European Chemicals Bureau

Institute for Health and Consumer Protection

European Chemicals Bureau

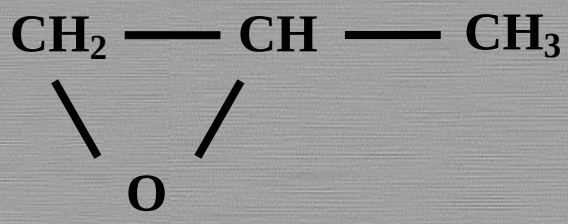
Existing Substances

European Union Risk Assessment Report

CAS No: 75-56-9

EINECS No: 200-879-2

methyloxirane (propylene oxide)



2nd Priority List

Volume: 23

EUROPEAN COMMISSION
JOINT RESEARCH CENTRE

EUR 20512 EN

CAS: 75-56-9
EC: 200-879-2

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23

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METHYLOXIRANE

(PROPYLENE OXIDE)

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RISK ASSESSMENT

Cataloguing data can be found at the end of this publication

Luxembourg: Office for Official Publications of the European Communities, 2002

Printed in Italy

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RISK ASSESSMENT

Final Report, 2002

United Kingdom

This document has been prepared by the UK rapporteur on behalf of the European Union. The scientific work on the environmental part was prepared by the Building Research Establishment (BRE) Ltd, under contract to the rapporteur.

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Date of Last Literature Search:	**1998**
Review of report by MS Technical Experts finalised:	**2000**
Final report:	**2002**

Foreword

We are pleased to present this Risk Assessment Report which is the result of in-depth work carried out by experts in one Member State, working in co-operation with their counterparts in the other Member States, the Commission Services, Industry and public interest groups.

The Risk Assessment was carried out in accordance with Council Regulation (EEC) 793/93[1] on the evaluation and control of the risks of "existing" substances. "Existing" substances are chemical substances in use within the European Community before September 1981 and listed in the European Inventory of Existing Commercial Chemical Substances. Regulation 793/93 provides a systematic framework for the evaluation of the risks to human health and the environment of these substances if they are produced or imported into the Community in volumes above 10 tonnes per year.

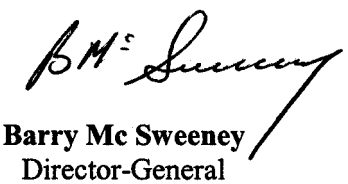
There are four overall stages in the Regulation for reducing the risks: data collection, priority setting, risk assessment and risk reduction. Data provided by Industry are used by Member States and the Commission services to determine the priority of the substances which need to be assessed. For each substance on a priority list, a Member State volunteers to act as "Rapporteur", undertaking the in-depth Risk Assessment and recommending a strategy to limit the risks of exposure to the substance, if necessary.

The methods for carrying out an in-depth Risk Assessment at Community level are laid down in Commission Regulation (EC) 1488/94[2], which is supported by a technical guidance document[3]. Normally, the "Rapporteur" and individual companies producing, importing and/or using the chemicals work closely together to develop a draft Risk Assessment Report, which is then presented at a Meeting of Member State technical experts for endorsement. The Risk Assessment Report is then peer-reviewed by the Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) which gives its opinion to the European Commission on the quality of the risk assessment.

If a Risk Assessment Report concludes that measures to reduce the risks of exposure to the substances are needed, beyond any measures which may already be in place, the next step in the process is for the "Rapporteur" to develop a proposal for a strategy to limit those risks.

The Risk Assessment Report is also presented to the Organisation for Economic Co-operation and Development as a contribution to the Chapter 19, Agenda 21 goals for evaluating chemicals, agreed at the United Nations Conference on Environment and Development, held in Rio de Janeiro in 1992.

This Risk Assessment improves our knowledge about the risks to human health and the environment from exposure to chemicals. We hope you will agree that the results of this in-depth study and intensive co-operation will make a worthwhile contribution to the Community objective of reducing the overall risks from exposure to chemicals.



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1 O.J. No L 084, 05/04/199 p.0001 – 0075

2 O.J. No L 161, 29/06/1994 p. 0003 – 0011

3 Technical Guidance Document, Part I – V, ISBN 92-827-801 [1234]

0 OVERALL RESULTS OF THE RISK ASSESSMENT

CAS no:	75-56-9
EINECS no:	200-879-2
IUPAC name:	methyloxirane
Synonyms:	propylene oxide

Environment

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

This conclusion applies to all environment endpoints for production and all uses of propylene oxide.

Human health

Human health (toxicity)

This substance has not been adequately tested for skin sensitisation and consequently the risk assessment does not evaluate the risks to any human population for this endpoint.

Workers

It is not currently possible to determine a threshold for mutagenic events and to identify a threshold for carcinogenicity. As a result, it is not possible to identify any level of exposure at which there would be no risk to human health. Therefore **conclusion (iiia)** is reached for workers for these endpoints. However, the occupational exposure assessment for the production and use of propylene oxide demonstrated that the industry currently employs and develops measures that reduce exposure to as low a level as is reasonably practicable. This conclusion is dependent upon the industry continuing to implement new procedures to reduce exposure when possible.

Any indication that this is not occurring would prompt a review of the risk assessment and might result in a revision of the conclusion.

Conclusion (iiia) Risks cannot be excluded for all other exposure scenarios, as the substance is identified as a non-threshold carcinogen. The adequacy of existing controls and the feasibility and practicability of further specific measures should be considered. However, the risk assessment indicates that risks are already low. This should be taken into account when considering the adequacy of existing controls and the feasibility and practicability of further specific risk reduction measures.

With respect to skin sensitisation no formal conclusion has been reached with this endpoint. It is therefore, concluded that, this substance has not been adequately tested for skin sensitisation, consequently the risk assessment does not evaluate the risks to any human population for this endpoint.

Consumers

Conclusion (iiia) is reached because it is not currently possible to determine a threshold for mutagenic or carcinogenic events. As a result, it is not possible to identify any level of exposure at which there would be no risk to human health. It is, however, noted that due to the half-life of 30-40 h and use in consumer products at very low concentrations, exposures to consumers are extremely low and therefore that the degree of risk is anticipated to be negligible.

Conclusion (iiia) Risks cannot be excluded for all other exposure scenarios, as the substance is identified as a non-threshold carcinogen. The adequacy of existing controls and the feasibility and practicability of further specific measures should be considered. However, the risk assessment indicates that risks are already low. This should be taken into account when considering the adequacy of existing controls and the feasibility and practicability of further specific risk reduction measures.

Humans exposed via the environment

Conclusion (iiia) is reached because it is not currently possible to determine a threshold for mutagenic events or carcinogenic events. As a result, it is not possible to identify any level of exposure at which there would be no risk to human health. It is, however, noted that exposures in local and regional scenarios are extremely low and therefore that the degree of risk is anticipated to be negligible.

Conclusion (iiia) Risks cannot be excluded for all other exposure scenarios, as the substance is identified as a non-threshold carcinogen. The adequacy of existing controls and the feasibility and practicability of further specific measures should be considered. However, the risk assessment indicates that risks are already low. This should be taken into account when considering the adequacy of existing controls and the feasibility and practicability of further specific risk reduction measures.

Combined exposure

A worst-case combined exposure scenario is composed of exposure in the workplace and to the highest local environmental exposure levels. No quantitative estimate of total exposure from inhalation, dermal and oral routes, is possible. For the main endpoints of concern, mutagenicity and carcinogenicity, no threshold of exposure below which there would be no cause for concern to human health can be identified. However, exposure is very low. In both cases of worker and exposure via the environment **conclusion (iiia)** is appropriate.

Conclusion (iiia) Risks cannot be excluded for all other exposure scenarios, as the substance is identified as a non-threshold carcinogen. The adequacy of existing controls and the feasibility and practicability of further specific measures should be considered. However, the risk assessment indicates that risks are already low. This should be taken into account when considering the adequacy of existing controls and the feasibility and practicability of further specific risk reduction measures.

Human health (risks from physico-chemical properties)

There are hazards associated with the extremely low flash point, high vapour pressure and flammmability of this substance. However, during the manufacture, storage and use of this substance the stringent control measures used ensure that risks arising from the physicochemical properties are small.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

CONTENTS

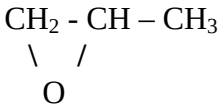
Euses Calculations can be viewed as part of the report at the website of the European Chemical Bureau: http://ecb.jrc.it

TABLES

1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS-No.: 75-56-9
EINECS-No.: 200-879-2
IUPAC name: methyloxirane
Synonyms: propylene oxide, 1,2-epoxypropene, propenoxide
Molecular formula: C_3H_6O
Structural formula:



Molecular weight: 58.08

1.2 PURITY, IMPURITIES AND ADDITIVES

The degree of purity given in the IUCLID entries ranges from 99% to 100%, with most being 99.9% or greater. A number of impurities are listed, none of which are present at more than 0.01% by weight. These include water, aldehydes, methanol and acetic acid. No other substances appear to be added to the commercial product.

1.3 PHYSICO-CHEMICAL PROPERTIES

1.3.1 Physical state (at n.t.p.)

The substance is a colourless liquid with a sweet, ether-like odour.

1.3.2 Melting point (freezing point)

The freezing point of propylene oxide (99.94 mole %), purified by distillation and degassed, has been determined by adiabatic calorimetry to be -112.16°C ± 0.05°C (Oetting, 1964). Other values presented with experimental detail were -112.13°C (McDonald et al., 1959) using freezing curve techniques and ~-111°C (BASF AG Material Safety Data Sheet, 1995) to DIN 53 171 (a distillation method quoted in Annex V for measuring boiling temperature). Values quoted with no supporting data were -111.9°C (BASF AG Technische Information, 1993) probably from Oetting (1964) and -104°C (Jefferson Chemicals, 1960). The latter, although not referenced, probably comes from the American Chemical Society Monograph Series: Glycols (1952) which quotes the freezing point as -104.4°C.

The theoretical freezing point of 100% pure propylene oxide is quoted as -111.94 ± 0.05°C.

Other literature/handbook values generally range between -111 and -112°C and it is probable that they are quoting one of the above sources. The value of -112.16°C will be taken as the best estimate as it is the most recently quoted value and has the most extensive supporting data.

1.3.3 Boiling point

A value of 34.1°C (Jefferson Chemicals, 1960) was quoted using a modified ASTM method (D-1078). Other values quoted without supporting data were 34°C at 101.325 kPa (BASF AG Material Safety Data Sheet, 1995), 34.3°C and 34°C (BASF AG Technische Information, 1993 and Dow Material Safety Data Sheet, 1987, respectively) and 34.3°C and 34°C at 101.3 kPa (BASF, 1981a and 1967, respectively). A value of 34.196°C at 101.325 kPa has been calculated from vapour pressure data, using the Antoine equation (ESDU, 1988). A measured boiling point of 33.9°C at 101.325 kPa (the American Chemical Society Monograph Series: Glycols, 1952) has also been quoted.

Other literature/handbook values generally range between 3.9 and 34.3°C, and it is probable that they are quoting one of the above sources.

For the environmental exposure assessment a value of 34.1°C is used.

1.3.4 Density

The density of propylene oxide (>99.8 mole % pure, containing 0.12 mole % water) was determined by pycnometer to be 831 $kg \cdot m^{-3}$ at 20°C (BASF, 1977b). This is equivalent to a relative density (D_4^{20}) of 0.831 and is in close agreement with the value of 0.8305 (Jefferson Chemicals, 1960) also determined by pycnometer.

Other literature/handbook values generally quote a relative density between 0.829 and 0.859 (the latter appears to come from the original work of Oser, 1860). The value of 0.831 will be used for the relative density.

1.3.5 Vapour pressure

There are extensive vapour pressure data available for propylene oxide. The key references are summarised in **Table 1.1**.

The vapour concentration could only be estimated at the flash point temperature since the vapour pressure was only reported to -24.17°C and the Antoine constants calculated by McDonald et al. (1959) were only valid to -20°C. Therefore, it was not possible to validate the lower explosive limit or flash point in this way.

The true value of the vapour pressure is probably between 58.4 and 61.2 kPa at 20°C. The middle of this range, 59.8 kPa, will be used in the environmental exposure assessment.

Table 1.1 Vapour pressure

Vapour pressure (kPa)	Temperature (°C)	Source	Comment
60.7	20	American Chemical Society Monograph Series: Glycols (1952)	99.7 mole% propylene oxide – method not stated
58.4	20	BASF (1977a)	Calculated using the Antoine equation
101.3	34.1	BASF (1981)	Method not stated
61.2	20	BASF (1967)	Dynamic method
71.55	25	Dow (1977)	No data or details of method provided
70.64-72.37	25	Gallant (1967) US EPA (1981)	No data or details of method provided
546.14	87.8	Kobe et al. (1956)	Dynamic method
51.97	17.05	McDonald et al. (1959)	Dynamic method, >99.5 mole% propylene oxide
55.46 76.53	19.00 27.00	Bott and Sadler (1966)	Static method, >99.9 mole% propylene oxide

1.3.6 Solubility

Propylene oxide is completely miscible with methanol, benzene, heptane, diethylether, carbon tetrachloride and acetone.

Propylene oxide and water are mutually soluble. Above 84.1°C propylene oxide and water are miscible in all proportions (Jefferson Chemicals, 1960); below this temperature a two-phase system exists. The composition of the phases varies according to temperature and pressure (**Table 1.2**).

Table 1.2 Solubility

Propylene oxide in water, % w/w (g/l *) at 36.4°C and 101.3 kPa	Water in propylene oxide, % w/w at 36.4°C and 101.3 kPa	Reference
38.73 [a] (385)	16.02	Wickert et al. (1979)
36.75 [b] (365)		BASF AG (1983)

[a] Husruhrmethode
[b] rubungstitration
* Calculated assuming density of water at 36.4°C is 993.5 kg · m^{-3}

The water solubility of propylene oxide is quoted as 395 g · l^{-1} at 20°C (Jefferson Chemicals, 1960). No method or data were provided and sample purity was not given. A value of 370 g · l^{-1} at 25°C (Amoore and Hautala, 1983) was quoted from the literature, but no reference was given and no further details were provided. In both cases the pH of the solutions was not reported. A solubility of ~400 g · l^{-1} at 20°C and pH 7 was reported (BASF, 1995). This was described as "valid with restrictions", however no further details were provided. A value of 405 g · l^{-1} is widely quoted in secondary literature, and apparently comes from the American Chemical Society Monograph Series: Glycols (1952). Co-incidentally, a value of 40.5% v/v (IARC, 1985) is quoted, equivalent to 336 g · l^{-1}. This seems rather low and could be a transcription error.

The solubility of water in propylene oxide is also given, as 12.8% by weight (Merck Index, no further details provided) and 12.5% by weight (Jefferson Chemicals, 1960 - details as above).

For all of these values, insufficient detail of the methods and analytical techniques makes it difficult to assess the accuracy of the data. A value of 400 $g \cdot l^{-1}$ at 20°C will be used as representative for the environmental exposure assessment.

1.3.7 n-Octanol-water partition coefficient (Kow)

Values for the octanol-water partition coefficient are in **Table 1.3.**

Table 1.3 Octanol-water partition coefficient

Experimental value	Reference
0.03	Hansch and Leo (1989), cited in Sangster (1989)
0.08 ± 0.05	Deneer et al. (1988)

The experimental values obtained are in reasonably close agreement (within the error margins of the experimental method). According to Deneer et al. (1988), a slow stirring method was employed to minimise the formation of emulsions and the test was conducted in triplicate at room temperature. Analysis was by gas-liquid chromatography (GLC).

A number of calculated log Kow values are quoted in IUCLID, ranging from -0.27 (Lipnick et al., 1987) to 0.35 (origin not known).

A value of 0.055 as the mean of the two measured log values will be used in the environmental exposure assessment.

1.3.8 Flash point

The flash point (closed cup) has been reported as -44°C (BASF AG Material Safety Data Sheet, 1995) and -37°C (Elm, R, cited in Ullmans Encyklopädie der technischen Chemie, 1980). Both tests were reportedly conducted using an accepted Annex V test method (Penskey-Martens apparatus) and although actual data were not provided, these values are supported by estimates based on vapour pressure and lower explosive limit data which gave values of between -43.4°C and -38.4°C. Values of -35°C and -37°C are widely quoted in secondary sources.

Without full details of the methods used/ignition source, it is not possible to explain the difference between values. All quoted values fall well within the limit for the classification of “Extremely Flammable”.

Flash points of -20°C (open cup, US Coast Guard, 1985) and of -20°C (calculated, Kirk-Othmer, 1991) and -29°C (TAG closed cup, Dow Material Safety Data Sheet) were also reported in the literature, although no details were provided. These were discounted in favour of the data generated using accepted Annex V methods.

1.3.9 Autoignition

Autoignition temperatures of 420°C (Elm, cited in Ullmans Encyklopädie der technischen Chemie, 1980) and 430°C (BASF AG, 1993) were reported. Both were conducted to an accepted Annex V test method (DIN 51794) although the actual test data were not provided. A value of 465°C (quoted in the NFPA handbook, 1994) could not be assigned.

1.3.10 Explosivity

Values reported for the explosive limits in air at normal temperature and pressure are given in **Table 1.4**.

Table 1.4 Explosivity

Lower explosive concentration (% by volume)	Upper explosive concentration (% by volume)	Reference
2.8	37	NIOSH (1985)
2.1	38.5	Jefferson Chemicals (1960)
2.5	21.5	American Chemical Society Monograph Series: Glycols (1952)
1.9	24	Ullmans Encyklopädie der technischen Chemie (1980)
2.1	21.5	Wood (1981)
1.9	45	Company data (1990)
1.85	36.25	ARCO Chemical Company (1975)
2.3	36	Dow Material Safety Data Sheet
2.1	37	ACGIH (1989) and NFPA (1994)

Of the above, only the ARCO Chemical Company (1975) provided actual measured data and details of the method of measurement. Therefore these values, 1.85 - 36.25, are the ones used in this assessment.

1.3.11 Oxidising properties

Testing for this property is not applicable due to the physical nature of this substance. Propylene oxide is not considered to be an oxidising agent, based on its chemical structure.

1.3.12 Surface tension

The surface tension of pure propylene oxide at 20°C is 23.5 $mN \cdot m^{-1}$ (Kobe et al., 1956, cited in Gallant, 1967; Yaws and Rackley, 1976). The surface tension of an aqueous solution was not provided (e.g. for comparison with water, which has a surface tension of 72.75 $mN \cdot m^{-1}$ at 20°C).

1.3.13 Other physico-chemical properties

The vapour density is quoted as 2.054 (air=1), although it is not stated whether this is a measured or calculated value (Oser, 1860).

Viscosity at 10°C is quoted as 0.38 mPa·s (BASF, 1995) and at 25°C as 0.28 mPa·s (Dow Chemical Company, 1977).

An air odour threshold of 44 ppm is quoted (Amoore and Hautala, 1983) although it will be detected by most people at 110 - 200 ppm (HSE, 1996).

1.3.14 Hazardous chemical reactions (particularly with water)

Hazardous polymerisation may occur when in contact with highly active catalytic sources, such as anhydrous chlorides of iron, tin or aluminium, peroxides of iron or aluminium and alkali metal hydroxides. Any change in the neutrality of propylene oxide can initiate polymerisation. Acids, bases oxidising materials and clay-based absorbent materials should be avoided (Dow Material Safety Data Sheet). Also, "reactions with other compounds, including water, may become violent if not properly controlled" (Dow Chemical Company, 1977), although no details were given.

1.3.15 Summary of physico-chemical properties

There are extensive physico-chemical data on propylene oxide but the reported experimental detail is limited. The values quoted in the consolidated IUCLID entry accurately reflect the values summarised in **Table 1.5**.

Table 1.5 Physico-chemical properties of propylene oxide

Property	Value
Molecular weight	58.08
Melting point	-112.16°C
Boiling point	33.9 - 34.3°C at 101.3 kPa (**34.1°C**)
Relative density	0.83
Vapour pressure	58.4 - 61.2 kPa at 20VC (**59.8 kPa**)
Water solubility	395 - 405 g·l^{-1} at 20°C (pH=7) (**400 g·l^{-1}**)
Log octanol/water partition coefficient	0.03 - 0.08 (**0.055**)
Flammability	Flash point: -37 to -44°C (closed cup)
Autoflammability	420 - 430°C
Explosive properties	Lower explosive limit: 1.9 - 2.8% v/v Upper explosive limit: 21.5 - 45% v/v
Vapour density	2.05 (air=1)
Surface tension	23.5 mN·m^{-1} at 20°C (propylene oxide)
Viscosity	0.28 mPa·s at 25°C
Conversion factor	1 ppm = 2.41 mg·m^{-3} at 25°C

Note: values in bold in parentheses are those used in the environmental exposure assessment

1.4 CLASSIFICATION AND LABELLING

Classification and labelling according to the 28th ATP of Directive 67/548/EEC[4]:

F+; R12	Extremely flammable
Carc. Cat. 2; R45	May cause cancer
Muta. Cat. 2; R46	May cause heritable genetic damage
Xn; R20/21/22	Also harmful by inhalation, in contact with skin and if swallowed
Xi; R36/37/38	Also irritating to eyes, respiratory system and skin
Nota E	
S45	In case of accident or if you feel unwell, seek medical advice immediately (show label where possible)
S53	Avoid exposure - obtain special instructions before use

Additional information – The CMR group concluded that the information on skin sensitisation did not meet the criteria for classification as a sensitiser.

No classification for the environment.

[4] The classification of the substance is established by Commission Directive 2001/59/EC of 6 August 2001 adapting to the technical progress for the 28th time Council Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances (OJ L 225, 21.8.2001, p.1).

2 GENERAL INFORMATION ON EXPOSURE

2.1 PRODUCTION METHODS

There are two main production routes to propylene oxide currently in use, the chlorohydrin process and the indirect oxidation process. Information in this section is taken from BUA (1992), Ashford (1994), and Reigel (1974).

2.1.1 Chlorohydrin process

In this process propylene is reacted with chlorine in water (hypochlorous acid) to give propylene chlorohydrin. The product is an isomeric mixture with 90% in the form of 1-chloro-2-propanol, which occurs as a hydrochloric solution of about 5%. The conversion rate is around 97% based on propylene. By-products from this step are 1,2-dichloropropane (4-8%), 2,2'-dichlorodiisopropylether (1.7%), propionaldehyde (0.3%) and others.

The chlorohydrin is then epoxidised without isolation by dehydrochlorinating at 105°C in a saponifier, with either excess $Ca(OH)_2$ or NaOH. The former gives a $CaCl_2$ solution, the latter a NaOH/NaCl solution. The raw yield of propylene oxide is ~93%. After coarse pre-treatment the product is stripped by distillation with a water-content of 10%. Then water, dichloropropane, aldehydes and other compounds are removed from the raw propylene oxide in a series of distillation columns.

2.1.2 Indirect oxidation

There are two major processes using the indirect oxidation route to make propylene oxide. In the first of these, isobutane is oxidised with air or pure oxygen to give t-butyl hydroperoxide. This is then used to oxidise propylene to propylene oxide with the aid of a soluble metal catalyst in the liquid phase; t-butanol is produced as a co-product. Raw propylene oxide is stripped out of the reaction mixture and separated from carbonyl compounds, ethylene oxide, unconverted propylene and hydrocarbons. Three tonnes of t-butanol are produced for each tonne of propylene oxide.

In the second process, ethylbenzene replaces isobutane as the second feedstock and ethylbenzene hydroperoxide is produced as the oxygen transfer agent. reacts with the raw hydroperoxide mixture in the presence of a solid or liquid catalyst to produce propylene oxide, with styrene as a co-product. After recovery about 2.8 tonnes of styrene are produced for each tonne of propylene oxide.

2.2 PRODUCTION VOLUMES

World capacity for propylene oxide production was estimated as 3,585,000 tonnes for 1990 (BUA, 1992).

From information in IUCLID the range of production in the EU is 580,000 to 2,750,000 tonnes per year, with seven companies producing propylene oxide. These figures include some imports as one company did not separate production and import. Separate import values were in the range 10,000 to 50,000 tonnes. Most of the values provided refer to 1992.

BUA (1992) estimated EU capacity in 1990 as 1,410,000 tonnes, which was expected to rise by a further 300,000 tonnes by 1994. The same report gave capacities for individual production plants in Europe. An article in European Chemical News (ECN, 1995) gave revised capacities for a number of propylene oxide plants. The capacity values from these two sources are considered more useful than the ranges from IUCLID in estimating the overall production tonnage. The values from ECN (1995) were combined with older values for other plants from BUA (1992) to give an estimate of 1,445,000 tonnes. This will be used as the total EU production volume later in the assessment. Combined with 50,000 tonnes as the maximum import figure this gives a total usage in the EU of 1,495,000 tonnes. Possible new plants or expansions could have increased this figure by 400,000 tonnes by 2000 (ECN, 1996a, b).

Table 2.1 shows the percentage of propylene oxide production using each route in Europe and worldwide (BUA, 1992).

Table 2.1 Breakdown of propylene oxide production by process used

Process	Europe	Worldwide
Chlorohydrin	53%	53%
t-Butanol	32%	27%
Styrene	15%	20%

Propylene oxide is transported by road and rail tanker, ship and by pipeline for captive use. Transport by ship may be by roll on/roll off ferries, lift on/lift off shipment in tanker containers or bulk sea-going vessels. There is understood to be no delivery by drums in the EU.

2.3 USES

Usages of propylene oxide fall into three areas: use as a monomer in polymer production; use as an intermediate in the synthesis of other substances; and direct applications of the substance itself. The last of these accounts for only a small proportion of the propylene oxide used.

Its use as a chemical intermediate is for the manufacture of the following:

- polyols used in polyurethane foam manufacture for the furniture and automotive industries, and coatings, adhesives and sealants.
- propylene glycol ethers for use as solvents in paints, inks, coatings, resins, cleaners and waxes.
- propylene glycols, which can be used in:
    1. the production of unsaturated polyester resins, especially in the textile and construction industries;
    2. as a solvent in food, pharmaceuticals and cosmetics;
    3. in engine coolants and aircraft de-icers.

- butanediol and related products for speciality resins and solvents.

(Sources: HSE EH65/21, 1996; IARC, 1994).

2.3.1 Polymer production

The main use of propylene oxide is to make polyether polyols, which are then largely used in the manufacture of polyurethane foams. Polyether polyols are propylene oxide polymers, made by a base-catalysed polymerisation of propylene oxide on a polyhydric alcohol. In this a "starter" is heated with a catalyst (KOH) to give an alkoxide, which then reacts with propylene oxide. Starters may have 2-8 OH groups, and common ones include propylene glycol, glycerol, trimethylol propane, pentaerythritol, sorbitol and sucrose. Nitrogen containing starters such as ethylene diamine can also be used. As propylene oxide is not symmetrical, the attack can occur at C1 or C2; the first of these is preferred by 10:1 and so the polyether produced is largely head-to-tail units, with some head-to-head and tail-to-tail. The molecular weight of the products ranges from 400 – 8,000.

In the production of polyurethane foams, polyether polyols are reacted with di- or poly-isocyanates. The hydroxyl end groups in the polyether chain react with the isocyanate groups, forming a substituted carbamic acid ester or urethane. This provides a basic step-growth polymerisation. The isocyanate groups also react with traces of water to produce carbon dioxide, which acts as a blowing agent for the foams.

The properties of the polymer can be improved as regards the production of PU foam by copolymerizing with ethylene oxide; this can also lead to the production of other materials. Three types of copolymer are possible: a random copolymer, in which mixed ethylene oxide and propylene oxide are polymerised; block copolymers, where ethylene oxide is polymerised into polyoxypropylene glycol, or vice versa; and randomised block copolymers which have elements of both. The randomised block copolymers are most widely used in foam applications. Block copolymers have a major use as surfactants. They consist of a hydrophobic polyoxypropylene base polyol with a molecular weight of 500 to 4,000, with polyoxyethylene end blocks of 4 to 100 oxyethylene units.

Modified polyether polyols can also be made. For example polymer polyols are conventional polyether polyols onto which polyvinyl fillers have been grafted, and PHD polyols are high molecular weight polyether triols containing dispersed particles of polyurea.

2.3.2 Use as an intermediate

(Kirk-Othmer, 1994; BUA, 1992)

The major product made from propylene oxide is propylene glycol. This is produced by the high pressure, high temperature, non-catalytic hydrolysis of propylene oxide. A large excess of water is used in the process, which gives a typical mixture of 90% mono-, and 10% di- and tri-propylene glycols. Excess water is removed in multi-effect evaporators and drying towers, and the glycols are purified by high vacuum distillation.

The most important commercial use of propylene glycol is in the manufacture of polyesters by reaction with a dibasic or polybasic acid. In the manufacture of unsaturated polyester resins a portion of the dibasic acid used is a vinyl reactive acid such as maleic acid. The polyester produced is diluted with a vinyl reactive monomer such as styrene, which in use reacts with the reactive group on the acid to give a highly cross-linked polymer system. This use accounted for 37% of the propylene glycol used in the USA in 1992. Other esters made from mono-, di- or tri-propylene glycol are used as plasticizers in polymer systems, as emulsifiers in foods and as part of acrylate resin systems.

Mono-propylene glycol is used as a solvent in a wide range of areas. It is also used as a low temperature heat transfer fluid. High purity grades are approved for use in foods and can be used in potential food contact applications. The use of monopropylene glycol in aeroplane and runway de-icing has increased in recent years, and it is also beginning to be used in automobile coolants. The di- and tri-propylene glycols have similar properties, but there are particular areas where they are more useful than other glycols.

Other non-polymeric products made from propylene oxide include mono-, di- and tri- propylene glycol alkyl ethers (largely used as solvents), mono-, di- and tri-isopropanol amines (used in brake fluids, as anti corrosive agents, and to produce isopropanol amides) and propylene carbonate (used in gas cleaning).

Propylene oxide is also used to make other monomers which are then used to produce other polymeric materials. A particular example is in acrylic resins. Propylene oxide reacts with acrylic and methacrylic acids to give hydroxyalkyl acrylic esters. These can be used to modify the properties of polymers produced from acrylates or methacrylates.

2.3.3 Direct applications

A small amount of propylene oxide is used without conversion into other substances. It is used as a stabiliser for dichloromethane and other chlorinated hydrocarbons. BUA (1992) also lists use as a stabiliser in fuels and heating oils, as an anti-corrosion additive for liquid coolants, and mentions that propylene oxide is a good solvent for nitrocellulose, cellulose acetate, adhesives etc.

IARC (1994) reports that propylene oxide is used for the fumigation of dried fruits and as a bulk fumigant for foodstuffs such as cocoa, spices, processed nutmeats, starch and gums. The United States Environmental Protection Agency reported that propylene oxide is approved by the Food and Drug Administration as a direct and indirect food additive. This approval is for use as an etherifying agent in the production of modified food starch (at levels up to 25%). It is also approved as a package fumigant for certain food products, and as a fumigant for bulk quantities of several food products. Specific limits are placed on the amount of residual propylene oxide. It is understood that it does not have such use in the EU.

Propylene oxide is used as a stabiliser in dichloromethane in grades used for degreasing. EU suppliers of dichloromethane reported that propylene oxide is used at levels of up to 0.5%. The extent of the use of propylene oxide as a stabiliser in dichloromethane was not established. It is, however, worth noting that dichloromethane is only one of many solvents used for degreasing. In addition, of the 133,000 tonnes of dichloromethane used in the EU in 1994, less than 10% was used for vapour degreasing (ECSA, 9/1995). Actual figures for vapour degreasing are not reported and the figure of 10% (13,300) relates to miscellaneous uses, including vapour degreasing. Assuming that all the 13,300 tonnes were used for degreasing and that it all contained 0.5% propylene oxide, then the EU consumption of propylene oxide as a stabiliser for dichloromethane would be a maximum of 66.5 tonnes. This is clearly an overestimate of the level of use of propylene oxide as a stabiliser in dichloromethane.

Propylene oxide is also used in the preparation of tissue samples for analysis by electron microscopy. Tissues can be dehydrated and infiltrated for epoxy resin embedding using a single substance, for example, ethanol. Propylene oxide may be used as an additional dehydration and infiltration agent after dehydration with ethanol. Propylene oxide mixes more readily with epoxy resin than ethanol, and thus acts as an intermediary between the ethanol and the epoxy resin. The extent of its use for electron microscopy was not established. Clearly there are numerous

research establishments using electron microscopy, therefore its use may be widespread. However, only very low volumes are used for the preparation work, therefore the total EU usage for this application is likely to be small.

2.3.4 Breakdown of use areas

The proportions of propylene oxide used in the various areas described above are given in **Table 2.2.**

Table 2.2 Propylene oxide use by product in 1982 (BUA, 1992)

Product	EU	USA	Canada
Polyether polyols	72%	64%	65%
Propylene glycols	23%	21%	29%
Other uses	5%	15%	6%

Assuming that the percentages for the EU are still applicable, the tonnages in each area based on a total usage of 1,495,000 tonnes are in **Table 2.3**.

Table 2.3 Tonnage of propylene oxide used by end use

Product	Tonnage used
Polyols	1,076,400
Glycols	343,850
Others	74,750

As partial confirmation of these figures, the capacity for propylene glycol production in the EU from IUCLID is in the range 185,000 - 460,000 tonnes.

The Danish Product Register (June 1997) indicated that 505 products were registered as containing propylene oxide, with a total tonnage of 8 tonnes per year. The majority of these products, 437, contained 0-1% by weight. The main product types were construction and insulation materials, fillers, adhesives and binding agents, and paints, lacquers and varnishes.

Information provided by Spain showed that 61,500 tonnes of propylene oxide were used in Spain in 1995, a combination of internal production and imported material.

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

3.1.1 Environmental releases

This section presents information on the release of propylene oxide to the environment at various points in its lifecycle. The main areas covered are production, use in the production of other substances, direct uses, and possible indirect sources. Information relating specifically to propylene oxide has been used where available, with default values from the Technical Guidance Document (TGD) being used to fill gaps in the data where appropriate. Information on releases to air and to water has been provided by Industry and this is used to estimate release factors in the sections on production and processing. It is also used to calculate site-specific predicted environmental concentrations (PECs) in later sections. The EUSES model output is given in Appendix D.

3.1.1.1 Release from production of propylene oxide

Release to air

Production and processing of propylene oxide may occur on the same site, but there are also sites where the chemical is brought in for use in the synthesis of other chemicals. Therefore the most appropriate Main Category for production (as defined in the TGD) for propylene oxide is 1c, i.e. isolated intermediate stored off-site. The default emission factor from the TGD for a chemical with a vapour pressure of ~60 kPa is 0.025, i.e. 25 kg/tonne. It is assumed throughout that production is continuous for 300 days per year.

Older estimates for release specifically from propylene oxide production are lower than the default value. BUA (1992) commented that values quoted for the early 1980s are 0.3-0.4 kg/tonne, and RIVM (1988) quoted values of 0.2-0.3 kg/tonne for modern plants in 1984, with 0.5 kg/tonne for older plants. These values are similar although the production processes involved are different.

BUA (1992) quotes producers of propylene oxide as claiming that considerable reductions in emissions have been achieved since 1983, and the more recent release estimates appear to support this. For the early 1990s a combined release of 10 tonnes/year to the atmosphere was estimated for three plants in Germany, including some release from further processing. The capacity of these three plants has been estimated as 659,000 tonnes (BUA, 1992) or 635,000 tonnes (ECN, 1995a); based on these values the average release factor is 0.016 kg/tonne.

Seven producers provided information on releases to air from production sites from which release factors were estimated. These range from $3.4 \cdot 10^{-5}$ to 0.11 kg/tonne.

The TGD default estimate is clearly much higher than those found in practice. The information from current producers covers 97% of the production capacity. Therefore the highest value from the range above, 0.11 kg/tonne, will be taken as representative of the current situation.

In the usual worst-case assessment this release factor would be applied to the largest realistic size of production site for the EU. From the information provided in IUCLID the largest production site in the EU at present is 500,000 tonnes (range 100,000-500,000). Applying the above factor

would give an annual release of 55 tonnes, or 183 kg/day. However, this type of calculation seems inappropriate in this case when information on actual releases is available for 97% of the production capacity (this will be used later to calculate PEC values for these sites). Instead emission estimates will be made for that part of the capacity which is not covered by the available information, assuming it is all at one site. This is a tonnage of 50,000 tonnes per year, giving a release of 5.5 tonnes/year, 18.3 kg/day.

On a regional scale, the capacity of the largest EU plant, at 500,000 tonnes, is greater than 10% of the total EU capacity, and so releases to the region will be based on this size of plant. This gives 55 tonnes per year. On the continental scale, applying the factor of 0.11 kg/tonne to the total production volume of 1,445,000 tonnes gives a release of 159 tonnes.

Release to water

The default emission factor from the TGD for chemicals used in synthesis is 0.003, i.e. 3 kg/tonne. A 1976 estimate of 6.3 kg/tonne is quoted in BUA (1992), with the comment from producers that improved control measures have reduced this considerably. A more recent estimate of 0.122 kg/tonne is presented in BUA (1992) based on the average concentration of propylene oxide in wastewater.

Information on releases to water has been provided by seven producers of propylene oxide, and from this information release factors have been calculated. A number of these will overestimate the release as they are based on detection limits, and others may also include propylene oxide releases from other processes on the same site. Values for releases before wastewater treatment range from $1.1 \cdot 10^{-5}$ to 0.26 kg/tonne. A value of $2 \cdot 10^{-3}$ kg/tonne for release after wastewater treatment was also derived. These sites cover both the chlorohydrin and indirect oxidation production routes, and there is no clear distinction between the values from the two methods.

The available information covers 97% of the EU production capacity and is therefore considered to be representative of the current situation. A value of 0.26 kg/tonne will be taken; this is likely to be an overestimate as it is derived from a detection limit of 2.2 mg/l. As with the releases to air above this will be applied to the production capacity not included in the available information, i.e. 50,000 tonnes. This gives a release of 13 tonnes/year, 43 kg/day.

On a regional scale, the capacity of the largest EU plant, at 500,000 tonnes, is greater than 10% of the total EU capacity, and so releases to the region will be based on this size of plant. This gives 130 tonnes per year. On the continental scale, applying the factor of 0.26 kg/tonne to the total production volume of 1,445,000 tonnes gives a release of 376 tonnes.

3.1.1.2 Releases from processing

Release to air

A number of estimates of release from the use of propylene oxide to produce other substances are available. Some of these refer to specific uses such as polymer production or glycol production, while others are more general. As the major processes appear to involve similar operations then the release factors will be applied to processing in general (although the particular area will be identified where appropriate). All values refer to release of propylene oxide, but may be defined in terms of tonnes of product or of tonnes of propylene oxide used.

A release factor of 132 g/tonne propylene oxide used to produce homo- and co-polymers was quoted by BUA (1992) as applying to the early 1980s, with the comment that definite reductions in emissions had occurred since then. BUA (1992) also presented more recent estimates: one processor estimated releases as 28.2 g/tonne of glycol produced, which corresponds to 37 g/tonne of propylene oxide used assuming a 1:1 conversion; a second processor gave an overall estimate from processing propylene oxide of 1-5 g/tonne used.

RIVM (1988) used a value of 100 g/tonne of product for polyols, propylene glycol and other products.

From information provided by a number of processors, emission factors in the range 0.04 to 14 g/tonne were calculated. A number of other production sites achieve zero emission of propylene oxide through acid hydrolysis of the waste streams (which produces propylene glycol from propylene oxide). The processors covered around 60% of the propylene oxide converted to other products. There are no clear indications of different emission rates from the various processes used.

The default release factor from the TGD is 5 kg/tonne for use as an intermediate (Table A3.3 in the TGD, MC=1c), and 50 kg/tonne for use in polymers (Table A3.10 in the TGD, Type I substance). As for the releases to air from production these are much larger than even the older values available. A value of 37 g/tonne will be used as a realistic worst-case estimate from measurements of emissions in the 1990s.

The TGD gives a fraction of 0.15 of the tonnage to be used on one site for use as an intermediate (or 0.05 for use in polymers). It will be assumed that both major processes of this type occur on the same site and so this fraction will be applied to the tonnage used to manufacture other substances. This is taken as the total usage, 1,495,000 tonnes, as only a small amount is used directly. This gives a tonnage for one site of 224,250 tonnes. This may be an overestimate as the largest site for which information was provided deals with 90,000 tonnes, and the largest production sites for propylene glycol listed in IUCLID have a capacity of 100,000 tonnes. Applying the fraction of main source to the regional tonnage (10% of the total) would result in a site processing 22,425 tonnes, which is considered to be an underestimate in this case.

Applying the release factor to this size of site gives an annual release of 8.3 tonnes, 28 kg/day. The regional release will be taken as the same value. For the continental scale the value is 55.3 tonnes/year.

Release to water

Again, releases to water are not always separated according to the different products and so they will be treated together. The default emission from the TGD for processing of intermediates is 7 kg/tonne (Table A3.3 in the TGD) and for use as a monomer it is 10 kg/tonne (Table A3.10 in the TGD, assuming a wet process).

For release into the wastewater stream, BUA (1992) has an estimate of 0 to 0.004 kg/tonne for processing in general. Data from four processing sites gave estimated release factors of $1.5 \cdot 10^{-5}$, $3.2 \cdot 10^{-4}$, 0.07 and 1.1 kg/tonne. The last of these is from a combined production and processing site, and is calculated as if all the emission arose only from processing. The fraction of the production volume processed on the site is only 25%. Therefore this value is not considered to be representative of releases from processing. In addition to these sites, four other sites had negligible releases of propylene oxide through recycling of process water, hydrolysis to propylene glycol and incineration of waste streams.

The information available from actual sites indicates that low levels of propylene oxide can be achieved in the wastewater from processing. The highest of the more specific estimates will be used, i.e. 0.07 kg/tonne or 70 g/tonne rather than the default value. Applying this factor to the processing volume identified above gives a release of 15.7 t per year, or 52 kg/day. The regional release is the same as the local release. The continental release is 105 tonnes/year.

3.1.1.3 Release from further processing and use of products

The polymers and other chemicals made from propylene oxide may contain residual amounts of unreacted propylene oxide. However levels of residual propylene oxide are low. Recent measurements on polyols provided by Industry show levels of ≤5 ppm. There is very little information available on what releases might occur in this area, so a number of assumptions have been made to make a worst-case estimate of what the releases might be.

Polyether polyols are used in the production of polyurethanes (see Section 2.3.1). The largest application is in the production of flexible slabstock foams. Woods (1982) describes the formation of flexible slabstock foams in a continuous process at a rate of up to 500 kg/minute, or 72,000 tonnes/year (for 8 hours/day, 300 days/year), on a single machine. A typical recipe for such foams is 100 parts polyol, 80-115 parts isocyanate and 1-200 parts filler, etc., all by weight. Thus the polyol makes up between 25% and 50% of the weight. Hence the usage of polyol would be 18,000-36,000 tonnes/year. Although the polyols are copolymers of propylene oxide and ethylene oxide, as a worst case and in the absence of any composition information it will be assumed that this is all propylene oxide based. Taking the figure of 5 ppm as the maximum possible propylene oxide content corresponds to 180 kg/year of monomer or 0.6 kg/day. The manufacture of polyurethanes involves only a small amount of water as a reactant and so release to water is unlikely. It will therefore be assumed that all of the above release goes to the air. This release is likely to be a large overestimate, as it is based on a detection limit value and also takes no account of any possible reaction between the residual monomer and other species during the further processing.

On a regional scale no information is available on the distribution of the use of polyols between polyurethane production and surfactant use. As a worst case it could be assumed that each in turn accounted for all of the use of polyols. Release from PU production is assumed to be to air, and release from surfactant use to be to water. Thus 10% of the total European usage of polyols, 107,640 tonnes/year, would give a maximum potential release of 0.54 tonnes to air from PU production, or 0.54 tonnes/year to water from surfactant use. Continental releases would be 5.4 tonnes to each compartment. In the calculation of regional and continental concentrations later in this section both of these releases will be included, recognising that this will be double counting.

The other major product from propylene oxide is propylene glycol. This substance is a high production volume chemical and has a IUCLID file. Propylene oxide is not included in the list of impurities (or additives) in the IUCLID entry for propylene glycol. Tests on a small number of glycol and glycol ether samples found no residual propylene oxide at a limit of detection of 0.5 ppm. It is therefore assumed that the content of propylene oxide monomer in this substance is negligible.

The estimates made above assume that all of the monomeric propylene oxide present in products manufactured in one year is released to the environment over the same timescale. This implies that there is no build up of products in use containing propylene oxide as residual monomer or that the average lifespan of products containing propylene oxide is less than one year.

3.1.1.4 Release from direct use

The only direct use of propylene oxide for which any information is available is as a stabiliser in chlorinated solvents, specifically dichloromethane. BUA (1992) estimated that 1,000 tonnes of dichloromethane were used in Germany in 1991, with a propylene oxide content of 0.5%. It is not clear if all the dichloromethane used contains propylene oxide; it is listed as an "impurity" in the IUCLID entry for dichloromethane. A survey of dichloromethane usage (DoE, 1994) estimated that 165,000 tonnes were used in Europe in 1992. There are a number of potential stabilisers available for dichloromethane so it is unlikely that propylene oxide would be used in the whole amount (it has been suggested that it is used when there is a requirement for no solid residue remaining when the solvent is evaporated to dryness). For the purposes of this assessment, the usage figure for Germany will be taken as representative of the usage in a region, which gives a value of 5 tonnes/year. It will be assumed that all of this is released unchanged during the year. For continental releases ten times this value will be used, i.e. 50 tonnes.

3.1.1.5 Release from indirect sources

Propylene oxide has been reported as being produced in the combustion of simple hydrocarbon fuels (Bogyo, 1980). RIVM (1988) found no quantitative data on the amount of propylene oxide in exhaust emissions, but deduced that the hydrocarbon fraction in exhaust gases may contain 0.01% propylene oxide (the basis of this deduction is not clear). This gave an estimated 10 tonnes/year release to the environment in The Netherlands. These two reports refer to studies carried out in the 1970s or earlier. More recent investigations into the composition of exhaust gases do not mention propylene oxide, though it cannot be judged whether this is because it is not found or because it is not looked for. As there is a lack of quantitative evidence as to whether propylene oxide is present in exhaust fumes and if so at what level, releases from this source cannot be estimated with any confidence.

3.1.1.6 Summary of releases

Table 3.1 shows a summary of the releases estimated in the preceding sections. These will be used to calculate the PECs later in the assessment. Site-specific release data will also be used to estimate PECs. The effects of wastewater treatment plants have not yet been taken into account, so some of the figures in the table will be altered before they are used in the distribution modelling later on.

Table 3.1 Summary of releases of propylene oxide

Activity	Release (tonnes/year)					
	Local scale		Regional scale		Continental scale	
	Air	Water	Air	Water	Air	Water
Production	5.5	13	55	130	159	376
Processing	8.3	15.7	8.3	15.7	55.3	105
Further processing	0.18 [a)]		0.54 [a)]	0.54 [a)]	5.4 [a)]	5.4 [a)]
Direct use			5		50	
Total			68.8	146	270	486

[a)] based on estimates from polyurethane production; larger scale estimates use this value for all further processing of propylene oxide, and assign all release to air and to water (i.e. these releases are double counted).

As a comparison with the regional release figure, information from the emission register of The Netherlands gives emissions to air of 59.6 tonnes of propylene oxide in 1995. This includes a significant number of producers and processors of propylene oxide, and is in reasonable agreement with the total regional release estimate in **Table 3.1**.

3.1.2 Environmental fate

3.1.2.1 Degradation

3.1.2.1.1 Abiotic degradation

Photolysis

Propylene oxide does not absorb solar radiation appreciably at wavelengths greater than 300 nm (it has a maximum absorption at 199.5 nm). Thus direct photolysis does not occur.

Photooxidation

Propylene oxide reacts with hydroxyl radicals in the atmosphere. The rate of this reaction has been determined by a number of investigators, and the results are summarised in **Table 3.2**.

Table 3.2 Photooxidation rate constants for the reaction of propylene oxide with OH radicals

Rate constant (10^{-12} $cm^3 \cdot molecule^{-1} \cdot s^{-1}$)	Half-life (days) *	Method	Reference
1.11±0.75	14.4	relative rate (n-butane as reference compound)	Edney et al. (1986)
0.495±0.052	32.3	absolute rate, flash photolysis resonance fluorescence	Wallington et al. (1988)
1.3±0.8	12.3	relative method	Winer et al. (1979) (in RIVM, 1988)
0.53±0.07	30.1	absolute method	Zetsch and Stahl (1981) (in RIVM, 1988)
2.4	6.6	smog chamber	Pitts (1979) (in IUCLID)

* using OH radical concentration of $5 \cdot 10^5$ molecule cm^{-3}

There is some variation in the results. As a reasonable worst case the longest half-life, 32 days, will be used.

The products of the reaction are expected to be acetyl formyl oxide, formaldehyde, formanhydride and methyl glyoxal which are expected to degrade further. RIVM (1988) described possible mechanisms for the formation of methyl glyoxal, which included the conversion of NO to NO_2, i.e. O_3 formation. However they considered that the low reactivity and relatively low concentration of propylene oxide meant that this was not important as a cause of photochemical air pollution. They considered that propylene oxide would eventually be transformed into carbon dioxide and water.

Reactions of propylene oxide with ozone and nitrogen oxides are considered to be negligible (Grosjean, 1990).

Hydrolysis

Epoxides such as propylene oxide can degrade in water through hydrolysis and related ionic reactions involving the cleavage of a carbon-oxygen bond. The hydrolysis reaction can be spontaneous (under neutral conditions), or acid or base catalysed. Bogyo et al. (1980) gave values for the rate constants for the three processes as shown in **Table 3.3**.

Table 3.3 Rate constants for hydrolysis of propylene oxide

Process	Rate constant (at 25°C)	Source
spontaneous hydrolysis	$6.9 \cdot 10^{-7}$ s^{-1}	Koskikallio and Whalley (1959)
acid catalysed	0.052 $l \cdot mole^{-1} \cdot s^{-1}$	estimated by Bogyo et al. (1980)
base catalysed	$8.7 \cdot 10^{-5}$ $l \cdot mole^{-1} \cdot s^{-1}$	Koskikallio and Whalley (1959)

In the environment the major reaction is expected to be the spontaneous process. A number of values have been reported for the rate constant for this process, and these are summarised in **Table 3.4**.

Table 3.4 Rate constants for spontaneous hydrolysis of propylene oxide in water

Temperature (°C)	Rate constant 10^{-6} s^{-1}	Half-life (days)	Reference
20	0.37	21.7	Nichols and Ingham (1955)
22	0.47	17.1	Nichols and Ingham (1955)
25	~0.55	14.6	Mabey and Mill (1978)
25	0.69	11.6	Koskikallio and Whalley (1959)
25	0.68 - 0.75	11.8 - 10.7	Sato et al. (1985)

The longest half-life from the table (which was also obtained at the most environmentally relevant temperature), i.e. 22 days, will be taken to represent the worst case. All the values are covered by a factor of two. The product of the hydrolysis reaction is propylene glycol (1,2-propanediol) which biodegrades rapidly in water.

As mentioned above propylene oxide can also react with other nucleophiles (anions or Lewis bases). In these cases the reactions can be spontaneous or acid catalysed. The most studied reaction is that with chloride ions, which is relevant to the fate of propylene oxide in salt water. A comparison of the rates of removal in fresh and salt water is given in **Table 3.5**. From this, it can be seen that removal in salt water is substantially accelerated over that in fresh water.

RIVM (1988) also considered the reaction of propylene oxide with OH radicals in water, with a rate constant of $1.4 \cdot 10^{-8}$ l $molecule^{-1}$ s^{-1}. For an average OH radical concentration (near the surface) of $4 \cdot 10^{-16}$ $mole \cdot l^{-1}$ ($2.4 \cdot 10^{8}$ $molecules \cdot l^{-1}$) this gives a half-life of 140 days. The authors expected this to be an underestimate of the actual reaction half-life, as the OH radical concentration decreases with water depth.

Table 3.5 Removal rates for propylene oxide in fresh and salt water.

	Half-life (days)			
Medium	**pH 5**	**pH 7**	**pH 9**	**Reference**
Fresh water	7.0	12.9		Meylan et al. (1986)
(NaCl 0.003%)	6.6	11.6	11.6	Bogyo et al. (1980)
Salt water	1.6	2.4		Meylan et al. (1986)
(NaCl 3%)	1.5	4.1	4.1	Bogyo et al. (1980)

3.1.2.1.2 Biodegradation

The available studies on the biodegradation of propylene oxide are reviewed in Appendix A. The overall picture is somewhat variable. There is one valid study that shows that propylene oxide is readily degradable but there are also studies which do not show ready degradability. In particular there appears to be greater removal when inocula from industrial wastewater treatment plants are used, or when the bacteria have been acclimated. This agrees with information from the producers discussed in Section 3.1.1.1, which indicates a high degree of removal in wastewater treatment plants. However this may not be due solely to biodegradation as both volatilisation and hydrolysis can also occur. Hydrolysis may also be a factor in the biodegradation studies, as the immediate product is 1,2-propanediol, which is readily degradable.

On the basis of the available evidence, it is clear that propylene oxide can be degraded biologically, but that this may not always happen under the conditions required for ready degradability. Therefore the substance is assumed to be inherently biodegradable for general releases and on the regional and continental scales. However, there is good evidence for ready biodegradability where the bacterial population has become acclimatised to the substance. Such conditions will apply where there are continuous releases of propylene oxide to a wastewater treatment plant, such as for large production and processing sites. Thus the substance can be assumed to be readily biodegradable in such cases.

The biodegradation rates used in the assessment are therefore as follows:

in acclimatised wwtp (ready)	$1\ h^{-1}$
in other wwtp (inherent)	$0.1\ h^{-1}$
in surface water (inherent)	$4.6 \cdot 10^{-3}\ day^{-1}$
in soil (inherent)	$2.3 \cdot 10^{-3}\ day^{-1}$
in sediment (inherent)	$2.3 \cdot 10^{-4}\ day^{-1}$

3.1.2.2 Distribution

Volatility

No measured value for the Henry's Law constant is available. A value can be estimated from the ratio of the solubility and vapour pressure, although this is less appropriate for chemicals with higher solubilities. This gives a value of 8.7 $Pa \cdot m^3 \cdot mole^{-1}$. The Syracuse Research Corporation's HENRY program, as described in the TGD, was used to estimate values from the structure of the molecule. The bond contribution method gave a value of 16.2 $Pa \cdot m^3 \cdot mole^{-1}$, while the group contribution method gave a value of 12.4 $Pa \cdot m^3 \cdot mole^{-1}$. These values indicate that volatilisation

from water may be important in some areas of environmental fate. For the purposes of this assessment, the average of the three estimates is taken, i.e. 12.4 $Pa \cdot m^3 \cdot mole^{-1}$.

Rain out

The high solubility of propylene oxide means that substance released to air may be dissolved in rain and thus removed to soil or water. RIVM (1988) estimated a scavenging rate for removal by wet deposition of $2.3 \cdot 10^{-6}$ s^{-1} by analogy with sulphur dioxide; this corresponds to a half-life of 60 to 100 hours.

3.1.2.3 Accumulation

Adsorption

No measured values for the organic carbon-water partition coefficient (K_{oc}) are available. The low value of the octanol-water partition coefficient (log K_{ow}=0.055) implies that propylene oxide will not be sorbed strongly to organic matter. Using the equation for non-hydrophobics in the QSAR section of the TGD gives a value for log K_{oc} of 1.05.

Bioconcentration

Again, propylene oxide is not expected to bioconcentrate due to its low log K_{ow} value. From the equation in the TGD, the predicted log BCF is -0.65. No measured values are available.

3.1.3 Aquatic Compartment (incl. sediment)

3.1.3.1 Measured levels

There is very little information on levels of propylene oxide in the aquatic environment. BUA (1992) reports that the substance was not listed in the annual reports of two German waterworks associations from 1986 to 1988. A Japanese study in 1980 did not find propylene oxide in water (36 samples, detection limit 0.2 µg/l) or in sediment (12 samples, detection limit 2.0 ng/kg) (DEHJ, 1985).

Measurements on the level of propylene oxide in treatment works effluent from production and processing sites were reported in BUA (1992). In both cases the levels were below the detection limits, which were 5 µg/l and 20 µg/l.

3.1.3.2 Calculation of PECs for the aquatic compartment on the local scale

3.1.3.2.1 Calculation of PEC_{local} for water

In this section the estimates of releases made in previous sections will be used to calculate predicted concentrations of propylene oxide in water. This will be done for production and for processing using default assumptions from the TGD. Following this calculations based on information from actual sites will be presented.

Production and processing

Estimates of releases to water from the production of propylene oxide were made in Section 3.1.1.1. In order to calculate the predicted concentration in water, account has to be taken of the removal and dilution processes that can occur. These are: removal in a wastewater treatment plant (WWTP), dilution of effluent in receiving waters, and adsorption to suspended matter. The TGD assumes that release occurs to a standard WWTP with a flow of 2,000 m^3/day, and that this discharges into a river with a standard dilution by a factor of 10. The concentration in the receiving water may be modified by adsorption to suspended solids; however the calculation for propylene oxide using the methods in the TGD shows that this has no significant effect on the aqueous concentrations.

As discussed in Section 3.1.2.1.2, propylene oxide is considered to be readily biodegradable when the bacterial population has become acclimated, as is expected to be the case for large production and use sites where discharges are continuous. From EUSES the fate of propylene oxide in the WWTP is as follows:

Degraded:	84.5%
To air:	4%
To water:	11.5%

Applying the default removal and dilution factors to the estimates of release from Section 3.1.1.1 gives the concentrations in **Table 3.6**.

Table 3.6 Calculated concentrations in water from propylene oxide (PO) production

Activity	Quantity of PO on site	Release (kg/day)	Concentration in WWTP effluent (mg/l)	Concentration in receiving water (mg/l)
Production	50,000	43	2.5	0.25
Processing	213,038	52	3.0	0.3

The concentration for production is based on a 50,000 tonne production site discharging into the standard WWTP and river. It is likely that the WWTPs treating wastewater from large plants will themselves be much larger than the default size. Information from producers gives the following sizes for treatment works receiving propylene oxide wastewaters: 31,200, 43,200, 60,000, $2.9 \cdot 10^5$, $4.1 \cdot 10^5$ and $5.9 \cdot 10^5$ m^3/day. The smallest of these, which serves a site of similar capacity, would result in a lowering of the PEC estimates by a factor of 15.

Processing sites too tend to be large; of the treatment works listed above, all but the $2.9 \cdot 10^5$ m^3/day works also serve processing sites. Similar considerations may also apply to the flows of the receiving waters, as larger plants tend to discharge to larger rivers or to estuaries. For example, the emission scenario document for intermediates in the TGD derives a flow of 60 m^3/s for receiving water. This is $5.2 \cdot 10^6$ m^3/day, compared to 20,000 m^3/day for the default flow rate used in the calculation above. Using the higher value would reduce concentrations by a factor of 25.

Site-specific PECs

Information has been provided by a number of producers and processors of propylene oxide which enables PECs to be calculated for some actual production and processing sites. The details of these calculations are not included in this report. The results are in **Table 3.7**.

As indicated above, these sites cover 97% of the production capacity and 60% of the processing capacity for propylene oxide. These are all lower values than those calculated above using the default WWTP and river sizes.

Table 3.7 PECs for actual production and processing sites

Site	Activity	Surface water concentration (µg/l)	Comments
1A	Production	$7.4 \cdot 10^{-3}$	
1B	Processing	$3 \cdot 10^{-4}$	
2	Production and processing	-	No emissions of PO to water - incineration of liquid waste streams
3	Production and processing	$7 \cdot 10^{-6}$	
3A	Processing	1.9	
4	Production and processing	-	No emission of PO, hydrolysed to propylene glycol
4A	Processing	-	No emission of PO, hydrolysed to propylene glycol
4B	Processing	-	No emission of PO, hydrolysed to propylene glycol
5	Production and processing	0.36	
6	Production and processing	0.22	
7	Production and processing	$1.7 \cdot 10^{-3}$	
7A	Processing	-	No emissions of PO, acid hydrolysis
7B	Processing	-	No emissions of PO, acid hydrolysis

3.1.3.2.2 Calculation of PEC_{local} for sediment

The TGD describes an equilibrium partitioning method to calculate the concentration in sediment corresponding to the surface water concentration. The required parameters are the suspended matter-water partition coefficient (1.12, see Appendix B), and the bulk density of suspended matter, 1,150 $kg \cdot m^{-3}$ from the TGD. Applying this procedure to the water concentrations calculated above gives the results in **Table 3.8**.

Table 3.8 Calculated concentrations in sediment

Activity	Site code	Concentration (µg/kg)	Activity	Site code	Concentration (µg/kg)
Production		241	Site-specific	4A	-
Processing		292	Site-specific	4B	-
Site-specific	1A	$7.2 \cdot 10^{-3}$	Site-specific	5	0.35
Site-specific	1B	$2.9 \cdot 10^{-4}$	Site-specific	6	0.21
Site-specific	2	-	Site-specific	7	$1.7 \cdot 10^{-3}$
Site-specific	3	$6.8 \cdot 10^{-6}$	Site-specific	7A	-
Site-specific	3A	1.9	Site-specific	7B	-
Site-specific	4	-			

3.1.3.3 Calculation of $PEC_{regional}$ and $PEC_{continental}$ for the aquatic compartment

The regional and continental scale concentrations have been calculated using the EUSES program (Appendix D). This implements the distribution modelling for the default European environment in the TGD. Local emissions and concentrations were not calculated; instead release rates were entered for the regional and continental scales directly.

The release rates were summarised in **Table 3.1**. These need to be modified to take account of removal and stripping in wastewater treatment plants before entry into the EUSES model. For propylene oxide, all releases from production and initial processing have been considered to go through a WWTP, and to be readily degradable. Releases from further processing may not all pass through a WWTP, and so a figure of 70% connection has been used, with inherent biodegradability. The resulting releases are in **Table 3.9**.

Table 3.9 Releases on regional and continental scales (tonnes/year)

		Regional		Continental	
Activity	direct/WWTP	air	water	air	water
Production	direct	55		159	
	WWTP	5.2	15.0	15	43
Processing	direct	8.3		55.3	
	WWTP	0.63	1.8	4.2	12.1
Further processing	direct	0.54	0.16	5.4	1.6
	WWTP	0.045	0.19	0.45	1.9
Direct use	direct	5		50	
Total		75	17	289	59
(in kg/day)		205	47	792	161

Note: the figures in the continental column are the total releases on this scale. The regional emissions were subtracted from these before entering as continental releases into EUSES.

The resulting concentrations for the aquatic compartment are in **Table 3.10**.

Table 3.10 Calculated regional and continental concentrations of propylene oxide in the aquatic compartment.

Compartment	Regional	Continental
Water (mg/l)	$6.7 \cdot 10^{-5}$	$2.2 \cdot 10^{-6}$
Sediment (mg/kg)	$5.5 \cdot 10^{-5}$	$1.8 \cdot 10^{-6}$

3.1.3.4 Summary of PECs for the aquatic compartment

In the preceding sections, local and regional concentrations in water and sediment have been calculated using default emission scenarios and site-specific data. The regional concentration is considered to be the background concentration, and so to obtain the PEC_{local} this needs to be added to the local concentrations already calculated. The PEC_{local} is the concentration obtained during release episodes, which will be used in the aquatic risk characterisation. In addition for the indirect human exposure and secondary poisoning assessments the annual average concentrations will be calculated (all the releases described above are assumed to occur over 300 days - these are spread out over 365 days to obtain the annual average). The resulting PEC values are in **Table 3.11**. Sediment concentrations were calculated from the water concentrations using the equilibrium partitioning method after the local and regional water concentrations were combined. An alternative method would have been to combine the local and regional sediment concentrations; this would have given slightly (but not significantly) different results. Only sites giving rise to concentrations in the aquatic compartment have been included.

Table 3.11 PEC values for the aquatic compartment

Activity	Site code	$PECloca l_{water}$ (µg/l)	$PECloca l_{water,ann}$ (µg/l)	$PECloca l_{sed}$ (µg/kg)	$PECloca l_{sed,ann}$ (µg/kg)
Production		250	210	240	200
Processing		300	250	290	240
Site specific	1A	0.074	0.061	0.072	0.059
	1B	0.067	0.055	0.065	0.053
	3	0.067	0.055	0.065	0.053
	3A	2.0	1.6	1.9	1.6
	5	0.43	0.35	0.42	0.35
	6	0.29	0.24	0.28	0.23
	7	0.069	0.057	0.067	0.055

It is clear from **Table 3.11** that the concentrations calculated for specific sites are much lower than those estimated using default values. This is largely due to the much larger wastewater treatment plants to which the large production and processing sites discharge, and to greater dilution in receiving waters. The emission factors estimated for actual sites are also much lower than the default value in the TGD. The information available for specific sites covers 97% of the production and 60% of the processing of propylene oxide. Some of the sites combine both

production and processing at the same location. The processing sites include large capacity plants, up to 180,000 tonnes per year. It is therefore considered that the actual information available is sufficiently representative of the production and use of propylene oxide to be used in the risk assessment. The PEC for the aquatic environment is therefore taken as the highest of the site-specific values, 2 µg/l (1.6 µg/l for the annual average). The corresponding values for sediment are 1.9 µg/kg and 1.6 µg/kg, respectively.

3.1.4 Air compartment

3.1.4.1 Measured levels

There are no reported values of ambient air concentrations of propylene oxide available.

3.1.4.2 Calculation of PECs for the air compartment on the local scale

Estimates of the release to air of propylene oxide during production and processing were made in Sections 3.1.1.1 to 3.1.1.3. The TGD gives a method for calculating the concentration in air at 100 metres from a source; the concentration is proportional to the source strength and so the concentrations are estimated by multiplying the actual emission rate by the concentration from a source of 1 $kg \cdot day^{-1}$. In addition to the direct releases emissions from wastewater treatment plants also need to be taken into account. The estimation of the fate of propylene oxide in the WWTP gives a release of 4% of the influent amount to the air.

The results of applying this calculation to the release estimates are in **Table 3.12**. Also included are the results of similar calculations for a number of actual sites.

Table 3.12 Calculated concentrations in air from emissions from production and processing

Activity	Source or site code	Release rate (kg/day)	Concentration (µg/m³)	Annual average concentration (µg/m³)
Production	direct	18.3	5.1	4.2
	via WWTP	1.3	0.36	0.30
Processing	direct	28	7.8	6.4
	via WWTP	2.1	0.58	0.48
Further processing	direct	0.6	0.17	0.14
Site specific	1A direct	75	21	17
	1A via WWTP	0.058	0.016	0.013
	1B direct	32	9	7.4
	1B via WWTP	$8.6 \cdot 10^{-3}$	$2.4 \cdot 10^{-3}$	$2 \cdot 10^{-3}$
	2 direct [a)]	0.015	0.004	$3.3 \cdot 10^{-3}$
	3 direct	67	19	16
	3 via WWTP	$4 \cdot 10^{-4}$	$1.1 \cdot 10^{-4}$	$9.0 \cdot 10^{-5}$
	3A direct	3.3	0.9	0.74
	4A direct [a,b)]	4.2	1.2	0.99
	4B direct [a,b)]	2.1	0.58	0.48
	5 direct	58	16	13
	5 via WWTP	1.0	0.28	0.23
	6 direct	5.9	1.6	1.3
	6 via WWTP	5.3	1.5	1.2
	7 direct	0.83	0.23	0.19
	7 via WWTP	0.037	0.01	$8.2 \cdot 10^{-3}$

[a)] no release to WWTP at this site so no indirect air emissions.
[b)] no site information, release estimated using factor from Section 3.1.1.2 for processing (37 g/t).
Sites 4, 7A and 7B have no direct releases to air (closed systems, N2 padding and acid hydrolysis of flue gases).

All the emission rates are based on 300 days of operation; the annual average concentrations were calculated by spreading these over 365 days as described in the TGD.

Where there are both direct releases and releases through a WWTP, the TGD states that the higher of the two values should be used as the PEC. In all the cases above the direct release gives the higher concentration. The highest value is 20 µg/m^3 from a specific site.

3.1.4.3 Calculation of $PEC_{regional}$ and $PEC_{continental}$ for the air compartment

Section 3.1.3.3 described the methods used to calculate the regional and continental scale concentrations. The results for the air compartment were: regional concentration $5.4 \cdot 10^{-3}$ µg/m^3; continental concentration $1.5 \cdot 10^{-3}$ µg/m^3.

3.1.4.4 Summary of PECs for air compartment

To calculate the final PEC_{local} for air, the regional background concentration needs to be added to the estimates from Section 3.1.4.2. As indicated previously, the higher concentrations resulting from direct releases will be taken rather than those arising from WWTPs. For the air compartment the annual average concentration is used rather than that during a release episode. The resulting concentrations ($PEClocal_{air,ann}$) are in **Table 3.13**.

Table 3.13 $PEClocal_{air,ann}$

Activity	$PEClocal_{air,ann}$ (µg/m³)
Production	4.2
Processing	6.4
Further processing	0.15
Site specific (Site 1A)	17

3.1.4.5 Calculation of the deposition fluxes from air emissions

The TGD provides a method for calculating the deposition of a chemical through wet and dry processes and incorporating particulate-adsorbed deposition. For these calculations the emissions from WWTPs are combined with the direct emissions. Only the largest of the site-specific values has been used in these calculations.

The fraction of chemical associated with particulate material in the air is calculated as $1.7 \cdot 10^{-9}$ (see Appendix B). The resulting estimated deposition rates are in **Table 3.14**. The values are used later in the assessment to estimate concentrations in soil.

Table 3.14 Deposition rates to soil from propylene oxide emission to air

Activity	Release rate ($kg \cdot day^{-1}$)	Concentration ($\mu g \cdot m^{-3}$)	Total deposition ($mg \cdot m^{-2} \cdot day^{-1}$)	Annual deposition rate ($mg \cdot m^{-2} \cdot day^{-1}$)
Production	19.6	5.5	$7.8 \cdot 10^{-3}$	$6.4 \cdot 10^{-3}$
Processing	30.1	8.4	0.012	$9.9 \cdot 10^{-3}$
Further processing	0.6	0.17	$2.4 \cdot 10^{-4}$	$2.0 \cdot 10^{-4}$
Site specific (1A)	75	21	0.03	0.025

3.1.5 Soil compartment

3.1.5.1 Measured levels

There are no reported measured levels of propylene oxide in soil available.

3.1.5.2 Calculation of PECs for soil compartment on the local scale

A substance can reach the soil compartment by three routes: direct application, deposition from air and sludge application. No direct application routes have been found for propylene oxide. The calculation of the fate of propylene oxide in a wastewater treatment plant indicates no removal on sludge, and so this route is not considered significant. Therefore the only route for soil exposure is through deposition from air.

The steps in the calculation of the PEC for soil from deposition are in Appendix C. Removal of propylene oxide from soil is relatively rapid so there is no build up of chemical in the soil. The most important removal process is volatilisation, followed by biodegradation and then leaching. Although three soil types (natural, agricultural and grassland) are considered in the calculations, there is no difference in the levels for natural and agricultural soils. This is because the only difference between the calculations for these two soil types is the time for averaging (30 days or 180 days). There is no sludge application and so the input to soil is continuous from deposition, hence the concentration is the same at both times. The results are presented in **Table 3.15**.

Table 3.15 Predicted concentrations in soil after 10 years deposition

	Concentration (µg/kg)	
Source	Natural/agricultural	Grassland
Production	0.84	0.84
Processing	1.3	1.3
Further processing	0.026	0.026
Site specific (Site 1A)	3.2	3.3

3.1.5.3 Calculation of $PEC_{regional}$ and $PEC_{continental}$ for the soil compartment

Section 3.1.3.3 described the methods used to calculate the regional and continental scale concentrations. The results for the soil compartment are shown in **Table 3.16**.

Table 3.16 Regional and continental concentrations in soil

	Regional	**Continental**
Pore water (mg/l)	$1.2 \cdot 10^{-6}$	$3.3 \cdot 10^{-7}$
Natural soil (mg/kg)	$4.1 \cdot 10^{-7}$	$1.1 \cdot 10^{-7}$
Agricultural soil (mg/kg)	$3.9 \cdot 10^{-7}$	$1.0 \cdot 10^{-7}$
Industrial soil (mg/kg)	$4.1 \cdot 10^{-7}$	$1.1 \cdot 10^{-7}$

3.1.5.4 Summary of PECs for soil

To calculate the PEC values to be used in the assessment, the background concentration for natural soil on the regional scale is added to the values calculated in Section 3.1.5.2. Pore water concentrations are also estimated from the soil concentrations by the methods in the TGD. The results are in **Table 3.17**.

Table 3.17 Local concentrations in soil and porewater

Activity	$PEClocal_{soil}$ (µg/kg)		$PEClocal_{soil,porew}$ (µg/l)	
	Natural/agric	Grassland	Natural/agric	Grassland
Production	0.84	0.84	2.5	2.5
Processing	1.3	1.3	3.9	3.9
Further processing	0.026	0.026	0.079	0.079
Specific site (Site 1A)	3.2	3.3	9.7	10

3.1.6 Secondary poisoning

Propylene oxide has a low octanol-water partition coefficient, and there are no indications that it will accumulate in the food chain. Neither is it persistent. Therefore an assessment of non-specific exposure will not be carried out.

There are a number of measurements of propylene oxide levels in foodstuffs dating back to the 1960s. These all arose as a result of treating the foodstuffs with propylene oxide as a sterilant or disinfectant. As propylene oxide is no longer used in the EU for such applications, these measured levels are not considered in this assessment.

3.2 EFFECTS ASSESSMENT: HAZARD IDENTIFICATION AND DOSE (CONCENTRATION) - RESPONSE (EFFECT) ASSESSMENT

3.2.1 Aquatic compartment (incl. sediment)

3.2.1.1 Toxicity test results

Few acute aquatic toxicity tests have been reported. Those for which data are available are summarised in **Tables 3.18 and 3.19**.

3.2.1.1.1 Toxicity to fish

From **Table 3.18** it can be seen that the majority of tests reported have looked at short-term toxicity. The most sensitive species appears to be the rainbow trout (*Oncorhynchus mykiss*) with a 96-hour LC_{50} of 52 mg/l and a 72-hour LC_{100} of 100 mg/l (Shell Research 1986). Other freshwater species show similar, if slightly lower, sensitivity with LC_{50} values ranging from 141 mg/l to 215 mg/l. The only saltwater species reported is the common mullet (*Mugil cephalus*) which shows a similar sensitivity to the freshwater species, having a 96-hour LC_{50} of 89 mg/l (Crews 1974).

The only longer-term toxicity test reported was that carried out by Deneer et al. (1988) with the guppy (*Poecilia reticulata*). They reported a 14-day LC_{50} of 31.9 mg/l.

The lowest no-observable effect concentration (NOEC) reported for any species was a 96-hour NOEC of 20 mg/l for *Oncorhynchus mykiss* (Shell Research 1986).

3.2.1.1.2 Toxicity to aquatic invertebrates

The only reported test on aquatic invertebrates was that carried out on the water flea (*Daphnia magna*) for Shell Research (1986) (see **Table 3.19**). The effect concentrations determined were a 24-hour EC_{50} of 650 mg/l and a 48-hour EC_{50} of 350 mg/l. The 95% fiducial limits were 550-760 mg/l and 290-420 mg/l respectively.

Table 3.18 Acute toxicity tests to fish

Species	Size (mm)	pH	Dissolved oxygen (mg/l)	Water hardness (mg/l $CaCO_3$)	Water temperature (°C)	Flow/static	Effect concentration * n - nominal concentration m - measured concentration	Data validity	Reference
Freshwater species									
Bluegill *Lepomis macrochirus*	30-40				23	static	96-hr NOEC 150 mg/l (n) 96-hr LC_{50} 215 mg/l (n) 24- hr LC_{100} 240 mg/l (n)	Use with care 2)	Crews (1974)
Mosquito fish *Gambusia affinis*	20-30				23	static	96-hr NOEC 130 mg/l (n) 96-hr LC_{50} 141 mg/l (n) 48-hr LC_{100} 180 mg/l (n)	Use with care 2)	Crews (1974)
Goldfish *Carrasius auratus*	62±7	6-8	>4		20±1	static	24-hr LC_{50} 170 mg/l (m)	Use with care 2)	Bridié et al. (1979)
Rainbow trout *Oncorhynchus mykiss*	44-51	8-8.4	8-10.2	218-228	18.5	static renewal	96-hr NOEC 20 mg/l (n) 96-hr LC_{50} 52 mg/l (n) 72-hr LC_{100} 100 mg/l (n)	Valid 1)	Shell Research (1986)
Guppy *Poecilia reticulata*		6.8-7.1	>4.6			semi-static	14-day LC_{50} 549.5 µmol/l =31.9 mg/l (n)	Not valid 3)	Deneer et al. (1988)
Saltwater species									
Common mullet *Mugil cephalus*	70-80				23	static	96-hr NOEC 80 mg/l (n) 96-hr LC_{50} 89 mg/l (n) 48-hr LC_{100} 100 mg/l (n)	Use with care 2)	Crews (1974)

* NOEC and LC_{50} based on survival

1) EPA test

2) APHA Guideline

3) Insufficient experimental detail

Table 3.19 Acute toxicity of propylene oxide to other aquatic organisms

Species	pH	Dissolved oxygen (mg/l)	Water hardness (mg/l$CaCO_3$)	Water temp (°C)	Flow/static	Effect concentration (all nominal)	Reference
Daphnia magna	8.0-8.1	9.0-9.2	168	18-22	static	24-hr EC_{50} 650 mg/l 48-hr EC_{50} 350 mg/l	Shell Research (1986)
Selenastrum capricornutum		7.2-7.5		23	static	96-hr EC_{50} 240 mg/l 96-hr NOEC 100 mg/l	

Note: *D. magna* values based on immobilisation, *S. capricornutum* values based on growth
Validity of tests: *Daphnia* valid (EPA test); *Selenastrum* use with care (modification of EPA test)

3.2.1.1.3 Toxicity to aquatic plants

Shell Research (1986) reported acute toxicity testing on the planktonic alga *Selenastrum capricornutum*. A four-day growth experiment was carried out, with incubation cell counts being made after two and four days using a Coulter counter. The 96-hour EC_{50} value of 240 mg/l was calculated from the reduction in cell numbers of the exposed organisms as compared to the mean cell number at day four in the controls. The calculation was done by probit analysis using log transformed concentration values. The 96-hour NOEC was 100 mg/l.

3.2.1.2 Calculation of PNEC for aquatic organisms

3.2.1.2.1 PNEC for water

Only a limited amount of information is available on the aquatic toxicity of propylene oxide. Short-term studies are available for fish, aquatic invertebrates and algae. The validity of the studies is indicated in the tables, and there are valid studies for each of the endpoints. The only long-term NOEC available is for algae, but this cannot be used to derive the PNEC if it is not supported by other long-term studies. Therefore the PNEC will be derived from the lowest short-term toxicity value, which is 52 mg/l for the rainbow trout (*Oncorhynchus mykiss*). An assessment factor of 1,000 is appropriate for this limited dataset. This gives a $PNEC_{water}$ of 52 µg/l.

3.2.1.2.2 PNEC for sediment

No data are available on the effects of propylene oxide on sediment-dwelling organisms. In the absence of such information the TGD suggests that the PNEC may be calculated using the equilibrium partitioning method. Applying this method to the PNEC for water from above, with a $K_{sed\text{-}water}$ value of 1.08 (see Appendix B) gives a $PNEC_{sed}$ of 43.2 µg/kg.

3.2.1.2.3 PNEC for microorganisms

There are no direct assessments of the effect of propylene oxide on microorganisms available. Some of the studies on biodegradation contain indications that the substance had no inhibitory effect on bacteria. Miller and Watkinson (1985) stated that there was no measurable inhibition of microbial activity in the closed bottle test at 3 mg/l. In the Japanese MITI test (MITI, 1988)

93-98% of propylene oxide was degraded at a concentration of 100 mg/l. It is not possible to derive a realistic PNEC from this information; however the balance of the evidence suggests that propylene oxide is not likely to be inhibitory to microorganisms under the conditions of these tests. Also, information from one site indicates a high level of removal in a wastewater treatment plant, again suggesting little or no inhibition. There is evidence for effects on soil bacteria at high exposure levels (see below).

3.2.2 Terrestrial compartment

Most toxicological testing on epoxides has been aimed at evaluating mutagenic activity and carcinogenic potential. The only studies available of relevance to the toxicity of propylene oxide in the terrestrial compartment deal with the sterilising effects of the substance on soil. These studies were intended to assess the suitability of propylene oxide to sterilise soil prior to its use in other experiments and hence involved relatively high exposure levels.

3.2.2.1 Toxicity to soil invertebrates and microbes

Alphei and Scheu (1993) found that fumigation of soil rich in organic carbon with propylene oxide as the fumigant defaunated the soil of protozoa and nematodes as well as eliminating microbial populations. Their fumigation method was to place a beaker containing 150 ml of propylene oxide in a desiccator with a 600 g (fresh weight) soil sample, distributed to about 2 cm thickness prior to evacuation of the desiccator. The desiccator was kept closed for 48 hours, after which the propylene oxide was removed by eight evacuation-ventilation cycles. The fumigation process was then repeated. Subsamples of the treated soil were tested to evaluate sterility and the degree of defaunation. Samples were also incubated in the dark for 115 days after being inoculated with a soil solution made from fresh soil. The authors found that as well as acting as a biocide, propylene oxide caused a strong increase in soil respiration throughout the incubation experiment, and resulted in almost total immobilisation of nitrate within the first 14 days of the incubation experiment. The treatment level in this experiment was around 200 g/kg wet weight.

3.2.2.2 Toxicity to terrestrial plants

Skipper and Westermann (1973) also found that propylene oxide sterilised soil (initial concentration 0.8 and 1.7 g propylene oxide for 25 g dry soil, i.e. 32 and 68 g/kg dry weight respectively). In addition they noted that the germination and growth of wheat and alfalfa were retarded in propylene oxide-treated soil. Germination was reduced by 50-60% and plant stems were twisted and distorted, with alfalfa appearing to be more resistant than wheat. There is therefore a possibility that propylene oxide residues in soil could hinder subsequent plant growth. However Agnihotri (1971) noted that propylene oxide used as a fumigant against the soilborne fungus *Waitea circinea*, which causes root rot of coniferous seedlings, left the seedlings healthy in appearance.

3.2.2.3 PNEC for soil

A PNEC for soil cannot be derived from the test results described above, and so the equilibrium partitioning method has to be used in accordance with the TGD. From the $PNEC_{water}$ of 52 µg/l, the $K_{soil\text{-}water}$ of 0.54 m^3/m^3 (see Appendix B) and the density of soil of 1,700 kg/m^3, the $PNEC_{soil}$ value is 16.5 µg/kg.

Propylene oxide has been used as a biocide (fumigant), and so some further consideration of the requirement for actual soil toxicity data is needed. This is addressed in the risk characterisation section.

3.2.3 Air compartment

There are no data on the effects of propylene oxide through atmospheric exposure other than those from mammalian toxicity tests (see Section 4). Propylene oxide has been used as a biocide (fumigant). There is no indication in the limited information available that the substance has been used against specific types of organism, although the use in soil sterilisation (see Section 3.2.2) suggests a general broadband toxicity at high doses. Further toxicity testing for exposure via the gaseous phase (e.g. for plants) could be considered. However, since the calculated concentrations of propylene oxide in ambient air are low it is not expected that these levels will cause adverse effects on organisms exposed through this route.

Propylene oxide reacts with hydroxyl radicals in the atmosphere with a moderate half-life. RIVM (1988) did not consider the substance to be important as a cause of photochemical air pollution. Although some of the potential products of propylene oxide breakdown in the atmosphere have relatively high photochemical ozone creation potentials, they are unlikely to be formed at a rate that could give rise to local air pollution problems.

3.2.4 Secondary poisoning

As discussed in Section 3.1.6 propylene oxide is not persistent and shows no indications of accumulating in the food chain, and therefore an assessment of secondary poisoning will not be carried out.

3.3 RISK CHARACTERISATION

The risk characterisation is performed by comparing the PEC with the relevant PNEC for each environmental compartment/endpoint. A ratio above 1 indicates a concern.

3.3.1 Aquatic compartment (incl. sediment)

3.3.1.1 Aquatic organisms

The $PNEC_{water}$ is 52 µg/l (Section 3.2.1.2.1). The highest PEC for a site-specific calculation (representative of production and processing) is 2 µg/l (Section 3.1.3.4). This gives a PEC/PNEC ratio of 0.04.

The regional concentration estimated in Section 3.1.3.3 was 0.067 µg/l; this gives a PEC/PNEC ratio of $1.3 \cdot 10^{-3}$.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

3.3.1.2 Sediment organisms

The predicted no-effect concentration for sediment organisms estimated in Section 3.2.1.2.2 is 43.2 µg/kg. The highest PEC for sediment (Section 3.1.3.4) is 1.9 µg/kg. This gives a PEC/PNEC ratio of 0.04.

The regional concentration estimated in Section 3.1.3.3 was 0.055 µg/kg; this gives a PEC/PNEC ratio of $1.3 \cdot 10^{-3}$.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

3.3.1.3 Sewage treatment plant

It is not possible to derive a realistic PNEC but the balance of evidence suggests that propylene oxide is not likely to be inhibitory to microorganisms under environmentally relevant conditions.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

3.3.2 Terrestrial compartment

Propylene oxide has been shown to have effects on soil organisms when used as a fumigant. The studies described in Section 3.2.2 do not allow specific endpoints to be determined, and the exposure concentrations were very high. The equilibrium partitioning method was used to derive a $PNEC_{soil}$ of 16.5 µg/kg. Comparing this with the predicted local soil concentrations (taking the grassland levels as the higher values) from **Table 3.17** gives the ratios in **Table 3.22**.

The regional concentration in soil was estimated to be $4.1 \cdot 10^{-4}$ µg/kg for natural soil; this gives a PEC/PNEC ratio of $2.4 \cdot 10^{-5}$.

All the PEC/PNEC ratios for soil are less than 1.

Table 3.20 PEC/PNEC ratios for soil

Activity	$PEClocal_{soil}$ (µg/kg)	PEC/PNEC ratio
Production	0.84	0.05
Processing	1.3	0.08
Further processing	0.026	$1.6 \cdot 10^{-3}$
Site-specific (Site 1A)	3.3	0.2

Propylene oxide has been used as a biocide (fumigant), and so some further consideration on the requirement for actual soil toxicity data is needed. There is no indication in the limited information available that the substance has been used against specific types of organism, although the use in soil sterilisation suggests a general broadband toxicity at high doses. The levels used to sterilise soil are 200 g/kg, 32 g/kg or 68 g/kg. It is presumed that these give complete sterilisation, but there is obviously no information on thresholds. The only information on effects on microorganisms relates not to soil organisms but to biodegradation tests. In these, 100 mg/l in water was not found to be inhibitory.

Data relating to plants are also available. The germination and growth of wheat and alfalfa were retarded by 50-60% in propylene oxide-treated soil (initial concentration 0.8 and 1.7 g propylene oxide for 25 g dry soil, i.e. 32 and 68 g/kg dry weight respectively). However propylene oxide used as a fumigant against the soil-borne fungus *Waitea circinea*, which causes root rot of coniferous seedlings, left the seedlings healthy in appearance - the treatment levels were 0.69 and 1.38 g/kg soil (dry or wet not specified). This suggests that the threshold for effects on plant germination may be around 1 g/kg.

The calculations of local levels in soil include input from the air through deposition based on the level of local emissions to air; in fact this is the only route to soil as the amounts on sewage sludge are negligible. The calculation method includes wet and dry deposition. The regional background calculations also incorporate deposition and volatilisation from water. The calculated levels in soil are 3.3 µg/kg for the highest local level, and 0.4 ng/kg for the regional background. The calculated level in pore water for soil (local scenario) is 10 µg/l.

The local level is therefore seven orders of magnitude lower than the levels used to sterilise the soil. There are also four orders of magnitude between the highest expected soil pore water concentration and a level found not to be inhibitory to microorganisms.

Taking all of these points into account it appears unlikely that the calculated levels of propylene oxide in soil will have an adverse effect on terrestrial organisms.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

3.3.3 Air compartment

It is not possible to assess the direct effects of propylene oxide on organisms via air exposure in view of the lack of toxicity data. However, levels of propylene oxide in the air are expected to be low and adverse effects are unlikely. Propylene oxide has moderate reactivity and is not expected to contribute to low level photochemical air pollution. It will not contribute to stratospheric ozone depletion.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

3.3.4 Secondary poisoning

Propylene oxide is not persistent and shows no indications of accumulating in the food chain, and so an assessment of secondary poisoning has not been carried out.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure Assessment

4.1.1.1 Occupational exposure

4.1.1.1.1 General introduction

Definitions and sources

In this document, unless otherwise stated, the term exposure is used to denote personal exposure as measured or otherwise assessed without taking into account the attenuating effect of any respiratory protective equipment (RPE) which might have been worn. The effect of RPE is dealt with separately. This definition permits the effects of controls, other than RPE, to be assessed and avoids the considerable uncertainty associated with attempting to precisely quantify the attenuation of exposure brought about by the proper use of RPE.

The sections entitled “inhalation exposure (general discussion)” and “dermal exposure (general discussion)” summarise the more important issues arising from the exposure assessments and bring together measured exposure data with that predicted from the EASE (Estimation and Assessment of Substance Exposure) model. EASE is a general-purpose predictive model for workplace exposure assessments. It is an electronic, knowledge-based, expert system which is used where measured exposure data are limited or not available. The model is in widespread use across the European Union for the occupational exposure assessment of new and existing substances.

All models are based upon assumptions. Their outputs are at best approximate and may be wrong. EASE is only intended to give generalised exposure data and works best in an exposure assessment when the relevance of the modelled data can be compared with and evaluated against measured data.

EASE predicts exposures as ranges in the form of conventional 8-hour time weighted averages (TWAs). It does not directly predict short-term exposures. However, because these exposures are process specific, they can be thought of as those experienced for that process either over the whole 8 hours or over any shorter period. These shorter periods can be further time weighted to construct other 8-hour time weighted averages. Although this device allows short-term exposures to be dealt with by EASE, such constructs should be regarded with caution. Dermal exposure is assessed by EASE as potential exposure rate predominantly to the hands and forearms (approximately 2,000 cm^2).

Overview of exposure

Propylene oxide is almost exclusively used as a chemical intermediate, with seven EU producers and an estimated 150 to 300 user plants. The total number of people exposed was estimated to be between 500 and 1,600.

HSE has no occupational exposure data for propylene oxide in its National Exposure Data Base (NEDB). A considerable amount of data have been received from Industry through CEFIC. This showed occupational exposure to propylene oxide to be between 0 and 30 ppm 8-hour TWA, with most exposures less than 3 ppm 8-hour TWA, the majority of which were less than 1 ppm 8-hour TWA. Occupational exposures during its use as a stabiliser in dichloromethane and in the preparation of samples for analysis by electron microscopy were predicted to be lower than during its use as a chemical intermediate.

Dermal exposure primarily occurs as a result of splashes on the skin. Contaminated surfaces are unlikely to be a source of exposure because of the high volatility of propylene oxide.

Occupational exposure limits

Table 4.1 below details occupational exposure limits for EU member states.

Table 4.1 Occupational Exposure Limits in the EU for propylene oxide

Country	**8-hour TWA**		**Reference (these are assumed to be the current limits)**
	ppm	**mg·m^{-3}**	
Austria	2.5	6	CEFIC
Belgium	21	50	IARC (1994)
Denmark	5	12	CEFIC
Finland	5	12	CEFIC
France	20	50	CEFIC
Germany	2.5	6	CEFIC
Italy	100	240	IARC (1994)
Netherlands	100	240	CEFIC
Norway +	1	2	CEFIC
Sweden	2	5	CEFIC
	10 **	25 **	
Switzerland	2.5	6	CEFIC
United Kingdom	5	12.5	EH40/97 Occupational Exposure Limits 1997. Table 1 Maximum Exposure Limits

Exposure limits provided by CEFIC and references copied from their source
** Short-term exposure limit
+ Norway is listed here due to its involvement with the ESR programme

Germany, Denmark, Norway and Switzerland provide notification with the above limit values that propylene oxide can be absorbed through the skin.

4.1.1.1.2 Occupational exposure during the production of propylene oxide and its use as a chemical intermediate

The manufacture of propylene oxide and its use as a chemical intermediate are carried out in closed systems. There are an estimated 35 to 70 workers exposed during its manufacture and 450 to 1,500 workers exposed during its use throughout the EU. A typical plant is likely to have only about 3 to 5 workers routinely working on the plant, one of whom will be in the control room. This number increases significantly when contracted workers are included. It is difficult to estimate this; however, one company reported that the number of contracted workers increased from 20 to about 1,200 for plant shutdowns lasting 2 to 3 weeks. Occupational exposure for workers on these closed plants will be intermittent and as a result of tasks where the system is breached. Consequently 8-hour TWA exposure arises from a series of short-term exposures. The nature of these tasks and the approach of companies to controlling emissions are likely to be similar for both producers and users. Occupational exposure may also occur from fugitive emissions, for example, leaks from pump seals. Occupational exposure during production and use as a chemical intermediate, for example in the production of polyols or propylene glycol, can therefore be considered together. In many cases the use of propylene oxide is on the same site as its production. The tasks that give rise to this occupational exposure will include the following.

Material sampling

During use as a chemical intermediate, exposure will be progressively more to the reaction products and not propylene oxide. Therefore the actual exposure may be significantly less than during production. This exposure is likely to very short (less than 1 minute) and dependent on how the emission is controlled.

Filling road and rail tankers, and ships

Although this work may take about 30 minutes, the actual exposure time will again be very short and primarily when the delivery line is uncoupled. Exposure, however, may be for the duration of the filling if contaminated air displaced from the road or rail tanker, or storage vessel is not controlled. Exposure during coupling is likely to be negligible, assuming lines are clean. The significance of the release during uncoupling will depend on how this is carried out and controlled.

Planned routine breaches, for example, renewing catalyst

With this task the potential for exposure exists for the duration of the time taken to remove the old catalyst and replace with new. The significance of exposure will depend on the steps taken to ensure the system is uncontaminated prior to breaching.

Periodic and unplanned maintenance

The potential for exposure is similar for renewing the catalyst and will again depend on the steps taken to ensure the system is uncontaminated prior to breaching. Periodic maintenance to inspect and renew plant takes place every 2 years or more and takes several weeks.

Fugitive emissions

In addition to the above tasks, exposure may also arise from process leaks, which will depend on the integrity of the equipment and again the industry's approach to monitoring and controlling such leaks.

The nature of the above tasks and the potential for exposure are similar for all chemical manufacturing processes. The significance of the resulting exposure will depend on the industries and the individual companies approach to controlling or preventing emissions. The control of propylene oxide is also influenced by its high flammability as well as concerns over its toxicity.

Two plants were visited in Holland and one in Germany in order to study the control regimes employed by producers and users of propylene oxide. Two were both producers and users and the third was a user. The philosophy adopted by these companies is to employ and develop measures to reduce exposure to as low a level as reasonably practicable, and not simply to reduce exposure below the numerical value of the national exposure limit. This is in line with some national exposure limits which require exposure to be as far as reasonably practicable below the exposure limit, for example the UK MEL or German TRK. It is understood that the development and use of these measures are seen as an industry objective and not on an individual company basis. This is achieved in part through the CEFIC sector group for propylene oxide and propylene glycols. This group is understood to represent the producers, although many of these companies are also users, and act as a focal point for the exchange of information in the industry. It is therefore likely that the approach to the control of propylene oxide found at the plants visited is similar at most producer and user sites. There may, however, be some variation in the control regimes used by manufacturers and users of propylene oxide in different member states and at different sites. At the sites visited steps had been taken to reduce occupational exposure during tasks where the system was breached. These steps included:

Sampling points

The minimum standard found was continuous circuit sampling points. However most sampling points employed were enclosed with vapour return, referred to as the “Dopak” system. Two of the three sites visited used the “Dopak” system with the third considering its use. It was reported that companies are generally moving over to this sampling system. This “Dopak” system involves pushing a sample bottle with a rubber seal direct onto an injection needle with vapour return for the displaced air. This allows propylene oxide to be released in to the closed bottle with minimal emission. One plant reported that vented air is passed through a charcoal filter. Release with this system is only likely to result from residual propylene oxide on the needle once the bottle is removed. It is understood that this system cannot be used where there is the potential for blockage of the needle by contaminants in the raw product.

Where use as a chemical intermediate is captive there is unlikely to be any sampling on the plant using propylene oxide, with sampling only post reaction where the concentration of propylene oxide is significantly reduced.

Filling and emptying of road and rail tankers

A significant proportion of propylene oxide has captive use and is thus transported on site by pipeline. One major producer reported 80% captive use of propylene oxide.

Where delivery is to or from road and rail tankers, steps are taken to minimise release during coupling / uncoupling and from displaced contaminated air. Dry break coupling systems were in use at the plants visited and it was reported that there is a move to this method by many companies in this industry. With this system, only a very small amount of propylene oxide is released when the delivery line is uncoupled. This is achieved by the flanges being immediately at the ends of the delivery line. Propylene oxide is allowed to flow through the line when the male and female flanges are pushed together. After delivery of propylene oxide the lines are purged with nitrogen

for dry break and traditional coupling systems. All three plants reported the use of vapour returns to allow displaced contaminated air from the road or rail tanker, or storage vessel to be controlled.

It is understood that delivery to ship bulk storage tank does not employ dry break couplers.

System breaching

The companies visited had specified procedures in place for situations where process lines or vessels have to be breached to carry out, for example, catalyst change and periodic or unplanned maintenance. In general these procedures included initial draining of the line or vessel, purging with nitrogen and blowing through with steam. When the vessel or pipeline is opened and before entry by the workers, the air is tested for total hydrocarbons and oxygen levels. In general it was reported that the operator wears respiratory protective equipment when the system is first breached and if exposure is likely to occur after breaching. One company reported that, if the concentration is greater than half the exposure limit, RPE (see below) is worn during the work.

On one plant using propylene oxide it was reported that catalyst changes are carried out by vacuum withdrawal of the catalyst and then adding new catalyst without entering the vessel.

During periodic shutdowns, usually every 2 years or more, this continual breaching of plant may result in a steady build up of propylene oxide until all the plant is open. This work may take several weeks and RPE is worn where the potential for exposure exists.

Respiratory protective equipment

All three companies visited reported the use of RPE. This ranged from the use of airfed RPE to orinasal cartridge respirators. Airfed RPE was generally used when opening process lines or vessels, although generally only as a precautionary measure. Orinasal respirators are generally worn during the filling or emptying of road and rail tankers. RPE is generally only used as a precautionary measure and not only when exposure is known to be above the relevant occupational exposure limit.

Fugitive emissions

One company reported an extensive fugitive emission monitoring programme where propylene oxide measurements are taken at thousands of locations according to internal sampling criteria. Where concentrations are found to be high, by comparison with in-house standards, measures are taken to rectify the emission. A further plant reported the use of detectors to continuously monitor propylene oxide. This system, however, was set to alarm at 10% of the lower explosive limit, which is considerably higher than any existing occupational exposure limit.

One company visited reported the use of magnetic delivery pumps (canned pumps) on their plant. These have the advantage of being completely sealed and therefore minimise the opportunity for fugitive emissions. It is, however, understood that they are not used where there is the chance of particulate clogging the pump.

The extent to which the above measures were employed varied between the sites visited and clearly will vary when compared to other EU producers and users. There is, however, no reason to believe that the approach to the control of occupational exposure to propylene oxide at sites not visited will vary significantly from that described above.

Industry exposure data (CEFIC)

Occupational exposure data were received from seven companies through the CEFIC Propylene Oxide and Propylene Glycols Sector Group. Companies collated and submitted the occupational exposure data to CEFIC who then anonymised it before passing it to HSE. Four of these companies sent exposure data for both production and use as a chemical intermediate. These occupational exposure data were from plants in several unidentified EU member states. The occupational exposure data for 8-hour TWAs and short-term exposure measurements are presented in **Tables 4.2** and **4.3** respectively.

The CEFIC collated exposure data represent measurements carried out in the last 5 years and in most cases the last 3 years. Occupational exposure information dating back to 1989 was also collected from the German Competent Authority and is presented for comparison with the CEFIC data to illustrate reductions achieved over the past few years.

Details were not provided, other than those in **Tables 4.2** and **4.3**, on the nature of the work or the specific controls used. The data are therefore discussed in general terms and are assumed to relate to the control regimes described earlier in Section 4.1.1.1.2.

As part of this review the industry provided through CEFIC (**Table 4.2**) a total of 458 8-hour TWA air sampling results, 350 of which were from seven manufacturing plants and 108 from four user plants. These four users plants were companies which also produced propylene oxide and a few of the results from one site were from fixed location measurements. The results overall ranged from 0 ppm to 30 ppm 8-hour TWA; 0 ppm to 30 ppm for manufacturing and 0.002 to 1 ppm for user plants. A results distribution was not provided for any of the sites. Without this distribution it was not possible to state exactly what proportion of results were above national limits. There were, however, no results for user plants above the lowest national exposure limit shown in **Table 4.1** (Norway 1 ppm 8-hour TWA). For manufacture the arithmetic means are, with the exception of three for plant 7, all below this limit. This suggests that the higher results, which are still in the region of most national limits, only represent a few samples. The highest results also represent the oldest data received from CEFIC, although it is not known whether this particular plant has improved control.

For occupational exposure during manufacture a total of 188 8-hour TWA exposure results were received for plant operators. These are assumed to be operators whose exposure only arises from routine activities, such as sampling, with long periods of no exposure. These results ranged from 0 ppm to 6.7 ppm 8-hour TWA. Individual mean / median results ranged from 0.07 ppm to 1.08 ppm 8-hour TWA. Details were not provided to explain the higher results, although its is likely that these are from occasional non-routine activities or unforeseen releases.

Plant operators exposures at user sites were lower than the above: 60 results from two plants were less than 0.01 to 1 ppm 8-hour TWA. The results at one of these sites were all less than 0.12 ppm. These lower exposures may result from operators carrying out less activities than at production sites that require breaching of the system. Three of these user plants were on the same site as the production plant. Therefore they may not carry out any pre-synthesis sampling and delivery may be by pipeline.

Table 4.2 Occupational exposure to propylene oxide during manufacture and its use as a chemical intermediate - 8-hour TWAs
(collated by CEFIC 1996)

Plant [1]	Year of sampling	Job	No of samples	Range (ppm)	Arithmetic mean (ppm)
During manufacture					
1	1996	plant operator	21	0.01 to 2.75	0.27
		maintenance	12	0.02 to 3.01	0.76
		laboratory technician	8	0.02 to 2.46	0.54
2	1993 to 96	plant operator	72	<0.01 to 2.1	0.07
		mini plant	5	<0.01 to 0.17	0.05
		laboratory	8	0.01 to 0.45	0.23
3	1993 to 96	plant operator	25	<0.01 to 2.1	0.13 [2]
4	1993 to 95	plant operator	21	<0.12 to 1.2	<0.1 [2]
		maintenance	21	<0.12 to 0.75	<0.1 [2]
		tanker / drum filling +	41	<0.12 to 0.87	<0.1 [2]
		laboratory technicians	17	<0.12 to 1.1	<0.1 [2]
5	1995	plant operator	4	<0.1 to 0.33	0.16
6	1995	plant operator	15 [3]	0.1 to 1.6	0.23
7	1991	shift officer	4	0 to 0.7 [4]	0.19
		dashboard man	4	0 to 1.3	0.34
		plant operator	30	0 to 6.7	1.08
		laboratory technician	16	0 to 10.9	1.35
		foreman	9	0 to 30	3.51
		tank operator	8	0 to 1.3	0.44
		waste operator	9	0 to 1.9	0.4
During use as a chemical intermediate					
1 (off-site use)		Unloading railcars	17	0.002 to 0.94	0.62
3 (on-site use)	1993 to 96	plant operator	47	<0.01 to 1	0.065 [2]
		Laboratory technicians	8	<0.01 to 0.45	not reported
		pilot plant	5	<0.01 to 0.17	not reported
4 (on-site use)	1993 to 95	plant operator	13	all <0.12	-
		Maintenance	6	all <0.12	-
		Laboratory technicians	9	all <0.12	-
5 (on-site use)	1996	plant operators	3	all <0.01	-

[1] The plant numbers for manufacturing and user sites correlate to the same company
[2] Reported as median
[3] Results include some static air sampling measurements
[4] No detection limit provided
\+ These results are listed as "tanker / drum filling, although it is understood that no transport by drums is used. This may therefore just represent minimal drum usage or a results reporting category used by the company

The highest exposures generally did not appear to correlate with those tasks where operators would be more likely to come in to contact with propylene oxide. For example, the highest exposure was for "foreman" at manufacturing plant 7; 30 ppm 8-hour TWA. Whereas the 39 results for maintenance workers at both manufacturing and user sites ranged from less than 0.12 ppm to 3.01 ppm, and the results for tanker/drum filling at manufacturing site 4 ranged from 0.12 ppm to 0.87 ppm 8-hour TWA. The higher results for "foreman" were the oldest, taken in 1991, and all the results for manufacturing plant 7 are generally higher than other plants. The results for "laboratory technician" for plant 7, presumably from taking and analysing samples, were up to 10.9 ppm 8-hour TWA. These measurements may therefore reflect older plant control measures. The lower results for tasks where higher exposures might be expected could also indicate that these tasks have been identified as potentially higher risk activities and have been adequately controlled. During routine plant work the results are more likely to include occasional exposures from unforeseen releases.

The above 8-hour TWAs reflect the operator's exposure for the shift, however, they take no account of the level of exposure during specific tasks. Only limited short-term exposures were received which are detailed in **Table 4.3**. These data show that higher exposures are experienced over 15-minute periods.

Table 4.3 Occupational exposure to propylene oxide during manufacture and its use as a chemical intermediate - short term [1)]

Plant	Job	Year of sampling	No of samples	Range (ppm)	Arithmetic mean (ppm)
During manufacture					
1	loading railcars	1996	16	0.2 to 24.2	6.7
During use as a chemical intermediate					
1	unloading railcars	1992	25	0.06 to 14.3	3.3
	unloading railcars	1993	40	0.07 to 41.7	5.2
	unloading railcars	1994	16	0.06 to 6.1	1.2

[1)] Results assumed to represent 15-minute TWAs

These short-term results, 16 for manufacture and 81 for user plants, were all from one company and ranged from 0.06 to 41.7 ppm. These exposure data were all for loading and unloading railcars. It is likely that exposure resulted from peak emissions when the delivery pipeline was uncoupled. Such peak exposures are likely to last for less than 1 minute. This is further discussed in the section on modelled exposure data. The company reported that cartridge respirators were worn during both coupling and uncoupling of the delivery line.

German competent authority exposure data

Exposure data were also received from the German competent authority. These exposure data are presented in **Table 4.4**.

These data were compiled by the German Dangerous Materials Committee (1989) and published in the Technical Rules on Dangerous Materials. It is likely that some of these measurements were taken from sites also represented in **Table 4.2**.

Table 4.4 Personal exposure to propylene oxide in Germany (8-hour TWAs) [1)]

Task	No of samples	Mean (ppm)	Maximum (ppm)
Manufacturing	555	less than 2.5	125
Processing	92	0.5 to 5.3	not reported
Processing to polyols	467	0.5 to 100	not reported
Processing to other products	110 [2)]	less than 2.5	not reported
Maintenance	73	less than 2.5	10.3
Loading	292	0.5 to 3	21.2

1) Results received from Bundesanstalt für Arbeitsschutz (BUA, 1988). These are as reported and it was not established why some means were submitted as ranges with no maximum result
2) Static sampling results

The data in **Table 4.4** show occupational exposure up to 125 ppm 8-hour TWA. In general these results appear to be higher that those in **Table 4.2**, although a distribution was not provided to establish the significance of this. The measures in place to control the above exposure were not reported. However, it is likely that these results represent older regimes and thus poorer control.

Modelled exposure data

Only limited short-term exposure data were received which were specific to loading or unloading railcars. To further determine short-term exposure during loading and unloading of rail cars, modelling was also carried out using the EASE model. This was also used to model the exposure experienced during sampling. During these tasks there will be brief periods of exposure followed by longer periods of no exposure. For these predictions it is assumed that exposure during these periods of "no exposure" is negligible.

During the specific period of filling/emptying of road, rail and ship storage tankers releases are unlikely to be significant as vapour returns are understood to be in use. Releases will therefore only occur during uncoupling. During coupling the line is likely to be free of propylene oxide. The exposure during uncoupling is likely to last about 1 minute. The EASE scenario that best describes this is non-dispersive with dilution ventilation (i.e. natural ventilation). This results in an EASE prediction of 500 to 1,000 ppm for the period of the task. This can be converted to provide a short-term (15-minute reference period) exposure prediction. In this 15-minute reference period there will be 14 minutes of no exposure and 1 minute at 500 to 1,000 ppm, which results in a calculated 15-minute TWA of 33 to 67 ppm.

During sampling the operator will only be exposed for the short time to take the sample, which is likely to be about 30 seconds. The EASE scenario that best describes this short-term exposure is non-dispersive without ventilation (assuming some of these tasks may be inside with no ventilation). This results in an EASE prediction of greater than 1,000 ppm for the period of the task. This can be converted to provide a short-term (15-minute reference period) exposure prediction. In this 15-minute reference period there will be 14½ minutes of no exposure and 30 seconds at greater than 1,000 ppm, which results in a calculated short-term exposure of greater than 33 ppm.

These EASE predictions do not take any account of the control measures employed during uncoupling and during sampling. They are in this respect likely to be the maximum concentrations for propylene oxide when carrying out these tasks. The values for uncoupling are

similar to those at the top of the range in **Table 4.3**. It is possible from these figures that short-term releases can be up to 67 ppm, however, it is likely that most companies have taken steps to mitigate such emissions.

Modelled dermal exposure data

Dermal exposure can occur during the production and use of propylene oxide, where operators come into contact with surfaces contaminated from splashing or condensed vapour, or as a result of direct contact onto the skin. As processing is in closed systems, dermal exposure is only likely during activities such as sampling and the uncoupling of pipes. The contribution from condensed vapour is likely to be minimal due to its high volatility.

The best EASE scenario for this exposure is direct handling with incidental contact, where incidental refers to one significant contact in a shift, for example spilling propylene oxide whilst sampling or touching a wet surface. This results in a prediction of 0 to 0.1 mg/cm^2/day, although on most days no such accidental contacts will occur and exposure will be towards the bottom of this range.

4.1.1.1.3 Occupational exposure to residual propylene oxide

Occupational exposure to residual propylene oxide may occur during the processing of its derived products. Data on residual propylene oxide were received from industry through CEFIC. These data are provided in **Table 4.5**.

Table 4.5 Residual propylene oxide in glycols and glycol ethers (CEFIC)

Derivative	No of samples	No of results (ppm)		
		less than 1	1 to 5	greater than 5
Glycols				
Mono propylene glycol	3	all less than 0.5 [1)]	-	-
Dipropylene glycol	1	all less than 0.5 [1)]	-	-
Glycol ethers				
Methoxy propanol	2	all less than 0.5 [1)]	-	-
Methoxy propyl acetate	1	all less than 0.5 [1)]	-	-
Polyols	30	24	5	1

[1)] Limit of detection

For glycols and glycol ethers residual propylene oxide is not detected as **Table 4.5** shows. It is therefore unlikely that workers would be exposed to residual propylene oxide during further processing with glycols or glycol ethers. For polyols a small amount of residual propylene oxide is found which operators may be exposed to during further processing.

Further processing with polyols involves its reaction with an isocyanate to form polyurethane foams. This involves the blending of the polyol and isocyanate in the mixing head where it is then delivered in to a mould or on to a conveyor. Such applications are usually equipped with local exhaust ventilation (LEV) to control, in particular, the isocyanate.

Exposure during this process can be modelled using EASE. The scenario that best describes this is non-dispersive with LEV, which results in an EASE prediction of 100 to 200 ppm. This assumes that the operator is exposed to propylene oxide for the full shift. These values can be converted to take account of the fact that propylene oxide will only constitute a small percentage of the vapour. From **Table 4.5**, 5 ppm in the product is used as a worst-case scenario. This results in a predicted exposure of 0.0005 to 0.001 ppm 8-hour TWA for the residual propylene oxide, assuming the vapour and liquid composition are the same. Where polyol is sprayed, for example for coatings, EASE predicts the same values.

4.1.1.1.4 Occupational exposure to propylene oxide during degreasing operations using dichloromethane

Occupational exposure to propylene oxide may occur during degreasing operations using dichloromethane. These degreasing operations are carried out using hot vapour degreasing plant with appropriate engineering controls (cooling coils, thermostats, lip extraction) to reduce exposure to the volatile dichloromethane.

Modelled exposure data

Occupational exposure data were not available for this scenario, therefore the exposure was modelled using EASE. The scenario that best describes this is non-dispersive with LEV, which results in an EASE prediction of 100 to 200 ppm. These values can be converted to take account of the fact that propylene oxide only constitutes up to 0.5% of the dichloromethane. This results in a predicted exposure to propylene oxide of 0.5 to 1 ppm 8-hour TWA, assuming the vapour and liquid composition are the same. This range of exposure assumes that the operator is working at the degreasing bath for the full shift. The operator is more likely to spend periods away from the degreasing bath whilst components are left in the dichloromethane. The periods of loading and unloading of the degreasing bath are likely to amount to about 2 hours of exposure. The exposure range can therefore be refined to 0.13 to 0.25 ppm 8-hour TWA.

Modelled dermal exposure data

Dermal exposure can occur during degreasing operations, where operators come into contact with surfaces contaminated from splashing, or as a result of direct contact onto the skin. During the loading and unloading of components such contacts may be frequent where appropriate gloves are not worn.

The best EASE scenario for this exposure is direct handling with extensive contact, where extensive refers to greater than ten significant contacts in a shift. This results in a prediction of 1 to 5 mg/cm^2/day, which can be refined to take account of the low concentration (0.5%) of propylene oxide in the dichloromethane. This results in a calculated exposure of 0.005 to 0.025 mg/cm^2/day.

4.1.1.1.5 Occupational exposure to propylene oxide during the preparation of samples for electron microscopy analysis

Laboratory technicians may be exposed to propylene oxide during the preparation of samples for analysis by electron microscopy. This work involves firstly the dehydration of the tissue sample using ethanol and then propylene oxide, then infiltration using a mixture of propylene oxide and epoxy resin. Occupational exposure may occur during the mixing and handling of propylene oxide.

Modelled exposure data

Occupational exposure data were not obtained for this work and EASE was not used to model exposure data. Preparation of an individual sample may only involve handling 2 to 5 ml of propylene oxide. Exposures predicted using EASE, for scenarios where such small volumes are involved would be very unrealistic. It was reported that laboratories carry out this work in a fume cupboard, and thus exposures are likely to be low. This work may take a full shift where a large number of samples are being prepared. Clearly, if laboratories carried out this work on the open laboratory bench then exposures may be higher.

Modelled dermal exposure data

Dermal exposure can occur whilst preparing the samples, where laboratory technicians receive contact through splashing, or touch contaminated laboratory equipment.

The best EASE scenario for this exposure is direct handling with incidental contact, where incidental refers to one contact in a shift. Significant contacts are likely to be infrequent due to the low volumes in use. This results in a prediction of 0 to 0.1 mg/cm^2/day.

4.1.1.1.6 General discussion

Occupational exposure to propylene oxide occurs during its manufacture and use as a chemical intermediate. There were no direct uses for propylene oxide reported. Therefore it is always used in closed plant with exposures only arising as a result of breaches of the system. Visits were carried out in 1996 to EU producers and users of propylene oxide to obtain an understanding of the measures adopted by this industry to control exposure.

This industry's approach to the control of propylene oxide is to employ and develop measures that reduce exposure to as low a level as is reasonably practical. This includes the use of:

(a) enclosed sampling systems;
(b) dry break coupling systems for filling and emptying road and rail tankers;
(c) magnetic delivery pumps;
(d) systems for purging and testing process lines and vessels prior to breaching;
(e) the use of RPE where the potential for exposure exists; and
(f) the monitoring and control of fugitive emissions.

Occupational exposure data were received through CEFIC from all seven producers and for four user plants operated by producers. Occupational exposure ranged from 0 to 30 ppm 8-hour TWA for manufacture and 0.002 to 1 ppm for users. Detailed information on the control of propylene oxide specific to each set of results was not provided. The means values of exposure for all the plants, with the exception of three for production plant 7, were all less than 1 ppm 8-hour TWA. In general, the results were all of the order of national exposure limits, with the majority of the results less than these limits.

The higher exposures were mostly for production plant 7 where the data were the oldest received from CEFIC (i.e. 1991). It is therefore likely that these data represent older control regimes. Data were also received from the German authorities which showed exposures up to 125 ppm 8-hour TWA. These exposure data were from 1989 and likely to represent older control regimes.

Short-term exposures were between 0.06 and 41.7 ppm for loading and unloading rail cars. This exposure is likely to be as a result of uncoupling. This exposure, and that experienced during sampling was also modelled using EASE. Calculated exposures from these EASE predictions were 33 to 67 ppm 15-minute TWA for uncoupling and greater than 33 ppm 15 minute-TWA for sampling. These predictions take no account of the measures employed to control exposure and are therefore likely to represent the maximum exposures. Where the potential for short-term exposure still exists, after reductions have been achieved by engineering and procedural means, RPE is worn. Although this RPE is often worn only as a precautionary measure.

During degreasing operations using dichloromethane stabilised with propylene oxide, operators may be exposed during loading and unloading operations, which were predicted using EASE to give exposures of 0.13 to 0.25 ppm 8-hour TWA. It was not possible to predict exposures for its use in the preparation of samples for analysis by electron microscopy, due to the very low volumes used in the laboratory. However, it was concluded that exposures are likely to be low as this work is undertaken inside a fume cupboard. Clearly, if laboratories carry out this work on the open bench then exposures may be higher.

It is likely that propylene oxide exposure is less than 3 ppm 8-hour TWA, with the majority less than 1 ppm 8-hour TWA.

Dermal exposure can occur during the production and use of propylene oxide, where operators come into contact with surfaces contaminated from splashing or condensed vapour, or as a result of direct contact onto the skin. As processing is in closed systems, dermal exposure is only likely during activities such as sampling and the uncoupling of pipes. The contribution from condensed vapour is likely to be minimal due to its volatility. EASE predicted this to be 0 to 0.1 mg/cm^2/day based on the assumptions of non-dispersive use, should it occur, although on most days no such accidental contacts will occur and exposure will be towards the bottom of this range. However, the upper end of the range may reflect exposure during maintenance activities where dermal contact is greater. Similar dermal exposures were predicted for laboratory technicians handling propylene oxide during electron microscopy work. For operators using dichloromethane stabilised with propylene oxide dermal exposures were predicted to be 0.005 to 0.025 mg/cm^2/day.

Operators are likely to wear gloves where the potential for skin contact exists and thus further reduce the above-predicted exposure.

4.1.1.2 Consumer exposure

4.1.1.2.1 Introduction

Propylene oxide has no direct consumer use as a monomer. It is, however, used in the production of other chemical intermediates. These intermediates, which may contain residual amounts of the monomer, may in turn be used in substances or products used by the consumer.

The intermediates derived from propylene oxide are mainly glycols, glycol ethers and polyether polyols. These have a variety of applications including use in de-icers in industrial applications (aircraft de-icers), hydraulic fluids, foodstuffs, medicinal products and cosmetic applications and as a component of paint and varnish solvents. Other products include mono, di- and tri-isopropanolamines which have application in brake fluids, anti-corrosion agents, cement production and as vulcanisation accelerators. Consumers would probably only come into contact with foodstuffs, medicinal products, and hydraulic fluids (brake fluid for cars) although it is

unclear as to the exact end use of the hydraulic fluids containing materials derived from propylene oxide.

4.1.1.2.2 Glycols and glycol ethers

There are no real data on consumer exposure to propylene oxide from these substances. Concentrations of propylene oxide in glycols and glycol ethers are below the 0.5 ppm limit of detection (CEFIC, private communication). If the propylene glycol is then used as a component of a mixture in a resulting consumer product (brake fluid or paint for example), the concentration of any propylene oxide would be further reduced and dispersed within that product. If the propylene glycol contained a maximum of 0.5 ppm of propylene oxide and the glycol was 10% of the final product, the concentration of propylene oxide would be 0.05 ppm. Furthermore, it is reasonable to assume that residual propylene oxide, being highly reactive, would combine chemically with other components of the mixture. Any exposure resulting from this use will be critically dependent upon the actual concentration in the final product, the amount of product used and the skills with which it is handled. However the amount available for inhalation or dermal contact are likely to be negligible.

4.1.1.2.3 Polyether polyols

Residual levels of propylene oxide in polyether polyols are generally less than 1 ppm with levels of up to 5 ppm only in a small minority of samples. These are, in turn, used of these materials is in the manufacture of polyurethane foams for use in upholstery (such as car seats). There are no real data but it is reasonable to assume that in reacting the polyols to produce the foams very little propylene oxide would remain un-reacted. Any remaining propylene oxide would be held in the foam. There are no data but it is likely that the diffusion of this remaining propylene oxide through and out of the foam will give rise to negligible exposure.

4.1.1.2.4 Isopropanolamines

Propylene oxide is used to manufacture isopropanolamines which may be used by consumers as a component of some brake fluids. The most likely exposure scenario is the topping up of brake fluid reservoirs in cars. No work has been done to identify which brake fluids contain isopropanolamines and there are no data on residual levels of propylene oxide in the intermediates (mono, di- and tri-isopropanolamines) or in the final products. However, it is reasonable to assume that on the basis of the chemistry of the production process that such amounts would be negligible. Any residual propylene oxide would be diluted in the final product.

These compounds are also be used as corrosion inhibitors in anti-freeze mixtures for commercial applications.

4.1.1.2.5 Conclusions

Consumer exposure to propylene oxide in consumer products is considered to be negligible, but cannot be excluded. No data are being taken forward for consumer risk characterisation.

4.1.1.3 Humans exposed via the environment

Concentrations in various environmental compartments were estimated in Section 3.1. The values obtained are summarised in **Tables 4.6** and **4.7**.

Table 4.6 Predicted environmental concentrations for indirect exposure assessment on local scale

Compartment	PEC	Comment
$PEClocal_{water,ann}$	250 $\mu g \cdot l^{-1}$	generic calculation (1.9 $\mu g \cdot l^{-1}$ site-specific)
$PEClocal_{air,ann}$	17 $\mu g \cdot m^{-3}$	highest site-specific value
$PEClocal_{grassland}$	2.6 $\mu g \cdot kg^{-1}$	highest site-specific value
$PEClocal_{agric\ soil,porew}$	7.9 $\mu g \cdot l^{-1}$	highest site-specific values
$PEClocal_{grassland,porew}$	8.2 $\mu g \cdot l^{-1}$	highest site-specific values
$PEClocal_{grw}$	7.9 $\mu g \cdot l^{-1}$	same as local agricultural soil porewater concentration

Table 4.7 Predicted environmental concentrations for indirect exposure assessment on regional scale

Compartment	PEC
$PECregional_{water}$	0.07 $\mu g \cdot l^{-1}$
$PECregional_{air}$	$4.8 \cdot 10^{-3}$ $\mu g \cdot m^{-3}$
$PECregional_{agric,soil}$	$3.5 \cdot 10^{-4}$ $\mu g \cdot m^{-3}$
$PECregional_{agric,porew}$	$1.1 \cdot 10^{-3}$ $\mu g \cdot l^{-1}$

These values were used to derive concentrations in leaf and root crops, fish, meat and milk using the methods in the TGD (**Table 4.8**). These were then converted into estimates of daily intake using the default consumption values for each food type, for air and for drinking water. The results are in **Table 4.9**. The regional calculation represents a background intake, the local calculation a worst case in which all food comes from the local area.

Table 4.8 Summary of concentrations for indirect exposure

	Local	Regional
Drinking water ($\mu g \cdot l^{-1}$)	250	0.07
Fish ($\mu g \cdot kg^{-1}$)	55	$1.5 \cdot 10^{-2}$
Leaf crops ($\mu g \cdot kg^{-1}$)	3.1	$8.4 \cdot 10^{-4}$
Root crops ($\mu g \cdot kg^{-1}$)	$7.5 \cdot 10^{-3}$	$1 \cdot 10^{-6}$
Meat ($\mu g \cdot kg^{-1}$)	$1.3 \cdot 10^{-2}$	$3.6 \cdot 10^{-6}$
Dairy products ($\mu g \cdot kg^{-1}$)	0.13	$3.6 \cdot 10^{-5}$
Air ($\mu g \cdot m^{-3}$)	17	$4.8 \cdot 10^{-3}$

Table 4.9 Daily intake of propylene oxide from the environment (values are for 70 kg human)

	Consumption (day^{-1})	Uptake (μg)	
		Local	Regional
Drinking water	2 l	500	0.14
Fish	0.115 kg	6.3	$1.7 \cdot 10^{-3}$
Leaf crops	1.2 kg	3.7	10^{-3}
Root crops	0.384 kg	$2.9 \cdot 10^{-3}$	$3.8 \cdot 10^{-7}$
Meat	0.301 kg	$3.9 \cdot 10^{-3}$	$1.1 \cdot 10^{-6}$
Dairy	0.561 kg	$7.3 \cdot 10^{-2}$	$2 \cdot 10^{-5}$
Inhalation	20 m^3	255	$7.2 \cdot 10^{-2}$
Total		765	0.21

These figures give a total uptake of 11 μg/kg bw/day for the local scenario and 3 ng/kg/day for the regional scenario. The largest single contribution comes from drinking water. The concentration in drinking water used here is the surface water concentration derived for a generic production site using default dilution factors. As discussed above (Section 3.1.1) this is a higher concentration than is estimated for any of the actual sites. The highest surface water concentration calculated for a specific site is 1.9 $\mu g \cdot l^{-1}$, which is lower than the highest pore water concentration calculated for a specific site (8.2 $\mu g \cdot l^{-1}$). Using the pore water value gives an uptake from drinking water of 16 μg/day (with changes to the uptake from fish, dairy and meat as well) and the overall daily uptake is 3.9 μg/kg bw/day. This is considered to be a more realistic worst case than that using the default values. In this local scenario, inhalation accounts for 91% of the uptake of propylene oxide.

4.1.1.4 Combined exposure

A worst-case combined exposure scenario is composed of exposure in the workplace and to the highest local environmental exposure levels. No quantitative estimate of total exposure from inhalation, dermal and oral routes, is possible. As described above, exposure in the workplace will be kept to a minimum due to the controls in place to minimise exposure to isocyanates. Exposure via the environment is also very low.

4.1.2 Effects Assessment: hazard identification and dose (concentration) – response assessment

4.1.2.1 Toxicokinetics, metabolism and distribution

4.1.2.1.1 Studies in animals

There are very few studies on the toxicokinetics of propylene oxide.

Studies *in vitro*

From *in vitro* experiments, two pathways for propylene oxide metabolism have been suggested (Tachizawa et al., 1982). These are conjugation with glutathione, and hydrolysis. Propylene oxide has been shown to be a substrate for rat liver glutathione S-transferases to give S-(2-hydroxypropyl)glutathione. This conjugate is further transformed to cysteine derivatives and mercapturic acids, for which excretion in the urine would be anticipated (Fjellstedt et al., 1973; Duus et al., 1989). Alternatively, there is evidence that propylene oxide is hydrolysed to 1,2-propanediol by epoxide hydrolase from rat liver microsomes (Guengerich and Mason, 1980; Dent and Schnell, 1981).

Non-enzymic hydrolysis to 1,2-propanediol is slow; the half-life for the uncatalysed reaction in neutral medium at 37°C was found to be 87 hours (Ross, 1950). However, Ehrenberg and Hussain (1981) have estimated the half-life for this reaction in the conditions of the stomach (pH 1 and 37°C) to be approximately 1 minute.

Studies i*n vivo*

In a carefully conducted study, depletion of tissue non-protein sulfhydryls and blood concentrations of propylene oxide were measured in groups of 9 male rats immediately following inhalation exposure, for 6 hours to 80-904 ppm (time weighted average) propylene oxide (Nolan et al., 1980). A dose-related, statistical significant depression of hepatic non-protein sulfhydryls relative to non-exposed controls occurred in rats exposed to 217 ppm propylene oxide and above. A minimal depression (<10%) was observed in rats exposed to 143 ppm propylene oxide, and no change was observed at 80 ppm. These observations indicate that conjugation with glutathione is a major pathway of propylene oxide detoxification. Depression of lung and kidney but not blood non-protein sulfhydryls was observed in an additional group of rats exposed to 625 ppm propylene oxide. The apparently low blood concentration of propylene oxide provides further evidence that propylene oxide is rapidly absorbed into the tissues and metabolised by, the rat. There was a disproportionate increase in blood concentration of propylene oxide after exposures above 143 ppm, indicating that the relative capacity to detoxify can become diminished. The changes in non-protein sulfhydryl levels observed in the liver and kidney provide evidence that propylene oxide is widely distributed following uptake via the lungs.

Blood levels of propylene oxide in groups of 3-8 rats exposed nose-only to 14 ppm propylene oxide for 2, 6, 10 or 60 minutes were measured by Maples and Dahl (1993). The concentration of propylene oxide increased during the first 10 minutes of exposure, levelling at approximately 3 ng/g blood. No other useful information was available.

In a limited study, conducted to compare the toxicokinetics of propylene and propylene oxide, groups of 2 male Sprague-Dawley rats were exposed, whole-body, to various concentrations of

propylene oxide (Golka et al., 1989). The exposure times were not specified. No saturation kinetics were observed for propylene oxide up to 3,000 ppm (7,110 $mg \cdot m^{-3}$), at which exposure level "systemic toxicity" was observed. From the clearance data, it was deduced by the authors that most of the inhaled propylene oxide was metabolised (96%) and only small amounts were exhaled unchanged (3%).

Thus, taking all the information into account it is likely that propylene oxide is almost completely absorbed, distributed widely throughout the body and rapidly metabolised. Elimination is likely to be via the urine, involving conjugation with glutathione, and also in expired air, following conversion to carbon dioxide.

4.1.2.1.2 Interactions with macromolecules

Studies in extracellular systems

Walles (1974) reported that propylene oxide causes single-strand breaks in isolated calf thymus DNA, probably by alkylation of the phosphodiester bond. Lawley and Jarman (1972) found that two alkylated DNA adducts, *N*7-(2-hydroxypropyl)guanine and *N*3-(2-hydroxy propyl)adenine were formed following incubation with naked DNA preparations.

Using an early post-labelling technique, Randerath et al. (1981) reported a total of 15 different calf thymus DNA adducts of propylene oxide; it was calculated that 1.3% of the nucleosides in the DNA molecule had been altered.

Hemminki and Vainio (1980) studied the alkylation of guanosine and deoxyguanosine by epoxides and glycidyl ethers. Propylene oxide was found to be one of the least active alkylating agents of those tested, having an alkylation rate only 28% of the most reactive compound, phenyl glycidyl ether. In addition, Hemminki et al. (1980) demonstrated that propylene oxide forms *N*7-alkylguanine and *N*6-alkyladenine adducts with deoxyguanosine and deoxyadenosine, respectively. No reaction products with cytosine were detected.

Solomon et al. (1988) further investigated the adduction of propylene oxide with calf thymus DNA. Following a 10 hour incubation period, the following adducts were identified: *N*6-(3-hydroxypropyl)deoxyadenine, 3-(2-hydroxypropyl)adenine, *N*7-(2-hydroxypropyl)guanine and 3-(2-hydroxy)deoxyuridine. It was shown that the uracil adduct was formed following adduction of propylene oxide with deoxycytidine by a hydrolytic deamination reaction. This conversion of cytidine to uracil is a mutagenic change.

Studies *in vivo*

In rats, haemoglobin alkylation by propylene oxide has been established at the amino-acids cysteine, valine and histidine (Farmer et al., 1982; Svensson and Osterman-Golkar, 1984).

Farmer et al. (1982) conducted a preliminary study to determine if exposure to propylene oxide would produce alkylated haemoglobin. Groups of 4 female Wistar rats were exposed by inhalation to 0-2,000 ppm (0-4,740 $mg \cdot m^{-3}$) propylene oxide for 4 hours. Haemoglobin was then isolated from erythrocytes and the level of N-3'-(2-hydroxypropyl)histidine determined. Apparently, a linear dose-related increase in alkylation was reported (data not shown). No adducts were found in control samples.

Segerback et al. (1992; 1994) studied (2-hydroxypropyl)histidine adduct levels in haemoglobin of 3 species. Groups of 10 mice and 5 rats were administered a single dose of propylene oxide by

intraperitoneal injection (3.1 or 7.6 $mg \cdot kg^{-3}$) or exposed by inhalation for 5 hours (two concentrations; exposure levels not given, expressed as amount of [^{14}C]propylene oxide absorbed). Additionally, groups of 2 Beagle dogs were exposed to 100 or 500 ppm propylene oxide for 1 hour. Rats and mice were killed after 2 hours, dogs after 4 hours. The measured adduct levels in each species were found to be related to dose.

In a very small study involving 2 cynomolgus monkeys, N-(2-hydroxypropyl)valine was quantified in haemoglobin from erythrocytes collected at 7 and 24 hours following administration of single high or low intravenous doses of propylene oxide (116 and 29 $mg \cdot kg^{-3}$ propylene oxide, respectively) (Couch et al., 1996). A disproportionate dose-related increase in adduct levels was observed suggesting that this may indicate a saturation in the removal (detoxification) of propylene oxide from blood at the higher dose level, which is consistent with the observations of others (see under Section 4.1.2.1.1).

Segerback et al. (1994) reported the DNA adduct, *N*7-(2-hydroxypropyl)guanine, in liver and lung samples from mice, rats and dogs exposed to [^{14}C]propylene oxide, and in brain DNA from exposed rats. In the rodents, adduct levels were generally higher in lung and brain than in liver following both inhalation and intraperitoneal exposure. Similarly, adduct levels in the dog were higher in lung tissue than in the liver following intravenous administration of propylene oxide. The authors suggested that efficient DNA repair in the liver might have contributed to these tissue differences but evidence for this was not presented. At comparable dose levels, there were no marked species differences in the levels of this adduct.

Following on from this study, Segarback et al. (1998) investigated the tissue distribution of the DNA adduct *N*7-(2-hydroxypropyl)guanine (7-HPG) in groups of 3 to 10 Fischer rats following exposure to 500 ppm, for 4 weeks, 6 h/d, 5d/week. DNA was isolated by enzyme incubation and solvent extraction from tissue samples of the lungs, liver, spleen, testes, nasal tract and lymphocytes. Levels of 7-HPG in DNA was determined using the ^{32}P-postlabelling assay with anion-exchange cartridges for adduct enrichment. Following exposure, 7-HPG adduct levels (Mol adduct/10^6) were determined in the DNA from respiratory mucosa (98.1+/-1.7), olfactory mucosa (58.5+/-11), lung (16.3+/-1.4), lymphocytes (9.92+/-1.3), spleen (9.26+/-0.5), liver (4.64+/-0.4), and testis (2.95+/-0.1). Three days after exposure these values were lower by between 63 and 75%.

The extent and persistence of DNA binding of inhaled propylene oxide in rat respiratory mucosa were measured by Snyder and Solomon (1993). Groups of 3 male F344 rats were exposed, head only, to 6, 12, 18, 28 or 46 ppm [^{3}H]propylene oxide. The exposures were continued for approximately 2 hours, until each rat had inhaled about 201 of air. Immediately after exposure, DNA was purified from nasal mucosa, trachea and lung. The radioactive content of the purified DNA (including covalently bound and other associated molecules) was measured.

In each of the tissues, the total DNA binding of propylene oxide was dose-related (levels expressed as mean adducts/10^6 bases). Furthermore, there was a gradient for the binding at each exposure concentration, such that the highest levels occurred in the nasal mucosa (4.2-17), followed by the trachea (0.5-5.8), with the lowest levels in lung tissue (0.11-3.3). This gradient was most pronounced at the lowest exposure concentrations. There was no statistical analysis of the data, but the variation of binding levels in different animals was relatively low and the results are biologically plausible.

In a second experiment, groups of 3 rats were exposed to 20 ppm [^{3}H] propylene oxide with recovery periods of 0, 1, 4, 7 and 10 days. Binding levels in the nasal tissue decreased with apparent bi-exponential kinetics; there was a rapid phase of half-time 8 hours and a slow phase

of 5.3 days. In contrast, binding levels in the trachea and lungs remained constant. After 7-10 days, the level of binding in the nasal tissue was comparable to that in the trachea. Although these observations imply that different processes exist for the clearance of total DNA-bound propylene oxide in the respiratory tract, the mechanisms involved (e.g. cell turnover, DNA repair) remain unproven. It should be noted that in this study non-covalently bound propylene oxide may have contributed to the total adduct levels measured.

Studies in the mouse have demonstrated that the degree of *in vivo* alkylation of DNA (as N-7-guanine) after intraperitoneal administration of propylene oxide is comparable in liver, kidney, spleen, lung and testis (Svensson et al., 1991).

4.1.2.1.3 Studies in humans

Propylene oxide was found to cause dose-dependent and reproducible inhibition of erythrocyte glutathione S-transferase (GST) in situ as well as the inhibition of purified erythrocyte GST (Ansari et al., 1987). This suggests that propylene oxide may be a substrate for human glutathione transferases *in vivo.*

Osterman-Golkar et al. (1984) measured (2-hydroxypropyl)histidine in haemoglobin from a small group of 7 workers producing hydroxypropylated starch and known to have been exposed to propylene oxide. Adduct levels ranged from 0.65-13 $nmol \cdot g^{-1}$ haemoglobin. The adduct levels differed significantly from background levels measured in 14 non-exposed controls (<0.1-0.38 $nmol \cdot g^{-1}$ haemoglobin).

Kautiainen and Tornqvist (1991) reported the detection of low levels N-(2-hydroxy-propyl)valine in human haemoglobin, although did not provide any details on the history of the blood donors. Therefore it is not clear if these adducts, in this study, were formed as a result of exposure to propylene oxide.

4.1.2.1.4 Summary of toxicokinetics

There are few data available on the toxicokinetics of propylene oxide in humans. However, based on the information that is available, propylene oxide and/or its metabolites are readily absorbed through the gastrointestinal and respiratory tracts and widely distributed to the major organs. No data are available for dermal absorption but acute toxicity data indicate the potential for dermal absorption of the liquid. No conclusions can be drawn regarding the potential for dermal absorption of the vapour. Studies in animals have suggested that clearance from the blood may be limited at higher levels of exposure, indicating saturation of metabolism. Metabolism involves conjugation with glutathione or hydrolysis by epoxide hydrolase. Excretion of propylene oxide and its metabolites is expected to be primarily via urine and expired air. Propylene oxide binds to, or reacts with, tissue proteins and nucleic acids *in vitro* and *in vivo.*

Haemoglobin adducts have been quantified in animals and humans exposed to propylene oxide. Although DNA binding in humans has not been studied, binding as assessed by adduct formation has been observed in several animal tissues following inhalation exposure, including nasal mucosa, trachea, lung, liver, brain and testes. Alkylation of cytosine (with subsequent deamination to a modified uracil) has also been reported.

4.1.2.2 Acute toxicity

4.1.2.2.1 Studies in animals

Inhalation

The four-hour inhalation LC_{50} of propylene oxide vapour is reported to be 1,740 ppm (4,124 $mg \cdot m^{-3}$) for mice (Jacobson et al., 1956). Values of 4,000 ppm (9,480 $mg \cdot m^{-3}$) and 4,197 ppm have been reported for rats (Weil et al., 1963; Blair and Osborne, 1977).

As part of a large comprehensive inhalation investigation carried out for the National Toxicology Program (NTP, 1985), results were reported of a single 4-hour exposure to propylene oxide vapour in F344/N rats and $B6C3F_1$ mice. Rats (5 per sex per group) were exposed to 1,277, 2,970, 3,794 and 3,900 ppm (3,033, 7,055, 9,012 and 9,204 $mg \cdot m^{-3}$). Mortalities were 0, 1, 4 and 3 males, and 0, 2, 4 and 3 females. Clinical observations at the three higher concentrations included dyspnoea and red nasal discharge. Mice (5 per sex per group) were exposed to 387, 859, 1,102, 1,277 and 2,970 ppm (919, 2,041, 2,618, 3,033 and 7,054 $mg \cdot m^{-3}$). Mortalities were 0, 0, 2, 2 and 5 males, and 1, 0, 4, 5 and 5 females. Dyspnoea occurred in all groups. Lachrymation occurred in animals exposed to the highest dose.

Jacobson et al. (1956) exposed groups of rats to propylene oxide vapour for 30 minutes. Mortality was 100% with 14,400 ppm (34,128 $mg \cdot m^{-3}$), and 50% with 7,200 ppm (17,064 $mg \cdot m^{-3}$). Exposure to 3,600 ppm (8,532 $mg \cdot m^{-3}$) for 2 hours killed 4/10 animals.

In studies conducted by Rowe et al. (1956), groups of ten rats and five guinea-pigs were exposed to propylene oxide vapour at concentrations of 2,000, 4,000, 8,000 and 16,000 ppm (4,740, 9,480, 18,960 and 37,920 $mg \cdot m^{-3}$) and for periods from 0.25-7.0 hours. Exposure to 4,000 ppm for 4 hours caused 4/10 deaths among rats and 1/5 deaths among guinea-pigs. Exposure to 2,000 ppm for 7 hours caused no deaths in either species. During the exposures, rats and guinea pigs exhibited irritation of the eyes and nasal passages, difficulty in breathing, drowsiness, weakness, and occasional inco-ordination. The seventy of response was dependent on the concentration and duration of exposure. Survivors showed temporary loss of body weight gain, but recovered weight gain within 14 days of exposure.

Mice inhaling 20 ppm propylene oxide for 3 hours showed no statistically significant changes in mortality from experimentally-induced *Streptococcal* pneumonia and pulmonary bactericidal activity (Aranyi et al., 1986).

Oral

In studies conducted by Rowe et al. (1956) in rats, a single oral dose, by gavage, of 1,000 $mg \cdot kg^{-1}$ resulted in 100% mortality, while no deaths occurred at 300 $mg \cdot kg^{-1}$. This suggests that the LD_{50} is below 1,000 $mg \cdot kg^{-1}$ and the slope of the dose-effect relationship is quite steep.

Smyth et al. (1969) reported a rat LD_{50} of 1.14 ml/kg (950 $mg \cdot kg^{-1}$). In another study, the oral LD_{50} values for the rat, mouse and guinea pig are reported to be 520 $mg \cdot kg^{-1}$, 630 $mg \cdot kg^{-1}$ and 660 $mg \cdot kg^{-1}$, respectively (Antonova et al., 1981). A guinea pig LD_{50} of 690 $mg \cdot kg^{-1}$ has also been reported (Smyth et al, 1941).

Dermal

Dermal LD_{50} values for the rabbit of 1,250 $mg \cdot kg^{-1}$ and 1.15 $ml \cdot kg^{-1}$ (950 $mg \cdot kg^{-1}$) have been reported (Weil et al., 1963; Smyth et al., 1969).

4.1.2.2.2 Studies in humans

Gosselin et al. (1984) provide a short summary of a case (1 male) of poisoning reported in Russia. The exposure concentration was given as 1,500 ppm (w/v) and, after 10 minutes, symptoms included respiratory tract and eye irritation. After 2 hours the man became cyanotic and collapsed, but with medical assistance recovery was complete after 24 hours. No further details regarding the nature of the exposure or exposure measurement is provided in this secondary source reference and the reliability of the observations is questionable.

4.1.2.2.3 Summary of acute toxicity

There is only very limited information on acute toxicity in humans; this does not contribute much to the picture available from studies in animals.

In studies in rodents, propylene oxide is harmful by inhalation, oral or dermal routes of exposure. Signs of respiratory tract irritation were observed in these studies. Classification according to Annex I of Directive 67/548/EC, see Section 1.

4.1.2.3 Irritation

4.1.2.3.1 Skin

Studies in animals

A brief report of a skin irritation study in 2 female White rabbits was provided by BASF (1981b). Undiluted propylene oxide was applied semi-occlusively for 4 hours. Neither redness nor oedema was observed at 1, 2 and 8 days; results for earlier time points were not recorded. The use of a semi-occlusive exposure may not have been appropriate due to the volatile nature of propylene oxide. This study appears to indicate that propylene oxide is non-irritating to rabbit skin, at least from 24 hours post-exposure, although the possibility that the test material evaporated from the surface of the skin during the exposure period cannot be discounted.

In a poorly reported dermal application study conducted in rabbits (numbers not stated), skin contact with undiluted propylene oxide or 10% and 20% aqueous solutions for periods of 1-60 minutes produced signs of irritation (Rowe et al., 1956). Erythema and oedema resulted from all applications of duration longer than 6 minutes. The more severe exposures resulted in scar formation. This study suggests that skin irritation may occur shortly after exposure to propylene oxide.

No skin irritation studies have been performed using propylene oxide vapour. One of several whole-body inhalation studies reported an increased incidence of benign skin tumours in rats exposed to high concentrations for 2 years (see Section 4.7.2.8.7). The significance of this finding to skin irritation is unclear.

Studies in humans

No information is available on skin irritation in humans following single exposure to propylene oxide.

4.1.2.3.2 Eyes and respiratory tract

Studies in animals

There are no conventional eye irritation studies available.

Carpenter and Smyth (1946) used a method they developed to judge the relative potency ranking of industrial chemicals to examine the irritant potential of undiluted propylene oxide to rabbit eyes. Apparently, application of 5-20 µl of propylene oxide to the corneal surface of the eye evoked a significant irritant response at a single, 18-24 hours, observation point. However, methodological details and results were presented without sufficient detail to enable this study to be interpreted according to contemporary standards. Furthermore, the report mentions that some test substances were "somewhat impure" and it is unclear if this applied to the propylene oxide samples. It is not possible to draw any meaningful conclusions from this study.

Signs of eye and respiratory tract irritation were observed in a number of animal species at high exposure concentrations exposed to propylene oxide vapour in single exposure studies (see Section 4.1.2.2.1). Signs of eye irritation were observed in mice following 4 hours exposure to 2,970 ppm and rats and guinea-pigs following 7 hours exposure to 2,000 ppm.

Studies in humans

Accidental exposure of the eyes of 3 individuals to unspecified concentrations of propylene oxide (not stated if liquid or vapour) resulted in alterations in the cornea and conjunctiva, described as "burns" (McLauglin, 1946). This report suggests that propylene oxide can produce severe eye irritation in humans.

In the case of one man exposed to propylene oxide vapour for 10 minutes, symptoms of respiratory tract and eye irritation were reported (Gosselin et al., 1984; see Section 4.1.2.2.2).

4.1.2.3.3 Summary of irritation

No information is available from human experience regarding skin irritation following dermal exposure to liquid propylene oxide. Furthermore, a skin irritation study in animals performed to regulatory standards is not available. A relatively old study in rabbits indicated that application of undiluted or 10-20% aqueous propylene oxide may cause signs of skin irritation within minutes and scar formation with more lengthy exposures. In a more recent study, in which propylene oxide may have evaporated from the test sites, no skin irritation was observed at 1, 2 and 8 days after exposure. Overall, it appears that propylene oxide liquid may cause local irritation on contact with the skin.

With respect to the vapour, there is no consistent evidence to indicate that propylene oxide vapour poses a significant skin irritation hazard. Exposure to the vapour has caused irritation of the eyes and upper respiratory tract in humans, and this has been confirmed by observations in mice, rats and guinea pigs. Although there are no useful data, in light of eye irritation following

exposure to propylene oxide vapour it is considered that the liquid also has the potential to produce eye irritation. Classification according to Annex I of Directive 67/548/EC, see Section 1.

4.1.2.4 Corrosivity

There are no data available to suggest propylene oxide is corrosive.

4.1.2.5 Sensitisation

4.1.2.5.1 Skin

Studies in animals

No conventional skin sensitisation studies have been reported.

In a split-adjuvent study, Carreon and Wall (1982) applied 0.1 ml of 10% propylene oxide to clipped and depilated backs of 10 Hartley guinea pigs four times in 10 days. The doses were applied on a gauze patch covered with adhesive tape. Freund's adjuvant was injected locally at the time of the third application. No negative control animals were used, but it appears from the scoring of skin effects in exposed animals, that there were no consistent signs of irritation following dosing during the induction period. After 2 weeks, the animals were challenged on distal sites with 10% propylene oxide. No signs of sensitisation were observed at 24 or 48 hours. This split-adjuvent study included a positive control group of 10 guinea pigs that were induced similarly with an “in-house” known skin sensitiser (an epoxy resin given the code DER 331). A positive response (slight/moderate redness) was observed in 8/10 of these animals at challenge. Although a negative result was achieved with propylene oxide, the level of sensitivity of this protocol to standard sensitisers with moderate potency used in current regulatory test methods is not known.

Studies in humans

Four cases of allergic contact dermatitis resulting from exposure to propylene oxide solution are available. In each case, the individuals were employed as laboratory assistants. Detailed accounts of work histories were not documented and, therefore, it is unclear if exposure to other potential allergens had occurred in these workers.

Van Ketel (1986) described a case of a female electron microscope technician who had eczema on her hands for 8 months. A standard patch test gave a clear positive reaction to propylene oxide. In a control group of 16 individuals, only one had a positive reaction to propylene oxide; this individual had also had previous daily contact with propylene oxide.

Steinkraus and Hausen (1994) report a case of a 52-year old laboratory assistant with allergic contact dermatitis due to propylene oxide exposure at work. The woman was particularly responsive to propylene oxide, developing erythema and oedema on the back of her hands. Standard patch tests with propylene oxide (diluted 1:10,000, 1:3,000 and 1:1,000) were positive and testing with disinfectants and rubber constituents was negative. No reactions to propylene oxide were seen in 10 negative control subjects.

Jensen (1981) reported briefly signs of contact dermatitis in two individuals who had used a commercial disinfecting swab containing 1% propylene oxide and 70% propan-2-ol on damaged skin. Patch tests with the ICDRG standard series gave negative results in both individuals. They both responded with an allergic-type reaction to 0.5% or 1% propylene oxide. One of them also responded to propan-2-ol and, therefore, a skin biopsy was taken 24 hours after a subsequent patch test with propylene oxide. This revealed spongiosis in the basal epidermis, oedema in the corium and infiltration of mononuclear cells (data not presented) which further suggest an allergic reaction to propylene oxide had occurred. A control group of 25 individuals (no further description) gave no positive response to propylene oxide in patch tests. These results suggest that propylene oxide has the potential to cause skin sensitisation in humans, although the effect may be facilitated by passage through broken skin. No explanation was given for the response of one individual to propan-2-ol, a substance regarded in the EU as a non-sensitiser, but this is not considered to detract from the conclusions regarding propylene oxide.

4.1.2.5.2 Respiratory sensitisation

There are no data available.

4.1.2.5.3 Summary of sensitisation

A small number of dermatitis cases in workers provide some limited evidence that propylene oxide may cause skin sensitisation. There have been no conventional studies of skin sensitisation potential with propylene oxide application to animal skin. In the only available study, the result was negative. Overall, although the evidence is unclear, propylene oxide has demonstrated some potential to cause skin sensitisation and given the alkylating properties of the substance, it is plausible that it could bind to tissue proteins to produce a hapten and hence elicit an immunological response.

There are no reports of propylene oxide causing respiratory sensitisation and it is not possible to draw any conclusions regarding this endpoint.

4.1.2.6 Repeated-dose toxicity

4.1.2.6.1 Studies in animals

Inhalation: NTP studies

As part of a large comprehensive and well-conducted investigation of propylene oxide, carried out for the National Toxicology Program (NTP, 1985), results were reported from three repeated exposure studies, all conducted in F344/N rats and $B6C3F_1$ mice. A summary of these studies is presented in sequence below.

In a 2-week study (NTP, 1985), rats (5 per sex per group) were exposed to air containing propylene oxide at concentrations of 0, 47.2, 98.5, 196, 487 and 1,433 ppm (0, 112, 233, 465, 1,154 and 3,396 $mg \cdot m^{-3}$) for 6 hours/day, 5 days/week, for 2 weeks (10 exposures). Daily observations, bodyweight measurements and gross necropsy were performed. The only death that occurred was one male receiving 1,433 ppm. Dyspnoea, hypoactivity, gasping, ataxia, and diarrhoea were observed at 1,433 ppm only. No other aspects were investigated.

In the same study, groups of mice (5 per sex per group) were similarly exposed to air containing propylene oxide at concentrations of 0, 20.1, 47.2, 98.5, 196 and 487 ppm (0, 48, 112, 233, 465 and 1,154 $mg \cdot m^{-3}$). There were no deaths, but dyspnoea was observed in animals receiving 196 and 487 ppm. Again, no other aspects were investigated.

In a 13-week study (NTP, 1985), conducted to determine the concentrations to be used in a subsequent 2-year study, groups of rats and mice (10 per sex per group) were exposed to air containing propylene oxide at concentrations of 0, 31, 63, 125, 250 and 500 ppm (0, 73, 149, 296, 593 and 1,185 $mg \cdot m^{-3}$) for 6 hours/day, 5 days/week, for 13 weeks. No deaths occurred in rats. There was only one death in mice (at 125 ppm) but this is not considered to have been related to propylene oxide exposure. At the conclusion of the study period, final mean body weight was depressed in animals receiving 500 ppm, compared to controls (rats by approx. 6%, mice by approx. 14%). No gross or microscopic pathological effect attributable to propylene oxide was observed in any animals at any dose; however chronic pneumonia was found in all groups of rats, which affected the ability to observe any changes in the respiratory tract. In view of the descriptions of microscopic changes induced in the respiratory tract of rodents in other studies (see below), this study is considered insufficient for the purpose of identifying a no effect level.

Taking into account the effect on body weight produced by 500 ppm in this 13-week study, exposure concentrations of 200 ppm and 400 ppm were selected for the 2-year study, 400 ppm being considered by the NTP to be the maximum tolerated dose (MTD).

In the 2-year bioassay (NTP, 1985; also reported by Renne et al., 1986), groups of 50 of each species and sex were exposed whole-body to 0, 200 or 400 ppm (0, 474 and 948 $mg \cdot m^{-3}$) for 6 hours/day, 5 days/week, for 24 months. Routine observations included clinical signs of toxicity, bodyweight, macroscopic- and microscopic pathology. In mice and rats exposed to 400 ppm, mean body weight gain was reduced, compared to controls, during the second year. However, in rats, the mean terminal body weight was within 10% of controls and there was no effect on survival. In mice at 400 ppm, only 29/50 males and 10/50 females survived to scheduled termination, compared to 34/50 male and 29/50 females at 200 ppm and 42/50 males and 38/50 females in controls.

A dose-related increase in the incidence of rhinitis was observed in all groups of mice and rats. In mice, serous rhinitis, characterised by accumulation of fluid in the nasal cavity, with few inflammatory cells, was seen in 2%, 19% and 4% of animals at 0, 200 and 400 ppm, respectively; suppurative rhinitis, characterised by a predominantly neutrophilic exudate in the lumen and adjacent nasal mucosa, was seen in 0%, 24% and 27% of animals at 0, 200 and 400 ppm, respectively. In some areas of severe rhinitis, degeneration and necrosis of the mucosal epithelium were evident. Rhinitis, with mucosal and submucosal infiltration of lymphocytes, histiocytes and plasma cells, was seen in 1%, 28% and 56% at 0, 200 and 400 ppm, respectively. In some mice, fibroplasia was seen with the rhinitis. Angiectasis of submucosal vessels beneath the respiratory epithelium was seen in 3 males and 3 females only at 400 ppm.

In rats, suppurative rhinitis was seen in 12% of controls, 26% exposed to 200 ppm propylene oxide, and 61 % exposed to 400 ppm. There was also a dose-related increase in the incidence of squamous metaplasia and hyperplasia of the respiratory epithelium of the nasal mucosa and the epithelium of the mucosal glands. The epithelial lesions were located on the greater curvature of the nasal or maxillary turbinates or on the adjacent lateral wall of the nasal cavity between the nasal and maxillary turbinates. There were no other treatment-related gross or microscopic findings in either species.

Inhalation: studies by Reuzel and Kuper

In a range finding study for a subsequent carcinogenicity study, Wistar Cpb:WU rats of both sexes were exposed whole-body to concentrations of 0, 75, 150, 300 or 600 ppm (0, 178, 356, 711 or 1,422 $mg \cdot m^{-3}$) propylene oxide vapour for 6 hours/day, 5 days/week, for 13 weeks (Reuzel and Kuper, 1981). Routine observations included clinical signs of toxicity, food intake, bodyweight, macroscopic- and microscopic pathology. Body weight gain was reduced at 300 and 600 ppm. Degenerative and hyperplastic epithelial changes in the nasal passages were observed in both sexes at the highest dose (600 ppm). No effects were observed at 150 ppm (356 $mg \cdot m^{-3}$) in this range-finding study.

In the carcinogenicity study conducted by these same authors, groups of 100 male and 100 female Wistar Cpb:WU rats were exposed, whole-body, to propylene oxide vapour at 0, 30, 100 or 300 ppm (0, 71, 237 or 711 $mg \cdot m^{-3}$) for 6 hours/day, 5 days/week, for 123-124 weeks (Reuzel and Kuper, 1982). No adverse effect of treatment was observed on general health, behaviour, food consumption, serum biochemistry, urinalysis and haematology, compared to controls. During the first year, body weight gain was reduced in both sexes at 300 ppm, but the animals adapted and recovered body weight in the second year. Mortality was increased by week 115 in both sexes at 300 ppm, and by week 119 in females at 100 ppm. A contributory factor to mortality amongst females was the occurrence of mammary gland tumours. Neoplastic findings are discussed under Carcinogenicity.

Most gross changes observed were common background findings in Wistar rats. Nevertheless, a significant increase in non-neoplastic nasal changes was seen in the respiratory and olfactory epithelium, in females exposed to 100 and 300 ppm and in males at 300 ppm. In the olfactory epithelium there were degenerative changes and focal hyperplasia of the basal cells. At all exposure levels, “nest-like infolds” were reported in the respiratory epithelium, sometimes with glandular formations, on the nasal septum and turbinates. Such changes represent a limited hyperplastic response. Although a dose-related trend in this finding was apparent, at 30 ppm the incidence of nest-like infolds in 18/125 exposed animals was described as slight and compared closely to the incidence in 8/130 control animals. There were no pathological findings attributable to propylene oxide exposure in any other tissues.

Inhalation: other studies

The effects of propylene oxide inhalation on the upper respiratory tract of F344 rats were further investigated by Eldridge et al. (1995). In this well conducted study, 5 sub-groups of 10 male F344 rats were each exposed whole body to 0, 10, 20, 50, 150, or 525 ppm (approx. 0, 24, 48, 121, 362, 1,267 $mg \cdot m^{-3}$) propylene oxide vapour 6 hours/day, 5 days/week, for 4 weeks. Thus each dose group consisted of 50 rats. After 1 and 4 weeks exposure, and after 1 and 4 weeks post-exposure, 10 rats from each dose-group were sacrificed for gross evaluation of all organs and histopathologic examination of the nasal cavity. Sixteen hours after the last exposure for each time-point, 5 of the 10 rats were injected ip with 5-bromo-2'-deoxyuridine (BrdU) in saline, for evaluation of cell proliferation in respiratory and olfactory epithelia. Two hours after BrdU injection, animals were killed for necropsy. The remaining 10 rats in each dose group appear to have been killed at the end of the study and not to have been investigated further.

No deaths occurred during the study. Although body weight gain was significantly decreased in the 525 ppm group after the first week of exposure, body weights of control and exposed animals at the end of the study were similar. No other clinical signs of toxicity were observed.

Exposure-related effects included hyperplasia of the respiratory epithelium and degeneration of the olfactory epithelium. Respiratory epithelial hyperplasia was most common in the 525 ppm group, ie. 5/10, 9/9, 2/10 and 1/10, for the time-points 1 week of exposure, 4 weeks of exposure, 1 week after 4 weeks of exposure, and 4 weeks after 4 weeks of exposure, respectively, and to a lesser extent in the 150 ppm group, ie. 3/10, 7/10, 2/10, 1/10, respectively. The hyperplasia was generally a minimal to mild recoverable change. However, 2 rats from the 525 ppm group exposed for 4 weeks showed moderate hyperplasia, although it is not reported whether this was observed in the 1- or 4-week recovery groups. Minimal hyperplasia of the respiratory epithelium also occurred in a few animals in the other groups, including two control animals. Minimal to mild degeneration of the olfactory epithelium, consisting of variably sized clear cystic spaces, occurred in 1/10, 8/9, 7/10 and 3/10 animals in the 525 ppm groups, in the same order as above. Animals in other groups were not affected similarly by exposure. Minimal degeneration of the olfactory epithelium was seen in one control animal (study week 5).

Propylene oxide also induced a proliferative response in the respiratory and olfactory epithelia. Significant increases in the labelling index, of 5- and 7-fold, were seen in the respiratory epithelium of 525 ppm group rats at weeks 1 and 4 of exposure, respectively. There were no increases in other exposure concentrations and the effect at 525 ppm was not seen in the post-exposure groups. Smaller, concentration-related, increases in olfactory epithelial cell proliferation (1.6-2.4 fold over control; $p<0.05$) were seen at week 1 in the 50, 150 and 525 ppm groups. This proliferation remained only in the 150 and 525 ppm groups at week 4 of exposure (1.6- and 2.3 fold, respectively), and in the 525 ppm group at 1 week post-exposure (1.9 fold). There are no agreed criteria for what constitutes a toxicologically significant increase in nasal epithelial cell proliferation; the study authors suggested that a labelling index 2-fold or more over controls would be significant.

These results demonstrate reversible proliferative changes induced by propylene oxide in the nasal mucosa of male F344 rats. Since the increase in olfactory cell proliferation observed in rats exposed to 50 ppm at week 1 was slight and was not sustained at week 4, this is not viewed as a toxicologically significant effect, hence, it is concluded that a NOAEL of 50 ppm propylene oxide can be identified from this 4-week study.

Rowe et al. (1956) reported several studies in which rats (10 or 20 per sex per group), guinea pigs (8 per sex per group), rabbits (2 per sex per group) and rhesus monkeys (1 or 2 females) were exposed, whole-body, to 102, 195 or 457 ppm (242, 462, 1,083 $mg \cdot m^{-3}$) propylene oxide vapour for 7 hours/day, 5 days/week for periods between 35 and 218 days. Rabbits and monkeys did not show any adverse effect of this treatment on appearance, behaviour, mortality, growth, organ weight and gross- or histopathology. Rats and guinea pigs showed no evidence of toxic effect at 102 and 195 ppm, but at 457 ppm in rats there was irritation of the eyes and respiratory passages and an increased mortality due to pneumonia. After 37-39 days exposure to 457 ppm, microscopic examination of rat lungs revealed alveolar haemorrhage and oedema, and interstitial oedema and hyperaemia. Guinea pigs also showed irritation of the eyes and respiratory passages at 457 ppm, but no increase in mortality. After 157 days, microscopic examination of guinea pig lungs revealed alveolar haemorrhage and oedema, and interstitial oedema and hyperaemia.

Lynch et al. (1984a) conducted a long-term inhalation study in which groups of 80 male F344 rats were exposed, whole-body, to 0, 100 or 300 ppm propylene oxide vapour for 7 hours/day, 5 days/week, for 24 months. Body weight gain in both exposure groups was significantly reduced compared to controls. However, from about 16 months, all rats in this study were affected by *Mycoplasma pulmonis* infection. This condition, alone or in combination with exposure to propylene oxide, affected survival of exposed rats and influenced the development

of proliferative lesions in the nasal mucosa. No treatment-related changes in clinical chemistry or urinalysis were seen.

Lung weight was significantly increased in both propylene oxide exposure groups, in a dose-related manner. However this was also probably complicated by the intercurrent infection. Kidney weight was reduced in a dose-related manner but other organ weight changes appeared to be related to reduced body weight. Neoplastic changes are discussed below in Section 4.1.2.8.

Skeletal myopathy was observed at 300 ppm, consisting of multifocal areas of atrophy and degeneration, however no lesions were seen in the sciatic nerves by light microscopy. Rats exposed to propylene oxide had increased incidence and greater severity of inflammatory lesions in the lungs, nasal cavity, trachea and middle ear - all characteristic of rodent chronic respiratory disease. However, in spite of this there was a dose-related increase in the incidence of complex epithelial hyperplasia in the nasal passages (controls 0/76; 100 ppm 2/77; 300 ppm 11/78). The proliferative lesions in the nasal mucosa appeared to be treatment related, but it is difficult to judge how much this was influenced by the respiratory infection.

In a 10-day study, groups of 3 male and 3 female rats were exposed for 6 hours/day to 0, 997 or 1,940 ppm propylene oxide (Blair and Osbome, 1977). At 1,940 ppm, 1 animal died during study and the remaining 5 were killed moribund on day 9. Congested and patchy lungs were observed in these animals together with microscopic signs of irritation in the nasopharynx, trachea and bronchi. Decreased terminal body weight and microscopic signs of respiratory irritation were seen at 997 ppm. Signs of eye irritation were also seen in this relatively limited investigation of repeated exposure toxicity.

Inhalation: studies on neurotoxic effects

Sprinz et al. (1982) investigated the possibility that propylene oxide might induce neuropathy. Groups of 2 male cynomolgus monkeys were exposed to 0, 100 or 300 ppm (0, 237 or 711 $mg \cdot m^{-3}$) for 6 hours/day, 5 days/week, for 24 months. Brain, spinal cord, and peripheral nerves (ulnar and sciatic) were examined histologically after exposure. Clinical signs, if any, were not reported. According to the authors, evaluation of the peripheral nerves was seriously compromised by fixation artefacts resembling myelin degeneration, but evaluation of spinal cord and brain sections was possible. The only treatment-related neuropathy was in the medulla oblongata, where there were signs of neuroaxonal dystrophy in the nucleus gracilis in the 4 treated monkeys, with no apparent dose-response relationship. However, the same lesion was also observed in 1/2 control monkeys, and since there was no detectable clinical or functional consequence of this change, nor any detectable change in the peripheral nerves, it is not clear what significance it has regarding exposure to propylene oxide. Neuroaxonal dystrophy is a relatively non-specific finding which increases with age and is present in a wide variety of human and animal conditions which are not necessarily neurologic diseases. No demyelination was seen in the propylene oxide exposed monkeys. Overall, no conclusion can be drawn from this study regarding the neurotoxic potential of propylene oxide.

Young et al. (1985) also investigated the neurotoxic potential of propylene oxide in groups of 10 male F344 rats exposed to 0, 100 or 300 ppm (0, 237 or 711 $mg \cdot m^{-3}$) for 6 hours/day, 5 days/week, for approximately 24 weeks, as part of a 2-generation reproduction study. Neurotoxicologic assessment of the rats consisted of periodic observation during exposure, sensory, motor and behavioural tests, an open field test and a hind-limb grip strength test. At the end of the exposure period, neuropathologic examination of the central and peripheral nervous system (sciatic and tibial nerves) was undertaken.

No treatment-related changes in demeanour or behaviour were observed, nor any significant difference between groups in the results of the functional and behavioural tests. There were no significant gross pathology or histopathology changes attributable to treatment. The most frequent microscopic change seen was very slight axonal degeneration in the cervical spinal cord and mild neuroaxonal dystrophy in the region of the nucleus gracilis but these occurred in equivalent incidences in the control group and the 300 ppm exposure group. These effects were therefore not related to exposure to propylene oxide. In conclusion, this study provides no evidence of neurotoxicity in male rats exposed to sufficiently high concentrations of propylene oxide to produce a reduction in body weight gain and respiratory tract irritation. The findings are similar to those reported by Sprinz et al. (1982) for Cynomolgus monkeys (above). Neuroaxonal dystrophy in rats is probably an age related condition, as it is in other species (Jellinger, 1973).

In the long-term inhalation toxicity study in F344 rats reported above (Lynch et al., 1984a), skeletal myopathy was observed at 300 ppm, consisting of multifocal areas of atrophy and degeneration, but no lesion was seen in the sciatic nerves by light microscopy.

More recently, Ohnishi et al. (1988) subjected 11 male Wistar rats by inhalation in exposure chambers to 1,500 ppm (3,555 $mg \cdot m^{-3}$) propylene oxide vapour for 6 hours/day, 5 days/week, for 7 weeks. A group of 11 control animals was exposed to filtered air. All treated animals developed signs of neuropathy, as ataxia of the hindlimbs without obvious foot drop or muscle atrophy. The main pathological change was axonal degeneration of the myelinated fibres in hindleg nerves and the fasciculus gracilis. These effects are considered to be compatible with a central-peripheral distal axonopathy resulting from exposure to this relatively high concentration of propylene oxide.

Oral administration

Following repeated daily oral doses by gavage in five rats per sex per group (18 doses in 24 days), a slight reduction in body weight gain, gastric irritation, and slight liver damage (not specified) were seen at 300 $mg \cdot kg^{-1}$. No effect was noted at 100 or 200 $mg \cdot kg^{-1}$ (Rowe et al., 1956).

Dunkelberg (1982) administered 0, 15 or 60 $mg \cdot kg^{-1}$propylene oxide by gavage, twice weekly for 150 weeks to groups of 50 female Sprague-Dawley rats. Survival of the propylene oxide treated animals did not differ significantly from vehicle controls. The principal findings were reactive changes (epithelial hyperplasia) in the squamous epithelium and associated neoplasms of the forestomach. Neoplastic findings in this study are described in more detail under Carcinogenicity.

Dermal

No information is available on repeated dermal application.

4.1.2.6.2 Studies in humans

Stocker and Thiess (1979) reported on 279 employees from 8 plants in Germany where alkene oxides were produced or processed. The workers were employed for an average of 10.8 years and were generally exposed to a mixture of alkene oxides, including propylene oxide, together with other volatile substances. It was stated that the average concentration of propylene oxide under normal conditions was 1 ppm or less. Exposure of workers to propylene oxide was measured using personal samplers over periods of up to 10 hours, and in each case the average exposure over a working shift was below the MAK (maximum allowable concentration at the

workplace) value of 100 ppm (237 $mg \cdot m^{-3}$). No clinical abnormality was included in this report to indicate an adverse effect attributable to propylene oxide, but in any event the mixed exposure limits the value of this study.

4.1.2.6.3 Summary of repeated dose toxicity

There are no useful data describing the effects of repeated exposure to propylene oxide in humans. In rats and mice, repeated inhalation exposure to propylene oxide for two years produces chronic irritation of the nasal epithelium, with such effects being only marginal in nature at 30 ppm. However, concentrations of 100 ppm and above produce pronounced epithelial damage. In a 4-week study in rats, small and reversible increases in nasal epithelium irritation occurred at 525 ppm propylene oxide. There is some evidence to indicate neurotoxicity in rats at the relatively high exposure level of 1,500 ppm (7 weeks exposure). No signs of neurotoxicity were observed in rats exposed to 300 ppm for 24 weeks.

Repeated oral administration caused reduced body weight gain and gastric irritation, seen microscopically as reactive changes in the squamous epithelium of the forestomach. No data are available on the toxicity of propylene oxide following repeated dermal exposure. The absence of significant toxic sequelae distant from the site of application following inhalation or oral administration suggests that concerns about target organ toxicity can be focused almost exclusively on tissues at the sites of initial contact.

4.1.2.7 Mutagenicity

4.1.2.7.1 Studies *in vitro*

Studies in bacteria

In Salmonella typhimurium, propylene oxide has been shown to cause mutation in strains TA100 and TA1535 in the absence and presence of metabolic activation, however it has not been reported to cause mutation reproducibly in strains TA1537, TA1538 and TA98 (Wade et al., 1978; Bootman et al., 1979; McMahon et al., 1979; Hemminki and Falck, 1979; Pfeiffer and Dunkelberg, 1980; Dean et al., 1985; Djuric et al., 1986; Hughes et al., 1987; Agurell et al., 1991; Canter et al., 1986). Propylene oxide was also mutagenic in TA1535 with and without activation by Aroclor-induced rat liver S9 in a modified SOS-Chromotest test (Ong et al., 1987).

Propylene oxide was also mutagenic without metabolic activation in spot tests in *Escherichia coli* strain WP2 (Bootman et al., 1979; Hemminki and Falck, 1979; Dean et al., 1985), strains CM891 and CM871 (Bootman et al., 1979) and in *Klebsiella pneumoniae* (Voogd et al., 1981). In the SOS-Chromotest propylene oxide, tested up to a cytotoxic concentration, was non-mutagenic to *E coli* strain PQ37 in the absence and presence of metabolic activation (von der Hude et al., 1990).

Garro and Phillips (1980) described a positive result in a novel mutagenesis assay using *Bacillus subtilis* to detect mutations in phage DNA previously exposed to propylene oxide at 42°C. Positive results were also reported for other alkylating agents.

Studies in fungi

Incubation of *Schizosaccharomyces pombe* with 3-30 mM propylene oxide for 6 hours in sealed test-tubes caused a significant increase in forward mutations (Migliore et al., 1982). Mutation frequencies were similar in the absence and presence of erogenous metabolic activation. Propylene oxide also caused reverse mutations in a purple adenine auxotrophic strain of *Neurospora crassa* (Kolmark and Giles, 1955).

Studies *in vitro*: mammalian cells - cytogenetics assays

In a chromosome aberration assay, Bootman et al. (1979) incubated cultures of human lymphocytes for 24 hours with 1.85 or 9.25 $\mu g \cdot ml^{-1}$ propylene oxide in the absence of metabolic activation. Control cultures received sterile water, and positive controls were incubated with chlorambucil. Propylene oxide treatment produced a dose-related increase in the frequency of aberrations (excluding gaps), ie 1% (control), 5.5% (1.85 $\mu g \cdot ml^{-1}$), 17.5% (9.25 $\mu g \cdot ml^{-1}$). The lesions induced by propylene oxide included chromosome and chromatid breaks and chromosome exchanges. Propylene oxide thus showed clastogenic activity in the absence of erogenous metabolic activation in this test system.

A chromosome aberration assay using Chinese hamster ovary (CHO) cells was reported by Gulati et al. (1989). Without metabolic activation, cells were exposed to 5-500 $\mu g \cdot ml^{-1}$ propylene oxide for approximately 10 hours and harvested at 12-13 hours. In the presence of Aroclor-induced rat liver S9, cells were exposed to 50-1,600 $\mu g \cdot ml^{-1}$ for 2 hours. In both instances, reproducible, dose-related increases in aberration frequency were observed. Levels of cytotoxicity were not described, but this study provides further evidence of the clastogenicity of propylene oxide.

In another chromosome aberration test, Dean and Hodson-Walker (1979) exposed an epithelial-type cell line (RLI) derived from rat liver to 25-100 $\mu g \cdot ml^{-1}$ propylene oxide for 24 hours. There was a dose-related increase in chromatid gaps (1.1, 5.3, 17.5, 31.3 and 53.7%, at 0, 25, 50, 75 and 100 $\mu g \cdot ml^{-1}$), and deletions (0.3, 1.3, 3.3 and 6.0%, at 0, 25, 50 and 75 $\mu g \cdot ml^{-1}$). The results from this relatively old, non-standard test are consistent with the positive findings of the other chromosome aberration studies.

Recently, propylene oxide was used as the positive control in a micronucleus test with human lymphocytes (Jorritsma et al., 1995). Cell cultures were exposed to propylene oxide for 72 hours, with addition after 44 hours of a cytokinesis-blocking agent. The method was specifically adapted for the testing of volatile and gaseous substances and involved application of propylene oxide via a syringe into sealed tissue culture vessels. In both of 2 independent experiments, a dose-related significant increase in the frequency of micronucleated binucleated cells was observed. At the higher concentrations only, cytotoxicity was also observed. These results further indicate the potential of propylene oxide to damage chromosomes.

In a sister chromatid exchange (SCE) study, Tucker et al. (1986) exposed phytohaemagglutinin-stimulated human peripheral lymphocytes to propylene oxide at a concentration of 2.5%. The SCE frequency was increased from 8.7% per cell in controls to 22.7% per cell in treated cells, thus demonstrating a positive result for propylene oxide in this system.

In a similar study, but without the use of concurrent controls, Agurell et al. (1991) investigated the comparative ability of ethylene oxide and propylene oxide to cause SCE in phytohaemagglutinin-stimulated human lymphocytes *in vitro*. Both test substances produced

equivalent frequencies of SCE. However, in the absence of a negative control, no conclusions can be drawn from this study.

Propylene oxide gave a reproducible, dose-related increase in the frequency of SCEs in Chinese hamster V79 cells (von der Hude et al., 1991). This positive result was obtained in the absence of an erogenous metabolic activation system. A marked increase in SCE frequency was also observed in CHO cells exposed to propylene oxide both in the presence and absence of Aroclor-induced rat liver S9 (Gulati et al., 1989).

Studies *in vitro*: mammalian cells - gene mutation assays

Zamora et al. (1983) tested propylene oxide vapour in a CHO cell *hprt* gene mutation test. Propylene oxide was vapourised by briefly heating the flask and the cells were incubated for 1 hour at 37°C. A clear dose-related increase in mutants was observed.

McGregor et al. (1991) used the L5178Y mouse lymphoma assay *(tk* locus) modified for gases and volatile liquids. Cultures of cells were exposed to propylene oxide vapour at various concentrations (0.04-1.25%) for 4 hours in the absence of erogenous metabolic activation. Propylene oxide demonstrated dose-related mutagenic activity at concentrations between 0.04% and 1.25%. Concentrations greater than 1.25% were lethal to the test cells.

Studies *in vitro*: mammalian cells - other assays

Sina et al. (1983) reported single strand breaks in DNA, evaluated by alkaline elution, in isolated rat hepatocytes exposed to propylene oxide at concentrations that were not toxic and as low as 1.7 $\mu g \cdot ml^{-1}$.

4.1.2.7.2 Studies in *Drosophila*

Hardin et al. (1983b) tested propylene oxide for mutagenic activity in the *Drosophila melanogaster* sex-linked recessive lethal assay. Male flies were exposed to propylene oxide vapour at a concentration of 645 ppm (1,530 $mg \cdot m^{-3}$) for 24 hours, and then mated to Muller-5 (Basc) females on days 2-3 and 7-8 post-exposure. F_1 females were mated with Muller-5 males and the resulting offspring scored for wild-type F_2 males. The total incidence of sex-linked recessive lethal mutations was significantly increased in propylene oxide-exposed flies (4.28%) compared to controls (0.25%).

4.1.2.7.3 Studies *in vivo*: somatic cells - cytogenetics assays

Propylene oxide has been tested in the mouse bone marrow micronucleus assay (Bootman et al., 1979). In a well-conducted study, consisting of 3 separate experiments, groups of 5 to 10 male CD-1 mice were administered two oral doses by gavage at 30 and 6 hours prior to killing, or were given 2 intraperitoneal injections on the same schedule. The individual oral doses were 100, 250 or 500 $mg \cdot kg^{-1}$, and those injected intraperitoneally were 75, 150 or 300 $mg \cdot kg^{-1}$. Positive control groups received either cyclophosphamide or chlorambucil, and vehicle controls received 0.5% gum tragacanth.

Micronucleated cells per 1,000 polychromatic erythrocytes were scored. No increase in the number of micronucleated cells was seen after oral administration of propylene oxide. However, there was a significant increase in micronucleated cells in mice receiving $2 \cdot 300$ $mg \cdot kg^{-1}$ by the

intraperitoneal route (6.5/1,000 cells) compared to the vehicle controls (3/1,000 cells). For comparison, chlorambucil produced a higher response (43/1,000 cells). No signs of toxicity were reported; it was not stated if propylene oxide by either route of administration produced an effect on the ratio of polychromatic to normochromatic erythrocytes. This study has demonstrated that propylene oxide has the potential to induce mutagenic lesions in somatic cells *in vivo*. The positive result following intraperitoneal injection is considered to indicate the potential for mutagenicity at sites of initial contact in the body.

The genotoxicity of propylene oxide to mouse bone marrow following intraperitoneal injection was confirmed by Farooqi et al. (1993). Four groups of 4 female Swiss albino mice were administered a single injection of 30-450 $mg \cdot kg^{-1}$ propylene oxide. A negative control group was also included, but it is not clear how these animals were treated. The mice were killed with a fixation time of 24 hours. At the two highest dose levels only (300 and 450 $mg \cdot kg^{-1}$) the mean frequency of micronuclei was very high (44 and 67 per 1,000 polychromatic erythrocytes, respectively) indicating a positive result. Mean values in other groups ranged from 0.5-4 per 1,000 cells. Whether or not systemic toxicity and/or cytotoxic damage to the bone marrow cells occurred at these relatively high intraperitoneal doses was not reported.

In a mouse bone marrow chromosome aberration assay, 5 groups of 4 female Swiss albino mice were administered 30-450 $mg \cdot kg^{-1}$ propylene oxide by intraperitoneal injection (Farooqi et al., 1993). A negative control group was also included, but it is not clear how these animals were treated. The mice were killed with a fixation time of 24 hours. The results, presented in graphical form, showed that propylene oxide produced a dose-related increase in the frequency of aberrations per cell in all treatment groups. The majority of the aberrations were apparently chromatid or isochromatid breaks. Although the data were presented in a non-conventional way, and no descriptions of the level of toxicity observed were provided, this study is further evidence that propylene oxide administered intraperitoneally is clastogenic to mouse bone marrow cells.

Farooqi et al. (1993) also studied the effect of propylene oxide on SCE frequency in mouse bone marrow cells. As in the other cytogenetics assays in this study, groups of 4 female Swiss mice received 30-450 $mg \cdot kg^{-1}$ propylene oxide by intraperitoneal injection. These mice had received bromodeoxyuridine immediately before exposure and were killed for SCE analysis after 28 hours. A dose-related, significant increase in the number of SCEs per cell compared with the negative controls was observed, providing further confirmation of the genotoxicity of propylene oxide.

Lynch et al. (1984b) investigated the induction of chromosomal aberrations and SCE in peripheral lymphocytes obtained and cultured from groups of 12 cynomolgus monkeys that had been exposed to 0, 100 or 300 ppm (0, 237, and 717 $mg \cdot m^{-3}$) propylene oxide vapour for 7 hours/day, 5 days/week, for 2 years. Blood was collected in month 24 and lymphocyte cultures established. The duration of culture was 68-74 hours. There was no significant increase in the incidence of chromosome aberrations or SCE in lymphocytes from exposed monkeys compared to controls. However, pre-exposure blood was not collected for cytogenetic assay at the start of the study, and the culture time used (68-74 hours) was probably a little too long; there may have been a depletion of affected cells. Nevertheless, by comparison, in the same study, lymphocytes from monkeys previously exposed to ethylene oxide (50 or 100 ppm) showed a significant increase in chromosome aberrations and SCE.

Studies *in vivo*: germ cells - dominant lethal assays

Propylene oxide has been tested for germ cell genotoxic activity by inhalation in a dominant lethal assay (Hardin et al., 1983b). A group of 10 male Sprague-Dawley rats was exposed, whole-body, to 300 ppm (711 $mg \cdot m^{-3}$) for 7 hours/day, for 5 days. A group of 10 males of the

same strain, breathing filtered air, served as controls. Commencing two days after final exposure, each male was mated with 2 virgin females, each week, for 6 consecutive weeks. Mating periods were 5 days, followed by a 2-day rest period. Females were killed and examined internally approximately 15 days after the first day of pairing with the male. Pregnancy rate, corpora lutea, implantations, early deaths, and late deaths were recorded. There was no difference between controls and treated animals regarding any of the reproductive parameters to indicate a genotoxic effect of propylene oxide.

Bootman et al. (1979) also conducted a dominant lethal assay in groups of 10 male CD-1 mice receiving 14 daily doses of 50 or 250 $mg \cdot kg^{-1}$ propylene oxide orally by gavage. A positive control group received 3 daily doses of 200 $mg \cdot kg^{-1}$ ethylmethanesulphonate (EMS), and vehicle controls received 0.5% gum tragacanth. Males were mated for 7-day periods with 2 virgin females each week for 6 consecutive weeks. Females were killed 18 days after the first day of pairing with the male. Implants, early deaths, and late deaths were recorded. Pregnancy rate, total implants/sire, and post-implantation loss did not differ significantly between controls and propylene oxide-treated groups. The positive control group (EMS) exhibited a significant reduction in pregnancy rate in weeks 2 and 5, and an increase in implant deaths after weeks 1 and 2 of mating.

4.1.2.7.4 Studies in humans

Thiess et al. (1981), investigated chromosomal aberrations in peripheral lymphocytes from 43 males aged 27-63 years (mean 47.1) who worked in ethylene oxide manufacturing or processing plants and were concurrently exposed to propylene oxide. The observed individuals were divided into four groups; 11 exposed more than 20 years, 6 exposed less than 20 years, 21 long-term exposure plus involvement in an ethylene oxide accident, and 5 short-term high exposure (ethylene oxide accident). The control group comprised 21 male employees from the Occupational Health Department and office staff, aged 24 to 58 years (mean 38.6), however this report gives no indication of whether they were smokers or not, or how they were matched to the observed groups. Exposure of workers to propylene oxide was measured using personal samplers over periods of up to 10 hours, and in each case the average exposure over a working shift was below the MAK value of 100 ppm (237 $mg \cdot m^{-3}$).

The percentage of lymphocytes with aberrant chromosomes (6.4%) (including gaps) was significantly increased ($p<0.005$) only for those workers with more than 20 years exposure, compared to the percentage observed in controls (4.0%). Statistically significant differences were not found in the other groups. However, a conclusion cannot be drawn regarding the specific mutagenic effect of propylene oxide based on this study because the group showing an increased frequency of aberrant chromosomes also had multiple and possibly long-term exposure to a variety of potential mutagens, including ethylene oxide.

As part of an extensive, cross-sectional study into the clastogenic potential of a number of substances, de Jong et al. (1988) measured chromosome aberration frequencies in peripheral blood lymphocytes from 27 workers involved in the manufacturing of chemicals using propylene oxide, ethylene oxide and epichlorohydrin (ECH) for between 1 and 15 years. The analyses were made during the first quarter of 1978. Exposure to propylene oxide was not measured, but was considered by the authors of the study to be low because use was limited to closed systems. Exposure to ethylene oxide was similarly considered to be low, whereas measured concentrations determined from personal air samples taken during 1977 and 1978 indicated a range of ECH exposure levels. A series of 6 control groups of workers who were believed not to be exposed occupationally to genotoxins were also included in this study, the most appropriate to

this test group being a group of 27 men working in another plant with phenol, acetone and bisphenol A. These individuals were matched with the test group for age and smoking habits, and were sampled during 1978. Additionally, 37 men from the same plant were sampled in 1980.

For chromosome aberration analysis, cells were harvested after 48 hours in culture. Overall, 2,471 cells were scored giving a mean aberration frequency (excluding gaps) of 0.97 aberrations/100 cells for the test group. This was greater than the mean value of 0.11 determined in 2,700 cells from the control group in 1978, and lower than the control value in 1980 (2.11 from 3,700 cells). It should be noted also that the values obtained in the 1978 control group were the lowest among the series of 6 control groups (range of means 0.11-2.26). Furthermore, all these aberration frequencies are relatively small and are within the range observed generally in control human lymphocytes. Consequently, it is unlikely that a clastogenic effect was observed in this situation. In view of the small scale of the study and the limited exposure to propylene oxide in the exposed group, no useful information can be obtained regarding the potential genotoxic effects of propylene oxide.

From 1978 to 1981, Van Sittert and de Jong (1985) conducted a prospective study of structural chromosome aberrations in peripheral lymphocytes from plant workers exposed to either to propylene oxide or styrene, or to both these substances. Precise data on exposure levels were utilised in this study of 116 male test subjects and 20 controls, matched by age and smoking habit. The levels of propylene oxide exposure during the study had been monitored (< 1 ppm, 8-hour TWA) and were probably below the detection level of the method. It was concluded that the very minor changes in the frequency of chromosome aberrations in lymphocytes during the period 1978-81 were not significant, and in any event were unlikely to have been of occupational origin. This study was also reported by de Jong et al. (1988).

In a study conducted without concurrent controls, Hogstedt et al. (1990) measured chromosome aberrations and micronuclei in peripheral lymphocytes from workers exposed to propylene oxide in a factory producing alkylated starch. The study group consisted of 20 male individuals, aged 22-59, of which 16 were smokers, who worked in a plant producing alkylated starch and were potentially exposed for between 1 and 20 years. The workers were mainly exposed to non-reacted propylene oxide evaporating from the starch after the reaction. This operation was carried out about 150 times per year, so exposure was not continuous. During exposure periods, concentrations of propylene oxide (breathing zones) varied between 0.33 and 11.4 ppm (average measured during 2-4 hours). With shorter sampling periods (20 minutes) a peak concentration of 56 ppm was measured.

All blood samples were taken within a two-month period. Lymphocytes were cultured for 72 hours. One hundred metaphases were scored for each individual for chromosome aberrations, or l,000 cells scored for intracytoplasmic micronuclei. Adduct levels of hydroxypropylvaline in haemoglobin were determined as a measure of *in vivo* exposure to propylene oxide.

The mean percentage of total chromosomal abnormalities in propylene oxide exposed workers was 4.7%, and the mean frequency of intracytoplasmic micronuclei was 2.6%. These results do not appear to differ significantly from findings in non-exposed individuals and under these exposure conditions no discernible clastogenic activity was observed. However, in the absence of concurrent control values it is not clear how useful these results are.

Pero et al. (1982; 1985) looked at unscheduled DNA synthesis (UDS) induced *in vitro* by the mutagen N-acetoxy-2-acetylaminofluorene (NAc-AAF) in peripheral lymphocytes from workers who had been exposed to propylene oxide for between 1 and 20 years (mean 10). The study group comprised 23 workers, aged 25-59 years (mean 41) from a factory producing alkylated

starch. Estimates of exposure were obtained using personal and background (or static) sampling; the time-weighted average (TWA) was 0.6-12 ppm for 2 to 6 hours per day, and so was normally below 12 ppm (28 $mg \cdot m^{-3}$). However, short-term exposures of up to 1,000 ppm (2,370 $mg \cdot m^{-3}$) were recorded for some workers. A control group consisted of 13 unexposed subjects, aged 24 to 55 years (mean 47.0), apparently matched for smoking habit. UDS was measured by exposing the cultured lymphocytes to a standardised dose of NAc-AAF and measuring thymidine incorporation.

NAc-AAF-induced UDS was significantly lower ($p<0.001$) in the propylene oxide exposed group, suggesting these individuals had a reduced capacity to repair DNA damage. At the same time, alkylated haemoglobin was significantly higher ($p<0.001$) than in the unexposed group. It is not clear what significance, if any, these results have for human health. No conclusion can be drawn regarding the genotoxicity of propylene oxide from these results.

In a poorly conducted study, cytogenetic analysis was performed on the blood of workers exposed to propylene oxide or ethylene oxide (Viktorova et al., 1994). A sample of 57 male workers (aged between 22 and 57 years) with a working service in the production facilities of 1-14 years was included in the study. Previous work histories were not reported and it is unclear whether the ethylene oxide facility was on the same site. A control group consisted of 20 males who lived in the same geographical area, but further matching, such as whether they were smoked tobacco or not, was not reported. Details of air sampling methods were not specified.

Lymphocytes were sampled at the same time for all groups, twice within a period of a year. There were statistically significant increases in the frequency of chromatid and chromosomal aberrations in lymphocytes from exposed workers compared to controls. The highest values were found in lymphocytes from workers who were considered to have received the highest exposures to propylene oxide.

The use of apparently unmatched controls, especially with respect to tobacco smoking status, and possibility that workers were exposed to various other substances including ethylene oxide the considerably weakens the toxicological significance of the findings. No conclusions regarding the mutagenic potential of propylene oxide can be drawn from this study.

4.1.2.7.5 Summary of mutagenicity

No conclusions about the mutagenicity or propylene oxide in humans can be drawn from the available human studies. The ability of propylene oxide to react directly with nucleic acids and proteins *in vitro and in vivo* has been demonstrated (see Section 4.1.2.1.2).

In *in vitro* genotoxicity studies, propylene oxide exerts a clear, direct-acting positive effect in a wide variety of standard test systems, causing mutations in bacteria, fungi, and mammalian cells in the absence of exogenous metabolic activation. *In vivo,* in an unconventional study in monkeys, no evidence for propylene oxide induced chromosomal aberrations or SCE was obtained following inhalation exposure for 2 years to up to 300 ppm. Negative results were obtained in mouse bone marrow micronucleus tests following oral exposure. In contrast, positive results were obtained for this endpoint following intraperitoneal administration. Positive results were also obtained for chromosomal aberrations and SCE in mouse bone marrow cells following intraperitoneal dosing. Therefore, it is clear that propylene oxide is a somatic cell mutagen *in vivo.* The general toxicological profile for propylene oxide suggests that its potential to produce genetic damage might be expressed only at sites of initial contact. It is not possible to establish an exposure level at which there would be no increased risk of mutagenicity. In relation to the potential of propylene oxide to induce heritable mutations in germ cells, dominant lethal tests

involving inhalation exposure of rats and oral exposure of mice have given negative results. There is no additional evidence that propylene oxide causes heritable mutations in germ cells. However, studies of DNA adduct formation indicate that very low levels of DNA adducts were observed in the testes following repeated inhalation exposure to 500 ppm propylene oxide vapour. There are many uncertainties surrounding this finding both in terms of the biological significance of the adduct formed and the level of adduct formation in relation to background levels but overall it would be prudent to assume that propylene oxide has the potential to reach the germ cells. Given that propylene oxide is a direct-acting mutagen then the possibility that it might express this activity within the germ cells cannot be discounted. Classification according to Annex I of Directive 67/548/EC, see Section 1.

4.1.2.8 Carcinogenicity

4.1.2.8.1 Studies in animals

Inhalation: NTP studies

In a thorough study conducted for the National Toxicology Program (NTP), groups of 50 male and 50 female F344/N rats were exposed to 200 or 400 ppm (474 or 948 $mg \cdot m^{-3}$ propylene oxide vapour for 6 hours/day, 5 days/week, for 103 weeks (NTP, 1985; Renne et al., 1986). These doses were selected to represent the MTD (400 ppm) and 50% MTD (200 ppm) as estimated from a preceding 13-week toxicity study. Control groups of 50 males and 50 females were exposed in the inhalation chambers to room air. Cageside observations and bodyweight were recorded regularly, and gross and microscopic pathology performed on decedents and animals surviving until termination of the study at week 103. The non-tumour pathology has been described earlier, in the "Repeated-dose toxicity" Section (4.1.2.6).

At the end of the exposure period, mortality rates were similar (60 - 70%) between exposed and non-exposed animals. Slightly decreased bodyweights (<9%) were recorded from week 20 in males, and week 40 in females. Increases were observed in the incidences of suppurative inflammation of the mucosa, epithelial hyperplasia, squamous cell metaplasia of the respiratory epithelium of the nasal turbinates and papillary adenoma involving the respiratory epithelium and underlying submucosal glands of the nasal turbinates.

Table 4.10 Incidences of nasal cavity tumours in 2-year inhalation study

	Male rats			Female rats		
Propylene oxide (ppm)	0	200	400	0	200	400
Numbers examined	50	50	50	50	48	48
Number with:						
Suppurative inflamation	9	21	38	3	5	23
Epithelial hyperplasia	0	1	11	1	0	5
Squamous cell metaplasia	1	3	21	1	2	11
Papillary adenoma	0	0	2	0	0	3

The incidence of papillary adenoma in the respiratory epithelium and submucosal glands of the nasal cavity was significant (p=0.037) compared to controls when determined by trend analysis (but not otherwise). Although the incidence of these adenomas was low, they are considered to be treatment-related in view of their rarity in control animals. NTP historical control tumour incidence data in F344 rats show that the background levels of nasal cavity papillomas are 0.1% and 0% in male and female rats respectively (Haseman et al., 1990).

In high-dose females, the incidences of thyroid C-cell adenoma and C-cell carcinoma were increased, but only the combined incidence was statistically significant; 2/45 control, 2/35 (200 ppm), 7/37 (400 ppm). In NTP studies the frequency of these tumours in control female F344 rats is relatively high (8.3%) and, also because the degree of C-cell hyperplasia was similar in control and exposed rats in this study, the C-cell tumours are considered to be chance findings unrelated to propylene oxide exposure.

A slight increase in the incidence of skin keratoacanthoma was also observed in males exposed to 400 ppm propylene oxide compared to controls (10% versus 2%, respectively).

In the same study (NTP, 1985; Renne et al., 1986), groups of 50 male and 50 female $B6C3F_1$, mice were similarly exposed to 200 or 400 ppm in the same regime. At 400 ppm, decreased survival rates were observed in males and females, 60% and 10% respectively, compared to controls, 86% and 78% respectively. Slightly decreased bodyweights were recorded from week 29 in males (<22%) and in females (<33%). The non-tumour pathology has been described earlier, in the "Repeated-dose toxicity" Section (4.1.2.6). Propylene oxide caused increased incidence and severity of inflammation of the respiratory epithelium of the nasal turbinates. Squamous cell metaplasia in the nasal cavity was observed in one low-dose male and two high-dose females. One squamous cell carcinoma and one papilloma occurred in the nasal cavity of two high-dose males, and two high-dose females (4.0%) had adenocarcinoma of the nasal cavity. None of these tumours was observed in controls or low-dose animals in this study, and furthermore had not been observed in historical controls.

Vascular neoplasms in the nasal cavities, haemangiomas and haemangiosarcomas, were observed in mice receiving 400 ppm propylene oxide. In the high-dose group, haemangioma developed in 5/50 males and 3/50 females, and haemangiosarcoma developed in 5/50 males and 2/50 females. Differentiation between these neoplasms was based on the degree of anaplasia and invasive features. Haemangiomas were composed of well-differentiated endothelial cells, flattened and with small nuclei with few or no mitotic figures. Haemangiosarcomas were composed of endothelial cells with large vesicular nuclei and a high mitotic index and had features of cancer, ie invasion of the maxillary sinus, turbinate bones, maxilla, and subcutis. These data reveal a gradation of response in the submucosal vasculature, with angiectasis the mildest vascular change, followed by haemangioma and haemangiosarcoma. These vascular tumours were not observed in the nasal turbinates of low-dose or control mice and compared to controls these incidences were significantly increased ($p<0.05$).

There was a statistically significant positive trend in the incidence of adenocarcinoma of the mammary gland in female mice: 0150 (controls), 3/50 (200 ppm), 3/50 (400 ppm). These incidences were within the historical control range for contemporary NTP studies (0/50 - 6/50: mean 1.4%) and it is considered that this finding is not related to propylene oxide exposure and may represent a stress-related effect.

The conclusion from this study is that there were carcinogenic responses associated with exposure to propylene oxide in both rats and mice. In rats there was an increased incidence of papillary adenoma of the nasal epithelium in animals exposed to 400 ppm but not at 200 ppm,

and in mice increased incidences of haemangioma and haemangiosarcoma in the nasal mucosa, as well as nasal cavity carcinoma and papilloma were observed at 400 ppm, but not at 200 ppm.

Inhalation: studies by Reuzel and Kuper

Reuzel and Kuper (1982) conducted an inhalation carcinogenicity study in which groups of 100 male and 100 female Wistar Cpb:WU rats were exposed, whole body, to propylene oxide vapour at 0, 30, 100 or 300 ppm (0, 70, 242 or 712 $mg \cdot m^{-3}$) for 6 hours/day, 5 days/week, for 123-124 weeks (this study is also reported as Kuper et al., 1988). Mortality was increased in both sexes at 300 ppm (55/100 males and 55/100 females) compared to controls (32/100 males and 30/100 females) and a similar tendency appeared for females at 100 ppm (43/100). A contributory factor to mortality amongst females was the occurrence of mammary gland tumours. Though most of these were benign, many females had to be killed because of the presence of large or several tumour masses which severely hampered movement, feeding or drinking, or as a result of tumour ulceration. Thus in females at least, part of the difference in mortality could be related to the occurrence of mammary tumours.

Increased incidence of degenerative changes (slight to moderate “nest”- like infolds) of the nasal mucosa was observed in all exposed groups. Hyperplasia of the nasal epithelium was observed at 300 ppm.

Nasal ameloblastic fibrosarcoma was seen in one low-dose male (1/61), and squamous-cell carcinoma occurred in one low-dose male (1/61) and one high-dose male (1/63). Nasal squamous-cell carcinoma is not uncommon in Wistar rats (historical control data indicate 0 to 3%). Squamous cell metaplasia was not observed. There were no tumours in the nasal turbinates, though there was a dose-related increase in focal hyperplasia. Four males (4/63) at 300 ppm had a carcinoma in the larynx/pharynx, trachea or lungs, whereas no such tumours were seen in controls or lower-dose males. However, pulmonary adenomas were observed in 2 control rats. Carcinoma in these parts of the respiratory tract is rare in Wistar rats and thus it seems justifiable to associate these malignant tumours with exposure to 300 ppm propylene oxide.

The number of females bearing benign tumours of the mammary glands (mainly fibroadenoma) was significantly increased at 300 ppm only, compared to controls. In addition, the mean number of mammary fibroadenomas per tumour-bearing animal was increased in females of all exposed groups, in a dose-related manner (1.3 at 0 ppm; 2.1 at 30 ppm; 2.2 at 100 ppm; 2.4 at 300 ppm). The incidence of malignant mammary tumours (tubulo-papillary carcinoma) in females was also increased in the exposed groups (6/71 at 30 ppm, 5/69 at 100 ppm, 8/70 at 300 ppm) compared to controls (3/69). However these incidences were within the range of historical controls at CIVO-TNO (0 to 15%) and therefore it is unlikely this finding can be attributed to an effect of propylene oxide. This effect was not seen in rats in the NTP study (NTP, 1985) or in the study by Lynch et al. (1984a - see below).

Overall, the results of this study provide evidence for the ability of propylene oxide to produce site of contact carcinogenicity of propylene oxide in rats.

The present study was revisited by the authors in view of a statistically significant, dose-related, increase in the incidence of brain tumours in a long-term carcinogenicity study of ethylene oxide in F344 rats (Snellings et al., 1981). Brain material in the present study was specifically re-examined for tumours. It was concluded there was no evidence that propylene oxide exposure induced brain tumours in Wistar rats (Reuzel and Kuper, 1984).

Inhalation: studies by Lynch et al.

The chronic inhalation toxicity and carcinogenicity of propylene oxide and ethylene oxide was evaluated in a 2-year study conducted by Lynch et al. (1984a). Groups of 80 male F344 rats were exposed whole-body to 0, 100, and 300 ppm propylene oxide for 7 hours/day, 5 days/week, for 104 weeks.

There was a dose-related increase in the incidence of complex epithelial hyperplasia in the nasal passages, and two adenomas occurred in the nasal passages in animals receiving 300 ppm. However, all rats in this study were affected by *Mycoplasma pulmonis* infection from about 16 months, and this intercurrent disease, alone or in combination with exposure to propylene oxide, undoubtedly affected survival of the rats and influenced the development of proliferative lesions in the nasal mucosa.

An increased incidence of phaeochromocytoma in both propylene oxide exposed groups was reported, but this was not dose-related, (8/78 in controls, 25/78 in the low-dose group, and 22/80 in the high-dose group). Adrenal tumours occur with a high background incidence in rats and are considered to have been associated with physiological stress of the animals.

An unusual finding in this study was an increased incidence of peritoneal mesothelioma in exposed animals (8/78 at 100 ppm and 9/80 at 300 ppm) compared to controls (3/78). However, these incidences were not statistically significant, and in view of their location relative to the route of administration of propylene oxide they are not considered to represent a consequence of exposure.

Overall, it is difficult to draw any firm conclusion from this study with regard to the carcinogenic action of propylene oxide. Although the findings may have been influenced by *Mycoplasma* infection, the changes in rat nasal epithelium are consistent with those seen in the NTP carcinogenicity study (NTP, 1985).

Oral

Dunkelberg (1982) administered 0, 15 or 60 $mg \cdot kg^{-1}$ propylene oxide by gavage, twice weekly, to groups of 50 female Sprague-Dawley rats for 150 weeks. One control group of 50 females received vehicle only, another was untreated. An exposure-free period occurred between weeks 79 and 82 due to an outbreak of pneumonia.

Survival of treated rats was comparable to controls. Treatment with propylene oxide resulted in a dose-related increased incidence of epithelial hyperplasia, papilloma, and squamous cell carcinoma of the forestomach. In the groups receiving 0, 15 and 60 $mg \cdot kg^{-1}$ the combined incidence of hyperkeratosis, hyperplasia, and papilloma was 0/50, 7/50, and 17/50 respectively, and of squamous cell carcinoma was 0/100, 2/50, and 19/50. At 60 $mg \cdot kg^{-1}$ one adenocarcinoma of the pylorus was also observed. No increase in the incidence of tumours at other sites was observed. A positive control group, receiving 30 $mg \cdot kg^{-1}$ beta-propiolactone had a high incidence of forestomach tumours (46/50). The conclusion from this study is that propylene oxide can produce neoplasms at the site of application.

Dermal

No studies have been reported on the carcinogenicity of propylene oxide following dermal application.

Subcutaneous

Dunkelberg (1979, 1981) injected propylene oxide in tricaprylin subcutaneously to groups of 100 female NMRI mice at doses of 0.1, 0.3, 1.0 or 2.5 mg (per mouse), once per week for 95 weeks. Controls were untreated (200) and receiving tricaprylin (200). Survival in all groups was comparable. However, propylene oxide induced local tumours, mostly fibrosarcoma. The incidences of fibrosarcoma and pleomorphic sarcoma were 0/200 (unexposed), 4/200 (vehicle control) 3/100 (at 0.1 mg), 2/100 (at 0.3 mg), 12/100 (at 1.0 mg), 15/100 (at 2.5 mg). Tumours other than local sarcomas occurred at similar incidences both in exposed and control animals and consequently were not considered to indicate an effect of treatment with propylene oxide. A positive control group of 100 NMRI mice receiving weekly injections of 2.5 μg benzo[α]pyrene for 95 weeks developed 81/100 local sarcomas.

In an overview of the carcinogenic action of alkylating agents, Walpole (1958) briefly reported the results of studies conducted on selected epoxides, including propylene oxide. When propylene oxide in arachis oil was injected subcutaneously, a total dose of 1,500 $mg \cdot kg^{-1}$ over 325 days caused injection-site sarcomas in 8/12 rats. Injection of propylene oxide in water, using the same regimen, produced sarcomas in 3/12 rats. However, no experimental details or associated observations were included in this report and consequently its value is very limited.

The presence of any unphysiological substance in the subcutis is likely to produce pathological changes, and it is known that hypertonic saline, concentrated aqueous glucose and also arachis oil have been reported to produce sarcomata by this route (Walpole, 1958). Consequently, the findings presented in these reports of subcutaneous injection are not considered to provide useful information on the carcinogenic activity of propylene oxide.

Other related studies (including *in vitro* transformation assays)

Groups of 50 male Sprague-Dawley rats were exposed to propylene oxide by inhalation for 6 hours/day, 5 days/week, for 30 days, and were then allowed to survive under observation until spontaneous death or termination due to condition (Sellakumar et al., 1987). Exposure to 1,740 ppm (4,124 $mg \cdot m^{-3}$) propylene oxide produced significant mortality after 8 exposures, and this dose was discontinued. The remaining doses were 435 and 870 ppm (1,031 and 2,062 $mg \cdot m^{-3}$).

The median life-span of the exposed animals did not differ significantly from air-breathing controls. At necropsy (times and exposures not specified), primary lesions were in the upper respiratory tract and limited to the anterior portion of the nasal cavity. The respiratory epithelium showed necrosis, ulceration and acute inflammation. Approximately 80% animals exposed to propylene oxide exhibited rhinitis, and approximately 10% and 25% exhibited squamous metaplasia at 435 and 870 ppm respectively. However, no nasal tumours were seen in any animals receiving propylene oxide.

Kolman and Dusinska (1995) demonstrated that propylene oxide induces transformation in Syrian hamster embryo (SHE) cells and mouse embryo fibroblasts (C3H/10T1/2). In both experiments, propylene oxide gave a dose-related increase in transformation frequency above that in vehicle control cultures following incubation under standardised conditions. The non-genotoxic tumour promoter, 12-0-tetradecanoylphorbol-13-acetate (TPA), also induced cell transformation in these tests and was found to potentiate the effect of propylene oxide in both systems.

4.1.2.8.2 Studies in humans

In extending an earlier investigation, Stocker and Thiess (1979) and Thiess et al. (1982) carried out a retrospective study of 602 employees in 8 German production plants. Mortality of the workers was compared with that in 3 sub-sets of the German population over the period 1928-80. Control data came from a styrene plant and from national statistics. Propylene oxide levels, measured by personal sampling from 1978 to 1980 were reported to be below a TWA of 100 ppm (237 $mg \cdot m^{-3}$) over a working shift of 12 hours. Higher levels were measured for brief periods. Overall, 56 deaths were observed in the observed group, compared with 71 to 76 based on the reference populations. The number of deaths that occurred in each cancer category was not significantly higher than expected. Although negative, the statistical power of this study is considered too low to provide adequate reassurance of a lack of carcinogenicity in humans.

4.1.2.8.3 Summary of carcinogenicity studies

There are no useful data on the potential carcinogenicity of propylene oxide in humans. Inhalation studies in animals have shown that propylene oxide produces a spectrum of upper respiratory tract changes, from inflammation and degeneration to metaplasia and neoplasia. In $B6C3F_1$ mice the development of squamous cell carcinoma and adenocarcinoma as well as haemangioma and haemangiosarcoma in the nasal cavity occurred following exposure to 400 ppm for 2 years. In similarly exposed F344/N rats, there was evidence of papillary adenoma development in the nasal cavity. A similar study in Wistar rats exposed to 300 ppm showed degenerative and hyperplastic changes of the nasal mucosal epithelium and a significant incidence of carcinoma at slightly more distal sites in the respiratory tract including the larynx, pharynx, trachea and lung. Repeated oral administration by gavage in rats induced carcinoma in the epithelium of the forestomach.

It is evident that carcinogenic responses to propylene oxide are primarily confined to the sites of initial contact. The relative contribution to the carcinogenic process made by irritation, consequential proliferative response, and genotoxicity is unclear based on current scientific knowledge. Due to its direct acting nature and its mutagenic activity, the carcinogenic hazard of propylene oxide expressed in animals is considered relevant to humans. In view of the potential genotoxic contribution to the carcinogenic mechanism of propylene oxide, it is not possible to establish an exposure level at which there would be no increased risk of carcinogenicity.

Classification according to Annex I of Directive 67/548/EC, see Section 1.

4.1.2.9 Toxicity to reproduction

4.1.2.9.1 Studies in animals

Reproductive toxicity studies have been conducted in mice, rats and rabbits.

Fertility

In a well-conducted two-generation reproduction study (Hayes et al., 1985; 1988), groups of 30 male and 30 female F344 rats were exposed to 0, 30, 100, 300 ppm (0, 70, 240 and 710 $mg \cdot m^{-3}$) propylene oxide vapour, whole body, for 6 hours/day, 5 days/week for 14 weeks prior to mating. Thereafter, during mating, gestation and lactation, exposure periods were increased to 7 days/week. Nevertheless, dams were not exposed from day 21 of pregnancy through day four post-partum.

After weaning, 30 F_1 pups/sex/group were similarly exposed to propylene oxide for 17 weeks and then mated to produce F_2. Reproductive parameters examined included fertility, litter size, neonatal growth and survival. All adults and weanlings were examined for gross and microscopic lesions.

No deaths occurred, and there were no treatment-related alterations in demeanour or physical appearance in any of the animals during the pre-mating periods. Toxicity was evident as reduced body weight gain in F_0 (8%) and F_1 (16%) rats at 300 ppm, however there was no evidence of treatment-related adverse effect on fertility in F_0 or F_1 matings. Growth and survival of F_1 and F_2 offspring was not adversely affected by exposure of either generation of parents at any dose. Mating and conception were not significantly affected in either F_0 or F_1 matings. Litter size was not adversely affected.

Detailed pathology examination of adults and weanlings revealed no changes considered attributable to propylene oxide exposure. The results indicate that inhalation exposure to levels up to 300 ppm over two generations did not produce any adverse effect on reproductive function.

Other studies

Hardin et al. (1983b) looked for effects of propylene oxide on sperm head morphology. Groups of 10 male C3H-He mice were exposed, whole-body, to 300 ppm, 7 hours/day for 5 days, and were killed at 1, 3, 5, 7 and 9 weeks post-exposure to evaluate sperm head morphology. A group of 10 control mice were exposed to filtered air. There were no significant differences between controls and exposed mice regarding the frequency of abnormal sperm.

In spite of the absence of adverse effects on fertility in rats following inhalation exposure to propylene oxide, the possibility of testicular toxicity in exposed rats was investigated recently by Omura et al. (1994). They administered 0, 23, 47, 93 or 186 $mg \cdot kg^{-1}$ propylene oxide by intraperitoneal injection to groups of eight or nine Wistar rats for up to three days/week for six weeks. The top dose resulted in the deaths of 3 animals; testicular atrophy was observed in these animals at necropsy. At this dose, epididymal weight and sperm count (in the body plus tail of the epididymis) decreased, and there was a significant increase in immature, teratic sperm and sperm without a head. Testicular weight and sperm count in the testis and the head of the epididymis were not changed.

At 93 and 47 $mg \cdot kg^{-1}$ there were no effects on epididymal or testicular weights. Small increases in immature sperm and sperm without a head only were observed. There were no histopathological changes in the seminiferous tubules, Leydig cells or the interstitium of the testes and no effects on serum testosterone levels. Given that the top dose caused deaths and that the findings at lower dose levels were limited to small increases in abnormal sperm, these results suggest that propylene oxide has no specific deleterious effect on the male rat reproductive system.

In a limited study provided by Dow Chemical Co. (Environmental Health Research and Testing Inc, 1982; summarised in Lynch et al., 1984c), male cynomolgus monkeys were exposed for 24 months to 0, 100 or 300 ppm (237 or 711 $mg \cdot m^{-3}$) propylene oxide for 7 hours/day, 5 days/week. A total of 7 animals of these animals were examined at necropsy for effects of treatment on sperm characteristics. No effect on the frequency of sperm head abnormality was observed in the exposed animals. In both exposure groups mean values for sperm motility and sperm count were reduced to approximately 80% of control values. However, due to the small number of samples and the absence of a consistent dose-relationship these changes are of doubtful toxicological significance.

Antonova et al. (1981) claimed that male rats exposed to a single oral dose of 520 $mg \cdot kg^{-1}$ showed reduced sperm motility and damage to primary spermatocytes. When these males were mated with

untreated females between 2 and 10 weeks after exposure, 50% of males appeared “infertile”. However, the doses used in these studies were close to the oral LD_{50} range for propylene oxide and could have produced significant generalised toxicity, and therefore no definite conclusion can be reached from these results about the specific reproductive toxicity of propylene oxide.

Development

The National Institute for Occupational Safety and Health (NIOSH) commissioned an inhalation reproductive toxicity study of propylene oxide in rats and rabbits (Hackett et al., 1982; Hardin et al., 1983a) as part of an investigation of ethylene oxide, propylene oxide, butylene oxide and styrene oxide. Study groups consisted of 32-45 female Sprague-Dawley rats and 23-30 female New Zealand White rabbits, exposed in a dynamic inhalation chamber to 500 ppm (1,188 $mg \cdot m^{-3}$) propylene oxide vapour. Rats were exposed daily, for 7 hours/day in three time-schedules, as follows: Group 2 animals - on days 7-16 of gestation; Group 3 animals - on days 1-16 of gestation; Group 4 animals - on 5 days/week for 3 weeks prior to mating, and daily thereafter through days 1-16 of gestation. All rats were killed and examined on day 21 of gestation. Rabbits were exposed daily on days 7-19 of gestation (Group 2), or on days 1-19 of gestation (Group 3). All rabbits were killed and examined on day 30 of gestation. For both species, control groups (Group 1) were exposed to filtered air.

All rat and rabbit foetuses were examined for external defects, then in 50% the heads were examined by thick serial slice technique. All foetuses were examined for visceral abnormality by open dissection, and were then prepared for skeletal examination by alizarin-red staining.

There was no treatment-related maternal mortality in either species. In rabbits, there were no treatment-related effects on maternal body weight gain, reproductive capacity or developmental toxicity. In rats, body weight gain was significantly reduced in relation to exposure, the most marked effect being observed in Group 4, where weight gain at gestation day 21 compared to study day 1 was 89%, compared to 106% in controls. Furthermore, in Group 4 only, the mean number of corpora lutea (13.8) was reduced compared to controls (15.4), and as a consequence of this the numbers of implantations and surviving live foetuses were correspondingly decreased. Detailed foetal examination revealed no significant teratologic finding. Nevertheless, in Group 4, an increase in the incidence of minor anomalies e.g. “wavy ribs” and reduced ossification of vertebrae and ribs, indicated some degree of toxicity to foetuses exposed in utero to propylene oxide. This is considered to be an indirect consequence of maternal toxicity resulting from the exposure.

Harris et al. (1989) also investigated the potential developmental toxicity of propylene oxide by inhalation. Groups of 25 female F344 rats were exposed, whole-body, to 0, 100, 300, and 500 ppm (0, 237, 711 and 1,188 $mg \cdot m^{-3}$) for 6 hours/day, on gestation days 6-15 inclusive. Caesarean sections were conducted on day 20 of gestation and the foetuses were removed and examined. All foetuses were examined externally, and 50% were placed in Bouin's fixative for subsequent internal morphological examination by thick serial slice technique. The remaining 50% were eviscerated and prepared for skeletal examination by alizarin-red staining.

No maternal deaths occurred, but mean maternal body weight gain was significantly lower over the period of exposure in darns receiving 500 ppm propylene oxide, compared to controls. Even so, no evidence of embryotoxicity or fetotoxicity was seen. Mean numbers of corpora lutea, implantations, viable foetuses, and post-implantation losses, were all comparable among the treatment groups and controls.

The incidence of foetal malformations was minimal and showed no relationship to exposure.

Among the developmental variations that were seen, increased cervical rib variation provided some indication of foetal toxicity but generally the findings were not considered toxicologically significant or attributable to propylene oxide exposure.

In a series of poorly reported experiments (Antonova et al., 1981), pregnant rats were administered 260 $mg \cdot kg^{-1}$ propylene oxide by gavage during the first two weeks of gestation. It was claimed that treatment produced embryotoxicity and lower offspring body weight compared to controls. No information on maternal toxicity was provided. No conclusions about the toxicity of propylene oxide can be drawn from this poorly reported study.

4.1.2.9.2 Studies in humans

No data are available.

4.1.2.9.3 Summary of toxicity to reproduction

No data are available on the potential reproductive effects of propylene oxide in humans. The reproductive effects of propylene oxide have been reasonably well studied in animals.

In a well conducted inhalation 2-generation fertility study in rats, no evidence for any effects on fertility were observed. The highest concentration tested in this study was 300 ppm (1,188 $mg \cdot m^{-3}$), a concentration at which parental toxicity was observed. A number of studies have examined the effects of propylene oxide on various sperm parameters but toxicologically significant effects were only produced atant nearly lethal concentrations. The developmental toxicity of propylene oxide has been investigated in rats and rabbits exposed by inhalation to concentrations of up to 500 ppm (1,185 $mg \cdot m^{-3}$), an exposure level causing maternal toxicity in rats. Overall, no evidence for developmental toxicity was observed at non-matemally toxic dose levels suggesting that propylene oxide is not a specific developmental toxicant.

4.1.3 Risk characterisation

4.1.3.1 General aspects

There are few data available on the toxicokinetics of propylene oxide in humans. However, based on the information that is available, propylene oxide and/or its metabolites are readily absorbed through the gastrointestinal and respiratory tracts and widely distributed to the major organs. No data are available for dermal absorption but acute toxicity data indicate the potential for dermal absorption of the liquid. No conclusions can be drawn regarding the potential for dermal absorption of the vapour. Studies in animals have suggested that clearance from the blood may be limited at higher levels of exposure, indicating saturation of metabolism. Metabolism involves conjugation with glutathione or hydrolysis by epoxide hydrolase. Excretion of propylene oxide and its metabolites is expected to be primarily via urine and expired air. Propylene oxide binds to, or reacts with, tissue proteins and nucleic acids *in vitro* and *in vivo.*

Haemoglobin adducts have been quantified in animals and humans exposed to propylene oxide. Although DNA binding in humans has not been studied, binding as assessed by adduct formation has been observed in several animal tissues following inhalation exposure, including nasal mucosa, trachea, lung, liver, kidney, brain and testes. Alkylation of cytosine (with subsequent deamination to a modified uracil) has also been reported.

There is only very limited information on acute toxicity in humans which does not contribute much to the picture available from studies in animals. In studies in rodents, propylene oxide is harmful by the inhalation, oral and dermal routes of administration. Liquid propylene oxide is irritating to the skin, and is probably irritating to the eyes and respiratory tract in view of the fact that propylene oxide vapours has caused irritation of the eyes and upper respiratory tract (but not the skin) in humans. Eye irritation has been confirmed by observations in mice, rats and guinea-pigs following exposure to high concentrations of 2,000 ppm and above.

A small number of dermatitis cases in workers provides some limited evidence that propylene oxide may cause skin sensitisation. There have been no conventional skin sensitisation studies with propylene oxide in animals. In the only available study, the result was negative. Overall, although the evidence is unclear, propylene oxide has demonstrated some potential to cause skin sensitisation and given the alkylating properties of the substance, it is plausible that it could bind to tissue proteins to produce a hapten and hence elicit an immunological response. This substance has not been adequately tested for skin sensitisation and consequently the risk assessment does not evaluate the risks to any human population for this endpoint.

There are no reports of propylene oxide causing respiratory sensitisation and it is not possible to draw any conclusions regarding this endpoint.

There are no useful data describing the effects of repeated exposure to propylene oxide in humans. In rats and mice, repeated inhalation exposure to propylene oxide for two years produces chronic irritation of the nasal epithelium, with such effects being only marginal in nature at 30 ppm. However, concentrations of 100 ppm and above produce pronounced epithelial damage. In a 4-week study in rats, small and reversible increases in nasal epithelium irritation occurred at 525 ppm. There is some evidence for neurotoxicity in rats at the relatively high exposure level of 1,500 ppm (7 weeks exposure). No signs of neurotoxicity were observed in rats exposed to 300 ppm for 24 weeks. Based on a 2-year study in rats, a NOEL of 30 ppm (71 $mg \cdot m^{-3}$) can be identified for systemic toxicity via inhalation exposure.

Repeated oral administration caused reduced body weight gain and gastric irritation, seen microscopically as reactive changes in the squamous epithelium of the forestomach. No data are available on the toxicity of propylene oxide following repeated dermal exposure. The absence of significant toxic sequalac distant from the site of application following inhalation or oral administration suggests that concerns about target organ toxicity can be focused almost exclusively on tissues at the sites of initial contact.

No conclusions about the mutagenicity or propylene oxide in humans can be drawn from the available human studies. The ability of propylene oxide to react directly with nucleic acids and proteins *in vitro* and *in vivo* has been demonstrated. Binding of propylene oxide or its metabolites to DNA has been reported in nasal mucosa, trachea, lung, liver, kidney and brain of rodents exposed by the inhalation route.

In *in vitro* genotoxicity studies, propylene oxide exerts a clear, direct-acting positive effect in a wide variety of standard test systems, causing mutations in bacteria, fungi, and mammalian cells in the absence of erogenous metabolic activation. *In vivo*, in an unconventional study in monkeys, no evidence for propylene oxide induced chromosomal aberrations or SCE was obtained following inhalation exposure for 2 years to up to 300 ppm. Negative results were obtained in mouse bone marrow micronucleus tests following oral administrations. In contrast, positive results were obtained for this endpoint following intraperitoneal administration. Positive results were also obtained for chromosomal aberrations and SCE in mouse bone marrow cells following intraperitoneal dosing. Therefore, it is clear that propylene oxide is a somatic cell mutagen *in vivo*. The general toxicological profile for propylene oxide suggests that its potential to produce genetic damage might be expressed only at sites of initial contact. In relation to the potential of propylene oxide to induce heritable mutations in germ cells, dominant lethal tests involving inhalation exposure of rats and oral exposure of mice have given negative results. There is no additional evidence that propylene oxide causes heritable mutations in germ cells. However, studies of DNA adduct formation indicate that very low levels of DNA adducts were observed in the testes following repeated inhalation exposure to 500 ppm propylene oxide vapour. There are many uncertainties surrounding this finding both in terms of the biological significance of the adduct formed and the level of adduct formation in relation to background levels but overall it would be prudent to assume that propylene oxide has the potential to reach the germ cells. Given that propylene oxide is a direct-acting mutagen then the possibility that it might express this activity within the germ cells cannot be discounted.

There are no useful data on the potential carcinogenicity of propylene oxide in humans. Inhalation studies in animals have shown that propylene oxide produces a spectrum of upper respiratory tract changes, from inflammation and degeneration to metaplasia and neoplasia. In $B6C3F_1$ mice the development of squamous cell carcinoma and adenocarcinoma as well as haemangioma and haemangiosarcoma in the nasal cavity occurred following exposure to 400 ppm for 2 years. In similarly exposed F344/N rats, there was evidence of papillary adenoma development in the nasal cavity. A similar study in Wistar rats exposed to 300 ppm showed degenerative and hyperplastic changes of the nasal mucosal epithelium and a significant incidence of carcinoma at slightly more distal sites in the respiratory tract including the larynx, pharynx, trachea and lung. Repeated oral administration by gavage in rats induced carcinoma in the epithelium of the forestomach.

It is evident that carcinogenic responses to propylene oxide are primarily confined to the sites of initial contact. The relative contribution to the carcinogenic process made by irritation, consequential proliferative response, and genotoxicity is unclear based on current scientific knowledge. Due to its direct acting nature and its mutagenic activity, the carcinogenic hazard of propylene oxide expressed in animals is considered relevant to humans. In view of the potential

genotoxic contribution to the carcinogenic mechanism of propylene oxide, it is not possible to establish an exposure level at which there would be no increased risk of carcinogenicity.

No data are available on the potential for reproductive effects of propylene oxide in humans. The reproductive effects of propylene oxide have been reasonably well studied in animals. In a well conducted inhalation 2-generation fertility study in rats, no evidence for any effects on fertility were observed. The highest concentration tested in this study was 300 ppm (1,188 $mg \cdot m^{-3}$), a concentration at which parental toxicity was observed. The developmental toxicity of propylene oxide has been investigated in rats and rabbits exposed by inhalation to concentrations of up to 500 ppm (1,185 $mg \cdot m^{-3}$), a concentration causing maternal toxicity in the rat. Overall, no consistent evidence for developmental toxicity was observed at non-matemally toxic dose-levels suggesting that propylene oxide is not a specific developmental toxicant.

Overall, the critical health concerns are for mutagenicity and carcinogenicity. In addition, there are concerns for repeat-dose toxicity. The position regarding skin sensitisation is unclear. With regard to local effects, inhalation exposure to propylene oxide produces chronic inflammation of the nasal epithelium in rats and mice; at 30 ppm such effects are only marginal in nature, whereas concentrations of 100 ppm and above produce pronounced nasal epithelial damage. It is possible that the rat is particularly susceptible to these local effects in view of the morphological features of the rat nasal turbinates leading to air flow patterns which may enhance localised deposition in the upper respiratory tract in this species. The absence of significant toxic sequelae distant from the site of application following inhalation or oral administration suggests that concerns about target organ toxicity, can be focused almost exclusively on tissues at the sites of initial contact.

Propylene oxide is clearly a direct-acting mutagen *in vitro* and animal data indicate that propylene oxide is capable of producing somatic cell mutation *in vivo*, particularly in the tissues at the site of contact. In relation to the potential of propylene oxide to cause germ cell mutation, negative results were obtained in dominant lethal studies by relevant routes of exposure. There are no other data relating to the ability of propylene oxide to cause heritable mutations in germ cells; toxicokinetic data indicate that propylene oxide can reach the testes following a physiological route of administration. Given that propylene oxide is a direct-acting mutagen then the possibility that it might express this activity within the germ cells cannot be discounted.

Propylene oxide is a respiratory tract carcinogen in animals and it is presumed that the mechanism of carcinogenesis involved is relevant to human health. It is possible that inflammation is a key influence in the production of cancer, and in this regard it is noteworthy that typical occupational exposures are an order of magnitude below the levels at which respiratory tract irritation is observed in rats. It isn't known whether the carcinogenic mechanism can arise in the absence of chronic inflammation. It is not currently possible to determine a threshold for mutagenic events and so it is not possible to identify a threshold for carcinogenicity. Therefore, it is not possible to identify a safe level of exposure at which there would be no risk to human health.

4.1.3.2 Workers

Occupational exposure to propylene oxide occurs during its manufacture and use as a chemical intermediate. It is therefore always used in closed plant with exposures arising during tasks where the system is breached. These tasks include sampling, tanker filling and emptying, and unplanned and periodic maintenance. This industry employs and develops measures to reduce exposure to as low a level as reasonably practicable, such as the use of enclosed sampling points and dry break coupling systems for tanker filling and emptying. Occupational exposure data

received from industry indicate that exposure can be controlled to less than 3 ppm 8-hour TWA, and that the majority of these exposures would be less than 1 ppm 8-hour TWA. Short-term exposures of between 0.06 and 41.7 ppm have been reported during uncoupling. These exposure data, and that experienced during sampling were modelled using EASE. Calculated exposures from EASE were 33 to 67 ppm 15-minute TWA for uncoupling and greater than 33 ppm 15-minute TWA for sampling.

4.1.3.2.1 Inhalation exposure

In relation to inhalation exposure the risks to human health which need to be addressed are those related to the effects of concern of single and repeat exposure, mutagenicity and carcinogenicity.

With respect to single and repeated exposure, effects are restricted to the site-of-contact toxicity. Hence, in order to conduct a risk assessment, workplace inhalation exposures can be compared directly with information from animal inhalation studies. It is not necessary to calculate systemic body-burdens.

For single exposures, the 4-hour LC_{50} value in rats is >1,740 ppm (4,124 $mg \cdot m^{-3}$) with no mortalities or clinical signs of toxicity developing after 4-hour exposures to 1,277 ppm. The highest single exposure levels to which workers may be exposed are 33-67 ppm for 15-min TWAs. Comparison of the concentration producing no clinical signs of toxicity and the maximum short-term exposure level shows the margin of safety to be 19. There is also the potential for eye irritation following single exposure to the vapour. However, the animal data indicate that this occurs following very high exposures of $\geq$2,000 ppm which is 2 orders of magnitude greater than exposures encountered in the workplace. Hence, there are no grounds for concern for acute toxicity following single peak exposures to propylene oxide.

For repeat exposures, minimal nasal epithelial changes occur in rats at 30 ppm, with more evident changes at 100 ppm. Hence, the margin of safety between the "minimal" LOAEL of 30 ppm for nasal epithelial effects in the rat and the majority of current occupational exposures of generally <1 ppm as an 8-hour TWA is $\geq$30. Some scenarios may result in exposures of up to 3 ppm and hence the margin of safety, in such situations is $\geq$10. This suggests that there would be no grounds for concern regarding respiratory tract inflammation in workers particularly in view of the anatomical differences in the upper respiratory tract of the rat and human.

For both mutagenicity and carcinogenicity it is not possible to identify a threshold level of exposure below which there would be no risk to human health and it is not possible to derive a toxicologically valid margin of safety. Therefore, the level of risk to workers under current occupational exposure conditions is uncertain and exposure to propylene oxide should be controlled to as low a level as is reasonably practical.

Table 4.11 Summary of inhalation exposure data.

Key health effect	Human exposure	Quantitative animal toxicity data	MOS	Conclusions for risks to human health
Acute toxicity	67 ppm	systemic NOAEL 1,277 ppm	19	ii
Repeated dose toxicity	<1 3	systemic LOAEL 30 ppm	$\geq$30 $\geq$10	ii

4.1.3.2.2 Dermal exposure

In relation to skin contact, the risks which need to be addressed are irritation, skin sensitisation and genotoxicity at the site of contact.

With respect to skin irritation it is not possible to identify a threshold level of exposure below which there would be no risk to human health and therefore it is not possible to conduct a quantitative risk assessment. However, occupational hygiene data suggest the potential for skin exposure is extremely low and infrequent, and furthermore, is attenuated by, the wearing of personal protective equipment which is standard practice in the chemical industry. Overall, there is low concern.

The potential risk for skin sensitisation from prolyene oxide cannot be assessed since this endpoint has not been adequately tested.

With respect to genotoxicity upon dermal exposure it is not possible to identify a threshold level of exposure below which there would be no risk to human health and therefore it is not possible to derive a toxicologically valid margin safety. Therefore, the level of risk to workers under current occupational exposure conditions is uncertain and, hence exposure to propylene oxide should be controlled to as low a level as is reasonably practical.

Provided personal protective equipment is worn, there is considered to be a low risk for the development of irritant, sensitising and mutagenic effects on the skin.

4.1.3.2.3 Oral exposure

There is no indication of any potential for ingestion; hence it is concluded there is no risk of adverse health effects to workers.

4.1.3.2.4 Summary of risk characterisation for workers

Propylene oxide is currently classified as a Category 2 Carcinogen and is labelled R45 – “May cause cancer”. Hence, it is already subject to the stringent requirements of the Carcinogens Directive 90/394/EEC and its amendments, and therefore should be currently subject to sufficient and appropriate risk control measures as long as industry continues to adopt best practice and continues to take steps to further reduce exposures. To this end, industry's approach to the control of propylene oxide is to employ and develop measures that reduce exposure to as low a level as is reasonably practicable.

This includes use of:

a. enclosed sampling systems,
b. dry break coupling systems for filling and emptying road and rail tankers,
c. magnetic delivery pumps,
d. systems for purging and testing process lines and vessels prior to breaching,
e. respiratory protective equipment where the potential for exposure exists,
f. monitoring and control of fugitive emissions.

As a substance for which no thresholds have been identified below which there would be no cause for concern for human health for the endpoints of carcinogenicity and mutagenicity,

conclusion (iiia) is reached for workers for these endpoints. This conclusion is dependent upon the industry continuing to implement new procedures to reduce exposure when possible.

Any indication that this is not occurring would prompt a review of the risk assessment and might result in a revision of the conclusion to allow for the development of a risk reduction strategy.

Conclusion (iiia) Risks cannot be excluded for all other exposure scenarios, as the substance is identified as a non-threshold carcinogen. The adequacy of existing controls and the feasibility and practicability of further specific measures should be considered. However, the risk assessment indicates that risks are already low. This should be taken into account when considering the adequacy of existing controls and the feasibility and practicability of further specific risk reduction measures.

It is not possible to characterise the risk to workers for skin sensitisation (see Section 4.1.2.5).

4.1.3.3 Consumers

Conclusion (iiia) is reached because it is not currently possible to determine a threshold for mutagenic events or for carcinogenic events. Therefore, it is not possible to identify any level of exposure at which there would be no risk to human health. It is, however, noted that exposures are negligible and therefore the degree of risk is anticipated to be very low.

Conclusion (iiia) Risks cannot be excluded for all other exposure scenarios, as the substance is identified as a non-threshold carcinogen. The adequacy of existing controls and the feasibility and practicability of further specific measures should be considered. However, the risk assessment indicates that risks are already low. This should be taken into account when considering the adequacy of existing controls and the feasibility and practicability of further specific risk reduction measures.

4.1.3.4 Humans exposed via the environment

The figures in Section 4.1.1.3 give a total uptake of 3.9 µg/kg bw/day for the local scenario and 3 ng/kg/day for the regional scenario. The largest single contribution in the local exposure scenario comes from inhalation.

With respect to inhalation exposure a risk characterisation is presented for repeated dose effects (**Table 4.12**)**.** None is generated for acute effects (see Section 4.1.3.2) since this is not considered an endpoint of concern for those exposed via the environment.

Table 4.12 Risk characterisation for repeated dose effects via inhalation

	Exposure/ ppm	MOS (based on LOAEL(30ppm))	Conclusion
Local	7% 10^{-3}	4,253	ii
Regional	2% 10^{-6}	$1.5 \cdot 10^{7}$	ii

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Conclusion (iiia) is reached for mutagenicity and carcinogenicity because it is not currently possible to determine a threshold for these events. Therefore, it is not possible to identify any level of exposure at which there would be no risk to human health. Risk reduction measures which are already being applied should be taken into account. It is, however, noted that exposures in local and regional scenarios are extremely low and therefore that the degree of risk is anticipated to be very low.

Conclusion (iiia) Risks cannot be excluded for all other exposure scenarios, as the substance is identified as a non-threshold carcinogen. The adequacy of existing controls and the feasibility and practicability of further specific measures should be considered. However, the risk assessment indicates that risks are already low. This should be taken into account when considering the adequacy of existing controls and the feasibility and practicability of further specific risk reduction measures.

4.1.3.5 Combined exposure

A worst-case combined exposure scenario is composed of exposure in the workplace and to the highest local environmental exposure levels. No quantitative estimate of total exposure from inhalation, dermal and oral routes, is possible. For the main endpoints of concern, mutagenicity and carcinogenicity, no threshold of exposure below which there would be no cause for concern to human health can be identified. However, exposure is very low. In both cases of worker and exposure via the environment **conclusion (iiia)** is appropriate.

Conclusion (iiia) Risks cannot be excluded for all other exposure scenarios, as the substance is identified as a non-threshold carcinogen. The adequacy of existing controls and the feasibility and practicability of further specific measures should be considered. However, the risk assessment indicates that risks are already low. This should be taken into account when considering the adequacy of existing controls and the feasibility and practicability of further specific risk reduction measures.

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

4.2.1 Risk characterisation

The physico-chemical properties of propylene oxide are well known. There is a general consensus over the values of particular parameters although validation can be difficult to obtain.
Propylene oxide is a highly flammable gas that has a large vapour pressure at ordinary temperature. It is also explosive over a wide range of concentrations when mixed with air. Propylene oxide is a defined substance under COMAH, the level of control under the regulations being related to tonnage. Current controls are considered sufficient and therefore **conclusion (ii)** is reached.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

5 RESULTS

Propylene oxide is produced in large quantities, 1,445,000 tonnes annually in the EU (based on data from 1995). The vast majority of this is used to make other chemicals and polymers.

5.1 ENVIRONMENT

Local releases of propylene oxide to the environment may occur during production and use. These releases have been quantified in the assessment and used to calculate PECs for various environmental compartments.

The PEC/PNEC ratio is <1 for the aquatic (including sediment) and terrestrial compartments from local sources for production and use. Although a PNEC could not be derived, no risks are expected for sewage treatment plant or the atmosphere. An assessment of secondary poisoning is unnecessary based on the properties of the substance.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

5.2 HUMAN HEALTH

5.2.1 Human health (toxicity)

Whilst a range of health hazards is associated with exposure to propylene oxide, the main issues are those of skin sensitisation, repeated-dose toxicity, genotoxicity, and carcinogenicity. Generally, there is very limited information from humans exposed to propylene oxide.

The picture regarding skin sensitisation is not clear. Evidence of contact dermatitis in workers is available in a few case reports. However, a split-adjuvant skin sensitisation test in guinea pigs was negative. Although the evidence is unclear, propylene oxide has demonstrated some potential to cause skin sensitisation and given the alkylating properties of the substance, it is plausible that it could bind to tissue proteins to produce a hapten and hence elicit an immunological response. This substance has not been adequately tested for skin sensitisation and consequently the risk assessment does not evaluate the risks to any human population for this endpoint. Given the high level of control currently exercised on worker exposures and the negligible level of dermal exposure to people exposed via the environment, it is proposed that no further testing on this endpoint is required at this time.

Propylene oxide produces chronic inflammation of the nasal epithelium in rats and mice. Effects at 30 ppm were marginal. For genotoxic effects, propylene oxide is a direct acting mutagen and is mutagenic *in vivo* to somatic cells. In relation to potential germ cell effects, dominant lethal tests involving inhalation exposure of rats and oral administration of propylene oxide to mice gave negative results. There are no other data relating to the ability of propylene oxide to cause heritable mutations in germ cells; toxicokinetic data indicate that propylene oxide can reach the testes following a physiological route of administration. Given that propylene oxide is a direct acting mutagen then the possibility that it might express this activity within the germ cells cannot be discounted.

Propylene oxide is a respiratory tract carcinogen in animals and it is presumed that the mechanism of carcinogenesis involved is relevant to human health. Propylene oxide also produces inflammation of the respiratory tract with a minimal effect level of 30 ppm. It is possible that inflammation is a key influence in the production of cancer, and in this regard it is noteworthy that typical occupational exposures are an order of magnitude below the levels at which respiratory tract inflammation is observed. It is not known whether the carcinogenic mechanism can arise in the absence of chronic inflammation. Propylene oxide is an *in vivo* somatic cell mutagen, and therefore the possibility that substance-related genetic damage is intimately involved in the mechanism of carcinogenesis cannot be discounted. It is not currently possible to determine a threshold for mutagenic events and so it is not possible to identify a threshold for carcinogenicity. Therefore, it is not possible to identify an exposure level at which there would be no risk to human health, hence, whether or not contemporary occupational exposure levels might confer a risk to workers is uncertain.

5.2.1.1 Workers

Exposure to propylene oxide by any route represents a cause for concern to human health and must be properly controlled. The available information on occupational exposure indicates that exposure to propylene oxide is stringently controlled, to the limits of technology that is currently available. Within the EU there are different approaches to the control of genotoxic substances in the workplace. In the UK, a maximum exposure limit (MEL) is in place of 5 ppm (12.5 $mg \cdot m^{-3}$; 8-hour TWA) but this carries a duty to reduce exposure below that level as far as reasonably practicable. The result of the occupational assessment is that **conclusion (iiia)** applies.

As a substance for which no thresholds have been identified below which there would be no cause for concern for human health for the endpoints of carcinogenicity and mutagenicity, **conclusion (iiia)** is reached for workers for these endpoints. This conclusion is dependent upon the industry continuing to implement new procedures to reduce exposure when possible.

Any indication that this is not occurring would prompt a review of the risk assessment and might result in a revision of the conclusion to allow for the development of a risk reduction strategy.

Conclusion (iiia) Risks cannot be excluded for all other exposure scenarios, as the substance is identified as a non-threshold carcinogen. The adequacy of existing controls and the feasibility and practicability of further specific measures should be considered. However, the risk assessment indicates that risks are already low. This should be taken into account when considering the adequacy of existing controls and the feasibility and practicability of further specific risk reduction measures.

It is not possible to characterise the risk to workers for skin sensitisation therefore no formal conclusion has been reached.

5.2.1.2 Consumers

Conclusion (iiia) is reached because it is not currently possible to determine a threshold for mutagenic or carcinogenic events. As a result, it is not possible to identify any level of exposure at which there would be no risk to human health. It is, however, noted that due to the half-life of 30-40 h and use in consumer products at very low concentrations, exposures to consumers are extremely low and therefore that the degree of risk is anticipated to be negligible.

Conclusion (iiia) Risks cannot be excluded for all other exposure scenarios, as the substance is identified as a non-threshold carcinogen. The adequacy of existing controls and the feasibility and practicability of further specific measures should be considered. However, the risk assessment indicates that risks are already low. This should be taken into account when considering the adequacy of existing controls and the feasibility and practicability of further specific risk reduction measures.

5.2.1.3 Humans exposed via the environment

Humans are exposed indirectly via the environment via several sources, the principal source being drinking water. As it is not currently possible to determine a threshold for mutagenic events or carcinogenic events, it is not possible to identify any level of exposure at which there would be no risk to human health. It is, however, noted that exposures in local and regional scenarios are extremely low and that the degree of risk is anticipated to be very low. Therefore, **conclusion (iiia)** applies.

Conclusion (iiia) Risks cannot be excluded for all other exposure scenarios, as the substance is identified as a non-threshold carcinogen. The adequacy of existing controls and the feasibility and practicability of further specific measures should be considered. However, the risk assessment indicates that risks are already low. This should be taken into account when considering the adequacy of existing controls and the feasibility and practicability of further specific risk reduction measures.

5.2.1.4 Combined exposure

A worst-case combined exposure scenario is composed of exposure in the workplace and to the highest local environmental exposure levels. No quantitative estimate of total exposure from inhalation, dermal and oral routes, is possible. For the main endpoints of concern, mutagenicity and carcinogenicity, no threshold of exposure below which there would be no cause for concern to human health can be identified. However, exposure is very low. In both cases of worker and exposure via the environment **conclusion (iiia)** is appropriate.

Conclusion (iiia) Risks cannot be excluded for all other exposure scenarios, as the substance is identified as a non-threshold carcinogen. The adequacy of existing controls and the feasibility and practicability of further specific measures should be considered. However, the risk assessment indicates that risks are already low. This should be taken into account when considering the adequacy of existing controls and the feasibility and practicability of further specific risk reduction measures.

5.2.2 Human health (risks from physico-chemical properties)

There are hazards associated with the extremely low flash point, high vapour pressure and flammmability of this substance. However, during the manufacture, storage and use of this substance the stringent control measures used ensure that risks arising from the physicochemical properties are small.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

6 REFERENCES

ACGIH (1989). Documentation of the Threshold Limit Values and Biological Exposure Indices, Pub. American Conference of Government Industrial Hygienists, Inc., Cincinnati, OH.

Agnihotri VP (1971). Effects of certain fungitoxicants on the viability and pathogenicity of sclerotia of *Waitea circinata*. Phytopath., 70, 71-80.

Alguire DE (1976). Regulation of ethylene oxide and propylene oxide in food processing and packaging applications. Food Prod. Develop., 10, 52-53.

Alphei J and Scheu S (1993). Effects of biocidal treatments on biological and nutritional properties of a mull-structured woodland soil. Geoderma, 56, 435-448.

American Chemical Society (1952). Monograph series: Glycols, Eds Curme GO Jr, Johnston F, Reinhold Publishing Corporation, New York.

Amoore JE and Hautala E (1983). Odour as an aid to chemical safety: Odour thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution, J. Appl. Toxicol., 3(6), 272-290.

Annex V to Commission Directive 92/69/EEC of 31 July 1992 adapting to technical progress for the seventeenth time Council Directive 67/548/EEC on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances as published in the Official Journal of the European Communities, 29 December 1992, Volume 35, L383A.

Ansari GAS, Singh SV, Gan JG and Awasthi YC (1987). Human erythrocyte glutathione s-transferase: a possible marker of chemical exposure. Toxicology Letters, 37, 57-62.

Antonova VI, Zommer EA, Kuznetsova AD and Petrova NA (1981). Toxicology of propylene oxide and regulation of its level in water. Gig. Sanit., 7, 76-79.

Aranyi C, O'Shea WJ, Graham JA and Miller JA (1986). The effects of inhalation of organic chemical air contaminanats on murine lung host defenses. Fundam Appl Toxicol, 6, 713-720.

ARCO Chemical Company (1975). The flammability limits of propylene oxide in oxygen and nitrogen mixtures, Hazards Research Corporation, Report no. 3465.

Ashford RD (1994). Dictionary of Industrial Chemicals. Wavelength Publications, London.

BASF AG (1967). Analytisches Labor, unveroeffentlichte Untersuchung, TA/PV-Vg L 540.

BASF AG (1977a). Analytisches Labor, unveroeffentlichte Untersuchung, BRU 77.34.

BASF AG (1977b). Analytisches Labor, unveroeffentlichte Untersuchung, BRU 77.119.

BASF AG (1981). Analytisches Labor, unveroeffentlichte Untersuchung, Ber. -Nr.: 171.375.1.

BASF AG (1981a). Analytisches Labor, unveroeffentlichte Untersuchung, BRU 81.57.

BASF AG (1981b). Rabbit skin irritation study with propylene oxide (substance code 80/84), unpublished.

BASF AG (1983). Analytisches Labor, unveroeffentlichte Untersuchung, BRU 83.115.

BASF AG (1984). Unveroeffentlichte Untersuchung, Ber. -Nr.: 183.0003.1.

BASF AG (1993). Technische Information 1,2-Propyleneoxid, TI/ES 1044 d.

BASF AG (1995). Sicherheitsdatenblatt Propylenoxid.

Blair D and Osborne GP (1977). Acute toxicity studies on propylene oxide: acute inhalation toxicity and 10 day repeated exposure study. Report TLGR.0032.77 from Shell Research Ltd, London.

Bogyo DA, Lande SS, Meylan WM, Howard PH and Santodonato J (1980). Investigation of selected potential environmental contaminants: epoxides. Report prepared for Office of Toxic Substances, US EPA. Report number EPA-560/11-80-005.

Bootman J, Lodge DC, Whalley HE (1979). Mutagenic activity of propylene oxide in Bacterial and Mammalian systems. Mutation Research 67, 101-112.

Bott TR and Sadler HN (1966): Vapour Pressure of Propylene Oxide, J. Chem. Eng. Data 11, 25.

Bridié AL, Wolff CJM and Winter M (1979). The acute toxicity of some petrochemicals to goldfish. Water Research, 13, 623-626.

BUA (1988). Begründungen zu den TRK-Werten - Annex to TRGS 102 - edition March 1988, Bundesarbeitsblatt, 3/1988, 86-87.

BUA (1992). GDCh - Advisory Committee on Existing Substances of Environmental Relevance (BUA). Propylene oxide. BUA Report 94 (June 1992), English version 1994. S Hirzel Verlag, Stuttgart.

Canter DA, Zeiger E, Haworth S, Lawlor T, Mortelmans K and Speck W (1986). Comparative mutagenicity of aliphatic epoxides in Salmonella. Mutation Research, 172, 105-138.

Carreon RE and Wall JM (1982). Propylene oxide: skin sensitisation potential. Toxicology Research Laboratory, Dow Chemical USA, Midland, Michigan 48640.

Carpenter CP and Smyth HF Jr (1946). Chemical burns of the rabbit cornea. Amer. J. Ophthalmol., 29, 1363-1372.

Couch R, Ehrenberg L, Magnusson A-L, Nilsson R, de la Rosa ME and Tornqvist M (1996). *In vivo* dosimetry of ethylene oxide and propylene oxide in the cynomologus monkey. Mutation Research 357, 17-23.

CRC Handbook of Chemistry and Physics, 75th Edition (1994), Eds. Weast RC, Astle MJ and Beyer WH.

Crews RC (1974). Effects of propylene oxide on selected species of fishes. Eglin Air Force Base, Florida, US Air Force Armament Center. NTIS/AD/A-003637.

Dean BJ and Hodson-Walker G (1979). An *in vitro* chromosome assay using cultured rat liver cells. Mutation Research, 64, 329-337.

Dean BJ, Brooks TM, Hodson-Walker G, Hutson DH (1985). Genetic toxicology testing of 41 industrial chemicals. Mutation Research, 153, 57-77.

DEHJ (1985). Chemicals in the Environment. Department of Environmental Health, Japan. (in BUA 1992).

De Jong G, Van Sittert NJ and Natarajan AT (1988). Cytogenetic monitoring of industrial populations potentially exposed to genotoxic chemicals and of control populations. Mutation Research 204, 451-464.

Deneer JW, Sinnige TL, Seinen W, and Hermens JLM, (1988). Quantitative Structure-Activity Relationship for the Acute Toxicity of Some Epoxy Compounds to the Guppy. Aquatic Toxicology, 13, 195-204.

Dent JG and Schnell SR (1981). Inhibition of microsomal-membrane bound and purified epoxide hydrolase by C2-C8 1,2-alkene oxides. Biochem Pharmacol, 30, 1712-1714.

Deutsche Forschungsgemeinschaft, List of MAK and BAT values 1995. Commission for the Investigation of Health Hazards of Chemical Compounds in the Work area; Report No.31.

Djuric Z, Hooberman BH, Rosman L, Sinsheimer JE (1986). Reactivity of mutagenic propylene oxide with deoxynucleosides and DNA. Environmental Mutagenesis, 8, 369-383.

DoE (1994). Environmental Hazard Assessment: Dichloromethane. Toxic Substances Division, Department of the Environment, UK. TSD/18.

Dow Material Safety Data Sheet (1987).

Dow (1977). Among the most versatile of intermediates... Alkylene Oxides from Dow, Pub, The Dow Chemical Company, Michigan USA.

Dow (1990). Unveroeffentlichter Bericht, 1-10.

Dunkelberg H (1979). On the oncogenic activity of ethylene oxide and propylene oxide in mice. Brit. J. Cancer 39, 588-589.

Dunkelberg H (1981). Carcinogenic activity of ethylene oxide and its reaction products 2-chloroethanol, 2-bromoethanol, ethylene glycol and diethylene glycol. I. Carcinogenicity of ethylene oxide in comparison with 1,2-propylene oxide after subcutaneous administration in mice Zbl Bakt Hyg I Abt Orig B 174, 383-404.

Dunkelberg H (1982). Carcinogenicity of ethylene oxide and 1,2-propylene oxide upon intragastric administration to rats. Brit J Cancer, 4, 924-933.

Duus U, Osterman-Golkar S, Tornqvist M, Mowrer J, Holm S, Ehrenberg L (1989). Studies of determinants of tissue dose and cancer risk of ethylene oxide exposure. In, Proceedings, Symposium on Management of Risk from Genotoxic Substances in the Environment, Stockholm, October 3-5, 1988, 141-153. Swedish National Chemicals Inspectorate, Solna, Sweden.

ECN (1995). Outage puts the squeeze on PO/PG. European Chemical News, 14-20 August, 1995, 10.

ECN (1996a). Dow aims to hike PO by 250,000 t/year. European Chemical News, 1-14 January 1996, 33.

ECN (1996b). Shell/BASF team up for major styrene venture. European Chemical News, 26 February - 3 March 1996, 26.

ECSA (1995). Methylene chloride: an update on human and environmental effects. European Chlorinated Solvent Association, September 1995.

Edney EO, Kleindienst TE and Corse EW (1986). Room temperature rate constants for the reactions of OH with selected chlorinated and oxygenated hydrocarbons. Int. J. Chem. Kinet., 18, 1355-1371.

Ehrenberg L, Hiesche KD, Osterman-Golkar S, Wennberg I (1974). Evaluation of genetic risks of alkylating agents: Tissue doses in the mouse from air contaminated with ethylene oxide. Mutation Research, 24, 83-103.

Ehrenberg L, and Hussain S (1981). Genetic toxicity of some important epoxides. Mutation Research, 86, 11-13.

Eldridge SR, Bogdanffy MS, Jokinen MP, Andrews LS (1995). Effects of propylene oxide on nasal epithelial cell proliferation in F344 rats. Fundam Appl Toxicol, 27, 25-32.

Elm R (1980), cited in Ullmanns Encyklopädie der technischen Chemie. ESDU Data Item No. 88017 and 88020 (1988). Thermophysical properties of propylene oxide.

European Chemical News, Chemscope. 10-12, September, 1996.

Farmer PB, Gorf SM, Bailey E (1982). Determination of hydroxypropylhistidine in haemoglobin as a measure of exposure to propylene oxide using high resolution gas chromatography mass spectrometry. Biomedical Mass Spectrometry, 9, 69-71.

Farmer PB, Bailey E and Shuker DEG (1983). The determination of *in vivo* alkylation of haemoglobin and DNA using gas chromatography-mass spectrometry. In Hayes AW et al. (eds), Development in the Science and Practice of Toxicology, Elsevier Science Publishers, Netherlands.

Farooqi Z, Tornqvist M, Ehrenbe L and Natarajan AT (1993). Genotoxic effects of ethylene oxide and propylene oxide in mouse bone marrow cells. Mutation Research, 288, 223-228.

Fjellstedt TA, Allen RH, Duncan BK, Jakoby WB (1973). Enzymatic conjugation of epoxides with glutathione. J. Biol. Chem., 248, 3702-3707.

Focus on Solvents. The Royal Society of Chemistry. November 1996.

Gallant RW (1967). Physical Properties of Hydrocarbons Part 12 - C2 - C4 Oxides, Hydrocarbon Processing, 46 (3), 143-150.

Garro AJ and Phillips RA (1980). Detection of mutagen-induced lesions in isolated DNA by marker rescue of Bacillus subtilus phage 105 Mutation Research, 73, 1-13.

GCDh-Advisory Committee on Existing Chemicals of Environmental Relevance (BUA) Propylene Oxide, Report 94 (June 1992).

Golka K, Peter H, Denk B, and Filser JG (1989). Pharmacokinetics of propylene and its reactive metabolite propylene oxide in Sprague-Dawley rats. Arch. Toxicol., Suppl. 13, 240-242.

Gosselin R et al. (1984). Propylene oxide. In Williams and Wilkins (eds), Clinical toxicology of commercial products, 5th edition, part 2, Baltimore, pp 97-98.

Grosjean D (1990). Atmospheric chemistry of toxicants. 2. Saturated aliphatics: acetaldehyde, dioxane, ethylene glycol ethers, propylene oxide. J. Air Waste Manage. Assoc., 40, 1522-1531.

Guengerich FP and Mason PS (1980). Alcohol dehydrogenase-coupled spectrophotometric assay of epoxide hydratase activity. Anal. Biochem., 104, 445-451.

Gulati DK, Witt K, Anderson B, Zeiger E, Shelby MD (1989). Chromosome aberration and sister chromatid exchange tests in Chinese hamster ovary cells *in vitro* III: results with 27 chemicals. Environ. Molec. Mutagen., 13, 133-193.

Hackett PL, Brown MG, Buschbom RL, Clark ML, Miller RA, Music RL, Rowe SC Schirmer RL and Sikov MR (1982). Battelle Pacific Northwest Laboratories, Richland, WA. Final report to the National Institute for Occupational Safety and Health (NIOSH) PB-83-258038.

Hansch C, Leo AJ (1989). Medchem Project, Pomona College, Claremont CA.

Hardin BD, Niemeier RW, Sikov MR and Hackett PL (1983a). Reproductive toxicologic assessment of the epoxides ethylene oxide, propylene oxide, butylene oxide and styrene oxide. Scand J Work Environ Health, 9, 94-102.

Hardin BD, Schuler RL, McGinnis PM, Niemeier RW, Smith RJ (1983b). Evaluation of propylene oxide for mutagenic activity in 3 *in vivo* test systems. Mutation Research, 117, 337-344.

Harris SB, Schardein JL, Ulrich CE and Ridlon SA (1989). Inhalation developmental toxicity study of propylene oxide in Fischer 344 rats. Fundam. Appl. Toxicol., 13, 323-331.

Haseman JK, Huff J and Boorman GA (1984). Use of historical control data in carcinogenicity studies in rodents. Toxicol. Pathol., 12, 126-135.

Hayes WC, Gushow TS, Kirk HD and Young JT (1985). Propylene oxide: Two-generation inhalation reproduction study in Fischer 344 rats. Report (D-1734) of the Mammalian and Environmental Toxicology Research Laboratory, Health and Environmental Sciences, Dow Chemical, Midland, MI 48640, USA.

Hayes WC, Kirk HD, Gushow TS and Young JT (1988). Effect of inhaled propylene oxide on reproductive parameters in Fischer 344 rats. Fundam. Appl. Toxicol., 10, 82-88.

Hemminki K and Falck K (1979). Correlation of mutagenicity and 4-(p-nitro-benzyl)-pyridine alkylation by epoxides. Toxicology Letters 4, 103-106.

Hemminki K and Vainio H (1980). Alkylation of nucleic acid bases by epoxides and glycidyl ethers. In: Mechanism of toxicity and hazard evaluation: proceedings of the 2nd international congress on toxicology, Brussels. Eds. Holmstedt B, Lauwerys B, Mercier M, Roberfroid M, Dev Toxicol Environ Sci, 8, 241-244.

Hemminki K, Paasivirta J, Kurkirinne T and Virkki L (1980). Alkylation products of DNA bases by simple epoxides. Chem-Biol. Interact., 30, 259-270.

Hogstedt B, Bergmark E, Tornqvist M, Osterman-Golkar S (1990). Chromosomal aberrations and micronuclei in lymphocytes in relation to alkylation of haemoglobin in workers exposed to ethylene oxide and propylene oxide. Hereditas, 113, 133-138.

HSE (1990). 1-chloro-2,3-epoxypropane (Epichlorohydrin). Health and Safety Executive, Toxicity Review 24, Part 2 HSE Books.

HSE (1996). Approved Supply List. Chemicals (Hazard Information and Packaging for Supply) Amendment Regulations. HSE Books, Sudbury, Suffolk, UK.

HSE (1996). Propylene Oxide - Criteria Document for an Occupational Exposure Limit, Pub. HMSO; ISBN 0-7176-1056-X.

Hughes TJ, Simmons DM, Monteith LG, Caxton LD (1987). Vaporization technique to measure mutagenic activity of volatile organic chemicals in the Ames/Salmonella assay. Environ. Mutagen., 9, 421-441.

IARC (1986). International Agency for Research on Cancer (IARC). Allyl compounds, Aldehydes, Epoxides and Peroxides, 36, 227.

IARC (1994). International Agency for Research on Cancer. Monographs on the Evaluation of Carcinogenic Risks to Humans, 60, 181-213.

IISRP (1994). Worldwide Rubber Statistics 1994. International Institute of Synthetic Rubber Producers, Inc., Houston, Texas.

Jacobson KH, Hackley EB, Feinsilver L (1956). The toxicity of inhaled ethylene oxide and propylene oxide vapours. A. M. A. Arch. Industr. Health, 13, 237-244.

Jefferson Chemical Company (1960). Technische Broschuere Propylene Oxide.

Jellinger K. (1973). Neuroaxonal dystrophy: Its natural history and related disorders. In: Progress in Neuropathology, Volume II. Ed. H M Zimmerman, Grune and Stratton, New York.

Jensen O (1981). Contact allergy to propylene oxide and isopropyl alcohol in a skin disinfectant swab. Contact Dermatitis, 7, 148-150.

Jensen RH, Langlois RG, Bigbee WL (1986). Determination of somatic mutations in human erythrocytes by flow cytometry. In: Genetic toxicology of environmental chemicals, part B - Genetic effects and applied mutagenesis. Liss AR Inc., pp 177-184.

Jorritsma U, Cornet M, Van Hummelen P, Bolt HM, Vercruysse, Kirsch-Volders M and Rogiers V (1995). Comparative mutagenicity of 2-methylpropane (isobutene), its epoxide 2-methyl-1,2-epoxypropane and propylene oxide in the *in vitro* micronucleus test using human lymphocytes. Mutagenesis, 10, 101-104.

Kautiainen A and Törnqvist M (1991). Monitoring exposure to simple epoxides and alkenes through gas chromatographic determination of hemoglobin adducts. Int. Arch. Environ. Health, 63, 27-31.

Kirk-Othmer (1994). Encyclopedia of Chemical Technology, 4th Edition, Volume 12. Wiley Interscience, New York.

Kirk-Othmer (1982). Encyclopaedia of Chemical Technology. Third Edition, Volume 19.

Kobe KA et al. (1956). Critical Properties and Vapour Pressures of Some Ethers and Heterocyclic Compounds, J. Chem. Eng. Data, 1, 50–56.

Kolman A and Dusinska M (1995). Comparison of propylene oxide and epichlorohydrin effects in two transformation tests (C3H/10T1/2 and SHE cells). Toxicol. Lett., 81, 213-221.

Kolmark G and Giles NH (1955). Comparative studies of monoepoxides as inducers of reverse mutations in Neurospora. Genetics, 40, 890-902.

Koskikallio J and Whalley E (1959). Effect of pressure on the spontaneous and the base-catalysed hydrolysis of epoxides. Can. J. Chem., 37, 783-787.

Kuper CF, Reuzel PGJ, Feron VJ, Verschuuren H (1988). Chronic inhalation toxicity and carcinogenicity study of propylene oxide in Wistar rats. Food Chem. Toxic., 26, 159-167.

Lawley PD, and Jarman M (1972). Alkylation by propylene oxide of deoxyribonucleic acid, adenine, guanosine and deoxyguanylic acid. Biochem. J., 126, 893-900.

Lipnick RL, Watson KR and Strausz KR (1987). A QSAR study of the acute toxicity of some industrial organic chemicals to goldfish. Narcosis, electrophile and proelectrophile mechanisms, Xenobiotica, 17, no. 8, 1011–1025.

Lynch DW, Lewis TR, Moorman WJ, Burg JR, Groth DH, Khan A, Ackerman LJ, Cockrell BY (1984a). Carcinogenic and toxicologic effects of inhaled ethylene oxide and propylene oxide in F344 rats. Toxicol. Appl. Pharmacol., 76, 69-84.

Lynch DW, Lewis TR, Moorman WJ, Burg JR, Gulati DK, Kaur P, Sabharwal PS (1984b). Sister-chromatid exchanges and chromosome aberrations in lymphocytes from monkeys exposed to ethylene oxide and propylene oxide by inhalation. Toxicology and Applied Pharmacology, 76, 85-95.

Lynch DW, Lewis TR, Moorman WJ, Sabharwal PS, Burg JR (1984c). Toxic and mutagenic effects of ethylene oxide and propylene oxide on spermatogenic functions in cynomolgus monkeys. Toxicologist, 3, 60.

Mabey W and Mill T (1978). Critical review of hydrolysis of organic compounds in water under environmental conditions. J. Phys. Chem. Ref. Data, 7, 383-415.

Maples KR and Dahl AR (1993). Levels of epoxides in blood during inhalation of alkenes and alkene epoxides. Inhalation. Toxicol., 5, 43-54.

McCoy GD, Rosenkranz HS, Klopman G (1990). Non-mutagenic carcinogen are primarily hydrophobic. Carcinogenesis, 11(7), 1111–1117.

McDonald RA, Shrader SA, and Stull DR (1959). Vapour Pressure and Freezing Points of 30 Organics, J. Chem. and Eng. Data, 4 (4), 311-313.

McGregor D, Brown AG, Cattanach P, Edwards I, McBride D, Riach C, Shepherd W, Caspary WJ (1991). Responses of the L5178Y mouse lymphoma forward mutation assay: V. Gases and vapours. Environ. Molec. Mutagen., 17, 122-129.

McLaughlin R (1946). Chemical burns of the human cornea. Am. J. Opthal., 29, 1355-1362.

McMahon RE, Cline JC, Thompson CZ (1979). Assay of 855 test chemicals in ten tester strains using a new modification of the Ames test for bacterial mutagens. Cancer Research, 39, 682-693.

Meylan W, Papa L, De Rosa CT and Stara JF (1986). Chemicals of current interest. Propylene oxide: health and environmental effects profile. Toxicol. Ind. Health, 2, 219-260.

Migliore L, Rossi AM, Loprieno N (1982). Mutagenic action of structurally related alkene oxides on Schizosaccharomyces pombe: the influence *in vitro* of mouse liver metabolising system. Mutation Research, 102, 425-437.

Miller RC and Watkinson RJ (1985). Propylene oxide: an assessment of ready biodegradability. Group Research Report SBGR.85.064, Shell Research Ltd, Sittingbourne Research Centre, Sittingbourne, UK.

MITI (1988). Biodegradation and bioaccumulation testing results on existing chemical substances. Ministry of International Trade and Industry, Japan. (reference not seen).

Nolan RJ, Smith FA, Karbowski RJ and Miller RR (1980). Effects of single 6-hour exposures to various concentrations of propylene oxide on liver non-protein sulfhydryls in male Wistar/Lewis rats. Dow Chemical Company, USA.

Nichols PL Jr and Ingham JD (1955). The inductive effect in ethylene oxide ring openings. Amer. Chem. Soc., 77, 6547-6551.

Nolan RJ, Smith FA, Karbowski RJ and Miller RR (1980). Effetcs of single 6-hour exposures to various concentrations of propylene oxide on liver non-protein sulfhydryls in male Wistar/Lewis rats. Dow Chemical Company, USA.

NFPA (1994). Fire Protection Guide to Hazardous Materials, 11th Edition, National Fire Protection Association.

NIOSH (1985). Pocket Guide to Chemical Hazards 5th Ed. Pub nI 85 - 114 Dept. of Health and Human Serv./Supt. of Documents, GPO.

NTP (1985). National Toxicology Program. Toxicology and carcinogenesis studies of propylene oxide in F344/N rats and B6C3F1 mice (inhalation studies). Technical Report No. 267, NTP-83-020.

Oetting FL (1964). Low-Temperature Heat Capacity and Related Thermodynamic Functions of Propylene Oxide, J. Chem. Physics, 41 (1), 149-153.

Ohnishi A and Murai Y (1993). Polyneuropathy due to ethylene oxide, propylene oxide and butylene oxide. Environmental Research, 60, 242-247.

Ohnishi A, Yamamoto T, Murai Y, Hori H, Tanaka I, Hayashida Y (1988). Propylene oxide causes central-peripheral distal axonopathy in rats. Archives of Environmental Health, 43, 353-356.

Omura M, Tanaka A, Mori K, Hirata M, Zao M and Inoue N (1994). Dose-dependent testicular toxicity of propylene oxide in rats induced by repeated intraperitoneal injections. Fukuoka Acta. Med., 85, 204-210.

Oser (1860). Über das Propylenoxyd, Bulletin de la Société chimique de Paris, séance du 12 Août.

Osterman-Golkar S, Ehrenberg L, Segerback D, Hallstrom I (1976). Evaluation of genetic risks of alkylating agents, II. Haemoglobin as a dose monitor. Mutation Research, 34, 1-10.

Osterman-Golkar S, Farmer PB, Segerback D, Bailey E, Calleman CJ, Svensson K, Ehrenberg L (1983). Dosimetry of ethylene oxide in the rat by quantitation of alkylated histidine in haemoglobin. Teratog. Carcinog. Mutagen., 3, 395-405.

Osterman-Golkar S, Bailey E, Farmer PB, Gorf SM, Lamb JH (1984). Monitoring exposure to propylene oxide through the determination of haemoglobin alkylation. Scand. J. Work Environ. Health, 10, 99-102.

Osterman-Golkar S and Bergmark E (1988). Occupational exposure to ethylene oxide: relation between *in vivo* dose and exposure dose. Scand. J. Work Environ. Health, 14, 372-377.

Pero RW, Bryngelsson T, Widegren B, Hogstedt B, Welinder H (1982). A reduced capacity for unscheduled DNA synthesis in lymphocytes from individuals exposed to propylene oxide and ethylene oxide. Mutation Research, 104, 193-200.

Pero RW, Osterman-Golkar S, Hogstedt B (1985). Unscheduled DNA synthesis correlated to alkylation of haemoglobin in individuals occupationally exposed to propylene oxide. Cell Biology and Toxicology, 1, 309-314.

Pfeiffer EH and Dunkelberg H (1980). Mutagenicity of ethylene oxide and propylene oxide and of the glycols and halohydrins formed from them during the fumigation of foodstuffs. Cosmet. Toxicol., 18, 115-118.

Pitts JN (1979). Chemical consequences of air quality standards and of control implementation programmes: roles of hydrocarbons, oxides of nitrogen, oxides of sulphur and aged smog in the production of photochemical oxidant and aerosol. CA State-wide Air Pollution Center (in IUCLID).

Reigel (1974). Reigel's Handbook of Industrial Chemistry, 7th Edition. Edited by JA Kent. Van Nostrand Reinhold, New York.

RIVM (1988). Integrated Criteria Document: Propylene oxide. W Sloof (ed). Report no 758473008, RIVM, Netherlands.

Randerath K, Reddy MV, Gupta RC (1981). 32P-labelling test for DNA damage. Proc. Natl. Acad. Sci., 78, 6126-6129.

Renne RA, Giddens WE, Boorman GA, Kovatch R, Haseman JE, Clarke WJ (1986). Nasal cavity neoplasia in F344/N rats and (C57Bl/6 x C3H)F1 mice inhaling propylene oxide for up to two years. J. Nat. Cancer Inst., 77, 573-582.

Reuzel PGJ, and Kuper CF (1981). Subchronic (13 week) inhalation toxicity study of propylene oxide in rats. CIVO Institutes TNO, Zeist, NL.

Reuzel PGJ, and Kuper CF (1982). Chronic (28 month) inhalation toxicity/carcinogenicity study of 1,2-propylene oxide in rats. Report no. V 82.215/280853. CIVO Institutes TNO, Zeist, NL.

Reuzel PGJ, and Kuper CF (1984). Addendum to report No. V 82.215/280853 - Chronic (28 month) inhalation toxicity/carcinogenicity study of 1,2-propylene oxide in rats. CIVO Institutes TNO, Zeist, NL.

Ross WCJ (1950). The reactions of certain epoxides in aqueous solutions. J. Chem. Soc., 2257-2271.

Rowe VK, Hollingsworth RL, Oyen F, McCollister DD, Spencer HC (1956). Toxicity of propylene oxide determined on experimental animals. A. M. A. Arch. Industr. Health, 13, 228-236.

Sangster J (1989). Octanol-Water Partition Coefficients of Simple Organic Compounds, J. Phys. Chem. Ref. Data, 18, No.3, 1111-1228.

Sato H, Kidata T and Hori M (1985). Sterilization of therapeutic immunoadsorbents with aqueous propylene oxide solutions. Int. J. Artif. Organs, 8, 109-114.

Segerback D (1983). Alkylation of DNA and hemoglobin in the mouse following exposure to ethene and ethene oxide. Chem.-Biol. Interact., 45, 139-151.

Segerback D, Nilsson R, Osterman-Golkar S and Molholt B (1992). Human cancer risk assessment of propylene oxide based on determination of tissue doese in experimental animals. Fresnius Envir. Bull., 1, 143-150.

Segerback D, Osterman-Golkar S, Molholt B and Nilsson R (1994). *In vivo* tissue dosimetry as a basis for cross-species extrapolation in cancer risk assessment of propylene oxide. Regul. Toxicol. Pharmacol., 20, 1-14.

Segerback D, Plna K, Faller T, Kreuzer PE, Hakansson K, Filser JG and Nilsson (1998). Tissue distribution of DNAadducts in male Fischer rats exposed to 500 ppm of propylene oxide: quantitative analysis of 7-(2-hydroxypropyl)guanine by 32P-postlabelling. Chemico-Biological Interactions, 115, 229-246.

Sellakumar AR, Snyder CA and Albert RE (1987). Inhalation carcinogenesis of various alkylating agents. J. Nat. Cancer Inst., 79, 285-289.

Shell Research (1986). Propylene oxide: acute toxicity (Salmo gairdneri, Daphnia magna and Selenastrum capricornutum) and n-octanol/water partition coefficient. Group Research report SBGR.85.250, Shell Research Ltd, Sittingbourne Research Centre, Sittingbourne, UK.

Sina JF, Bean CL, Dysart GR, Taylor VI, Bradley MO (1983). Evaluation of the alkaline elution/rat hepatocyte assay as a predictor of carcinogenic/mutagenic potential. Mutation Research, 113, 357-391.

Skipper HD and Westermann DT (1973). Comparative effects of propylene oxide, sodium azide and autoclaving on selected soil properties. Soil Biol. Biochem., 5, 409-414.

Smyth HF, Seaton J, Fischer L (1941). The single dose toxicity of some glycols and derivatives. J. Industr. Hygiene and Toxicol., 23, 259-268.

Smyth HF, Carpenter CP, Weil CS, Pozzani US, Striegel JA & Nycum JS (1969). Range finding toxicity data. (List VII). Am. Ind. Hyg. Assoc., 30, 470-476.

Snellings WM, Weil CS, Maronpot RR (1981). Final report on ethylene oxide two-year inhalation study in rats. Project report 44-20, Bushy Run Research Center (formerly Carnegie-Mellon Institute of Research).

Snyder CA and Solomon JJ (1993). The extent and persistence of binding to respiratory mucosal DNA by inhaled tritiated propylene oxide. Cancer Lett., 72, 157-161.

Solomon JJ, Mukal F, Fedyk J and Segal A (1988). Reactions of proylene oxide with 2'-deoxynucleosides and *in vitro* with calf thymus DNA. Chem-Biol. Interact., 67, 275-294.

Sprinz H, Matzke H, Carter J (1982). Neuropathological evaluation of monkeys exposed to ethylene and propylene oxide: Midwest Research Institute, Kansas City, MO. Doc. no. PB83-134817, NTIS, Springfield, VA.

Steinkraus V and Hausen BM (1994). Contact allergy to propylene oxide. Contact Dermatitis, 31, 120.

Stocker WG and Thiess AM (1979). Morbidity study on workers exposed to ethylene oxide/propylene oxide. In: The 7th Medichem Congress, Gera, 11-15 September, 1979.

Stump F, Tejada S, Ray W, Dropkin D and Black F (1990). The influence of ambient temperature on tailpipe emissions from 1985 to 1987 model year light-duty gasoline motor vehicles - II. Atmos. Environ., 24A, 2105-2122.

Svensson K, and Osterman-Golkar S (1984). Kinetics of metabolism of propene and covalent binding to macromolecules in the mouse. Toxicol. Appl. Pharmacol., 73, 363-372.

Svensson K, Olofsson K, Osterman-Golkar S (1991). Alkylation of DNA and haemoglobin in the mouse following exposure to propene and propene oxide. Chem.-Biol. Interact., 78, 55-66.

Tachizawa H, MacDonald TL, Neal RA (1982). Rat liver microsomal metabolism of propyl halides. Molecular Pharmacology, 22, 745-751.

The Merck Index, an Encyclopaedia of Chemicals, Drugs and Biologicals, 11th Edition (1989), Eds. Merck et al.

Thiess AM, Schwegler H, Fleig I, Stocker WG (1981). Mutagenicity study of workers exposed to alkylene oxides (ethylene oxide/propylene oxide) and derivatives. J. Occup. Med., 23, 343-347.

Thiess AM, Frentzel-Beyme R, Link R, Stocker WG (1982). Mortality study on employees exposed to alkylene oxides (ethylene oxide/propylene oxide) and their derivatives. In: Prevention of occupational cancer - international symposium; April 1981; Helsinki, Finland. International Labour Office, Geneva, Switzerland; Occupational safety and health series, no. 46, pp 249-259.

Tucker JD, Xu J, Stewart J, Baciu PC, Ong T-m. (1986). Detection of sister chromatid exchanges induced by volatile genotoxicants. Teratog. Carcinog. Mutagen., 6, 15-21.

Ullmanns Encyklopädie der technischen Chemie (1980), Band 19, S. 471-81.

US Coast Guard (1985). Dept. of Transportation, CHRIS hazardous Chemical Data, Vol. II.

Van Ketel WG (1979). Contact dermatitis from propylene oxide. Contact Dermatitis, 5, 191-192.

Van Sittert NJ and De Jong G (1985). Biomonitoring of exposure to potential mutagens and carcinogens in industrial populations. Food Chem. Toxicol., 23, 23-31.

Von der Hude W, Seelbach A, Basler A (1990). Epoxides: comparison of the induction of SOS repair in Escherichia coli PQ37 and the bacterial mutagenicity in the Ames test. Mutation Research, 231, 205-218.

Von der Hude W, Carstensen S, Obe G (1991). Structure-activity relationships of epoxides: induction of sister-chromatid exchanges in Chinese hamster V79 cells. Mutation Research 249, 55-70.

Voogd CE, Van der Stel JJ, Jacobs JJJAA (1981). The mutagenic action of aliphatic epoxides. Mutation Research, 89, 269-282.

Wade DR, Airy SC, Sinsheimer JE (1978). Mutagenicity of aliphatic epoxides. Mutation Research, 58, 217-223.

Walles SAS (1974). The influence of some alkylating agents on the structure of DNA *in vitro*. Chem.-Biol. Interact. 9, 97-103.

Wallington TJ, Liu R, Dagaut P and Kurylo MJ (1988). The gas phase reactions of hydroxyl radicals with a series of aliphatic ethers over the temperature range 240-440 K. Int. J. Chem. Kinet., 20, 41-49.

Walpole AL (1958). Carcinogenic action of alkylating agents. Ann. NY Acad. Sci., 68, 750-761.

Weil CS, Condra N, Haun C, Streigel JA (1963). Experimental carcinogenicity and acute toxicity of representative epoxides. Amer. Industr. Hygiene J., 24, 305-325.

Wickert JN, Tamplin WS and Shank RL (1979). Phase Equilibria in the system Propylene Oxide-Water, Chem. Techn. Jg., 4, April 1979.

Winer et al. (1979). Cited in Atkinson R, Darnall KR, Lloyd AC, Winer AM and Pitts JN Jr. Kinetics and mechanisms of the reactions of the hydroxyl radical with organic compounds in the gas phase. Advances in Photochemistry, 11, 3741 (from RIVM 1988).

Woods G (1982). Flexible Polyurethane Foams. Chemistry and Technology. Applied Science Publishers, London.

Wood RR (1981). NTIS/OTS 0206201 # 878210140.

Yaws CL, Rackley MP (1976). Lamar University, Chemical Engineering, 129-137.

Young JT, Mattsson JL, Albee RR, Schuetz DJ (1985). Propylene oxide: Assessment of neurotoxic potential in male rats.Report (D-1831) of the Mammalian and Environmental Toxicology Research Laboratory, Health and Environmental Sciences, Dow Chemical, Midland, MI 48640, USA.

Zamora PO, Benson JM, Li AP, Brooks AL (1983). Evaluation of an exposure system using cells grown on collagen gels for detecting highly-volatile mutagens in the CHO/HGPRT mutation assay. Environ. Mutagen., 5, 795-801.

Zetsch C and Stahl F (1981). Rate constants for reactions of OH with partly oxidised hydrocarbons: carbonic acids and epoxides. Paper presented during "Discussion meeting of working party 2" in Leuven, Belgium, February 11/12, 1981, in the framework of COST 61A bis "Physicochemical behaviour of atmospheric pollutants". (report prepared by RA Cox, AERE, Harwell).

ABBREVIATIONS

ADI	Acceptable Daily Intake
AF	Assessment Factor
ASTM	American Society for Testing and Materials
ATP	Adaptation to Technical Progress
AUC	Area Under The Curve
B	Bioaccumulation
BBA	Biologische Bundesanstalt für Land- und Forstwirtschaft
BCF	Bioconcentration Factor
BMC	Benchmark Concentration
BMD	Benchmark Dose
BMF	Biomagnification Factor
bw	body weight / *Bw*, *bw*
C	Corrosive (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
CA	Chromosome Aberration
CA	Competent Authority
CAS	Chemical Abstract Services
CEC	Commission of the European Communities
CEN	European Standards Organisation / European Committee for Normalisation
CEPE	European Committee for Paints and Inks
CMR	Carcinogenic, Mutagenic and toxic to Reproduction
CNS	Central Nervous System
COD	Chemical Oxygen Demand
CSTEE	Scientific Committee for Toxicity, Ecotoxicity and the Environment (DG SANCO)
CT_{50}	Clearance Time, elimination or depuration expressed as half-life
d.wt	dry weight / dw
dfi	daily food intake
DG	Directorate General
DIN	Deutsche Industrie Norm (German norm)
DNA	DeoxyriboNucleic Acid
DOC	Dissolved Organic Carbon
DT50	Degradation half-life or period required for 50 percent dissipation / degradation
DT90	Period required for 50 percent dissipation / degradation
E	Explosive (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
EASE	Estimation and Assessment of Substance Exposure Physico-chemical properties [Model]

EbC50	Effect Concentration measured as 50% reduction in biomass growth in algae tests
EC	European Communities
EC10	Effect Concentration measured as 10% effect
EC50	median Effect Concentration
ECB	European Chemicals Bureau
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECVAM	European Centre for the Validation of Alternative Methods
EDC	Endocrine Disrupting Chemical
EEC	European Economic Communities
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EN	European Norm
EPA	Environmental Protection Agency (USA)
ErC50	Effect Concentration measured as 50% reduction in growth rate in algae tests
ESD	Emission Scenario Document
EU	European Union
EUSES	European Union System for the Evaluation of Substances [software tool in support of the Technical Guidance Document on risk assessment]
F(+)	(Highly) flammable (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
FAO	Food and Agriculture Organisation of the United Nations
FELS	Fish Early Life Stage
foc	Organic carbon factor (compartment depending)
GLP	Good Laboratory Practice
HEDSET	EC/OECD Harmonised Electronic Data Set (for data collection of existing substances)
HELCOM	Helsinki Commission -Baltic Marine Environment Protection Commission
HPLC	High Pressure Liquid Chromatography
HPVC	High Production Volume Chemical (> 1000 t/a)
IARC	International Agency for Research on Cancer
IC	Industrial Category
IC50	median Immobilisation Concentration or median Inhibitory Concentration
ILO	International Labour Organisation
IPCS	International Programme on Chemical Safety
ISO	International Organisation for Standardisation
IUCLID	International Uniform Chemical Information Database (existing substances)
IUPAC	International Union for Pure and Applied Chemistry
JEFCA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues

Koc	organic carbon normalised distribution coefficient
Kow	octanol/water partition coefficient
Kp	solids-water partition coefficient
L(E)C50	median Lethal (Effect) Concentration
LAEL	Lowest Adverse Effect Level
LC50	median Lethal Concentration
LD50	median Lethal Dose
LEV	Local Exhaust Ventilation
LLNA	Local Lymph Node Assay
LOAEL	Lowest Observed Adverse Effect Level
LOEC	Lowest Observed Effect Concentration
LOED	Lowest Observed Effect Dose
LOEL	Lowest Observed Effect Level
MAC	Maximum Allowable Concentration
MATC	Maximum Acceptable Toxic Concentration
MC	Main Category
MITI	Ministry of International Trade and Industry, Japan
MOE	Margin of Exposure
MOS	Margin of Safety
MW	Molecular Weight
N	Dangerous for the environment (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC
NAEL	No Adverse Effect Level
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NOEC	No Observed Effect Concentration
NTP	National Toxicology Program (USA)
O	Oxidizing (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
OECD	Organisation for Economic Cooperation and Development
OEL	Occupational Exposure Limit
OJ	Official Journal
OSPAR	Oslo and Paris Convention for the protection of the marine environment of the Northeast Atlantic
P	Persistent
PBT	Persistent, Bioaccumulative and Toxic
PBPK	Physiologically Based PharmacoKinetic modelling
PBTK	Physiologically Based ToxicoKinetic modelling

PEC	Predicted Environmental Concentration
pH	logarithm (to the base 10) (of the hydrogen ion concentration $\{H^+\}$
pKa	logarithm (to the base 10) of the acid dissociation constant
pKb	logarithm (to the base 10) of the base dissociation constant
PNEC	Predicted No Effect Concentration
POP	Persistent Organic Pollutant
PPE	Personal Protective Equipment
QSAR	(Quantitative) Structure-Activity Relationship
R phrases	Risk phrases according to Annex III of Directive 67/548/EEC
RAR	Risk Assessment Report
RC	Risk Characterisation
RfC	Reference Concentration
RfD	Reference Dose
RNA	RiboNucleic Acid
RPE	Respiratory Protective Equipment
RWC	Reasonable Worst Case
S phrases	Safety phrases according to Annex III of Directive 67/548/EEC
SAR	Structure-Activity Relationships
SBR	Standardised birth ratio
SCE	Sister Chromatic Exchange
SDS	Safety Data Sheet
SETAC	Society of Environmental Toxicology And Chemistry
SNIF	Summary Notification Interchange Format (new substances)
SSD	Species Sensitivity Distribution
STP	Sewage Treatment Plant
T(+)	(Very) Toxic (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
TDI	Tolerable Daily Intake
TG	Test Guideline
TGD	Technical Guidance Document
TNsG	Technical Notes for Guidance (for Biocides)
TNO	The Netherlands Organisation for Applied Scientific Research
UC	Use Category
UDS	Unscheduled DNA Synthesis
UN	United Nations
UNEP	United Nations Environment Programme
US EPA	Environmental Protection Agency, USA
UV	Ultraviolet Region of Spectrum

UVCB	Unknown or Variable composition, Complex reaction products of Biological material
vB	very Bioaccumulative
VOC	Volatile Organic Compound
vP	very Persistent
vPvB	very Persistent and very Bioaccumulative
v/v	volume per volume ratio
w/w	weight per weight ratio
WHO	World Health Organization
WWTP	Waste Water Treatment Plant
Xn	Harmful (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
Xi	Irritant (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)

Appendix A Review of biodegradation studies

Studies on biodegradation of propylene oxide in IUCLID

1. MITI (1988). Ministry of International Trade and Industry. Biodegradation and bioaccumulation testing results on existing chemical substances. Details provided by MITI in response to letter from rapporteur. Test from 1988.

Standard MITI test in accordance with OECD Guideline 301C. Mixed activated sludge from 10 sites used at concentration of 30 mg/l suspended solids. Propylene oxide concentration 100 mg/l. Test vessels designed for volatile chemicals were used. BOD removal 93-98% after 28 days. Parent compound removal 89-90% (GC-FID measurement). Substance readily biodegradable.

This is considered a valid test.

2. Miller RC and Watkinson RJ (1985). Propylene oxide: an assessment of ready biodegradability. Group Research Report SBGR.85.064, Shell Research Ltd, Sittingbourne Research Centre, Sittingbourne UK. Report available.

Closed bottle test chosen because propylene oxide is volatile. Test procedure as in EC Directive 84/449 EEC (Official Journal L251). Chemical tested at 3 mg/l. Inoculum taken from local sewage treatment works. Sodium benzoate used as positive control and in tests for inhibition of degradation. Results were 12-14% degradation after 15 days, with little further degradation after 28 days. The authors concluded that propylene oxide was not readily biodegradable. There was no measurable inhibition of microbial activity in this test.

This is considered a valid test.

3. BASF AG (1977). Oekologielabor, unpublished report of BASF AG, May 6 1977.

Manometric respiration test method used (Sapromat test), measuring oxygen consumption. Inoculum taken from activated sludge from BASF wastewater treatment plant. Test concentration at 80 mg/l total organic carbon. Degradation over 14 days was 90%-100%.

Test method is standard but only few details reported. Inoculum likely to be adapted. Use with care.

4. Waggy GT and Payne JR (1974). Environmental Impact Analysis, Product Biodegradability Testing. Progress report, August 12 1974. File No 19751, Research and Development Department, Union Carbide Corporation.

Few experimental details available. Project described as a screening programme, using a non-adapted mixed inoculum of municipal and industrial sewage. For water soluble compounds, concentration chosen to give a potential oxygen demand of 5-12 mg/l. For a ThOD of 2.21 mg/mg this indicates an exposure concentration of 2.3-5.5 mg propylene oxide/l. Degradation was 14% after 5 days, 37% after 10 days, 65% after 15 days and 67% after 20 days.

Study appears to be sound, but only few details available, so use with care.

5. Bridié AL et al. (1979). BOD and COD of some petrochemicals. Water Research, **13**, 627 - 630.

Standard dilution method (APHA Standard Method No 219) used, with addition of allylthiourea to prevent nitrification. Large number of chemicals tested, five day BOD determination. Inoculum taken from biological sanitary waste treatment plant. In some cases an adapted seed

was prepared and used, although inducement of adaptation was not tried exhaustively. BOD as percentage of ThOD for propylene oxide was 8% for non-adapted and 9% for adapted seed.

Widely quoted study, considered valid, but only covering 5 days.

6. DOW (1978). NTIS/OTS 0509917 # 407875003. Reference available, but poor quality copy. Test dated July 1963.

Few details available. Industrial sewage used as inoculum. No details of specific test method used; degradation calculated by relating biochemical oxygen demand to theoretical oxygen demand (ThOD = 2.21 g O_2/g propylene oxide). Removal was 15.8% after 5 days, 55.7% after 11 days and 74.1% after 20 days.

Not enough information to judge reliability.

7. Hatfield R (1957). Ind Eng Chem **49**, 192-196. Reference not seen.

Few details available. Domestic sewage sludge, acclimated over 1 month using a fill-and-draw method. Exposure concentration ~176 mg/l. Removal based on chemical oxygen demand was 20% after 8 hours.

Not enough information to judge reliability.

8. De Bont JAM et al. (1982). Biochim Biophys Acta, **714**, 465-470. Reference available.

Experiment with bacteria enriched from soil. Isolated a bacterium (*Nocardia* A60) with capacity to utilise propylene oxide aerobically as carbon and energy source for growth. Propylene oxide was converted into 1,2-propanediol; authors able to show that this was not abiotic hydrolysis.

Not a biodegradation test as such, but indicating that propylene oxide may be biodegraded by acclimated bacteria.

9. Hou CT et al. (1979). Appl Environ Microbiol, **38**, 127-134. Reference not seen.

Bacteria (*Methylococcus capsulatus*) grown on methane, then incubated with propylene oxide at 560 mg/l for 24 hours. No significant disappearance of propylene oxide observed.

10. Gorban NS and Petrenko MB (1972). Participation of microorganisms in the transformation of propylene glycol, a component of wastewaters. Cited in Chemical Abstracts **79**, 23331d (1973). Reference not seen.

Available information in IUCLID indicates “purification” of wastewater containing propylene oxide using two *Pseudomonas* species; few details.

Not enough information to judge.

Appendix B Chemical data

Chemical Data on Propylene Oxide

This Appendix gives details of the chemical properties derived from the basic data available. It covers partition coefficients, fate in wastewater treatment and other removal processes.

1. Basic physico-chemical data (as described in Section 1.3)

Molecular weight	58.08
Melting point	-112.16 °C
Boiling point	34.1°C
Vapour pressure	59.8 kPa
Solubility	400 g/l
Log Kow	0.055

2. Partition coefficients

Sorption

Koc

Estimated from non-hydrophobics equation from Section 4.3 of Chapter on QSAR in the TGD.

Equation is: $\log K_{oc} = 0.52 \log Pow + 1.02$

$\text{Log } P_{ow} = 0.055$
$\log K_{oc} = 1.05$
$K_{oc} = 11.2$

Solid - Water partition coefficients

From Section 2.3.5 of the TGD (equation 8)

$$Kp_{comp} = F_{occomp} K_{oc} \qquad \text{with } comp \{soil, sed, susp\}$$

Using the fraction organic carbon values from Table 3 in the Technical Guidance:

$Kp_{soil} =$ 0.224 l/kg
$Kp_{sed} =$ 0.56 l/kg
$Kp_{susp} =$ 1.12 l/kg

The dimensionless form of Kp, or the total compartment-water partitioning coefficient, can be derived from equation 9:

$$K_{comp\text{-}water} = Fair_{comp} \bullet K_{air\text{-}water} + Fwater_{comp} + Fsolid_{comp} \bullet \frac{Kp_{comp}}{1000} \bullet RHOsolid$$

with comp $\in \{soil, sed, susp\}$

Using the values of $Fair_{comp}$, $F_{watercomp}$ and $F_{soilcomp}$ from Table 3 in the TGD, the value of $K_{air,water}$ from below and 2,500 $kg \cdot m^{-3}$ for RHOsolid, gives the following:

$K_{soil,water}$ = 0.54
$K_{sed,water}$ = 1.08
$K_{susp,water}$ = 1.18

Air partition coefficients

Henry's law constant

Section 3.1.2.2 of the risk assessment gives three estimations of the Henry's law constant. These are all very similar. Taking the average of these gives a value for H of 12.42 $Pa \cdot m^3 \cdot mole^{-1}$.

$K_{air,water}$

The air-water partition coefficient is the dimensionless form of the Henry's law constant, or H/RT. The value for H above leads to $K_{air,water}$ as $5.2 \cdot 10^{-3}$.

Adsorption to aerosol particles

The fraction of chemical associated with aerosol particles can be estimated from equation 5 in the Technical Guidance:

$$Fass_{aer} = \frac{CONjunge \bullet SURF_{aer}}{VP + CONjunge \bullet SURF_{aer}}$$

With $CONjungeSURF_{aer}$ set to 10^{-4} Pa, this gives $Fass_{aer} = 1.7 \cdot 10^{-9}$.

3. Degradation rates

Hydrolysis

This is discussed in Section 3.1.2.1.1 of the risk assessment, and the value for the half-life taken is 22 days. This corresponds to a rate constant of 0.03/day.

Photooxidation

This is discussed in Section 3.1.2.1.1 of the risk assessment, and the value for the half-life taken is 32 days. This corresponds to a rate constant of 0.02/day.

Wastewater treatment plant removal

Biodegradation is discussed in Section 3.1.2.1.2. As the data are not completely clear, both ready and inherent biodegradation is considered. The removal and fate according to the tables in the TGD are as follows:

Ready biodegradability:	To air -	3%
	To water -	12%
	To sludge -	0%
	Degraded -	85%
	Total removal -	88%
Inherent biodegradability:	To air -	8%
	To water -	53%
	To sludge -	0%
	Degraded -	39%
	Total removal -	47%

Other biodegradation rates

Section 2.3.6 of the TGD gives methods for estimating the biodegradation rates in surface water, soil and sediments. Using these methods and assuming inherent biodegradability gives the following results:

4. Removal rates from soil

Volatilisation

The rate constant for volatilisation from soil, k_{volat}, is given by equation 41 in the TGD:

$$\frac{1}{k_{volat}} = \left(\frac{1}{Kasl_{air} \cdot K_{air\text{-}water}} + \frac{1}{kasl_{soilair} \cdot K_{air\text{-}water} + Kasl_{soilwater}} \cdot Ksoil\text{-}water \right) \cdot DEPTHSoil$$

Taking the values from the TGD as follows:

$kasl_{air}$ =	120 m/day
$kasl_{soilair}$ =	0.48 m/day
$kasl_{soilwater}$ =	$4.8 \cdot 10\text{-}5$ m/day
$DEPTH_{soil}$ =	0.2 or 0.1 m depending on soil type

and the values for partition coefficients from above gives the rate constants:

k_{volat} (0.2) =	0.023/day
k_{volat} (0.1) =	0.047/day

Leaching

The rate constant for leaching, k_{leach}, is given by equation 42 in the TGD:

$$k_{leach} = \frac{Finf_{soil}}{K_{soil\text{-}water} \cdot DEPTH_{soil}} \cdot \frac{RAINrate}{}$$

Taking the values from the TGD as follows:

$Finf_{soil}$ =	0.25
$RAIN_{rate}$ =	$1.92 \cdot 10^{-3}$ m/day
$DEPTH_{soil}$ =	0.2 or 0.1 m depending on soil type

and the value for $K_{soil,water}$ from above gives the rate constants:

k_{leach} (0.2) =	$4.4 \cdot 10^{3}$/day
k_{leach} (0.1) =	$8.9 \cdot 10^{3}$/day

Overall removal rate

The overall removal rate is the sum of the three processes volatilisation, leaching and biodegradation. The overall results for the two depths are:

k(0.2) =	0.0297/day
k(0.1) =	0.0582/day

Appendix C Calculation of local soil concentrations

Calculation of local soil concentrations

As discussed in Section 3.1.5.2 of the risk assessment propylene oxide is not sorbed significantly to sewage sludge and so the only route to the soil compartment to be considered is through aerial deposition. Annual deposition rates were calculated in Section 3.1.4.5 and the results presented in **Table 3.16**. From the TGD, the deposition rate is converted into an aerial deposition flux (mg chemical per kg soil per day) by using equation 36:

$$Dair = \frac{DEP_{total,ann}}{DEPTH_{soil} \cdot \rho_{soil}}$$

where $DEP_{total,ann}$ comes from **Table 3.16**, RHO_{soil} is 1,700 $kg \cdot m^{-3}$, and $DEPTH_{soil}$ is 0.2 m for natural and agricultural soil and 0.1 for grassland. The values for D_{air} obtained are in **Table C.1**.

Table C.1 Aerial deposition fluxes (D_{air}, mg/kg/day)

Source	$DEP_{total,ann}$	Soil type	
		Natural, agricultural	Grassland
Production	$6.4 \cdot 10^{-3}$	$1.9 \cdot 10^{-5}$	$3.8 \cdot 10^{-5}$
Processing	$9.0 \cdot 10^{-3}$	$2.6 \cdot 10^{-5}$	$5.3 \cdot 10^{-5}$
Further processing	$2.0 \cdot 10^{-4}$	$5.9 \cdot 10^{-7}$	$1.2 \cdot 10^{-6}$
Site-specific (site 1A)	0.03	$7.4 \cdot 10^{-5}$	$1.5 \cdot 10^{-4}$

The concentration on soil after 10 years of continuous deposition is given by equation 43 in the TGD:

$$C_{depsoil10}(0) = \frac{D_{air}}{k} - \frac{D_{air}}{k} \cdot e^{-365 \cdot 10 \cdot k}$$

Applying this equation and using k(0.2) for natural and agricultural soil and k(0.1) for grassland gives the values in **Table C.2**.

Table C.2 Concentrations in soil from aerial deposition (mg/kg).

Source	Natural/agricultural soil	Grassland
Production	$6.4 \cdot 10^{-4}$	$6.5 \cdot 10^{-4}$
Processing	$8.8 \cdot 10^{-4}$	$9.1 \cdot 10^{-4}$
Further processing	$2.0 \cdot 10^{-5}$	$2.1 \cdot 10^{-5}$
Site-specific (Site 1A)	$2.5 \cdot 10^{-3}$	$2.6 \cdot 10^{-3}$

Equation 43 gives the concentration at the beginning of the 10^{th} year but as all the input of chemical is continuous and the overall half-life is much less than 1 year, then the concentration is the same throughout the year. The effect of the different depths of soil largely cancels out so that concentrations in all types of soil are roughly the same.

The corresponding concentrations in soil pore water are given in **Table C.3.**

Table C.3 Concentrations in soil pore water (mg/l)

Source	Natural/agricultural soil	Grassland
Production	$2.0 \cdot 10^{-3}$	$2.0 \cdot 10^{-3}$
Processing	$2.8 \cdot 10^{-3}$	$2.9 \cdot 10^{-3}$
Further processing	$6.3 \cdot 10^{-5}$	$6.6 \cdot 10^{-5}$
Site-specific (Site 1A)	$7.9 \cdot 10^{-3}$	$8.2 \cdot 10^{-3}$

Appendix D EUSES output

The EUSES model was used to calculate the regional and continental concentrations. The emissions on these scales were calculated in the main assessment report and entered directly as the total emissions in EUSES. The intermediate results for Use Pattern 1 and the local emissions in this output were not used and should be ignored, as should the risk characterisation for Production.

Euses Calculations can be viewed as part of the report at the website of the European Chemicals Bureau: http://ecb.jrc.it.

Appendix E Measurement and Biological Monitoring

Position regarding a Biological Monitoring Guidance Value for Propylene Oxide

When the criteria for deciding if a BMGV is appropriate are applied to propylene oxide the following criteria are satisfied:

1) Will air sampling techniques alone not give a reliable indication of exposure and/or uptake?

There are no data on dermal absorption of propylene oxide vapour. It is possible that in some industries control of exposure relies on RPE.

2) Will a BMGV be of practical use in the workplace?

Biological monitoring has been used to monitor occupational exposure in the workplace, Osterman-Golkar et al. (1984) monitored haemoglobin adducts of propylene oxide in 7 workers and found a good agreement between the levels of adducts and the estimated exposure.

An unpublished industry report (Van Der Giesen, 1996) describes the results of haemoglobin adduct estimations on 77 workers in surveys carried out in 1990, 1993 and 1995. This survey was part of a health surveillance programme and used the biological monitoring results as a guide to the efficacy of control procedures. The report describes an in-house "biological limit value" of 340 $pmol \cdot g^{-1}$ globin but does not say where this limit comes from or which adducts is measured.

3) Does a suitable measurement method exist or can one be developed?

Analytical methods for the determination of propylene oxide-haemoglobin adducts based on N-(2-hydroxypropyl) histidine have been published and used to monitor occupational exposure in 7 workers (Osterman-Golkar, 1984). Methods for propylene oxide-haemoglobin adducts based on N-(-2-hydroxypropyl valine) have been proposed, but not used, for monitoring occupational exposure.

However, there are the following contraindications for proposing a biological monitoring guidance value.

4) Are sufficient data currently available or can it be collected?

The Shell report does not give sufficient detail to determine the adequacy of control measures or describe the analytical method used. Although the study covers 77 workers in 5 shifts in 3 different years it is not possible to say whether this is a cross-sectional study or representative of industry with good hygiene practices and so it can not be used to set a biological monitoring benchmark value.

Measurement

An analytical method for the measurement of N-(-2-hydroxypropyl) histidine in blood is based on the isolation of globin followed by hydrolysis and purification of the aminoacids on an ion exchange column followed by derivatisation and detection by capillary gas chromatography mass spectrometry (Osterman-Golkar et al., 1984).

The method for N-(2-hydroxypropyl) valine is based on a modified Edman degradation (Mowrer et al. 1986; Kautiainen and Tornqvist 1991) followed by capillary gas chromatography mass spectrometry detection of the phenylthiocarbamoyl derivatives.

Summary

Biological monitoring of occupational exposure to propylene oxide is possible and has been used. However, there is insufficent data at this time for HSE to propose a biological monitoring benchmark value.

References

Osterman-Golkar S, Bailey E, Farmer PB, Gorf SM, Lamb JH (1984). Monitoring exposure to propylene oxide through the determination of hemoglobin alkylation. Scand. J. Work Environ. Health, 10 99-102.

Van Der Giesen K (1996). Periodiek Bedrijfs Gezondheidskundig Onderzoek (Periodic Occupational Health Checks) MBGD Shell Moerdijk Report no 96/008 14.5.96 File MSPO 1-21 (HSE Translation 15601).

Kautiainen A, Tornqvist M (1991). Monitoring exposure to simple epoxides and alkenes through gas chromatographic determination of haemoglobin adducts. Int. Arch. Occup. Environ. Health, 63 (1) 27-31.

Mowrer J, Tornqvist M, Jensen S, Ehrenberg L (1986). Modified Edman degradation applied to hemoglobin for monitoring occupational exposure to alkylating agents. Toxicol. & Environ. Chem., 11 215-231.

Appendix F Propylene oxide research programme submitted by Industry

Background

Animal studies have shown that long-term inhalation exposure to high concentrations (300-400 ppm) of propylene oxide results in the formation of upper respiratory tract tumours in rats and mice. No nasal tumours were seen at lower exposure levels, nor were any treatment-related tumours were found in other, more distal tissues in any of the exposure groups.

Microscopic examination of nasal epithelial tissue from the inhalation bioassays showed evidence of concurrent inflammatory damage, with the greatest response seen in those animals exposed at the highest concentration (300-400 ppm) of propylene oxide vapour. This damage preceded and coincided with the development of tumours. Since both the magnitude of these inflammatory changes and the induction of tumours were dose-related, a working hypothesis was developed to explain these findings. This suggested that the carcinogenicity of propylene oxide vapour was a two-stage process dependent upon an initial genotoxic event within nasal cell DNA, followed by colonel expansion and tumour development as a consequence of long-term epithelial inflammation and cell proliferation.

The objective of the current research programme is to test this hypothesis and generate mechanistic data which will better characterise the hazards and human health risks associated with occupational exposure to low concentrations of propylene oxide vapour. DNA and haemoglobin adducts will be used as “dosimeters” to determine the internal concentration in target (nasal) and non-target (liver, testes) tissues following inhalation exposure of animals to propylene oxide. This information will be linked with metabolic data to develop a physiologically-based pharmacokinetic (PBPK) model to describe the disposition and fate of propylene oxide in rodents and, ultimately, humans.

Methods development, to allow accurate and reproducible quantitation of very low levels of DNA adducts in target and non-target tissues, commenced in 1995. The main programme is planned for 1998-1999. Findings will be published in the open literature.

The work is funded by the major European and North American manufacturers of propylene oxide, and jointly managed by the CEFIC Propylene Oxide Sector Group and the CMA Propylene Oxide Panel.

Programme design

Phase 1: Methods development

In the first part of the project, male F344 rats will be exposed to 500 ppm PO vapour, 6 hr/d, 5 d/wk for 4 wk. Following the last exposure, aliquots of blood together with samples of liver, spleen, lung, nasal tract tissue and testes will be immediately harvested and DNA adducts quantified. PO levels in whole blood, as well as PO adducts to haemoglobin, will be also quantitated. The measurements will be repeated in a further group of animals 3 days after last exposure. Method development and validation for measurement of haemoglobin (hydroxy propyl valine) and DNA adducts (N7(2-hydroxy propyl) guanine) are a major portion of this phase of the work. A number of *in vitro* studies will also be included to measure tissue partition coefficients and metabolic constants for rat, mouse and human tissues, and used as a first step in developing a PBPK model for PO.

A preliminary communication of results from this work has been accepted for publication in *Mutation Research*. A copy of the abstract is attached for information.

Phase 2: repeat vapour exposure study

During Phase 2, male F344 rats will be exposed to PO vapour at concentrations of 5, 25, 50, 300 and 500 ppm, 6 hr/d, for 3 or 21 days. The internal concentration of PO, together with together with PO-haemoglobin adduct levels, will be determined at steady state in blood. Samples of nasal respiratory epithelium, larynx/pharynx, trachea, lung and liver will be analysed for DNA adducts (N7(2-hydroxy propyl) guanine), and cellular fractions assayed for glutathione content. A satellite group of animals will be used to quantify cell proliferation (antibromodeoxyuracil antibody technique) in these same tissues, with a complimentary microscopic examination (H&E staining) to assess histopathological changes.

Collaborating Scientists and Institutes

Prof Dr JG Filser, GSF-Forschungszentrum fur Umwelt und Gesundheit, Neuherberg, Germany.
Dr S Osterman-Golkar, Stockholm University, Sweden.
Dr D Segerbäck, Karolinska Institute, Huddinge, Sweden.
Dr J Swenberg, University of North Carolina, Chapel Hill, NC, USA.

Propylene Oxide: mutagenesis, carcinogenesis and molecular dose

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Abstract

The results from mutagenic and carcinogenic studies of propylene oxide (PO) and the current efforts to develop molecular dosimetry methods for PODNA adducts are reviewed. PO has been shown to be active in several bacterial and mammalian mutagenicity tests and induces site of contact tumors in rodents after long-term administration. Quantitation of N7(2-hydroxypropyl)-guanine (7-HPG) in nasal and hepatic tissues of male F344 rats exposed to 500 ppm PO (6 hours/day; 5 days/week for 4 weeks) by inhalation was performed to evaluate the potential of high concentrations of PO to produce adducts in the DNA of rodent tissues and to obtain information necessary for the design of molecular dosimetry studies. The persistence of 7-HPG in nasal and hepatic tissues was studied in rats sacrificed three days after cessation of a 4-week exposure period. DNA samples from exposed and untreated animals were analyzed for 7-HPG by two different methods. The first method consisted of separation of the adduct from DNA by neutral thermal hydrolysis, followed by electrophoric derivatization of the adduct and gas chromatography-high resolution mass spectrometry (GC-HRMS) analysis. The second method utilized ^{32}P-postlabeling to quantitate the amount of this adduct in rat tissues. Adducts present in tissues from rats sacrificed immediately after cessation of exposure were 835.4-80.1 (respiratory), 396.8-53.1 (olfactory) and 34.6-3.0 (liver) pmol adduct/mol guanine using GC-HRMS. Lower values, 592.7-53.3, 296.5-32.6 and 23.2-0.6 pmol adduct/mol guanine were

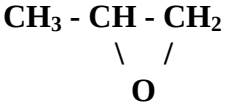
found in respiratory, olfactory and hepatic tissues of rats sacrificed after three days of recovery. Analysis of the tissues by ^{32}P-postlabeling yielded the following values: 445.7±8.0 (respiratory), 301.6±49.2 (olfactory) and 20.6±1.8 (liver) pmol adduct/mol guanine in DNA of rats killed immediately after exposure cessation and 327.1-21.7 (respiratory), 185.3-29.2 (olfactory) and 15.7-0.9 (liver) pmol adduct/mol guanine after recovery. Current methods of quantitation did not provide evidence for the endogenous formation of this adduct in control animals. These studies demonstrated that the target tissue for carcinogenesis has much greater alkylation of DNA than liver, a tissue that did not exhibit a carcinogenic response.

Full paper to be published in Mutation Research, 1997.

Appendix G Submission from Norway Competent Authrority

T25 Calculation of cancer risk estimate

CA Name: methyloxirane
CAS No: 75-56-9
EINECS No: 200-879-2
EU classification: Carc cat 2, Mut cat 2



C_3H_6O Mol. wt: 58.08

Exposure levels and route of exposure:

Workers: 3 ppm, 7.23 mg/m^3, light work 13.9 m^3/8h equals 100.5 mg/8h = (100.5/70) **1.4 mg/kg/d**

Man via the environment:
Local: 765 μg/day = (765/70) 10.9 μg/kg/d
Regional: 0.21 μg/day= (0.21/70) 3 ng/kg/d

Workers, primarily inhalation; man via the environment, oral and inhalation.

Effective dose level in humans

No adequate human studies available.

Effective dose level in animals

The substance has been studied in mice and rats by inhalation. All studies are summarised in the "Risk assessment of methyloxirane". The quantitative risk assessment will be based on the NTP report (1) and a study by Dunkelberg (2).

MICE

B6C3F$_1$ mice, groups of 50 males and 50 females (6-7 weeks old) were exposed by inhalation to 0 (control), 200 ppm (482 mg/m^3) and 400 ppm (964 mg/m^3) propylene oxide 6 hours per day, 5 days per week for 103 weeks. It was concluded that there was *clear evidence of carcinogenicity*, in male and female mice, as indicated by increased incidences of hemangiomas or hemangiosarcomas of the nasal turbinates at the high dose. The main results are shown in **Table G.1**.

Table G.1 Tumour frequency in mice after administration of propylene oxide for 103 weeks.

Tumour type	0 mg/m³		482 mg/m³		964 mg/m³	
	Males	Females	Males	Females	Males	Females
Hemangioma og hemangiosarcoma	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	10/50 (20%)	5/50 (10%)

Remarks on study:

species, strain:	mice, B6C3F$_1$, males
route:	inhalation
tumour:	hemangioma or hemangiosarcoma
exposure:	103 weeks exposure

Lowest dose with a significant increased tumour-incidence

Control: 0/50 (0%)
Exposed: 10/50 (20%)
net%: 20%

Daily dose per mice during the exposure period

6 hours · inhalation volume x mg propylene oxide/m^3 · (5/7) (for 7 days a week)
6h · 2.5 l/h (def.)[5] · 964 · 1/1,000 · (5/7) = 10.3 mg/mice/day.

Daily dose per kg bodyweight during the exposure period

Bodyweight (based on data) 30 g
i.e. 1,000/30 · 10.3 = 343 mg propylene oxide/kg bodyweight per day.

T25 after 24 months

T25 = 25/20 · 343 mg/kg/day = 429 mg/kg bw/day.

T25 dose descriptor in mice exposed by inhalation is 429 mg/kg/day

RATS

F344 rats, groups of 50 males and 50 females (6 weeks old) were exposed by inhalation to 0 (control), 200 ppm (482 mg/m^3) and 400 ppm (964 mg/m^3) propylene oxide 6 hours per day, 5 days per week for 103 weeks. It was concluded that there was *some evidence of carcinogenicity*, in male and female rats, as indicated by increased incidences of papillary adenomas of the nasal turbinates at the high dose. The main results are shown in **Table G.2**.

[5](def.): In case bodyweights, feed consumption data etc. are not specified, the default data set is used.

Table G.2 Tumour frequency in rats after exposure to propylene oxide for 104 weeks.

Tumour type	0 mg/m³		482 mg/m³		964 mg/m³	
	Males	Females	Males	Females	Males	Females
Papillary adenoma	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/48 (0%)	2/50 (4%)	3/48 (6.25%)

Remarks on study:

species, strain: rat, F344, males
route: inhalation
tumour: papillary adenoma
exposure: 103 weeks
note:

Lowest dose with a significant increased tumour-incidence

Control: 0/50 (0%)
964 mg/m^3 2/50 (4%)
net %: 4%

Daily dose per rat during the exposure period

6 hours · inhalation volume x mg propylene oxide/m^3 · (5/7) (for 7 days a week)
6h · 20.5l/h (def) · 964 · 1/1,000 · (5/7) = 84.7 mg/rat/day.

Daily dose per kg bodyweight during the exposure period

Bodyweight specified: 410 gram
i.e. 1,000/410 · 84.7 = 206.6 mg propylene oxide/kg bodyweight per day.

T25 after 24 months

T25 = 25/4 · 206.6 mg/kg/day = 1,291 mg/kg bw/day.

T25 dose descriptor in male rats exposed by inhalation is 1291 mg/kg/day

Remarks on study:

species, strain: rat, F344, females
route: inhalation
tumour: papillary adenoma
exposure: 103 weeks
note:

Lowest dose with a significant increased tumour-incidence

Control: 0/50 (0%)
964 mg/m^3 3/48 (4%)
net%: 6.25%

Daily dose per rat during the exposure period

6 hours · inhalation volume x mg propylene oxide/m^3 · (5/7) (for 7 days a week)
6h · 15.7l/h (def) · 964 · 1/1,000 · (5/7) = 64.9 mg/rat/day.

Daily dose per kg bodyweight during the exposure period

Bodyweight specified: 290 gram
i.e. 1000/290 · 64.9 = 223.8 mg propylene oxide/kg bodyweight per day.

T25 after 24 months

T25 = 25/6.25 · 223.8 mg/kg/day = 895.2 mg/kg bw/day.

T25 dose descriptor in female rats exposed by inhalation is 895.2 mg/kg/day

Dunkelberg (2) administered 0, 15 or 60 mg/kg propylene oxide by gavage, twice weekly, to groups of 50 female Sprague-Dawley rats for 150 weeks. One control group of 50 females received vehicle only, another was untreated. An exposure-free period occurred between weeks 79 and 82 due to an outbreak of pneumonia. Survival of treated rats was comparable to controls. Treatment with propylene oxide resulted in a dose-related increased incidence squamous cell carcinoma of the forestomach. The incedence of squamous cell carcinoma was 0/100, 2/50, and 19/50. No increase in the incidence of tumours at other sites was observed.

Remarks on study

species, strain:	rat, Sprague-Dawley, females
route:	gavage
tumour:	forestomach carcinomas
exposure:	twice weekly for 150 weeks
note:	

Lowest dose with a significant increased tumour-incidence

Control:	0/50 (0%)
60 mg/kg	19/50 (38%)
net%:	38%

Daily dose per rat during the exposure period

Twice per week
60 (2/7) = 17.1 mg/rat/day.

Daily dose per kg bodyweight during the exposure period

Bodyweight (def): 350 gram
i.e. 1,000/350 · 17.1 = 49 mg propylene oxide/kg bodyweight per day.

T25 after 24 months

T25 = 25/38 · 49 mg/kg/day = 32.2 mg/kg bw/day.

T25 dose descriptor in female rats exposed by gavage is *32.2 mg/kg/day* (not adjusted for exposure time as the description is inadequate)

Elements that may influence the calculated lifetime cancer risks

Data-sets available: A mice and two rat studies are available. The risk calculations are based on T25 from the mice inhalation study (males). The T25 from the rat inhalation study (females and males) is 2-3 times higher than T25 from the mice study. The T25 from the female rat gavage study is slightly less than 1/10 of the mice study.

Epidemiological studies
No adequate study available.

Dose-response relationships

Site/species/strain/gender activity Tumours located at the nasal turbinates in both mice and rats and male and females after inhalation and forestomach in rats after gavage.

Mechanistic relevance to humans ----

Toxicokinetics

Other element

In previous calculations, default inhalation volumes of 1.8 l/h in mice and 6.0 l/h in rats were used. During our work with the Guidelines for quantitative risk assessments it has tentatively been agreed to increase these values. The new default inhalation volumes have been used in the calculations above. T25 with the previous default values was 309, 378 and 342 for male mice, male rats, and female rats, respectively.

Conclusion

Propylene oxide seems to induce tumours primarely at sites of contact (nasal turbinates after inhalation exposure in mice and rats and forestomach after gavage administration in rats). Accordingly, no scaling factor will be applied. The risk estimates after inhalation exposure from the rat study gives T25-values 2-3 times higher than from the study with male mice. The T25 after gavage administration in female rats was about 10 times lower than found in the inhalation studies. It is likely that irritation effects have enhanced the carcinogenic effects of propylene oxide in the gavage study. It was decided to use the T25 from the male mice study in the risk assessment.

Lifetime risk levels

Workers

HT25:	429 mg/kg bw/d
Exposure level:	1.4 mg/kg bw/d (3 ppm, light work)
Lifetime cancer risk level:	([1.4/2.8]/[429·4]) $2.9 \cdot 10^{-4}$

Man via the environment:

Local.

HT25:	429 mg/kg bw/d
Exposure level:	0.0109 mg/kg bw/d
Lifetime cancer risk level:	([0.0109]/[429·4]) $6.4 \cdot 10^{-6}$

Regional:
HT25: 429 mg/kg bw/d
Exposure level: 3 ng/kg bw/d
Lifetime cancer risk level: $([3 \cdot 10^{-6}]/[429 \cdot 4])$ $1 \cdot 10^{-9}$

Comments

The risk assessment above is based on a male mice inhalation study. A female rat study by gavage gave a considerable higher risk. However, irritation effects may have contributed to the higher risk. The rat inhalation studies gave lower risks. The above estimates is considered the best estimates, however, due to the large variations in the T25-values the risk estimates are subject to considerable uncertainties.

References

National Toxicology Program (1985). Toxicology and carcinogenesis studies of propylene oxide in F344/N rats and B6C3F1 mice. Department of Health and Human Services, Research Triangle Park.

Dunkelberg H (1982). Carcinogenicity of ethylene oxide and 1,2-propylene oxide upon intragastric administration to rats. Brit. J. Cancer, 4, 924-933.

European Commission

EUR 20512 EN **European Union Risk Assessment Report**
Methyloxirane (propylene oxide), Volume 23

Editors: B.G. Hansen, S.J. Munn, F. Berthault, M. Luotamo, C. Musset, J. de Bruijn, S. Pakalin, S. Vegro, G. Pellegrini, R. Allanou, S. Scheer.

Luxembourg: Office for Official Publications of the European Communities

2002 – X pp., 138 pp. – 17.0 x 24.0 cm

Environment and quality of life series

The report provides the comprehensive risk assessment of the substance methyloxirane (propylene oxide). It has been prepared by the United Kingdom in the frame of Council Regulation (EEC) No. 793/93 on the evaluation and control of the risks of existing substances, following the principles for assessment of the risks to man and the environment, laid down in Commission Regulation (EC) No. 1488/94.

The evaluation considers the emissions and the resulting exposure to the environment and the human populations in all life cycle steps. Following the exposure assessment, the environmental risk characterisation for each protection goal in the aquatic, terrestrial and atmospheric compartment has been determined. For human health the scenarios for occupational exposure, consumer exposure and humans exposed via the environment have been examined and the possible risks have been identified.

The human health risk assessment for methyloxirane (propylene oxide) concludes that there is at present concern for workers, consumers and humans exposed via the environment. The risk assessment concludes that a risk cannot be excluded as the substance is identified as a non-threshold carcinogen. The risks though are low and this should be taken into account when considering the feasibility and practicability of further specific risk reduction measures. The risk assessment for the environment concludes that there is at present no concern for the atmosphere, aquatic ecosystem, terrestrial ecosystem or for micro-organisms in the sewage treatment plant from sources of methyloxirane (propylene oxide) covered by Regulation 793/93.

The conclusions of this report will lead to risk reduction measures to be proposed by the Commission's Committee on risk reduction strategies set up in support of Council Regulation (EEC) 793/93.

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European Commission – Joint Research Centre
Institute for Health and Consumer Protection
European Chemicals Bureau (ECB)

European Union Risk Assessment Report

methyloxirane (propylene oxide)

CAS No: 75-56-9 EINECS No: 200-879-2

Series: 2nd Priority List Volume: 23

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