ARBETE OCH HÄLSA vetenskaplig skriftserie

1995:7

The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals

117. Propene

Brita Beije

ARBETS MILJÖ INSTITUTET
NATIONAL INSTITUTE OF OCCUPATIONAL HEALTH

A Center for Research on Occupational Health

Sweden´s National Institute of Occupational Health employs over 300 scientists in research on the work environment. The research is led by 30 professors. The Institute does mostly applied research, but some questions also require focused basic research.

The scientific competence of the Institute is organized into six areas: Physiology, Chemistry, Medicine, Psychology, Technology and Toxicology. This broad base of expertise provides solid support for the Institute's cross-disciplinary approach.

The Institute is responsible for training and educating personnel working within the occupational health services as physicians, nurses, physiotherapists, psychologists and safety and hygiene engineers.

Another of the Institute's responsibilities is disseminating information on occupational health research.

Arbete och Hälsa

Redaktör: Anders Kjellberg
Redaktionskommitté: Anders Colmsjö, Elisabeth Lagerlöf, Nils Stjernberg och Ewa Wigaeus Hjelm.
Grafisk produktion: Eva Nilsson

Arbetsmiljöinstitutet,
171 84 Solna, Sverige

ISBN 91-7045-298-9
ISSN 0346-7821
Tryckt hos Graphic Systems

Contents

1. Introduction 1
2. Substance Identification 1
3. Physical and Chemical Properties 1
4. Occurrence, Production and Use 2
5. Occupational Exposure and Uptake 4
6. Sampling and Analysis of Substance at Workplace 5
7. Toxicokinetics 5
   7.1 Uptake 5
   7.2 Distribution 5
   7.3 Biotransformation 6
   7.4 Elimination 7
   7.5 Kinetics 7
8. Biological Monitoring 10
   8.1 Hemoglobin adducts 10
   8.2. DNA adducts 12
9. Effects in Animals and in Vitro Studies 13
   9.1 Irritation and sensitization 13
   9.2 Acute toxicity 13
   9.3 Short-term toxicity 17
   9.4 Long-term toxicity/carcinogenicity 17
      9.4.1 Propene 17
      9.4.2 Propylene oxide 21
   9.5 Mutagenicity and genotoxicity 22
   9.6 Reproductive and developmental toxicity 23
10. Observations in Man 23
   10.1 Irritation and sensitization 23
   10.2 Acute effects by contact and systemic distribution 23
   10.3 Effects of repeated exposure on organ systems 23
   10.4 Genotoxic effects 24
   10.5 Carcinogenic effects 24
   10.6 Reproductive and developmental effects 24
11. Dose-Effect and Dose-Response Relationships 25
   11.1 Single/short-term exposure 25
   11.2 Long-term exposures 25
12. Previous Evaluations by (Inter)national Bodies 27
13. Evaluation of Human Health Risks 28
   13.1 Groups at extra risk 28
   13.2 Assessment of health risks 28
   13.3 Scientific basis for an occupational exposure limit 29
14. Research Needs 30
15. Summary 31
16. Summary in Swedish 31
17. References 32
18. Data Bases Used 37
Appendix 38
List of published NEG documents 39

1. Introduction

There is a large, world-wide, production of propene (PE) and polypropylene, and the general use of both compounds as important industrial chemicals indicate that exposure of workers is common. The general population is also exposed to PE as it appears as a contaminant in urban air as well as in cigarette smoke. Furthermore, it has been shown that the major PE metabolite in vivo is propylene oxide (PO), which is carcinogenic in experimental animals, and has been evaluated as "possibly carcinogenic to humans" (Group 2B) by IARC (38) There are no occuptional exposure limits for PE in the Nordic countries, the Netherlands or the USA. However, PE is listed as an asphyxiant by ACGIH (1).

2. Substance Identification

Chemical name	Propene
CAS registry number	115-07-1
Synonyms/Trade names	Methylethene, Methylethylene, NCI-C50077 1-Propene (9CI), Propylene, 1-Propylene
Molecular formula	C3-H6
Structural formula	CH_3-CH=CH_2
Molecular weight	42.08

3. Physical and Chemical Properties

Vapour pressure	1043 kPa (10.3 atm) at 21.1° C
Vapour density	1.48 (air=1)
Boiling point	-47.4° C
Melting point	-185.2° C
Critical temperature	92° C
Autoignition temperature	400° C
Oil/water partition coefficient	Log $P_{O/W}$ = 1.77
Conversion factor (25°C)	1 ppm = 1.72 mg/m^3; 1mg/m^3 = 0.58 ppm

Propene (PE) is an inflammable and colourless gas, at room temperature, with a mild odour. The lower flammable (explosive) limit is 2.4 %, and the upper flammable (explosive) limit is 10.3 %.

The odour threshold is 30 mg/m^3 (detection level), 100 mg/m^3 (recognition level), and 137.6 mg/m^3 (80 ppm) for 100 % recognition (6). PE is soluble in water (44.6 ml per 100 ml), ether (no figure given), ethanol (1250 ml/100 ml), and acetic acid (524.5 ml per 100 ml). PE may contain trace amounts of propane, ethane and acetylene. It polymerizes, at elevated temperature and pressure in the presence of a catalyst, by itself or with other monomers, to produce polypropylene and propylene copolymers.

PE is available in western Europe as a 92 % pure chemical grade and as a 99.8% pure polymerization grade. Impurities are butylene (0.020 ‰), ethylene (0.020 ‰), methyl-acetylene (0.010 ‰), butadiene (0.005 ‰), propadiene (0.005 ‰), and methanol (0.005 ‰).

In the US, PE is generally available as a chemical grade (min. purity 92 %) and as a polymerization grade (99.9 %).

There is also a refinary-grade PE, which contains about 50 - 70 % PE mixed with other low molecular mass hydrocarbons (21).

4. Occurrence, Production and Use

PE occurs *naturally*, to some extent. Thus, it has been found in the gaseous metabolites released from germinating beans, corn, cotton, and pea seeds (103). It has also been detected in the gases desorbed from coal samples (48). From Chinese rice fields, the average emission rate of PE was estimated to be 0.4 µg/m^2/h (46, 47) .From ash, elm, cypress and hackberry trees near Batton Rouge, LA, USA, PE was emitted at levels ranging from 5 to 20 µg/kg foliage/h (46). Annual emissions of PE from natural and anthropogenic sources in western Europe (between 35° and 50° N latitude) was calculated, in 1985, to 10.6 million tonnes and 2.3 million tonnes, respectively (91). In the USA the annual emission has been calculated to range between 440 and 600 thousand tonnes (5, 62) .The average atmospheric lifetime of PE is estimated to less than one day at low altitudes (79). PE is subject to photochemical degradation by reaction with OH radicals (91).

Air concentrations of PE have been measured in various countries round the world. In rural areas the concentrations are ranging from 0.02 to 8.3 µg/m^3 (7, 16, 34, 42, 54, 63, 80) . In urban and polluted air the PE concentrations are ranginging from 0.6 to 448 µg/m^3. For example, Delft, The Netherlands, had a highest value of 14 µg/m^3 (8 ppb) which occurred in the early morning with a southerly wind (13). In the air of a suburban community of Philadelphia, USA, near several industrial complexes, air concentrations ranged between 12 - 448 µg/m^3 (7 - 260 ppb) (28). A median PE level of 4.4 µg/m^3 from 39 US cities has been reported by (84) . See also Table 1.

In the 454 m long Tingstad tunnel in Gothenburg, Sweden, PE concentrations varied between 13 and 160 µg/m^3. Measuring time was 30 minutes. The measurements were done at different time points over one year (11). The higher concentrations could be explained by traffic congestion etc. The urban air concentration of PE at a road inter-section in Gothenburg, Sweden, during a winter inversion episode was 28 and 26 µg/m^3.

Samples taken at the road side of fast traffic contained 6.5 and 3.8 µg/m^3, and after cold starts in a garage the air concentration was 24 µg/m^3 (56) .

Table 1. Air concentrations of propene (PE) measured in some areas round the world.

Air conc. (µg/m^3)	Comments	Area	Ref.
0.5	(average of 192 samples)	Tokyo, Japan	(102)
0.6 - 4.7		Chicago, USA	(8)
0.7 - 32.3		Bombay, India	(64, 76)
5.7		Northwest England	(16)
12 - 55		Los Angeles, USA	(32)
12 - 448		Philadelphia, USA	(28)
14	(max value)	Delft, the Netherlands	(13)
100	Road tunnel, rushhours	Gothenburg, Sweden	(28)
9,15	Inside car, 2 separate days	-"-	-"-
37, 73	Café, cig. smoke 2 separate days	-"-	-"-
1.8-25.2	Suburban area, winter months*	Malmö, Sweden	(19)
5-70	Suburban area winter months*	Kiruna, Sweden	-"-

* wood-fired boilers

Combustion products of burning white pinewood have been found to contain 86 mg/m^3 (50 ppm) PE (69).

Exhaust gases from a jet engine contain PE (223 - 245 mg/m^3) (43) as well as exhaust gases from a diesel powered passenger car (12.9 mg/km) on commercial diesel fuel. In 1983, PE emissions from petrol exhaust in the UK were estimated at 13 300 tonnes (9, 10). When burning a standard US EPA smoke test fuel only 5.8 mg/km PE was produced (14).

Cigarette smoke is also a significant source of PE exposure; 1.3 - 1.4 mg PE is released from one cigarette (73) . PE concentrations of 40 and 70 mg/m^3 were found in two studies of tavern air during normal smoking conditions. The corresponding outdoor air concentrations at the time were 6 mg/m^3 in both studies (57).

Concentrations of PE *in water* has been measured in the Gulf of Mexico (0.1 - 16 nl/l), the Carribean Sea (0.2 - 5.8 nl/l), the Atlantic Ocean (trace - 11.0 nl/l) and the Pacific Ocean (0.6 - 3.6 nl/l) (52, 90).

Most PE is produced commercially as a by-product of either ethylene manufacture or refinery operations. Refinery off-gases from catalytic cracking contain large quantities of PE, and ethylene plants based on steam cracking of natural gas liquids, naphta and gas oil produce recoverable quantities of PE (90 - 318 g/kg ethylene) as a by-product (21, 81).

In 1993, the production of PE amounted to about 190 000 tonnes in *Sweden* , to 160 000 tonnes in *Norway*, and to 240 000 tonnes in *Finland*. In *Denmark* there was no production of PE during 1993. Total PE production in Europe has been estimated to about 12 million tonnes for 1993. In *the US*, 10.248 million tonnes PE were produced in 1992.

PE is a major chemical intermediate. In Sweden about 50 % of the PE produced is used in the paint industry and as a PVC softener. The pattern of use of PE as a chemical intermediate in the USA during 1992, was polypropylene (39 %), acrylonitrile (14 %), propylene oxide (11 %), and cumene (10 %). Other derivatives include, in order of decreasing PE use, oxo alcohols, isopropanol, acrylic acid, allyl chloride, ethylene-propylene elastomers, acrolein. Important areas of application of polypropylene are in plastics (injection moulding) and fibres (carpets), which accounts for about one-third of the US consumption, and in wire-insulating, film, and blow moulding.

Refinery production accounts for about 20 % of the chemical industry´s consumption of PE in Europe, and for more than 40% in the USA.

5. Occupational Exposure and Uptake

There are few data on occupational exposure levels. Jankovic et al (40) have studied PE exposure of fire-fighters. During the "knock-down" phase of a fire, the samples contained 13.8 mg/m^3 (8 ppm) PE, whereas no PE was detected in samples taken during the "overhaul" phase. No PE was detected in area samples taken in the vicinity of injection moulding, extrusion and welding machines in four plants in which polypropylene was processed (27, 74). In a National Occupational Exposure Survey conducted by NIOSH, between 1981 and 1983, it was indicated that 7 300 US employees were potentially exposed to PE at work. Of this number, 88 % were estimated to be exposed to PE and 12 % to materials containing PE. No measurements of actual exposures were made (65-67).

However, it may be hard to attain a careful characterization of occupational exposure over long periods of time. To bypass this problem Granath and collegues (30) have suggested a theoretical kinetic method using the relationships between adduct level and exposure concentration. The method suggests that a fairly accurate measure of this relationship can be obtained by measuring the adduct levels A_1, A_2, A_3 at three consecutive times t_1, t_2, t_3 with equal intervals t_1 - t_2 and t_2 - t_3. During one of the intervals, each in the order of 5-10 days, the person should be absent from the exposure source and during the other interval the exposure should be carefully measured. In a further study (30, 31) the model was evaluated with a possible application to work environment in mind. The aim was also to obtain improved data for the relationships between exposure of ethene and PE and in vivo doses of the respective epoxides formed metabolically, as well as the changes in hemoglobin (Hb) adduct levels. Thus, the changes in hemoglobin adduct levels were measured in two smokers, who abstained

from smoking for one week and then carefully recorded the smoking during the second week. The inhaled amount of PE per smoked cigarette was simultaneously measured. Due to the low levels of the N-(2-hydroxy-propyl)valine (HOPrVal) adducts from tobacco smoke, special statistical considerations were required, the results of which will be published later by these authors.

6. Sampling and Analysis of Substance at Workplace

PE can be detected in gaseous mixtures, using *infra-red spectrophotometry* of cryogenically-cooled gaseous mixtures, with a limit of detection of 1.7 µmol (78) or by absorption of infra-red radiation from a laser source, with a limit of detection of 5.2 µg/m^3 (3 ppb) (49).

Gas chromatographic methods for the separation and identification of PE has been used on ambient air, using a chemically-bonded stationary phase, with a limit of detection of 0.86 µg/m^3 (0.5 ppb) (107), a cryogenic temperature programming (28) or an automated system, with a limit of detection of 3.4 - 8.6 µg/m^3 (2 - 5 ppb) (41).

Gas chromatography combined with mass spectrometry has been used to determine PE in gaseous mixtures, with a detection limit of approximately 0.172 mg/m^3 (0.1 ppm) (53). One method is based on sample enrichment on a solid adsorbent, a Zeolite, at room temperature, followed by heat desorption for *gas chromatographic separation and flame ionization detection* (73).

7. Toxicokinetics

7.1 Uptake

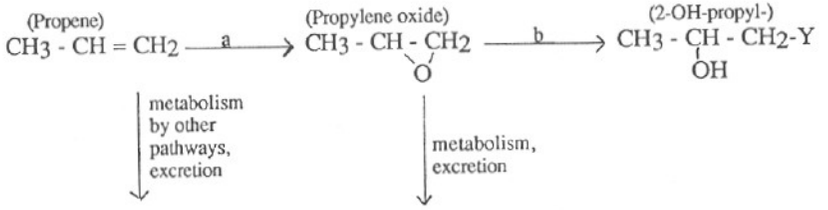
PE is a gas with moderate solubility in water and lipids, and furthermore, the molecules are of a small size and thus easily taken up by the lungs. However, no quantitative data on pulmonary uptake (retention) have been given. No data have been found on dermal uptake. See also 7.3.

7.2 Distribution

PE is metabolized to the epoxide, propylene oxide (PO), which binds to macromolecules, i.e. hemoglobin and DNA, forming 2-hydroxypropyl (HOPr-) adducts (see 7.3). Svensson and coworkers (88) measured such 2-hydroxypropyl adducts in hemoglobin and in DNA from various organs in the mouse after inhalation of 395.6 - 51 600 mg/m^3 (230 - 30 000 ppm) PE, or injection of PO. The data indicate a fairly even distribution in the body. See also 8.

7.3 Biotransformation

The following pathway has been proposed for PE (89):



a) metabolism

b) alkylation of nucleophilic sites; (Y-) e.g. in macromolucules

Osimitz and Conolly (70) have demonstrated that cytochrome P-450 dependent metabolism of PE is necessary for the in vivo bioactivation of PE to a hepatotoxic metabolite. They pretreated Sprague Dawley (SpD) rats with the polychlorinated biphenyl (PCB) mixture, Arochlor 1254 (100 mg/kg/day), for 3 days, followed by SKF-525A (75 mg/kg in saline, i.p. injection), 15 minutes before PE exposure at 75 680 mg/m^3 (44 000 ppm) for 4 h. PCB is a well-known inducer of some cytochrome P-450 species, whereas SKF-525A inhibits, irreversibly, cytochrome P-450-dependent metabolism, both in vivo and in vitro. The SKF-525A treatment totally abolished the hepatotoxic effects of PE observed in PCB-pretreated rats, as described in 9.2.

Svensson and Osterman-Golkar (89) performed a study which indicated that PE, like ethylene, is metabolized to the corresponding epoxide (propylene oxide, PO) and the oxidation is not stereospecific, but yields a racemic mixture. Male CBA mice, 15 in each group, were exposed to ^{14}C-PE (4 867.6 mg/m^3, 2 830 ppm) for 1 h, and to unlabeled PE (34 400 mg/m^3, 20 000 ppm) for 4 h/day and 8 consecutive days, for the identification of alkylated products in macromolecules. Assuming that PO, is the primary metabolite, the authors estimated the rate of epoxide formation at an air concentration of 34 400 mg/m^3 (20 000 ppm) PE to be 11 mg PO/kg bw/h. Further support of PO being the major PE metabolite was obtained in a later study, in which a linear relationship was reported between the concentration of HOPrVal (0.24 - 1.62 nmol/g Hb) (see also 8.1) and the amount of PO (0.3 - 1.3 mmol/kg bw; 17.4 - 75.4 mg/kg bw) formed in mice after an inhalation exposure dose of 2 770 - 361 200 mg/m^3 x h PE (230 - 30 000 ppm x 7h). This relationship had almost the same slope as that obtained after ip injection of 0.065 - 0.19 mmol/kg bw (3.8 - 11 mg/kg bw) ^{14}C-PO in saline (88). See also Table 2.

Maples and Dahl (59) measured the PO concentration in the blood of male Fisher 344/N (F344/N) rats exposed to two different PE concentrations, i.e. 1 032 mg/m^3 (600 ppm) PE for 0-480 minutes, or to 10.32 mg/m^3 (6 ppm) PE for 0-360 minutes. In the high exposure rats, the blood level of PO rose to approximately 740 ng PO/g blood within the first 5 minutes after exposure and dropped to about 10 ng/g blood after 8 - 10 minutes. The PO concentration remained at this low level for about 90 minutes, after

which it slowly increased to a level round 300 ng/g blood at 200 minutes and remained at this level to the end of exposure, i.e. to 480 minutes. Exposure to the low PE concentration gave rise to a peak of approximately 160 ng/g blood, 5-12 minutes after the exposure begun, after which the PO concentration went down to about 40 ng/g blood and remained at this level during the following 70 minutes. In rats exposed to 20.94 mg/m^3 (14 ppm) PO, the blood concentration of PO increased during the first 10 minutes of exposure and then leveled off at about 3 ng/g blood (60).

It has been estimated from the animal experiments that approximately 5 % of inhaled PE is metabolized to PO (87) and there are some indications of PO being detoxified 4-5 times faster than ethylene oxide. There are contradictory opinions about the detoxifiction of PO. In the above mentioned study by Osimitz and Conolly (70) it was suggested that glutathione may not play a major role in the detoxification of PE or its metabolites, nor in the repair of PE-induced lesions. This assumption was based on the fact that fasting the rat did not modify the toxic response to PE, which was observed with PCB-pretreated rats. However, the authors did not completely rule out a possible role of GSH in the PE metabolism. Törnquist (personal communication), on the other hand, suggests that glutathione S-transferase (GST) is involved in the detoxification of PO, as is the case with ethylene oxide.

7.4 Elimination

The metabolic elimination rate has been calculated by Becka et al (12) using 11 experiments carried out by Golka and coworkers (29) with SpD rats, as described below. The range of initial concentrations was from 8.6 to 13 416 mg/m^3 (5 to 7 800 ppm), and the measurements were taken from the first compartment (gas phase) in the two-compartment model. With initial concentrations smaller than 86 mg/m^3 (50 ppm), first-order elimination kinetics were assumed. Under standard conditions, the first-order rate constant for uptake was 0.405 (h^{-1}) and for exhalation 0.031 (h^{-1}). Up to an atmospheric concentration of 86 mg/m^3 (50 ppm), about 42 % of inhaled PE is exhaled unmetabolized (29).

7.5 Kinetics

The kinetics of PE metabolism have been studied by Svensson and Osterman-Golkar (89). Male CBA mice (15 in each group) were exposed, in a closed system, to 163.4 - 2 949.8 mg/m^3 (95 - 1 715 ppm) PE (initial concentrations). It was shown that the rate-limiting step was a saturable enzymatic process following Michaelis-Menten kinetics. The K_m and V_{max} were calculated to 1 376$\pm$103.2 mg/m^3 (800$\pm$60 ppm) and 8$\pm$0.5 mg/kg bw/h, respectively. It should be noted that it was not possible to distinguish between inhaled and exhaled PE.

Golka and coworkers (29) have studied the pharmacokinetics of PE and its reactive metabolite, PO, in SpD rats. Based on the pharmacokinetic parameters for PE and PO, determined for standard conditions according to Filser and Bolt (26), the pharmacokinetics for a single rat, 250 g bw, were calculated. The thermodynamic equilibrium constant for whole body/air was determined to be 1.6 for PE and 45 for PO. V_{max} for PE was 0.17 µmol/min, $K_{m(app)}$ was 220 nl PE-gas/ml tissue volume, and the atmospheric

Table 2. Degree of alkylation of Hb in mouse, rat, dog exposed to propene (PE) or propylene oxide (PO).

Species (n)	Agent	Exposure route	PE conc. (mg/m^3)+	Exposure time	Amount of PO formed* (mmol/kg bw)	Amount of PO administered (mg/kg bw)	HOPr Val a) (nmol/g Hb)	HOPr His (nmol/g Hb/h)	Ref
Mouse (12m)	PE	Inhalation	6 707	1 h				0.9x)	(89)
CBA (12m)			47 400	4 h, 8 d				2.2x)	
Mouse (18m)	PE	Inhalation	395.6	7 h	0.30		0.24b)		(88)
CBA (9m)			1 169.6	7 h	0.46		1.08b)		
(9m)			38 012	6 h	1.1		1.62b)		
(9m)			51 600	7 h	1.3		0.97; 1.4 b)		
Mouse (10m)	PO	Inhalation	-	5 h		6.5	0.27		(83)
B6C3F1(10m)				5 h		18.4	0.59		
Rat (5m)	PO	Inhalation	-	5 h		3.8	0.29		(83)
F344 (5m)	PO			5 h		10.9	0.72		
Dog (1m+1f)	PO	Inhalation	237	1 h			0.28		(83)
Beagle (1m+1f)			1 185	1 h			1.7		
Mouse (18m)	PO	I.p. inj.	-			5.61c)	0.13; 0.19 b)	0.18	(88)
CBA (5m)						3.65c)	0.075		
(5m)						10.66c)	0.25		

Table 2. Cont.

Species (n)	Agent	Exposure route	PE conc. (mg/m^3)+	Exposure time	Amount of PO formed* (mmol/kg bw)	Amount of PO administered (mg/kg bw)	HOPr Val a) (nmol/g Hb)	HOPr His (nmol/g Hb/h)	Ref
Mouse (10m)	PO	I.p. inj.	-	5 h		3.1	0.08;0.08b)		(83)
B6C3F1(10m)				5 h		7.6	0.20;0.18b)		
Rat (5m)	PO	I.p. inj.	-	5 h		3.1	0.18;0.17b)		(83)
F344 (5m)	PO			5 h		7.6	0.60;0.56b)		
Dog (1m+1f)	PO	I.v. inj.	-			4.1	0.26		(83)
Beagle (1m+1f)						20.2	1.4		
Man							0.07 (estimated value)		(83)

+ Calculated from ppm as given in the original paper.
* The calculation of in vivo formation of PO was based on inhalation K_m (800±60 ppm) and V_{max} (8±0.5 mg/kg bw/h) in the CBA mouse (89).
x) Analysed with HPLC:fluorescence.
a) Determined from the radioactivity of the pentafluorophenylthiohydantoin (PFPTH) derivative.
b) Determined by GC-MS.
c) Calculted from mmol/kg bw as given in the original paper.
f=female, m=male

concentration of PE corresponding to V_{max} / 2 was 447.2 mg/m^3 (260 ppm). Below 86 mg/m^3 (50 ppm), first order kinetics were found for PE, the clearance of metabolism being 11 ml/min. In contrast to PE, no saturation kinetics were observed for PO up to an initial concentration of 7 140 mg/m^3 (3 000 ppm) in the atmosphere of the exposure chamber. Of the inhaled PO, 96 % is metabolized and only 3 % is exhaled unchanged. At concentrations above 7 140 mg/m^3 (3 000 ppm) acute toxic effects were observed. The body burden of PO in rats was calculated for different conditions of continuous exposure to either PO or PE. At a concentration of 238 mg/m^3 (100 ppm) PO in the atmosphere, the calculated body burden was 124 nl PO-gas/ml tissue.

8. Biological Monitoring

Extensive research has been targeted on the ability of PO, formed in the metabolism of PE, to react covalently with hemoglobin and DNA, with a view to utilizing the adducts as biological dosimeters of cumulative dose and/or as a measure of genotoxic risk.

8.1 Hemoglobin adducts

The most sensitive method for the measurement of adducts from PE/PO is the "N-alkyl Edman method" (92, 95, 97) for masspectrometric determination of adducts to N-seminal *valine* in hemoglobin. Another possibility is to measure adducts to *histidine* in the interior of the globin chain after total hydrolysis of the protein, isolation and derivatization of adducted amino acids followed by GC/MS-analysis (24) Determination of *histidine adducts* was used in the first study of PO-exposed workers (71). The faster and more sensitive N-alkyl Edman method for the determination of *valine adducts* has been used in studies of animals exposed to PE in automobile exhaust (101), to PE or PO (44, 45, 83, 88), and in studies of humans exposed to PE in tobacco smoke (93, 94, 98) or with occupational exposure to PO (35).

In non-smokers, not occupationally exposed to PE, the back-ground level of *HOPrVal* of Hb was found to be 2 pmol/g Hb. It was estimated that smoking 10 cigarettes per day would induce an increment of about 2 pmol/g globin (94). Occupational exposure to PE at 1.72 mg/m^3 (1 ppm) (40 h time-weighted average) was assumed to be associated with an increment of about 5 pmol/g Hb (45). In workers exposed to PO for 1-20 years, the mean HOPrVal levels were 0.14 nmol/g Hb (range 0.05 - 0.26) for 3 non-smokers and 0.93 nmol/g Hb (range 0.03 - 3.5) for 16 smokers. The average concentration of PO in the breathing zone varied between 0.79 and 27.1 mg/m^3 (0.33 - 11.4 ppm) (35).

Svensson and Osterman-Golkar (71) exposed male CBA mice, 15 in each group, for 1 h with ^{14}C-PE at 4 867.6 mg/m^3 (2 830 ppm), and 4 h/day for 8 consecutive days with unlabeled PE, 34 400 mg/m^3 PE (20 000 ppm) for the identification of alkylated products in macromolecules. After ^{14}C-PE exposure for 1 h, the degree of alkylation of cysteine and histidine, i.e. *(S-(2-hydroxypropyl)cysteine* and *N^2-(2-hydroxypropyl)histidine (HOPrHis)* in hemoglobin was 2 nmol/g Hb and 0.9 nmol/g Hb, respectively (measured

Table 3. N-(2-hydroxypropyl)valine (HOPrVal) adducts in experimental animals exposed by inhalation to propene in petrol and diesel exhaust.

Species	Conc (mg/m^3)	Exposure time	Hb-adducts	Ref
Fisher 344 rats female	<0.17-1.24 (mean atmos conc.)	6 months (petrol & diesel exhaust)	44 pmol HOPrVal/g Hb (at highest dose) vs. 9 pmol HOPr Val/g Hb (background)	(101)
Syrian hamsters male & female	<0.17-1.24 (mean atmos conc.)	6 months (petrol & diesel exhaust)	47 pmol HOPrVal/g Hb (at highest dose) vs. 6 pmol HOPrVal/g Hb. (background) The increase was ~ linear with exp. dose	(101)

by ion exchange chromatography and radioactive determination). After the longer exposure time, the degree of histidine-alkylation was 70 nmol/g Hb, as compared to the control value of 12 nmol/g Hb (analysed by HPLC-fluorescence). In another study, a linear relationship was reported between the concentration of HOPrVal (0.24 - 1.62 nmol/g Hb) and the amount of PO (0.3 - 1.3 mmol/kg bw; 17.4 - 75.4 mg/kg bw) formed in mice after inhalation of 2 770 - 361 200 mg/m^3 x h PE (230 - 30 000 ppm x 7h). See also 7.3 and Table 2.

Svensson and coworkers (88) have used an improved version (101) of the N-alkyl Edman method to determine the degree of alkylation of *N-terminal valine* in hemoglobin as a method of biological monitoring. Using GC-MS analyses they measured hydroxypropyl adducts in hemoglobin, as well as in DNA from various organs in the mouse after inhalation of 395.6 - 51 600 mg/m^3 (230 - 30 000) ppm PE or injection of 0.10 - 0.19 mg/m^3 PO. Hb-adducts are not only a measure of exposure, they may also be an indication of genotoxic risk as there is fairly good evidens for a correlation between Hb-adducts and DNA-adducts of certain chemicals. See Table 2.

Adducts to *N-terminal valine* were analysed by GC-MS and radioactivity determination of pentafluorophenylthiohydantoin (PFPTH) derivatives of blood samples from CBA mice exposed to PE by inhalation or PO by i.p. injection. The amount of PO formed in vivo was calculated as described in 7.3 (89). PE concentrations were ranging from 395.6 to 51 600 mg/m^3. The level of HOPrVal formation was similar when comparing the amount of PO injected with the amount of PO formed from inhaled PE (82, 83) (See Table 2). In another study from the same lab, HOPrVal in Hb was determined in female Fisher 344 rats and in Syrian hamsters (of both sexes) after exposure for six months to petrol and diesel exhausts (mean atmospheric concentrations of PE were < 0.17 - 1.24 mg/m^3). Background values for HOPrVal were 9 pmol/g Hb in rats and 6 pmol/g Hb in hamsters. In hamsters, the levels of HOPrVal increased almost linearly with exposure dose and they were higher in females than in males. HOPrVal adduct increments at the

Table 4. Alkylation of guanine-N-7 in DNA from various organs after exposure of male CBA mice to propene (PE) or propylene oxide (PO) (88).

Agent	PO injected or formed (mmol/kg bw)	Measured product	Adduct level (pmol/mg DNA) 3 h	10 h
PE a)	1.3 b)	N-7-HOPrGua in DNA		
		liver	3	-
		kidney	3	-
		spleen	2	-
		lung	-	-
		testis	-	-
PO c)	0.10	N-7-HOPrGua in DNA		
		liver	0.39	0.40
		kidney	0.16	0.17
		spleen	0.26	-
		lung	0.09	0.12
		testis	0.15	0.15

a) Mice were exposed by inhalation for 7 h to 51 600 mg/m^3 (30 000 ppm) PE in the air, and killed immediately after exposure.
b) The in vivo formation of PO was calculated with inhalation K_m (800±60 ppm) and V_{max} (8±0.5 mg/kg bw/h) in CBA mice (89)
c) Mice killed 3 h or 10 h after i.p. injection.

highest dose were similar in female rats (44 pmol/g Hb) and hamsters (47 pmol/g Hb) (101). See Table 3.

Eide and collegues (20) exposed male SpD rats to PE 12 h/day for three consecutive days, with a mean exposure level of 505.2 mg/m^3 (293.7±6.9 ppm). Blood samples (Hb and lymphocyte DNA) and liver (DNA) were prepared immediately after the last exposure. The levels (mean±SD) were; HOPrVal in Hb , 2730±50 pmol/g, N-alkyl guanine in lymphocytes, 1.77±0.91 adducts/10^7 nucleotides; N-alkyl guanine in liver DNA, 2.82±0.92 adducts/10^7 nucleotides.

It should be noted that endogenously formed aldehydes give rise to a background level of HOPrVal, which is about 2 pmol/g globin in non-smokers, about 17 pmol/g globin in NMRI mice, and about 10 pmol/g globin in germ-free NMRI mice (44, 100).

8.2 DNA adducts

In the above mentioned study (89) with male CBA mice, 15 in each group, exposed for 1 h with ^{14}C-PE at 4 867.6 mg/m^3 (2 830 ppm), and 4 h/day for 8 consecutive days with unlabeled PE, 34 400 mg/m^3 (20 000 ppm), the amount of alkylated DNA products (2-hydroxypropylated guanine-N7) was below the detection limit (1 nmol/g DNA).

DNA alkylation at the N7 position of guanine was also investigated in male CBA mice exposed to atmospheric unlabeled PE or uniformly labelled ^{14}C-PE, and the adduct levels

Table 5. Levels of N-7-(2-hydroxypropyl)guanine in DNA of mice, rats and dogs exposed to propylene oxide (PO) (83).

Species	No of animal	Dose (mg/kg)	Route	Adduct level (pmol/g DNA per mg PO/kg bw) liver	lung	brain
Mouse	10	6.5	inhal (5h)	36	52	ND
B6C3F$_1$ (m)	10	18.4	inhal (5h)	19	28	ND
Rat	5	3.8	inhal (5h)	22	94	34
F344 (m)	5	10.9	inhal (5h)	21	75	ND
Mouse	10	3.1	i.p. inj.	17	ND	ND
B6C3F$_1$ (m)	10	7.6	i.p. inj.	21	ND	ND
Rat	4	3.1	i.p. inj.	38	26	ND
F344 (m)	4	7.6	i.p. inj.	28	48	56
Dog	2	4.1	i.v. inj.	17	61	ND
Beagles (m+f)	2	20.2	i.v. inj.	17	57	ND

(m); males, (m+f); 1 male and 1 female at each dose

were related to the concentration of PO (0.88 mmol/kg bw), calculated from the rate of PE metabolism. Immediately after expsure to 107 MBq uniformly labelled ^{14}C-PE (18.1 MBq/mmol PE) for 7 h in a closed exposure chamber, the mice were killed and 2-hydroxypropyl-DNA adducts were measured, the results being; 3000 pmol/g DNA in liver and kidney, 2 000 pmol/g DNA in spleen(88).

Segerbäck ea (83) measured levels of N-7-(2-hydroxypropyl)guanine in DNA in different tissues from mouse, rat, and dog exposed to PO by inhalation or injection (i.p. and i.v). Species differences, when considering the same tissue, were small. The DNA adduct levels in liver were slightly lower than in lung and brain. The data are shown in Tables 4 and 5.

9. Effects in Animals and in Vitro Studies

9.1 Irritation and sensitization

No data were found.

9.2 Acute toxicity

In a study from 1924 (18) the anaesthetic effect of PE was studied in cats. Anaesthesia was induced at a concentration of 37 % in oxygen or air, and the effect was maintained satisfactorily with concentrations between 31 and 20 % in oxygen or air. At 50 %, the

Table 6. Acute toxicity of propene (PE) in rats.

Species	Pretreatment	PE exposure (mg/m^3)*	Exp. time	Effect	Ref
SpD (m)	PB; 80 mg/kg/d, 3 d	688 000	4 h	Abnormal porphyrins in liver	(50)
SpD (m)	-	86 000	4 h	No hepatotoxic effects	(70)
SpD (m)	PCB; 100 mg/kg/d, 3 d	86 000	4 h	Liver weight; 7.66 ± 0.22 g/100 g bw vs 6.32 ± 0.33 ($p \leq 0.05$) SDH; 190 ± 36 U/ml serum vs 20.5 ± 4.8, no PE ($p < 0.05$)	(70)
SpD (m)	PCB; 100 mg/kg/d, 3d	86 000	2 h 4 h	Hepatic mic P-450; ~ 55% of ctrl (no PE) Hepatic mic P-450; 40% of ctrl (no PE) Hepatic mic AH; 80% of ctrl (no PE) Hepatic mic APD and G-6-P ase not effected	(70)
SpD (m)	PCB + SKF-525A; 75 mg/kg i.p. 15 min prior PE exposure	75 680	4 h	Liver weight; 5.91 ± 0.33 g/100 g bw vs 6.85 ± 0.26 no SKF ($p \leq 0.05$) SDH; 27.2 ± 6.8 U/ml serum vs 105 ± 19, no SKF ($p \leq 0.05$) ALT; 18.9 ± 7.61 IU/l serum vs 230 ± 79 no SKF ($p \leq 0.05$) (No PE no SKF; ALT 24.6 ± 9.51 IU/l serum)	(70)

Table 6. Cont.

Species	Pretreatment	PE exposure (mg/m^3)*	Exp. time	Effect	Ref
F 344/N (m)	-	1032	20 min	Hepatic mic P-450; 70% of ctrl (no PE) Ethmoturb mic P-450; ~ 60% of ctrl (no PE)	(59)
F 344/N (m)	-	1032	6 h	Maxilloturb mic P-450; ~ 41% of ctrl (no PE) Hepatic mic P-450; ~ 135% of ctrl (no PE) Ethmoturb mic P-450; ~ 90% of ctrl (no PE) Maxilloturb mic P-450; ~120% of ctrl (no PE)	(59)
F 344/N (m)	-	10.32	20 min	Hepatic mic P-450; ~ 90% of ctrl (no PE) Ethmoturb mic P-450; ~ 90% of ctrl (no PE) Maxilloturb P-450; ~ 55% of ctrl (no PE)	(59)
F 344/N (m)	-	10.32	6 h	Hepatic mic P-450; ~ 85% of ctrl (no PE) Ethmoturb mic P-450; ~ 120% of ctrl (no PE) Maxilloturb mic P-450; ~ 45% of ctrl (no PE)	(59)

* original data given as ppm, ALT; serum alamine leucine transaminase, SDH; serum sorbitol dehydrogenase, AH; aniline hydroxylase
APD; aminopyrine demethylase , G-6-P ase; glucos-6-phosphatase

anaesthetic effect was induced within two minutes. Symptoms of toxicity were produced within two minutes at concentrations above 70 %. However, the recovery was rapid and there were no negative aftereffects. There was no control of the oxygen concentration, when air was used. Thus, the anaesthetic effect in those experiments might have been due to oxygen deficiency rather than PE exposure.

Exposure of male SpD rats to 111 800 mg/m^3 (65 000 ppm) PE by inhalation for 4 h did not cause hepatotoxicity, as indicated by the serum levels of alanine-leucine transaminase (ALT), and sorbitol dehydrogenase (SDH) (17). However, the same PE concentration was acutely hepatotoxic when given to SpD rats, which had been pretreated with the polychlorinated biphenyl (PCB) mixture Arochlor 1254 (100 mg/kg/day) for 3 days. Inhalation of 111 800 mg/m^3 (65 000 ppm) PE for 4 h on the fourth day resulted, 24 h later, in a significant ($p<0.05$) increase in serum SDH level, i.e. 190$\pm$36 U/ml serum vs 20.5$\pm$4.8 U/ml serum in controls (PCB, no PE). The liver weight was also increased in these rats (PCB+PE) compared to the controls (PCB), from 6.32$\pm$0.33 g per 100 g bw to 7.66$\pm$0.22 g/100 g bw ($p<0.05$). Some PCB treated rats were given SKF-525A (75 mg/kg in saline, i.p. injection), 15 minutes before PE exposure at 75 680 mg per m^3 (44 000 ppm) for 4 h. The PE-induced elevation of SDH and liver weight/100 g bw was prevented. SDH was reduced from 105$\pm$19 SDH units /ml serum to 27.2$\pm$6.8, and the liver weight /100 g bw was reduced from 6.85$\pm$0.26 g/100 g bw to 5.91$\pm$0.33 g/100 g bw. Also the serum ALT activity was reduced from 230$\pm$79 IU/l serum (PCB+PE, no SKF) to 18.9 $\pm$ 7.6 IU/l serum by SKF treatment (PCB+PE+SKF), control value (PCB,no PE, no SKF) was 24.6$\pm$9.5 IU/l serum (70). See also Table 6.

Kunze et al (50) found that abnormal porphyrins had accumalated in the liver of phenobarbital-pretreated male SpD rats exposed to 40 % PE in air (688 000 mg/m^3) for 4h. It was concluded that the porphyrins resulted from alkylation of the prosthetic haem group of cytochrome P-450 during oxidation of PE which led to inactivation of the ezyme. An N-(2-hydroxypropyl) adduct at the pyrrole ring D was identified by nuclear magnetic resonance (NMR) analysis of alkylated porphyrins. In vitro, an NADPH-dependent reduction of total cytochrome P-450 by 32 % was measured in PE-exposed (5 % in air, 86 g/m^3, 30 min) liver microsomes isolated from phenobarbital-pretreated male SpD rats (Table 6).

The hepatic microsomal cytochrome P-450 levels were dramatically decreased in PCB-treated rats already 2 h after the exposure to 86 000 mg/m^3 (50 000 ppm) PE, and after 4 h the level was only 40 % of the control value (only PCB-treatment). The depression remained for at least 24 h. The hepatic microsomal aniline hydroxylase activity was also decreased (by 20 %) 4 h after exposure of PCB-treated rats to 86 000 mg/m^3 (50 000 ppm) PE. However, no effects were observed on the hepatic microsomal enzymes aminopyrine demethylase and glucose-6-phosphatase (70). See also Table 6.

The cytochrome P-450 content was measured in liver microsomes and nasal microsomes from F344/N rats exposed to 10.32 or 1 032 mg/m^3 (6 or 600 ppm) PE for 20 minutes. In both tissues, the P-450 contents were lower as compared to unexposed values (59) . This is in line with in vitro studies, in which P-450 has been inactivated by PE (70). After 6 h of exposure to 10.32 mg/m^3 (6 ppm) PE, the ethmoturbinate P-450 level increased to a value slightly greater (about 120 %) than the pre-exposure level.

However, both the maxilloturbinate and liver P-450 levels continued to decline throughout the exposure period. After 6 h exposure to 1 032 mg/m^3 (600 ppm) PE, the ethmoturbinate P-450 level had returned to approximately its initial level, whereas maxilloturbinate and liver values were still somewhat elevated (approx. 120 and 135 % of initial value) (59). See Table 6.

9.3 Short-term toxicity

Within the National Toxicology Program (68) *F344/N rats* and *B6C3F1 mice* were exposed for 14 days to PE at concentrations ranging from 1 075 - 17 200 mg/m^3 (625 to 10 000 ppm) for 6 h/day, 5 days/week. No toxic effects were observed, i.e. no compound-related deaths or clinical signs were observed, and no gross or microscopic pathologic effects (including nasal cavity).

Male *SpD rats* (50/group) were exposed to 1 031 or 2 062 mg/m^3 (435 or 870 ppm) PO (95 % purity) by inhalation for 6 h/day, 5 days/ week for 30 days, and 4 124 mg/m^3 (1 740 ppm) for eight days (due to high mortality) and then observed for life. Median lifespans were; controls 613 days, low concentration 655 days, mid-concentration 635 days, and high concentration 519 days. No nasal tumours were observed. Two mid-concentration rats had adenomas of the lung. No tumours of the respiratory tract of control rats (85).

9.4 Long-term toxicity/carcinogenicity

9.4.1 Propene

As part of the National Toxicology Program (68) F344/N rats and B6C3F1 mice were exposed for 14 weeks to PE at concentrations ranging from 1 075 - 17 200 mg/m^3 (625 to 10 000 ppm) for 6 h/day, 5 days/week. No toxic effects were observed, i.e. no compound-related deaths or clinical signs were observed, and no gross or microscopic pathologic effects (including nasal cavity).

Within the National Toxicology Program, Quest and coworkers (68, 75) conducted a two-year inhalation toxicity study of PE in *F344/N rats*. Groups of 50 rats of each sex were exposed to 0 (control), 8 600 or 17 200 mg/m^3 (5 000 or 10 000 ppm) PE for 6 h each day, 5 days a week for 103 weeks. The rats were killed at 102 weeks or when moribund. The highest PE concentration used, was decided by the risk of explosion. No compound related clinical signs were observed. However, in the nasal cavities of the exposed rats, three types of non-neoplastic changes were observed; *epithelial hyperplasia* was increased in females at 17 200 mg/m^3 (0/49 control; 4/50 low concentration; 9/50 high concentration); *squamous metaplasia* was increased in males at 8 600 mg/m^3 (2/50 control; 19/50 low concentration; 7/50 high concentration) and in females at both 8 600 and 17 200 mg/m^3 (0/49 control; 15/50 low concentration; 6/50 high concentration). *Inflammatory changes* were observed in males at both concentrations and in females at 17 200 mg/m^3. The changes were significantly higher than control values ($p<0.05$). No treatment related increase in tumour incidence was observed. Observations regarding

Table 7. Long term bioassays with rats exposed to propene (PE) by inhalation.

Species (n)	PE conc. (mg/m^3)	Exposure time	Effect	Ref
SpD rats (100 m+100 f)	344	7h/d 5d/w 104 w	No increase in benign or malignant tumours	(15,58)
	1 720	7h/d, 5d/w 104 w	Slight increase in mortality* (m) No increase in benign or malignant tumours	
	8 600	7h/d, 5 d/w 104 w	Slight increase in mortality* (m) No increase in benign or malignant tumours	
F344/N rats (50 m+50 f)	8 600	6h/d, 5d/w 103 w	Epithelial hyperplasia increased; 4/50 (f) vs 0/49(ctrl) Squamous metaplasia increased; 15/50 (f) vs 0/49(ctrl), $p<0.05$; 19/50 (m) vs 2/50(ctrl), $p<0.05$ Inflammation of nasal cavity; 10/50 (f) vs 8/49(ctrl), 21/50 (m) vs 11/50(ctrl), $p<0.05$	(68,75)
	17 200	6h/d, 5d/w 103 w	Epithelial hyperplasia increased; 9/50 (f) vs 0/49(ctrl), $p<0.05$; 5/50 (m) vs 2/50(ctrl) Squamous metaplasia increased; 6/50 (f) vs 0/49(ctrl), $p<0.05$; 7/50 (m) vs 2/50(ctrl) Inflammation of nasal cavity; 13/50 (f) vs 8/49(ctrl), 19/50 (m) vs 11/50(ctrl) No increase in tumour incidence	

ctrl=control, i.e. the same sex with no PE exposure; f=female, m=male; * no data given

neoplasm in rats were confined to the thyroid gland. There were significant ($p<0.05$) negative trends in the incidence of female rats with C-cell adenomas, as well as C-cell adenomas and C-cell carcinomas combined. However, these negative trends in thyroid tumour incidence were accompanied by a positive trend in the incidence of *C-cell hyperplasia* (control 2/39, low concentration 7/47, high concentration 6/47). When the three were combined, the observed negative trends disappeared. No changes in thyroid gland pathology were noticed in the male rats exposed to PE. See also Table 7.

As part of a large study to identify potential brain carcinogens in the petrochemical industry, Maltoni and coworkers (58) exposed *SpD rats* to PE by inhalation for 7 h/day, 5 days/week for 104 weeks, after which the incidence of brain tumours (giomas and meningiomas) was investigated. PE concentrations in the air were 344, 1 720 and 8 600 mg/m^3 (200, 1 000 and 5 000 ppm). Both males and females (100 of each sex) were included in each exposure group. There was no increase in brain tumours compared to control rats.

In a long-term carcinogenicity bioassay (15) PE (purity; 97.0% PE, and small amounts of propane, ethylene, ethane, and methane) was administered to *SpD rats* (120 of each sex). The rats were exposed by inhalation 7 h/day, 5 days/week for 104 weeks, and then kept under observation until spontaneous death. The exposure concentrations were 344, 1 720 and 8 600 mg/m^3 (200, 1 000 and 5 000 ppm). The treatment did not affect the survival rate of female rats. Among male rats the *mortality rate* was increased (no data given) at both 1 720 and 8 600 mg/m^3 (1 000 and 5 000 ppm). There was no increase in any of the types of tumours studied (mammary carcinomas, leukemias, pheochromocytomas, pheochromoblastomas) in the rats. See also Table 7.

Within the National Toxicology Program, Quest and coworkers (68, 75) also conducted a two-year inhalation toxicity study of PE in *B6C3F1 mice*. Groups of 50 mice of each sex were exposed to 0 (control), 8 600 or 17 200 mg/m^3 (5 000 or 10 000 ppm) PE for 6 h each day, 5 days a week for 103 weeks. The mice were killed at 104 weeks or when moribund. The highest PE concentration used, was decided by the risk of explosion. No compound related clinical signs were observed. However, PE produced a significantly ($p<0.05$) increased incidence of *chronic focal renal inflammation* in males (17/49 and 9/49, after low and high exposure, respectively, vs 0/50 for controls) and in females (7/49 and 6/49 for low and high exposure, respectively, vs 1/50 for controls). The involved glomeruli usually showed atrophy and mild fibrosis. Both increased and decreased tumorigenic responses were observed in mice. However, no neoplastic changes were observed in the nasal cavity, neither in females nor in males. Significant ($p<0.05$) positive trends in the incidence of females with *hemangiosarcomas* (0/50 for controls, 0/49 and 3/50 for low and high exposure, respectively) or *hemangiosarcomas and hemangiomas* (0/50 for controls, 1/49 and 4/50 for low and high exposure, resp.) were observed, but the incidences in the high concentration groups were not significantly higher than those in the controls. The lesions were not site specific; hemangiosarcomas occurred in subcutaneous tissue, spleen and uterus, and hemangiomas occurred in the liver. No differences in these tumour types were noted between exposed and control groups of the male mice. *Uterine endometrial stromal polyps* occurred with a significant ($p<0.05$) positive concentration response trend in female mice (0/47 for controls, 0/47 and 3/48 for low and high exposure, respectively). However, the incidence of this lesion in the high concentration group was not significantly greater than that in the controls. There was a significant ($p<0.05$) decrease in the incidences of hepatocellular adenomas (5/50 for control, 0/49 for low, and 3/49 for high concentration), and of alveolar/bronchiolar carcinomas (9/50 for control, 1/49 for low, and 4/50 for high concentration) in male mice exposed to the low PE concentration. Furthermore, there was a significant ($p<0.05$) negative concentration response trend in the incidence of alveolar/bronchiolar adenomas and carcinomas (combined) in males (16/50 for controls, 4/49 for low, and 7/50 for high concentration). However, the control rate of alveolar/bronchiolar tumours observed in this study was considerably higher than the historical control rate observed in the NTP carcinogenicity testing program, which makes the biological significance of these results questionable. See also Table 8.

In the long-term carcinogenicity bioassay by Ciliberti and coworkers (15), PE (purity; 97.0 % PE, and small amounts of propane, ethylene, ethane, and methane) was

Table 8. Long term bioassays with mice exposed to propene (PE) by inhalation.

Species (n)	PE conc. (mg/m^3)	Exposure time	Effect	Ref.
Swiss mice (100 m + 100 f)	344	7h/d, 5d/w, 78 w	No effect on mortality. No increase in tumours	(15)
	1 720	7h/d, 5d/w, 78 w	No effect on mortality. No increase in tumours	
	8 600	7h/d, 5d/w, 78 w	Slightly increased mortality rate* (m). No diff in tumour incidenses between groups	
$B6C3F_1$ mice (50 m+50 f)	8 600	6h/d, 5 d/w, 103 w	Haemangiosarcomas; 0/49(f) vs 0/50(ctrl) Haemangiosarc+Haemangiomas; 1/49(f) vs 0/50(ctrl) Focal renal inflamation; 7/49(f) vs 1/50(ctrl), p<0.05 17/49(m) vs 0/50(ctrl), p<0.05	(68,75)
	17 200	6h/d 5d/w, 103 w	Haemangiosarcomas; 3/50(f) vs 0/50(ctrl) Haemangiosarc+Haemangiomas; 4/50(f) vs 0/50(ctrl) Focal renal inflammation; 6/49(f) vs 1/50(ctrl), p<0.05 9/49(m) vs 0/50(ctrl), p<0.05	
	8 600-17 200	6h/d 5d/w, 103 w 4/50(high conc)	Uterine endometrial stromal polyps; pos. trend (p<0.05); 0/47(ctrl), 0/47(low conc), 3/48(high conc), Hep cell adenom decrease (m); 5/50(ctrl) vs 0/49 (low conc), p<0.05, 3/49(high conc) Alveol/bronchiol carcinom decrease (m); 9/50(ctrl) vs 1/49(low conc), p<0.05, Alveol/bronchiol adenom + carcinom (m); neg trend (p<0.05) in (m), 16/50(ctrl), 4/49(low conc), 7/50(high conc)	

ctrl=control, i.e. the same sex with no PE exposure; f=female, m=male; * no data given

administered to *Swiss mice* (100 of each sex). The mice were exposed by inhalation 7 h/day, 5 days/week for 78 weeks, and then kept under observation until spontaneous death. The exposure concentrations were 344, 1 720 and 8 600 mg/m^3 (200, 1 000 and 5 000 ppm). The treatment did not affect the survival rate of the mice, except at the highest concentration, i.e. 8 600 mg/m^3 (5 000 ppm), when male mice showed a slightly increased *mortality rate* (no data given). There was no increase in the types of tumours studied, i.e. mammary carcinomas, pulmonary tumours, leukemias, and hepatomas. See also Table 8.

9.4.2 Propylene oxide

Due to the limited information about PE and the fact that PE is metabolized in vivo to PO, it seems relevant to include cancer bioassays performed with PO.

Groups of 80 male weanling *F 344 rats* were exposed by inhalation to filtered air containing 0 (control), 237 or 711 mg/m^3 (100 or 300 ppm) PO (98 % purity) vapour for about 7 h/day, 5 days/week for 104 weeks. *Mortality* was increaesed in the PO exposed rats, the effect being significant in the high concentration group ($p<0.01$). PO exposure caused an increased incidence of *inflammatory leisons* in the respiratory system, which was dose dependent. Two rats in the high concentration group developed adenomas in the nasal cavity. *Adrenal pheochromocytomas* developed in 8/78 controls, 25/78 and 22/80 rats of the low concentration and high concentration group, respectively ($p<0.05$, X^2 test). A slight, nonsignificant increase in the incidence of peritoneal mesoentheliomas was also found in the exposed groups (control, 3/78; low concentration, 8/78; high concentration, 9/80) (55).

As part of the National Toxicology Program, Renne and coworkers (68, 77) exposed groups of *F344/N rats*, 50 of each sex, by inhalation to 0 (control), 474 or 948 mg/m^3 (200 or 400 ppm) PO (>99.9 % purity) vapour for 6 h/day, 5 days/week for 103 weeks. The same survival time was observed for both exposed and non-exposed rats. A dose related increase in the incidence of *rhinitis* was observed in the exposed rats; *suppurative rhinitis* in male rats, 9/50 (controls), 21/50 (low concentration), and 38/50 (high concentration), as well as in females, 3/50 (controls), 5/48 (low concentration), and 23/48 (high concentration); *epithelial hyperplasia* in males 0/50 (controls), 1/50 (low concen-tration), and 11/50 (high concentration), and in females 1/50 (controls), 0/48 (low concentration), and 5/48 (high concentration). Suppurative inflammation, epithelial hyperplasia and squamous metaplasia of the respiratory epithelium and underlying submucosal glands of the nasal turbinates were observed in exposed rats. Papillary adenomas of the nasal cavity occurred in 3/50 of females exposed to the high concen-tration, whereas no papillary adenomas were observed in the control group or the females exposed to the lower concentration. In male rats exposed to the high concentration, 2/50 had papillary adenomas, whereas controls and low exposure males had no papillary adenomas. Historical controls had an incidence of nasal cavity tumours of 3/1 523 in females and 1/1 477 in males. The combined incidences of *C-cell adenomas and C-cell carcinomas* of the thyroid were increased in females; 2/45 control, 2/35 low concen-tration, 7/37 high concentration ($p<0.05$).

Wistar rats (groups of 100 of each sex) were exposed to 0 (control), 71.1, 237 or 711 mg/m^3 (30, 100 or 300 ppm) PO (>99.99 % pure) for 6 h/day, 5 days/week for 124 weeks (males) and 123 weeks (females). After 12, 18 and 24 months, 10 rats of each group were killed for the measurements of haematological, biochemical and urinary parameters. By 115 weeks the *mortality* of the rats (both sexes) in the high concentration group was significantly higher than in controls; $p<0.05$ (females) and $p<0.01$ (males), and the significance was further increased at 123 weeks (males) and 119 weeks (females). Statistically significant increases in *non-neoplastic nasal changes* were found in males and females in all exposure groups, i.e.71.1, 237 and 711 mg/m^3 after 12, 18, 24, and 28 months. The changes occurred in the *respiratory epithelium*, and in the *olfactory epithelium* in both females and males of the highest exposure group at all four

exopsure times, as well as in the intermediate exposure group at 24 and 28 months exposure time. The changes were found in the dorso-medial region and on the septum and nasomaxillary turbinates. No statistically significant increase in incidence of any particular type of tumour other than mammary tumours could be identified when comparing the treated rats with the controls, although a number of different types of malignant tumours occurred at very low incidence in the high concentration group and not in the controls, or showed a slightly increased incidence compared to controls. Thus the total number of rats bearing malignant tumours was significantly increased in the high concentration group compared with the control group of both sexes. The incidence of *mammary gland tumours* was significantly higher in females exposed to the high concentration, i.e. fibroadenoma; 32/69 control, 30/71 low concentration, 39/69 mid-concentration, 47/70 high concentration ($p<0.04$), tubulopapillary adenocarcinoma; 3/69 control, 6/71 low concentration, 5/69 mid-concentration, 8/70 high concentration ($p<0.01$). The incidence of *degenerative and hyperplastic changes* in the nasal mucosa were increased in all treatment groups over that in controls. Three *malignant tumours* were found in the nasal cavity of treated males; one ameloblastic fibrosarcoma in a low concentration male, one squamous-cell carcinoma in a low concentration male and one in a high concentration male. Four males in the high concentration group had a *carcinoma* in larynx or pharynx, trachea or lungs. No such tumours were seen in low concentration or control rats (51).

Within the National Toxicology Program, Renne and collegues (68, 77) exposed groups of *B6C3F1 mice*, 50 of each sex, by inhalation to 0 (control), 474 or 948 mg/m^3 (200 or 400 ppm) PO (>99.9 % purity) vapour for 6 h/day, 5 days/week for 103 weeks. The *survival* to the end of the experiment was for males; 42/50 (controls), 34/50 (low concentration) and 29/50 (high concentration), $p< 0.005$, and for females; 38/50 (controls), 29/50 (low concentration) and 10/50 (high concentration), $p< 0.005$. One squamous-cell carcinoma and one papilloma of the nasal cavity were observed in two high concentration males. Two high concentration females showed adenocarcinoma of the nasal cavity. The combined incidences of *haemangiomas and haemangiosarcomas* of the nasal cavity were for males 0/50 (control and low concentration) and 10/50 (high concentration) $p<0.001$, and for females 0/50 (control and low concentration) and 5/50 (high concentration) $p<0.05$. Inflammation of the respiratory epithelium was observed after PO exposure. Squamous metaplasia was observed in one low concentration male and in two high concentration females. Three high concentration males and three high concentration females had focal angiectasis of the submucosal turbinate vessels.

9.5 Mutagenicity and genotoxicity

When PE was tested in the L5178Y mouse lymphoma forward mutation assay (61), no mutagenic effect was observed with atmospheres of up to 30 % (v/v) PE in the absence of an exogenous metabolic activating system (S9 mix). In the presence of S9 mix, the results varied between experiments in an erratic way. The authors concluded that the overall response was questionable and the mutagenic potential of PE could not be further

categorized. PE did not induce gene mutation in the reverse mutation assay with Salmonella typhimurium TA100 exposed to 20 % PE in air for 7 h, in the presence or absence of S9 mix (61), or exposed to 336 000 µg/ml in the atmosphere of the exposure chamber, with or without S9 mix (105).

The PE metabolite PO was active in about 70 % of the studies performed to test for mutagenicity and genotoxicity. Thus, PO induced DNA damage and gene mutation in bacteria, gene mutations in yeast and fungi, and induced sex-linked recessive lethal mutations in Drosophila melanogaster. In mammalian cells in vitro, PO induced DNA damage, gene mutation, sister chromatide exchange, and chromosomal aberrations. PO also induced chromosomal aberrations and micronuclei in mouse bone marrow cells, and sister chromatide exchange and chromosomal aberrations in human lymphocytes in vitro (25, 37, 38).

9.6 Reproductive and developmental toxicity

No information was found regarding embryo and fetal toxicity due to PE exposure. However, PO, at a concentration causing no mortality in nonpregnant or pregnant rats, but some reduction in the body weight gain and a significant increase in the relative kidney weight, showed some effects on the reproduction status. Sexually mature female SpD rats were exposed to 1 188 mg/m^3 (500 ppm) PO for 7 h/day, 5 days/week for three weeks before breeding, and days 1-16 of gestation. The exposure led to a significant ($p<0.01$) reduction in the number of corpora lutea (13.8$\pm$3.0, n=43 vs 15.4$\pm$3.1, n=46 for controls) and implants, number of live fetuses, fetal weight and length. No effect on resorptions was observed. Some skeletal alterations (rib dysmorphology and reduced ossification) were increased. Resorptions were increased in the rats exposed to PO only on days 7-16 of gestation, but not in those exposed only on days 1-16 of gestation. Rabbits appeared relatively unaffected by 1 188 mg/m^3 (500 ppm) PO (33).

10. Observations in Man

10.1 Irritation and sensitization

No data were found for PE.

10.2 Acute effects by contact and systemic distribution

PE gas is not irritating to the skin or the eye. However, liquid PE may cause frostbite. The main health concern has been the fact that PE can displace oxygen in the atmosphere and thus cause suffocation due to lack of oxygen (asphyxiation) (ACGIH). No toxic effects were seen in workers exposed to PE on a short-term basis in the workplace (86).

10.3 Effects of repeated exposure on organ systems

No data were found.

10.4 Genotoxic effects

No data were found for PE.

However, there is one study on chromosomal aberrations and micronuclei in lymphocytes in 20 workers exposed to PO for 1-20 years. The average concentration of PO in the breathing zone varied between 0.79 and 27.1 mg/m^3 (0.3 -11.4 ppm). With shorter sampling periods (20 minutes), a peak concentration of 133 mg/m^3 (56 ppm) was measured (35). Mean values were; micronuclei, 2.6 ‰ (range 0-6), total number of chromosomal aberrations, 4.7 % (range 1-11), gaps, 3.0 % (range 1-8), and breaks, 2.0 % (range 0-4). The results were only compared to those observed in ethylene oxide exposed workers, the results being significantly higher in the latter group. No data were given for unexposed individuals. This observation of a limited clastogenic potency of PO is in line with the findings by Lynch et al (55) that PO is practically unable to induce chromosomal aberrations and sister chromatid exchange in monkeys inhaling the compound for long periods of time. The PO exposed workers were also investigated with regard to N-acetoxy-2-acetylaminofluorene-induced unscheduled DNA sythesis (UDS) in mononuclear leukocytes. The PO exposed workers (28.5 mg/m^3 (12 ppm) for 1-20 years) had reduced levels of UDS, 495±31 cpm dTd/µg DNA as compared to the referent group, 648±81 cpm dTd/µg DNA ($p<0.05$). The authors concluded that exposure to relatively low doses of PO can cause individuals to be at increased risk due to a reduced capacity to repair DNA lesions (72).

10.5 Carcinogenic effects

Acquavella and coworkers (2) carried out a descriptive cohort study of 335 men who had been working in a polypropylene manufacturing plant for at least six months during 1960-85. Allowing a 10-year induction period from the first exposure, they found 7 incidences of colorectal cancers, when 1.3 was expected (a significant 5.6-fold colorectal cancer excess). On the same work force, a case (n=24)-control (n=72) study of adenomatous polyps and carcinoma in situ in the large bowel was carried out subsequently (3). Among the 24 cases there was a tendency towards having higher exposure to pre-extrusion polymer plus additives (OR=2.6, 90 % CI 1.5-15.3). Analyses by job area of the plant, however, did not indicate additional risk factors. PE was handled at the plant, but so were also several other chemicals. No classification of subjects according to PE-exposure was done in the studies. Thus, it is not possible to assess the risk in relation to PE-exposure specifically. The authors suggested that confirmatory experimental and epidemiological studies are needed (2, 3).

10.6 Reproductive and developmental effects

No data were found.

11. Dose-Effect and Dose-Response Relationships

11.1 Single/short-term exposure

There are few studies dealing with short-term effects, and no permanent adverse effects were observed after short-term exposure. Within 24 hours most affected functions/levels had returned back to normal.

In cats, anaesthesia was induced within 2 minutes by 50 % PE in oxygen or air, whereas 2 minutes exposure to 70 % PE in oxygen or air caused a toxic effect. However, the recovery back to normal was rapid (18).

F 344 rats exposed by inhalation to 10.32 mg/m^3 (6 ppm) PE for 20 minutes had significantly reduced levels of nasal (ethmoturbinate 90 %, and maxilloturbinate 55 %) and hepatic (90 %) microsomal cytochrome P-450 compared to control values, and this decrease was further reduced by the inhalation of 1 032 mg/m^3 (600 ppm) PE for 20 minutes, i.e. ethmoturbinate 60 %, maxilloturbinate 41 %, and hepatic 70 % of the control values. After 6 h exposure to the lower concentration, the maxilloturbinate and hepatic cytochrome P-450 remained reduced (45 % and 85 %, resp.) whereas the ethmoturbinate cytochrome P-450 level increased to 120 % of the control value. After 6 h exposure to the higher concentration, the maxilloturbinate and hepatic cytochrome P-450 levels were increased to 120 % and 135 %, respectively, whereas the ethmoturbinate cytochrome P-450 level was reduced to 90 % of the control value (59). See also Table 6.

In SpD rats exposed to 86 000 mg/m^3 PE for 2h and 4 h, respectively, no hepatotoxic effects were observed. However, pretreatment of the rats with PCB (ubiquitous environmental pollutant) followed by PE exposure, decreased the level of hepatic cytochrome P-450 compared to control levels (PCB, no PE), the effect being more marked after 4 h of PE exposure than 2 h of PE exposure (70). See Table 6.

Rats and mice exposed for 14 days to 1 075 - 17 200 mg/m^3 PE showed no signs of toxicity (nasal cavity was also studied). Neither did rats exposed to 1 031 or 2 062 mg/m^3 PO by inhalation for 30 days, or 4 124 mg/m^3 PO for eight days (due to high mortality) and then observed for life. No nasal tumours were observed. However, two mid-concentration rats had adenomas of the lung (85).

11.2 Long-term exposures

In the three long-term inhalation studies with rats and mice, no adverse effects (except a slight increase in mortality) were observed with SpD rats or Swiss mice, whereas F344 rats and B6C3F$_1$ mice exposed to similar PE concentrations showed some dose-related effects.

Exposure by inhalation to 344, 1 720 or 8 600 mg/m^3 PE for 104 weeks (SpD rats) or 78 weeks (Swiss mice) caused no increase in any of the types of tumours studied, including brain tumours, and the PE exposure did not affect the survival rate in the female rats and mice. However, in the male rats the mortality rate was increased at both 1 720 and 8 600 mg/m^3 and in the male mice the mortality rate was slightly increased at 8 600 mg/m^3 (no data given). No compound related clinical signs were observed in either species (15, 58).

Exposure of F344 rats and B6C3F$_1$ mice to 8 600 or 17 200 mg/m^3 PE, by inhalation, caused no compound related clinical signs in either species, and no neoplastic changes were observed in the nasal cavity. However, three types of non-neoplastic changes were observed in the nasal cavities of F344 rats, squamous metaplasia, epithelial hyperplasia, and inflammatory changes. There was a statistically significant increase in squamous metaplasia in the rats (both sexes) after exposure to 8 600 mg/m^3, but only in female rats at 17 200 mg/m^3. Epithelial hyperplasia was significantly increased ($p<0.05$ vs controls) in female rats exposed to the high PE concentration, with a small, non-significant increase (vs controls) at the lower concentration. An increased incidence ($p<0.05$ vs controls) of inflammatory changes was observed in male rats, although the increase was statistically significant only at the lower exposure level. In female F344 rats, there were negative trends in the incidence of thyroid C-cell adenomas, as well as C-cell adenomas and C-cell carcinomas combined, but a positive trend in the incidence of C-cell hyperplasia. Since C-cell hyperplasia, C-cell adenomas, and C-cell carcinomas appear to represent a continuous spectrum of progressive lesions in the rat, the three were combined, and thereby the observed negative trends disappeared. No changes in thyroid gland pathology were noticed in the male F344 rats. In the B6C3F$_1$ mice, PE produced a significantly ($p<0.05$) increased incidence of chronic focal renal inflammation in male and female mice exposed to both PE concentrations, i.e. 8 600 or 17 200 mg/m^3. Both increased and decreased tumorigenic responses were observed in the B6C3F$_1$ mice. Significant ($p<0.05$) positive trends in the incidence of female mice with hemangiosarcomas or hemangiosarcomas and hemangiomas combined were observed, but the incidences in the high concentration groups were not significantly higher than those in the controls. No differences in these tumour types were noted between exposed and control groups of male mice. Uterine endometrial stromal polyps occurred with a significant ($p<0.05$) positive concentration response trend in female mice. However, the incidence of this lesion in the high concentration group was not significantly greater than that in the controls. There was a significant ($p<0.05$) negative concentration response trend in the incidences of hepatocellular adenomas, and of alveolar/bronchiolar carcinomas in male mice exposed to the low PE concentration. However, the control rate of alveolar/bronchiolar tumours observed in this study was considerably higher than the historical control rate observed in the NTP carcinogenicity testing program, which makes the biological significance of these results questionable (68, 75). See also Tables 7 and 8.

Exposure of F344 rats and B6C3F$_1$ mice, by inhalation, to 474 or 948 mg/m^3 PO for 103 weeks caused a dose-related increase in the incidence of rhinitis in both species. When exposed to the high PO concentration, neoplastic lesions in the nasal cavity were observed in both species, as well as a significant ($p<0.05$) incidence of nasal haemangiomas and haemangiosarcomas in the mice. Papillary adenomas of the nasal cavity was increased ($p=0.037$ by trend test) in high concentration F344 rats, both sexes. No primary nasal cavity tumours were present in the low concentration group. The combined incidences of C-cell adenomas and C-cell carcinomas of the thyroid were significantly increased in the female rats. The same survival time was observed for both exposed and non- exposed rats. In the mice exposed to 948 mg/m^3 PO, one squamous-cell carcinoma, one papilloma, and one adenocarcinoma were observed in the nasal cavity. The combined

incidences of haemangiomas and haemangiosarcomas in the nasal cavity were significantly increased in both male and female mice. Inflammation of the respiratory epithelium and squamous metaplasia were observed. Three high concentration male and female mice had focal angietactis of the submucosal turbinate vessels. The survival to the end of the experiment was reduced in both male and female mice (68, 77).

In rats exposed to 71.1, 237 or 711 mg/m^3 PO for 124 weeks (Wistar), and 237 or 711 mg/m^3 PO for 104 weeks (F344), the incidence of mammary gland tumours was significantly higher in female Wistar rats exposed to the high concentration, and a dose dependent, increased incidence of inflammatory lesions was observed in the respiratory system of F344 rats. The incidence of degenerative and hyperplastic changes in the nasal mucosa was increased in all treatment groups over that in controls. Three malignant tumours were found in the nasal cavity of treated males. Four male rats in the high concentration group had carcinoma in larynx or pharynx, trachea or lungs. Two F344 rats in the high concentration group developed adenomas in the nasal cavity. Adrenal pheochromocytomas developed in both low concentration and high concentration rats. Mortality was increaesed in the PO exposed rats, the effect being significant in the high concentration group (51, 55).

The increase in mammary gland tumours observed by (51) occurred towards the end of their study which ran for 119 weeks. This late response might be one explanation for the lack of mammary tumours in the studies by Lynch et al (55) and (77) who stopped their studies at 104 weeks. Moreover, the different strains used may be another reason for this discrepancy. Exposure to PO increased the incidence of degenerative and hyperplastic changes in the nasal mucosa in all of the treatment groups compared to controls. The severity of these changes did not alter greatly during the course of the study.

In sum: Inhalation of PE on a long-term basis evoked non-neoplastic toxic changes in the nasal cavity of rats (i.e. epthelial hyperplasia, squamous metaplasia, and inflammatory changes) but not in mice (68, 75). However, in male mice the incidence of chronic focal renal inflammation was increased, and in female mice uterine endometrial stromal polyps were increased and, to a lesser extent, hemangiosarcomas as well as hemangiosarcomas and hemangiomas combined.

There was some evidence of carcinogenicity (68, 77) in F344 rats exposed to PO, as indicated by an increased incidence of papillary adenomas of the nasal epithelium in the rats, of both sexes. There was clear evidence of carcinogenicity (68, 77)as indicated by increased incidences of hemangiomas and hemangiosarcomas of the nasal mucosa in mice exposed to PO. Exposure to PO also caused suppurative inflammation, hyperplasia, and squamous metaplasia in the nasal epithelium of rats and inflammation in mice.

12. Previous Evaluations by (Inter)national Bodies

PE and PO have been evaluated as potential environmental pollutants in Sweden (104-106) . Cancer was concidered the critical effect for risk assessment. A quantitative risk assessment was done using a safety factor model, which gave a low risk level (life-time

risk of 1 in 10^5) of 200 ppb. The rad-equivalence and quantitative cancer risk assessment for PO gave a low risk level of 1-10 ppb, assuming that about 10 % of inhaled PE is metabolized to PO in humans. The authors suggested that the higher figure should be used. However, they pointed out that the calculations were based on very weak assumptions (104) Furthermore, it should be pointed out that these figures were calculated for a daily life-time exposure for 24 hours.

EPA (22, 23) has made a quantitative cancer risk assessment for PO, based on one dose level (952 mg/m^3) giving an increase in hemangioma and hemangiosarcoma in the nasal cavity of mice exposed in the NTP study (68) The EPA multi-stage model gave a unit risk of $3.7x10^{-6}$ per µg/m^3, which corresponds to $1x10^{-5}$ per 2.7 µg/m^3 or 1.1 ppb.

PE and PO were recently evaluated by IARC (37, 38) regarding their potential carcinogenic activity. IARC states that there is "inadequate evidence in experimental animals and humans for the carcinogenicity of PE". The overall evaluation states that "PE is not classifiable as to its carcinogenicity to humans (Group 3)". PO was degraded from group 2A to 2B ("PO is possibly carcinogenic to humans") due to inadequte genotoxicity data. The evaluation was based on "inadequate evidence in humans for the carcinogenicity of PO", and "sufficient evidence in experimental aimals for the carcinogenicity of PO". As comparison, the data on ethene, which was evaluated at the same meeting, were also regarded as "inadequate evidence in humans and experimental animals for the carcinogenicity of ethylene". The overall evaluation states that "Ethylene is not classifiable as to its carcinogenicity to humans (Group 3)". Ethylene oxide was uppgraded to Group 1, i.e. "Ethylene oxide is carcinogenic to humans". The evaluation was based on "limited evidence in humans, and sufficient evidence in experimental animals for the carcinogenicity of ethylene oxide" (36)

ACGIH and NIOSH have not established an occupational exposure limit for PE. However, ACGIH has pointed out that PE is an asphyxiant.

13. Evaluation of Human Health Risks

13.1 Groups at extra risk

There is no specific group that can be assumed to be at extra risk due to PE exposure.

13.2 Assessment of health risks

The limited human studies on effects of PE exposure indicate that PE gas is not irritating to skin or eyes, whereas liquid PE may cause frostbite. No toxic effects were observed after short-term exposure of workers. The two cancer studies on PE exposed workers indicated an increased risk in colorectal cancer incidence and carcinoma in situ of the large bowl. However, no PE measurements were done, and there was simultaneous exposure to several other chemicals.

The acute toxic effects observed in experimental animals disappeared rapidly after cessation of exposure. Short-term exposure caused no toxic effects in rats and mice.

Long-term exposure gave varying results. No significant tumour incidences were observed in rats in the three studies, whereas hemangiosarcomas developed in exposed mice. Some non-neoplastic, as well as, inflammatory changes were observed in the nasal cavity of exposed animals.

Rats exposed to PO showed a dose-related increase in rhinitis and, in female rats, papillary adenomas of the nasal cavity. Female rats also showed an increase in C-cell adenomas and C-cell carcinomas of the thyroid, as well as mammary gland tumours. The combined incidence of hemangioma and hemangiosarcoma was increased in mice exposed to PO.

According to the IARC (37) evaluation, there is inadequate evidence in both humans and experimental animals for the carcinogenicity of PE. However, the major PE metabolite in vivo is PO, and there are studies showing the presence of hydroxypropyl adducts in hemoglobin in humans and in hemoglobin and DNA from experimental animals exposed to PE by inhalation. The evidence for the carcinogenicity of PO in humans are inadequte, but there is sufficient evidence for the carcinogenicity of PO in animals. Although IARC has degraded PO in its latest evaluation (38, 39) it still evaluates PO as a possible carcinogen in humans.

Törnqvist and Ehrenberg (92, 94-97, 99) have calculated the cancer risk associated with PE exposure, using their risk estimates for ethene as the basis. From animal experiments, they have estimated that approximately 5 % of inhaled PE is metabolized to PO (87), which appears to be detoxified about 4 times faster than ethylene oxide in animals exposed to engine exhausts (101)and about 20 times faster than ethylene oxide in smokers (94). The two epoxides are equally effective point mutagens, although ethylene oxide is more effective than PO with respect to genetic effects involving recombination (4). Based on these data, the risk from PO is assumed to be five times less than the risk from ethylene oxide. With the rad-equivalence approach a life-time risk of $2x10^{-5}$ is expected. This would correspond to an estimated cancer risk, in Sweden, from PE in urban air pollution of 5 cancer cases/year at a mean exposure level of 2.3 µg/m^3. The estimation is based on 24 h exposure. The corresponding data for ethylene give 30 cancer cases/ year at a mean exposure level of 1.8 µg/m^3.

When setting an occupational exposure limit for PE, one should bear in mind the fact that workers occupationally exposed to PE also are exposed to PE as an air pollutant on a daily basis.

13.3 Scientific basis for an occupational exposure limit

On the data available, it is not possible to rule out PE as a carcinogen, albeit a very weak one. Thus, cancer should be regarded as the critical effect for the assessment of an occupational exposure limit.

14. Research Needs

For the estimation of cancer risks from PE in the occupational setting, knowledge of the target dose is essential, dose being defined as the time integral of the concentration in target tissues. In vivo doses from chronic or intermittent PE exposures can be determined from established steady-state levels of macromolecule (Hb) adducts of the reactive compound, i.e. PO. Thus, the measurement of Hb adducts should be done on humans exposed to PE for various lenghts of time. Moreover, carefully conducted epidemiological studies, in which the exposure levels are properly measured, are needed. The studies in humans could preferably be combined with Hb and DNA adduct studies in experimental animals. Reproductive and developmental toxicity due to PE exposure should be looked into, especially in view of the observed detrimental effects on the number of corpora lutea, implants and live fetuses, which were observed in PO exposed rats. PE exposure per se did not cause any hepatotoxic effects in experimental animals. However, in rats pretreated with the ubiquitous, environmental pollutant PCB, acute, hepatotoxic effects were induced by PE exposure. Thus, the interaction between PE and other chemicals with a similar action to PCB should be investigated.

15. Summary

Beije B. 117. Propene. The Nordic Expertgroup for Criteria Documentation of Health Risks from Chemicals. *Arbete och Hälsa* 1995;7:1-41.

Propene (PE) is an important industrial chemical, which is also present as a contaminant in urban air and cigarette smoke. PE is metabolized to propylene oxide (PO), which binds to macromolecules, i.e. hemoglobin and DNA. PE is an asphyxiant. Human data are scarce. Inhalation of PE on a long-term basis gave rise to non-neoplastic toxic changes in the nasal cavity of rats, but not of mice. In male mice the incidence of chronic focal renal inflammation was increased. In female mice, uterine endometrial stromal polyps increased and, to a leser extent, hemangiosarcoma as well as hemangiosarcoma and hemangioma combined. There are limited data on the potential health hazard to humans due to PE exposure. However, as the metabolite, PO, is carcinogenic to experimental animals, it is not possible at the present time to rule out PE as a human carcinogen.

Key words: Cancer, genotoxicity, non-neoplastic effects, occupational exposure limit, propene, propylene oxide.

16. Summary in Swedish

Beije B. 117. Propen. Nordiska expertgruppen för kriteriedokumentation av kemiska hälsorisker. *Arbete och Hälsa* 1995;7:1-41.

Propen (PE) är en viktig industrikemikalie, som även förekommer som förorening i tätortsluft och cigarettrök. PE metaboliseras till propylenoxid (PO), som binder till makromolekyler, såsom hemoglobin och DNA. PE är ett asfyxiant. Det finns få humandata. Inhalation av PE under lång tid ger upphov till icke-neoplastiska toxiska förändringar i näshålan hos råttor, men inte hos möss. Hos hanmöss ökade incidensen av kronisk fokal njurinflammation. Hos honmöss ökade antalet polyper i livmoderslem-hinnan, samt i midre utsträckning även hemangiosarkom och hemangiosarkom och hemangiom kombinerat. Det finns få data om potentiella hälsorisker för människa vid inandning av PE. Eftersom metaboliten, PO, är carcinogen i försöksdjur, kan man för närvarande inte utesluta att PE kan ge upphov till cancer.

Nyckelord: Cancer, genotoxocitet, hygieniskt gränsvärde, icke-neoplastiska effekter, propen, propylenoxid.

17. References

1. ACGIH. *Threshold Limit Values and Biological Exposure Indices for 1994-95*. Cincinnati, OH: American Conference of Governmental Industrial Hygienists, 1994.
2. Acquavella J, Douglass T, Phillips S. Evaluation of excess colorectal cancer incidence among workers involved in the manufacture of polypropylene. *J Occup Med* 1988;30:438-442.
3. Acquavella JF, Owen C, Bird M, Yarborough C, Lynch J. An adenomatous polyp case-control study to assess occupational risk factors following a workplace colorectal cancer cluster. *Am J Epidemiol* 1991;133:357-367.
4. Agurell E, Cederberg H, Ehrenberg L, Lindahl-Kiessling U, Rannug U, Törnqvist M. Genotoxic effects of ethylene oxide and propylene oxide: A comparative study. *Mutat Res* 1991;250:229-237.
5. Altshuller A. Review: natural volatile organic substances and their effect on air quality in the United States. *Atmos Environ* 1983;17:2131-2165.
6. Amoore JE, Hautala E. Odor as an aid to chemical safety: Odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. *J Appl Toxicol* 1983;3:272-290.
7. Anlauf K, Bottenheim J, Brice K, et al. Measurement of atmospheric aerosols and photochemical products at a rural site in SW Ontario. *Atmos Environ* 1985;19:1859-1870.
8. Aronian P, Scheff P, Wadden R. Wintertime source-reconciliation of ambiant organics. *Atmos Environ* 1989;23:911-920.
9. Bailey J, Gunary K, Schmidl B, Williams M. Speciated hydrocarbon emissions from vehicles operated over the normal speed range on the road. *Sci Total Environ* 1990;93:199-206.
10. Bailey J, Schmidl B, Williams M. Speciated hydrocarbon emissions from vehicles operated over the normal speed range on the road. *Atmos Environ* 1990;24A:43-52.
11. Barrefors G, Petersson F. Volatile hazardous hydrocarbons in a Scandinavian urban road tunnel. *Chemosphere* 1992;25:691-696.
12. Becka M, Bolt HM, Urfer W. Statistical analysis of toxicokinetic data by nonlinear regression (example: Inhalation pharmacokinetics of propylene). *Arch Toxicol* 1992;66:450-453.
13. Bos R, Guicherit R, Hoogeveen A. Distribution of some hydrocarbons in ambient air near Delft and the influence on the formation of secondary air pollutants. *Sci total Environ* 1977;7:269-281.
14. Braddock J, Bradow R. *Emission patterns of diesel-powered passenger cars*. Warrendale, Pa, Society of Automotive Engineers, Inc., 1975 (Paper No 750682).
15. Ciliberti A, Maltoni C, Perino G. Long-term carcinogenicity bioassays on propylene administered by inhalation to Sprague-Dawley rats and Swiss mice. *Ann N Y Acad Sci* 1988;534:235-45.
16. Colbeck I, Harrison R. The concentrations of specific C_2-C_6 hydrocarbons. *Atmos Environ* 1985;19:1899-1904.
17. Conolly RB, Osimitz TG. Mixed function oxidase system inducers and propylene hepatotoxicity. *Toxicologist* 1981;1:406.
18. Easson-Brown W. Experiments with anestethic gases propylene, methane, dimethyl-ether. *J Pharmacol Exp Ther* 1924;23:485-496.
19. Ehrenberg L, Törnqvist M. *Småskalig vedeldning och cancerrisker. Kunskapssammanställning*. Solna, Naturvårdsverket, 1993 (Rapport 4224). In Swedish.
20. Eide I, Hagemann R, Zahlsen K, et al. Uptake, distribution, and formation of hemoglobin and DNA adducts after inhalation of C2-C8 1-alkene (olefins) in the rat. *Carcinogenesis* 1995. In press.
21. Eisele P, Killpack R, ed. Propene. In. Elvers B, Hawkins S, Russey W, Schulz G, eds. *Ullmann's Encyclopedia of Indsutrial Chemistry; Vol. A22*. 5th ed. New York: VCH Publishers, 1993:211-222.
22. EPA/OTS. *Final statement to international joint study group on the long-term effects of propylene*. Enviroment Protection Agency/OTS doc FYI-OTS-0681-0116:Bologna Tumour CTR/Inst Oncolo.
23. EPA/OTS. *Photochemical reactivity of trichloroethylene and other chlorinated solvents in the presence of other organic materials in a simulated atmospheric environment as related*. Enviroment Protection Agency/OTS doc 878211062.

24. Farmer P, Bailey E, Gorf S, et al. Monitoring human exposure to ethylene oxide by the determination of hemoglobin adducts using gas chromatography-mass spectrometry. *Carcinogenesis* 1986;7:637-640.
25. Farooqi Z, Törnqvist M, Ehrenberg L, Natarajan AT. Genotoxic effects of ethylene oxide and propylene oxide in mouse bone marrow cells. *Mutat Res* 1993;288:223-228.
26. Filser JG, Bolt HM. Exhalation of ethylene oxide by rats on exposure to ethylene. *Mutat Res* 1983;120:57-60.
27. Frostling H, Hoff A, Jacobsson S, Pfäffli P, Vainotalo S, Zitting A. Analytical, occupational and toxicological aspects of the degradation products of polypropylene plastics. *Scand J Work Environ Health* 1984;10:163-169.
28. Giannovario JA, Grob R, Rulon P. Analysis of trace pollutants in the air by means of cryogenic gas chromatography. *J Chromatogr* 1976;121:285-294.
29. Golka K, Peter H, Denk B, Filser JG. Pharmacokinetics of propylene and its reactive metabolite PO in Sprague Dawley rats. *Arch Toxicol* 1989;Suppl 13:240-242.
30. Granath F, Ehrenberg L, Törnqvist M. Degree of alkylation of macromolecules in vivo from variable exposure. *Mutat Res* 1992;284:297-306.
31. Granath F, Rohlén O, Göransson C, Hansson L, Magnusson A-L, Törnqvist M. Relationship between dose in vivo of ethylene oxide and exposure to ethene studied in exposed workers. *Scand J Work Environ Health* 1995. Accepted.
32. Grosjean D, Fung K. Hydrocarbons and carbonyls in Los Angeles air. *J Air Pollut Control Assoc* 1984;34:537-543.
33. Hardin B, Niemeier R, Sikov M, Hackett P. Reproductive-toxicologic assessment of the epoxides ethylene oxide, propylene oxide, butylene oxide, and styren oxide. *Scand J Work Environ Health* 1983;9:94-102.
34. Hov Ø, Schmidbauer N, Oehme M. C_2-C_5 hydrocarbons i rural south Norway. *Atmos Environ* 1991;25A:1981-1999.
35. Högstedt B, Bergmark E, Törnqvist M, Osterman-Golkar S. Chromosomal aberrations and micronuclei in lymphocytes in relation to alkylation of hemoglobin in workers exposed to ethylene oxide and propylene oxide. *Hereditas* 1990;113:133-138.
36. IARC. Ethylene oxide. In: *IARC Monographs on the Evaluation of Carcinogenic Risks to Human: Some Industrial Chemicals*. Lyon: International Agency for Research on Cancer,1994;60:73-161.
37. IARC. Propylene. In: *IARC Monographs on the Evaluation of Carcinogenic Risks to Human: Some Industrial Chemicals*. Lyon: International Agency for Research on Cancer, 1994;60:161-181.
38. IARC. Propylene oxide. In: *IARC Monographs on the Evaluation of Carcinogenic Risks to Human: Some Industrial Chemicals*. Lyon: International Agency for Research on Cancer, 1994;60:181-215.
39. IARC. Propylene oxide (Group 2 A). In: *IARC monographs on the evaluation of carcinogenic risk of chemicals to man: Overall evaluations of carcinogenicity: An updating of IARC Monographs volymes 1-42*. Lyon: International Agency for Research on Cancer, 1987, Suppl 7: 328-329.
40. Jankovic J, Jones W, Burkhart J, Noonan G. Environmental study of firefighters. *Ann OccupHyg* 1991;35:581-602.
41. Jeltes R, Burghardt E. Automatic gas chromatographic measurement of C_1-C_5 hydrocarbons in air. *Atmos Environ* 1972;6:793-805.
42. Kanakidou M, Bonsang B, Lambert G. Light hydrocarbons vertical profiles and fluxes in a French rural area. *Atmos Environ* 1989;23:921-927.
43. Katzman H, Libby W. Hydrocarbon emissions from jet engines operated at simulated high-altitude supersonic flight conditions. *Atmos Environ* 1975;9:839-842.
44. Kautiainen A, Midtvedt T, Törnqvist M. Intestinal bacteria and endogenous production of malonaldehyde and alkylators in mice. *Carcinogenesis* 1993;14:2633-2636.
45. Kautiainen A, Tornqvist M. Monitoring exposure to simple epoxides and alkenes through gas chromatographic determination of hemoglobin adducts. *International Archives of Occupational and Environmental Health* 1991;63:27-31.

46. Khalil MAK, Rasmusen RA. Forest hydrocarbon emissions: relationships between fluxes and ambient concentrations. *J Air Waste Manag Assoc* 1992;42:810-813.
47. Khalil MAK, Rasmussen RA, Wang M-X, Ren L. Emissions of trace gases from Chinese rice fields and biogas generators: CH_4, N_2O, CO, CO_2, chlorocarbons, and hydrocarbons. *Chemosphere* 1990;20:207-226.
48. Kim A, Douglas L. *Gases desorbed from five coals of low gas content: Report of investigations.* Washington DC, Bureau of Mines, 1973 (7768).
49. Kreuzer L, Kenyon N, Patel C. Air pollution: sensitive detection of ten pollutants gases by carbon monoxide and carbon dioxide lasers. *Science* 1972;177:347-349.
50. Kunze K, Mangold B, Wheeler C, Beilan H, Montellano PO. The cytochrome P-450 active site. Regiospecificity of prosthetic heme alkylation by olefins and acetylenes. *J Biol Chem* 1983;258:4202-4207.
51. Kuper C, Reuzel P, Feron V, Verschuuren H. Chronic inhalation toxicity and carcinogenicity study of propylene oxide in Wistar rats. *Fd Chem Toxic* 1988;26:159-167.
52. Lamontagne R, Smith W, Swinnerton J. C1-C3 hydrocarbons and chlorophyll a concentrations in the equatorial Pacific Ocean. In: Gibb T, ed. *Analytical Methods in Oceanography, Advances in Chemistry Series. Vol 147* . Washington DC: American Chemical Society, 1975: 163-171.
53. Leigh D, Lynaugh N. Qualitative and quantitative analysis of dissolved gas by gas chromatography-mass spectrometry. *Adv Mass Spectrom*1974;6:463-470.
54. Lightman P, Kallend A, Marsh A, Jones B, Penkett S. Seasonal variation of hydrocarbons in the free troposphere at mid-latitudes. *Tellus* 1990;42B:408-422.
55. Lynch DW, Lewis TR, Moorman WJ, et al. Sister-chromatid exchanges and chromosome aberrations in lymphocytes from monkeys exposed to ethylene oxide and propylene oxide by inhalation. *Toxicol Appl Pharmacol* 1984;76:85-95.
56. Löfgren L, Petersson G. Proportions of volatile hazardous hydrocarbons in vehicle-polluted urban air. *Chemosphere* 1992;24:135-140.
57. Löfroth G, Burton RM, Forehand L, et al. Characterization of environmental tobacco smoke. *Environ Sci Technol* 1989;23:610-614.
58. Maltoni C, Ciliberti A, Carretti D. Experimental contributions in identifying brain potential carcinogens in the petrochemical industry. *Ann NY Acad Sci* 1982;381:216-249.
59. Maples KR, Dahl AR. Blood levels of propylene oxide during propylene inhalation and effect on hepatic and nasal cytochrome P-450 concentrations. *Drug Metabol Disp*1991;19:835-837.
60. Maples KR, Dahl AR. Levels of epoxides in blood during inhalation of alkenes and alkene oxides. *Inhal Toxicol* 1993;5:43-54.
61. McGregor D, Brown AG, Cattanach P, et al. Responses of the L5178Y mouse lymphoma forward mutation assay: V. Gases and vapors. *Environ Mol Mut agen*1991;17:122-129.
62. Middleton P, Stockwell WR, Carter WPL. Aggregation and analysis of volatile organic compound emissions for regional modeling. *Atmos Environ* 1990;24A:1107-1133.
63. Mowrer J, Lindskog A. Automatic unattended sampling and analysis of background levels of C_2-C_5 hydrocarbons. *Atmos Environ* 1991;25A:1971-1979.
64. Netravalkar AJ, Rao A. Seasonal variations in the concentrations of ethylene, acetylene and propylene at Trombay, Bombay. *Sci total Environ* 1984;35:33-40.
65. NIOSH. *Recommendations for Occupational Safety and Health* . Cincinnati OH: National Institute for Occupational Safety and Health, 1992 (Publication no 92-100).
66. NIOSH. Environmental study of firefighters. *Ann OccupHyg* 1991;35:581-602.
67. NIOSH. Properties of 220 Rn progency (212Pb) in the presence of trace gases. *Sci Total Environ* 1992;112:251-262.
68. NTP. *Toxicology and carcinogenesis studies of propylene in F 344/N rats and 86C3F1 mice (inhalation studies).* Research Triangle Park, NC: National Toxicology Program, 1985 (Technical Report Series 1985:272).
69. O'Mara M. The combustion products from synthetic and natural products-Part 1: Wood. *J Fire Flammability* 1974;5:34-53.

70. Osimitz T, Conolly R. Mixed function oxidase system induction and propylene hepatotoxicity. *J Toxicol Environ Health* 1985;15:39-49.
71. Osterman-Golkar S, Bailey E, Farmer P, Gorf S, Lamb J. Monitoring exposure to propylene oxide through the determination of hemoglobin alkylation. *Scand J Work Environ Health* 1984;10:99-102.
72. Pero R, Brygelsson T, Widegren B, Högstedt B, Welinder H. A reduced capacity for unscheduled DNA synthesis in lymphocytes from individuals exposed to propylene oxide and ethylene oxide. *Mutat Res* 1982;104:193-200.
73. Persson K-A, Berg S. Automatic determination of selected C_2-C_4 hydrocarbons in urban air by solid sorbent sampling and gas chromatography. *Chromatographia* 1989;27:55-59.
74. Purohit V, Orzel RA. Polypropylene: a literature review of the thermal decomposition products and toxicity. *J Am Coll Toxicol* 1988;7:221-242.
75. Quest JA, Tomaszewski JE, Haseman JK, Boorman GA, Douglas JF, Clarke WJ. Two-year inhalation toxicity study of propylene in F344/N rats and B6C3F_1 mice. *Toxicol Appl Pharmacol* 1984;76:288-295.
76. Rao AMM, Netravalkar AJ, Arora PK, Vohra KG. Determination of ethylene and other reactive hydrocarbons in the atmospheric air at Trombay, Bombay by gas chromatography using a chemiluminescent detector. *Atmos Environ*1983;17:1093-1097.
77. Renne R, Giddens W, Boorman G, Kovatch R, Haseman J, Clarke W. Nasal cavity neoplasia in F344/N rats and (C57BL/6XC3H)F1 mice inhaling propylene oxide for up to two years. *J Natl Cancer Inst* 1986;77:573-582.
78. Rochkind M. Infrared analysis of multicomponent gas mixtures. *Anal Chem* 1967;39:567-574.
79. Rudolph J, Koppmann R, Johnen F-J, Khedim A. *The distribution of light nonmethane hydrocarbons in the troposphere and their potential impact on photochemical ozone formation..* Hampton, VA: A. DEEPAK Publishing,1989:561-564.
80. Satsumabayashi H, Kurita H, Chang Y-S, Carmichael G, Ueda H. Diurnal variation of OH radical and hydrocarbons in a polluted air mass during long-range transport in central Japan. *Atmos Environ* 1992;26A:2835-2844.
81. Schoenberg MR, Blieszner JW, Papadopoulos CG. Propylene. In: Mark HF, Othmer DF, Overberger CG, Seaborg GT, Grayson M, eds. *Kirk-Othmer Encyclopedia of Chemical Technology Vol 19.* 3rd ed. New York: John Wiley, 1982: 228-246.
82. Segerbäck D, Nilsson R, Osterman-Golkar S, Molholt B. Human cancer risk assessment of propylene oxide based on determination of tissue dose in experimental animals. *Fresenius Envir Bull* 1992;1:143-150.
83. Segerbäck D, Osterman-Golkar S, Molholt B, Nilsson R. In vivo tissue dosimetry as a basis for cross-species extrapolation in cancer risk assessment of propylene oxide. *Regul Toxicol Pharmacol* 1994;20:1-14.
84. Seinfeld J. Urban pollution: state of the science. *Science* 1989;243:745-752.
85. Sellakumar A, Snyder C, Albert R. Inhalation carcinogenesis of various alkylating agents. *J Natl Cancer Inst* 1987;79:285-289.
86. Stephenson F. *Properties and essential information for safe handling and use of propylene.* Manufacturing Chemists Association, 1974 (Chemical Safety Data Sheet SD-59).
87. Svensson K. Studies of vinylchloride, urethane, 1,2-dichloroethane and propene with respect to metabolism, covalent binding to macromolecules and genotoxic risks. PhD Thesis. Stockholm University, 1988.
88. Svensson K, Olofsson K, Osterman-Golkar S. Alkylation of DNA and hemoglobin in the mouse following exposure to propene and propylene oxide. *Chem Biol Interact* 1991;78:55-66.
89. Svensson K, Osterman-Golkar S. Kinetics of metabolism of propene and covalent binding to macromolecules in the mouse. *Toxicol Appl Pharmacol* 1984;73:363-72.
90. Swinnerton J, Lamontagne R. Oceanic distribution of low-molecular-weight hydrocarbons. Baseline measurements. *Environ Sci Technol* 1974;8:657-663.

91. Tille K, Savelsberg M, Bäckmann K. Airborne measurements of nonmethane hydrocarbons over western Europe: vertical distributions, seasonal cycles of mixing ratios and source strenghs. *Atmos Environ* 1985;19:1751-1760.
92. Törnqvist M. Is ambient ethene a cancer risk factor? *Environ Health Perspect* 1994;102:157-160.
93. Törnqvist M, Almberg JG, Bergmark EN, Nilsson S, Osterman-Golkar SM. Ethylene oxide doses in ethene-exposed fruit store workers. *Scand J Environ Health* 1989;15:436-438.
94. Törnqvist M, Ehrenberg L. Approaches to risk assessment of automotive engine exhausts. In: Vainio H, Sorsa M, McMichael AJ, eds. *Complex Mixtures and Cancer Risks*. International Agency for Research on Cancer, Lyon: IARC Scientific Publications Vol 104, 1990.
95. Törnqvist M, Ehrenberg L. On cancer risk estimation of urban air pollution. *Environ Health Perspect* 1994;102(Suppl. 4):173-181.
96. Törnqvist M, Ehrenberg L. Risk assessment of urban air pollution. *Pharmacogenetics* 1992;2:297-303.
97. Törnqvist M, Hindsø Landin H. Hemoglobin adducts for in vivo dose monitoring and cancer risk estimation. *J Occup Environ Med* 1995. In press.
98. Törnqvist M, Gustafsson B, Kautiainen A, Harms-Ringdahl M, Granath F, Ehrenberg L. Unsaturated lipids and intestinal bacteria as sources of endogenous production of ethene and ethylene oxide. *Carcinogenesis* 1989;10(1):39-41.
99. Törnqvist M, Kautiainen A. Adducted proteins for identification of endogenous electrophiles. *Environ Health Perspect* 199;99:39-44.
100. Törnqvist M, Kautiainen A. Epoxide adducts to N-terminal valine of hemoglobin. *Methods in Enzymology* 1994;231:650-657.
101. Törnqvist M, Kautiainen A, Gatz RN, Ehrenberg L. Hemoglobin adducts in animals exposed to gasoline and diesel exhausts. 1. Alkenes. *J Appl Toxicol* 1988;8:159-170.
102. Uno I, Wakamatsu S, Wadden R, Konno S, Koshio H. Evaluation of hydrocarbon reactivity in urban air. *Atmos Environ* 1985;19:1283-1293.
103. Vancura V, Stotzky G. Gaseous and volatile exudates from germinating seeds and seedlings. *Can J Bot* 1976;54:518-532.
104. Victorin K. *Uppdaterad hälsoriskbedömning av etenoxid, eten och propen*. Insitutet för miljömedicin, Stockholm 1992:1-42.(IMM-rapport 8/92) In Swedish.
105. Victorin K, Stahlberg M. A method for studying the mutagenicity of some gaseous compounds in Salmonella typhimurium. *Environ Mol Mutagen* 1988;11:65-77.
106. Victorin K, Stahlberg M. Mutagenic activity of ultraviolet-irradiated mixtures of nitrogen dioxide and propene or butadiene. *Environ Res* 1989;49:271-82.
107. Westberg H, Rasmussen R, Holdren M. Gas chromatographic analysis of ambient air for light hydrocarbons using a chemically bonded stationary phase. *Anal Chem* 1974;46:1852-1854.

18. Data Bases Used

In search for literature the following data bases were used: Arbline, Medline, NIOSHTIC, RTECS, Toxline.

Submitted for publication April 25, 1995.

Appendix

Permitted or recommended maximum levels of propene in air

Country	ppm	mg/m^3	Comments	Year	Ref.
Denmark	-	-		1994	1
Finland	-	-		1993	2
Iceland	-	-		1989	3
Netherlands				1994	4
Norway	-	-		1994	5
Sweden	-	-		1993	6
USA (ACGIH)	-	-	simple asphyxiant	1994-95	7
(NIOSH)	-	-		1993-94	8

References

1. *Grænsværdier for stoffer og materialer*. Køpenhavn: Arbejdstilsynet,1994 (At-anvisning Nr.3.1.0.2) .
2. *HTP-värden 1993*. Tammerfors: Arbetsministeriet, 1993 (Säkerhetsmeddelande 25). ISBN 951-47-8343-3.
3. *Mengunarmörk og adgerdir til ad draga úr mengun*. Skrá yfir mengunarmörk. Reykjavik: Vinnueftirlit Rikisins,1989.
4. *De Nationale MAC-lijst 1994*. Den Haag: 1994 (Arbeidsinspectie P 145). ISBN 90-399-0600-9.
5. *Administrative normer for forurensinger i arbeitsatmosfaere*. Veiledning til arbeidsmiljøloven. Oslo: Direktoratet for arbeidstilsynet, 1994 (Bestillingsnr. 361).
6. *Hygieniska gränsvärden*.. Stockholm: Arbetarskyddsstyrelsen, 1993 (AFS 1993:9). ISBN 91-7930-046-4.
7. *Threshold Limit Values and biological exposure indices for 1994-95*. Cincinnati, Ohio: American Conference of Governmental Industrial Hygienists, 1994. ISBN 1-882417-06-2.
8. Rules and Regulations. *Federal Register Vol.58*. Washington: US Government, 1993.

The Criteria Documents are in a Scandinavian language, with summary in English. Those marked with * are in English. Those marked with D are published in collaboration with the Dutch Expert Committee for Occupational Standards (DECOS). Those marked with N are published in collaboration with NIOSH, USA.

Acetaldehyde	Arbete och Hälsa 1986:25
Acetone	Arbete och Hälsa 1986:39
Acetonitrile	Arbete och Hälsa 1989:22, 1989:37*
Acrolein	Arbete och Hälsa 1991:45
Acrylates	Arbete och Hälsa 1983:21
Acrylonitrile	Arbete och Hälsa 1985:4
Allyl alcohol	Arbete och Hälsa 1986:8
Aluminium	Arbete och Hälsa 1992:45, 1993:1*
Ammonia	Arbete och Hälsa 1986:31
Arsenic, inorganic	Arbete och Hälsa 1981:22, 1991:9, 1991:50*
Arsine	Arbete och Hälsa 1986:41
Asbestos	Arbete och Hälsa 1982:29
Benomyl	Arbete och Hälsa 1984:28
Benzene	Arbete och Hälsa 1981:11
Boric acid, Borax	Arbete och Hälsa 1980:13
1,3-Butadiene	Arbete och Hälsa 1994:36*, 1994:42
1-Butanol	Arbete och Hälsa 1980:20
Cadmium	Arbete och Hälsa 1981:29, 1992:26, 1993:1*
7/8 Carbon chain aliphatic monoketones	Arbete och Hälsa 1990:2*D
Carbon monoxide	Arbete och Hälsa 1980:8
Chlorine, Chlorine dioxide	Arbete och Hälsa 1980:6
Chloromequat chloride	Arbete och Hälsa 1984:36
4-Chloro-2-methylphenoxy acetic acid	Arbete och Hälsa 1981:14
Chlorophenols	Arbete och Hälsa 1984:46
Chromium	Arbete och Hälsa 1979:33
Cobalt	Arbete och Hälsa 1982:16
Cobalt and cobalt compounds	Arbete och Hälsa 1994:39*, 1994:42
Copper	Arbete och Hälsa 1980:21
Creosote	Arbete och Hälsa 1988:13, 1988:33*
Cyclohexanone, Cyclopentanone	Arbete och Hälsa 1985:42
n-Decane	Arbete och Hälsa 1987:25, 1987:40*
Deodorized kerosene	Arbete och Hälsa 1985:24
Diacetone alcohol	Arbete och Hälsa 1989:4, 1989:37*
Diesel exhaust	Arbete och Hälsa 1993:34, 1993:35*
2-Diethylaminoethanol	Arbete och Hälsa 1994:25*N
Diethylamine, Diethylenetriamine, Dimethylamine & Ethylenediamine	Arbete och Hälsa 1994:23*, 1994:42
Diisocyanates	Arbete och Hälsa 1979:34, 1985:19
Dimethyldithiocarbamates	Arbete och Hälsa 1990:26, 1991:2*
Dimethylethylamine	Arbete och Hälsa 1991:26, 1991:50*
Dimethylformamide	Arbete och Hälsa 1982:28
Dimethylsulfoxide	Arbete och Hälsa 1991:37, 1991:50*
Dioxane	Arbete och Hälsa 1982:6
Epichlorohydrin	Arbete och Hälsa 1981:10
Ethyl acetate	Arbete och Hälsa 1990:35*D
Ethylbenzene	Arbete och Hälsa 1986:19
Ethylene bisdithiocarbamates	Arbete och Hälsa 1993:24, 1993:35*