivo sur la souris. Rien n'indique qu'il provoque des mutations. On manque d'études adéquates à long terme sur son pouvoir cancérogène.

Par voie orale, respiratoire ou cutanée, le 2-propoxyéthanol présente une faible toxicité aiguë. Il ne se révèle pas être très irritant pour la peau ni avoir d'effet sensibilisateur cutané. Il provoque une irritation oculaire chez le lapin. Le principal effet de ce composé après une exposition répétée a été observé sur le sang. On n'a trouvé aucune donnée sur sa génotoxicité ou sa cancérogénicité. Lors d'une étude d'ampleur limitée, on n'a relevé ni embryotoxicité, ni foetoxicité, ni tératogénicité, mais un petit nombre d'anomalies ont été observées au niveau du squelette des fœtus à des doses qui étaient également toxiques pour la mère.

Malgré le caractère limité des données épidémiologiques, on a avancé que chez l'Homme, le sang et l'appareil reproducteur masculin pourraient être également la cible des effets toxiques du 2-éthoxyéthanol. On a ainsi observé une diminution de la production de spermatozoïdes chez des travailleurs exposées à des concentrations moyennes de 2-éthoxyéthanol égales à 9,9 ou 24 mg/m^3. Des effets hématologiques ont également été observés chez des peintres de chantiers navals exposés à une concentration moyenne d'acétate d'éthoxyéthyle équivalente à 11 mg/m^3 de 2-éthoxyéthanol. Il faut toutefois admettre que dans ces études, il y avait également exposition à d'autres substances.

Les études portant sur des sujets humains sont trop limitées pour que l'on puisse définir la valeur de la dose ou de la concentration de 2-éthoxyéthanol qui serait tolérable. D'après les études relatives aux effets toxiques de ce composé sur le développement de rats et de lapins, on peut fixer à 40 mg/m^3 la concentration sans effet indésirable observé (NOAEC). En se basant sur une exposition continue et en appliquant un facteur d'incertitude pour tenir compte des variations interspécifiques (10) et interindividuelles (10), on arrive à une concentration tolérable de 0,1 mg/m^3.

Les informations disponibles ne permettent pas de définir la valeur de la dose ou de la concentration tolérable de 2-propoxyéthanol.

Les données de la surveillance sont trop limitées pour permettre de parvenir à une estimation fiable qui soit représentative de l'exposition de la population générale au 2-éthoxyéthanol. Si l'on se fonde sur la limite supérieure approximative de l'exposition à ce composé observée dans l'environnement général (basée sur la limite de détection constatée dans une étude relative à l'exposition portant sur divers milieux), on a entre cette valeur et la concentration tolérable une marge de sécurité correspondant à un facteur d'environ 30. Si l'on compare la concentration tolérable à la concentration de 2-éthoxyéthanol la plus élevée effectivement mesurée dans l'air ambiant au Canada (mesure effectuée à l'extérieur d'une usine d'automobiles), on arrive à une marge de sécurité d'environ 120. Cependant, en s'appuyant sur les données incertaines dont on dispose au sujet de la composition type des produits de consommation qui pourraient contenir cette molécule, les estimations les plus pessimistes de l'exposition au 2-éthoxyéthanol résultant de l'usage de ces produits pourraient dépasser la concentration tolérable. Le degré de confiance que l'on peut avoir dans ces estimations est toutefois extrêmement faible et les données limitées dont on dispose indiquent qu'au Canada, aux Etats-Unis ou dans l'Union européenne, le 2-éthoxyéthanol n'est plus guère présent dans les produits de consommation. Il peut cependant y avoir encore des possibilités d'exposition en milieu professionnel, et les modalités de production et d'utilisation du produit donnent à penser que les

concentrations présentes sur le lieu de travail pourraient dépasser les valeurs qui produisent des effets chez l'Homme.

On ne disposait que de données limitées relatives aux effets du 2-éthoxyéthanol sur les organismes aquatiques. En ce qui concerne l'environnement terrestre, on s'est plutôt basé sur les valeurs critiques de la toxicité tirées d'études sur des mammifères de laboratoire. En se fondant sur les valeurs estimatives obtenues au Canada en ce qui concerne l'exposition des organismes terrestres, le sol et l'environnement aquatique, une caractérisation prudente du risque montre que le 2-éthoxyéthanol est présent à une concentration qui a peu de chances de provoquer des effets indésirables parmi les populations concernées de la faune et de la flore sauvages.

Le caractère très limité des données écotoxicologiques et le manque de données sur les concentrations dans l'environnement ne permettent pas d'évaluer le risque environnemental que représente le 2-propoxyéthanol.

RESUMEN DE ORIENTACIÓN

El presente Documento Internacional Conciso sobre Evaluación de Sustancias Químicas (CICAD)[1] relativo al 2-etoxietanol y el 2-propoxietanol fue preparado por Toxicology Advice & Consulting Ltd (Reino Unido). Para el 2-etoxietanol se basa en la documentación preparada como parte del Programa de Sustancias Prioritarias en el marco de la *Ley Canadiense de Protección del Medio Ambiente, 1999* (CEPA) (Ministerios de Medio Ambiente y de Salud del Canadá, 2002). La evaluación de las sustancias prioritarias en el marco de la CEPA tiene por objeto determinar los efectos potenciales sobre la salud de la exposición indirecta en el entorno general, así como las repercusiones para el medio ambiente. En el documento original se examinaron los datos identificados hasta enero de 2000. Las secciones sobre el 2-propoxietanol se basan en el informe preparado por consenso por el Grupo sobre los Criterios relativos a las Normas del Trabajo, de Suecia (Lundberg, 1994). En enero de 2004 se realizó una búsqueda bibliográfica amplia en varias bases de datos en línea para identificar cualquier referencia importante publicada después de las incorporadas a los documentos originales. La información sobre el carácter del examen colegiado y la disponibilidad de los documentos originales se presenta en el apéndice 2. La información relativa al examen colegiado del presente CICAD figura en el apéndice 3. Este CICAD se sometió a examen en la 12ª reunión de la Junta de Evaluación Final, celebrada en Hanoi (Viet Nam) del 28 de septiembre al 1º de octubre de 2004. La lista de participantes en esta reunión figura en el apéndice 4. El proyecto de documento se revisó teniendo en cuenta las opiniones expresadas en esa reunión y el nuevo texto se volvió a someter a un examen colegiado. Por último, este CICAD se examinó y aprobó como evaluación internacional en la 13ª reunión de la Junta de Evaluación Final, celebrada en Nagpur (India) del 31 de octubre al 3 de noviembre de 2005. Los participantes en esta reunión figuran en el apéndice 5. También se reproducen en este documento las Fichas internacionales de seguridad química para el 2-etoxietanol (ICSC 0060; IPCS, 2002), el 2-etoxietilacetato (que se metaboliza con rapidez a 2-etoxietanol) (ICSC 0364; IPCS, 2006) y el 2-propoxietanol (ICSC 0607; IPCS, 2004), preparadas por el Programa Internacional de Seguridad de las Sustancias Químicas (IPCS) en un proceso de examen colegiado independiente.

El 2-etoxietanol (Servicio de Resúmenes Químicos [CAS] Nº 110-80-5) y el 2-propoxietanol (CAS Nº 2807-30-9) son líquidos incoloros totalmente miscibles con el

[1] La lista de siglas y abreviaturas utilizadas en el presente informe figuran en el apéndice 1.

agua, con coeficientes de reparto octanol/agua (K_{ow}) bajos; no parecen encontrarse como productos naturales. El 2-etoxietanol se produce comercialmente a partir de óxido de etileno y un exceso de etanol anhidro.

Se ha informado de la utilización del 2-etoxietanol en pinturas, revestimientos, tintas, limpiadores, abrillantadores, líquidos de frenos y combustibles para reactores y tiene una aplicación amplia como disolvente, intermediario químico y acoplador de disolventes en mezclas, así como en formulaciones acuosas. Su presencia en los productos de consumo se suele considerar inaceptable y los programas de reducción de su utilización han llevado a una restricción generalizada de dicho uso. La producción y utilización de 2-etoxietanol como disolvente en la industria puede dar lugar a su liberación en el medio ambiente mediante diversas corrientes de desechos.

El 2-propoxietanol se utiliza en lubrificantes, pinturas, revestimientos de superficies y abrillantadores. Su producción y uso puede dar lugar a su liberación en el medio ambiente mediante diversas corrientes de desechos.

Los datos de vigilancia en los que se basan las estimaciones de la exposición de la población general al 2-etoxietanol son limitados. Se han establecido estimaciones de la exposición a partir del medio ambiente (sobre todo el aire y el agua) y de los productos de consumo. Hay datos relativos a la exposición ocupacional para diversos modelos de producción y de utilización de productos.

No se ha encontrado información que sirva de base para hacer estimaciones de la exposición de la población general al 2-propoxietanol.

La absorción de 2-etoxietanol a través de la piel puede ser una vía importante de exposición, sobre todo en el entorno profesional. El 2-etoxietanol también se absorbe con rapidez por inhalación y por vía oral y tras la absorción se distribuye ampliamente por todo el organismo.

Sobre la base de los estudios *in vitro*, es probable que la absorción cutánea del 2-propoxietanol sea rápida.

Las principales rutas metabólicas del 2-etoxietanol son la oxidación a 2-etoxiacetaldehído (EALD) y ácido 2-etoxiacético (EAA), probables metabolitos activos. Hay algunos indicios de que las personas pueden absorber la sustancia inhalada en mayor medida que las ratas y que su conversión en EAA es también más rápida, pero con una eliminación posterior más lenta.

No se han encontrado datos sobre el metabolismo del 2-propoxietanol, pero parece que en él intervienen la alcohol deshidrogenasa y la aldehído deshidrogenasa.

La toxicidad aguda del 2-etoxietanol tras la exposición oral es de baja a moderada, pero tras la respiratoria o cutánea es baja. Tiene un bajo potencial de irritación cutánea u ocular y no se ha demostrado su actividad como sensibilizador cutáneo. El 2-etoxietanol ha inducido de manera sistemática efectos hematológicos, reproductivos (efectos en los testículos y los parámetros del esperma y en la regularidad del estro) y en el desarrollo en numerosas especies de animales de laboratorio expuestos por distintas vías. Los ratones parecen ser menos sensibles que las ratas a los efectos del 2-etoxietanol. Se supone que los importantes efectos reproductivos, en el desarrollo y hematológicos observados en los animales de experimentación se deben al EAA formado durante el metabolismo del 2-etoxietanol. La información disponible sobre la genotoxicidad del 2-etoxietanol parece indicar que puede tener algún potencial de inducción de daños citogenéticos *in vitro*, aunque esto no se reflejó en los estudios *in vivo* realizados con ratones. No hay pruebas de que induzca mutaciones. Tampoco se dispone de estudios prolongados adecuados sobre su potencial carcinogénico.

La toxicidad aguda del 2-propoxietanol por las vías oral, respiratoria y cutánea es baja. No parece ser importante como irritante o sensibilizador cutáneo. En conejos produjo irritación ocular. El efecto principal tras la exposición repetida al 2-propoxietanol se observa en la sangre. No se encontraron datos sobre la genotoxicidad y la carcinogenicidad. En un estudio limitado no se observó embriotoxicidad, fetotoxicidad o teratogenicidad, pero se detectó un pequeño número de aberraciones óseas en los fetos con dosis que también indujeron toxicidad materna.

Aunque los datos epidemiológicos son limitados, hay indicios de que la toxicidad del 2-etoxietanol se manifiesta en las personas en la sangre y el sistema reproductor masculino. También se observó una disminución de la producción de esperma en los trabajadores expuestos a concentraciones medias de 2-etoxietanol de 9,9 ó 24 mg/m^3. Se detectaron efectos en la sangre de pintores de embarcaciones expuestos a una concentración media de 2-etoxietilacetato, equivalente a 11 mg de 2-etoxietanol/m^3. Sin embargo, hay que reconocer que en estos estudios también había exposición a otras sustancias.

Los estudios en las personas son demasiado limitados para establecer una ingesta o una concentración tolerable para el 2-etoxietanol. De los estudios de toxicidad en el desarrollo efectuados en ratas y conejos se puede derivar una concentración sin efectos adversos

observados (NOAEC) de 40 mg/m^3. Tras el ajuste para una exposición continua y utilizando factores de incertidumbre para la variación interespecífica (10) e intraespecífica (10) se puede derivar una concentración tolerable de 0,1 mg/m^3.

La información disponible no permite establecer una ingesta o una concentración tolerable para el 2-propoxietanol.

Las limitaciones de los datos de vigilancia para el 2-etoxietanol impiden establecer estimaciones fidedignas de la exposición normal de la población general. Utilizando una estimación bruta del límite superior de exposición al 2-etoxietanol en el medio ambiente general (basada en el límite de detección de un estudio de exposición en medios múltiples), el margen entre este valor y la concentración tolerable es de alrededor de 30. Si se compara la concentración tolerable con la concentración más elevada de 2-etoxietanol detectada realmente en el aire ambiente en el Canadá (en el exterior de una fábrica de automóviles), este margen sería de alrededor de 120. Sin embargo, teniendo en cuenta la incertidumbre de los datos sobre la composición de los productos de consumo de la muestra que pueden contener la sustancia, las estimaciones del caso peor de exposición al 2-etoxietanol a partir de su uso indican que los niveles pueden rebasar la concentración tolerable. No obstante, el grado de confianza en estas estimaciones de la exposición es muy bajo y los limitados datos disponibles ponen de manifiesto que el 2-etoxietanol ya no suele estar presente en los productos de consumo en el Canadá, los Estados Unidos de América o la Unión Europea. No obstante, los entornos profesionales pueden presentar todavía alguna posibilidad de exposición y los modelos de producción y uso de los productos parecen indicar que los niveles en el lugar de trabajo pueden rebasar los que tienen efectos en las personas.

Sólo se dispone de datos limitados sobre los efectos del 2-etoxietanol en los organismos acuáticos. Para los animales terrestres se han utilizado valores críticos de la toxicidad obtenidos de estudios en mamíferos de laboratorio. En caracterizaciones del riesgo prudentes basadas en los valores de la exposición estimada para la biota terrestre, el suelo y el medio acuático del Canadá, se estableció que era poco probable que concentraciones de 2-etoxietanol pudieran causar efectos adversos en las poblaciones correspondientes de fauna y flora silvestres.

La escasa disponibilidad de datos ecotoxicológicos y la ausencia de datos sobre concentraciones en el medio ambiente no permiten realizar una evaluación del riesgo del 2-propoxietanol para el medio ambiente.

PART D

2-BUTOXYETHANOL (UPDATE)

1. EXECUTIVE SUMMARY

This CICAD[1] on 2-butoxyethanol is an update of the CICAD published in 1998 (IPCS, 1998), which was based upon reviews prepared by NIOSH (1990) and ATSDR (1996) of the USA. Human health aspects of the CICAD have been extensively revised, as important new information on carcinogenicity and an assessment of the mode of action for tumour development observed in these studies have become available. Additional detailed information on potential exposure has also been incorporated as a basis for the sample risk characterization.[2] The update was prepared by Toxicology Advice & Consulting Ltd of the United Kingdom and is based primarily on documentation prepared as part of the Canadian Priority Substances Program under CEPA (Environment Canada & Health Canada, 2002). The objective of assessments on priority substances under CEPA is to assess potential effects of indirect exposure in the general environment on human health as well as environmental effects. Data identified as of October 1999 were considered in the source document. A comprehensive literature search of several online databases was conducted in February 2003 to identify any key references published subsequent to those incorporated in the source document. Information on the nature of the peer review and availability of the source document is presented in Appendix 2. Information on the peer review of this CICAD is presented in Appendix 3. This CICAD was approved as an international assessment at a meeting of the Final Review Board, held in Hanoi, Viet Nam, on 28 September – 1 October 2004. Participants at the Final Review Board meeting are listed in Appendix 4. The International Chemical Safety Cards for 2-butoxyethanol (ICSC 0059) and 2-butoxyethyl acetate (ICSC 0839), produced by IPCS (2003, 2005a), have also been reproduced in this document.

2-Butoxyethanol (CAS No. 111-76-2) is a colourless liquid that is miscible with water and most organic solvents. It has not been reported to occur as a natural product.

2-Butoxyethanol is used widely as a solvent in surface coatings, such as spray lacquers, quick-dry lacquers, enamels, varnishes, varnish removers, and latex paint. It is also used in metal and household cleaners.

Based upon limited data, ambient exposures in air are generally in the μg/m^3 range. Indirect exposure of the general population to 2-butoxyethanol is most likely from inhalation and dermal absorption during the use of products containing the chemical. Levels of airborne 2-butoxyethanol in occupational settings are typically in the mg/m^3 range.

2-Butoxyethanol is readily absorbed following inhalation, oral, and dermal exposure. The chemical is metabolized primarily via alcohol and aldehyde dehydrogenases, with the formation via BALD of BAA, the principal metabolite, although other metabolic pathways have also been identified.

2-Butoxyethanol has moderate acute toxicity and is irritating to the eyes and skin; it is not a skin sensitizer. The principal effect exerted by 2-butoxyethanol and its metabolite BAA is haematotoxicity. In vitro studies indicate that human red blood cells are not as sensitive as rat red blood cells to the haemolytic effects of 2-butoxyethanol and BAA and that the latter is the more potent haemolytic agent. In rats, adverse effects on the central nervous system, kidneys, and liver occur at higher exposure concentrations than do haemolytic effects. In animals, adverse effects on reproduction and development have been observed only at maternally toxic doses. Long-term studies in laboratory animals gave some evidence of carcinogenicity in mice (increased incidences of haemangiosarcomas of the liver or hepatocellular carcinomas in males and squamous cell papillomas or carcinomas of the forestomach in females) and equivocal evidence in female rats (a marginal increase in the incidence of benign or malignant phaeochromocytomas of the adrenal gland). The results of in vitro tests for mutagenicity of 2-butoxyethanol were inconsistent; 2-butoxyethanol was not genotoxic in vivo.

Based on limited data from case reports and one clinical study, similar acute effects — including haemolytic effects as well as effects on the central nervous system — are observed in humans and rats exposed to 2-butoxyethanol, although the effects are observed at much higher exposure concentrations in humans than in rats. A TC, making use of chemical-specific adjustment factors, for haemolytic effects of 11 mg/m^3 has been developed, based on BMCs. A TC of 0.04 mg/m^3 for lesions in the forestomach of mice was also established.

Levels of 2-butoxyethanol in ambient air in Canada are less than the TCs derived for effects on the blood or forestomach. For example, the mean concentration of 2-butoxyethanol in outdoor air reported in a multimedia exposure study was 8.4 μg/m^3, with a maximum of 243 μg/m^3. However, exposure to 2-butoxyethanol during use of products containing the substance could potentially exceed the TCs, based on limited data on emissions from products currently available.

[1] For a list of acronyms and abbreviations used in this report, please refer to Appendix 1.

[2] While there were minor differences in the environmental assessments between the source documents for CICAD 10 and the present CICAD, the final outcomes (i.e. the PNECs) are similar; thus, the environmental sections in the present CICAD were not revised.

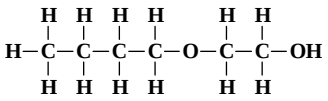
Conservative estimates of short-term indoor air concentrations resulting from emissions of some common household products ranged up to 62 mg/m^3.

Based upon extremely conservative assumptions, the highest predicted concentrations of 2-butoxyethanol in surface waters in the immediate vicinity of effluent streams may, in some cases, exceed PNECs. However, more realistic assumptions based on the available data suggest that risk to aquatic organisms is low. Owing to the short half-life of 2-butoxyethanol in the atmosphere, measured or predicted concentrations of this chemical in air are considered to have no environmental significance.

2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES

2-Butoxyethanol (CAS No. 111-76-2; $C_6H_{14}O_2$; relative molecular mass, 118.2), also known as monobutyl glycol ether and butyl cellosolve, is a synthetic glycol ether. It is a colourless liquid with a mild ether odour; the odour threshold is approximately 0.5 mg/m^3 (Amoore & Hautala, 1983). At ambient temperature, 2-butoxyethanol is miscible with water and most organic solvents. 2-Butoxyethanol has a boiling point of 171 °C, a vapour pressure of 0.1 kPa at 20 °C, and a log K_{ow} of 0.83. A calculated Henry's law constant is 0.551 Pa·m^3/mol (ASTER, 1996). Additional physical and chemical properties are presented in the International Chemical Safety Card for 2-butoxyethanol reproduced in this document.

The structural formula of 2-butoxyethanol is given below:



The conversion factors[1] for 2-butoxyethanol in air (at 20 °C and 101.3 kPa) are as follows: 1 ppm in air = 4.91 mg/m^3; 1 mg/m^3 = 0.204 ppm.

[1] In keeping with WHO policy, which is to provide measurements in SI units, all concentrations of gaseous chemicals in air will be given in SI units in the CICAD series. Where the original study or source document has provided concentrations in SI units, these will be cited here. Where the original study or source document has provided concentrations in volumetric units, conversions will be done using the conversion factors given here, assuming a temperature of 20 °C and a pressure of 101.3 kPa. Conversions are to no more than two significant digits.

3. ANALYTICAL METHODS

Laboratory analysis for 2-butoxyethanol in environmental samples is usually by GC in combination with FID, ECD, or MS detection; infrared absorption spectrophotometry is also sometimes used. The detection limits of these analytical methods in air include 0.15 mg/m^3 for a 48-litre sample (OSHA, 1990) and 0.01–0.02 mg for 2- to 10-litre samples (NIOSH, 1994). Multidimensional GC–MS has been used to improve the detection limit to 5–7 µg per sample (Kennedy et al., 1990).

GC methods combined with FID, ECD, or MS detection and HPLC methods coupled with ultraviolet or radiochemical detection have been developed for the analysis of 2-butoxyethanol and its metabolite BAA in urine and blood (Smallwood et al., 1984, 1988; Groeseneken et al., 1986, 1989; Johanson et al., 1986, 1988; Rettenmeier et al., 1993; Sakai et al., 1993, 1994; Corley et al., 1994). The detection limits for BAA range from 0.03 to 0.1 mg/l. 2-Butoxyethanol and BAA in rat and human blood can be analysed by a GC–MS derivatization method with a detection limit range of 16–18 ng/g blood (Bormett et al., 1995). NIOSH (1990) reviewed the available data and developed guidelines for the biological monitoring of BAA.

4. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

2-Butoxyethanol does not occur naturally. It is usually produced by reacting ethylene oxide with butyl alcohol, but also by the direct alkylation of ethylene glycol with an agent such as dibutyl sulfate (Rowe & Wolf, 1982).

2-Butoxyethanol is widely used as a solvent in surface coatings, such as spray lacquers, quick-dry lacquers, enamels, varnishes, varnish removers, and latex paint (Leaf, 1985; Sax & Lewis, 1987; Stemmler et al., 1997). It is also used as a coupling agent in metal and household cleaners; as an intermediate in 2-butoxyethyl acetate production; and in herbicides, automotive brake fluids, printing inks, spot removers, and cosmetics (Leaf, 1985; Stemmler et al., 1997; ATSDR, 1998). The average concentration of 2-butoxyethanol in household products marketed in the USA in 1977 was 2.8%. "Low-pollutant" paints contained up to 6% 2-butoxyethanol in a study conducted in Germany (Plehn, 1990). Levels of 2-butoxyethanol in industrial and household window-cleaning agents have been reported to range from 1% to 30% (v/v) (Vincent et al., 1993; ATSDR, 1998). Concentrations up to 10% have been reported in cosmetic

products, including hair dyes, nail polish, and nail polish removers (Health Canada, 1998a). 2-Butoxyethanol has also been used as an ice fog suppressant (USEPA, 1979). In 1994, 176 900 tonnes of 2-butoxyethanol were produced in the USA (USITC, 1996). Within the European Community, the total production capacity of 2-butoxyethanol was approximately 70 000–90 000 tonnes in the same year (ECETOC, 1994; CEFIC, 1995). Canadian production of 2-butoxyethanol was 182.7 tonnes in 1995 and 235.3 tonnes in 1996 (Environment Canada, 1997a,b). In 2002, production in the USA was between 45 400 and 227 000 tonnes; in 2003, production in Europe was 160 000 tonnes (OECD, 2005).

2-Butoxyethanol may be released into air or water by facilities that manufacture, process, or use the chemical (ATSDR, 1998; USNLM, 2002). Products containing 2-butoxyethanol may also release the substance into the air. Solvent-based building materials such as paints will release 2-butoxyethanol to air as they dry. There is potential for the release of 2-butoxyethanol from hazardous waste sites, although quantitative data have not been identified. 2-Butoxyethanol has been detected in samples of groundwater and surface water taken near municipal landfills and hazardous waste sites (ATSDR, 1998). Concentrations of 2-butoxyethanol in aqueous samples from a municipal and an industrial landfill in the USA ranged from <0.4 to 84 mg/l (Beihoffer & Ferguson, 1994). 2-Butoxyethanol was detected at a concentration of 0.23 μg/m^3 in the emissions of a municipal waste incineration plant in Germany (Jay & Stieglitz, 1995). The Canadian Chemical Producers' Association (CCPA, 1997, 1999a,b) reported total environmental emissions to air by member companies between 1992 and 1998 ranging from 1 to 3 tonnes per year. According to data reported under CEPA, 319 tonnes of 2-butoxyethanol were released into the air in Canada in 1996, while 63 tonnes were released as waste, 6.5 tonnes were released into landfills, and 2 tonnes were released into water (Environment Canada, 1997b).

5. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

In the atmosphere, 2-butoxyethanol is expected to exist in the vapour phase. Owing to 2-butoxyethanol's water solubility, wet deposition is likely to occur (ATSDR, 1998). The chemical will not persist in the atmosphere; it has an atmospheric half-life of approximately 17 h, based on an estimated rate constant for reaction with hydroxyl radicals (USNLM, 2002). Tuazon et al. (1998) reported that the gas-phase reaction products of 2-butoxyethanol with hydroxyl radicals in the presence of nitric oxide were *n*-butyl formate, 2-hydroxyethyl formate, propanal, 3-hydroxybutyl formate, an organic nitrate, and one or more hydroxycarbonyl products. Stemmler et al. (1997) irradiated synthetic air mixtures containing 2-butoxyethanol, methyl nitrite, and nitric oxide in a Teflon bag reactor at room temperature. The major oxidation products were butyl formate, ethylene glycol monoformate, butoxyacetaldehyde, 3-hydroxybutyl formate, and propionaldehyde, whereas minor products were 2-propyl-1,3-dioxolane, ethylene glycol monobutyrate, 2-hydroxybutyl formate, acetaldehyde, propyl nitrate, and butyraldehyde. Howard et al. (1991) estimated a half-life of 2-butoxyethanol in the air of 3.28–32.8 h.

The miscibility of 2-butoxyethanol with water, low log K_{ow}, and Henry's law constant suggest that volatilization from water, adsorption, and bioconcentration are not important fate processes and that the chemical should not significantly bioconcentrate in aquatic organisms (OECD, 1997). A bioconcentration factor of 2.5 was calculated (SRC, 1988).

Aerobic biodegradation rates suggest that the half-life of 2-butoxyethanol in surface water will range from 1 to 4 weeks (Howard et al., 1991).

Because of its low K_{oc}, 2-butoxyethanol should be highly mobile in soil and potentially could transfer to groundwater (OECD, 1997). Howard et al. (1991) estimated half-lives of 2-butoxyethanol of 2–8 weeks in groundwater and 1–4 weeks in soil, based on unacclimated aqueous aerobic biodegradation.

2-Butoxyethanol is not likely to undergo direct hydrolysis in the aquatic environment, and it is likely to be readily biodegraded (ATSDR, 1998). Five-day theoretical BOD values range from 5% (without acclimation) to 73% (with acclimation); 10-day theoretical BOD values range from 57% to 74%. The maximum theoretical BOD value reported is 88% for 20 days (USNLM, 2002). Biodegradation is likely to be the most important mechanism for the removal of 2-butoxyethanol from aerobic soil and water.

A Level III fugacity model has been used to estimate the environmental partitioning of 2-butoxyethanol when released into air, water, or soil. Values for input parameters were as follows: molecular mass, 118 g/mol; vapour pressure, 296 Pa[1]; water solubility, 63 500 mg/l; log K_{ow}, 0.84[2]; Henry's law constant, 0.551 Pa·m^3/mol; half-life in air, 17 h; half-life in water, 550 h; half-life in soil, 550 h; and half-life in sediment, 1700 h. Modelling

[1] This is the vapour pressure cited in the source document and used in the fugacity model. However, ICSC 0059 (IPCS, 2005a) provides a vapour pressure of 0.1 kPa.

[2] This is the log K_{ow} cited in the source document and used in the fugacity model. However, ICSC 0059 (IPCS, 2005a) provides a log K_{ow} of 0.83.

was based upon an assumed emission rate of 1000 kg/h, although the emission rate used would not affect the estimated percent distribution. If 2-butoxyethanol is emitted into air, EQC Level III fugacity modelling predicts that about 66% would be present in air, about 20% in water, and about 14% in soil. If 2-butoxyethanol is emitted into water, more than 99% would be present in water. Following its release to soil, about 75% would be present in soil and about 25% in water.

6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

6.1 Environmental levels

Few data on levels of 2-butoxyethanol in the environment have been identified. One study was conducted to determine concentrations of 2-butoxyethanol in multiple media in Canada to which humans are exposed, including drinking-water and indoor and outdoor air. Thirty-five participants were randomly selected from the Greater Toronto Area in Ontario, six from Queens Subdivision in Nova Scotia, and nine from Edmonton, Alberta. For each participant, samples of drinking-water and beverages and indoor, outdoor, and personal air were collected over a single 24-h period; however, samples of food were not analysed for 2-butoxyethanol. In outdoor air, levels of 2-butoxyethanol were above the limit of detection (0.84 μg/m^3) in 32% of the 50 samples. The maximum concentration found was 243 μg/m^3, and the mean concentration[1] was 8.4 μg/m^3. In indoor air, 2-butoxyethanol was detected in 66% of the 50 samples. The maximum and mean concentrations were 438 μg/m^3 and 27.5 μg/m^3, respectively. 2-Butoxyethanol was detected in 70% of the 50 personal air samples. Concentrations ranged from below the limit of detection to 275 μg/m^3, with a mean concentration of 31 μg/m^3. 2-Butoxyethanol was detected in 68% of the 50 drinking-water samples (detection limit 0.02 μg/l). Concentrations ranged from below the limit of detection to 0.94 μg/l, with a mean concentration of 0.21 μg/l. 2-Butoxyethanol was detected in 56% of the 50 beverage samples (detection limit 6.80 μg/l). Concentrations ranged up to 73.8 μg/l, and the mean concentration was 6.46 μg/l (Conor Pacific, 1998).

In samples of drinking-water collected between 1989 and 1995 from four sites in Ontario, Canada, concentrations of 2-butoxyethanol were above the limit of detection (not specified) in one sample from each site (i.e. in 9–17% of total samples at each site). The highest concentration measured was 5.0 μg/l (OMEE, 1996). 2-Butoxyethanol was detected (but not quantified) in a sample of paper and paperboard food packaging materials in the United Kingdom (Castle et al., 1997).

Reported levels of 2-butoxyethanol in samples of ambient air collected between 1990 and 1993 (including samples taken from Nepal, Europe, and Antarctica) have ranged from below the limits of detection to 100 μg/m^3 (Ciccioli et al., 1993, 1996; Daisey et al., 1994; Brinke, 1995; Shields et al., 1996). In Canada, the mean concentration of 2-butoxyethanol in samples of ambient air collected in the vicinity of an automotive plant were reported as 2.3 μg/m^3 (when concentrations in samples where 2-butoxyethanol was not detected were assumed to be equivalent to one half the limit of detection), and the maximum concentration was 7.3 μg/m^3 (OMEE, 1994). 2-Butoxyethanol was detected at a concentration of 23 μg/l in one of seven groundwater samples collected near the Valley of Drums, Kentucky, USA (ATSDR, 1998). Samples from the Hayashida River in Japan, where effluent entered the river from the leather industry, contained 2-butoxyethanol at 1310 and 5680 μg/l (Yasuhara et al., 1981). Information on levels in soils or sediments has not been identified. 2-Butoxyethanol levels below 100 μg/l have been reported in samples of industrial wastewater effluents in the USA (ATSDR, 1998).

ChemCAN4 (version 0.95) modelling has been used to estimate environmental concentrations of 2-butoxyethanol. This model is a Level III fugacity-based regional model developed to estimate the environmental fate of chemicals in Canada. According to a survey conducted under CEPA, the highest reported recent release of 2-butoxyethanol in Canada was 319 tonnes, from facilities in British Columbia, Ontario, and Quebec in 1996 (Environment Canada, 1997a). To make a conservative estimate of environmental concentrations of 2-butoxyethanol, it was assumed, for modelling purposes, that all of this was released into southern Ontario. "Ontario – Mixed Wood Plain" was therefore selected as the geographic region for ChemCAN4 modelling of 2-butoxyethanol. The 2-butoxyethanol input rate was 36.4 kg/h, all to the atmosphere. Chemical input values were as follows: molecular mass, 118 g/mol; vapour pressure, 296 Pa[2]; water solubility, 63 500 mg/l; log K_{ow}, 0.84[3]; Henry's law constant, 0.551 Pa·m^3/mol; half-life in air, 17 h; half-life in water, 550 h; half-life in soil, 550 h; and half-life in sediment, 1700 h. Modelling was

[1] In all outdoor air, indoor air, personal air, drinking-water, and beverage samples where 2-butoxyethanol was not detected, concentrations were assumed to be equivalent to one half the limit of detection for the calculation of the mean concentration.

[2] This is the vapour pressure cited in the source document and used in the fugacity model. However, ICSC 0059 (IPCS, 2005a) provides a vapour pressure of 0.1 kPa.

[3] This is the log K_{ow} cited in the source document and used in the fugacity model. However, ICSC 0059 (IPCS, 2005a) provides a log K_{ow} of 0.83.

based upon an assumed emission rate of 1000 kg/h, although the emission rate used would not affect the estimated per cent distribution. For Ontario – Mixed Wood Plain, environmental characteristics were as follows: total surface area, 169 000 km^2; percentage of area covered by water, 43.8%; average air height, 2 km; average water depth, 20 m; average soil depth, 10 cm; residence time in air, 1.71 days; residence time in water, 618 days; and environmental temperature, 7.4 °C. Environmental concentrations of 2-butoxyethanol in southern Ontario predicted by ChemCAN4 modelling (assuming all release is to the atmosphere) are as follows: 1.623 ng/m^3 in air; 3.02×10^{-4} µg/l in water; 4.28×10^{-3} ng/g dry weight in soil; and 1.64×10^{-4} ng/g dry weight in sediments. The ChemCAN4 model estimates average concentrations throughout the region; therefore, actual concentrations in the vicinity of releases could be higher than those estimated by the model.

Other than the multimedia exposure study described above (Conor Pacific, 1998), available data on concentrations of 2-butoxyethanol in residential indoor air are limited to detection of 2-butoxyethanol at a concentration of 8 µg/m^3 in one of six samples of indoor air collected over 4- to 7-day periods in 1983–1984 from homes in northern Italy (De Bortoli et al., 1986). Concentrations of 2-butoxyethanol in the other five samples were below the limit of detection, which was not specified.

2-Butoxyethanol was measured in indoor air samples (three per site) at concentrations up to 33 µg/m^3 during March and April 1991 at 70 office buildings in 25 states plus the District of Columbia across the USA (Shields et al., 1996). A specific limit of detection was not reported for 2-butoxyethanol; however, a general limit of detection of 0.5 µg/m^3 was reported for VOCs. Geometric mean concentrations calculated based on the assumption of half of this general limit of detection (0.25 µg/m^3) for samples in which the concentration of 2-butoxyethanol was below the limit of detection are reported for three categories of building. 2-Butoxyethanol was detected in 24% of the samples from 50 telecommunications offices at concentrations up to 33 µg/m^3; the geometric mean concentration was 0.1 µg/m^3. The compound was detected in 44% of the samples from nine data centres at concentrations up to 16 µg/m^3, with a geometric mean concentration of 0.2 µg/m^3. 2-Butoxyethanol was also detected in 73% of the samples from 11 administrative offices at concentrations up to 32 µg/m^3, with a geometric mean concentration of 1.0 µg/m^3 (Shields et al., 1996). In contrast, detectable concentrations of 2-butoxyethanol were not present in 70 samples of outdoor air collected in the immediate vicinities of these office buildings.

Indoor air was sampled between June and September 1990 in 12 office buildings in the San Francisco Bay area of northern California, USA. Concentrations of 2-butoxyethanol ranged from below the limit of detection (2 µg/m^3) to 130 µg/m^3. An arithmetic mean concentration was not reported. The geometric mean concentration was 7.9 µg/m^3 in indoor air, compared with 1.9 µg/m^3 in the air outside these buildings (Daisey et al., 1994; Brinke, 1995). However, the number of samples collected at each location, the frequencies of detection in indoor air, and key details of the sampling and analytical methods were not reported.

Based on information from the United States National Occupational Exposure Survey (NIOSH, 1983), the number of workers potentially exposed to 2-butoxyethanol in the workplace in the USA during 1981–1983 was estimated at about 1.7 million. Data on the occurrence of airborne 2-butoxyethanol in the workplace obtained from facilities in the USA indicate that, in general, most mean time-weighted average exposures are below 34 mg/m^3 (NIOSH, 1990; ATSDR, 1998). Time-weighted average 2-butoxyethanol exposures have ranged from 5.4 to 26 mg/m^3, with an average of 17 mg/m^3, for silk screening; average exposures of 33 mg/m^3 for silk screeners and 13 mg/m^3 for silk screen spray painters have also been reported (NIOSH, 1990; ATSDR, 1998). In a study of various industrial operations, geometric mean atmospheric exposures to 2-butoxyethanol ranged from 1.5 to 17.7 mg/m^3 for printing, from 3.4 to 93.6 mg/m^3 for painting, and from 0.2 to 1774 mg/m^3 in a mirror manufacturing plant (Veulemans et al., 1987). Workers employed in varnish production facilities have been reported to have individual exposures ranging from <0.5 to 39 mg/m^3 (Angerer et al., 1990; Sohnlein et al., 1993). In a study of automobile cleaners using products containing 2-butoxyethanol, time-weighted average personal exposures ranged from <0.5 to 36 mg/m^3 (Vincent et al., 1993).

6.2 Human exposure

Available data on levels of 2-butoxyethanol in environmental media in Canada upon which estimates of population exposure may be based are limited to air and drinking-water. These data are further limited by the lack of identification of reliable, quantitative, representative data on levels in residential indoor air, although available information is sufficient to indicate that such levels are higher than those in ambient air.

Therefore, point estimates of average daily intakes (on a body weight basis) were derived primarily as a basis for determining the relative contributions to total intake by the few media for which relevant data were identified (Table 1). These point estimates were based on the limited data on mean concentrations in ambient air, indoor air, and drinking-water reported in the Canadian multimedia exposure study (Conor Pacific, 1998) and reference values for body weight, inhalation volume, and

Table 1: Estimated average intake of 2-butoxyethanol by six age groups in the general population.

Route of exposure	Estimated average intake of 2-butoxyethanol by six age groups in the general population (µg/kg body weight per day)					
	0–6 months	6 months – 4 years	5–11 years	12–19 years	20–59 years	60+ years
Ambient air	0.3	0.6	0.5	0.3	0.2	0.2
Indoor air (inhalation)	6.7	14	11	6.4	5.5	4.8
Drinking-water	0.02	0.01	0.01	<0.01	<0.01	<0.01
Subtotal	7.0	15	12	6.7	5.7	5.0

amount of drinking-water consumed daily for six age groups in the general population in Canada. Although confidence in the results of the multimedia exposure study is low, due to limitations of the analytical methodology, this is one of the only studies in which exposure in residential indoor air, the likely principal medium of exposure for the general population (other than during the use of consumer products), was characterized; it is also the only investigation in which an attempt was made to characterize representative exposure of the general population of Canada. Mean concentrations in indoor air for this study, for which confidence in quantification is low, are similar to the single detected value for the only other identified investigation of a limited number of samples of residential indoor air in Italy, for which the limit of detection was not reported. Mean concentrations in the air in offices in well documented studies in other countries were lower, although maximum concentrations were often higher. The dermal uptake of 2-butoxyethanol from air can be estimated to be 0.47 µg/kg body weight per day using the following assumptions: an average K_p of 3 cm/h (Corley et al., 1997); exposure for 21 h/day (Health Canada, 1998b) to the average concentration of 2-butoxyethanol in indoor air (27.5 µg/m^3; Conor Pacific, 1998); an adult average total body surface area of 19 400 cm^2 (Health Canada, 1998b); and an average adult body weight of 70.9 kg (Health Canada, 1998b). This dermal uptake is roughly similar to the intake by inhalation of 2-butoxyethanol from ambient air containing an average concentration of 8.4 µg/m^3 (Conor Pacific, 1998) for 3 h/day (i.e., 0.2 µg/kg body weight per day for the adult age group in Table 1).

Since no monitoring data are available, it is not possible to determine the contribution of food to the overall intake of 2-butoxyethanol. However, 2-butoxyethanol's volatile nature, very low log K_{ow} (0.83), and low bioconcentration factor mean that it is unlikely to partition to food. Indeed, based on physical/chemical properties, the principal source of 2-butoxyethanol in food is likely to be water, for which reported concentrations are very low. In addition, if intake in food were estimated on the basis of concentrations predicted in terrestrial animals and plants by fugacity modelling, these values would be more than 2 orders of magnitude less than the estimated average intake from indoor air for an average adult. Exposure to 2-butoxyethanol in soil is likely to be negligible, based on its release patterns and the relatively small quantities of soil ingested.

Based upon available data, exposure of the general population to 2-butoxyethanol is most likely via inhalation and dermal absorption during the use of a variety of consumer products containing this chemical. 2-Butoxyethanol was detected in emissions from seven consumer products, including cleaners, nail polish remover, and hair colorant (selected as those considered most likely to contain the chemical), that had been purchased in Ottawa, Canada, at rates of up to 938 mg/m^3 per hour (Cao, 1999; Zhu et al., 2001).

Estimates of indoor air concentrations resulting from use of several cleaning products examined by Health Canada (Cao, 1999; Zhu et al., 2001) were derived on the basis of emission factors calculated from steady-state concentrations measured in emission chambers. Assuming a standard room volume, a conservative air exchange rate, and standard product use scenario information, estimated average concentrations of 2-butoxyethanol during the first 60 min following application range from 2.8 mg/m^3 for a glass cleaner to 62 mg/m^3 for an all-purpose spray cleaner (see Table 2).

Estimates of daily intake of 2-butoxyethanol via inhalation and dermal absorption associated with six common household cleaning tasks involving these spray and glass cleaners are also presented in Table 2. Because these products are used primarily by adults, estimated exposures have been derived for this age group only. (The differences in intake from a given medium among age classes, as a result of age-specific differences, would be small in relation to the variation in exposure from the various sources, in any case.) It is assumed that the hands become wetted by the cleaning products during performance of the various cleaning tasks. Dermal absorption from cleaning products was estimated using five different approaches, in order to characterize the

Table 2: Estimates of exposure to 2-butoxyethanol through inhalation and dermal uptake from use of household cleaning products.

Product identification	Task no.	Concentration of 2-butoxyethanol		Average task duration (h/task)	Average task frequency (tasks/day)	Estimated exposure per event (mg/task)		Estimated exposure (mg/kg body weight per day)	
		In product (mg/cm^3)	In room air (mg/m^3)			Dermal uptake	Intake by inhalation	Dermal uptake	Intake by inhalation
Spray cleaner #1	1	37.2	62	0.87	0.0329	36.4	70.1	0.017	0.032
	2			0.42	0.1316	25.3	33.8	0.047	0.063
	3			0.57	0.0658	29.5	45.9	0.027	0.043
	4			0.32	0.1316	22.1	25.8	0.041	0.048
	1–4			**all four tasks**		–	–	**0.132**	**0.186**
Spray cleaner #2	1	12.8	25	0.87	0.0329	12.5	28.3	0.006	0.013
	2			0.42	0.1316	8.7	13.6	0.016	0.025
	3			0.57	0.0658	10.l	18.5	0.009	0.017
	4			0.32	0.1316	7.6	10.4	0.014	0.019
	1–4			**all four tasks**		–	–	**0.045**	**0.074**
Glass cleaner #1	5	8.7	4.7	2.12	0.0109	14.8	13.0	0.002	0.002
	6			0.40	0.1316	5.8	2.4	0.011	0.004
	5–6			**both tasks**		–	–	**0.013**	**0.006**
Glass cleaner #2	5	5.0	2.8	2.12	0.0109	8.5	7.7	0.001	0.001
	6			0.40	0.1316	3.3	1.5	0.006	0.003
	5–6			**both tasks**		–	–	**0.007**	**0.004**

variety of estimates that could be derived using the available data.[1] The estimates of dermal absorption presented in Table 2 are based on the non-steady-state approach with a K_p of 0.0014 cm/h, estimated using the Guy & Potts (1993) equation relating K_p to log K_{ow} and molecular mass; this approach was considered preferable in view of the fact that the lag times and/or time to steady state are not far removed from the durations for each of the tasks modelled and the limitations in the available measured data on dermal absorption of 2-butoxyethanol.[2] The estimated K_p was within the same order of magnitude as the measured K_p based on an in vivo study in guinea-pigs exposed dermally to 2-butoxyethanol solutions (Johanson & Fernström, 1988) and within a factor of 5 of both the estimated and measured values reported in USEPA (1992) for 2-ethoxyethanol, a structurally similar compound. The estimated dermal absorption derived by the various approaches is fairly similar in any case, differing by 9- to 32-fold across all of them, depending on the cleaning product modelled.

The estimated overall daily intakes (i.e. intakes from all tasks combined) via inhalation range from 0.074 to 0.186 mg/kg body weight per day for all-purpose spray cleaners and from 0.004 to 0.006 mg/kg body weight per day for spray glass cleaners, assuming that the user is exposed only for the task duration, average frequency of use, standard values for breathing rate consistent with "light activity," and average adult body weight. (Note that these estimates assume that aerosol generated as overspray is not inhaled by the user and that additional inhalation of background concentrations of 2-butoxyethanol in the residential air following the cleaning activities are relatively low compared with the higher intakes during active use of the products.) Dermal absorption during the performance of these tasks could contribute an additional 0.045–0.132 mg/kg body weight per day for the all-purpose cleaners and 0.007–0.013 mg/kg body weight per day for the glass cleaners, assuming contact with the palms of both hands and an estimated K_p of 0.0014 cm/h and applying a non-steady-state approach. Based on these estimated values, therefore, both inhalation and dermal absorption contribute

[1] The five approaches were 1) a non-steady-state approach using a measured K_p; 2) measured flux values; 3) a steady-state approach using a measured K_p; 4) a non-steady-state approach using an estimated K_p; and 5) 100% absorption from a thin film.

[2] The first three approaches — 1) the non-steady-state approach using a measured K_p; 2) measured flux values; and 3) the steady-state approach using a measured K_p) — which were based on the K_p of 0.012 cm/h measured in an in vivo study in guinea-pigs exposed dermally to 5% and 10% solutions of 2-butoxyethanol (Johanson & Fernström, 1988), were considered less suitable approaches with which to estimate dermal absorption as a consequence of their high variability**,** lack of dose–response, and/or the substantially higher solution concentrations used in this study compared with the cleaning products being modelled.

significantly to intake of 2-butoxyethanol during use of domestic products containing the substance.

It should be noted that estimates of exposure to 2-butoxyethanol through use of consumer products were developed for only a few of the small number of products that were investigated by Health Canada and that exposure to the substance could also occur during use of a variety of other types of products. Little information was identified in the literature regarding measured human exposures from consumer products. Norbäck et al. (1995, 1996) reported that personal air samples collected in the breathing zone of Swedish house painters using water-based paints under "normal" working conditions contained a mean 2-butoxyethanol concentration of 59 μg/m^3 (maximum 730 μg/m^3). Concentrations were below limits of detection in personal air and area samples (i.e. <3.4 and <1.0 mg/m^3, respectively) for cleaners at a school in Australia using a diluted solution of a product containing 1% 2-butoxyethanol (NICNAS, 1996). Office window cleaners in France were exposed to 2-butoxyethanol at concentrations of <1.5–3.4 mg/m^3 during use of spray cleaners containing 0.9% or 9.8% of the substance (Vincent et al., 1993).

7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Results of animal and human studies (most of the available data are from studies conducted with rats) indicate that 2-butoxyethanol is readily absorbed following inhalation, oral, and dermal exposure (Jonsson & Steen, 1978). Absorption through the skin can be significant and may be influenced by the vehicle — water, for example, possibly facilitates percutaneous absorption (Johanson & Fernström, 1988; Wilkinson & Williams, 2002).

2-Butoxyethanol is metabolized primarily via alcohol and aldehyde dehydrogenases, with the formation of BALD and BAA, the principal metabolite (Ghanayem et al., 1987a; Medinsky et al., 1990). This is the favoured metabolic pathway for lower systemic doses of 2-butoxyethanol. Alternative pathways include *O*-dealkylation to ethylene glycol and conjugation to 2-butoxyethanol glucuronide and/or 2-butoxyethanol sulfate (Medinsky et al., 1990). In the study conducted by Medinsky et al. (1990), higher relative concentrations of BAA and ethylene glycol were obtained at lower vapour concentrations of 2-butoxyethanol; higher 2-butoxyethanol glucuronide levels were observed at the high exposures to 2-butoxyethanol, possibly owing to saturation of the oxidative and dealkylation pathways. In human studies, *N*-butoxyacetylglutamine (an amino acid conjugate of the parent compound) has been identified as a metabolite (Rettenmeier et al., 1993).

In general, the metabolism of 2-butoxyethanol to BAA is linearly related to exposure concentration up to levels causing mortality. In one study, after inhalation exposure in rats, 2-butoxyethanol and BAA were analysed in blood, muscle, liver, and testes. The kinetic profile of BAA tissue concentrations was similar to that of 2-butoxyethanol tissue concentrations. Sixty-four per cent of the inhaled dose of 2-butoxyethanol was eliminated in urine as BAA, and the rate of urinary excretion of BAA was dose-dependent (Johanson, 1994).

In humans exposed to 2-butoxyethanol via inhalation at 100 mg/m^3 for 2 h, the concentration of 2-butoxyethanol in the blood reached a plateau of 7.4 μmol/l within 1–2 h, and the chemical could no longer be detected in the blood 2–4 h after exposure. The mean elimination half-life was 40 min. Less than 0.03% of the total uptake of 2-butoxyethanol was excreted unchanged in the urine, whereas urinary excretion as BAA ranged from 17% to 55% (Johanson et al., 1986). Similarly, after percutaneous uptake of 2-butoxyethanol, the urinary excretion of BAA peaked 3 h after exposure and subsequently declined, with an average half-life of 3.1 h. The accumulated urinary excretion of BAA corresponded to 2.5–39% of uptake (Johanson et al., 1988).

Several PBPK models of increasing sophistication have been developed for 2-butoxyethanol (Johanson et al., 1986; Johanson & Boman, 1991; Shyr et al., 1993; Corley et al., 1994; Lee et al., 1998). The Corley et al. (1994) model accurately predicted pharmacokinetics data in animals at non-toxic dose levels but overpredicted the amount of BAA excreted in the urine at haemolytic doses, presumably due to toxicity in the kidneys. The model (Corley et al., 1994) suggested that dermal intake following whole-body exposure is approximately 21% of the total, rather than the 75% suggested by Johanson & Boman (1991). An additional study further addresses dermal uptake in humans from the vapour phase but does not address direct skin contact with liquid containing 2-butoxyethanol (Corley et al., 1997).

Jones et al. (2003) determined that in human volunteers exposed to 2-butoxyethanol vapours (250 mg/m^3 for 2 h), dermal absorption could account for around 11% of the total absorbed dose. This rose to as much as 39% when an industrial setting was simulated (the wearing of overalls, high temperature, and high humidity).

There are species- and sex-related variations in haematological response to 2-butoxyethanol, with rats being the most sensitive species tested to date. Alterations in haematological parameters were observed in

repeated inhalation studies in both rats and mice (NTP, 2000), but the changes in mice were consistent with normocytic anaemia, compared with the macrocytic anaemia observed in rats. In both rats and mice, females are more sensitive to the haematotoxicity of 2-butoxyethanol (see section 8). The data suggest that BAA is responsible for the haematological effects. Observed species- and sex-related variations in haematotoxicity are well correlated with differences in production and clearance of BAA. Mice appear to clear BAA from the blood much more quickly than rats, and the fall-off in the rate of elimination at increased duration of exposure is less marked in mice (Dill et al., 1998). Likewise, clearance of BAA from the blood is slower in female rats than in males (Dill et al., 1998); in addition, the activity of hepatic alcohol dehydrogenase enzyme, which is involved in the metabolism of 2-butoxyethanol to BAA, is greater in females than in males (Aasmoe et al., 1998). Ghanayem et al. (1987b) also observed older rats to be more susceptible to the haemolytic effects of acute 2-butoxyethanol exposure, which is consistent with the greater rate of elimination of metabolites in the urine of younger rats.

These models do not incorporate results of in vitro investigations, in which hepatocytes from rats metabolized 2-butoxyethanol to BAA more efficiently than cells from humans; this pathway was also saturated at much lower doses in human hepatocytes (Green et al., 1996).

Green et al. (2002) compared the metabolic capacity of the rat and mouse stomach to metabolize 2-butoxyethanol. 2-Butoxyethanol was metabolized in vitro in both mouse and rat forestomach and glandular stomach fractions by alcohol dehydrogenases, forming BALD, which was rapidly converted by aldehyde dehydrogenases to BAA. There were marked species differences in alcohol dehydrogenase activity between rats and mice, with the maximum rate up to 1 order of magnitude greater in mice than in rats.

Although data are limited, the acetate derivative of 2-butoxyethanol (2-butoxyethyl acetate) appears to be rapidly hydrolysed to 2-butoxyethanol via esterases in several tissues in the body (Johanson, 1988). Where available, data on the toxicity of 2-butoxyethyl acetate have, therefore, been included in this CICAD.

8. EFFECTS ON LABORATORY MAMMALS AND IN VITRO TEST SYSTEMS

8.1 Single exposure

Many acute toxicity studies of 2-butoxyethanol have led to the establishment of LC_{50}s or LD_{50}s in a variety of species by inhalation, oral, and dermal exposure. Inhalation LC_{50}s for 2-butoxyethanol of 2400 mg/m^3 (male rats, 4 h), 2200 mg/m^3 (female rats, 4 h), 3400 mg/m^3 (mice, 7 h), and >3200 mg/m^3 (guinea-pigs, 1 h) have been reported. Oral LD_{50}s for rats (2500 mg/kg body weight), mice (1400 mg/kg body weight), guinea-pigs (1200 mg/kg body weight), and rabbits (320 mg/kg body weight) have also been reported. Dermal LD_{50}s of 404–502 and 2000 mg/kg body weight have been reported for rabbits and guinea-pigs, respectively. Effects observed in rats, mice, and guinea-pigs exposed by inhalation to the LC_{50} or by ingestion at the LD_{50} include loss of coordination, ataxia, sluggishness, muscular flaccidity, enlarged kidney, blood in the bladder, haemoglobinuria, splenic lesions, and pulmonary congestion (Werner et al., 1943a; Carpenter et al., 1956; Dodd et al., 1983; Gingell et al., 1997). Inhalation exposures of female rats to 2-butoxyethanol at 299 mg/m^3 for 4-h periods resulted in increased osmotic fragility of erythrocytes (Carpenter et al., 1956).

Ghanayem et al. (1987b) indicated that the haemolytic activity of 2-butoxyethanol in rats is age-dependent, with older rats being more susceptible than younger animals. In their study, 2-butoxyethanol (0, 125, or 500 mg/kg body weight) was administered orally to young (4–5 weeks old) and adult (9–13 weeks old) male F344 rats. Although no significant haematotoxic effects were observed in the younger rats administered 2-butoxyethanol at 125 mg/kg body weight, effects in older animals administered this dose included a significant decrease ($P \leq 0.05$) in the number of red blood cells, haematocrit, and haemoglobin and an increase in free haemoglobin plasma levels ($P \leq 0.05$). Histopathological evaluation of tissues collected 24 h after administration of 2-butoxyethanol to rats of various ages revealed dose- and age-dependent liver and kidney changes. These histopathological changes exhibited signs of regression when examined 48 h following exposure. Severe acute haemolytic anaemia was evidenced by a decrease in circulating red blood cells, an increase in the concentration of free haemoglobin in plasma, and the development of haemoglobinuria. Ghanayem et al. (1987b) indicated that the acute anaemia in 2-butoxyethanol-exposed rats was caused by a time- and dose-dependent decrease in the number of red blood cells, in haemoglobin concentrations, and in haematocrit, with little or no change in mean cell volume. In a follow-up study, haematological profiles revealed a time- and dose-dependent increase in haematocrit and mean cell volume. Based on these data, Ghanayem et al. (1990) concluded that 2-butoxyethanol causes spherical swelling of red blood cells followed by haemolysis.

To investigate the induction of tolerance, Ghanayem et al. (1992) assessed haematological parameters in naive or previously bled rats administered a single 2-butoxyethanol dose of 125 or 250 mg/kg body weight. The

bled/recovered rats were less sensitive to 2-butoxyethanol than the naive animals. In vitro incubations with BAA revealed that red blood cells from the bled/recovered rats were less sensitive than those cells from naive animals. Ghanayem et al. (1992) concluded that young red blood cells formed during the regeneration process were less sensitive to BAA than older red blood cells. On chronic exposure to 2-butoxyethanol, some tolerance might be expected. The mechanism is probably related to the greater susceptibility of older cells to BAA; haemolysis of these cells during the initial exposure followed by their replacement with less susceptible younger cells may account for the development of tolerance.

Female rats appear to be more sensitive than males to the effects of 2-butoxyethanol exposure. The onset of haemolysis was faster and blood cell changes were observed earlier and more frequently in female F344 rats given 2-butoxyethanol at 250 mg/kg body weight by gavage than in males treated similarly (Ghanayem et al., 2000).

Toxic effects in the kidneys have been observed in rabbits exposed percutaneously to 2-butoxyethanol (Carpenter et al., 1956). Necropsy of rabbits exposed for 24 h to undiluted 2-butoxyethanol (0.48–0.64 ml/kg body weight) revealed congestion of the kidneys, haemoglobinuria, pale livers, and engorged spleens (Carpenter et al., 1956).

When 2-butoxyethanol (200, 260, 320, 375, or 500 mg/kg body weight) was applied to the shaved dorsal skin of groups of female rats, blood effects (increased mean cell volume, a lowered erythrocyte count and haemoglobin level, and haemoglobinuria) were observed at all doses except the lowest. However, there was no discernible dose–response relationship, which was attributed to the inherent biological variation in percutaneous absorption and haemolytic susceptibility and to the small number of animals ($n = 3$) in these dose groups (Bartnik et al., 1987).

8.2 Irritation and sensitization

2-Butoxyethanol is irritating to the eyes and skin. In rabbits, instillation of an unspecified amount of 2-butoxyethanol caused severe eye irritation, including conjunctival hyperaemia and oedema (von Oettingen & Jirouche, 1931), while 30% and 70% concentrations were moderately irritating (Kennah et al., 1989). When applied to the skin of rabbits for 4 h, 2-butoxyethanol caused mild irritation; extending the period of contact increased the severity of irritation (Tyler, 1984). 2-Butoxyethanol was classified as a severe skin irritant when the Draize method was used (Zissu, 1995).

2-Butoxyethanol did not induce skin sensitization in guinea-pigs (Unilever, 1989; Zissu, 1995).

8.3 Short-term exposure

Haematotoxic effects (e.g. increased osmotic fragility, decreased haemoglobin, decreased numbers of red blood cells) have been observed in rats (270–1600 mg/m^3), dogs (1000–1900 mg/m^3), and monkeys (1030 mg/m^3) exposed repeatedly via inhalation to 2-butoxyethanol for up to approximately 30–35 days (Werner et al., 1943b; Carpenter et al., 1956). Indications of haemoglobinuria, together with histopathological changes in the kidney, were also observed in rabbits exposed for 30 days to 2-butoxyethyl acetate at 2600 mg/m^3 (equivalent to a 2-butoxyethanol concentration of 2000 mg/m^3) (Truhaut et al., 1979).

Dodd et al. (1983) exposed Fischer 344 rats of both sexes to 2-butoxyethanol at 0, 100, 420, or 1200 mg/m^3, 6 h/day for 9 days in total (5 consecutive days of exposure, followed by 2 days of no exposure, then 4 additional consecutive days of exposure). In both sexes, exposure to 1200 mg/m^3 was associated with a significant reduction in red blood cell counts ($P < 0.001$), haemoglobin levels ($P < 0.001$), and mean cell haemoglobin concentration ($P < 0.01$), as well as a significant increase ($P < 0.001$ in all cases) in mean cell volume, nucleated red blood cells, and reticulocytes. Fourteen days post-exposure, a substantial recovery of the affected erythroid parameters was observed; however, statistically significant differences from controls were still observed for the males — i.e. red blood cell count ($P < 0.01$), mean cell volume ($P < 0.001$), and mean cell haemoglobin ($P < 0.001$). Exposure of both sexes to 2-butoxyethanol at 420 mg/m^3 was associated with a significant but less profound effect on erythroid parameters. The NOAEC in this study is 100 mg/m^3.

In a study designed primarily to assess developmental effects, Tyl et al. (1984) exposed pregnant Fischer 344 rats (36 per group) and New Zealand white rabbits (24 per group) to 2-butoxyethanol (0, 120, 250, 490, or 980 mg/m^3) for 6 h/day on days 6–15 of gestation for the rats and on days 6–18 of gestation for the rabbits. In rats, the blood picture was normal at 250 mg/m^3; at 490 mg/m^3 and above, effects included reductions in red blood cell count, mean cell haemoglobin concentration, and increases in haemoglobin, haematocrit, mean cell volume, and mean cell haemoglobin. In the rabbits, statistically significant increases in haemoglobin content and haematocrit were observed at a 2-butoxyethanol concentration of 490 mg/m^3 ($P < 0.01$) but not at 980 mg/m^3, suggesting that rabbits are less sensitive than rats. The NOAEC in this study is 250 mg/m^3.

The oral administration of 2-butoxyethanol at doses of 500 or 1000 mg/kg body weight per day for 4 consecutive days to male F344 rats produced a pronounced dose-dependent effect on circulating red and white blood cells (Grant et al., 1985); however, some effects were

reversible following the end of exposure. Reduced erythrocyte counts, haematocrit, haemoglobin levels, and leukocyte counts and elevated mean cell volume, reticulocyte counts, and mean cell haemoglobin concentration ($P < 0.001$) were observed in animals in the high-dose group. Similar, although less severe, effects were observed in the low-dose group. The LOAEL was 500 mg/kg body weight per day.

To assess the development of tolerance to the haemolytic effects of 2-butoxyethanol exposure in laboratory animals, male F344 rats were administered (by gavage) 2-butoxyethanol at 125 mg/kg body weight per day for 0, 1, 2, 3, 6, and 12 days, and haematological parameters (red blood cell counts, haemoglobin content, haematocrit) were determined after exposure (Ghanayem et al., 1987b). Administration of 2-butoxyethanol for 2 and 3 days caused significant haemolysis of red blood cells. After 3 or more days of exposure, however, there was a gradual increase in the number of red blood cells and haemoglobin content. After 12 days of exposure, red blood cells and haemoglobin approached pre-exposure levels, indicative of the development of tolerance to the haemolytic effects of 2-butoxyethanol. In a follow-up study, Ghanayem et al. (1992) assessed the haemolytic effects of 2-butoxyethanol (administered as a single dose of 0, 125, or 250 mg/kg body weight) in untreated (control) or 2-butoxyethanol-pretreated male F344 rats. The pretreated animals were administered (by gavage) 2-butoxyethanol at 125 mg/kg body weight per day for 3 days and then allowed to recover for 7 days prior to study. The pretreated animals were less sensitive than the untreated controls to the haemolytic effects of subsequent exposure to 2-butoxyethanol. In vitro incubations with BAA revealed that red blood cells from the 2-butoxyethanol-pretreated group were less sensitive than cells from the untreated controls. The investigators suggested that the development of tolerance to the haemolytic effects of 2-butoxyethanol might be due in part to the greater resilience of young erythrocytes formed during the blood regeneration process.

In mice orally administered 2-butoxyethanol at 500 or 1000 mg/kg body weight per day, 5 days/week for 5 weeks, no effect upon white blood cell counts, mean cell volume, or haemoglobin levels was observed; however, red blood cell counts were reduced at both doses (Nagano et al., 1979). The oral administration of 2-butoxyethanol to male rats at 222, 443, or 885 mg/kg body weight per day, 5 days/week for 6 weeks, principally affected red blood cells, whereas white blood cell counts were unaffected (Krasavage, 1986).

In a study in which F344/N rats and B6C3F1 mice were administered 2-butoxyethanol in drinking-water daily for 2 weeks, estimates of 2-butoxyethanol intake by rats and mice ranged from 70 to 300 mg/kg body weight per day and from 90 to 1400 mg/kg body weight per day, respectively (NTP, 1993). Survival was not affected. Decreased thymus weights were noted in male mice receiving 2-butoxyethanol at 400 or 650 mg/kg body weight per day. No haematological tests were conducted in this study.

Female B6C3F1 mice were given oral doses (0, 50, 150, or 500 mg/kg body weight) of 2-butoxyethanol or BAA daily for 10 days. Marked hyperkeratosis in the forestomach was observed, with BAA being more toxic than 2-butoxyethanol. The NOEL for the former was 50 mg/kg body weight, whereas that for the latter was 150 mg/kg body weight (Green et al., 2002).

Oral administration of neat 2-butoxyethanol to male and female B6C3F1 mice (400, 800, or 1200 mg/kg body weight per day for 2 days, reduced to 200, 400, and 600 mg/kg body weight per day for a further 2 days because of unexpected mortality) caused dose-related forestomach lesions (epithelial hyperplasia and inflammation) (Poet et al., 2003), similar to those reported in long-term inhalation studies in mice (NTP, 2000). Forestomach lesions were also observed in mice administered 400 mg/kg body weight per day for 4 days by intraperitoneal or subcutaneous injection (Poet et al., 2003).

8.4 Medium-term exposure

In an inhalation study in F344/N rats exposed at 150–2500 mg/m^3 for 14 weeks (NTP, 2000), there were changes in haematological parameters characteristic of macrocytic, normochromic, responsive anaemia (i.e. increased mean cell volume, lack of change in mean cell haemoglobin values, and increased reticulocyte count). Females were more sensitive than males (LOECs of 150 mg/m^3 and 610 mg/m^3, respectively); the NOEC in males was considered to be 310 mg/m^3. Severity of these effects increased with concentration, and there was no evidence of amelioration over time. Females at the higher concentrations had an increased incidence of thrombosis in the blood vessels of several tissues as well as bone infarction, which was hypothesized to have resulted from severe acute haemolysis or anoxic damage to endothelial cells, causing compromised blood flow. Other effects consistent with regenerative anaemia observed in both male and female rats included excessive haematopoietic cell proliferation in the spleen, haemosiderin pigmentation in the hepatic Kupffer cells and renal cortical tubules, and bone marrow hyperplasia. Inflammation and/or hyperplasia of the forestomach also occurred in rats of both sexes exposed to the higher concentrations of 1200 and 2500 mg/m^3, while changes in relative kidney and liver weights were noted at 310 mg/m^3 and above in females and 1200 mg/m^3 and above in males.

Dodd et al. (1983) exposed Fischer 344 rats of both sexes (16 per group) to 2-butoxyethanol at 0, 25, 120, or

380 mg/m^3 by inhalation, 6 h/day, 5 days/week, for 13 weeks. After 6 weeks, animals exposed to 380 mg/m^3 had a slight but statistically significant decrease in red blood cell counts ($P < 0.01$) and haemoglobin level (statistics not reported), accompanied by an 11% increase in mean cell haemoglobin concentration ($P < 0.001$). At the end of the study, these effects had either lessened or returned to the ranges of control values (contrary to the observations in this strain of rats by the NTP [2000]). The only significant haemolytic effect for male rats in the 380 mg/m^3 exposure group was a 5% decrease in red blood cell count after 66 exposures to 2-butoxyethanol (statistics not provided). The NOAEC in this study is 120 mg/m^3.

Alterations in haematological parameters indicative of haemolytic anaemia (haemoglobin, haematocrit, and erythrocyte counts) were also the most sensitive end-points observed in B6C3F1 mice exposed for 14 weeks (NTP, 2000). However, the anaemia in mice was considered to be normocytic, normochromic, and responsive (compared with the macrocytic anaemia noted in rats), as 2-butoxyethanol did not induce any changes in mean cell volume. In addition, based on the magnitude of the changes, the anaemia was less severe in mice than in rats, although females were again more sensitive than males (LOECs in females and males were 150 mg/m^3 and 610 mg/m^3, respectively). As in rats, effects consistent with regenerative anaemia (haemosiderin pigmentation and increased haematopoiesis in the spleen) were also observed. The incidence of hyperplasia of the forestomach was increased in female mice exposed to 610 mg/m^3 or more and in males at the highest concentration, 2500 mg/m^3; various lesions also appeared in other tissues in females at 2500 mg/m^3 (a concentration that was also associated with increased mortality in both sexes).

In older studies, haematotoxic effects (e.g. increased osmotic fragility, decreased haemoglobin, decreased red blood cell numbers) have been observed in mice (490–2000 mg/m^3), dogs (2000 mg/m^3), and monkeys (490 mg/m^3) exposed repeatedly by inhalation to 2-butoxyethanol for up to approximately 90 days (Werner et al., 1943c; Carpenter et al., 1956).

Groups of F344/N rats and B6C3F1 mice (10 per sex per concentration) were administered 2-butoxyethanol in drinking-water (0, 750, 1500, 3000, 4500, or 6000 mg/l) daily for 13 weeks; estimated intakes ranged from 70 to 500 mg/kg body weight per day in rats and from 100 to 1300 mg/kg body weight per day in mice (NTP, 1993). Effects observed in both species included decreased body weight gain and water consumption. In rats, reduced red blood cell counts and histopathological lesions in the liver, spleen, and bone marrow were observed in males and females (at concentrations of 3000–6000 mg/l and 750–6000 mg/l, respectively). Reduced thymus weights (at concentrations of 4500 and 6000 mg/l in males and females, respectively), diminished uterine size (at 4500 and 6000 mg/l in females), and diminished sperm concentration (at 750–6000 mg/l in males) were also noted. A NOAEL could not be identified in rats owing to a mild to moderate anaemia present in most dose groups. In mice, the only effect observed was reduced body weight gain in males and females at concentrations of 3000–6000 mg/l, although haematological parameters may not have been examined in mice.

Siesky et al. (2002) investigated the hepatic effects of 2-butoxyethanol in rodents. Male B6C3F1 mice and male F344 rats were given 2-butoxyethanol by gavage at 225, 450, or 900 mg/kg body weight per day (mice) or 225 or 450 mg/kg body weight per day (rats) for up to 90 days. DNA synthesis, oxidative damage, haematocrit, and iron deposition in the liver were assessed. There was an increase in haemolysis (as indicated by a decrease in haematocrit and an increase in relative spleen weight) in both rats and mice. The percentage of iron-stained Kupffer cells was increased following treatment with 450 or 900 mg/kg body weight per day in mice and in all treated rats. In the mouse liver, a biphasic increase in oxidative damage (elevated 8-hydroxydeoxyguanosine and malondialdehyde) was observed after 7 and 90 days of treatment, whereas no such effect was seen in treated rats. Vitamin E levels were reduced in both mouse and rat liver following treatment with 2-butoxyethanol, although (importantly) the basal level of vitamin E was approximately 2.5-fold higher in the rat than in the mouse. There was also a biphasic induction of DNA synthesis following 2-butoxyethanol treatment in the mouse; increased DNA synthesis was observed in hepatocytes at 90 days and in endothelial cells at 7 and 14 days at all doses. No change in DNA synthesis was seen in 2-butoxyethanol-treated rat liver.

No overt signs of toxicity and no effects on the weight or microscopic appearance of unspecified organs or on haematology (including osmotic fragility tests) were observed in rabbits administered daily dermal 2-butoxyethanol applications (covered) of up to 150 mg/kg body weight per day for 13 weeks (CMA, 1983).

8.5 Long-term exposure and carcinogenicity

Results are available for inhalation bioassays in which F344/N rats and B6C3F1 mice were exposed (whole body) for 6 h/day, 5 days/week, for up to 2 years to 2-butoxyethanol concentrations of 0, 153, 308, or 614 mg/m^3 (rats) and 0, 308, 614, or 1230 mg/m^3 (mice) (NTP, 2000). In rats, chronic exposure to 2-butoxyethanol at 153 mg/m^3 (the lowest concentration tested) or greater resulted in haemolytic anaemia (characterized as macrocytic, normochromic anaemia, based on decreases in haematocrit, haemoglobin concentrations, and

erythrocyte counts, increases in mean cell volume and mean cell haemoglobin, and the lack of effect on mean cell haemoglobin concentration). Consistent with results observed in earlier studies and toxicokinetic data that indicate slower clearance of the active metabolite (i.e. BAA) and greater activity of the relevant isoenzyme in females, the severity of haematological effects was, in general, greater in females than in males; alterations in multiple parameters were observed at the lowest concentration tested in female rats (i.e. 153 mg/m^3, considered to be the LOEC), while only mean cell volume was affected in males at this concentration. The severity of these effects increased with exposure level, and the effects were persistent throughout the 12 months during which haematological parameters were monitored; there was no indication of amelioration over time in males, while in females, there were slight decreases in the magnitude of the changes in some parameters at 12 months. The anaemia was considered to be responsive, based on the observation of increased reticulocyte and nucleated erythrocyte counts and a decrease in the myeloid to erythroid ratios.

There was a marginal increase in the incidence of phaeochromocytomas (primarily benign, with one malignant tumour) of the adrenal gland in female rats at the highest concentration (614 mg/m^3), which, while not statistically significantly elevated compared with concurrent controls, was greater than the incidence of this lesion observed in historical controls at the NTP. (Incidences of benign or malignant phaeochromocytomas combined were 3/50, 4/50, 1/49, and 8/49 in the 0, 153, 308, and 614 mg/m^3 exposure groups.) There was also a non-statistically significant increase in the incidence of hyperplasia of the adrenal medulla of females at 614 mg/m^3. No such increases were observed in males. Other exposure-related histopathological changes observed in rats included increased incidences of minimal hyaline degeneration of the olfactory epithelium (which was considered to be adaptive/protective rather than adverse), increased incidences of Kupffer cell pigmentation in the liver of both sexes at the two highest concentrations, and an increase in splenic fibrosis in males at 308 mg/m^3 and above. Based on the results of this study, the NTP concluded that there was no evidence of carcinogenic activity in male F344/N rats and equivocal evidence of carcinogenic activity in female rats of this strain, since the slight increase in phaeochromocytomas could not be attributed with certainty to exposure to 2-butoxyethanol.

As in shorter-term studies, B6C3F1 mice were less sensitive than rats to the haematological effects associated with exposure to 2-butoxyethanol. Anaemia, characterized by decreases in haematocrit, haemoglobin concentrations, and erythrocyte count, was present in mice exposed to the two higher concentrations (614 and 1230 mg/m^3), and there was some evidence of anaemia in females at 308 mg/m^3, but only at one time point. In general, based on the lack of consistent changes in mean cell volume and mean cell haemoglobin concentrations, the effects were consistent with normocytic, normochromic anaemia. Although the anaemia was considered responsive, based on the increased reticulocyte counts, this response ameliorated over time. In addition, contrary to the observations in rats, there were no decreases in myeloid to erythroid ratios. Thrombocytosis (increase in platelet counts) was present at all concentrations. Females were again more sensitive than males, with alterations in haematological parameters generally occurring earlier and at lower exposure levels in female mice.

There were increased incidences of papillomas or carcinomas (combined) of the forestomach in both sexes, which were statistically significant in females exposed to 1230 mg/m^3 compared with concurrent and historical controls and in males at 614 and 1230 mg/m^3 compared with historical controls (but not study controls). (Incidences of squamous cell papilloma were 1/50, 1/50, 2/49, and 2/49 in male mice and 0/50, 1/50, 2/50, and 5/50 in female mice at concentrations of 0, 308, 614, and 1230 mg/m^3, respectively. Incidences of squamous cell papilloma or carcinoma combined in female mice were 0/50, 1/50, 2/50, and 6/50 at concentrations of 0, 308, 614, and 1230 mg/m^3, respectively. In addition, the incidence of hyperplasia of the epithelium of the forestomach was significantly increased in a concentration-related manner in all exposed groups, which was accompanied by a concentration-related trend in the incidence of ulcers of the forestomach in female mice. The severity of the epithelial hyperplasia in females also increased with exposure level, as mean severity scores in animals with lesions were 1.8, 2.0, 2.4, and 2.9 at 0, 308, 614, and 1230 mg/m^3, respectively.

There was also a concentration-related increase in the incidence of haemangiosarcomas of the liver in male mice (significant at 1230 mg/m^3). (Incidences were 0/50, 1/50, 2/49, and 4/49 in mice exposed to 0, 308, 614, and 1230 mg/m^3, respectively.) Haemangiosarcomas were also detected in the bone marrow of two mice exposed to 1230 mg/m^3 (one of which also had a haemangiosarcoma in the spleen, while the other had a haemangiosarcoma in the heart) and in one mouse exposed to 308 mg/m^3. A significant increase in the incidence of hepatocellular carcinomas was also observed in males at the highest concentration, although the incidence was within the range observed in historical controls. In addition, the incidences of hepatocellular adenomas were lower in exposed mice than in controls, and there was no indication of an association between exposure and induction of a related preneoplastic lesion. In spite of these facts, a potential role of 2-butoxyethanol in the development of malignant liver tumours could not be ruled out, and it was concluded that they may be exposure-related.

Haemosiderin pigmentation of the Kupffer cells of minimal severity was also noted in the liver of exposed mice.

Based on the increased incidence of hemangiosarcoma of the liver (males) and squamous cell papillomas or carcinomas of the forestomach (females), it was concluded by the investigators that there was some evidence of carcinogenic activity of 2-butoxyethanol in male and female B6C3F1 mice, and the LOAEC for non-neoplastic effects (haematotoxicity and forestomach lesions) was 308 mg/m^3 in both sexes (NTP, 2000).

8.6 Genotoxicity and related end-points

2-Butoxyethanol has been tested for genotoxicity in a range of in vitro and in vivo assays.

In vivo mutagenicity tests have yielded uniformly negative results for 2-butoxyethanol. These assays have included three bone marrow micronucleus tests utilizing intraperitoneal injection in rats and mice (Elias et al., 1996; Elliott & Ashby, 1997; NTP, 2000); a [^{32}P]post-labelling assay for DNA adducts in the brain, kidney, liver, spleen, and testes of orally dosed rats (Keith et al., 1996); an assay for DNA methylation in the brain, kidney, liver, spleen, and testes of rats and in FVB/N transgenic mice carrying the v-Ha-*ras* oncogene (Keith et al., 1996); as well as a test for tumour formation in FVB/N transgenic mice (Keith et al., 1996). Although the results of in vitro tests for mutagenicity of 2-butoxyethanol are inconsistent, the negative results from in vivo studies suggest that 2-butoxyethanol does not have significant in vivo genotoxic potential.

In standard tests in bacteria, 2-butoxyethanol was not mutagenic in *Salmonella typhimurium* strains TA1535, TA1537, TA97, TA98, TA100, and TA102 (Zeiger et al., 1992; Hoflack et al., 1995; Gollapudi et al., 1996). However, the results for strain TA97a were inconsistent, with one report of mutagenicity observed in both the presence and absence of metabolic activation (Hoflack et al., 1995) and another report of no mutagenicity (Gollapudi et al., 1996).

2-Butoxyethanol was not mutagenic at the *HPRT* locus in Chinese hamster ovary cells in either the presence or absence of metabolic activation (McGregor, 1984; Chiewchanwit & Au, 1995). However, there was evidence that it caused gene mutations at the *HPRT* locus in Chinese hamster lung (V79) cells (Elias et al., 1996). An in vitro assay for unscheduled DNA synthesis in rat hepatocytes yielded equivocal results (Elliott & Ashby, 1997). 2-Butoxyethanol produced sister chromatid exchanges in human peripheral lymphocytes but not in Chinese hamster lung (V79) or ovary cells. In vitro cytogenetic assays conducted with human lymphocytes, Chinese hamster lung (V79) cells, and Chinese hamster ovary cells revealed no induction of chromosomal aberrations. An in vitro micronucleus assay in Chinese hamster lung (V79) cells, which incorporated a test for aneuploidy, yielded equivocal results (Elliott & Ashby, 1997). 2-Butoxyethanol failed to produce cell transformation in Syrian hamster embryo cells tested at concentrations up to 20 mmol/l with 7-day exposures (Park et al., 2002).

Mutagenicity studies have also been performed on two metabolites of 2-butoxyethanol: BAA and BALD. BAA was not mutagenic in a series of in vitro assays, in addition to an in vivo micronucleus assay in mice administered the chemical by intraperitoneal injection (Hoflack et al., 1995; Elias et al., 1996; Elliott & Ashby, 1997). BAA (tested at up to 20 mmol/l for 7 days) failed to produce cell transformation in Syrian hamster embryo cells (Park et al., 2002). BALD exhibited genotoxic potential in several in vitro studies (including tests for *HPRT* gene mutation, chromosomal aberrations, micronuclei, aneuploidy, and sister chromatid exchange); however, in the absence of data from in vivo studies, it is not possible to reach a firm conclusion concerning the possible mutagenic hazard of this metabolite (Chiewchanwit & Au, 1995; Hoflack et al., 1995; Elias et al., 1996; Elliott & Ashby, 1997).

8.7 Reproductive toxicity

8.7.1 Effects on fertility

Heindel et al. (1990) used a continuous breeding protocol (Heindel et al., 1989) to assess the reproductive toxicity of 2-butoxyethanol. Male and female Swiss CD-1 mice were administered 2-butoxyethanol in drinking-water (0, 0.5, 1, or 2%; equivalent to 0, 700, 1300, and 2100 mg/kg body weight per day) 7 days prior to and during a 98-day cohabitation period (20 pairs of mice per dose). Exposure to 1% or 2% 2-butoxyethanol in drinking-water was associated with increased mortality in the females and a significant reduction ($P < 0.05$) in the number of live pups per litter, the proportion of pups born alive, and the live pup weights (both absolute and adjusted). Other signs of maternal toxicity included decreased body weight, decreased water consumption, and increased kidney weight. Necropsy revealed that testes and epididymis weights were normal, as were sperm number and motility. The reproductive toxicity of 2-butoxyethanol was evident only in female mice, at doses that also elicited general toxicity (Heindel et al., 1990). (It has been hypothesized that fetal deaths may have been due to hydrops foetalis, associated with severe anaemia induced by 2-butoxyethanol or its metabolite, BAA, transported across the placenta [Atkins, 1999]; however, no description of the possible cause of fetal death was presented in the report of this study.) The NOAEL was 700 mg/kg body weight per day.

Effects on male and female reproductive organs (including reduced weight or histopathological changes in the epididymis or testes, decreased sperm concentration, altered sperm morphology, or uterine atrophy) were noted in F344 rats and B6C3F1 mice exposed to 2-butoxyethanol in the subchronic studies conducted by the NTP (1993, 2000), although some of these effects were not considered to be of biological significance and occurred only at doses or concentrations that also induced haematological and other effects.

Effects on the testes were not observed in studies in which Alpk/Ap (Wistar-derived) rats were exposed by inhalation to 2-butoxyethanol at 4000 mg/m^3 for 3 h (Doe, 1984), JCL-ICR mice were orally administered 2-butoxyethanol at doses ranging from 500 to 2000 mg/kg body weight per day, 5 days/week, for 5 weeks (Nagano et al., 1979), or rats were administered 2-butoxyethanol (by gavage) at doses ranging from 222 to 885 mg/kg body weight per day, 5 days/week, for 6 weeks (Krasavage, 1986). Testicular damage was not observed in groups of Alpk/Ap (Wistar-derived) rats administered a single oral dose of BAA at 174, 434, or 868 mg/kg body weight (Foster et al., 1987).

8.7.2 Developmental toxicity

No adverse effects were observed in either the dams or pups (number of resorptions, fetal weights, and incidence of malformations) in a study in which Sprague-Dawley rats were exposed by inhalation for 7 h/day on days 7–15 of gestation to 2-butoxyethanol at 740 or 980 mg/m^3. Adults died at 1200 or 2500 mg/m^3 (Nelson et al., 1984).

Tyl et al. (1984) exposed Fischer 344 rats (36 per group) and New Zealand white rabbits (24 per group) to 2-butoxyethanol at 0, 120, 250, 490, or 980 mg/m^3 for 6 h/day on days 6–15 of gestation for the rats and on days 6–18 of gestation for the rabbits. No adverse reproductive or developmental effects were observed in rats or rabbits exposed to 2-butoxyethanol at concentrations up to 250 mg/m^3. At 490 mg/m^3 and above, signs of delayed ossification were seen in the rats, and maternal toxicity (decreased weight gain and increased resorptions) was evident at 980 mg/m^3. In rabbits, maternal toxicity (reduced weight gain) and delayed ossification were seen at 980 mg/m^3.

Maternal deaths and a reduction in the number of viable litters were observed when CD-1 mice were orally administered 2-butoxyethanol at 4000 mg/kg body weight per day on days 7–14 of gestation (Schuler et al., 1984).

No maternal, embryotoxic, fetotoxic, or teratogenic effects were detected when 2-butoxyethanol (106 mg, about 1.6 g/kg body weight per day) was applied to the shaved interscapular skin of female Sprague-Dawley rats, 4 times daily on days 7–14 of gestation (Hardin et al., 1984).

8.8 Immunological and neurological effects

Effects on the immune system have been examined in rats. In one study, Sprague-Dawley rats were administered 2-butoxyethanol at 0, 2000, or 6000 mg/l (males) or 0, 1600, or 4800 mg/l (females) in drinking-water for 21 consecutive days. Treatment had no effect on antibody production, delayed-type hypersensitivity reactions, and interferon or interleukin-2 production. However, natural killer cell cytotoxicity responses were enhanced ($P \leq 0.05$) in rats receiving the lowest concentrations of 2-butoxyethanol (Exon et al., 1991). In a second study, male Fischer rats were administered (by gavage) 2-butoxyethanol at 0, 50, 100, 200, or 400 mg/kg body weight per day for 2 consecutive days, following immunization with trinitrophenyl-lipopolysaccharide. A reduction ($P < 0.05$) in the serum haemagglutination titre was observed 3 days later in rats administered 2-butoxyethanol at 200 mg/kg body weight per day. All animals in the highest dose group died (Smialowicz et al., 1992).

An abstract reports that statistically significant effects on indicators of immune function were observed in BALB/c mice administered repeated oral 2-butoxyethanol doses of 50 mg/kg body weight per day or more for 10 days. There was an increase in the mixed lymphocyte reaction and concanavalin A mitogenic stimulation of splenocytes at all tested doses. Increased cytotoxic T lymphocyte activity and elevated lipopolysaccharide stimulation of splenocytes were reported at the higher dose levels (Morris et al., 1996). Effects on immune function were also observed in a study in which BALB/c mice were given dermal doses of 100, 500, 1000, or 1500 mg/kg body weight per day for 4 days. Reduced splenic T cell proliferative response to concanavalin A and mixed lymphocyte response to allogeneic antigen were observed at 500 mg/kg body weight per day, whereas there was an increase in spleen cellularity and spleen to body weight ratio at the top dose (Singh et al., 2001). Dermal exposure also resulted in a decrease in oxazolone-induced contact hypersensitivity response in female BALB/c mice. Application of 4 mg of 2-butoxyethanol in 4:1 acetone and olive oil vehicle at the time of induction of sensitization, challenge, or both decreased the contact hypersensitivity response (evaluated by measuring ear thickness before and after challenge) by 18%, 18%, and 22%, respectively (Singh et al., 2002).

Reduced weights or histopathological changes were observed in the thymus or spleen of both mice and rats exposed to 2-butoxyethanol by repeated inhalation; however, these effects were considered likely to be

secondary to haemolysis and decreased body weight (NTP, 1993, 2000).

No specific investigations on potential neurological effects associated with exposure to 2-butoxyethanol were identified. However, adverse effects on the central nervous system associated with exposure to high doses or concentrations of 2-butoxyethanol have been observed in short-term studies. These included loss of coordination, sluggishness, narcosis, muscular flaccidity, and ataxia (Carpenter et al., 1956; Dodd et al., 1983; Hardin et al., 1984; Krasavage, 1986).

8.9 In vitro haemolytic effects

Bartnik et al. (1987) examined the effects of 2-butoxyethanol and BAA on human (from healthy males) and rat (four male Wistar) erythrocytes in vitro. The lowest concentration of BAA administered (1.25 mmol/l) resulted in 25% haemolysis of rat erythrocytes after 180 min, whereas 3.75 mmol/l caused complete lysis. In contrast, BAA at 15 mmol/l did not produce measurable haemolysis in human erythrocytes over the same time. Complete lysis of rat and human cells occurred at 2-butoxyethanol concentrations of 200 mmol/l and 175 mmol/l, respectively. These results indicate that rats may be more susceptible than humans to the haemolytic effects of 2-butoxyethanol and its metabolite BAA (Bartnik et al., 1987).

The addition of 2-butoxyethanol at concentrations of 5 or 10 mmol/l in rat blood had no effect on haematocrit, whereas a concentration of 20 mmol/l caused significant haemolysis ($P < 0.05$). The addition of BAA to rat erythrocytes to concentrations of 0.5 or 1 mmol/l caused a time- and concentration-dependent increase in haematocrit followed by haemolysis. Incubation with BAA at 2 mmol/l caused a faster time-dependent increase in haematocrit, with the haematocrit reaching a maximum after 2 h, followed by nearly complete haemolysis after 4 h. Also examined was the effect of BAA (0.5, 1, 2, 4, or 8 mmol/l) on human blood obtained from healthy young male and female volunteers (Ghanayem, 1989). No significant changes in haematocrit or haemolysis were observed at BAA concentrations of 4 mmol/l or less; at 8 mmol/l, there was a slight but significant increase in haematocrit ($P < 0.05$), followed by a slight but significant haemolysis ($P < 0.05$) of erythrocytes (Ghanayem, 1989).

In a subsequent study, Ghanayem & Sullivan (1993) assessed the haemolytic activity of BAA (1 or 2 mmol/l) in blood collected from rats, mice, hamsters, baboons, rabbits, pigs, guinea-pigs, dogs, cats, and humans. BAA caused a time- and concentration-dependent increase in mean cell volume and haematocrit of blood from rats, rabbits, hamsters, mice, and baboons. However, no or minimal effects were observed on blood from humans, guinea-pigs, dogs, cats, and pigs (Ghanayem & Sullivan, 1993), demonstrating the sensitivity of rat erythrocytes and the relative insensitivity of human erythrocytes to the haemolytic effects of BAA.

Udden (2000) compared the morphological appearance of rat erythrocytes with that of erythrocytes derived from humans when each was exposed in vitro to BAA. Stomatocytes (cup-shaped cells) and spherocytes were the principal morphological features of cells from rats, whereas none of these was observed in human red blood cells incubated with BAA at up to 2.0 mmol/l. In a subsequent study, Udden (2002) reported that human erythrocytes required exposure to a concentration (up to 10 mmol/l) of BAA that was 100-fold greater than that required by rat erythrocytes in order to develop sub-haemolytic effects (loss of deformability, increased osmotic fragility, and increased erythrocyte sodium); the investigators suggested that such a high concentration is not likely to occur under normal human use of 2-butoxyethanol-containing products. The results give further support to the role of BAA in the haemolytic effect of 2-butoxyethanol in the rat and the higher sensitivity of rats compared with humans.

The effect of BAA on red blood cells from healthy young and older individuals (Udden & Patton, 1994) and individuals with a possible susceptibility to 2-butoxyethanol-induced haemolysis (i.e. sickle cell and spherocytosis patients) (Udden, 1994, 1996) has also been examined. Along with haemolysis, BAA at 0.2 and 2 mmol/l caused decreased red blood cell deformability and increased mean cellular volume in rat red blood cells (Udden & Patton, 1994). However, none of the human blood samples exhibited prehaemolytic changes (i.e. decreased deformability and increased mean cellular volume) or haemolysis after BAA treatment at 2 mmol/l for up to 4 h (Udden, 1994, 1996; Udden & Patton, 1994). The results of these in vitro studies provide further evidence that rat erythrocytes are more susceptible than human erythrocytes to BAA-induced haemolysis.

8.10 Mode of action for carcinogenicity

8.10.1 Forestomach papillomas and carcinomas in female mice

Mechanisms by which 2-butoxyethanol may induce tumours in the forestomach have been assessed (USEPA, 2005). The first stage in the proposed sequence of steps is the deposition of 2-butoxyethanol/BAA in the stomach and forestomach via consumption or reingestion of 2-butoxyethanol-laden mucus, salivary excretions, or fur material. 2-Butoxyethanol/BAA may be retained in food particles in the forestomach long after being cleared from other organs. 2-Butoxyethanol is metabolized to BALD, which is then rapidly converted to BAA systemically and in the forestomach. Irritation of the target cells

leads to hyperplasia and ulceration, with continued injury and degeneration resulting in high cell proliferation and turnover. The final stage on the path to tumour formation is the high cell proliferation and turnover leading to clonal growth of spontaneously initiated forestomach cells (USEPA, 2005).

The weak positive effects induced by 2-butoxyethanol at high concentrations in some in vitro DNA repair, sister chromatid exchange, and cell transformation assays make it difficult to completely exclude the potential for contribution from direct interaction of a 2-butoxyethanol metabolite with DNA. Although these positive findings may be due to study design artefacts such as changes in pH or osmolarity associated with high 2-butoxyethanol concentrations, they may also be due to the short-lived metabolite BALD, which has caused clastogenic changes in Chinese hamster lung and human lymphocyte cells. Available evidence from PBPK modelling, modified to include kinetics for the metabolism of BALD, suggests that the conditions in the in vitro assays for genotoxicity (no metabolic activation; high cytotoxic concentrations of BALD) have little relevance to the expected target organ environment (high metabolic activity; low concentrations of BALD). Additional research to verify the PBPK modelling and explore further the relevance of genotoxic activity would enable a more definitive determination regarding the possible role of BALD in the formation of forestomach tumours in female mice.

8.10.2 Liver tumours in male mice

A mode of action for the development of haemangiosarcomas of the liver and hepatocellular carcinomas in male mice has been proposed (USEPA, 2005).[1] The first stage in the proposed sequence of steps is haemolysis of red blood cells by the 2-butoxyethanol metabolite BAA. This haemolysis leads to the accumulation of haemosiderin (iron) in phagocytic cells of the liver of both rats and mice. Oxidative damage and increased synthesis of endothelial hepatocyte DNA are initiated by the generation of reactive oxygen species from iron within Kupffer cells and perhaps from within hepatocytes and sinusoidal endothelial cells and/or by the activation of Kupffer cells to produce cytokines/growth factors that suppress apoptosis and promote cell proliferation. Recent research indicates that the mouse is more or uniquely sensitive to these effects. It is hypothesized that these events can contribute to the transformation of the endothelial cells to haemangiosarcomas and of hepatocytes to hepatocellular carcinomas in male mice.

[1] As an application of the IPCS framework for the assessment of the mode of action in carcinogenesis, the induction of tumours in the liver in mice is being analysed as part of the IPCS Harmonization Project. The analysis is expected to be published in 2006.

As described above (see section 8.10.1) for forestomach tumours observed in female mice, the weak positive effects induced by 2-butoxyethanol at high concentrations in some in vitro genotoxicity assays and the reported clastogenicity of the 2-butoxyethanol metabolite BALD make it difficult to completely exclude the potential for contribution from direct interaction of a 2-butoxyethanol metabolite with DNA. Again, PBPK modelling suggests that the conditions in the in vitro genotoxicity assays (no metabolic activation; high cytotoxic concentrations of BALD) are of little relevance to the expected target organ environment (high metabolic activity; low concentrations of BALD). As in the case for the forestomach tumours, additional research to verify the PBPK modelling and explore further the relevance of genotoxic activity would enable a more definitive determination regarding the role of BALD in the formation of liver tumours in male mice.

9. EFFECTS ON HUMANS

Information on human health effects associated with exposure to 2-butoxyethanol are limited to a few case reports, a clinical investigation, and a cross-sectional survey. The principal human health effects attributed to 2-butoxyethanol exposure have involved the central nervous system, the blood, and the kidneys (ATSDR, 1998).

In a cross-sectional survey, slight, but statistically significant, changes in some haematological parameters (haematocrit and mean corpuscular haemoglobin concentration) were observed in a group of 31 men occupationally exposed to average concentrations of 2-butoxyethanol of 3.64 or 2.20 mg/m^3 compared with unexposed workers. However, there was no correlation with levels of BAA in the urine, and information on exposure was limited to personal monitoring samples taken during only one workshift (Haufroid et al., 1997).

In one report involving a number of small studies, the exposure of two males to 2-butoxyethanol at 560 mg/m^3 for 4 h produced nose and eye irritation as well as disturbed taste, but there was no evidence of haemolytic effects. Similar effects were observed in a second study in which two males and one female were exposed to 2-butoxyethanol at 960 mg/m^3 for two 4-h periods, separated by a 30-min period of no exposure. When two males and two females were exposed to 2-butoxyethanol at 490 mg/m^3 for 8 h, the effects included vomiting and headache. No clinical signs of haemolysis were observed in any of the subjects (Carpenter et al., 1956).

Haemoglobinuria, erythropenia, hypotension, metabolic acidosis, shock, non-cardiogenic pulmonary oedema, albuminuria, hepatic laboratory abnormalities, haematuria, and mental status depression have been reported in case-studies of individuals who had attempted suicide by ingesting 2-butoxyethanol-containing cleaning solutions (involving an estimated ingestion of 25–60 g 2-butoxyethanol) (Rambourg-Schepens et al., 1988; Gijsenbergh et al., 1989; Bauer et al., 1992; Gualtieri et al., 1995, 2003; McKinney et al., 2000). In several of the cases, haemodialysis was employed, and all patients recovered fully with appropriate treatment. A survey of paediatric poisonings identified 24 children who had ingested 5–300 ml of glass cleaners containing 2-butoxyethanol (Dean & Krenzelok, 1992). The two children with the highest intake exhibited no evidence of haemolytic effects. Other effects characteristic of poisoning with ethylene glycol (a metabolite of 2-butoxyethanol in humans), such as coma, metabolic acidosis, and renal effects, as well as changes in levels of hepatic enzymes (of uncertain biological significance), have been reported in several cases or cross-sectional studies (e.g. Rambourg-Schepens et al., 1988; Collinot et al., 1996; Haufroid et al., 1997; Nisse et al., 1998). 2-Butoxyethanol is reportedly not a skin sensitizer in humans (Greenspan et al., 1995).

10. EFFECTS EVALUATION

10.1 Evaluation of health effects

10.1.1 Hazard identification and dose–response assessment

Few data were identified on the potential effects of 2-butoxyethanol in humans. Although effects on the blood have been observed in exposed workers and in several cases of incidental exposure (Rambourg-Schepens et al., 1988; Gijsenbergh et al., 1989; Bauer et al., 1992; Haufroid et al., 1997), limitations of these studies mean that characterization of health hazards associated with 2-butoxyethanol is based primarily on studies in laboratory animals.

10.1.1.1 Haematological effects

The majority of toxicological investigations with 2-butoxyethanol have been conducted in rats, in which the most sensitive target tissue is the blood. Alterations in haematological parameters characteristic of haemolytic anaemia have been observed in this species following single, short-term, medium-term, and long-term exposure to 2-butoxyethanol via inhalation, ingestion, and dermal application (Carpenter et al., 1956; Dodd et al., 1983; Bartnik et al., 1987; Ghanayem et al., 1987b; NTP, 1989). In some of these studies, the effects appeared to be reversible after cessation of exposure, as the severity of the haematological changes decreased with increasing time since exposure (Grant et al., 1985; Krasavage, 1986; NTP, 1989; Ghanayem et al., 1992). Similarly, tolerance, or autoprotection, was suggested by the results of two studies in which the haematological effects were less severe in rats that had been exposed to 2-butoxyethanol prior to administration than in rats receiving only the subsequent doses, although the protective effect declined with increasing time between exposures. In addition, bleeding rats prior to acute exposure to 2-butoxyethanol reduced the severity of the haematotoxicity (Ghanayem et al., 1992; Sivarao & Mehendale, 1995). These data suggest that older red blood cells are more susceptible to 2-butoxyethanol-induced effects (which has also been demonstrated in in vitro studies); as they are replaced by more resilient younger cells, the severity of the haematotoxic response declines.

However, such reversibility or autoprotection is likely limited, since it was not observed in rats repeatedly exposed to 2-butoxyethanol for longer durations. In rats exposed to 2-butoxyethanol in the drinking-water for 13 weeks, symptoms of regenerative haemolytic anaemia were still present at the end of the study in females at all doses tested (NTP, 1993). Similar effects were also noted in the same strain of rats exposed via inhalation for 14 weeks to 2-butoxyethanol at all concentrations tested, based on results of studies conducted by the NTP (2000). The anaemia was considered to be macrocytic, normochromic, and responsive. Other indicators of regenerative anaemia, including increased haematopoiesis, haemosiderin accumulation in the liver and kidney, and bone marrow hyperplasia, were also observed in both sexes; thrombosis, likely associated with severe acute haemolysis, was also noted in females at the higher exposure levels. In addition, in the chronic study conducted by the NTP (2000), in which rats were exposed to 2-butoxyethanol by inhalation for up to 2 years, haemolytic anaemia was evident in animals monitored at regular intervals up to 12 months. The anaemia, which was again characterized as macrocytic, normochromic, and responsive, was observed at all concentrations; the severity of the effects increased with exposure level and did not ameliorate significantly over time.

2-Butoxyethanol-induced haematological effects have also been observed in other species of laboratory animals. In mice, a decrease in red blood cell count was noted following short-term oral exposure (Nagano et al., 1979, 1984), while alterations in haematological parameters were reported in subchronic and chronic inhalation studies (NTP, 2000), although, as discussed above, mice appear to be less sensitive than rats to 2-butoxyethanol-induced haematotoxicity. Haematological effects were also noted in limited short-term studies in rabbits, dogs,

and monkeys (Carpenter et al., 1956; Truhaut et al., 1979; Union Carbide, 1980; Tyl et al., 1984), although available data are inadequate to allow the evaluation of differences in species sensitivity. In general, these effects were observed only at doses greater than those that induced similar, more severe effects in rats.

There is also some evidence that the blood is a sensitive target tissue in the developing young following in utero exposure to 2-butoxyethanol in both rats and mice. Haematological effects were reported in the fetuses of rats exposed to doses of 2-butoxyethanol that were also haematotoxic in the dams (NTP, 1989), while an increase in fetal mortality in mice (Heindel et al., 1990) has been hypothesized to be due to hydrops foetalis, associated with severe anaemia induced by 2-butoxyethanol or its metabolite, BAA, transported across the placenta (Atkins, 1999); however, no description of the possible cause of fetal death was presented in the report of this study.

In view of the extensive database that indicates that 2-butoxyethanol is haematotoxic in multiple laboratory species and the limited evidence of changes in haematological parameters in occupationally and incidentally exposed humans, 2-butoxyethanol is considered likely to be haematotoxic in humans.

Although limited, available data from toxicokinetic studies and comparative in vitro investigations suggest that humans may be less sensitive than rats to 2-butoxyethanol-induced haematotoxicity (although few data were identified on interindividual sensitivity in humans); rats appear to be the most sensitive of the animal species investigated.

10.1.1.2 Other non-neoplastic effects

Other target organs of 2-butoxyethanol-induced effects in various species (rats, mice, rabbits, or guinea-pigs) following single, short-term, or long-term exposure (Carpenter et al., 1956; Truhaut et al., 1979; Krasavage, 1986; Bartnik et al., 1987; Ghanayem et al., 1987b; NTP, 1993, 2000) include the liver, kidney, spleen, and bone marrow. Many of the observed effects, such as accumulation of haemosiderin pigment, increased haematopoiesis and cellularity, and haemoglobinuria, are considered to be secondary or in response to haemolytic anaemia (NTP, 2000), while other effects, such as alterations in relative organ weights and some histopathological changes, occurred only at doses that were also haemolytic. Although cytoplasmic changes were noted in the liver of male rats exposed over the medium term to oral doses lower than those that induced alterations in blood parameters (although these doses were haematotoxic in females), these effects may have been related to the induction of enzymes involved in the metabolism of 2-butoxyethanol (NTP, 1993).

The forestomach was also a critical target for 2-butoxyethanol-induced toxicity in mice. In the chronic inhalation study in mice, increased incidences of inflammation, epithelial hyperplasia, and/or ulceration were noted. Females were more sensitive than males, and there was some evidence of concentration-related trends in incidence and severity of forestomach lesions. These effects were also observed in both mice and rats exposed over the medium term to higher concentrations that also induced haematological changes (NTP, 2000). These effects on the forestomach are also in concordance with neoplastic lesions at this site in mice. Forestomach lesions have also been observed in mice administered 2-butoxyethanol by intraperitoneal or subcutaneous injection.

In investigations of the potential developmental toxicity of 2-butoxyethanol in rats, mice, or rabbits, embryotoxic or fetotoxic effects or malformations have generally been observed only at or above doses that are also maternally toxic (Hardin et al., 1984; Schuler et al., 1984; Wier et al., 1987; NTP, 1989; Heindel et al., 1990). Similarly, effects on female reproductive ability or on male and female reproductive organs (some of which were not considered to be of biological significance) were observed only at doses or concentrations that were associated with high mortality or that were greater than those that induced haematotoxicity (Heindel et al., 1990; NTP, 1993, 2000).

Based on limited data, 2-butoxyethanol does not appear to induce immunological effects at doses lower than those associated with haematotoxicity or other adverse effects (Exon et al., 1991; Smialowicz et al., 1992). Data on the potential effects of 2-butoxyethanol on the nervous system are insufficient for evaluation.

10.1.1.3 Carcinogenicity and genotoxicity

In the chronic bioassays conducted by the NTP (2000), incidences of tumours were significantly increased (often only marginally) only at the higher concentrations tested (in some cases only when compared with historical controls).

While it was concluded that there was some evidence of carcinogenicity in mice (based on increased incidences of haemangiosarcomas of the liver in males and squamous cell papillomas of the forestomach in females), the evidence in female rats was considered only equivocal (based on a marginal increase in the incidence of benign or malignant phaeochromocytomas of the adrenal gland).

As outlined in section 8.10.1, it is thought that 2-butoxyethanol/BAA deposits in the forestomach following inhalation exposure as a result of grooming and ingestion of material condensed on the skin and fur or

ingestion of mucus and salivary secretions. Metabolites cause cellular damage, increased cell replication, and hyperkeratosis, changes that are believed to lead to the tumours seen in the mouse studies. Liver carcinogenicity induced by 2-butoxyethanol in male mice has been proposed to be mediated via iron-catalysed oxidative stress and Kupffer cell activation, as outlined in section 8.10.2. Weak positive effects were induced by 2-butoxyethanol (at high concentrations) in some in vitro genotoxicity assays, and the metabolite BALD has caused clastogenic changes in hamster and human cells in culture. Although it is thought that these genotoxicity test results may have little relevance to the expected target organ environments, additional research would be required to enable the possible role of direct interaction of a 2-butoxyethanol metabolite with DNA in the formation of tumours to be assessed with confidence.

10.1.2 Criteria for setting tolerable intakes and concentrations

Based on available data, inhalation in indoor air is an important route of exposure to 2-butoxyethanol for the general population, particularly for those using consumer products that contain the substance. Since intake from food is highly uncertain (relevant monitoring data have not been identified) but is expected to be low (levels in water, the likely principal source in food, are low), exposure–response relationships for health effects associated with 2-butoxyethanol have been quantified for the inhalation route only.

The principal critical effects for exposure–response analyses for characterization of risk to humans are the haematological effects in rats and mice. Owing to the consistency of their observation in a wide range of studies at lowest doses or concentrations, these effects are emphasized. BMCs for a variety of haematological end-points have been derived on the basis of long-term studies in animals. Non-neoplastic lesions in the forestomach of mice are also considered critical, and a BMC has also been derived for this end-point. A BMC was also derived for Kupffer cell pigmentation (see Appendix 5), primarily for comparison with those determined for the effects considered critical.

A TC for haematological effects (for the derivation of the TCs, see Appendix 5) was calculated as:

$$TC = 5.3 \text{ mg/m}^3 / 0.5$$

$$= 11 \text{ mg/m}^3$$

where:

- 5.3 mg/m^3 is the lower end of the range of BMC_{05}s for haematological effects in the long-term rat study (data for the rat being considered more sufficient and robust than those for the mouse), and
- 0.5 is the total uncertainty factor, with components of 0.5 (interspecies, toxicokinetics) × 0.1 (interspecies, toxicodynamics) × 3.2 (intraspecies, toxicokinetics) × 3.2 (intraspecies, toxicodynamics).

A TC for non-neoplastic forestomach lesions was developed as follows:

$$TC = 4.3 \text{ mg/m}^3 / 100$$

$$= 0.04 \text{ mg/m}^3$$

where:

- 4.3 mg/m^3 is the BMC associated with a 5% increase in the incidence of hyperplasia of the forestomach epithelium in female B6C3F1 mice exposed to 2-butoxyethanol for 2 years (NTP, 2000), and
- 100 is the uncertainty factor (×10 for intraspecies variation and ×10 for interspecies variation).

This TC for forestomach lesions is considered to be protective for squamous cell papillomas or carcinomas of the forestomach in mice. TCs derived on the basis of the incidence of tumours at other sites, although the weight of evidence for an association with 2-butoxyethanol is considered quite limited, are higher than those for tumours of the forestomach.

It is noteworthy that the TC based on forestomach lesions is 275-fold lower than that derived for 2-butoxyethanol-induced haematological effects. However, it is important to keep in mind that the BMC_{05}s for non-neoplastic lesions in the forestomach were derived on the basis of the incidences of lesions of all severities (combined), including those considered to be minimal; however, if lesions of minimal severity were excluded, the resulting BMC_{05}s would be within 3-fold of those presented here. In addition, the association between exposure to 2-butoxyethanol and haemolysis has been much more thoroughly investigated than the association with effects on the forestomach, with some evidence (albeit quite weak) of haematological effects in humans.

10.1.3 Sample risk characterization

Based on the limited data available on levels of 2-butoxyethanol in environmental media, inhalation in air appears to be a principal route of exposure to 2-butoxyethanol for the general population in Canada. The mean concentration of 2-butoxyethanol in outdoor air reported in the multimedia exposure study was 8.4 μg/m^3, with a maximum of 243 μg/m^3. However, as discussed below, the confidence in these values is low, due to the analytical methodology employed, although they are

considered conservative. Indeed, in the only other Canadian study identified (in which the confidence is greater), the maximum outdoor air concentration reported near a likely source (an automotive plant) was lower (i.e. 7.3 μg/m^3). Exposure in indoor air is generally greater than that in outdoor air. In the multimedia exposure study, the mean concentration of 2-butoxyethanol in 50 samples from Canadian residences was 27.5 μg/m^3, with a maximum measured concentration of 438 μg/m^3. However, exposure to 2-butoxyethanol through use of some consumer products could be much higher. For example, conservative estimates of short-term indoor air concentrations resulting from emissions of some common household products recently investigated in Canada range up to 62 mg/m^3. Intake of 2-butoxyethanol via inhalation and dermal exposure through use of such consumer products was estimated to be much greater than intake from background environmental sources.

Based on evaluation of available data (principally toxicological investigations in laboratory animals), haematotoxicity is considered to be the principal effect for characterization of potential risk to humans associated with exposure to 2-butoxyethanol. As described above (see also Appendix 5), a TC of 11 mg/m^3 (11 000 μg/m^3) was derived for 2-butoxyethanol on the basis of BMCs determined for alterations in haematological parameters based on observations in rats and mice following long-term exposure, taking into consideration interspecies differences in toxicokinetics and toxicodynamics. A more conservative TC of 0.04 mg/m^3 (40 μg/m^3) was derived for non-neoplastic forestomach lesions reported in mice exposed over a 2-year period, although confidence in this latter value is lower.

Comparison of measured exposure levels in outdoor air with the TCs indicates that average exposure in the ambient environment does not exceed either the TC for haematological effects (in which there is greater confidence) or the more conservative TC for lesions of the forestomach. Likewise, mean concentrations in indoor air reported in the multimedia exposure study are less than the TCs. However, maximum concentrations reported in outdoor and indoor air in the multimedia exposure study exceed the more conservative TC for forestomach lesions.

The elevated exposure in indoor air is likely due to use of consumer products containing 2-butoxyethanol. Indeed, crude estimates of exposure through direct use of such products, although based on limited data, greatly exceed the TCs for adverse health effects. The maximum estimated short-term indoor air concentration of 2-butoxyethanol based on monitored emissions from a few common household products is about 1550-fold greater than the more conservative TC (based on long-term exposure) for forestomach lesions; this predicted indoor air concentration resulting from emissions from consumer products is also 6-fold greater than the TC in which confidence is greater (i.e. haematological effects).

10.1.4 Uncertainties in the evaluation of health risks

There is a high degree of uncertainty in the estimates of population exposure that have been developed for this assessment primarily as a basis for determining principal media of exposure, due to the paucity of data on levels of 2-butoxyethanol in environmental media. Although estimates of average exposures were based on data reported in the multimedia exposure study conducted in Canada, the methodology employed in this study is considered experimental, and confidence in the results is low. For example, recovery was relatively low (i.e. 52% in air), and concentrations in "blanks" were high and variable, perhaps due in part to the use of non-standard desorbing solvents to extract 2-butoxyethanol from these samples. However, while likely conservative, the range of concentrations is similar to the single reported value for residential indoor air outside Canada. These estimates also do not take into account intake via dermal absorption of airborne 2-butoxyethanol, which, although less than the amount inhaled from indoor air, could be significant. In addition, there is a moderate degree of uncertainty concerning the relative contribution of food to total intake of 2-butoxyethanol, as no relevant monitoring data were identified, and this might be an appropriate area of additional investigation.

Confidence in the estimates of exposure to 2-butoxyethanol through use of products containing the substance is low to moderate for those few substances for which measured emissions permitted development of such estimates. For example, a conservative room ventilation rate of 0.5 air change per hour was incorporated into the calculations of indoor air concentrations resulting from typical use of spray cleaning products; if a higher rate of 1.0 air change per hour were applied, concentrations in indoor air resulting from the use of these products would be about 2-fold lower. Conversely, the estimates of dermal uptake of 2-butoxyethanol were based on a non-steady-state approach; these estimates are up to an order of magnitude lower than they would be if other, more conservative approaches were adopted. However, in spite of these uncertainties, confidence in these estimates based on measured emissions is greater than confidence in estimates that could be derived on the basis of product composition data. The inhalation and dermal exposures estimated in this assessment are for the average durations and frequencies of performance of specific tasks. However, based on the 95th percentiles reported in USEPA (1997), a significant fraction of the population performs some of these tasks on a daily basis and for roughly 3–4 times as long as the durations assumed here, and they would have correspondingly

greater exposures. It should also be noted that the values presented here were based on extrapolation of emission factors for only a few of the potentially large number of products containing 2-butoxyethanol available to the consumer and, therefore, may significantly underestimate overall exposure associated with the use of numerous products containing this glycol ether on a regular basis in the home. Acquisition of additional data on the content of 2-butoxyethanol in consumer products and its emissions from these products is considered to be a high priority.

While there is a moderate degree of certainty that haematotoxicity is the principal critical end-point for 2-butoxyethanol, based on the observations in short- and long-term studies in multiple species of laboratory animals, there is only limited evidence that 2-butoxyethanol induces haematological effects in humans; in fact, available data from in vitro investigations suggest that humans may be less sensitive than rats. This lesser sensitivity of humans with respect to haematological effects is accounted for in the small uncertainty factor applied to the BMC_{05} in the derivation of the TC, and limited available data from studies in humans indicated that the TC is protective. The component for interspecies toxicokinetics of the total compound-specific adjustment or uncertainty factor (IPCS, 2005b) was based on data for a limited number of time points. However, the database for the component that has greater impact on deviation from default for the uncertainty factor (i.e. that of interspecies variations in dynamics) is much more extensive.

However, it should be noted that no data were available on the effects of 2-butoxyethanol on haematological parameters in rodents in the critical studies beyond 12 months. In addition, the sizes of the groups of animals in which blood was examined at each time point were small. Although the subchronic study conducted by the NTP (2000) involved a greater number of exposure levels, because of the high concentrations, modelling of these data would not improve characterization of exposure–response in the region of the BMC_{05}s.

The TC was derived on the basis of point estimates for the BMCs, as opposed to the 95% LCLs; however, use of the 95% LCLs would not change the TC substantially, since for most parameters, the 95% LCL was less than 3-fold lower than the midpoint estimate. In addition, if the BMCs for haematological effects had been determined on the basis that 10% of the control population was considered "abnormal" (as opposed to 5% used in derivations presented), the resulting values would vary by less than 1.5-fold.

There is a moderate to high amount of uncertainty concerning the TC derived on the basis of the BMC for non-neoplastic lesions of the forestomach in mice (although these effects were consistently observed in subchronic studies in rats and mice and in the only chronic study in mice). The profile of effects suggests a progression from irritation to ulceration and tumour formation. Owing to the limited information on the mode of induction of these lesions, including the nature of delivery to the target site and the role of putatively toxic metabolites, their relevance to humans is unknown but cannot be completely precluded. (It is noteworthy that, in the only relevant clinical trials in humans, irritation of the eyes and upper respiratory tract was the most sensitive effect reported.) If these lesions are local effects resulting from ingestion, mice are likely to be considerably more sensitive due to longer residence time in the forestomach (and its low acidity) compared with the human oesophagus. Because the animals were exposed to 2-butoxyethanol via inhalation, preening may have contributed to exposure at the target site.

If ingestion via preening or mucociliary clearance were significant, then the TC based on BMCs derived on the basis of the airborne exposure concentrations would likely overestimate the risk to humans (i.e. there would not be the additional exposure via ingestion). On the other hand, dermal absorption of airborne 2-butoxyethanol by humans (which could be significant, i.e. up to 27% of total uptake, based on clinical investigations in humans; Corley et al., 1997) has also not been considered in the determination of the TC. In addition, the BMC_{05}s upon which the TC is based were derived on the basis of inclusion of forestomach lesions of all severities combined; if lesions of minimal severity were excluded, the resulting BMC_{05}s would be within 3-fold of the values presented here.

There is also some uncertainty associated with the characterization of risk, in that the TCs derived on the basis of long-term studies in rodents are compared with estimates of short-term exposure associated with use of a small number of consumer products containing 2-butoxyethanol. However, although estimated exposures were based on average use patterns, a proportion of the general population uses these products more frequently (up to 22 times more) and for longer duration (up to 4-fold longer) than average (USEPA, 1997). As well, as noted above, several products containing the substance may be used throughout the day, thereby potentially increasing the magnitude and duration of exposure. In addition, haematological effects, similar to those observed in the chronic bioassay, have been reported in acute and short-term studies in experimental animals, indicating that prolonged exposure is not requisite for induction of haematotoxicity by 2-butoxyethanol. Thus, it was considered appropriate to characterize risk on the basis of these data.

10.2 Evaluation of environmental effects[1]

The evaluation of environmental effects has not been updated from CICAD 10 (IPCS, 1998) and is reprinted here. The environmental effects data from CICAD 10 (IPCS, 1998) are presented in Appendix 6.

10.2.1 Aquatic environment

Data on measured levels of 2-butoxyethanol in surface waters are insufficient for risk characterization. However, a sample risk characterization for the aquatic environment is presented in which the ratio between a PEC_{local} and a PNEC is calculated.

PEC_{local}s for surface waters have been derived based upon data from Australia (OECD, 1997) as well as information on all reported releases to the environment in 1993 from individual industrial plants in the USA (Staples et al., 1998). Calculations of expected surface water concentration were based on worst-case scenarios for local river flows identified from a United States Geological Survey database. Site-specific estimates were made for 36 industrial plants, of which 26 discharged through sewage treatment plants and 10 discharged directly to rivers. Both studies relied on fugacity modelling to predict the environmental distribution of 2-butoxyethanol, yielding slightly different results. However, both approaches indicated that most (84–96%) of the chemical will partition to water, with almost all of the remainder volatilizing to air. There is negligible binding of 2-butoxyethanol to particulates, and no bioconcentration in organisms is expected. In addition, 2-butoxyethanol is readily degraded by microorganisms.

A PEC for surface water in Sydney, Australia, based on the assumption that all local usage passes through a single sewage treatment plant and releases at a point source to a river, was calculated as follows:

$$PEC_{local\ (water)} = C_{effluent}/[(1 + K_{p(susp)} \times C_{(susp)}) \times D]$$

$$= 50.4\ \mu g/l$$

where:

- $C_{effluent}$ is the concentration (g/l) of the chemical in the sewage treatment plant effluent, calculated as $C_{effluent} = W \times (100 - P)/(100 \times Q)$
  where:
  W = emission rate: 1400 kg/day (OECD, 1997)
  P = % removal by biodegradation in the sewage treatment plant (modelled as 91% using the SIMPLETREAT model)
  Q = volume of wastewater: 250 000 m^3/day (OECD, 1997)

- $K_{p(susp)}$ is the suspended matter/water adsorption coefficient, calculated as $K_{p(susp)} = F_{oc(susp)} \times K_{oc}$
  where:
  $F_{oc(susp)}$ = the fraction of organic carbon in suspended matter (0.01)
  K_{oc} = $0.411 \times K_{ow}$
  where:
  K_{ow} = the octanol/water partition coefficient (6.76)

- $C_{(susp)}$ is the concentration of suspended matter in river water (default value = 15 mg/l)

- D is the dilution factor for river flow (default value = 10)

As degradation in the sewage treatment plant is a large component of the assumptions, and as it cannot be assumed that this level of sewage treatment occurs in all countries globally, this calculation can be revised assuming no sewage treatment (i.e. $P = 0$), yielding a PEC of 560 µg/l. This value assumes that all local release is diluted with general wastewater from the urban centre. No values were available for individual industrial plants in Sydney, Australia, and therefore concentrations released directly to rivers cannot easily be calculated.

Using the other approach of site-specific estimation (Staples et al., 1998), 36 industrial plants in the USA were selected from 814 reporting emissions, on the basis of availability of river flow values and worst-case releases. Calculations were based on local stream flows, taking a value for the lowest flow expected over any single 7-day period once in 10 years. For plants emitting via a sewage treatment system, degradation rates of 90% were assumed. Calculated concentrations are "instantaneous," assuming no dilution by the receiving stream, no degradation in the receiving waters, and no distribution to media other than water. These are conservative assumptions. Calculated in-stream concentrations ranged from 0.0002 to 21.7 mg/l for emissions via sewage treatment (annual release ranged from 18 000 to 974 000 kg for the 26 plants with sewage treatment) and from 0.000 01 to 4.66 mg/l for untreated emissions (annual release ranged from 1870 to 35 000 kg for the 10 plants with no sewage treatment). The highest reported concentration of 2-butoxyethanol in surface waters was 5.7 mg/l following release by the leather industry into the Hayashida River in Japan, before treatment was introduced (Yasuhara et al., 1981). These measured and

[1] While there are minor differences in the environmental assessments between the source documents of CIDAD 10 and the present CICAD, the final outcomes (i.e. the PNECs) are similar.

estimated surface water concentrations are summarized in Table 3.

Table 3: PEC/PNEC ratios.

Location	Sewage treatment	Highest concentration (mg/l)	PEC/PNEC ratio[a]
Australia[b] (Sydney)	Yes	0.05	0.3
	No	0.56	3.4
USA (site specific)[c]	Yes	21.7	131.5
	No	4.66	28.2
Japan[d]	No	5.7	34.5

[a] Based on a PNEC of 165 µg/l (see text).
[b] Modelled.
[c] Modelled, but based on known annual release for each site.
[d] Measured.

As a guide for those wishing to perform similar calculations using local use/release figures, the Staples et al. (1998) study estimates that the annual release of total glycol ethers (assuming that 50% of released compounds would be 2-butoxyethanol) leading to instantaneous 2-butoxyethanol concentrations in surface waters of 1 mg/l would be 18 000 kg with sewage treatment and 1800 kg without sewage treatment for streams with very low flow at 0.03 m^3/s (equivalent to 2.5 million litres per day).

A PNEC for surface waters may be calculated as follows:

PNEC = (165 mg/l)/1000
= 165 µg/l

where:

- 165 mg/l is the lowest reported effect level for a lethality end-point in aquatic species (48-h LC_{50} in the golden ide [*Leuciscus idus melanotus*], a freshwater fish) (see Table A-1 in Appendix 6), and
- 1000 is the uncertainty factor. The range of organisms tested in short-term tests would justify application of an uncertainty factor of 100, yielding a PNEC of 1.65 mg/l, based on the lowest reported LC_{50} in fish. However, there is some indication that estuarine species may be more sensitive, although the lowest reported LC_{50} for the grass shrimp (*Palaemonetes pugio*) (96-h LC_{50} = 5.4 mg/l) is such an extreme outlier compared with the range of other data that it is difficult to justify its use as the basis for the PNEC calculation. Application of an uncertainty factor of 1000 to the lowest freshwater value would be protective for both freshwater and estuarine environments, yielding margins relative to the 96-h LC_{50}s for the grass shrimp (5.4 mg/l) and the oyster (*Crassostrea virginica*) (89 mg/l), the most sensitive of the estuarine invertebrates, of 33 and 540, respectively. For freshwater organisms, the threshold concentration for inhibition of growth in algae (long-term effect) cannot be justified as the basis for application of uncertainty factors to establish a PNEC.

As the highest measured concentration in surface waters (at 5.7 mg/l) is almost identical to the lowest reported LC_{50} concentration (at 5.4 mg/l for the grass shrimp), it is not surprising that high risk factors are generated. High-volume usage and emissions to surface waters in a range of industries would lead to locally high concentrations, principally where sewage treatment was not in operation and river flow was low. It can be expected that concentrations would exceed those likely to produce effects in some aquatic species under these circumstances. However, the majority of reported acute toxicity effect levels are 100 mg/l or higher, and most exceed 800 mg/l. Four of 38 estimated surface water concentrations exceed 2 mg/l, with the remainder less than, and usually substantially less than, 1 mg/l (Figure 1). Most of these estimates also fail to account for dilution in rivers. Using an uncertainty factor of 100, justified by the range of toxicity data, on the lowest reported freshwater LC_{50} and typical estimates of water concentrations yields PEC/PNEC ratios of ≤1. Therefore, for most releases to surface waters, the risk is considered to be low. It is also unlikely that 2-butoxyethanol would be toxic to sewage treatment plant bacteria, as the only reported effect level for bacteria is an IC_{50} of >1000 mg/l (Union Carbide, 1989).

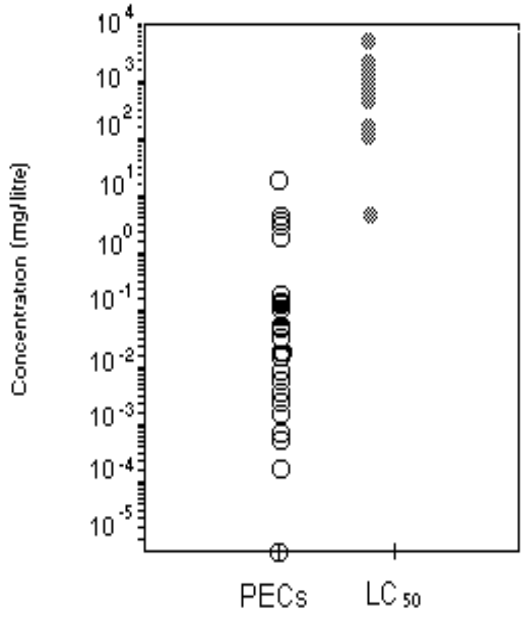


Figure 1: Plot of estimated and measured concentrations in surface waters and reported acute toxicity values for 2-butoxyethanol

10.2.2 Terrestrial environment

Data are inadequate to characterize the risks to terrestrial organisms of exposure to 2-butoxyethanol. A $PEC_{local(air)}$ of 537 $\mu g/m^3$, based upon the use patterns of this chemical in Australia, has been reported (OECD, 1997). Although available monitoring data are limited, this predicted concentration is much higher than levels measured in ambient air (see section 6). As 2-butoxyethanol is expected to have a half-life in the atmosphere of less than 1 day, these concentrations are considered to have no environmental significance.

11. PREVIOUS EVALUATIONS BY IOMC BODIES

IARC (2004) has classified 2-butoxyethanol as *not classifiable as to the carcinogenicity to humans*, due to *inadequate evidence* in humans and *limited evidence* in experimental animals.

Evaluations by JECFA or JMPR were not identified. A SIDS Initial Assessment Report has been prepared under the OECD's High Production Volume Chemicals Programme (OECD, 1997). Information on international hazard classification and labelling is included in the International Chemical Safety Card that has been reproduced in this document.

REFERENCES

Aasmoe L, Winberg J-O, Aarbakke J (1998) The role of liver alcohol dehydrogenase isoenzymes in the oxidation of glycol-ethers in male and female rats. *Toxicology and Applied Pharmacology*, 150:86–90.

Amoore JE, Hautala E (1983) Odor as an aid to chemical safety: odor threshold compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. *Journal of Applied Toxicology*, 36(6):272–290.

Angerer J, Lichterbeck E, Begerow J, Jekel S, Lehnert G (1990) Occupational chronic exposure to organic solvents: XIII. Glycol ether exposure during the production of varnishes. *International Archives of Occupational and Environmental Health*, 62(2):123–126.

ASTER (1996) *ASTER (Assessment Tools for the Evaluation of Risk) ecotoxicity profile*. Duluth, MN, United States Environmental Protection Agency, National Health and Environmental Effects Research Laboratory.

Atkins HL (1999) Personal communication (letter dated 25 March 1999). Ottawa, Ontario, Ottawa Hospital, General Campus, Bone Marrow Transplantation and Cancer Research [cited in Environment Canada & Health Canada, 2002].

ATSDR (1996) *Toxicological profile for 2-butoxyethanol and 2-butoxyethanol acetate* (draft). Atlanta, GA, United States Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, August.

ATSDR (1998) *Toxicological profile for 2-butoxyethanol and 2-butoxyethanol acetate*. Atlanta, GA, United States Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry.

Bartnik FG, Reddy AK, Klecak G, Zimmermann V, Hostynek JJ, Kunstler K (1987) Percutaneous absorption, metabolism, and hemolytic activity of *n*-butoxyethanol. *Fundamental and Applied Toxicology*, 8:59–70.

Bauer PH, Weber M, Mur JM, Protois JC, Bollaert PE, Condi A, Larcan A, Lambert H (1992) Transient noncarcinogenic pulmonary edema following massive ingestion of ethylene glycol butyl ether. *Intensive Care Medicine*, 18:250–251.

Beihoffer J, Ferguson C (1994) Determination of selected carboxylic acids and alcohols in groundwater by GC-MS. *Journal of Chromatographic Science*, 32:102–106.

Bormett GA, Bartels MJ, Markham DA (1995) Determination of 2-butoxyethanol and butoxyacetic acid in rat and human blood by gas chromatography–mass spectrometry. *Journal of Chromatography*, B665:315–325.

Bridie AL (1979) The acute toxicity of some petrochemicals to fish. *Water Research*, 13:623–626.

Bringmann G, Kuhn R (1977) Results of the damaging effects of water pollutants on *Daphnia magna. Zeitschrift für Wasser und Abwasser Forschung*, 10:161–166.

Bringmann G, Kuhn R (1980a) Comparison of the toxicity thresholds of water pollutants to bacteria, algae, and protozoa in the cell multiplication test. *Water Research*, 14:231–241.

Bringmann G, Kuhn R (1980b) Determination of the toxicity of water pollutants to protozoa. II. Bacteriovorous ciliates. *Zeitschrift für Wasser und Abwasser Forschung*, 13:26–31.

Bringmann G, Kuhn R (1982) Results of the toxic action of water pollutants on *Daphnia magna* Straus tested by an improved standardized procedure. *Zeitschrift für Wasser und Abwasser Forschung*, 15:1–6.

Brinke JT (1995) *Development of new VOC exposure metrics and their relationship to "sick building syndrome" symptoms* [Ph.D. thesis]. Berkeley, CA, University of Calfornia.

Cao XL (1999) *Emissions of glycol ethers from consumer products — a final report for 1998/1999 CEPA project*. Ottawa, Ontario, Health Canada, June.

Carpenter CP, Pozzani UC, Woil CS, Nair JH, Keck GA, Smyth HF Jr (1956) The toxicity of butyl cellosolve solvent. *American Medical Association Archives of Industrial Health*, 14:114–131.

Castle L, Offen CP, Baxter MJ, Gilbert J (1997) Migration studies from paper and board food packaging materials. 1. Compositional analysis. *Food Additives and Contaminants*, 14(1):35–44.

CCPA (1997) *Reducing emissions 4. A Responsible Care initiative. 1995 emissions inventory and five year projections.* Ottawa, Ontario, Canadian Chemical Producers' Association.

CCPA (1999a) *Reducing emissions 6. A Responsible Care initiative. 1997 emissions inventory and five year projections.* Ottawa, Ontario, Canadian Chemical Producers' Association.

CCPA (1999b) *Reducing emissions 7. A Responsible Care initiative. 1998 emissions inventory and five year projections.* Ottawa, Ontario, Canadian Chemical Producers' Association.

CEFIC (1995) *CEFIC Document 486/95/7/stat/year, Oxygenated Solvents S.G. — Statistical Investigation 1994*. Brussels, European Chemical Industry Council, 23 February 1995 [cited in OECD, 1997].

Chiewchanwit T, Au WW (1995) Mutagenicity and cytotoxicity of 2-butoxyethanol and its metabolite, 2-butoxyacetaldehyde, in Chinese hamster (CHO-AS52) cells. *Mutation Research*, 334(13):341–346.

Ciccioli P, Brancaleoni E, Cecinato A, Sparapani R, Frattoni M (1993) Identification and determination of biogenic and anthropogenic volatile organic compounds in forest areas of northern and southern Europe and a remote site of the Himalaya region by high-resolution gas chromatography–mass spectrometry. *Journal of Chromatography*, 643:55–69.

Ciccioli P, Cecinato A, Brancaleoni E, Frattoni M, Bruner F, Maione M (1996) Occurrence of oxygenated volatile organic compounds (VOC) in Antarctica. *International Journal of Analytical Chemistry*, 62:245–253.

CMA (1983) *90-day subchronic dermal toxicity study in rabbits with ethylene glycol monobutyl ether*. Washington, DC, Chemical Manufacturers Association [cited in Tyler, 1984].

CMA (1994) *HEDSET for ethylene glycol butyl ether.* Prepared for the European Union Existing Substances Programme. Washington, DC, Chemical Manufacturers Association.

Collinot JP, Collinot F, Deschamps D, Decolin G, Siest G, Galteau MM (1996) Evaluation of urinary D-glucaric acid excretion in workers exposed to butyl glycol. *Journal of Toxicology and Environmental Health*, 48:349–358.

Conor Pacific (1998) *A report on multimedia exposures to selected PSL2 substances*. Prepared on contract by Conor Pacific Environmental Technologies Inc. for Health Canada (Project No. 741-6705) [cited in Environment Canada & Health Canada, 2002].

Corley RA, Bormett GA, Ghanayem BI (1994) Physiologically-based pharmacokinetics of 2-butoxyethanol and its major metabolite, 2-butoxyacetic acid, in rats and humans. *Toxicology and Applied Pharmacology*, 129(1):61–79.

Corley RA, Markham DA, Banks C, Delorme P, Masterman A, Houle JM (1997) Physiologically-based pharmacokinetics and the dermal absorption of 2-butoxyethanol vapor by humans. *Fundamental and Applied Toxicology*, 39:120–130.

Crump KS, Van Landingham C (1996) *BENCH_C: A Fortran program to calculate benchmark doses from continuous data.* Ruston, LA, ICF Consulting.

Daisey JM, Hodgeson AT, Fisk WJ, Mendell MJ, TenBrinke J (1994) Volatile organic compounds in twelve California office buildings: classes, concentrations and sources. *Atmospheric Environment*, 28(22):3557–3562.

Dawson GW, Jennings AL, Drozdowski D, Rider E (1977) The acute toxicity of 47 industrial chemicals to fresh and saltwater fishes. *Journal of Hazardous Materials*, 1:303–318.

Dean BS, Krenzelok EP (1992) Clinical evaluation of pediatric ethylene glycol monobutyl ether poisonings. *Journal of Toxicology and Clinical Toxicology*, 30(4):557–563.

De Bortoli M, Knöppel H, Pecchio E, Peil A, Rogora L, Schauenburg H, Schlitt H, Vissers H (1986) Concentrations of selected organic pollutants in indoor and outdoor air in northern Italy. *Environment International*, 12:343–350 [cited in Environment Canada & Health Canada, 2002].

Dill DC (1995) *Environmental summary for Dowanol EB and DB glycol ethers.* Unpublished report. Midland, MI, Dow Chemical Company.

Dill JA, Lee KM, Bates DJ, Anderson DJ, Johnson RE, Chou BJ, Burka LT, Roycroft JH (1998) Toxicokinetics of inhaled 2-butoxyethanol and its major metabolite, 2-butoxyacetic acid, in F344 rats and B6C3F1 mice. *Toxicology and Applied Pharmacology*, 153:227–242.

Dodd DE, Snelling WM, Maronpot RR, Ballentyne B (1983) Ethylene glycol monobutyl ether: acute 9-day and 90-day vapor inhalation studies in Fischer 344 rats. *Toxicology and Applied Pharmacology*, 68:405–414.

Doe JE (1984) Further studies on the toxicology of the glycol ethers with emphasis on rapid screening and hazard assessment. *Environmental Health Perspectives*, 57:199–206.

Dow (1979) *Toxicity of Dowanol EB to freshwater organisms*. Unpublished report. Midland, MI, Dow Chemical Company (Report No. ES-330).

Dow (1988) *Dowanol EB glycol ether: evaluation of the toxicity to the green alga,* Selenastrum capricornutum. Unpublished report. Midland, MI, Dow Chemical Company.

ECETOC (1994) *Butoxyethanol criteria document. Including a supplement for 2-butoxyethyl acetate.* Brussels, European Chemical Industry Ecology and Toxicology Centre, April (Special Report No. 7).

Elias Z, Daniere MC, Marande AM, Poirot O, Terzelti F, Schneider O (1996) Genotoxic and/or epigenetic effects of some glycol ethers: results of different short-term tests. *Occupational Hygiene*, 2:187–212.

Elliott BM, Ashby J (1997) Review of the genotoxicity of 2-butoxyethanol. *Mutation Research*, 387:89–96.

Environment Canada (1997a) *Results of the CEPA Section 16 notice respecting the second Priority Substances List and di(2-ethylhexyl)phthalate*. Hull, Quebec, Environment Canada, Commercial Chemicals Evaluation Branch, Use Patterns Section.

Environment Canada (1997b) Notice respecting the second Priority Substances List and di(2-ethylhexyl)phthalate. *Canada Gazette*, Part I, 15 February 1997, pp. 366–368.

Environment Canada (1997c) *Canadian Environmental Protection Act. Priority Substances List supporting documentation — 2-Butoxyethanol. Vol. 2* (draft). Hull, Quebec, Environment Canada, pp. 187–212.

Environment Canada (1999) *Canadian Environmental Protection Act. Priority Substances List supporting documentation for the environmental assessment of 2-methoxyethanol, 2-ethoxyethanol, 2-butoxyethanol.* Hull, Quebec, Environment Canada, Commercial Chemicals Evaluation Branch.

Environment Canada, Health Canada (2002) *Canadian Environmental Protection Act, 1999. Priority Substances List assessment report: 2-Butoxyethanol.* Ottawa, Ontario, Government of Canada.

Exon JH, Mather GG, Bussiere JL, Olson DP, Talcott PA (1991) Effects of subchronic exposure of rats to 2-methoxyethanol or 2-butoxyethanol: thymic atrophy and immunotoxicity. *Fundamental and Applied Toxicology*, 16(4):830–840.

Foster PMD, Lloyd SC, Blackburn DM (1987) Comparison of the in vivo and in vitro testicular effects produced by methoxy-, ethoxy- and *n*-butoxy acetic acids in the rat. *Toxicology*, 43:17–30.

Ghanayem BI (1989) Metabolic and cellular basis of 2-butoxyethanol-induced hemolytic anemia in rats and assessment of human risk in vitro. *Biochemical Pharmacology*, 38(10):1679–1684.

Ghanayem BI, Sullivan CA (1993) Assessment of the haemolytic activity of 2-butoxyethanol and its major metabolite, butoxyacetic acid, in various mammals including humans. *Human Experimental Toxicology*, 1214:305–311.

Ghanayem BI, Burka LT, Sanders JM, Matthews H (1987a) Metabolism and disposition of ethylene glycol monobutyl ether (2-butoxyethanol) in rats. *Drug Metabolism and Disposition*, 15:478–484.

Ghanayem BI, Blair PC, Thompson MB, Maronpot RR, Matthews HB (1987b) Effect of age on the toxicity and metabolism of ethylene glycol monobutyl ether (2-butoxyethanol) in rats. *Toxicology and Applied Pharmacology*, 91:222–234.

Ghanayem BI, Ward SM, Blair PC, Matthews HB (1990) Comparison of the hematologic effects of 2-butoxyethanol using two types of hematology analyzers. *Toxicology and Applied Pharmacology*, 106(2):341–345.

Ghanayem BI, Sanchez IM, Matthews HB (1992) Development of tolerance to 2-butoxyethanol-induced hemolytic anemia and studies to elucidate the underlying mechanisms. *Toxicology and Applied Pharmacology*, 112(2):198–206.

Ghanayem BI, Ward SM, Chanas B, Nyska A (2000) Comparison of the acute hematotoxicity of 2-butoxyethanol in male and female F344 rats. *Human and Experimental Toxicology*, 19:185–192.

Gijsenbergh FP, Jenco M, Veulemans H, Groesenken D, Verberckmoes R, Delooz HH (1989) Acute butyl-glycol intoxication: a case report. *Human Toxicology*, 8:243–245.

Gingell R, Boatman RJ, Lewis S (1997) *Comparative acute toxicity of ethylene glycol mono*-n-*butyl ether in several species.* Arlington, VA, Chemical Manufacturers Association.

Gollapudi BB, Barber ED, Lawlor TE, Lewis SA (1996) Re-examination of the mutagenicity of ethylene glycol monobutyl ether to *Salmonella* tester strain TA97a. *Mutation Research*, 370:61–64.

Grant D, Slush S, Jones HB, Gangolli SD, Butler WH (1985) Acute toxicity and recovery in the hemopoietic system of rats after treatment with ethylene glycol monomethyl and monobutyl ethers. *Toxicology and Applied Pharmacology*, 77:187–200.

Green CE, Gordon GR, Cohen PM, Nolen HW, Peters JH, Tyson CA (1996) In vitro metabolism of glycol ethers by human and rat hepatocytes. *Occupational Hygiene*, 2:67–75.

Green T, Toghill A, Lee R, Moore R, Foster J (2002) The development of forestomach tumours in the mouse following exposure to 2-butoxyethanol by inhalation: studies on the mode of action and relevance to humans. *Toxicology*, 180:257–273.

Greenspan AH, Reardon RC, Gingell R, Rosica KA (1995) Human repeated insult patch test of 2-butoxyethanol. *Contact Dermatitis*, 33:59–60.

Groeseneken D, Van Vlem E, Veulemans H, Masschelein R (1986) Gas chromatographic determination of methoxyacetic and ethoxyacetic acid in urine. *British Journal of Industrial Medicine*, 43:62–65.

Groeseneken D, Veulemans H, Masschelein R, Van Vlem E (1989) An improved method for the determination in urine of alkoxyacetic acids. *International Archives of Occupational and Environmental Health*, 61:249–254.

Gualtieri J, Harris C, Roy R, Corley R, Manderfield C (1995) Multiple 2-butoxyethanol intoxications in the same patient: clinical findings, pharmacokinetics, and therapy. *Journal of Toxicology and Clinical Toxicology*, 33(5):550–551.

Gualtieri JF, DeBoer MD, Harris CR, Corley R (2003) Repeated ingestion of 2-butoxyethanol: case report and literature review. *Journal of Toxicology and Clinical Toxicology*, 41(1):57–62.

Guy RH, Potts RO (1993) Penetration of industrial chemicals across the skin: a predictive model. *American Journal of Industrial Medicine*, 23:711–719.

Hardin BD, Goad PT, Burg JR (1984) Developmental toxicity of four glycol ethers applied cutaneously to rats. *Environmental Health Perspectives*, 57:69–74.

Haufroid V, Thirion F, Mertens P, Buchet JP, Lison D (1997) Biological monitoring or workers exposed to low levels of 2-butoxyethanol. *International Archives of Occupational and Environmental Health*, 70:232–236.

Health Canada (1998a) Personal communication on glycol ethers in cosmetics products from C. Denman, Health Protection Branch, Ottawa, Ontario [cited in Environment Canada & Health Canada, 2002].

Health Canada (1998b) *Exposure factors for assessing total daily intake of priority substances by the general population of Canada* (draft). Ottawa, Ontario, Health Canada, Environmental Health Directorate, Priority Substances Section, March [cited in Environment Canada & Health Canada, 2002].

Heindel JJ, Lamb JC IV, Chapin RE, Gulati DK, Hope E, George J, Jameson CW, Teague J, Schwetz BA (1989) *Reproductive toxicity testing by continuous breeding: Test protocol in Swiss (CD-1) mice.* Available from National Technical Information Service, United States Department of Commerce, Springfield, VA (NTIS No. PB89152451AS).

Heindel JJ, Gulati DK, Russell VS, Reel JR, Lawton AD, Lamb JC IV (1990) Assessment of ethylene glycol monobutyl and monophenyl ether reproductive toxicity using a continuous breeding protocol in Swiss CD-1 mice. *Fundamental and Applied Toxicology*, 15(4):683–696.

Hoflack JC, Lambolez L, Elias Z, Vasseur P (1995) Mutagenicity of ethylene glycol ethers and of their metabolites in *Salmonella typhimurium* his$^-$. *Mutation Research*, 341(4):281–287.

Howard PH, Boethling RS, Jarvis WF, Meylan WM, Michalenko EM (1991) *Handbook of environmental degradation rates.* Chelsea, MI, Lewis Publishers Inc.

Howe RB (1995) *THRESH: A computer program to compute a reference dose from quantal animal toxicity data using the benchmark dose method*. Ruston, LA, KCF Kaiser Engineers, Inc.

IARC (2004) *Formaldehyde, 2-butoxyethanol, and 1*-tert-*butoxy-2-propanol.* Lyon, International Agency for Research on Cancer (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 88) (in preparation; http://www-cie.iarc.fr/htdocs/indexes/vol88index.html).

IPCS (1998) *2-Butoxyethanol*. Geneva, World Health Organization, International Programme on Chemical Safety (Concise International Chemical Assessment Document 10).

IPCS (2003) *2-Butoxyethyl acetate*. Geneva, World Health Organization, International Programme on Chemical Safety (International Chemical Safety Card 0839; http://www.ilo.org/public/english/protection/safework/cis/products/icsc/dtasht/_icsc08/icsc0839.pdf).

IPCS (2005a) *Ethylene glycol monobutyl ether*. Geneva, World Health Organization, International Programme on Chemical Safety (International Chemical Safety Card 0059; http://www.ilo.org/public/english/protection/safework/cis/products/icsc/dtasht/_icsc00/icsc0059.pdf).

IPCS (2005b) *Chemical-specific adjustment factors for interspecies differences and human variability: guidance document for use of data in dose/concentration–response assessment.* Geneva, World Health Organization, International Programme on Chemical Safety (Harmonization Project Document No. 2).

Jay K, Stieglitz L (1995) Identification and quantification of volatile organic components in emissions of waste incineration plants. *Chemosphere*, 30:1249–1260.

Johanson G (1988) *Toxicokinetics of butoxyethanol. Uptake, distribution, metabolism, and excretion in man and laboratory animals*. Solna, National Institute of Occupational Health, 78 pp. (Arbete Och Halsa 3).

Johanson G (1994) Inhalation toxicokinetics of butoxyethanol and its metabolite butoxyacetic acid in the male Sprague-Dawley rat. *Archives of Toxicology*, 68(9):588–594.

Johanson G, Boman A (1991) Percutaneous absorption of 2-butoxyethanol vapor in human subjects. *British Journal of Industrial Medicine*, 48(11):788–792.

Johanson G, Fernström P (1988) Influence of water on the percutaneous absorption of 2-butoxyethanol in guinea pigs. *Scandinavian Journal of Work, Environment and Health*, 14:95–100.

Johanson G, Kronborg H, Naslund PH, Nordqvist MB (1986) Toxicokinetics of inhaled 2-butoxyethanol (ethylene glycol monobutyl ether) in man. *Scandinavian Journal of Work, Environment and Health*,12:594–602.

Johanson G, Boman A, Dynesius B (1988) Percutaneous absorption of 2-butoxyethanol in man. *Scandinavian Journal of Work, Environment and Health*, 14:101–109.

Jones K, Cocker J, Dodd LJ, Fraser I (2003) Factors affecting the extent of dermal absorption of solvent vapours: a human volunteer study. *Annals of Occupational Hygiene*, 47:145–150.

Jonsson AK, Steen G (1978) *n*-Butoxyacetic acid, a urinary metabolite from inhaled *n*-butoxyethanol (butylcellosolve). *Acta Pharmacologica et Toxicologica*, 42:354–356.

Junke I, Ludemann D (1978) Results of the examination of the effects of 200 chemical compounds on fish toxicity using the golden orfe test. *Zeitschrift für Wasser und Abwasser Forschung*, 11:161–164.

Keith G, Coulais C, Edorh A, Bottin MC, Rihn B (1996) Ethylene glycol monobutyl ether has neither epigenetic nor genotoxic effects in acute treated rats and in subchronic treated v-Ha-*ras* transgenic mice. *Occupational Hygiene*, 2:237–249.

Kennah HE II, Hignet S, Laux PE, Dorko JD, Barrow CS (1989) An objective procedure for quantitating eye irritation based upon changes of corneal thickness. *Fundamental and Applied Toxicology*, 12(2):258–268.

Kennedy ER, O'Connor PF, Grote AA (1990) Application of multidimensional gas chromatography–mass spectrometry to the determination of glycol ethers in air. *Journal of Chromatography*, 522:303–333.

Koenemann H (1981) Quantitative structure–activity relationships in fish toxicity studies. Part 1. Relationships for 50 industrial pollutants. *Toxicology*, 19:209–221.

Krasavage WJ (1986) Subchronic oral toxicity of ethylene glycol monobutyl ether in male rats. *Fundamental and Applied Toxicology*, 6:349–355.

Leaf DA (1985) *Glycol ethers: an overview.* Washington, DC, United States Environmental Protection Agency, Office of Pesticides and Toxic Substances.

Lee KM, Dill JA, Chou BJ, Roycroft JH (1998) Physiological based pharmacokinetic model for chronic inhalation of 2-butoxyethanol. *Toxicology and Applied Pharmacology*, 153:211–226.

McGregor DB (1984) The genotoxicity of glycol ethers. *Environmental Health Perspectives*, 57:97–103.

McKinney PE, Palmer RB, Blackwell W, Benson BE (2000) Butoxyethanol ingestion with prolonged hyperchloremic metabolic acidosis treated with ethanol therapy. *Clinical Toxicology*, 38(7):787–793.

Medinsky MA, Singh G, Bechtold WE, Bond JA, Sabourin PJ, Birnbaum LS, Henderson RF (1990) Disposition of three glycol ethers administered in drinking water to male F344/N rats. *Toxicology and Applied Pharmacology*, 102(3):443–455.

Morris BJ, Shipp BK, Bartow TA, Baylock BL (1996) Oral exposure to 2-butoxyethanol alters immune response in BALB/c mice. *Toxicologist*, 30(1–2):342 (Abstract 1756).

Nagano K, Nakayama E, Koyano M, Oobayashi H, Adachi H, Yamada T (1979) Mouse testicular atrophy induced by ethylene glycol monoalkyl ethers. *Japanese Journal of Industrial Health*, 21:29–35.

Nagano K, Nakayama E, Koyano M, Oobayashi H, Nishazawa T, Okuda H, Yamazaki K (1984) Experimental studies on toxicity of ethylene glycol alkyl ethers in Japan. *Environmental Health Perspectives*, 57:75–84.

Nelson BR, Setzer JV, Brightwell WS, Mathinos PR, Kuczuk MH, Weaver TE, Goad PT (1984) Comparative inhalation teratogenicity of four glycol ether solvents and an amino derivative in rats. *Environmental Health Perspectives*, 57:261–271.

NICNAS (1996) *Priority Existing Chemicals, Chemical No. 6. 2-Butoxyethanol in cleaning products*. Canberra, Australian Government Publishing Service, National Industrial Chemicals Notification and Assessment Scheme.

NIOSH (1983) *National Occupational Exposure Survey (NOES), 1981–83: estimated total and female employees, actual observation and trade-named exposure to EGEE, EGHE, EGBE, and their acetates*. Unpublished database. Cincinnati, OH, United States Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Division of Surveillance, Hazard Evaluations, and Field Studies, Surveillance Branch.

NIOSH (1990) *Criteria for a recommended standard. Occupational exposure to ethylene glycol monobutyl ether and ethylene glycol monobutyl ether acetate*. Cincinnati, OH, United States Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Division of Standards Development and Technology Transfer (DHHS [NIOSH] Publication No. 90-118).

NIOSH (1994) *Manual of analytical methods*, 4th ed. Cincinnati, OH, United States Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health (DHHS [NIOSH] Publication No. 94-113).

Nisse P, Coquelle-Couplet V, Forceville X, Mathieu-Nolf M (1998) Renal failure after suicidal ingestion of window cleaner. A case report. *Veterinary and Human Toxicology*, 40(3):173.

Norbäck D, Wieslander G, Edling C (1995) Occupational exposure to volatile organic compounds (VOCs) and other air pollutants from the indoor application of water-based paints. *Annals of Occupational Hygiene*, 39(6):783–794.

Norbäck D, Wieslander G, Edling C, Johanson G (1996) House painters' exposure to glycols and glycol ethers from water-based paints. *Occupational Hygiene*, 2:111–117.

NTP (1989) *Teratologic evaluation of ethylene glycol monobutyl ether (CAS No. 111-76-2) administered to Fischer-344 rats on either gestational days 9 through 11 or days 11 through 13*. Research Triangle Park, NC, National Institutes of Health, National Toxicology Program (PB89-165849).

NTP (1993) *NTP technical report on toxicity studies of ethylene glycol ethers 2-methoxyethanol, 2-ethoxyethanol, 2-butoxyethanol administered in drinking water to F344/N rats and B6C3F1 mice.* Research Triangle Park, NC, United States Department of Health and Human Services, Public Health Service, National Institutes of Health, National Toxicology Program (NIH Publication No. 93-3349).

NTP (2000) *Toxicology and carcinogenesis studies of 2-butoxyethanol (CAS no. 111-76-2) in F344/N rats and B6C3F1 mice (inhalation studies).* Research Triangle Park, NC, United States Department of Health and Human Services, National Institutes of Health, National Toxicology Program (NTP TR 484).

OECD (1997) *Screening information dataset (SIDS) initial assessment report on 2-butoxyethanol*. 6th SIDS Initial Assessment Meeting. Paris, Organisation for Economic Co-operation and Development.

OECD (2005) *Screening information dataset (SIDS) initial assessment report on monoethyleneglycols category*. 15th SIDS Initial Assessment Meeting. Paris, Organisation for Economic Co-operation and Development.

OMEE (1994) *Windsor Air Quality Study: TAGA 6000 survey results.* Toronto, Ontario, Queen's Printer for Ontario; Ontario Ministry of Environment and Energy, Windsor Air Quality Committee (PIBS 3152E; ISBN 0-7778-2831-6) [cited in Environment Canada & Health Canada, 2002].

OMEE (1996) Personal communication, dated 20 June 1996, from J. McGrachan, Ontario Ministry of Environment and Energy, Etobicoke, Ontario, to J. Sealy, Health Canada, Ottawa, Ontario, concerning concentration of 2-butoxyethanol in water samples [cited in Environment Canada & Health Canada, 2002].

OSHA (1990) *2-Butoxyethanol (butyl cellosolve) and 2-butoxyethyl acetate (butyl cellosolve acetate).* Salt Lake City, UT, United States Department of Labor, Occupational Safety and Health Administration, Organic Methods Evaluation Branch, OSHA Analytical Laboratory.

Park J, Kamendulis LM, Klaunig JE (2002) Mechanisms of 2-butoxyethanol carcinogenicity: studies on Syrian hamster embryo (SHE) cell transformation. *Toxicological Sciences*, 68:43–50.

Plehn W (1990) Solvent emission from paints. In: *Proceedings of the 5th International Conference on Indoor Air Quality and Climate, Indoor Air '90, Vol. 3*. Toronto, Ontario, July, pp. 563–568.

Poet TS, Soelberg JJ, Weitz KK, Mast TJ, Miller RA, Thrall BD, Corley RA (2003) Mode of action and pharmacokinetic studies of 2-butoxyethanol in the mouse with an emphasis on forestomach dosimetry. *Toxicological Sciences*, 71:176–189.

Price KS, Waggy GT, Conway RA (1974) Brine shrimp bioassay and seawater BOD of petrochemicals. *Journal of the Water Pollution Control Federation*, 46:63–77.

Rambourg-Schepens MD, Buffet M, Bertault R, Jaussaud M, Journe B, Fay R, Lamiable D (1988) Severe ethylene glycol butyl ether poisoning. Kinetics and metabolic pattern. *Human Toxicology*, 7:187–189.

Rettenmeier AW, Hennigs R, Wodarz R (1993) Determination of butoxyacetic acid and *n*-butoxyacetylglutamine in urine of lacquerers exposed to 2-butoxyethanol. *International Archives of Occupational and Environmental Health*, 65(1) (Suppl.):S151–S153.

Rowe VK, Wolf MA (1982) Derivatives of glycols. In: Clayton GD, Clayton EF, eds. *Patty's industrial hygiene and toxicology*, 3rd rev. ed. *Vol. 2*. New York, NY, John Wiley and Sons, pp. 3909–4052.

Sakai T, Araki T, Masuyama Y (1993) Determination of urinary alkoxyacetic acid by rapid and simple method for biological monitoring of workers exposed to glycol ethers and their acetates. *International Archives of Occupational and Environmental Health*, 64:495–498.

Sakai T, Araki T, Morita Y, Masuyama Y (1994) Gas chromatographic determination of butoxyacetic acid after hydrolysis of conjugated metabolites in urine from workers exposed to 2-butoxyethanol. *International Archives of Occupational and Environmental Health*, 66:249–254.

Sax NI, Lewis RJ (1987) *Hawley's condensed chemical dictionary*, 11th ed. New York, NY, Van Nostrand Reinhold Company, pp. 488–489.

Schuler RL, Hardin BD, Niemeier RW, Booth G, Hazelden K, Piccirillo V (1984) Results of testing 15 glycol ethers in a short-term in vivo reproductive toxicity assay. *Environmental Health Perspectives*, 57:141–146.

Shields HC, Fleischer DM, Weschler CJ (1996) Comparisons among VOCs measured in three types of U.S. commercial buildings with different occupant densities. *Indoor Air*, 6:2–17.

Shyr LJ, Sabourin PJ, Medinsky MA, Birnbaum LS, Henderson RF (1993) Physiologically-based modeling of 2-butoxyethanol disposition in rats following different routes of exposure. *Environmental Research*, 63(2):202–218.

Siesky AM, Kamendulis LM, Klaunig JE (2002) Hepatic effects of 2-butoxyethanol in rodents. *Toxicological Sciences*, 70:252–260.

Singh P, Zhao S, Baylock BL (2001) Topical exposure to 2-butoxyethanol alters immune responses in female BALB/c mice. *International Journal of Toxicology*, 20:383–390.

Singh P, Morris, B, Zhao S, Baylock BL (2002) Suppression of the contact hypersensitivity response following topical exposure to 2-butoxyethanol in female BALB/c mice. *International Journal of Toxicology*, 21:107–115.

Sivarao DV, Mehendale HM (1995) 2-Butoxyethanol autoprotection is due to resilience of newly formed erythrocytes to hemolysis. *Archives of Toxicology*, 69:526–532.

Smallwood AW, DeBord KE, Lowry LK (1984) Analyses of ethylene glycol monoalkyl ethers and their proposed metabolites in blood and urine. *Environmental Health Perspectives*, 57:249–253.

Smallwood AW, DeBord KE, Burg J, Moseley C, Lowry LK (1988) Determination of urinary 2-ethoxyacetic acid as an indicator of occupational exposure to 2-ethoxyethanol. *Applied Industrial Hygiene*, 3(2):47–50.

Smialowicz RJ, Williams WC, Riddle HH, Andres DL, Luebke RW, Copeland CB (1992) Comparative immunosuppression of various glycol ethers orally administered to Fischer 344 rats. *Fundamental and Applied Toxicology*, 18(4):621–627.

Sohnlein B, Letzel S, Weltle D, Rüdiger HW, Angerer J (1993) XIV. Examinations concerning the evaluation of a limit value for 2-ethoxyethanol and 2-ethoxyethylacetate and the genotoxic effects of these glycol ethers. *International Archives of Occupational and Environmental Health*, 64(7):479–484.

SRC (1988) *Syracuse Research Corporation calculated values.* Syracuse, NY, Syracuse Research Corporation [cited in Environment Canada & Health Canada, 2002].

Staples CA, Boatman RJ, Cano ML (1998) Ethylene glycol ethers: An environmental risk assessment. *Chemosphere*, 36:1585–1613.

Stemmler K, Mengen DJ, Kinnison DJ, Kerr JA (1997) OH radical-initiated oxidation of 2-butoxyethanol under laboratory conditions related to the troposphere: product studies and proposed mechanism. *Environmental Science and Technology*, 31:1496–1504.

Truhaut R, Dutertre-Catella H, Phu-Lich N, Huyen VN (1979) Comparative toxicological study of ethylglycol acetate and butylglycol acetate. *Toxicology and Applied Pharmacology*, 51:117–127.

Tuazon EC, Aschmann SM, Atkinson R (1998) Products of the gas-phase reactions of the OH radical with 1-methoxy-2-propanol and 2-butoxyethanol. *Environmental Science and Technology*, 32:3336–3345.

Tyl RW, Millicovsky G, Dodd DE, Pritts IM, France KA, Fisher LC (1984) Teratologic evaluation of ethylene glycol monobutyl ether in Fischer 344 rats and New Zealand white rabbits following inhalation exposure. *Environmental Health Perspectives*, 57:47–68.

Tyler TR (1984) Acute and subchronic toxicity of ethylene glycol monobutyl ether. *Environmental Health Perspectives*, 57:185–191.

Udden MM (1994) Hemolysis and deformability of erythrocytes exposed to butoxyacetic acid, a metabolite of 2-butoxyethanol: II. Resistance in red blood cells from humans with potential susceptibility. *Journal of Applied Toxicology*, 14(2):97–102.

Udden MM (1996) Effects of butoxyacetic acid on human red cells. *Occupational Hygiene*, 2:283–290.

Udden MM (2000) Rat erythrocyte morphological changes after gavage dosing with 2-butoxyethanol: a comparison with the *in vitro* effects of butoxyacetic acid on rat and human erythrocytes. *Journal of Applied Toxicology*, 20:381–387.

Udden MM (2002) In vitro sub-hemolytic effects of butoxyacetic acid on human and rat erythrocytes. *Toxicological Sciences*, 69:258–264.

Udden MM, Patton CS (1994) Hemolysis and deformability of erythrocytes exposed to butoxyacetic acid, a metabolite of 2-butoxyethanol: I. Sensitivity in rats and resistance in normal humans. *Journal of Applied Toxicology*, 412:91–96.

Unilever (1989) *2-Butoxyethanol: Skin sensitisation study in guinea-pigs*. United Kingdom, Unilever Research [cited in ECETOC, 1994].

Union Carbide (1980) *Butyl cellosolve: 9-day repeated dermal application to rabbits*. South Charleston, WV, Union Carbide Corporation, Corporate Applied Toxicology (Bushy Run Research Center Project Report 43-76) [cited in Tyler, 1984].

Union Carbide (1989) *Ecological fate and effects data on four selected glycol ether products.* Unpublished report. South Charleston, WV, Union Carbide Chemicals and Plastic Co. Inc.

USEPA (1979) *Ice fog suppression using thin chemical films*. Washington, DC, United States Environmental Protection Agency, January. Available from National Technical Information Service, United States Department of Commerce, Springfield, VA (NTIS Report PB-294 275).

USEPA (1984) *Acute toxicity studies on Wellaid 31.* Study submitted to the United States Environmental Protection Agency by Amoco Corporation [cited in OECD, 1997].

USEPA (1992) *Dermal exposure assessment: principles and applications. Interim report.* Washington, DC, United States Environmental Protection Agency, Office of Health and Environmental Assessment, Exposure Assessment Group, January (EPA/600/8-91/011B) [cited in Environment Canada & Health Canada, 2002].

USEPA (1997*) Exposure factors handbook. Vol. III. Activity factors*. Washington, DC, United States Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, August (EPA/600/P-95/002Fc) [cited in Environment Canada & Health Canada, 2002].

USEPA (2005) *An evaluation of the human carcinogenic potential of ethylene glycol butyl ether*. Washington, DC, United States Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment.

USITC (1996) *Preliminary report on U.S. production of selected synthetic organic chemicals (including synthetic plastics and resin materials).* Washington, DC, United States International Trade Commission, pp. 2–12 (Series C/P-96-2; No. 26, Totals, 1995).

USNLM (2002) *Hazardous substances data bank*. Bethesda, MD, United States National Library of Medicine, National Toxicology Information Program (last revision on 11 August 2002).

Verschueren K (1983) *Handbook of environmental data on organic chemicals*, 2nd ed. New York, NY, Van Nostrand Reinhold Company, 1310 pp.

Veulemans H, Groeseneken D, Masschelein R, Van Vlem E (1987) Survey of ethylene glycol ether exposures in Belgian industries and workshops. *American Industrial Hygiene Association Journal*, 48(8):671–676.

Vincent R, Cicolella A, Subra I, Rieger B, Parrot P, Pierre F (1993) Occupational exposure to 2-butoxyethanol for workers using window cleaning agents. *Applied Occupational and Environmental Hygiene*, 8(6):580–586.

von Oettingen WF, Jirouche EA (1931) The pharmacology of ethylene glycol and some of its derivatives in relation to their chemical constitution and physical chemical properties. *Journal of Pharmacology and Experimental Therapeutics*, 42(3):355–372.

Werner HW, Mitchell JL, Miller JW, von Oettingen WF (1943a) The acute toxicity of vapors of several monoalkyl ethers of ethylene glycol. *Journal of Industrial Hygiene and Toxicology*, 25:157–163.

Werner HW, Nawrocki CZ, Mitchell JL, Miller JW, von Oettingen WF (1943b) Effects of repeated exposure of rats to monoalkyl ethylene glycol ether vapors. *Journal of Industrial Hygiene and Toxicology*, 25:374–379.

Werner HW, Mitchell JL, Miller JW, von Oettingen WF (1943c) Effects of repeated exposure of dogs to monoalkyl ethylene glycol ether vapors. *Journal of Industrial Hygiene and Toxicology*, 25:409–414.

Wier PJ, Lewis SC, Traul KA (1987) A comparison of developmental toxicity evident at term to postnatal growth and survival using ethylene glycol monoethyl ether, ethylene glycol monobutyl ether and ethanol. *Teratogenicity, Carcinogenicity and Mutagenicity*, 7:55–64.

Wilkinson SC, Williams FM (2002) Effects of experimental conditions on absorption of glycol ethers through human skin in vitro. *International Archives of Occupational and Environmental Health*, 75:519–527.

Yasuhara A, Shiraisi H, Tsuji M, Okuno T (1981) Analysis of organic substances in highly polluted river water by mass spectrometry. *Environmental Science and Technology*, 15:570–573.

Zeiger E, Anderson B, Haworth S, Lawlor T, Mortelmans K (1992) *Salmonella* mutagenicity tests: V. Results from the testing of 311 chemicals. *Environmental and Molecular Mutagenesis*, 19(Suppl. 21):2–141.

Zhu J, Cao X-L, Beauchamp R (2001) Determination of 2-butoxyethanol emissions from selected consumer products and its application in assessment of inhalation exposure associated with cleaning tasks. *Environment International*, 26:589–597.

Zissu D (1995) Experimental study of cutaneous tolerance to glycol ethers. *Contact Dermatitis*, 32(2):74–77.

APPENDIX 1—ACRONYMS AND ABBREVIATIONS

ATSDR	Agency for Toxic Substances and Disease Registry (USA)
BAA	2-butoxyacetic acid
BALD	2-butoxyacetaldehyde
BMC	benchmark concentration
BMC_{05}	concentration associated with a 5% increase in the absolute risk of seeing an "adverse" response
BOD	biological oxygen demand
CAS	Chemical Abstracts Service
CCRIS	Chemical Carcinogenesis Research Information System
CEPA	*Canadian Environmental Protection Act*
CICAD	Concise International Chemical Assessment Document
CIS	Chemical Information System
DART	Developmental & Reproductive Toxicology
DNA	deoxyribonucleic acid
EC_{50}	median effective concentration
ECD	electron capture detection
EHC	Environmental Health Criteria
EMIC	Environmental Mutagen Information Center
EQC	Equilibrium Criterion
ETIC	Environmental Teratology Information Center
FAO	Food and Agriculture Organization of the United Nations
FID	flame ionization detection
GC	gas chromatography
GENE-TOX	Genetic Toxicology
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substances Data Bank
IARC	International Agency for Research on Cancer
IC_{50}	median inhibitory concentration
ICSC	International Chemical Safety Card
IOMC	Inter-Organization Programme for the Sound Management of Chemicals
IPCS	International Programme on Chemical Safety
IRIS	Integrated Risk Information System
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
K_{oc}	organic carbon sorption coefficient
K_{ow}	octanol–water partition coefficient
K_p	permeability coefficient
LC_{50}	median lethal concentration
LCL	lower confidence limit
LD_{50}	median lethal dose
LOAEC	lowest-observed-adverse-effect concentration
LOAEL	lowest-observed-adverse-effect level
LOEC	lowest-observed-effect concentration
LOEL	lowest-observed-effect level
MS	mass spectrometry
NOAEC	no-observed-adverse-effect concentration
NOAEL	no-observed-adverse-effect level
NOEC	no-observed-effect concentration
NOEL	no-observed-effect level
NTIS	National Technical Information Service (USA)
NTP	National Toxicology Program (USA)
OECD	Organisation for Economic Co-operation and Development
PBPK	physiologically based pharmacokinetic
PEC	predicted environmental concentration
PEC_{local}	predicted local environmental concentration
PNEC	predicted no-effect concentration
ppm	part per million
RTECS	Registry of Toxic Effects of Chemical Substances
SI	International System of Units (Système international d'unités)
SIDS	screening information data set
TC	tolerable concentration
TSCA	*Toxic Substances Control Act* (USA)
USA	United States of America
VOC	volatile organic compound
v/v	volume to volume
WHO	World Health Organization

APPENDIX 2—SOURCE DOCUMENT

The original CICAD (IPCS, 1998) was based on reviews prepared by NIOSH (1990) and ATSDR (1996) of the USA. This update is based principally on additional information identified in the following source document:

Environment Canada & Health Canada (2002)

Copies of the *Canadian Environmental Protection Act* Priority Substances List assessment report on 2-butoxyethanol are available from:

Inquiry Centre
Environment Canada
Main Floor, Place Vincent Massey
351 St. Joseph Blvd.
Gatineau, Quebec
Canada K1A 0H3

or on the Internet at:

http://www.ec.gc.ca/substances/ese/eng/psap/final/main.cfm

Unpublished supporting documentation, which presents additional information, is available upon request from:

Existing Substances Branch
Environment Canada
14th Floor, Place Vincent Massey
351 St. Joseph Blvd.
Gatineau, Quebec
Canada K1A 0H3

or

Existing Substances Division
Environmental Health Centre
Health Canada
Tunney's Pasture
Address Locator 0801C2
Ottawa, Ontario
Canada K1A 0L2

Sections of the assessment report related to the environmental assessment of 2-butoxyethanol and the environmental supporting document (Environment Canada, 1999) were prepared or reviewed by the members of the Environmental Resource Group, established by Environment Canada to support the environmental assessment: D. Boersma, Environment Canada; R. Breton, Environment Canada; P. Cureton, Environment Canada; N. Davidson, Environment Canada; R. Desjardins, Environment Canada; L. Hamel, Union Carbide Canada Inc.; B. Lee, Environment Canada; S. Lewis, Chemical Manufacturers' Association; B. Sebastien, Environment Canada; and K. Taylor, Environment Canada (lead for the environmental assessment)

Sections of the assessment report relevant to the environmental assessment and the environmental supporting document (Environment Canada, 1999) were also reviewed by C. Staples, Assessment Technologies Inc.

A summary of data relevant to assessment of the potential risk to human health associated with exposure to 2-butoxyethanol was prepared in 1996 by BIBRA Toxicology International. Additional recent reviews were also used for the identification of relevant data, including those prepared for IPCS (1998) and ATSDR (1998). Additional and more recent data were identified through literature searches, the strategies for which are described below.

The health-related sections of the assessment report and the background supporting documentation were prepared by the following staff of Health Canada: K. Hughes, M.E. Meek, D. Moir, L. Turner, and M. Walker.

H. Atkins (Ottawa Hospital, General Campus) provided advice on the biological significance of haematological effects. A. Renwick (University of Southampton) provided advice on the adequacy of the data as a basis for replacement of default components of uncertainty factors. Input on this aspect was also received at an IPCS workshop on uncertainty and variability in risk assessment, held in Berlin, Germany, on 9–11 May 2000.

Comments primarily on the adequacy of data coverage in the sections of the supporting documentation related to health effects were provided in a written review by members of the American Chemistry Council Ethylene Glycol Ethers Panel, including R. Boatman, Eastman Kodak (for Eastman Chemical); R. Gingell, Shell Chemical; S. Lewis, American Chemistry Council; A. Schumann, Dow Chemical; and T. Tyler, Union Carbide Corporation.

Comments on accuracy of reporting, adequacy of coverage, and defensibility of conclusions with respect to hazard identification were provided in written review by BIBRA Toxicology International and H. Atkins (Ottawa Hospital, General Campus).

Accuracy of reporting, adequacy of coverage, and defensibility of conclusions with respect to hazard characterization and exposure–response analyses were considered in written review of the completed assessment report by H. Clewell, K.S. Crump Group, Inc., ICF Kaiser International, Inc.; J. Delic, United Kingdom Health and Safety Executive; J. Gift, National Center for Environmental Assessment, United States Environmental Protection Agency; and J. Roycroft, National Institute for Environmental Health Sciences, United States Department of Health and Human Services.

The health-related sections of the assessment report were reviewed and approved by the Healthy Environments and Consumer Safety Branch Risk Management meeting of Health Canada.

The entire assessment report was reviewed and approved by the Environment Canada/Health Canada CEPA Management Committee.

Search strategies employed for identification of relevant data

In addition to studies included in the review prepared by BIBRA Toxicology International and relevant studies included in reports published by IPCS (1998) and ATSDR (1998), recent data were identified through searching the following databases beginning in August 1996 using the chemical name or the CAS number for both 2-butoxyethanol and 2-butoxyethyl acetate: Canadian Research Index, DIALOG (CancerLit, Environmental Bibliography, Waternet, Water Resources Abstracts, Enviroline, CAB Abstracts, Food Science and Technology Abstracts, Pollution Abstracts, and NTIS), Medline, Toxline Plus and TOXNET (CCRIS, United States National Cancer Institute), GENE-TOX (United States Environmental Protection Agency), and EMIC (Oak Ridge National Laboratory). Data acquired as of October 1999 were considered for inclusion in this report.

As well as these databases, officials at the Product Safety Bureau and Drugs Directorate of Health Canada, along with the

Pest Management Regulatory Agency, were contacted to obtain information relevant to this assessment.

A comprehensive literature search was conducted in February 2003 by Toxicology Advice & Consulting Ltd, United Kingdom, in order to identify critical data published since publication of the source document. Databases searched included:

- ChemID*plus* (The ChemID*plus* system searches and/or identifies literature from a wide range of online databases and databanks, including ATSDR, CancerLit, CCRIS, DART/ETIC, GENE-TOX, HSDB, IRIS, Medline, Toxline Core, Toxline Special, and TSCA Chemical Inventory);
- INCHEM (the INCHEM database consolidates information from a number of intergovernmental organizations, including JECFA [evaluations and monographs], JMPR, IARC, CIS, IPCS [EHC documents], and SIDS); and
- RTECS.

APPENDIX 3—CICAD PEER REVIEW

The draft CICAD on 2-butoxyethanol was sent for review to institutions and organizations identified by IPCS after contact with IPCS national Contact Points and Participating Institutions, as well as to identified experts. Comments were received from:

M. Baril, Institut de Recherche en Santé et en Sécurité du Travail du Québec, Montreal, Quebec, Canada

B. Benson, Drinking Water Program, United States Environmental Protection Agency, Denver, CO, USA

R. Chhabra, National Institute for Environmental Health Sciences, United States Department of Health and Human Services, Research Triangle Park, NC, USA

E. Frantik, National Institute of Public Health, Prague, Czech Republic

P. Howe, Centre for Ecology and Hydrology, Monks Wood, United Kingdom

I. Indans, Health and Safety Executive, Bootle, United Kingdom

G. Johanson, Karolinska Institute, Stockholm, Sweden

S.A. Lewis, American Chemistry Council, Arlington, VA, USA

P.A. Schulte, National Institute for Occupational Safety and Health, Cincinnati, OH, USA

G. Ungvary, József Fodor National Centre for Public Health, Budapest, Hungary

R. Wiger, Norwegian Institute of Public Health, Oslo, Norway

K. Ziegler-Skylakakis, Commission of the European Communities, Luxembourg

APPENDIX 4—CICAD FINAL REVIEW BOARD

Hanoi, Viet Nam
28 September – 1 October 2004

Members

Mr D.T. Bai, Centre of Environmental Protection & Chemical Safety, Institute of Industrial Chemistry, Hanoi, Viet Nam

Dr R. Chhabra, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA

Mr P. Copestake, Toxicology Advice & Consulting Ltd, Surrey, United Kingdom

Dr C. De Rosa, Agency for Toxic Substances and Disease Registry, Centres for Disease Control and Prevention, Atlanta, GA, USA

Dr S. Dobson, Centre for Ecology & Hydrology, Monks Wood, Abbots Ripton, Huntingdon, Cambridgeshire, United Kingdom

Dr G. Dura, National Institute of Environmental Health of József Fodor National Centre of Public Health, Budapest, Hungary

Ms C.W. Fang, National Institute of Occupational Safety and Health Malaysia, Selangor, Malaysia

Dr L. Fishbein, Fairfax, VA, USA

Dr L. Fruchtengarten, Poison Control Center of São Paulo, São Paulo, Brazil

Dr C.L. Geraci, Document Development Branch, Centers for Disease Control and Prevention / National Institute for Occupational Safety and Health, Cincinnati, OH, USA

Dr H. Gibb, Sciences International, Alexandria, VA, USA

Dr R.F. Hertel, Federal Institute for Risk Assessment, Berlin, Germany

Mr P. Howe, Centre for Ecology & Hydrology, Monks Wood, Abbots Ripton, Huntingdon, Cambridgeshire, United Kingdom

Dr S. Ishimitsu, Division of Safety Information on Drug, Food and Chemicals, National Institute of Health Sciences, Tokyo, Japan

Dr J. Kielhorn, Fraunhofer Institute of Toxicology and Experimental Medicine, Hanover, Germany

Dr S. Kunarattanapruke, Food & Drug Administration, Ministry of Public Health, Nonthaburi, Thailand

Dr Y. Liang, Department of Occupational Health, Fudan University School of Public Health, Shanghai, China

Ms M.E. Meek, Existing Substances Division, Environmental Health Directorate, Health Canada, Ottawa, Ontario, Canada

Mr F.K. Muchiri, Directorate of Occupational Health and Safety Services, Nairobi, Kenya

Dr O. Sabzevari, Food and Drug Quality Control Laboratories, Ministry of Health and Medical Education, Tehran, Islamic Republic of Iran

Dr J. Stauber, CSIRO Energy Technology, Menai, New South Wales, Australia

Dr M.H. Sweeney, United States Embassy, Hanoi, Viet Nam

Mr P. Watts, Toxicology Advice & Consulting Ltd, Surrey, United Kingdom

Ms D. Willcocks, National Industrial Chemicals Notification and Assessment Scheme, Sydney, New South Wales, Australia

Dr K. Ziegler-Skylakakis, European Commission, Luxembourg

Secretariat

Dr A. Aitio, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

APPENDIX 5—DERIVATION OF TOLERABLE INTAKES AND CONCENTRATIONS FOR BUTOXYETHANOL[1]

In view of the sufficient weight of evidence for the haematotoxicity of 2-butoxyethanol in short- and long-term studies in experimental animals (with the lowest LOEC being 31.2 ppm), BMCs for a variety of haematological end-points were derived on the basis of the long-term studies in animals in which adequate exposure–response data were presented.

Although haemosiderin pigmentation was considered to be secondary to haemolytic anaemia, BMCs were also derived on the basis of the incidence of haemosiderin pigmentation of chronically exposed rodents, since this effect was also observed in rats and mice at concentrations as low as 31.2 ppm; these BMCs are derived as a discrete measure of 2-butoxyethanol-induced effects, primarily for comparison with those based on the continuous data for haematological parameters.

Although less consistently observed, the forestomach was also a sensitive target organ in rodents exposed to 2-butoxyethanol via inhalation, with non-neoplastic effects being induced in a chronic study in mice at the lowest concentration investigated (62.5 ppm) and at higher concentrations in a subchronic study in rats (>250 ppm).

Based on the available data from short- and long-term studies in various laboratory species and in vitro investigations in blood cells from animals and humans, as well as information on toxicokinetics and metabolism of 2-butoxyethanol, rats appear to be more sensitive than other species to the haematotoxic effects induced by the substance. Variations in sensitivity are well correlated with production and clearance rates of BAA. Available data indicate that BAA is principally responsible for the haematological effects associated with 2-butoxyethanol. The major pathways of metabolism and disposition of 2-butoxyethanol are qualitatively similar in rats, mice, and humans, with BAA being a major circulating metabolite in all species and being eliminated primarily by renal excretion. However, while there is considerable evidence that BAA is the putatively toxic entity, and hence an appropriate surrogate for interspecies and intraspecies (interindividual) adjustment for the toxicokinetic component of the uncertainty factor for a TC for critical haematological effects (i.e. haemolysis), the relevance of the systemic disposition of BAA to lesions of the forestomach in mice is not fully known. Therefore, values for these two effects have been developed separately here, with inclusion of compound-related adjustment factors for which data are sufficient for one (haemolysis in rats) but not the other (forestomach lesions in female mice).

Haematological effects

The studies considered most appropriate for derivation of BMCs for use in characterizing the risk of haematological effects in human health associated with exposure to 2-butoxyethanol in the environment are those conducted by the NTP (2000), in which rats and mice were exposed to the substance for up to 2 years. In addition, the lowest effect levels for these end-points were derived from these studies. In these investigations, groups of up to 50 male or female F344/N rats were exposed to concentrations of 0, 31.2, 62.5, or 125 ppm for 6 h/day, while similar groups of B6C3F1 mice were exposed to concentrations of 0, 62.5, 125, or 250 ppm. Various haematological parameters in 10 animals per exposure group were measured at several time points throughout the first 12 months of exposure. Statistically significant changes in several parameters were noted at these intervals in both species; therefore, BMC_{05}s were calculated for these effects using data at the 12-month time point.

The BMC_{05} is defined as the concentration associated with a 5% increase in the absolute risk of seeing an "adverse" response.

The Weibull model was fit to each of the end-points using BENCH_C (Crump & Van Landingham, 1996):

$$P(d) = p_0 + (1 - p_0) \cdot [1 - e^{-(\beta d)^k}]$$

where d is dose, $P(d)$ is the probability of an adverse response at dose d, and k, β, and p_0 are parameters to be estimated. The BMC_{05} was then calculated as the concentration C such that

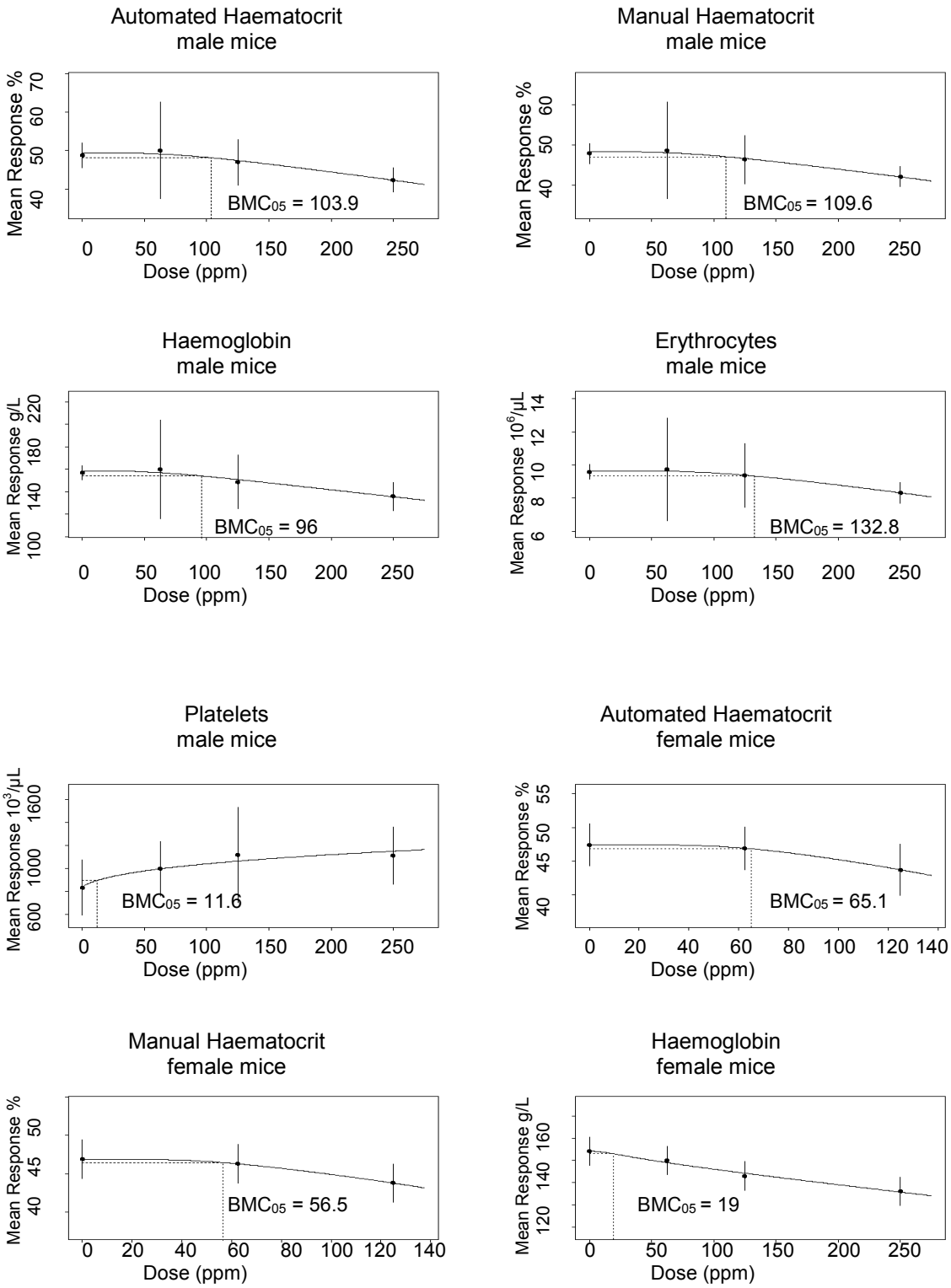
$$P(C) - P(0) = 0.05$$

Plots of the data and fitted curves are shown in Figure A-1. Although the BMC_{05}s were derived on the basis of studies in which animals were exposed for a duration of less than lifetime, it was not considered appropriate to amortize exposure over a 2-year period (as is done for many chronic effects), in view of the shorter time course for formation, ageing, and elimination of blood cells. Values were adjusted, however, to account for non-continuous exposure of only 6 h/day and 5 days/week by multiplying by 6/24 × 5/7. In general, the BMC_{05}s for each parameter are lower for rats than for mice (although there are some exceptions in females) and generally lower in female rats than in male rats. The BMC_{05}s for haematological effects, adjusted for non-continuous exposure, range from 1.1 to 13.2 ppm in rats and from 2.1 to 23.7 ppm in mice.

A TC was developed on the basis of the BMC_{05}s for haematological effects in rats, quantitatively taking into account interspecies variations in kinetics and dynamics. The lower end of the range of BMC_{05}s for haemological effects in the long-term rat study was 1.1 ppm.

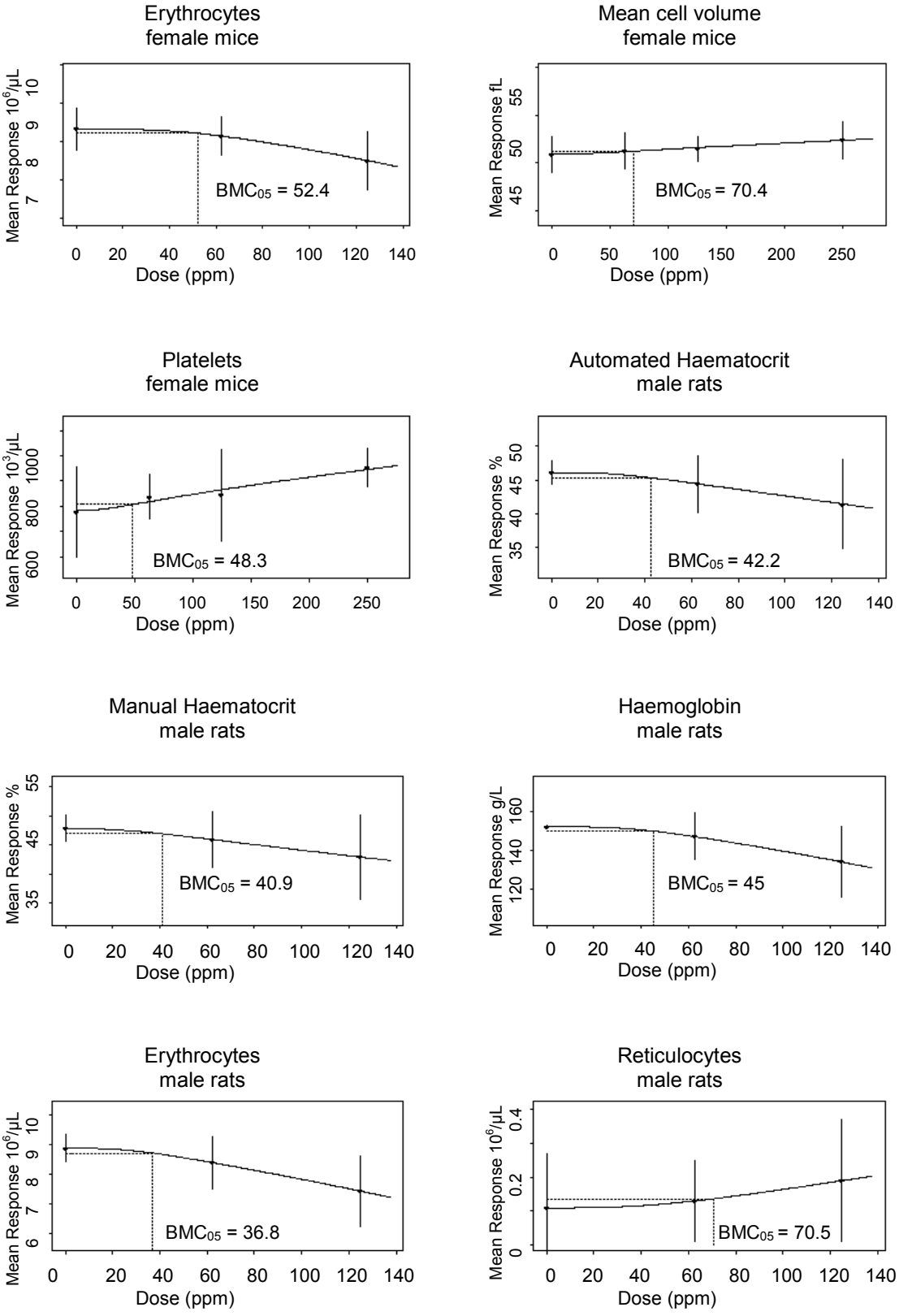
Information relevant to consideration of both the interspecies and intraspecies (interindividual) dynamic components of uncertainty or adjustment factors is available from several studies in which the direct effects of BAA on several measures of haemolysis in rat and human erythrocytes have been examined in vitro (i.e. Bartnik et al., 1987; Ghanayem, 1989; Udden, 1994; Udden & Patton, 1994). Based on these investigations, there is consistent evidence that human erythrocytes are at least 10-fold less sensitive than rat erythrocytes; therefore, the default factor for the interspecies component for dynamics (2.5) can be replaced with a value of 0.1 (and this would still be conservative). It is noteworthy that the end-points in these studies on which this adjustment is based (haematocrit and haemoglobin concentration) are consistent with some of the end-points in in vivo studies for which TCs were lowest. However, available data on intraspecies (interindividual) variation in dynamics are limited primarily to one study in vitro in blood from various potentially sensitive subgroups of the population (i.e. seniors and patients with sickle cell disease and spherocytosis) in which no response was observed at the administered concentration (n = 9, 9, 7, and 3) (Udden, 1994). In several other studies, haemolysis was examined in generally pooled blood samples from unspecified or very small numbers of

[1] The studies upon which this appendix is based and the calculations of BMC_{05} in the source document expressed the concentrations of 2-butoxyethanol in the air in ppm, and therefore this metric is also used in this appendix. The tolerable concentrations derived are given in SI units, in line with WHO policy. These figures are identical, independent of which temperature convention (20 °C or 25 °C) is used.



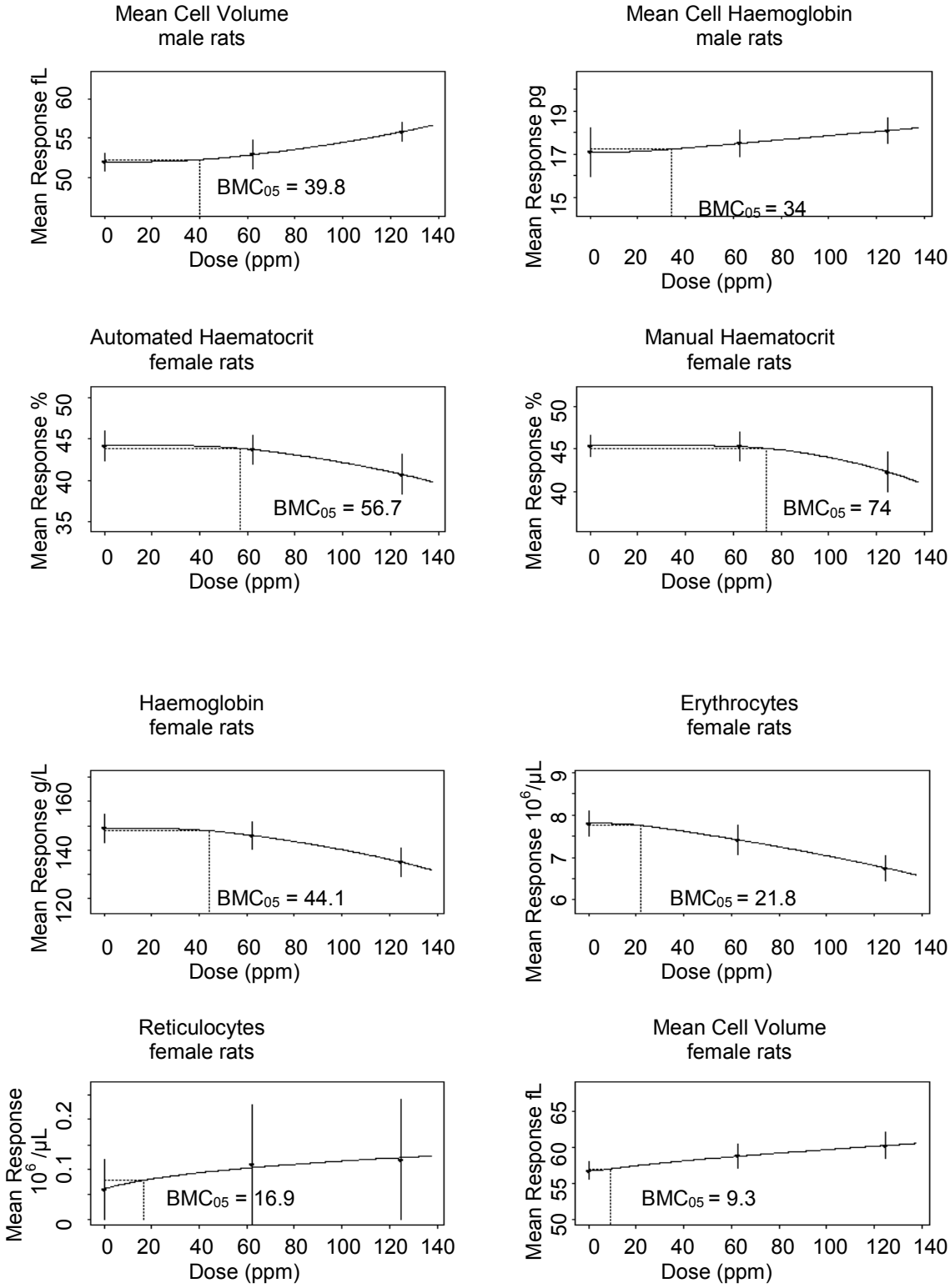
BMC_{05} unadjusted for non-constant dosing

Fig. A-1. Exposure–response curves for haematological effects in mice and rats.



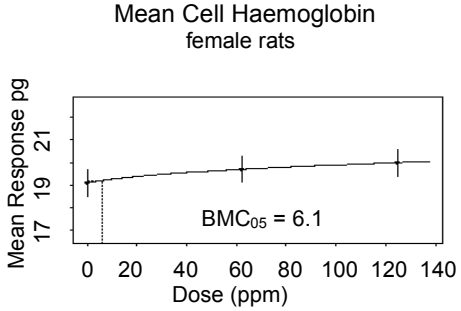
BMC_{05} unadjusted for non-constant dosing

Fig. A-1. Exposure–response curves for haematological effects in mice and rats (contd).



BMC_{05} unadjusted for non-constant dosing

Fig. A-1. Exposure–response curves for haematological effects in mice and rats (contd).



BMC_{05} unadjusted for non-constant dosing

Fig. A-1. Exposure–response curves for haematological effects in mice and rats (contd).

individuals (n = 3) as a basis solely for estimation of the central tendency for interspecies comparison (Bartnik et al., 1987; Ghanayem, 1989; Udden & Patton, 1994). These data are inadequate to meaningfully quantitatively inform the replacement of default with a data-derived adjustment factor; hence, the default value of 3.2 is maintained.

The total compound-specific adjustment factor is, therefore, 0.5 (interspecies, toxicokinetics) × 0.1 (interspecies, toxicodynamics) × 3.2 (intraspecies, toxicokinetics) × 3.2 (intraspecies, toxicodynamics) = 0.5.

Based on the above considerations regarding relative sensitivity to 2-butoxyethanol-induced haematotoxicity, the TC has been derived as follows:

TC = [6.1 ppm × 5/7 × 6/24] / 0.5

= 1.1 ppm / 0.5

= 5.3 mg/m^3 / 0.5

= 11 mg/m^3

where:

- 6.1 ppm is the BMC_{05} for mean cell haemoglobin in female rats (see Figure A-1),
- 5/7 and 6/24 are adjustment factors for continuous exposure, and
- 0.5 is the compound-specific adjustment factor (see above).

While limitations of the monitoring data in the single identified relevant cross-sectional study of workers preclude its utility in bounding the TC developed on the basis of studies in animals, the value developed above is protective, based on the early, shorter-term clinical study (Carpenter et al., 1956).

Other (non-haematological) effects

BMC_{05}s were derived for other non-cancer effects, including Kupffer cell pigmentation of the liver (although considered secondary to haemolysis), as well as ulceration and hyperplasia of the forestomach (all severities combined), based on the observations in rats and mice exposed to 2-butoxyethanol for up to 2 years (NTP, 2000). For such discrete end-points, the BMC_{05} is defined as the concentration of the substance associated with a 5% increase in incidence over background response rate. It is calculated by first fitting the following model to the exposure–response data (Howe, 1995):

$$P(d) = q_0 + (1 - q_0) \cdot [1 - e^{-q_1 d - \ldots - q_k d^k}]$$

where d is dose, k is the number of dose groups in the study, $P(d)$ is the probability of the animal developing the effect at dose d, and $q_i > 0$, i = 0,...,k are parameters to be estimated.

The models were fit to the incidence data using THRESH (Howe, 1995), and the BMC_{05}s were calculated as the concentration C that satisfies:

$$[P(C) - P(0)] / [1 - P(0)] = 0.05$$

Resulting BMC_{05}s were adjusted for the non-constant exposure pattern by multiplying by 6/24 × 5/7. BMC_{05}s for these non-cancer end-points, adjusted for non-continuous exposure, range from 0.89 ppm (95% LCL = 0.73 ppm) for hyperplasia of the forestomach epithelium in female mice to 16.5 ppm (95% LCL = 10.9 ppm) for Kupffer cell pigmentation in male mice. In concordance with the greater sensitivity of rats compared with mice to 2-butoxyethanol-induced haemolysis, lower BMC_{05} values (1.1 ppm and 2.2 ppm for males and females, respectively) were determined for Kupffer cell pigmentation in rats.

A TC was developed on the basis of the lower end of the range of the BMC_{05}s for these effects (i.e. that for hyperplasia of the forestomach epithelium in female mice), although the range of these values is relatively small. In addition, haemosiderin pigmentation is considered to be secondary to haemolysis, rather than an adverse effect directly associated with exposure to 2-butoxyethanol. The TC was developed as follows:

TC = [5 ppm × 5/7 × 6/24] / 100

= 0.89 ppm / 100

= 4.3 mg/m^3 / 100

= 0.04 mg/m^3

where:

- 5 ppm is the BMC associated with a 5% increase in the incidence of hyperplasia of the forestomach epithelium in female B6C3F1 mice exposed to 2-butoxyethanol for 2 years (NTP, 2000),
- 5/7 and 6/24 are adjustment factors for continuous exposure, and
- 100 is the default uncertainty factor (×10 for intraspecies variation and ×10 for interspecies variation). Available data are insufficient as a basis to replace default values for intra- and interspecies variations in toxicokinetics and toxicodynamics by compound-specific adjustments — i.e. the putatively toxic metabolite in the induction of local irritant effects is unknown, and relative sensitivity has not been investigated.

APPENDIX 6—EFFECTS ON THE ENVIRONMENT[1]

Aquatic environment

Results of acute and long-term studies on toxicity to aquatic organisms are summarized in Table A-1. Long-term studies are restricted to microorganisms and unicellular algae, for which 72 h is the cut-off point for the designation of acute/long-term studies.

Terrestrial environment

Information on the toxicological effects of 2-butoxyethanol on terrestrial organisms was not identified.

[1] Reproduced from CICAD 10, as no relevant new information was revealed in the literature searches in 2004.

Table A-1: Acute and long-term studies on toxicity to aquatic organisms.

Species	End-point[a]	Concentration (mg/l)	Reference
Freshwater			
Bacterium (*Pseudomonas putida*)	16-h LOEC (growth)	700	Bringmann & Kuhn, 1980a
Sewage sludge bacteria	16-h IC_{50}	>1000	Union Carbide, 1989
Protozoan (*Entosiphon sulcatum*)	72-h LOEC (growth)	91	Bringmann & Kuhn, 1980a
Protozoan (*Chilomonas paramecium*)	48-h EC_5 (growth)	911	Bringmann & Kuhn, 1980b
Protozoan (*Uronema parduczi*)	48-h EC_5 (growth)	463	Bringmann & Kuhn, 1980b
Cyanobacterium (*Microcystis aeruginosa*)	8-day LOEC (growth)	35	Bringmann & Kuhn, 1980a
Green alga (*Scenedesmus quadricaudata*)	7-day LOEC (growth)	900	Bringmann & Kuhn, 1980a
Green alga (*Selenastrum capricornutum*)	7-day NOEC	125	Dow, 1988
	7-day EC_{50}	>1000	
Water flea (*Daphnia magna*)	24-h LC_{50}	1720	Bringmann & Kuhn, 1977
	24-h LC_{50}	1698–1940	Bringmann & Kuhn, 1982
	24-h LC_{50}	5000	CMA, 1994
	48-h LC_{50}	835	Dow, 1979
Guppy (*Poecilia reticulata*)	7-day LC_{50}	982	Koenemann, 1981
Golden ide (*Leuciscus idus melanotus*)	48-h LC_{50}	165–186	Junke & Ludemann, 1978
	48-h LC_{50}	1880	CMA, 1994
Bluegill (*Lepomis macrochirus*)	96-h LC_{50}	1490	Dawson et al., 1977
Goldfish (*Carassius auratus*)	24-h LC_{50}	1700	Bridie, 1979
	24-h LC_{50}	1650	Verschueren, 1983
Fathead minnow (*Pimephales promelas*)	96-h LC_{50}	2137	Dow, 1979
Emerald shiner (*Notropus atherinoides*)	72-h LC_{50}	>500	Dill, 1995
Rainbow trout (*Oncorhynchus mykiss*)	96-h LC_{50}	>1000	Environment Canada, 1997c
Estuarine/marine			
Oyster (*Crassostrea virginica*)	96-h LC_{50}	89	USEPA, 1984
White shrimp (*Penaeus setiferus*)	96-h LC_{50}	130	OECD, 1997
Grass shrimp (*Palaemonetes pugio*)	96-h LC_{50}	5.4	Environment Canada, 1997
Brown shrimp (*Crangon crangon*)	48-h LC_{50}	600–1000	Verschueren, 1983
	96-h LC_{50}	550–950	
Brine shrimp (*Artemia salina*)	24-h LC_{50}	1000	Price et al., 1974
Inland silverside (*Menidia beryllina*)	96-h LC_{50}	1250	Dawson et al., 1977
Sheepshead minnow (*Cyprinodon variegatus*)	96-h LC_{50}	116	OECD, 1997

2-BUTOXYETHYL ACETATE

ICSC: 0839
November 2003

CAS #	**112-07-2**	**Butyl glycol acetate**
RTECS #	**KJ8925000**	**Ethylene glycol monobutyl ether acetate**
EC Annex 1 Index #	**607-038-00-2**	**2- Butoxyethanol acetate**
EC/EINECS #	**203-933-3**	**Butyl cellosolve acetate**
		$C_8H_{16}O_3$ / $C_4H_9OCH_2CH_2OOCCH_3$
		Molecular mass: 160.2

TYPES OF HAZARD / EXPOSURE	ACUTE HAZARDS / SYMPTOMS	PREVENTION	FIRST AID / FIRE FIGHTING
FIRE	Combustible.	NO open flames.	Powder, alcohol-resistant foam, water spray, carbon dioxide.
EXPLOSION	Above 71°C explosive vapour/air mixtures may be formed.	Above 71°C use a closed system, ventilation.	
EXPOSURE		**PREVENT GENERATION OF MISTS!**	
Inhalation	Cough. Headache. Dizziness. Drowsiness. Nausea.	Ventilation, local exhaust, or breathing protection.	Fresh air, rest. Refer for medical attention.
Skin	MAY BE ABSORBED! Redness. Dry skin.	Protective gloves. Protective clothing.	Remove contaminated clothes. Rinse and then wash skin with water and soap.
Eyes	Redness.	Safety goggles.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion	Burning sensation in the throat and chest. Vomiting. (Further see Inhalation).	Do not eat, drink, or smoke during work.	Rinse mouth. Give one or two glasses of water to drink. Do NOT induce vomiting. Refer for medical attention.

SPILLAGE DISPOSAL

Personal protection: filter respirator for organic gases and vapours adapted to the airborne concentration of the substance. Ventilation. Collect leaking liquid in sealable containers. Absorb remaining liquid in sand or inert absorbent and remove to safe place.

PACKAGING & LABELLING

EU Classification
Symbol: Xn
R: 20/21
S: (2-)24

EMERGENCY RESPONSE

NFPA Code: H 1; F 2; R 0;

STORAGE

Separated from strong oxidants, and strong bases. Cool. Keep in the dark.

IPCS
International Programme on Chemical Safety

WHO ILO UNEP

Prepared in the context of cooperation between the International Programme on Chemical Safety and the Commission of the European Communities

SEE IMPORTANT INFORMATION ON BACK

2-BUTOXYETHYL ACETATE

ICSC: 0839

IMPORTANT DATA

PHYSICAL STATE; APPEARANCE
COLOURLESS LIQUID , WITH CHARACTERISTIC ODOUR.

CHEMICAL DANGERS
The substance can presumably form explosive peroxides. Reacts with strong oxidants and strong bases, causing fire and explosion hazard.

OCCUPATIONAL EXPOSURE LIMITS
TLV: 20 ppm as TWA; A3; (ACGIH 2003).
MAK: (sum of concentrations in air of 2-butoxyethanol and 2-butoxyethyl acetate) 10 ppm, 66 mg/m³; Peak limitation category: I(2); skin absorption (H); Carcinogen category: 4; Pregnancy risk group: C; (DFG 2009).

ROUTES OF EXPOSURE
The substance can be absorbed into the body by inhalation of its vapour, through the skin and by ingestion.

EFFECTS OF SHORT-TERM EXPOSURE
The vapour is irritating to the eyes, the skin and the respiratory tract. The substance may cause effects on the central nervous system. Exposure far above the OEL may result in unconsciousness. The substance may cause effects on the blood , resulting in lesions of blood cells and kidney impairment.

EFFECTS OF LONG-TERM OR REPEATED EXPOSURE
The liquid defats the skin. The substance may have effects on the blood , resulting in anaemia and kidney impairment.

PHYSICAL PROPERTIES

Boiling point: 192°C
Melting point: -64°C
Relative density (water = 1): 0.94
Solubility in water: moderate (1.7 g/100 ml at 20°C)
Vapour pressure, Pa at 20°C: 31
Relative vapour density (air = 1): 5.5

Relative density of the vapour/air-mixture at 20°C (air = 1): 1.00
Flash point: 71°C c.c.
Auto-ignition temperature: 340°C
Explosive limits, vol% in air: 0.9 (93°C) - 8.5 (135°C)
Octanol/water partition coefficient as log Pow: 1.51

ENVIRONMENTAL DATA

The substance is harmful to aquatic organisms.

NOTES

Check for peroxides prior to distillation; eliminate if found. Card has been partially updated in April 2010: see Occupational Exposure Limits, Ingestion First Aid, Spillage Disposal.

ADDITIONAL INFORMATION

ETHYLENE GLYCOL MONOBUTYL ETHER

ICSC: 0059
May 2003

CAS #	**111-76-2**	**2-Butoxyethanol**
RTECS #	**KJ8575000**	**Monobutyl glycol ether**
UN #	**2810**	**Butyl oxitol**
EC Annex 1 Index #	**603-014-00-0**	**EGBE**
EC/EINECS #	**203-905-0**	**Butyl cellosolve**
		$C_6H_{14}O_2$ / $CH_3(CH_2)_2CH_2OCH_2CH_2OH$
		Molecular mass: 118.2

TYPES OF HAZARD / EXPOSURE	ACUTE HAZARDS / SYMPTOMS	PREVENTION	FIRST AID / FIRE FIGHTING
FIRE	Combustible.	NO open flames.	Powder, alcohol-resistant foam, water spray, carbon dioxide.
EXPLOSION	Above 60°C explosive vapour/air mixtures may be formed.	Above 60°C closed system, ventilation.	In case of fire: keep drums, etc., cool by spraying with water.
EXPOSURE		**PREVENT GENERATION OF MISTS!**	
Inhalation	Cough. Dizziness. Drowsiness. Headache. Nausea. Weakness.	Ventilation, local exhaust, or breathing protection.	Fresh air, rest. Refer for medical attention.
Skin	MAY BE ABSORBED! Dry skin. (Further see Inhalation).	Protective gloves. Protective clothing.	Remove contaminated clothes. Rinse skin with plenty of water or shower. Refer for medical attention.
Eyes	Redness. Pain. Blurred vision.	Safety goggles or eye protection in combination with breathing protection.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion	Abdominal pain. Diarrhoea. Nausea. Vomiting. (Further see Inhalation).	Do not eat, drink, or smoke during work.	Rinse mouth. Give one or two glasses of water to drink. Refer for medical attention.

SPILLAGE DISPOSAL

Personal protection: filter respirator for organic gases and vapours adapted to the airborne concentration of the substance. Collect leaking and spilled liquid in sealable containers as far as possible. Wash away remainder with plenty of water. Remove all ignition sources.

PACKAGING & LABELLING

Airtight. Do not transport with food and feedstuffs.
EU Classification
Symbol: Xn
R: 20/21/22-36/38
S: (2-)36/37-46
UN Classification
UN Hazard Class: 6.1
UN Pack Group: III

EMERGENCY RESPONSE

Transport Emergency Card: TEC (R)-61GT1-III
NFPA Code: H2; F2; R0

STORAGE

Separated from strong oxidants, food and feedstuffs.
Cool. Keep in the dark.

IPCS
International Programme on Chemical Safety

WHO UNEP

SEE IMPORTANT INFORMATION ON BACK

ETHYLENE GLYCOL MONOBUTYL ETHER

ICSC: 0059

IMPORTANT DATA

PHYSICAL STATE; APPEARANCE
COLOURLESS LIQUID , WITH CHARACTERISTIC ODOUR.

CHEMICAL DANGERS
The substance can form explosive peroxides. Reacts with strong oxidants causing fire and explosion hazard.

OCCUPATIONAL EXPOSURE LIMITS
TLV: (as TWA) 20 ppm; A3 (confirmed animal carcinogen with unknown relevance to humans); (ACGIH 2004).
MAK: (sum of concentrations in air of 2-butoxyethanol and 2-butoxyethyl acetate) 10 ppm, 49 mg/m³; Peak limitation category: I(2); skin absorption (H); Carcinogen category: 4; Pregnancy risk group: C; (DFG 2009).

ROUTES OF EXPOSURE
The substance can be absorbed into the body by inhalation and through the skin, and by ingestion.

INHALATION RISK
A harmful contamination of the air will be reached rather slowly on evaporation of this substance at 20°C.

EFFECTS OF SHORT-TERM EXPOSURE
The substance is irritating to the eyes, the skin and the respiratory tract. The substance may cause effects on the central nervous system, blood, kidneys and liver.

EFFECTS OF LONG-TERM OR REPEATED EXPOSURE
The liquid defats the skin.

PHYSICAL PROPERTIES

Boiling point: 171°C
Melting point: -75°C
Relative density (water = 1): 0.90
Solubility in water: miscible
Vapour pressure, kPa at 20°C: 0.10
Relative vapour density (air = 1): 4.1

Relative density of the vapour/air-mixture at 20°C (air = 1): 1.03
Flash point: 60°C c.c.
Auto-ignition temperature: 238°C
Explosive limits, vol% in air: 1.1 at 93°C-12.7 at 135°C
Octanol/water partition coefficient as log Pow: 0.830

ENVIRONMENTAL DATA

NOTES

Check for peroxides prior to distillation; eliminate if found. Card has been partly updated in October 2006: see sections Occupational Exposure Limits, Ingestion first aid. Card has been partially updated in April 2010: see Occupational Exposure Limits.

ADDITIONAL INFORMATION

RÉSUMÉ D'ORIENTATION

Ce CICAD[1] consacré au 2-butoxyéthanol est une mise à jour du CICAD publié en 1998 (IPCS, 1998) qui reposait sur des comptes rendus analytiques préparés aux Etats-Unis par le NIOSH (1990) et l'ATSDR (1996). Les points du CICAD portant sur la santé humaine ont été très largement révisés du fait que l'on dispose maintentant d'informations nouvelles et importantes sur la cancérogénicité et que l'on a analysé le mode d'action à l'origine des tumeurs observées dans les études en cause. Des données détaillées supplémentaires sur les possibilités d'exposition ont également été ajoutées comme point de départ pour la caractérisation du risque type.[2] C'est Toxicology Advice & Consulting Ltd qui a préparé la mise à jour en s'appuyant principalement sur une documentation rédigée dans le cadre du Programme canadien d'évaluation des substances prioritaires, en application de la *Loi canadienne sur la protection de l'environnement* (LCPE) (Environnement Canada & Santé Canada, 2002). Les évaluations des substances prioritaires effectuées en application de cette loi portent sur les effets que pourraient avoir ces produits sur la santé humaine en cas d'exposition indirecte dans l'environnement ainsi que sur l'environnement lui-même. Le document de base prend en compte les données répertoriées jusqu'à octobre 1999. Une analyse exhaustive de la littérature a été effectuée en février 2003 sur plusieurs bases de données en ligne à la recherche de références bibliographiques importantes publiées postérieurement à celles qui ont été prises en compte dans le document de base. L'appendice 2 donne des informations sur la nature de l'examen par des pairs et sur la disponibilité des sources documentaires. Des renseignements sur l'examen par des pairs du présent CICAD sont donnés à l'appendice 3. Ce CICAD a été approuvé en tant qu'évaluation internationale lors de la réunion du Comité d'évaluation finale qui s'est tenue à Hanoï (Viet Nam) du 28 septembre au 1er octobre 2004. La liste des participants à cette réunion figure l'appendice 4. Les fiches internationales sur la sécurité chimique du 2-butoxyéthanol (ICSC 0059) et de l'acétate de 2-butoxyéthyle (ICSC 0839), établies par le Programme international sur la sécurité chimique (IPCS, 2003, 2005), sont également reproduites dans le présent document.

[1] Pour la liste des acronymes et des abréviations utilisées dans le présent rapport, voir l'appendice 1.

[2] En dépit de différences mineures dans l'évaluation de l'impact environnemental entre les documents de base du CICAD 10 et ceux du présent CICAD, les résultats finals (c'est-à-dire la concentration sans effet prévisible) sont similaires; les parties du présent CICAD relatives à l'impact environnemental n'ont donc pas été révisées.

Le 2-butoxyéthanol (No CAS 111-76-2), se présente sous la forme d'un liquide incolore qui est miscible à l'eau et à la plupart des solvants organiques. On ne le connaît pas à l'état naturel.

Le 2-butoxyéthanol est très utilisé comme solvant dans les revêtements de surface, comme les laques à pulvériser, les laques à séchage rapide, les vernis divers, les dissolvants pour vernis et les peintures au latex. Il entre également dans la composition de produits pour le décapage des métaux et de produits d'entretien domestiques.

Des données limitées indiquent que l'exposition à ce composé dans l'air ambiant est de l'ordre du microgramme par m^3. L'exposition de la population générale au 2-butoxyéthanol se produit très probablement par inhalation ou absorption transcutanée lors de l'utilisation de produits qui en contiennent. La concentration du 2-butoxyéthanol dans l'atmosphère des lieux de travail est habituellement de d'ordre du milligramme par m^3.

En cas d'exposition par la voie respiratoire, orale ou cutanée, le 2-butoxyéthanol est rapidement absorbé. Il est métabolisé sous l'action des alcool- et aldéhyde-déshydrogénases, essentiellement en acide 2-butoxy-acétique (BAA), son principal métabolite, avec formation de 2-butoxyacétaldéhyde (BALD) comme intermédiaire, mais il existe d'autres voies métaboliques.

Le 2-butoxyéthanol présente une toxicité aiguë modérée et il est irritant pour la peau et les yeux; il ne produit pas de sensibilisation cutanée. Le principal effet du 2-butoxyéthanol et de l'acide 2-butoxyacétique est leur hématotoxicité. Les études in vitro montrent que les érythrocytes humains ne sont pas aussi sensibles que ceux du rat à l'effet hémolytique du 2-butoxyéthanol et du BAA, ce dernier étant celui dont le pouvoir hémolytique est le plus marqué. Chez le rat, on observe des effets indésirables sur le système nerveux central, le rein et le foie à des concentrations supérieures à celles auxquelles se produisent les effets hémolytiques. Chez l'animal, des effets nocifs sur la reproduction et le développement n'ont été observés qu'aux doses toxiques pour la mère. Les études de longue durée effectuées sur des animaux de laboratoire ont permis de relever quelques signes de cancérogénicité chez la souris (augmentation de l'incidence des hémangiosarcomes du foie ou des carcinomes hépatocellulaires chez les mâles et de celle des papillomes ou des carcinomes spino-cellulaires au niveau de l'aire glandulaire de l'estomac chez les femelles) et chez le rat - mais ambigus dans ce cas (augmentation marginale de l'incidence des phéochromocytomes bénins ou malins de la surrénale). Les tests de mutagénicité in vitro donnent des résultats irréguliers et le 2-butoxyéthanol ne se révèle pas génotoxique in vivo.

Selon les données limitées que l'on peut tirer de divers rapports médicaux et d'une étude clinique, des effets aigus similaires - notamment une hémolyse et des effets sur le système nerveux central - s'observent chez l'Homme et chez le rat en cas d'exposition au 2-butoxyéthanol, encore qu'à concentration beaucoup plus élevée chez l'Homme que chez le rat. On a établi à 11 mg/m^3 la valeur de la concentration tolérable (CT) pour les effets hémolytiques, en utilisant des facteurs de correction chimiospécifiques et en s'appuyant sur les concentrations de référence. On a également établi une CT de 0,04 mg/m^3 pour les lésions de l'aire glandulaire gastrique de la souris.

Au Canada, la concentration de 2-butoxyéthanol dans l'air ambiant est inférieure à la CT pour les effets hémolytiques ou les lésions de l'aire glandulaire gastrique. Ainsi, la concentration moyenne de ce composé dans l'air extérieur indiquée dans une étude d'exposition au sein de divers milieux était de 8,4 µg/m^3, avec une valeur maximum de 243 µg/m^3. Toutefois, lors de l'utilisation de produits contenant ce composé, l'exposition au 2-butoxyéthanol pourrait dépasser la valeur de ces CT, du moins d'après les données limitées que l'on possède au sujet de l'émission de 2-butoxyéthanol par les produits existants. Selon des estimations prudentes, la concentration dans l'air intérieur du 2-butoxyéthanol émis par certains produits ménagers courants pourrait aller jusqu'à 62 mg/m^3.

Sur la base d'hypothèses extrêmement prudentes, la concentration maximale prédite du 2-butoxyéthanol dans les eaux superficielles à proximité immédiate de rejets d'effluents pourrrait dans certains cas dépasser la concentration prédite sans effet toxique (PNEC). Toutefois, des hypothèses plus réalistes reposant sur les données disponibles indiquent que le risque pour les organismes aquatiques est faible. En raison de la brève demi-vie du 2-butoxyéthanol dans l'atmosphère, on estime que les concentrations mesurées ou prédites de ce composé dans l'air n'ont aucun impact sur l'environnement.

RESUMEN DE ORIENTACIÓN

Este CICAD[1] sobre el 2-butoxietanol es una actualización del CICAD publicado en 1998 (IPCS, 1998), que se basó en los exámenes preparados por el NIOSH (1990) y la ATSDR (1996) de los Estados Unidos. Los aspectos relativos a la salud humana de este CICAD han sido objeto de una revisión exhaustiva, porque se dispone de nueva información importante sobre la carcinogenicidad y de una evaluación del mecanismo de acción en la formación de tumores observado en estos estudios. Se ha incorporado asimismo información detallada adicional sobre la exposición potencial como base para una caracterización del riesgo de muestra.[2] La actualización fue preparada por Toxicology Advice & Consulting Ltd del Reino Unido y se basa fundamentalmente en la documentación preparada como parte del Programa Canadiense de Sustancias Prioritarias en el marco de la CEPA (Departamento de Medio Ambiente del Canadá & Departamento de Sanidad del Canadá, 2002). El objetivo de las evaluaciones sobre las sustancias prioritarias previsto en la CEPA es evaluar los efectos potenciales de la exposición indirecta en el medio ambiente general para la salud humana, así como los efectos en el medio ambiente. En el documento original se examinaron los datos identificados hasta octubre de 1999. En febrero de 2003 se realizó una búsqueda bibliográfica amplia de varias bases de datos en línea para localizar cualquier referencia importante publicada después de las incorporadas al documento original. La información sobre el carácter del examen colegiado y la disponibilidad del documento original se presenta en el apéndice 2. La información sobre el examen colegiado de este CICAD figura en el apéndice 3. Este CICAD se aprobó como evaluación internacional en una reunión de la Junta de Evaluación Final, celebrada en Hanoi (Viet Nam) del 28 de septiembre al 1º de octubre de 2004. La lista de participantes en esta reunión aparece en el apéndice 4. También se han reproducido en el presente documento las fichas internacionales de seguridad química para el 2-butoxietanol (ICSC 0059) y el 2-butoxietilacetato (ICSC 0839), preparadas por el IPCS (2003, 2005).

El 2-butoxietanol (CAS Nº 111-76-2) es un líquido incoloro miscible en agua y en la mayor parte de los disolventes orgánicos. No se ha informado de que se encuentre como producto natural.

[1] La lista de siglas y abreviaturas utilizadas en el presente informe figura en el apéndice 1.

[2] Si bien entre los documentos originales del CICAD 10 y el presente CICAD había diferencias insignificantes en las evaluaciones del medio ambiente, los resultados finales (es decir, las PNEC) son semejantes; así pues, en este CICAD no se revisaron las secciones relativas al medio ambiente.

El 2-butoxietanol se utiliza ampliamente como disolvente en revestimientos de superficie, como lacas nebulizadas, lacas de secado rápido, esmaltes, barnices, eliminadores de barnices y pintura de látex. También se utiliza en productos limpiadores de metales y domésticos.

Basándose en datos limitados, puede indicarse que la exposición ambiental en el aire es en general del orden de $\mu g/m^3$. La exposición indirecta de la población general al 2-butoxietanol se produce muy probablemente por inhalación y absorción cutánea durante el empleo de productos que contienen la sustancia química. Las concentraciones de 2-butoxietanol en el aire de entornos laborales suelen ser del orden de mg/m^3.

El 2-butoxietanol se absorbe fácilmente después de la exposición por inhalación o por las vías oral y cutánea. El producto químico se metaboliza principalmente por acción de la deshidrogenasa de alcoholes y aldehídos, con formación de 2-butoxiacetaldehído y de ácido 2-butoxiacético, el principal metabolito, aunque también se han identificado otras vías metabólicas.

El 2-butoxietanol presenta una toxicidad aguda moderada y es irritante para los ojos y la piel; no es un sensibilizador cutáneo. El principal efecto del 2-butoxietanol y de su metabolito, el ácido 2-butoxiacético, es la hematotoxicidad. Los estudios *in vitro* muestran que los eritrocitos humanos no son tan sensibles como los de rata a los efectos hemolíticos del 2-butoxietanol y del ácido 2-butoxiacético y que este último es el agente hemolítico más potente. En la rata, los efectos adversos sobre el sistema nervioso central, los riñones y el hígado se producen con concentraciones de exposición más altas que las que dan lugar a efectos hemolíticos. En animales sólo se han observado efectos adversos sobre la reproducción y el desarrollo con dosis tóxicas para la madre. En estudios prolongados con animales de laboratorio se obtuvieron algunas pruebas de carcinogenicidad en ratones (mayor incidencia de hemangiosarcomas de hígado o de carcinomas hepatocelulares en machos y de papilomas en células escamosas o carcinomas del antro cardíaco en hembras) y pruebas equívocas en ratas hembras (un aumento marginal de la incidencia de feocromocitomas benignos o malignos de la glándula adrenal). Los resultados de las pruebas *in vitro* para la mutagenicidad del 2-butoxietanol fueron contradictorios; el 2-butoxietanol no fue genotóxico *in vivo*.

Basándose en datos limitados procedentes de estudios de casos y de un estudio clínico, se han señalado efectos agudos análogos (incluidos efectos hemolíticos y sobre el sistema nervioso central) en personas y en ratas expuestas al 2-butoxietanol, aunque los efectos se observaron con concentraciones de exposición mucho más altas en personas que en ratas. Se ha establecido una concentración tolerable, utilizando los factores de ajuste de sustancias químicas específicas, para los efectos hemolíticos de 11 mg/m^3, tomando como base las concentraciones de referencia. También se estableció una concentración tolerable de 0,04 mg/m^3 para las lesiones en el antro cardíaco de ratones.

Los niveles de 2-butoxietanol en el aire ambiente del Canadá son inferiores a la concentración tolerable obtenida a partir de los efectos en la sangre o el antro cardíaco. Por ejemplo, la concentración media de 2-butoxietanol en el aire exterior notificada en un estudio de exposición en diversos medios fue de 8,4 $\mu g/m^3$, con un máximo de 243 $\mu g/m^3$. Sin embargo, basándose en datos limitados sobre emisiones de productos actualmente disponibles, la exposición al 2-butoxietanol durante la utilización de estos productos podría potencialmente superar las concentraciones tolerables. Estimaciones prudentes de concentraciones breves en el aire de espacios cerrados debidas a las emisiones de algunos productos domésticos comunes ascendieron hasta 62 mg/m^3.

Sobre la base de supuestos extremadamente prudentes, las concentraciones máximas previstas de 2-butoxietanol en aguas superficiales situadas cerca de corrientes de efluentes pueden, en algunos casos, exceder de las concentraciones previstas sin efectos. Sin embargo, supuestos más realistas basados en los datos disponibles permiten indicar que el riesgo para los seres acuáticos es escaso. Debido a la corta semivida del 2-butoxietanol en la atmósfera, las concentraciones medidas o previstas de este producto químico en el aire se consideran exentas de importancia ambiental.

APPENDIX A

STRUCTURE–ACTIVITY RELATIONSHIP (SAR) ANALYSIS OF 2-ALKOXYETHANOLS

First draft prepared by
Patricia Ruiz, Hana Pohl, Moiz Mumtaz, Jewell Wilson,
Mike Fay, Dennis Jones, Eugene Demchuk,
Sam Keith, Hugh Hansen and Christopher De Rosa,
Agency for Toxic Substances and Disease Registry

A1. COMPUTATIONAL TOXICOLOGY

In recent years, computational toxicology (CT) has been used as a predictive tool to fill information gaps in toxicological databases used for the hazard and risk characterization of chemicals (El-Masri et al., 2002). This information has been especially used in priority setting for toxicity testing.

One such CT tool is computer-assisted structure–activity relationship (SAR)-based toxicity assessment (Richard, 1998). Two general approaches are used for SAR analysis. The first is a "top-down" empirical approach that relies on statistically derived algorithms for extracting useful generalizations from existing data, usually a large (training) data set. Examples of this approach include TOPKAT, CASE and MULTICASE (Klopman, 1984; Gombar et al., 1995; Enslein et al., 1997; Enslein, 1998; Cronin et al., 2003; Klopman et al., 2004; Patlewicz et al., 2007). The second approach is an expert system– or knowledge-based approach that attempts to extend generalizations from individual chemicals to entire chemical classes based on prior knowledge, heuristics, expert judgement and chemical and biological mechanism considerations. Examples include DEREK and OncoLogic (Sanderson & Earnshaw, 1991).

A2. STRUCTURE–ACTIVITY RELATIONSHIP (SAR) MODELLING

The building of any computer-assisted toxicity assessment model or method begins with collecting results from previously completed experimental studies and bioassays. In order to obtain a meaningful SAR assessment, bioassay data generated under uniform conditions must be used to develop the model. This is achieved through careful review and organization of the data, identifying differences in chemicals used, bioassays, test animal species, and exposure routes and durations. A model thus developed is limited in its ability to assess only those types of bioassay results that were used in the development of the model. Another important limitation is the availability of consistent and unequivocal study results on different end-points for chemicals representing different chemical structures.

TOPKAT 6.2 software (Accelrys, 2004) is one such computer-assisted SAR tool. This allows the prediction of a range of inherent properties of a chemical, including its physical/chemical properties, its disposition within a biological system and a range of toxicological end-points based solely on the chemical structure. This software has modules designed to predict carcinogenicity (both sex and species specific), mutagenicity, developmental toxicity, chronic adverse effect levels, and median lethal dose (LD_{50}), median lethal concentration (LC_{50}) and median effective concentration (EC_{50}) values.

A2.1 Structure descriptors

Models for assessing toxicity solely from molecular structure are based on information-rich structure descriptors that quantify transport, bulk and electronic attributes of a chemical structure. These descriptors have been reported to capture processes leading to the toxic responses of chemicals (Kier, 1986; Gombar & Jain, 1987; Gombar & Enslein, 1990; Hall et al., 1991). A number of theoretically calculated and experimentally measured property values (Hansch & Leo, 1995) have been employed to numerically encode these structural features, including the theoretically calculated descriptors for three-dimensional molecular geometry or two-dimensional molecular topology (Gombar & Enslein, 1990), as described below.

Electro-topological state values (E-values) encode information about the electron content (valence, sigma, pi and lone-pair), topology and environment of an atom, or a group of atoms, in a molecule. An E-value accounts for the effects of both intrinsic and environmental features, and it changes even with subtle variations in the structure (Hall et al., 1991). The size-corrected E-values computed from a rescaled count of valence electrons are used for quantification of molecular bulk (Hall et al., 1991).

Molecular shape and symmetry also influence molecular transport. Therefore, topological shape descriptors (Kier, 1986; Gombar & Jain, 1987) as well as indices of molecular symmetry (Gombar, 1991) have also been included for effective quantification of molecular shape.

These descriptors, based on the principles of linear free energy relationships and cross-validated quantitative structure–activity relationships (QSARs), contribute to the development of robust models and associated databases (Gombar & Enslein, 1990). Unique to the TOPKAT system are algorithms to evaluate whether a given chemical is within the optimum prediction space (OPS) of the model as well as methods to assign confidence to the calculated toxicity (Enslein et al., 1994, 1997; Enslein, 1998).

A2.2 Model development

A model is statistically tested for robustness and validated before it is used for predictive purposes (see Figure A1; Enslein et al., 1994). The development of the discriminant function starts with a frequency check of all the structural descriptors (shape indices, symmetry

indices, counts, E-values and size-corrected E-values). Any variables having values for fewer than three chemicals are excluded as predictor variables. In order to reduce problems due to possible co-linearity of variables, pairwise correlations of these variables are examined. If two variables have a correlation coefficient of 0.9 or higher, only one variable is retained in the descriptor set. To select the variables that have the greatest power to distinguish between the two outcome groups, linear discriminant analysis is employed. The ensuing preliminary discriminant function is then analysed by multiple linear regression analysis. First, influential cases are identified—i.e. cases whose elimination would significantly affect the discriminant function coefficients. For influential cases, the compound is dropped from the model if the variable is significant; if the variable is not significant, the variable is dropped. Every time a compound is dropped, the variables are rechecked for frequency (≥3). Then, the surviving set of compounds is checked for outliers (≥2.5 standard deviations [SD]). The process is iterated until no further influential cases or outliers are identified; a tentative discriminant function (QSAR model) is reached; this is then validated (Enslein et al., 1994).

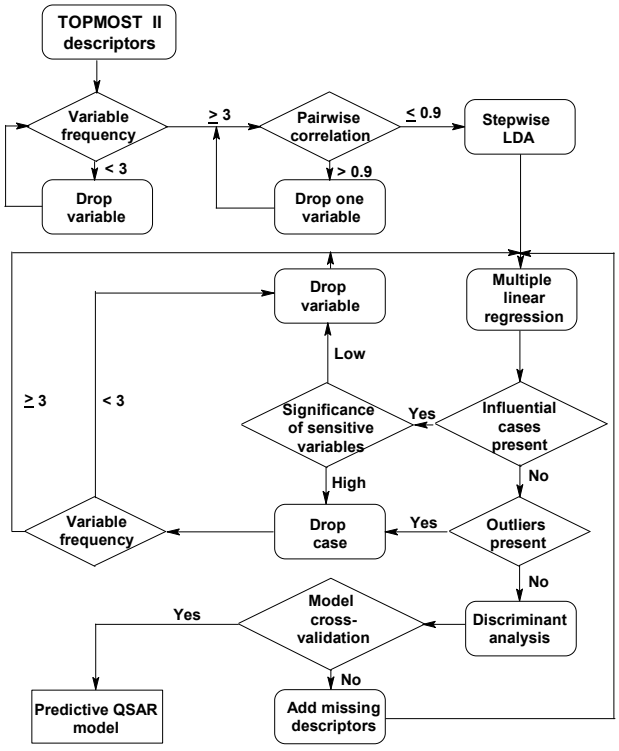


Figure A1. Steps involved in developing TOPKAT QSAR models (Enslein et al., 1994)

The validation is performed using the original database by 1) "resubstitution" or 2) "cross-validation", also called "jack-knife classification". In resubstitution, the compounds originally in the learning data set are analysed using the developed model, and the proportion of correct and incorrect predictions is calculated. The process is essentially a circular argument, but it has been reported that the error from this procedure is not significantly different from that obtained from an independent validation, provided that 1) a no-decision zone is defined, 2) the two outcome groups are sufficiently separated and 3) the group sizes are large. In the cross-validation, each compound in turn is evaluated using a discriminant function, from the development of which this compound was withheld. The developers of the model consider the cross-validation to be satisfactory if 1) not many compounds are classified as indeterminate, 2) the difference in the number of misclassifications in resubstitution and cross-validation is not large and 3) the misclassified compounds do not have common structural features (Enslein et al., 1994).

A2.3 Defining optimum prediction space (OPS)

Any model, TOPKAT included, is limited by the chemical compounds available for use in the training data set. In addition to predicting the specific outcome queried, TOPKAT also analyses whether the chemical studied can be reliably analysed—in other words, are there enough similar compounds in the training data set, i.e. is the query model within the multivariate space called the OPS (Enslein et al., 1997)? Toxicity of chemicals within and near the periphery of this space can be assessed using the model. It is important to note that just because a chemical is inside the OPS does not mean that the calculated value of the dependent variable for that chemical will have concordance with the experimental value. All it implies is that the model is applicable to this chemical, and the probability of concordance between the calculated and the actual values is as high as it is for the training set of chemicals on which the model is based.

A2.4 Application of the model

In the application of the model for a specific chemical compound, the input datum is the chemical formula in the simplified molecular input linear entry system (SMILES) (Weininger, 1988). The model first checks if the compound is in the training set, and, if so, gives the input data as results. It then determines if the compound is within the OPS or in its vicinity. If this is the case, for categorical end-points (mutagenicity, carcinogenicity, developmental toxicity, dermal sensitization), the model produces the probability of the query end-point, between 0 and 1. The results are interpreted as negative if the probability is less than 0.3 and positive if the probability is greater than or equal to 0.7. Values in the range 0.3–0.7 are indeterminate.

A2.5 TOPKAT module protocols

A2.5.1 Mutagenicity module

The Ames mutagenicity module was developed from compounds assayed according to the United States Environmental Protection Agency (USEPA) GeneTox protocol (Enslein et al., 1994). In this protocol, a chemical is tested against five strains of *Salmonella typhimurium*—namely, TA98, TA100, TA1535, TA1537 and TA1538—using the histidine reversion assay. Tests are performed both with and without S9 activation. A chemical is labelled a mutagen if a positive response is observed in one or more strains, with or without S9 activation; this positive response is defined as a significant increase in the number of reversions compared with background reversions. A chemical is a non-mutagen if there is no significant increase in the number of reversions compared with background reversions in any of the five bacterial strains, with or without S9 activation (Zeiger et al., 1996).

In a validation study of 1265 chemicals from different mutagenicity databases, 1213 were suitable for modelling (Enslein et al., 1994). Of these, 35 were excluded because of equivocal results in the mutagenicity assays, 17 because descriptors could not be generated (organometallics, polymers, cuboids, etc.) and 130 as influentials/outliers. The cross-validation of the results is presented in Table A1.

In a study that aimed at independent and anonymous modelling, the chemical structures of 100 chemicals were sent to the TOPKAT operators for a mutagenicity prediction (Zeiger et al., 1996). TOPKAT could not be applied to 26 chemicals, and for 13, the result was indeterminate. Of the remaining 61, mutagens were correctly identified in 71%, and non-mutagens in 76%.

In a study on the predictive power of TOPKAT and DEREK (Cariello et al., 2002), the concordance of the predicted mutagenicity was compared with actual Ames test data for 414 chemicals studied over 15 years in a pharmaceutical company. Of these, 332 were non-mutagenic and 82 mutagenic. Of the 414 chemicals, 5 could not be processed by the model, 96 were outside the OPS, and 10 compounds gave an indeterminate result (probability between 0.3 and 0.7); all these were excluded from the analysis. This left 303 compounds in the analysis, out of which 250 were non-mutagenic and 53 mutagenic. The performance of TOPKAT in this database is depicted in Table A2.

A2.5.2 Carcinogenicity module

The carcinogenicity module is composed of four species/sex combinations—namely, male or female, F344 rats or B6C3F1 mice (Enslein et al., 1997). These models are derived from studies selected after critical review of technical reports on 366 rodent carcinogenicity studies conducted by the United States National Cancer Institute (NCI) and the United States National Toxicology Program (NTP) using oral (diet) administration. The training set compounds are classified as carcinogens (NTP "clear evidence" or "some evidence") or non-carcinogens ("no evidence"). The cross-validation data by the model developer are reproduced in Table A3.

Prival (2001) assessed the performance of TOPKAT as a predictor of carcinogenicity using NTP studies not included in the TOPKAT training data set (mostly studies performed after the model had been developed). Chemicals that gave equivocal results in the bioassay as well as those that fell outside the OPS were excluded; for comparative reasons, studies using inhalation and dermal exposure routes were also included. The results of this independent validation are given in Table A4; the results for male and female rats and male and female mice are pooled.

A2.5.3 Developmental toxicity potential module

The developmental toxicity potential module (Gombar et al., 1995) is composed of three models for three different groups of organic chemicals: "heteroaromatics" (any compound containing one or more heteroaromatic rings), "carboaromatics" (any compound containing one or more aromatic rings but no heteroaromatic rings) and "aliphatics" (all other organic chemicals). For the development of these models, 5559 open literature citations were analysed. Out of 1238 oral studies in rats, 374 studies were retained for the model development. Two types of studies were removed from the database prior to further evaluation: single-dose studies in which developmental toxicity as well as maternal toxicity were observed at that dose, and studies in which neither developmental nor maternal toxicity was observed at the highest dose; exclusion of these studies left 273 studies that were used finally for the model development.

Developmental toxicity included reduced fetal growth, fetal death, resorptions, abnormal brain, cleft palate, skeletal abnormalities, limb defects, external malformations, haemorrhage, runting and visceral defects.

Studies in which no developmental toxicity was observed even at maternally toxic levels were scored as negative for developmental toxicity. Studies in which 1) strict concordance between developmental toxicity and maternal toxicity (i.e. no developmental toxicity or maternal toxicity at one dose, and both developmental toxicity and maternal toxicity at a higher dose) was observed, 2) developmental toxicity was observed at the dose lower than that at which maternal toxicity was

Table A1: Cross-validation of mutagenicity analysis of 1265 chemicals.[a]

(a) Ames test result

		Predicted class in cross-validation test		
	Total number of chemicals	**Mutagen**	**Indeterminate**	**Non-mutagen**
Mutagen	669	648	7	14
Non-mutagen	414	5	1	408

(b) Distribution of chemicals

	N	**%**
Number of compounds in database	1265	
Number suitable for modelling	1213	
Number included in training set	1083	
Mutagens correctly identified	648	96.9
Non-mutagens correctly identified	408	99.3

[a] From Enslein et al. (1994).

Table A2: Performance of TOPKAT mutagenicity model.[a]

	TOPKAT mutagenic	**TOPKAT non-mutagenic**
Number Ames positive	21	32
Number Ames negative	49	201
Sensitivity (%)	40	
Specificity (%)	80	
Positive predictivity (%)	30	
Negative predictivity (%)	86	
Concordance (%)	73	

[a] From Cariello et al. (2002). For definitions of sensitivity, specificity, positive predictivity, negative predictivity and concordance, see Table A4.

Table A3: The cross-validation of TOPKAT carcinogenicity prediction.[a]

Species, sex	**Number of compounds**	**Carcinogens correctly identified (%)**	**Non-carcinogens correctly identified (%)**	**Indeterminate, *n***
Rat, male	202	82	82	11
Rat, female	165	91	93	1
Mouse, male	210	90	94	1
Mouse, female	238	88	87	5

[a] From Accelrys (2004).

Table A4: Independent validation of the TOPKAT carcinogenicity model.[a,b,c]

	Oral	**Oral + inhalation**	**Oral + inhalation + skin**
Sensitivity	0.18	0.33	0.31
Specificity	0.80	0.78	0.80
Positive predictivity	0.45	0.64	0.63
Negative predictivity	0.51	0.49	0.51
Concordance	0.50	0.53	0.54

[a] From Prival (2001).

[b] The sensitivity of TOPKAT was calculated as the proportion of NTP positive findings of carcinogenicity that were correctly predicted by TOPKAT (true positives / (true positives + false negatives)). Specificity is the proportion of NTP non-carcinogen results predicted by TOPKAT to be negative (true negatives / (true negatives + false positives)). Positive predictivity is the proportion of results predicted by TOPKAT to be positive for carcinogenicity that were reported by NTP to be positive (true positives / (true positives + false positives)). The proportion of negative TOPKAT predictions that were reported by the NTP as negative results (true negatives / (true negatives + false negatives)) is the negative predictivity. The overall fraction of NTP results that were correctly predicted by TOPKAT is the concordance.

[c] For classification as a non-carcinogen, the probability <30% was used, and for carcinogenicity, ≥70%. Excludes data found outside OPS by TOPKAT.

observed and 3) studies in which developmental toxicity was observed at least two dose levels below that which produced maternal toxicity were considered as indicating developmental toxicity.

The results of the cross-validation of the model are given in Table A5.

A2.5.4 Skin sensitization module

The skin sensitization module (Enslein et al., 1997) is composed of two models. The first separates non-sensitizers from sensitizers. Sensitizers are subsequently analysed in the second model in order to separate weak or moderate sensitizers from strong sensitizers. Each model comprises two submodels that are applicable to a specific class of chemicals: "aromatics" (organic chemicals containing more than one aromatic ring) and "aliphatics and single benzenes" (organic chemicals containing fewer than two aromatic rings). Guinea-pig maximization test assay data from 335 studies identified from published literature were used to develop these models.

When data on the per cent positive results were available, they were used to assign data to four classes as defined by Barratt et al. (1994) (Table A6). For those chemicals for which only the Magnusson & Kligman (1969) classes were available, Classes I and II were assigned to weak, Class III to moderate and Classes IV and V to strong. Owing to the fact that there were insufficient data for model development purposes in the weak and moderate groups, these two were combined into a single class.

Data were also screened for consistency and, in some cases, harmonized when conflicting information existed for a given compound in different sources.

The identification of sensitizers and non-sensitizers is performed in the TOPKAT standard fashion—that is, compounds with a probability greater than or equal to 0.7 are considered sensitizers, and compounds with a probability below 0.3, non-sensitizers. Also, in the separation of the weak/moderate and strong sensitizers model, a probability of 0.7 or more indicates a strong sensitizer, and a probability below 0.3 indicates a weak or moderate sensitizer. Probability values between 0.3 and 0.7 refer to an indeterminate region.

The results of the cross-validation accuracy of the two pairs of classes for three groups of chemicals are given in Table A7 (Enslein et al., 1997; Accelrys, 2004).

In a subset of 25 compounds not included in the training set, Enslein et al. (1997) noted that the specificity of the model was 92%, and the sensitivity, 83% (excluding indeterminates).

The accuracy of the TOPKAT (version 6.2) sensitization prediction has been analysed in a database of 211 chemicals that had been assessed for dermal sensitization using the local lymph node assay (LLNA) (Patlewicz et al., 2007). Of the 211 chemicals, 105 could be analysed, and 106 were excluded because they could not be analysed by the model, were outside the OPS or gave indeterminate results. The results for the compounds that could be analysed are presented in Table A8.

A3. RESULTS OF SAR ANALYSIS OF 2-ALKOXYETHANOLS

SAR analysis was used to assess the following toxicity end-points for the 2-alkoxyethanols: mutagenicity, carcinogenicity, developmental toxicity and dermal sensitization. This was performed for both the parent 2-alkoxyethanol compounds as well as their metabolites.

For ease of interpretation of results, the structure of these 2-alkoxyethanols can be represented by two distinct toxicophore areas (Figure A2):

- R_1 representing the alkyl ether group (the methoxy-, ethoxy-, propoxy- or butoxy- group); and
- R_2 representing the ethyl acetate and alcohol groups and their metabolites (acetaldehyde, acetic acid).

Model assessments for the above four end-points are shown in Tables A9 through A11.

A3.1 Mutagenicity

The model predicted that the 2-alkoxyethyl acetates, 2-alkoxyethanols and their metabolites are negative for mutagenicity (Tables A9 and A10).

A3.2 Carcinogenicity

The model predicted that 2-methoxyethyl acetate, 2-methoxyethanol and their oxidized metabolites are carcinogenic in male and female rats; for female mice, the prediction is carcinogenic or indeterminate. The other 2-alkoxyethyl acetates were predicted to be carcinogenic in male rats, whereas carcinogenicity was predicted for all 2-alkoxyacetic acids in female rats. 2-Propoxyacetaldehyde and 2-butoxyacetaldehyde were predicted to be carcinogenic in male rats (Tables A10 and A11).

Table A5: Cross-validation of the TOPKAT model for developmental toxicity.[a]

	Aliphatics	Carboaromatics	Heteroaromatics
Number toxic to development	44	53	41
Number not toxic to development	35	39	49
Sensitivity (%)	88.6	87.0	86.1
Specificity (%)	88.6	97.4	86.0
Concordance (%)	88.6	91.4	86.0
Indeterminate (%)	2.5	2.2	5.5

[a] From Gombar et al. (1995). For definitions of sensitivity, specificity, positive predictivity, negative predictivity and concordance, see Table A4.

Table A6: TOPKAT grouping of guinea-pig maximization test data into sensitization classes.

Magnusson & Kligman (1969)		Barratt et al. (1994)	
Category	**% animals positive**	**Category**	**% animals positive**
Non	0	Non	
I	1–8	Weak	1–30
II	9–28		
III	29–64	Moderate	30–70
IV	65–80	Strong	70–100
V	81–100		

Table A7: Cross-validation of the TOPKAT dermal sensitization model.[a]

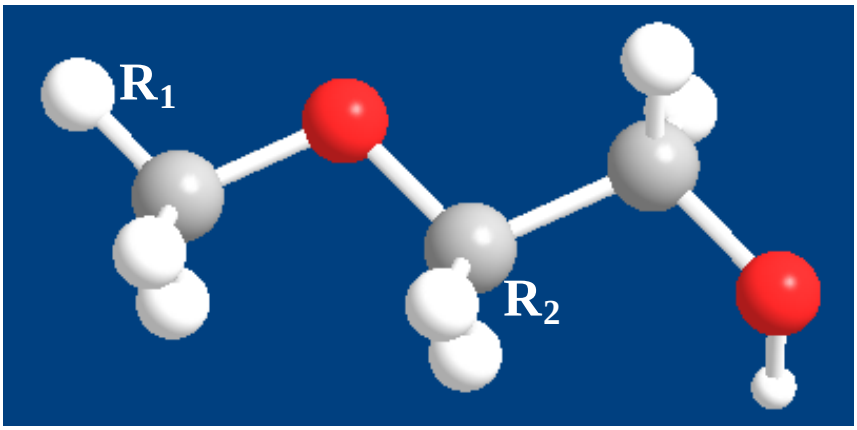
	Number of compounds	Specificity (%)	Sensitivity (%)	Indeterminate (%)
Non-sensitizers versus sensitizers				
Aliphatics and single benzenes	252	91	93	3
Aromatics (excluding single benzenes)	75	81	95	1
Weak/moderate sensitizers versus strong sensitizers				
Aliphatics and single benzenes	158	89	85	6
Aromatics (excluding single benzenes)	59	90	92	3

[a] From Accelrys (2004).

Table A8: Performance of the TOPKAT dermal sensitization module in a database of chemicals tested for dermal sensitization by the local lymph node assay.[a]

	TOPKAT sensitizer	TOPKAT non-sensitizer
Number LLNA positive	65	18
Number LLNA negative	12	10
Sensitivity (%)	78	
Specificity (%)	46	
Positive predictivity (%)	84	
Negative predictivity (%)	36	
Concordance (%)	71	

[a] From Patlewicz et al. (2007). For definitions of sensitivity, specificity, positive predictivity, negative predictivity and concordance, see Table A4.



R_1 (alkoxy) moieties		R_2 (ethanol) moieties	
$-OCH_3$	2-Methoxy-	$-CH_2CH_2OCOCH_3$	Ethyl acetate group
$-OCH_2CH_3$	2-Ethoxy-	$-CH_2CH_2OH$	Ethanol group
$-OCH_2CH_2CH_3$	2-Propoxy-	$-CH_2COH$	Acetaldehyde group
$-OCH_2CH_2CH_2CH_3$	2-Butoxy-	$-CH_2COOH$	Acetic acid group

Figure A2. Toxicophore elements for the 2-alkoxyethyl acetates, 2-alkoxyethanols and their metabolites for QSAR analysis.

A3.3 Developmental toxicity

The model predicted that 2-methoxyethyl acetate, but not the other acetates, are developmental toxicants. Of the 2-alkoxyethanols, all except 2-butoxyethanol, and of the 2-alkoxyacetic acids, all except 2-butoxyacetic acid, were predicted to be developmental toxicants. None of the aldehyde derivatives were predicted to be developmental toxicants (Tables A10 and A11).

A3.4 Skin sensitization

The skin sensitization model predicted that, of the compounds studied, 2-alkoxyacetaldehydes were skin sensitizers (Table A10).

A3.5 The model and observed data

Although the TOPKAT predictions are in general well in line with the experimental data, there are some points to notice.

The models for carcinogenicity and developmental toxicity potential were developed and validated using the oral administration route. This may lead to inaccuracies in the predictions for 2-alkoxyethanols and their acetates, as the routes of exposure are mostly inhalation (or, for humans, dermal).

The models predict in some instances different results for a 2-alkoxyethyl acetate and the corresponding alkoxyethanol. As the former is rapidly and practically quantitatively metabolized to the latter, this is unlikely to be true, although little experimental evidence is available to prove or disprove this. The most conspicuous such occurrence is the predicted lack of developmental toxicity of 2-propoxyethyl acetate and developmental toxicity of 2-propoxyethanol. There is a similar difference in the predicted carcinogenicity in male rats for 2-ethoxyethanol/acetate, 2-propoxyethanol/acetate and 2-butoxyethanol/acetate (although in the opposite direction).

Further down in the metabolic scheme of 2-alkoxyethanols, the model predicts that the acetic acid metabolites of 2-methoxyethanol, 2-ethoxyethanol and 2-propoxyethanol are developmental toxicants, but the short-lived aldehyde metabolite, which is oxidized to the acid, is not.

The model predicts that 2-methoxyethanol and 2-ethoxyethanol are developmental toxicants and that 2-butoxyethanol is not; this is all well in line with the experimental data. This is, however, not a strong argument for the general validity of the model, as these data were all in the input data to the model.

One inhalation study with 2-propoxyethyl acetate, another with 2-propoxyethanol in rats and one with 2-propoxyethanol in rabbits as well as one oral study in mice with 2-propoxyethanol did not demonstrate developmental toxicity except skeletal variations at maternally toxic doses, but the model predicted that 2-propoxyethanol is a developmental toxicant. However, the model has been developed and validated using oral

Table A9: Comparison between experimental and calculated mutagenicity in bacteria in vitro.

Alkoxyethanol	Experimental data	Calculated data
2-Methoxyethanol	−	−
2-Methoxyacetaldehyde	+/−[a]	−
2-Methoxyacetic acid	−	−
2-Ethoxyethyl acetate	−	−
2-Ethoxyethanol	−	−
2-Ethoxyacetaldehyde	−	−
2-Ethoxyacetic acid	−	−
2-Propoxyethanol	n/a	−
2-Butoxyethanol	−	−
2-Butoxyacetic acid	−	−

n/a, not available; +, positive; −, negative

[a] Positive with *Salmonella typhimurium* strain TA97A, negative with strains TA98, TA100 and TA102.

Table A10: QSAR (TOPKAT) assessment of the mutagenicity, carcinogenicity, developmental toxicity and skin sensitization of 2-alkoxyethanol derivatives.

		Carcinogenicity					
Alkoxyethanol derivative	Mutagenicity	Rat, male	Rat, female	Mouse, male	Mouse, female	Developmental toxicity	Skin sensitization
2-Methoxyethyl acetate	−	+	+	−	+	+	−
2-Methoxyethanol	−	+	+	−	IND	+ (DB)	− (DB)
2-Methoxyacetaldehyde	−	+	+	−	+	−	+
2-Methoxyacetic acid	−	+	+	−	IND	+	−
2-Ethoxyethyl acetate	−	+	−	−	−	−	−
2-Ethoxyethanol	− (DB)	−	IND	−	−	+ (DB)	− (DB)
2-Ethoxyacetaldehyde	−	IND	−	−	−	−	+
2-Ethoxyacetic acid	−	−	+	−	−	+	−
2-Propoxyethyl acetate	−	+	−	−	−	−	−
2-Propoxyethanol	−	−	−	−	−	+	−
2-Propoxyacetaldehyde	−	+	−	−	IND	−	+
2-Propoxyacetic acid	−	−	+	−	−	+	−
2-Butoxyethyl acetate	−	+	−	−	−	−	−
2-Butoxyethanol	− (DB)	−	−	−	−	− (DB)	− (DB)
2-Butoxyacetaldehyde	−	+	−	−	IND	−	+
2-Butoxyacetic acid	−	−	+	−	−	−	−

+, positive; −, negative; DB, in input data in the training data set; IND, indeterminate

Table A11: Compilation of experimental and calculated data for carcinogenicity and developmental toxicity of 2-alkoxyethanols.

	Carcinogenicity								Developmental toxicity	
	Experimental data				Calculated data					
Alkoxyethanol	Rat M	Rat F	Mouse M	Mouse F	Rat M	Rat F	Mouse M	Mouse F	Experimental data	Calculated data
2-Methoxyethanol	n/a	n/a	n/a	n/a	+	+	−	IND	+	+
2-Ethoxyethanol	n/a	n/a	n/a	n/a	−	IND	−	−	+	+
2-Propoxyethanol	n/a	n/a	n/a	n/a	−	−	−	−	−	+
2-Butoxyethanol	−	IND	IND	IND	−	−	−	−	−	−

+, positive; −, negative; F, female; IND, indeterminate; M, male; n/a, not available

studies in rats, so this is not necessarily a clear-cut discrepancy.

The model predicted that 2-methoxyacetaldehyde is not mutagenic in *Salmonella*. The strains used in the development and validation of the model were TA98, TA100, TA1535, TA1537 and TA1538. Experimental studies were negative with TA98, TA100 and TA102, but positive with strain TA97A, in both the presence and the absence of S9.

Published studies on carcinogenicity are available only for 2-butoxyethanol; equivocal evidence has been found for female and male mice and female rats. TOPKAT predicts non-carcinogenicity for 2-butoxyethanol and carcinogenicity for 2-methoxyethyl acetate and 2-methoxyethanol, expecially in rats (Tables A10 and A11).

REFERENCES

Accelrys (2004) *TOPKAT user guide Version 6.2*. Burlington, MA, Accelrys, Inc.

Barratt M, Basketter D, Chamberlain M, Admans G, Langowski J (1994) An expert system rulebase for identifying contact allergens. *Toxicology In Vitro*, 8:1053–1060.

Cariello NF, Wilson JD, Britt BH, Wedd DJ, Burlinson B, Gombar V (2002) Comparison of the computer programs DEREK and TOPKAT to predict bacterial mutagenicity. *Mutagenesis*, 17:321–329.

Cronin MT, Jaworska JS, Walker JD, Comber MH, Watts CD, Worth AP (2003) Use of QSARs in international decision-making frameworks to predict health effects of chemical substances. *Environmental Health Perspectives*, 111:1391–1401.

El-Masri H, Mumtaz M, Choudhary G, Cibulas W, De Rosa C (2002) Applications of computational toxicology methods at the Agency for Toxic Substances and Disease Registry. *International Journal of Hygiene and Environmental Health*, 205:63–69.

Enslein K (1998) QSTR applications in acute, chronic, and developmental toxicity, and carcinogenicity. In: Reiss C, Parvez S, Labbe G, Parvez H, eds. *Advances in molecular toxicology.* Zeist, VSP BV, pp. 141–164.

Enslein K, Gombar VK, Blake BW (1994) Use of SAR in computer-assisted prediction of carcinogenicity and mutagenicity of chemicals by the TOPKAT program. *Mutation Research*, 305:47–61.

Enslein K, Gombar VK, Blake BW, Maibach HI, Hostynek JJ, Sigman CC, Bagheri D (1997) A quantitative structure–toxicity relationships model for the dermal sensitization guinea pig maximization assay. *Food and Chemical Toxicology*, 35:1091–1098.

Gombar V (1991) *Toxicology Newsletter No. 13.* Rochester, NY, Health Designs, Inc.

Gombar V, Enslein K (1990) Quantitative structure–activity relationship (QSAR) studies using electronic descriptors calculated from topological and molecular orbital (MO) methods. *Quantitative Structure–Activity Relationships*, 9:321–325.

Gombar V, Jain D (1987) Quantification of molecular shape and its correlation with physico-chemical properties. *Indian Journal of Chemistry*, 26A:554–555.

Gombar VK, Enslein K, Blake BW (1995) Assessment of developmental toxicity potential of chemicals by quantitative structure–toxicity relationship models. *Chemosphere*, 31:2499–2510.

Hall L, Mohney B, Kier L (1991) The electrotopological state: structure information at the atomic level for molecular graphs. *Journal of Chemical Information and Computer Sciences*, 31:76–82.

Hansch C, Leo A (1995) *Exploring QSAR: fundamentals and applications in chemistry and biology. Vol. 1.* Washington, DC, American Chemical Society.

Kier L (1986) Shape indices of orders one and three from molecular graphs. *Quantitative Structure–Activity Relationships*, 5:1–7.

Klopman G (1984) Artificial intelligence approach to structure–activity studies: computer automated structure evaluation of biological activity of organic molecules. *Journal of the American Chemical Society*, 106:7315–7321.

Klopman G, Zhu H, Fuller MA, Saiakhov RD (2004) Searching for an enhanced predictive tool for mutagenicity. *SAR & QSAR in Environmental Research*, 15:251–263.

Magnusson B, Kligman AM (1969) The identification of contact allergens by animal assay. The guinea pig maximization test. *Journal of Investigative Dermatology*, 52:268–276.

Patlewicz G, Aptula A, Uriarte E, Roberts D, Kern P, Gerberick G, Kimber I, Dearman R, Ryan C, Basketter D (2007) An evaluation of selected global (Q)SARs/expert systems for the prediction of skin sensitisation potential. *SAR & QSAR in Environmental Research*, 18:515–541.

Prival MJ (2001) Evaluation of the TOPKAT system for predicting the carcinogenicity of chemicals. *Environmental and Molecular Mutagenesis*, 37:55–69.

Richard AM (1998) Commercial toxicology prediction systems: a regulatory perspective. *Toxicology Letters*, 102–103:611–616.

Sanderson D, Earnshaw C (1991) Computer prediction of possible toxic action from chemical structure; the DEREK system. *Human & Experimental Toxicology*, 10:261–273.

Weininger D (1988) SMILES, a chemical language and information system. 1. Introduction to methodology and encoding rules. *Journal of Chemical Information and Computer Sciences*, 28:31–36.

Zeiger E, Ashby J, Bakale G, Enslein K, Klopman G, Rosenkranz HS (1996) Prediction of *Salmonella* mutagenicity. *Mutagenesis*, 11:471–484.

THE CONCISE INTERNATIONAL CHEMICAL ASSESSMENT DOCUMENT SERIES

Acrolein (No. 43, 2002)
Acrylonitrile (No. 39, 2002)
Arsine: Human health aspects (No. 47, 2002)
Asphalt (bitumen) (No. 59, 2004)
Azodicarbonamide (No. 16, 1999)
Barium and barium compounds (No. 33, 2001)
Benzoic acid and sodium benzoate (No. 26, 2000)
Benzyl butyl phthalate (No. 17, 1999)
Beryllium and beryllium compounds (No. 32, 2001)
Biphenyl (No. 6, 1999)
Bromoethane (No. 42, 2002)
1,3-Butadiene: Human health aspects (No. 30, 2001)
2-Butenal (No. 74, 2008)
2-Butoxyethanol (No. 10, 1998)
Butyl acetates (No. 64, 2005)
Carbon disulfide (No. 46, 2002)
Chloral hydrate (No. 25, 2000)
Chlorinated naphthalenes (No. 34, 2001)
Chlorine dioxide (No. 37, 2001)
4-Chloroaniline (No. 48, 2003)
Chlorobenzenes other than hexachlorobenzene: environmental aspects (No. 60, 2004)
Chloroform (No. 58, 2004)
Coal tar creosote (No. 62, 2004)
Cobalt and inorganic cobalt compounds (No. 69, 2006)
Crystalline silica, Quartz (No. 24, 2000)
Cumene (No. 18, 1999)
Cyclic acid anhydrides: human health aspects (No. 75, 2009)
1,2-Diaminoethane (No. 15, 1999)
3,3′-Dichlorobenzidine (No. 2, 1998)
1,2-Dichloroethane (No. 1, 1998)
1,1-Dichloroethene (Vinylidene chloride) (No. 51, 2003)
2,2-Dichloro-1,1,1-trifluoroethane (HCFC-123) (No. 23, 2000)
Diethylene glycol dimethyl ether (No. 41, 2002)
Diethyl phthalate (No. 52, 2003)
N,*N*-Dimethylformamide (No. 31, 2001)
Diphenylmethane diisocyanate (MDI) (No. 27, 2000)
Elemental mercury and inorganic mercury compounds: human health aspects (No. 50, 2003)
Ethylenediamine (No. 15, 1999)
Ethylene glycol: environmental aspects (No. 22, 2000)
Ethylene glycol: human health aspects (No. 45, 2002)
Ethylene oxide (No. 54, 2003)
Formaldehyde (No. 40, 2002)
2-Furaldehyde (No. 21, 2000)
Glyoxal (No. 57, 2004)
HCFC-123 (No. 23, 2000)
Heptachlor (No. 70, 2006)

(continued on back cover)

THE CONCISE INTERNATIONAL CHEMICAL ASSESSMENT DOCUMENT SERIES
(continued)

Hydrogen cyanide and cyanides: human health aspects (No. 61, 2004)
Hydrogen sulfide: human health aspects (No. 53, 2003)
Inorganic chromium(III) compounds (No. 76, 2009)
Iodine and inorganic iodides: human health aspects (No. 72, 2009)
Limonene (No. 5, 1998)
Manganese and its compounds (No. 12, 1999)
Manganese and its compounds: environmental aspects (No. 63, 2004)
Methyl and ethyl cyanoacrylates (No. 36, 2001)
Methyl chloride (No. 28, 2000)
Methyl methacrylate (No. 4, 1998)
N-Methyl-2-pyrrolidone (No. 35, 2001)
Mono- and disubstituted methyltin, butyltin, and octyltin compounds (No. 73, 2006)
Mononitrophenols (No. 20, 2000)
N-Nitrosodimethylamine (No. 38, 2002)
Phenylhydrazine (No. 19, 2000)
N-Phenyl-1-naphthylamine (No. 9, 1998)
Polychlorinated biphenyls: human health aspects (No. 55, 2003)
Resorcinol (No. 71, 2006)
Selected 2-alkoxyethanols (No. 67, 2010)
Silver and silver compounds: environmental aspects (No. 44, 2002)
Strontium and strontium compounds (No. 77, 2010)
1,1,2,2-Tetrachloroethane (No. 3, 1998)
Tetrachloroethene (No. 68, 2006)
1,1,1,2-Tetrafluoroethane (No. 11, 1998)
Thiourea (No. 49, 2003)
Tin and inorganic tin compounds (No. 65, 2005)
o-Toluidine (No. 7, 1998)
2,4,6-Tribromophenol and other simple brominated phenols (No. 66, 2005)
Tributyltin oxide (No. 14, 1999)
1,2,3-Trichloropropane (No. 56, 2003)
Triglycidyl isocyanurate (No. 8, 1998)
Triphenyltin compounds (No. 13, 1999)
Vanadium pentoxide and other inorganic vanadium compounds (No. 29, 2001)

To order further copies of monographs in this series, please contact WHO Press,
World Health Organization, 1211 Geneva 27, Switzerland
(Fax No.: +41 22 791 4857; E-mail: bookorders@who.int).
The CICAD documents are also available on the web at http://www.who.int/ipcs/en/

ISBN 978 92 4 153067 5