Social Europe

Recommendation from the Scientific Committee on Occupational Exposure Limits for propylene oxide

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8-hour TWA:	1 ppm [2.41 mg/m^3]
STEL (15 min):	not assigned
Notation:	none
BLV:	3 nmol N-(3-hydroxypropyl) valine/ g globin in blood haemoglobin
SCOEL carcinogen group:	C *(genotoxic carcinogen for which a practical threshold is supported and a health –based OEL is proposed)*

Substance identification: 1,2-propylene oxide. [The compound exists in two optical isomers, the commercial propylene oxide representing a racemic mixture (IARC 1994).]

Synonyms: methyloxirane, 1,2-epoxypropane, propene oxide, methyl ethylene oxide

Structural formula: $CH_2(O)CH\text{-}CH_3$

CAS no.: 75-56-9
Molecular formula: C_3H_6O
Molecular weight: 58.08
Melting point: -111°C
Boiling point: 34°C
EU Classification:

Flam. Liq. 1	H224	Extremely flammable liquid and vapour
Carc. 1B	H350	May cause cancer
Muta. 1B	H340	May cause genetic defects
Acute Tox. 4 *	H332	Harmful if inhaled
Acute Tox. 4 *	H312	Harmful in contact with skin
Acute Tox. 4 *	H302	Harmful if swallowed
Eye Irrit. 2	H319	Causes serious eye irritation
STOT SE 3	H335	May cause respiratory irritation
Skin Irrit. 2	H315	Causes skin irritation

Conversion factor: 1 ppm = 2.41 mg/m^3; 1 mg/m^3 = 0.41 ppm

1 Occurrence/use and occupational exposure

Propylene oxide is an important basic chemical intermediate. Nearly all of the propylene oxide produced is converted within the chemical industry into derivatives, often for applications similar to those of ethylene oxide derivatives. Propylene oxide is used primarily to produce polyether polyols, propylene glycols and propylene glycol ethers. Most of the propylene oxide is used as an intermediate for polyether polyols, which are used mainly in the manufacture of polyurethanes (IARC 1994). Therefore, in contrast to ethylene oxide relevant occupational exposure to propylene oxide is, in first instance, confined to the chemical industry.

2 Health significance

2.1 Toxicokinetics

Propylene oxide is a weak electrophilic compound that directly alkylates macromolecules, introducing a hydroxypropyl group at nucleophilic centres.
Its chemical reactivity is about 4 times less than that of the related ethylene oxide (Pauwels and Veulemans 1998). There is some evidence of enantioselective reactivity of the two optical isomers of propylene oxide (Peter et al. 1991). However, all studies on toxicokinetics and toxicity of propylene oxide were performed with the racemate, which is also used industrially.
As ethylene oxide, also propylene oxide is metabolized *via* two pathways: conjugation with glutathione and hydrolysis to 1,2-propanediol (see IARC 1994).

2.1.1 Human data

Similar to ethylene oxide, also propylene oxide is a substrate of the human glutathione S-transferase hGSTT1-1 (Thier et al., 1999).
The adducts of propylene oxide at the imidazol ring of histidine (HOPrHis) and at the N-terminal valine (HOPrVa1) of haemoglobin (Hb) are used to biologically monitor the internal dose in humans (see chapter 2.1. 3).
With human blood in vitro, a half-life time of 13.6 h was determined for propylene oxide, about 4 times longer than that of ethylene oxide (Pauwels and Veulemans, 1998).

2.1.2 Animal data

Propylene oxide (1mM) was hydrolysed to 1,2-propanediol by two forms of epoxide hydrolase obtained from liver microsomes of male Sprague-Dawley rats which had been pretreated with phenobarbital. The metabolic rate of propylene oxide hydrolysis was reported to be lower than that of other epoxides tested (Guengerich & Mason, 1980).

The inhalation pharmacokinetics of propylene oxide in male Sprague-Dawley rats was first studied by gas uptake in closed exposure chambers, in which the atmospheric concentration-time course was measured after injection of a single dose into the chamber atmosphere (Golka et al., 1989). This was later extended by Csanády and Filser (2007), see 2.1.4. In male Fischer 344/N rats exposed by nose only for 60 min to 14 ppm propylene oxide, the blood concentrations increased during the first 10 min, then reaching a plateau at about 3 ng/g blood (Maples & Dahl, 1993).
As high concentrations of propylene oxide induced inflammation in the respiratory nasal mucosa of rodents (see chapter 2.5.2), and as concentrations at or above 300 ppm

caused nasal tumours (see chapter 2.8.2), the glutathione depletion was determined in tissues of propylene oxide exposed male Fischer 344/N rats (Lee et al., 2005). Rats were exposed once (6 h) to concentrations between 0 and 750 ppm, and repeatedly for up to 20 days (6 h, 5 days/week) to concentrations between 0 and 500 ppm. At the end of the exposures, propylene oxide in blood and non-protein sulhydryls in tissues were determined. Propylene oxide in blood was dependent on concentration and duration of exposure. After the 1-day exposures, non-protein sulhydryl depletion was most distinctive (rat nasal mucosa > liver > lung). Compared to controls, non-protein sulfhydryl levels were 43% at 50 ppm propylene oxide in nasal mucosa and 16% at 300 ppm in both nasal mucosa and liver. Lung non-protein sulfhydryls fell linearly to 20% at 750 ppm. After repeated exposures over 3 and 20 days to 5, 25, 50, 300, and 500 ppm, non-protein sulfhydryl losses were less pronounced. At both time points, non-protein sulfhydryls were 90%, 70%, 50%, 30%, and 30% of the control values in nasal mucosa. Liver non-protein sulfhydryls decreased to 80% and 50% at 300 and 500 ppm, respectively. After 20 days, lung non-protein sulfhydryls declined to 70% (300 ppm) and 50% (500 ppm). Notably, at the inhalation concentration of 5 ppm the glutathione level (non-protein sulfhydryls) was maintained at 90% of the control level (Lee et al. 2005; see also Recommendation).

The depletion of glutathione in rat nasal epithelium due to propylene oxide inhalation and its coherence with cell proliferation was further studied by Khan et al. (2009). Because cell proliferation was suggested to result after depletion of glutathione (GSH) in rat nasal epithelium, cell proliferation was measured by bromodeoxyuridine incorporation into DNA of the epithelium lining middle septum, dorsal medial meatus, and medial and lateral surfaces of the nasoturbinate in transverse nasal sections taken immediately posterior to the upper incisor teeth, and water-soluble non-protein thiol (consisting mostly of gluthathione) in the epithelium was determined after exposing male Fischer 344 rats to 50ppm, 100ppm, 200ppm, or 300ppm propylene oxide (6h/day, 3 days). Both parameters were also investigated after treating rats for 3 days with diethylmaleate (2 x 250mg/kg/day or 500+150mg/kg/day) or buthionine sulfoximine (500mg/kg/day). Exposure to 50 ppm propylene oxide and treatment with 2 x 250mg/kg/day diethyl maleate resulted in non-protein thiol levels approximating 50% and 80% of the level in untreated controls, respectively. Cell proliferation did not increase under these conditions. After exposures to ≥100 ppm propylene oxide or treatment with buthionine sulfoximine or 500+150mg/kg/day diethyl maleate, non-protein thiols were depleted to ≤1/3 of the control level, and cell proliferation increased 2.0–3.7-fold the control value. Yet, the statistically significant induction of nasal respiratory cell proliferation quantified following 3 days of exposure to 100 ppm propylene oxide was not at the tumour target site; it was in the nasal septum. Cell proliferation was significantly elevated in part of the tumour target site (medial surface of the nasoturbinate) following 3 days of exposure to 200 ppm propylene oxide; the lateral surface of the nasoturbinate transitional epithelium, which was also part of the tumour target, showed significant increased cell proliferation following 3 days of exposure to 300 ppm propylene oxide. The authors concluded that the profound depletion of the glutathione represents a critical step in propylene oxide-induced rat nasal carcinogenicity (Khan et al. 2009; see also 2.7.3).

2.1.3 Biological monitoring

Biological monitoring programmes were developed and practically used in the European chemical industry, based on detection of the haemoglobin adduct of propylene oxide, N-(3-hydroxypropyl) valine (HOPrVal) (Törnqvist et al. 1986; Boogaard, 2002).
In a study in a starch alkylation factory, the concentrations of HOPrVal were determined to be below 20 pmol/g Hb in controls, including smokers and nonsmokers, and from 230 to 3500 pmol/g Hb in exposed workers. The adduct levels correlated with the mean

concentrations in the breathing zones, which varied between 0.33 and 11.4 ppm during sampling periods of 2-4 h (Högstedt et al., 1990). The steady-state background concentration of HOPrVa1 adducts in Hb was 2 pmol/g Hb in unexposed people (Törnqvist & Ehrenberg, 1990). The increment in workers exposed for 40 h/week to 1 ppm propylene oxide (TWA) was estimated to be about 500 pmol/g Hb (Kautiainen & Törnqvist, 1991).

In another study, HOPrVal adduct concentrations in Hb were found to be slightly higher in propylene oxide manufacturing and loading workers than in controls, after correction for smoking (van Sittert & van Vliet, 1994).

Boogaard (2002) described a limit of detection of HOPrVal of 0.1 pmol/g globin. In comparison to ethylene oxide, the dependence of HOPrVal on external propylene oxide exposure was established in industrial settings (Boogaard et al., 1999; Boogaard, 2002). The induced adduct level was about one order of magnitude lower compared to the same external exposure concentrations of ethylene oxide, which mostly resembles the lower systemic reacticity of propylene oxide vs. ethylene oxide. At steady-state, it was deduced that a repetitive exposure to 2 ppm propylene oxide resulted in a HOPrVal level of 2.56 ± 0.34 (S.E.) nmol HOPrVal/g globin (Boogaard, 2002). This is consistent with quantitations based on studies in rats by Osterman-Golkar et al. (2003) [see also Albertini & Sweeney, 2007]. In consequence of these data, for 8h-TWA exposure conditions to 1 ppm propylene oxide a steady-state haemoglobin adduct level of 1.3 nmol HOPrVal per g globin can be deduced (see Recommendation section).

There is one small field study by Czene et al. (2002) on eight Chinese workers repetitively exposed to propylene oxide and eight controls, which also measured DNA adducts. The propylene oxide concentrations in air varied from 0.9 to 6.9 ppm; workers were present in the areas of highest exposure (3.7 to 6.9 ppm) for 1 to 1.5 h per day. The HOPrVal adduct levels ranged from 0.13 to 4.91 nmol/g globin, with a mean of 2.69 (± 1.52) nmol/g globin. Values for controls ranged from 0.005 to 0.008 nmol/g globin. These data are consistent with the general coherence of external propylene oxide exposure and HOPrVal levels, according to Boogaard (2002). The results on DNA adducts obtained in this study by Czene et al. (2002) are discussed below in chapter 2.7.

2.1.4 Toxicokinetic modelling (PB-PK)

Considering the nose as the most relevant target organ for propylene oxide-induced tumorigenicity, Csanády and Filser (2007) developed a physiological toxicokinetic model for propylene oxide in rats and humans. Under identical conditions of PO exposure, similar PO concentrations in rat nasal mucosa were modelled for rats and humans. Also PO concentrations in blood were similar in both species, according to the modelling.

2.2 Acute toxicity

2.2.1 Human data

Irritation of the skin and eyes and some cases of contact dermatitis after direct contact with
1,2-propylene oxide have been described (DFG 1993).

2.2.2 Animal data

The data on acute toxicity of 1,2-propylene oxide were reviewed by DFG (1993). According to earlier data, the acute toxicity of 1,2-propylene oxide was reported to be one half to one third of that of ethylene oxide. Rats survived inhalation of 4000 ppm for 0.5 hours, 2000 ppm for 2 hours and 1000 ppm for 7 hours. Upon a 4 h inhalation, LC_{50} values were reported of 1740 ppm in mice and 4000 ppm in rats (DFG 1993).

2.3 Irritation and corrosivity

2.3.1 Human data

Three cases of corneal burns after exposure to propylene oxide have been described (McLaughlin, 1946). Van Ketel (1979) described the development of hand eczema in a female laboratory analyst who was working with pure propylene oxide or a concentrated solution (50%). Two cases of contact dermatitis from a disposable swab containing 70% isopropyl alcohol and 1% propylene oxide were reported by Jensen (1981).

2.3.2 Animal data

Data on skin and eye irritation are summarized in the EU Risk Assessment Report (ECB 2002).

2.4 Sensitisation

2.3.1 Human data

No data have been reported.

2.3.2 Animal data

No data have been reported.

2.5 Repeated dose toxicity

2.5.1 Human data

See chapter 2.6.2.

2.5.2 Animal data

Rowe et al. (1956) exposed animals of several species (rat, guinea pig, rabbit, monkey) to 1,2-propylene oxide and found that 200 ppm, 7 hours daily on 5 days per week for 6 months, had no effects except on female guinea pigs in which the lung weights were slightly increased at the end of the study. Exposure to 100 ppm had no effects at all. The authors suggested 150 ppm as a threshold concentration.

In another experiment (Hine & Rowe 1962), groups of 5 young female rats were given a total of 18 oral doses of 0.1, 0.2 or 0.3 g/kg and day of 1,2-propylene oxide in olive oil by gavage, 3 days per week. In the two lower dose groups, no effects on clinical, gross pathological or micropathological parameters were detected. In the highest

dose group reduced body weights, irritation of the stomach mucosa and slight liver damage were found.

The subchronic toxicity of 1,2-propylene oxide was also investigated in the rat in a 13-week inhalation study (Reuzel & Kuper 1981) with concentrations of 75, 150, 300 and 600 ppm, 6 hours daily on 5 days per week. Ten male and ten female rats were exposed in each dose group. Delayed body weight gain was seen in both sexes in the 600 ppm group and as a transient effect in the males of the 300 ppm group. In addition, slight degenerative and hyperplastic alterations of the nasal epithelium developed in the highest dose group in both sexes. Of unclear toxicological significance was the finding of hypoglycaemia, retention of urine and dehydration in the highest dose group.

Male Fischer 344 rats were exposed to 0, 10, 20, 50, 150 or 525 ppm propylene oxide vapour for up to four weeks followed by recovery for up to four weeks, and toxicity and cell proliferation were examined in the nasal cavity. Respiratory epithelial hyperplasia, degeneration of olfactory epithelium and cell proliferation at both sites were dose- and time-dependent and reversible upon cessation of exposure. No effect was observed at 50 ppm propylene oxide (Eldridge et al., 1995).

Exposure of male Wistar rats to 1500 ppm propylene oxide (6 h/day, five days/week, seven weeks) by inhalation caused ataxia in the hindlegs without muscular atrophy. A central-peripheral distal axonopathy was verified histologically by the observation of axonal degeneration of myelinated fibres in hindleg nerves and in the fasciculus gracilis (Ohnishi et al., 1988; Ohnishi & Murai, 1993).

Data from chronic bioassays are described in chapter 2.7.2.

2.6 Genotoxicity

Comprehensive reviews have been presented by IARC (1994) and by Albertini & Sweeney (2007).

2.6.1 In vitro

Propylene oxide induced DNA damage and gene mutation in bacteria. It caused gene mutation in yeast and fungi, and in one study it induced mitotic gene conversion in Saccharomyces cerevisiae. Induction of sex-linked recessive lethal mutations in Drosophila was reported in a single study. Propylene oxide induced DNA damage, gene mutation, sister chromatid exchange and chromosomal aberrations in mammalian cells in vitro. It also induced sister chromatid exchange and chromosomal aberrations in human lymphocytes in vitro (IARC 1994).

Propylene oxide binds covalently to DNA. Using ^{32}P-postlabelling, Randerath et al. (1981) detected 15 different DNA adducts after incubation (12 h, 37 °C, pH 5.8) of propylene oxide (200 mmol/L) with calf thymus DNA (3 mmol/L).

After incubation (48 h, 37 °C, pH 7.4) of propylene oxide with calf thymus DNA (0.2 mmol propylene oxide per mg DNA), the yields of alkylated nucleosides were: deoxyguanosine (46% reacted) > deoxyadenosine (38% reacted) > deoxycytidine (24% reacted) > deoxythymidine (15% reacted) (Djuric et al., 1986).

After incubation (10 h, 37 °C, pH 7.5) of propylene oxide (2 mol/L) with calf thymus DNA (3 mg/ml), the following 2-hydroxypropyl adducts were found: 7-guanine (133 nmol/mg DNA), 3-adenine (14 nmol/mg DNA), 3-uracil (13 nmol/mg DNA) and N^6-adenine
(1 nmol/mg DNA). The 2-hydroxypropyl adduct at 3-uracil was formed from the corresponding cytosine adduct by hydrolytic deamination of the imino group (Solomon et al., 1988).

2.6.2 In vivo – Human data

In persons who had been exposed to 1,2-propylene oxide for more than 20 years, Thiess et al. (1981a) found an increase in chromosomal aberrations in circulating leukocytes; however, the exposures had also involved other epoxides, particularly ethylene oxide.

Results from the analysis of chromosomal aberrations and micronuclei in peripheral blood lymphocytes from 20 male workers exposed to propylene oxide during the production of alkylated starch were inconclusive because no data were available on controls (Högstedt et al., 1990).

Sister chromatid exchange (SCE) frequencies were also reported in a short communication by Czene et al. (2002), conducted on a limited number of propylene oxide exposed persons in China (for his study, see also chapters 2.1.3 and 2.6.4). The group mean SCE frequency by the technique employed was 3.7 ± 2.11% in exposed workers and 2.0 ± 0.52% in controls, the difference being significant (p=0.011). At lower levels of propylene oxide exposure (below 2 ppm), however, no difference to the background fluctuation in controls could be seen (Figure 2B of Czene et al., 2002). [SCOEL noted that the relevance of these data may be questioned, in view of the general background fluctuation in non-exposed controls; for discussion, see also Albertini, 2003.]

2.6.3 In vivo – Animal data

In vivo mutagenic effects have only been found under extreme conditions (IARC, 1994). Negative results were obtained in a dominant lethal test in the male mouse after oral administration of 1,2-propylene oxide doses of 50 or 250 mg/kg daily for 14 days and in a micronucleus test in the male mouse after oral administration of twice 500 mg/kg (the solvents were water and "gum traganth solution"). On the other hand, positive results were, obtained in a micronucleus test after administration of twice 300 mg/kg by intraperitoneal injection (Bootman et al. 1979). However, this application route also produced negative results with lower doses (twice 75 mg/kg or twice 150 mg/kg) (Bootman et al. 1979).

Hardin et al. (1983) investigated the mutagenic potential of 1,2-propylene oxide in animals exposed to 300 ppm using the dominant lethal test in rats and the sperm head morphology test in mice. Groups of 10 male rats were exposed for 7 hours daily on 5 consecutive days and then mated for a period of 6 weeks with a different group of two females each week. In the females from the first week of mating the preimplantation losses were increased and there were a smaller number of viable implants relative to the number of corpora lutea. This was not interpreted as a mutagenic effect; an increased mutagenicity index is indicated by an increased incidence of dead implants. The above results are rather indicative of toxic effects. The study of sperm head morphology in mice exposed according to the same protocol did not yield positive results. There was enormous scatter in the data, even in

the control group. The authors considered that both the dominant lethal test and sperm head test had yielded negative results. In contrast, these authors found an unequivocal increase in recessive lethal mutations in Drosophila melanogaster exposed to 1,2-propylene oxide (treated group 4.28%, controls 0.25%).

2.6.4 Quantitative aspects of DNA adduct formation, related to genotoxicity

A variety of studies have shown that propylene oxide reacts primarily with cyclic ring nitrogens in DNA *via* S_N2 mechanisms, producing hydroxypropyl adducts primarily at N^7G, but also at N^3A and N^1A, N^3C and N^3T (Solomon 1999; Koskinen & Plna 2000; Osterman-Golkar et al. 2003). The N^7G and N^3A lesions are non-promutagenic, but may cause apurinic site because of labilisation of the imidazol ring structure by a positive charge. N^7-(2-Hydroxypropyl) guanine is the major DNA lesion caused by propylene oxide. Normally, apurinic sites are rapidly repaired, and there is a physiological background of such lesions from endogenous sources at about 1 per 10^5 nucleotides (Albertini and Sweeney, 2007). In tissues of rats exposed to 500 ppm propylene oxide no significant differences were found in the number of apurinic sites between the exposed animals and controls, even when assessed immediately after exposure (Ríos-Blanco et al. 2000).

N^7-(2-Hydroxypropyl) guanine was detected in DNA hydrolysates of various organs obtained from male mice 3 h and 10 h after intraperitoneal injection of ^{14}C-propylene oxide (Svensson et al. 1991). In mice, rats and dogs, the levels of DNA adducts in liver (pmol/g DNA per mg propylene oxide per kg bw) were 17 in mice, 38 in rats and 17 in dogs after intraperitoneal or intravenous injection, and somewhat higher after exposure by inhalation in mice (Segerbäck et al. 1994). From these data IARC (1994) calculated a "covalent binding index" [i.e., (µmol adduct/mol DNA nucleotide)/(mmol chemical/kg bw)] of 0.3 for mouse liver DNA, at 6 h after intraperitoneal injection. Compared to other alkylating carcinogens, this was considered as being low (IARC 1994).

In view of the local toxicity and carcinogenicity of propylene oxide on the rat nasal mucosa (see chapters 2.5.2 and 2.8.2) quantitations of the DNA adduct N^7-(2-hydroxypropyl) guanine were performed in nasal and hepatic tissues of male Fischer 344 rats exposed to 500 ppm propylene oxide (6 h/day; 5 days/week for 4 weeks) by inhalation (Ríos-Blanco et al. 1997). Specifically, the persistence of N^7-(2-hydroxypropyl) guanine in nasal and hepatic tissues was studied in rats killed three days after cessation of a 4-week exposure period. DNA samples from exposed and untreated animals were analyzed for N^7-(2-hydroxypropyl) guanine by two different methods. The first method consisted of separation of the adduct from DNA by neutral thermal hydrolysis, followed by electrophoretic 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 killed immediately after cessation of exposure were 835.4 +/- 80.1 (respiratory mucosa), 396.8 +/- 53.1 (olfactory mucosa) and 34.6 +/- 3.0 (liver) pmol adduct/micromol guanine using GC-HRMS. Lower values of 592.7 +/- 53.3, 296.5 +/- 32.6 and 23.2 +/- 0.6 pmol adduct/micromol guanine were found in respiratory, olfactory and hepatic tissues of rats killed after three days of recovery. Analysis of the tissues by 32P-postlabeling yielded the following values: 445.7 +/- 8.0 (respiratory), 301.6 +/- 49.2 (olfactory) and 20.6 +/- 1.8 (liver) pmol adduct/micromol 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/micromol guanine after recovery. There was no evidence for the endogenous formation of this adduct in control animals. These studies were interpreted by the authors to demonstrate that the target nasal tissue for carcinogenesis displays higher alkylation of

DNA than liver, a tissue that does not exhibit a carcinogenic response experimentally (Ríos-Blanco et al. 1997).

As already mentioned (chapter 2.1.3), there is one published occupational field study on a limited number of Chinese workers exposed to propylene oxide that also measured DNA adducts (Czene et al. 2002). The propylene oxide concentrations in air varied from 0.9 to 6.9 ppm; workers were present in the areas of highest exposure (3.7 to 6.9 ppm) for 1 to 1.5 h per day. The HOPrVal adduct levels ranged from 0.13 to 4.91 nmol/g globin, with a mean of 2.69 (± 1.52) nmol/g globin. [Using the derivations of Boogaard (2002; see chapter 2.1.3), this points to a mean TWA exposure of 2 ppm propylene oxide.] In the study by Czene et al. (2002), the quantitatively minor DNA adduct 1-hydroxypropyl-adenine (N1HPA) was assessed; compared to *N*^{7}-(2-hydroxypropyl)–guanine, the N1HPA adduct concentrations generally range at about 2% (Segerbäck et al., 1998; Plna et al., 1999). Czene et al. (2002) detected N1HPA adducts in DNA from 7 of the 8 exposed workers, but not in controls, obtaining a mean value for the exposed group of 0.66 ± 0.34 adducts per 10^9 nucleotides [detection limit: 0.1 per 10^9nucleotides]. In consequence, this would correspond to a mean frequency for the major N^7-(2-hydroxypropyl)guanine adduct of 3.3 x 10^8, using the conversions given above, for a mean TWA exposure of 2 ppm propylene oxide (see also the Recommendation section).

2.7 Carcinogenicity

2.7.1 Human data

Several cohort studies on ethylene oxide included some workers who were also exposed to propylene oxide (Hogstedt et al., 1979, 1986; Thiess et al., 1981b; Hogstedt, 1988). No conclusion could be drawn regarding a risk for cancer in relation to exposure to propylene oxide specifically (IARC 1994).

2.7.2 Animal data

The available experimental carcinogenicity data have been compiled in detail and evaluated by IARC (1994). Especially the inhalation studies within the U.S. National Toxicology Program have demonstrated that propylene oxide is a nasal carcinogen in rats and mice, in both sexes (Haseman and Hailey 1997).

<u>Studies with subcutaneous administration</u>
Groups of 100 female NMRI mice, six to eight weeks old, received subcutaneous injections of propylene oxide (purity, 99%) in tricaprylin at 0.1, 0.3, 1.0 or 2.5 mg/mouse once a week for 95 weeks (mean total dose, 6.8, 21,7, 72.8 or 165.4 mg/mouse, respectively). Groups of 200 untreated and 200 tricaprylin-treated mice served as controls. Survival rates in the animals treated with propylene oxide were comparable to those in controls. The incidences of sarcomas at the site of injection were: untreated control, 0/200; tricaprylin control, 4/200; 0.1 mg, 3/100; 0.3 mg, 2/100; 1.0 mg, 12/100; and 2.5 mg, 15/100 [$p<0.001$, Cochran-Armitage test for trend]. No increase in tumour incidence at other sites was found (Dunkelberg, 1981).

Of 12 rats [age, sex and strain unspecified] given a total of 1500 mg/kg bw propylene oxide [purity unspecified] in arachis oil by subcutaneous injection over a period of 325 days [dosing schedule unspecified], eight developed local sarcomas after 507-739 days. In a similar experiment, in which 1500 mg/kg bw propylene oxide in water were injected subcutaneously, 3/12 rats developed a local sarcoma after 158 days and two developed local sarcomas after 737 days (Walpole, 1958).

Oral studies

Groups of 50 female Sprague-Dawley rats, about 100 days old, were administered 0 (control), 15 or 60 mg/kg bw propylene oxide (purity, 99%) in a commercial vegetable oil by gastric intubation twice a week for 109.5 weeks (average total dose, 2714 or 10 798 mg/kg bw, respectively) and observed for life time. Another untreated control group consisting of 50 females was also available. Survival rates in rats treated with propylene oxide were comparable to those of controls. Treatment with propylene oxide resulted in a dose-dependent increase in the incidence of forestomach tumours, which were mainly squamous-cell carcinomas. The incidences of squamous-cell carcinomas of the forestomach were 0/50 and 0/50 in control groups, 2/50 in the low-dose group and 19/50 in the high-dose group; one additional animal in the high-dose group had a carcinoma in situ, and a further animal had an adenocarcinoma of the glandular stomach. In addition, 7/50 1ow-dose and 17/50 high-dose animals developed papillomas, hyperplasia and hyperkeratosis of the forestomach. The incidences of tumours at other sites in treated animals were no greater than those in controls (Dunkelberg, 1982).

Inhalation studies

Groups of 50 male and 50 female B6C3F1 mice, seven to nine weeks old, were exposed by inhalation to 0 (control), 200, or 400 ppm propylene oxide (purity > 99.9%) vapour for 6 h per day on five days per week for 103 weeks. Fewer treated than control animals survived to the end of the experiment: males-control, 42/50; low-dose, 34/50; high-dose, 29/50 ($p = 0.006$); females-control, 38/50; low-dose, 29/50; high-dose, 10/50 ($p < 0.001$). One squamous-cell carcinoma and one papilloma of the nasal cavity occurred in two high-dose male mice, and two high-dose female mice had adenocarcinomas of the nasal cavity. The (combined) incidences of haemangiomas and haemangiosarcomas in the nasal cavity were: males - 0/50 control, 0/50 low-dose and 10/50 high-dose ($p < 0.001$, Fisher exact test); females - 0/50 control, 0/50 low-dose and 5/50 high-dose ($p = 0.028$, Fisher exact test). Propylene oxide caused inflammation of the respiratory epithelium of the nasal turbinates; squamous metaplasia was observed in one low-dose male and in two high-dose female mice. Three high-dose males and three high-dose females had focal angiectasis of the submucosal turbinate vessels (US National Toxicology Program, 1985; Renne et al., 1986).
Groups of 80 male weanling Fischer 344 rats were exposed by inhalation to filtered air containing 0 (control), 100 or 300 ppm propylene oxide (purity, 98%) vapour for about 7 h per day on five days per week for 104 weeks. Increased mortality over that in controls was observed in the two groups of rats exposed to propylene oxide, which was significant in the high-dose group ($p < 0.01$). Rats exposed to 100 or 300 ppm propylene oxide had an increased incidence of inflammatory lesions of the respiratory system and of a “complex epithelial hyperplasia” in the nasal cavity, which was dose dependent (control, 0/76; low-dose, 2/77; high-dose, 11/78). Two rats in the high-dose group developed adenomas in the nasal cavity, which were not seen in controls. Adrenal phaeochromocytomas developed in 8/78 controls, 25/78 rats of the low-dose group and 22/80 rats of the high-dose group ($p < 0.05$, chi^2 test). A slight, non-significant increase in the incidence of peritoneal mesotheliomas was also found in the exposed groups (control, 3/78; low-dose, 8/78; high-dose, 9/80) (Lynch et al., 1984).

Groups of 50 male and 50 female Fischer 344/N rats, seven to eight weeks of age, were exposed by inhalation to 0 (control), 200 or 400 ppm propylene oxide (purity, > 99.9%) vapour for 6 h per day on five days per week for 103 weeks. Survival of rats exposed to propylene oxide was comparable to that of controls; terminal body weights were lower in high-dose males and high-dose females than in controls. Suppurative inflammation, epithelial hyperplasia and squamous metaplasia of the respiratory epithelium and underlying submucosal glands of the nasal turbinates were observed in exposed rats. Papillary adenomas of the nasal cavity occurred in 0/50 control, 0/50 low-dose and

3/50 high-dose females (p = 0.037, Cochran-Armitage trend test) and in 0/50 control, 0/50 low-dose and 2/50 high-dose males ($p > 0.05$). In historical controls, the incidence of nasal cavity tumours was 3/1523 in females and 1/1477 in males. In female rats, the combined incidences of C-cell adenomas and C-cell carcinomas of the thyroid were increased (control, 2/45; low-dose, 2/35; high-dose, 7/37; p = 0.023, Cochran-Armitage trend test). The incidence in historical controls was 122/1472 (8.3 ± 4.3% [S.D.]) (US National Toxicology Program, 1985; Renne et al., 1986).

Groups of 50 male Sprague-Dawley rats, 11-12 weeks old, were exposed by inhalation to 435 or 870 ppm (1031 or 2062 mg/m^3) propylene oxide (purity, > 95%) vapour in air for 6 h per day on five days per week for 30 days. A group of 50 rats was exposed to 1740 ppm (4124 mg/m^3) propylene oxide for only eight days because of high mortality. A control group of 98 male rats was exposed to air alone. All animals were observed for life. Median lifespans were: control, 613 days; low-dose, 655 days; mid-dose, 635 days; and high-dose, 519 days. No nasal tumour was observed in any group receiving propylene oxide; two mid-dose animals had adenomas of the lung. Control animals developed no tumour in any part of the respiratory tract (Sellakumar et al., 1987).

Groups of 100 male and 100 female Wistar rats, 34-38 days old, were exposed by inhalation to 0 (control), 30, 100 or 300 ppm (71.1, 237 or 711 mg/m^3) propylene oxide (purity > 99.99%) vapour for 6 h per day on five days per week for 124 weeks (males) and 123 weeks (females). The body weights of exposed males in the high-dose group were lower than those of the controls throughout the study and lower than those of treated females only during the first year. After 12, 18 and 24 months, 10 rats of each sex from each group were killed. By week 115, mortality of male and female rats in the high-dose group was higher than that in controls; at week 119, the mortality of females in the mid-dose group was also higher than that in controls. The incidences of mammary gland tumours were significantly higher in high dose females: fibroadenoma - control, 32/69; low-dose, 30/71; mid-dose, 39/69; high-dose, 47/70 ($p < 0.04$); tubulopapillary adenocarcinoma - control, 3/69; low-dose, 6/71; mid-dose, 5/69; high-dose, 8/70 ($p < 0.01$; Cox's test, adjusted for time of tumour appearance). The mean numbers of benign mammary tumours per tumour-bearing rat were: control, 1.3; low-dose, 2.1; mid-dose, 2.2; high-dose, 2.4. Exposure to propylene oxide increased the incidences of degenerative and hyperplastic changes in the nasal mucosa in all of the treatment groups over that in controls. Three malignant tumours were found in the nasal cavity of treated males: one tumour described as an “ameloblastic fibrosarcoma” in a low-dose male, one squamous-cell carcinoma in a low-dose male and one in a high-dose male. Four males in the high-dose group had a carcinoma in the larynx or pharynx, trachea or lungs; no such tumour was seen in any of the controls or low-dose males (Kuper et al., 1988).

2.7.3 Evaluation of carcinogenicity and mode of action

Propylene oxide is a weakly DNA-reactive genotoxic agent. In addition to results of experimental studies, its genotoxicity for humans has been assessed by biomarker studies. IARC (1994) has evaluated the evidence of carcinogenicity in humans of propylene oxide as being “inadequate” and the evidence in experimental animals as being “sufficient”.

As explained above (2.7.2), propylene oxide, when administered by oral gavage to rats, produced tumours of the forestomach, which were mainly squamous-cell carcinomas. In mice exposed by inhalation, propylene oxide produced haemangiomas and haemangiosarcomas of the nasal cavity and a few malignant nasal epithelial tumours. In a study in rats of each sex exposed by inhalation, papillary adenomas of the nasal cavity

were observed in males and females and thyroid adenomas and carcinomas were-found in females; in the second study, in males, papillary adenomas of the nasal cavity and an increased incidence of adrenal phaeochromocytomas were observed in the third study, in females, increased incidences of mammary fibroadenomas and adenocarcinomas were observed. Subcutaneous administration of propylene oxide to mice produced local sarcomas; the study in rats was inadequate for evaluation. Thus, propylene oxide induces tumours in rodents, although at high concentrations and mainly confined to the portals of entry.

Since the 1990s, there have been considerable efforts to elucidate modes of action of rodent nasal carcinogens (Bogdanffy et al. 1997). As outlined in detail by Albertini and Sweeney (2007) and Sweeney et al. (2009), the overall weight of evidence for propylene oxide indicates that this is genotoxic, but that its potency as a DNA-reactive mutagen is weak. Aspects of target tissue toxicity appear especially relevant, namely with attention to a severe concentration-dependent glutathione (GSH) depletion (see 2.1.1), and to cell proliferation, cell death, and necrosis at the nasal tissue target. Toxic tissue responses occur in the same anatomical regions in rodents as do the tumours. Some of these tissue toxicities may produce effects that either augment the DNA-reactive mutagenicity or are genotoxic by themselves.

Taking these arguments together, the DNA reactivity of propylene oxide appears to be a necessary prerequisite of its genotoxicity and of its experimental carcinogenicity in rodents. However, this seems not to be sufficient for cancer induction, and the associated tissue toxicities, which are rate-limiting, appear as major quantitative determinants (Eldridge et al., 1995; Ríos-Blanco et al., 2003). Since these are threshold effects, a practical threshold for overall cancer outcomes has been inferred (Albertini and Sweeney, 2007; Sweeney et al. 2009).

2.8 Reproductive toxicity

2.8.1 Human data

No data have been reported.

2.8.2 Animal data

New Zealand white rabbits were exposed by inhalation to 0 (17 animals) or 500 ppm propylene oxide (purity, 99%) vapour for 7 h per day on gestation days 7-19 (11 animals) or 1-19 (19 animals). Fetuses were examined on day 30. Food consumption, but not maternal body weight, was generally depressed in the treated groups during the periods of exposure. Fertility was low in all groups, but the overall resorption rate was not increased, and no adverse effect was observed in the fetuses in the treated groups. Sprague-Dawley rats were exposed by inhalation to 0 (46 animals) or 500 ppm propylene oxide (purity, 99%) vapour for 7 h per day either from three weeks before gestation to day 16 of gestation (43 animals) or on days 1-16 (41 animals) or 7-16 of gestation (44 animals). Fetuses were examined on day 21. Food consumption was reduced in females that received the pregestational exposure, and maternal weight gain tended to be lower in all treated groups during exposure. Fetal growth was lower in all treated groups than in controls. No major malformation related to treatment was seen, but the incidence of rib dysmorphology (primarily wavy ribs) was increased in all treated groups (Hardin et al., 1983a).

Hayes et al. (1988) exposed Fischer 344 rats to propylene oxide (> 99.7% pure) by inhalation (whole-body exposure) for two generations. Groups of 30 males and 30

females were exposed to 0, 30, 100 or 300 ppm propylene oxide for 6 h per day on five days per week (seven days per week from mating to end of lactation, except for four to five days during parturition) for 14 weeks, and then mated. Groups of offspring (F1) were exposed after weaning to the same levels for 17 weeks and then mated to produce F2 litters. Other than decreased body weight gain at the highest dose level, no adverse effect was seen on fertility, litter size, development or postnatal survival. Gross and histological examination of the high-dose and control pups (F1 and F2) showed no adverse effects.

A teratology study was carried out on groups of 20-23 pregnant Fischer 344 rats exposed (whole-body) to 0, 100, 300 or 500 ppm propylene oxide (> 99% pure) for 6 h per day from days 6 to 15 of gestation and killed on day 20. Maternal body weight gain was depressed at the highest dose level, but no adverse effect was observed on litter size, resorptions or fetal weight, and no increase in malformations was seen. The incidence of seventh cervical ribs was increased (13.6% versus 2.8% in controls [p = 0.026]) in the highest dose group only (Harris et al., 1989).

Recommendation

The primary aspect to be considered in deriving an OEL for propylene oxide is its local carcinogenicity with the nasal epithelium as primary target, which is well established experimentally in rats and mice. So far, there is no evidence of carcinogenity of propylene oxide from studies in humans.

Propylene oxide is the methyl homologue of ethylene oxide. Like ethylene oxide, it has alkylating properties. This leads to hydroxypropylation of biological macromolecules. Hydroxypropylation of the *N*-terminal valine in haemoglobin is used as a means of biological monitoring, and hydroxypropylation of DNA bases is viewed in conjunction with genotoxicity. Compared to ethylene oxide, the alkylating power of propylene oxide is about 4 times lower (Pauwels and Veulemans, 1998). The metabolism of both, ethylene oxide and propylene oxide, is qualitatively similar, *via* glutathione transferase and expoxide hydrolase, but differs quantitatively. At similar conditions of human industrial exposure, the levels of haemoglobin alkylation produced by propylene oxide are about 10 times lower compared to ethylene oxide exposure (Boogaard, 2002).

In contrast to ethylene oxide, the primary target of both toxicity and carcinogenicity of propylene oxide is at the port of entry into the organism. With inhalation exposure, this is the nasal epithelium. The carcinogenic potency at this site of propylene oxide is relatively weak. In long-term experiments mice, nasal tumours were observed at 400 ppm, and no tumours were seen at 200 ppm. In rats, such tumours were detected at 300 ppm, and no tumours were seen at the lower concentration of 100 ppm (chapter 2.8.2).

The EU Risk Assessment Report (ECB 2002) has addressed propylene oxide to be a genotoxic carcinogen, without an identifiable threshold. Yet, recent investigations into the mode of action of rodent nasal carcinogenesis due to propylene oxide inhalation point to decisive contributions of several factors besides genotoxicity. Upon propylene oxide inhalation, glutathione depletion is most marked in nasal respiratory mucosa, where a level of only 43% of control was observed following a single exposure of rats to 50 ppm for 6 h. At inhalation of 5 ppm the gluthathione level at this site was maintained at 90% (Lee et al., 2005; see chapter 2.1.1). This is important, because gluthatione has an important scavenging function in the detoxification of propylene oxide. For cytotoxic and proliferative changes in the nasal epithelium Eldridge et al. (1995) determined a NOAEL of 50 ppm in a 4-week study in rats (see chapter 2.5.2). Similarly, Kuper et al. (1988) found focal hyperplasia of the nasal turbinates and degenerative changes and proliferative

hyperplasia of the nasal epithelium, particularly at the highest concentration tested (300 ppm propylene oxide). At 30 ppm these responses were rated „slight“and of low incidence (and only identified in the 28-month treatment group), compared to the greater incidence of „moderate“ effects at 100 ppm (Reuzel and Kuper, 1983, Kuper et al., 1988). This study therefore points to a LOAEL of 30 ppm.

Apart from the local toxic and neoplastic effects of propylene oxide at the portal of entry into the organism, a systemic genotoxicity must be considered. Occupational genotoxicity studies performed on propylene oxide are scarce compared to those on ethylene oxide (Preston, 1999; Albertini and Sweeney, 2002). Czene et al. (2002), using the parameter of sister chromatid exchanges (SCE) in human lymphocytes, found that SCE frequencies at low occupational exposures (below 2 ppm propylene oxide) are not distinguished from those of non-exposed controls (see chapter 2.6.2). However, in view of the scattering of the general background of this parameter and of other arguments (Albertini 2003) the practical relevance of this finding is not clear.

Because there is a well-established mode of action for the local carcinogenicity (Albertini and Sweeney, 2002), propylene oxide is assigned to the SCOEL carcinogen group C, which is characterised by a practical threshold (Bolt & Huici-Montagud, 2008).

Considering (i) a LOAEL shown for local changes at the rat nasal epithelium at 30 ppm and (ii) an only minimal local glutathione depletion in the nasal tissue of the rats at 5 ppm, a health-based OEL should be set well below 5 ppm. A species scaling with regard to humans is not required in this case, as it is generally accepted that the nasal epithelium of rodents is more susceptible to irritation and irritation-based carcinogenicity than that of humans. Therefore, it is proposed to set the health-based OEL for propylene oxide at 1 ppm [2.41 mg/m^3]. This also takes into account the results of Czene et al. (2002) of a no observed SCE effect in workers below 2 ppm exposure.

According to Boogaard (2002; see chapter 2.1.3) this OEL corresponds to a BLV of 1.3 nmol N-(3-hydroxypropyl)-valine haemoglobin adduct per g globin.
There is no data available to propose a STEL.

This OEL and BLV derivation is also supported by the following:

(i) In chapter 2.6.4 it has been deduced that a mean TWA exposure of 2 ppm propylene oxide would correspond to a mean DNA adduct frequency of N^7-(2-hydroxypropyl)guanine of 3.3 x 10^8. Accordingly, the frequency of this major propylene oxide DNA adduct, induced at the proposed OEL, would be 1.65 x 10^8. This is a factor of 20 below the physiological level of the corresponding ethylene oxide adduct, N^7-(2-hydroxyethyle) guanine, in human lymphocytes of non-smokers (Zhao & Hemminki 2002; see also SCOEL/SUM/160 for ethylene oxide), and confirms that no substantial genotoxic risk is associated with the proposed OEL and BLV.

(ii) Just recently, Sweeney et al. (2009) have again compiled all arguments, based on mode of action, that propylene oxide represents a carcinogen with a practical threshold. In addition to this, they also performed calculations, based on benchmark dose modelling, of a "human reference concentration" (RfC), according to current guidance of the U.S. Environmental Protection Agency (EPA 2005). Their resulting RfC values were in a range of 0.4 - 0.7 ppm, which is close to the OEL proposed here based on threshold assumption and experimental NOAEL/LOAEL.

There are no data at present on skin absorption of propylene oxide, which could serve as a data base for a skin notation.

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