

PROPYLENE OXIDE

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Explanation

Propylene oxide is the International Organization for Standardization (ISO)–approved name for methyloxirane (International Union of Pure and Applied Chemistry) (Chemical Abstracts Service No. 75-56-9). Propylene oxide is a highly reactive, volatile compound (boiling point 34 °C) that is used, as a gas or pressurized liquid, for fumigation and sterilization to control insect infestations and microbial spoilage in a range of food commodities (e.g. herbs, spices and nuts). The primary residues detected after propylene oxide use are propylene oxide, propylene chlorohydrin (chloropropanol), propylene bromohydrin (bromopropanol) and propylene glycol.

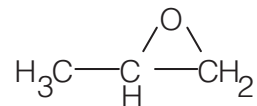
Propylene oxide was reviewed for the first time by the Joint FAO/WHO Meeting on Pesticide Residues at the request of the Codex Committee on Pesticide Residues.

The database for propylene oxide and propylene chlorohydrin consists mainly of published papers, often with limited levels of detail and no statements of compliance with good laboratory practice.

The conversion factor for propylene oxide in air is: 1 part per million (ppm) of propylene oxide is equal to 2.4 mg/m³ at 25 °C (ECB, 2002).

The structure of propylene oxide is shown in Figure 1.

Figure 1. Structure of propylene oxide



Evaluation for acceptable daily intake

1. Biochemical aspects

1.1 Absorption, distribution and excretion

(a) Oral route

No data were submitted.

(b) Dermal route

No data were submitted.

(c) Inhalation route

A review by the USEPA (2006) stated that, like ethylene oxide, propylene oxide will probably be completely absorbed, distributed throughout the body and rapidly metabolized following inhalation.

A review by ECB (2002) described a study (Nolan et al., 1980) demonstrating that male rats exposed to propylene oxide by inhalation (6 hours; 80–904 ppm) had low blood concentrations of propylene oxide (levels not stated), but there was a disproportionate increase in blood levels above 143 ppm, indicating a saturation of metabolism and/or elimination. This is contrary to the findings of another study (Golka et al., 1989), also reviewed in ECB (2002), which is cited as reporting no saturation at up to 3000 ppm.

Male F344 rats (five per group) were exposed to propylene oxide (99.99% pure; Lyondell Chemicals) by inhalation, 6 hours/day, for 1 day (10–750 ppm), 1–5 days (50 or 100 ppm) or 3–28 days (5 days/week; 5–500 ppm). At sacrifice, blood samples were taken within 2 minutes, and nasal tissues, liver and major organs were removed. Analyses were performed for propylene oxide levels in blood and for non-protein sulfhydryls in liver, blood, lung and nasal tissues. Single exposures gave a relationship between propylene oxide concentrations in blood and air, with an air concentration of 300 ppm propylene oxide equating to a concentration of approximately 12.5 $\mu\text{mol/l}$ in blood. Repeated exposures indicated a non-linear increase in propylene oxide concentrations in blood at air concentrations above 300 ppm. Non-protein sulfhydryl groups were reduced by more than 50% in nasal mucosa, lung and liver after single exposures to propylene oxide at concentrations of 300 ppm and above. After repeated exposures, the reductions in non-protein sulfhydryls were less marked in liver and lung, but still marked in nasal mucosa (Lee et al., 2005).

A physiologically based pharmacokinetic model was developed based on the results of Lee et al. (2005). The primary focus was to provide a comparison of human and rat exposures to propylene oxide following inhalation. The model indicated that systemic exposures and local concentrations in the nasal mucosa would be similar in rats and humans following inhalation exposure (Csanady & Filser, 2007).

There are no reliable data that would permit a reliable conversion of an inhalation exposure level to a systemic dose. For the purposes of this assessment, a simplistic conversion between inhalation exposures and oral dosing has been performed. For rats, this conversion assumed standard breathing rates and volumes, a body weight of 250 g and 100% absorption via each exposure route. The conversion resulted in an atmospheric concentration of 100 ppm (240 mg/m^3) inhaled for 6 hours/day, 5 days/week, being approximately equivalent to an oral dose of 40 mg/kg body weight (bw) per day in rats. The corresponding value for mice is considered to be approximately double that for rats, giving 100 ppm equivalent to 80 mg/kg bw per day. These are likely to be conservative estimates for systemic propylene oxide exposures via the oral route.

1.2 Biotransformation

Based on in vitro hydrolysis data, propylene oxide is predicted to hydrolyse very rapidly, with a half-life for hydrolysis of approximately 1 minute under the conditions found in the mammalian stomach (pH 1, 37 °C) (Meylan et al., 1986). This rapid hydrolysis was confirmed for human synthetic gastric juice (pH 1.46), with a half-life of approximately 2 minutes, but not for rat synthetic gastric juice (pH 4.8), in which the half-life was estimated to be greater than 2 hours (Todhunter, 2000). With human blood samples in vitro, the half-life was cited as being 13.6 hours (SCOEL, 2009).

A review by ECB (2002) described a study indicating that male rats exposed to propylene oxide by inhalation (6 hours; > 217 ppm) had reduced levels of hepatic non-protein sulfhydryl groups. Depression of lung and kidney sulfhydryl groups was observed at 625 ppm. This indicates a possible role for glutathione conjugation in the metabolism of propylene oxide. This review also cited the authors of a 1989 paper (Golka et al., 1989) who deduced that 96% of inhaled propylene oxide was metabolized, although the underlying reasoning is unknown.

An in vitro study with Sprague-Dawley rat liver microsomes showed that propylene oxide was a substrate for epoxide hydrolase, being hydrolysed to 1,2-propylene glycol. Of all the epoxides tested, the rate of hydrolysis was slowest for propylene oxide (Guengerich & Mason, 1980).

The limited data available indicate that the majority of propylene oxide ingested is unlikely to be systemically available. Ingested propylene oxide is likely to be hydrolysed to propylene chlorohydrin or propylene glycol in the acidic conditions of the stomach. Any absorbed propylene oxide will be extensively metabolized to propylene glycol in the liver or bound to sulfhydryl groups.

Table 1. Acute toxicity studies with propylene oxide

Species	Strain	Sex	Route	LD ₅₀ (mg/kg bw)	LC ₅₀ (mg/l)	Purity (%); batch	Vehicle	Reference
Mouse	—	—	Oral	630	—	—	Not stated	Antonova et al. (1981)
Rat	—	—	Oral	300–1000	—	—	Not stated	Rowe et al. (1956)
Rat	—	—	Oral	950	—	—	Not stated	Smyth et al. (1969)
Rat	—	—	Oral	520	—	—	Not stated	Antonova et al. (1981)
Guinea-pig	—	—	Oral	660	—	—	Not stated	Antonova et al. (1981)
Guinea-pig	—	—	Oral	690	—	—	Not stated	Smyth, Seaton & Fischer (1941)
Rabbit	—	—	Dermal	1250	—	—	Not stated	Weil et al. (1963)
Rabbit	—	—	Dermal	950	—	—	Not stated	Smyth et al. (1969)
Mouse	—	—	Inhalation 4 h	—	4.1	—	None	Jacobson, Hackley & Feinsilver (1956)
Mouse	—	—	Inhalation 4 h	—	1.0–1.5 ^a	—	None	NTP (1985); USEPA (2006)
Rat	—	—	Inhalation 4 h	—	9.5	—	None	Weil et al. (1963)
Rat	—	—	Inhalation 0.5 h	—	17	—	None	Jacobson, Hackley & Feinsilver (1956)
Rat	—	—	Inhalation 4 h	—	3.2–3.4 ^a	—	None	NTP (1985); USEPA (2006)

LC₅₀, median lethal concentration; LD₅₀, median lethal dose

^a Values calculated by USEPA (2006) based on data in NTP (1985).

2. Toxicological studies

2.1 Acute toxicity

(a) Lethal doses

Propylene oxide was of moderate acute toxicity via the oral and dermal routes and of moderate acute toxicity via the inhalation route (Table 1).

(b) Dermal and ocular irritation and dermal sensitization

A review by ECB (2002) presented conflicting results for the skin irritating properties of propylene oxide. In one study in rabbits, propylene oxide was considered to be non-irritating following a 4-hour exposure, but in another study, severe erythema and oedema progressing to scar tissue were reported in rabbits exposed for longer than 6 minutes. Propylene oxide vapour is reported to be irritating to the eye and respiratory tract (ECB, 2002). A review by USEPA (2006) categorized propylene oxide as a severe irritant to both skin and eyes.

2.2 Short-term studies of toxicity

(a) Oral administration

Mice

No data were available.

Rats

In a 1956 study cited by ECB (2002), a no-observed-adverse-effect level (NOAEL) of 200 mg/kg bw per day was reported for rats (five of each sex per group) administered propylene oxide by

gavage 18 times over 24 days. Reduced body weight gain, increased gastric irritation and unspecified hepatotoxicity were seen at 300 mg/kg bw per day (Rowe et al., 1956).

In a 1981 study, a NOAEL of 0.0052 mg/kg bw per day was reported for rats administered propylene oxide in drinking-water for 26 weeks. At 0.052 mg/kg bw per day, mild haematological effects were reported. At the highest dose of 0.52 mg/kg bw per day, polyuria, haematological changes, altered serum protein levels and increased activity of intestinal mucosa enzymes were reported (Antonova et al., 1981).

The reason for the apparent difference in NOAELs in these studies (4 orders of magnitude) is unknown. The results in the Antonova et al. (1981) paper were inconsistent with other data on propylene oxide, and the methodology was poorly described. The Meeting decided not to use the findings in the risk assessment for propylene oxide.

Dogs

No data were available.

(b) Dermal application

No data were available.

(c) Exposure by inhalation

A number of published studies have been summarized in reviews by IPCS (1985), ECB (2002) and USEPA (2006). The most appropriate reports are considered to be those from the United States National Toxicology Program (NTP, 1985), which are summarized below.

Mice

Groups of B6C3F1 mice (five of each sex per concentration) were exposed to propylene oxide (99.9% pure; lot No. UC 5/10/76) in an inhalation chamber for 6 hours/day, 10 times over 12 days. Concentrations in the chamber were 0, 20, 47, 99, 196 and 487 ppm. Animals were observed daily, weighed on days 0, 4 and 8 and at termination and subjected to a terminal gross necropsy. No histopathological examination was performed. The only finding reported was dyspnoea at 196 and 487 ppm.

Within the limitations of the study protocol, the no-observed-adverse-effect concentration (NOAEC) was 99 ppm (~240 mg/m³), based on dyspnoea at 196 ppm (NTP, 1985).

Groups of B6C3F1 mice (10 of each sex per concentration) were exposed to propylene oxide (99.9% pure; lot No. UC 5/10/76) in an inhalation chamber for 6 hours/day, 5 days/week, for 13 weeks (63 exposures). Mean time-weighted concentrations in the chamber were 0, 31, 63, 125, 250 and 500 ppm. Animals were observed daily, weighed weekly and subjected to a terminal gross necropsy. Histopathological examination was performed on a wide range of tissues from control and 500 ppm animals.

One male from the 125 ppm group died. Body weight gains were depressed approximately 40–55% at 500 ppm. No adverse effects were reported at either gross or microscopic examination.

A NOAEC of 250 ppm (600 mg/m³) can be determined, based on the body weight effects at 500 ppm (NTP, 1985).

Rats

Groups of F344/N rats (five of each sex per concentration) were exposed to propylene oxide (99.9% pure; lot No. UC 5/10/76) in an inhalation chamber for 6 hours/day, 10 times over 12 days. Concentrations in the chamber were 0, 47, 99, 196, 487 and 1433 ppm. Animals were observed daily, weighed on days 0, 4 and 8 and at termination and subjected to a terminal gross necropsy. No histopathological examination was performed. One male exposed at 1433 ppm died. Rats exposed at

1433 ppm lost weight (males) or failed to gain weight (females) and exhibited dyspnoea, hyperactivity, gasping ataxia and diarrhoea.

Within the limitations of the study protocol, the NOAEC was 487 ppm ($\sim 1200 \text{ mg/m}^3$), based on body weight loss and clinical signs at 1433 ppm (NTP, 1985).

Groups of F344/N rats (10 of each sex per concentration) were exposed to propylene oxide (99.9% pure; lot No. UC 5/10/76) in an inhalation chamber for 6 hours/day, 5 days/week, for 13 weeks (62 exposures). Mean time-weighted concentrations in the chamber were 0, 31, 63, 125, 250 and 500 ppm. Animals were observed daily, weighed weekly and subjected to a terminal gross necropsy. Histopathological examination was performed on a wide range of tissues from control and 500 ppm animals.

There were no deaths. Body weight gains were depressed approximately 15% at 500 ppm. No adverse effects were reported at either gross or microscopic examination.

A NOAEC of 250 ppm (600 mg/m^3) can be determined, based on the body weight effects at 500 ppm (NTP, 1985).

2.3 Long-term studies of toxicity and carcinogenicity

(a) Oral administration

Mice

No data were available.

Rats

Female SD rats (50 per group) received propylene oxide (99% pure; Merck-Schuschar dt) by gavage at a dose level of 15 or 60 mg/kg bw twice per week for up to 150 weeks (equal to 4.3 and 17 mg/kg bw per day). Both untreated, vehicle (salad oil) and β -propiolactone control groups were included. At necropsy, gross examinations were performed, and “pathologically noteworthy” organs were fixed, stained and examined histopathologically.

Survival was similar in untreated, vehicle and propylene oxide groups, with greater than 50% survival until approximately week 105. Within the limitations of the investigative procedure, the only organ with an increased incidence of non-neoplastic lesions and tumours was the stomach/forestomach (data not presented separately). The tumour incidence in the stomach/forestomach showed a clear dose-response relationship and is shown in Table 2. Only the most severe finding is presented in the results in the paper; that is, an animal with hyperkeratosis and carcinoma would be recorded only under the carcinoma heading. This makes it impossible to determine any association between hyperkeratosis and tumours or the absolute incidence of hyperkeratosis.

With the limited level of tissue investigation and data presentation, this study is unable to demonstrate a NOAEL for chronic toxicity because of the presence of hyperkeratosis at 4.3 mg/kg bw per day, the lowest dose tested. The lowest dose level had a slight, but not statistically significant, increase in squamous cell carcinoma of the stomach, compared with 0 in 100 control animals. The NOAEL for carcinogenicity could not be determined and would be less than 4.3 mg/kg bw per day (Dunkelberg, 1982).

(b) Exposure by inhalation

Mice

Groups of B6C3F1 mice (50 of each sex per concentration) were exposed to propylene oxide (99.9% pure; lot No. 64772) in an inhalation chamber for 6 hours/day, 5 days/week, for 2 years. Mean

Table 2. Stomach tumour and lesion incidences in female rats exposed to propylene oxide

Tumour type	Incidence of finding		
	Controls (untreated and vehicle; <i>n</i> = 100)	Propylene oxide (15 mg/kg bw; <i>n</i> = 50)	Propylene oxide (60 mg/kg bw; <i>n</i> = 50)
Squamous cell carcinoma	0	2	19
Adenocarcinoma	0	0	1
Carcinoma in situ	0	0	1
Hyperkeratosis/hyperplasia/papilloma	—	7	17
Animals with stomach tumours	0	2	20

From Dunkelberg (1982)

— incidence not specified

time-weighted concentrations in the chamber were 0, 200 (495 exposures) and 400 ppm (491 exposures). Animals were observed daily, weighed weekly and subjected to a terminal gross necropsy. Histopathological examination was performed on a wide range of tissues from all animals.

Survival was reduced in both treated groups during the second half of the study (Table 3). The survival in the 400 ppm females became less than 50% at week 88 and might have compromised the ability to investigate carcinogenic potential. Body weights were significantly lower in the 400 ppm groups during the second half of the study. No compound-related clinical signs were reported. Inflammation of the nasal epithelia was seen in all propylene oxide-treated groups (Table 3). Low incidences of squamous cell carcinoma and adenocarcinoma were present in high-dose animals; both tumours were described as arising from the submucosal glands and spread along the nerve sheaths. There was also an increase in haemangiosarcoma and haemangioma of the vascular plexus below the nasal epithelium (Table 3). These nasal tumours had not been reported in previous studies, but the degree of examination, involving three levels of the nasal turbinates, is much greater than in many other NTP mouse studies in which the turbinates were not always examined or were examined only at one level. An increase in mammary gland adenocarcinoma was seen in females, which was statistically significant in the high-dose group when corrected for survival; the incidences are within the historical control range and considered to be not clearly treatment related.

A NOAEC for site of contact toxicity cannot be derived for this study due to the inflammation of the nasal epithelia seen at both concentrations. The NOAEC for carcinogenicity was 200 ppm (480 mg/m³), based on the nasal tumours seen at 400 ppm. The NOAEC for systemic toxicity was 200 ppm, based on reduced body weight gain at 400 ppm (NTP, 1985).

Rats

Wistar rats (70 of each sex per group) were exposed to propylene oxide (> 99.9% pure, Dow Chemicals) at 0, 30, 100 or 300 ppm in the air for 6 hours/day, 5 days/week, for up to 28 months. Additional satellite groups of 10 rats of each sex were sacrificed after 12, 18 or 24 months. Animals were housed in whole-body inhalation chambers. Routine observations of morbidity, mortality and body weight were performed. Samples for haematological, clinical chemistry and urine analyses were taken at sacrifice of the satellite group animals. A gross pathological examination was performed on all animals. Major organs from all satellite animals and 20 of each sex per group at terminal sacrifice were weighed. Microscopic histopathological examinations were performed on a wide range of tissues from all control and 300 ppm animals from the 12- and 24-month satellite groups and animals killed at study termination. A limited histopathological examination, concentrating on the respiratory tract and tumours, was performed on the 18-month satellite groups and intermediate-exposure groups at the end of the study. Lungs were examined in control and 300 ppm groups only at termination.

Table 3. Findings in mice exposed to propylene oxide by inhalation for 2 years

	Incidence of finding (n = 50)					
	0 ppm		200 ppm		400 ppm	
	Males	Females	Males	Females	Males	Females
<i>Survival to termination (%)</i>	84	74	68	58	54	10
<i>Body weight (week 90) (g)</i>	38	32	37	30	30*	27*
Nasal epithelia suppurative inflammation	0	0	8*	16*	4	23*
Nasal epithelia acute/chronic inflammation	0	0	14*	14*	38*	18*
Nasal epithelia squamous metaplasia	0	0	1	0	0	2
Nasal epithelia squamous cell carcinoma (HC)	0 (0)	0 (0)	0	0	1	0
Nasal epithelia adenocarcinoma (HC)	0 (0)	0 (0)	0	0	0	2
Nasal cavity haemangiosarcoma (HC)	0 (0)	0 (0)	0	0	5*	2
Nasal cavity haemangioma (HC)	0 (0)	0 (0)	0	0	5*	3
Mammary gland adenocarcinoma (HC)	—	0 (0–12%; 2.4%)	—	3	—	3

From NTP (1985)

HC, historical control range and mean; * $P < 0.05$

Mean measured air concentrations were within 3% of nominal. Survival was greater than 50% in all groups at week 105, but subsequently there was a statistically significant ($P < 0.05$) increase in deaths in the 300 ppm groups from week 115 and in 100 ppm females at week 119. Body weights were reduced in the 300 ppm groups. There were no consistent effects on clinical chemistry, urinalysis or organ weights that were related to propylene oxide exposure. Increases in relative liver weights (10–15%) were statistically significant at 300 ppm in males sacrificed at 24 and 28 months and in females sacrificed at 24 months. Body weights were reduced slightly ($< 5\%$) in treated groups during the initial stages of the study, but not at termination; this is not considered to be biologically relevant. There were indications of increased leukocyte counts in samples taken after 100 weeks from animals exposed at 300 ppm. Local effects on the basal mucosa, nasal turbinates and olfactory epithelium were seen at 300 ppm and occasionally at 100 ppm from 12 months onwards (Table 4). Non-neoplastic findings were seen in the heart, liver, lung and kidneys at 300 ppm; the effects at 100 and 30 ppm are unclear due to the limited number of tissues examined (Table 4). There were no increases in tumour incidence in the nose or respiratory tract. Increased incidences of a number of tumours of the mammary glands and thyroid were recorded in the main groups of animals (Table 4). The incidences of multiple mammary gland tumours were increased in all treated female groups, but were reported to be within historical control ranges.

The NOAEC for systemic toxicity was 100 ppm, based on body weight gain reductions at 300 ppm. The increased mortality at 100 ppm after week 115 is not considered relevant, as this is beyond the typical lifespan of laboratory rats. The NOAEC for tumours was 300 ppm, the highest dose tested (Reuzel & Kuper, 1983).

Groups of F344/N rats (50 of each sex per concentration) were exposed to propylene oxide (99.9% pure; lot No. 6477-22) in an inhalation chamber for 6 hours/day, 5 days/week, for 2 years (491 exposures). Mean time-weighted concentrations in the chamber were 0, 200 and 400 ppm. Animals were observed daily, weighed weekly and subjected to a terminal gross necropsy. Histopathological examination was performed on a wide range of tissues from all animals.

Survival was similar in all groups and greater than 50% at study termination. Body weights were slightly lower ($< 10\%$) in the 400 ppm groups. Inflammation of the nasal cavity was increased

Table 4. Tumour and non-neoplastic lesion incidences in rats exposed to propylene oxide by inhalation

	Incidence of lesions (<i>n</i> = 70)						
	Males ^a			Females ^b			
	Control	100 ppm	300 ppm	Control	30 ppm	100 ppm	300 ppm
<i>Deaths, week 109</i>	17	18	24	14	—	18	26*
<i>No. surviving to scheduled sacrifice</i>	37	35	14*	36	—	27	15*
Mammary gland mass / suspected tumour	7	3	3	33	—	46*	48*
Mammary gland (fibro)adenoma (HC 19–67%)	1	0	0	32	30	39	47*
Multiple fibroadenoma	0	0	0	2	8*	13*	22*
Mean fibroadenomas	0	0	0	1.3	2.1	2.2	2.4
Mammary gland tubulopapillary carcinoma	0	0	0	3	6	5	8*
Brain glial cell tumour	2	0	5	0	—	0	1
Thyroid follicular adenoma	1	0	5	1	—	0	7*
Thyroid parafollicular adenoma	3	1	6	6	—	0	10
Uterus endometrial polyp	—	—	—	9	—	14	18*
Rats with tumours	49	34	53	52	—	61	67
Rats with malignant tumours	19	22	34*	6	—	14	26*
Liver, hepatocellular necrosis	1	0	6*	0	—	1	4*
Myocardial degeneration	15	1	18	3	—	0	10*
Thrombi of the heart	2	4	9*	3	—	1	3
Dilated renal tubules	9	0	11	0	—	3	7*
Olfactory epithelia basal cell hyperplasia (12 months, <i>n</i> = 10)	0	2	5*	0	—	0	7*
Olfactory epithelia basal cell hyperplasia (termination, <i>n</i> = 70)	4	10	24*	0	—	9*	33*
Alveolar bronchiolization	5	2	10	3	—	0	7

From Reuzel & Kuper (1983)

* *P* < 0.05^a No data for 30 ppm are presented, as there were no notable findings.^b Most data for 30 ppm are not presented, as there were few notable findings.

at 400 ppm and in males at 200 ppm (Table 5). Tumours of the nasal cavity (papillary adenoma) were increased in both sexes at 400 ppm, outside the historical control range. Other tumours showing increased incidences were mammary gland, uterus and thyroid tumours in females (Table 5). The uterine stromal sarcoma incidences did not exhibit a dose–response relationship, but were above the historical control range at both concentrations of propylene oxide. The thyroid gland C-cell tumours were at the upper end of the historical control range, and as there was no related increase in hyperplasia, the relationship to propylene oxide is considered equivocal. The mammary gland tumours are consistent with results in other studies but are not statistically significant and are within the historical control range; their relationship to propylene oxide is equivocal.

The NOAEC for tumours was 200 ppm, based on the increase in papillary adenomas of the nasal cavity at 400 ppm. The NOAEC for systemic toxicity was 200 ppm, based on reduced body weight gain at 400 ppm. A NOAEC for chronic site of contact toxicity could not be determined and would be less than 200 ppm, based on nasal cavity inflammation (NTP, 1985).

Table 5. Findings in rats exposed to propylene oxide by inhalation for 2 years

	Incidence of finding (<i>n</i> = 50)					
	0 ppm		200 ppm		400 ppm	
	Males	Females	Males	Females	Males	Females
<i>Survival to termination (%)</i>	60	70	66	64	62	64
<i>Body weight (week 90) (g)</i>	442	309	435	291	409	284
Nasal cavity suppurative inflammation	7	3	19*	5	33*	20*
Nasal epithelia hyperplasia	0	1	1	0	11*	5
Nasal epithelia squamous metaplasia	0	1	3	2	21*	11*
Nasal cavity papillary adenoma (HC)	0 (1/1477)	0 (3/1523)	0	0	2	3
Mammary gland fibroadenoma	0	7	2	13	2	13
Mammary gland adenocarcinoma	0	1	0	1	0	1
Thyroid C-cell adenoma/carcinoma (HC)	1	2 (mean 8%; range 2–18%)	2	2	4	7*
Uterus endometrial stromal sarcoma (HC)	—	0 (0–2%)	—	4	—	2
Adrenal medulla focal hyperplasia	2	2	2	2	10*	3
Splenic fibrosis	4	0	8	8	5	6

From NTP (1985)

HC, historical control incidence; * *P* < 0.05

2.4 Genotoxicity

Testing of the genotoxicity of propylene oxide has been performed in a wide range of assays. The overall database is considered adequate to conclude that propylene oxide is an *in vitro* genotoxin and is a potential site of contact alkylating agent *in vivo*. The level of information in many of the studies was such that it was not possible to make an independent evaluation but necessary to rely on the conclusions of the authors.

Key data on the genotoxicity of propylene oxide are summarized in [Table 6](#).

There are no *in vivo* genotoxicity data from tissues directly exposed to propylene oxide rather than its metabolites. Special investigative studies have reported that propylene oxide produces deoxyribonucleic acid (DNA) adducts (primarily *N*⁷G, plus *N*³A, *N*³C and *N*¹A) in respiratory mucosa and liver of exposed rats (IARC, 2010; see also [section 2.6](#)).

2.5 Reproductive toxicity

(a) Multigeneration studies

No data are available via the oral route.

Mice

No data are available.

Table 6. Results of studies of genotoxicity with propylene oxide

Vehicle	End-point	Test object	Concentration	Purity (%); supplier	Result	Reference
In vitro						
Water, DMSO, 0.5% tragacanth	Reverse mutation	<i>Salmonella typhimurium</i> strains TA98, TA100, TA1535, TA1537, TA1538 <i>Escherichia coli</i> WP2uvrA, CM871	1.1–700 µg/plate, with and without S9 mix	99.5; BDH	Positive with TA100 and TA1535 (±S9); negative with other strains	Bootman, Lodge & Whaley (1979)
—	Reverse mutation	<i>S. typhimurium</i> strains TA98, TA100, TA1535, TA1537, TA1538, G46, C3076, D3052 <i>E. coli</i> WP2, WP2uvrA	2.5–20 µl/plate in volatile liquid apparatus; –S9	Not specified	Positive with TA100, TA1535 and <i>E. coli</i>	McMahon, Cline & Thompson (1979)
Water	Forward mutation	<i>Schizosaccharomyces pombe</i> P1	3, 10, 30 mmol/l (sealed tube); ±S9	Not specified; Merck	Positive (±S9)	Migliore, Rossi & Loprieno (1982)
Acetone	Reverse mutation	<i>S. typhimurium</i> strains TA98, TA100, TA1535, TA1537	Up to 200 µmol/plate; –S9	99; Merck-Schuscharhardt	Positive with TA100 and TA1535	Pfeiffer & Dunkelberg (1980)
—	Reverse mutation	Chinese hamster ovary (CHO-K ₁ -BH ₄) cells	8–40 µg/cm ³ (protocol optimized for volatile compounds) (1 h)	Not specified; Kodak Chemical Co.	Positive at ≥ 8 µg/cm ³	Zamora et al. (1983)
—	Sister chromatid exchange	Human lymphocytes (two non-smoking donors)	2.5% in air (30–300 s)	Not specified; Matheson Gas	Positive at 100 and 300 s; negative at 30 s	Tucker et al. (1986)
Water	Chromosomal aberration	Human lymphocytes (two male donors)	1.85, 9.25 µg/ml; –S9 (24 h)	99.5; BDH	Positive	Bootman, Lodge & Whaley (1979)
Water or DMSO	Chromosomal aberration	Rat liver epithelial cells	25, 50, 75, 100 µg/ml; ±S9 (24 h)	Not specified; Shell Chemicals, United Kingdom	Positive (±S9)	Dean & Hodson-Walker (1979)
Methanol	DNA base reactivity	Pure chemicals from calf thymus	0.5 nmol/mg (deoxyadenosine; 68 h) 0.5 nmol/mg (deoxyguanosine; 24 h) 0.2 nmol/mg (DNA)	Not specified; Aldrich Chemical Co.	Positive	Djuric et al. (1986)

Table 6 (continued)

Vehicle	End-point	Test object	Concentration	Purity (%); supplier	Result	Reference
In vivo						
0.5% gum tragacanth	Micronucleus assay	CD-1 mouse bone marrow (gavage)	0, 100, 250, 500 mg/kg bw, twice (30 h)	99.5; BDH	Negative	Bootman, Lodge & Whaley (1979)
0.5% gum tragacanth	Micronucleus assay	CD-1 mouse bone marrow (intraperitoneal)	0, 75, 150, 300 mg/kg bw, twice (30 h)	99.5; BDH	Positive at 300 mg/kg bw	Bootman, Lodge & Whaley (1979)
0.5% gum tragacanth	Dominant lethal	Male CD-1 mouse (gavage)	0, 50, 250 mg/kg bw per day for 14 days	99.5; BDH	Negative	Bootman, Lodge & Whaley (1979)
—	Dominant lethal	Male rats	300 ppm in air; 7 h/day for 5 days prior to mating	98; Eastman Kodak	Negative	Hardin et al. (1983a)
—	Sperm head morphology	Male mice	300 ppm in air (720 mg/m ³); 7 h/day for 5 days; investigations on days 1, 3, 5, 7 and 9 post-exposure	98; Eastman Kodak	Negative	Hardin et al. (1983a)
—	Sex-linked recessive lethal	<i>Drosophila melanogaster</i>	645 ppm in air (1550 mg/m ³); 24 h	98; Eastman Kodak	Positive	Hardin et al. (1983a)

DMSO, dimethyl sulfoxide; DNA, deoxyribonucleic acid; S9, 9000 × g supernatant from livers of rats

Rats

Groups of F344 rats (30 of each sex per group) were exposed to propylene oxide (> 99.7% pure) in whole-body inhalation chambers in a two-generation reproduction study. Exposures were at 0, 30, 100 or 300 ppm, 6 hours/day, 5 days/week, during pre-mating and 7 days/week from mating to weaning. Exposures started 14 weeks prior to first mating. Offspring of the first mating were selected and exposed in a similar manner to give the F₂ generation.

There were no effects reported on mating performance, fertility, litter size, pup survival or development. Reduced body weight gain was seen in parental animals and pups at 300 ppm. There were no adverse effects reported on gross or histopathological examination of pups from control or 300 ppm groups.

The NOAEC for reproductive toxicity was 300 ppm (720 mg/m³), the highest dose tested. The NOAEC for parental and pup toxicity was 100 ppm (240 mg/m³), based on reduced body weight gain at 300 ppm (Hayes et al., 1988).

(b) Developmental toxicity

No data are available via the oral route.

Mice

No data are available.

Rats

Groups of 25 mated Fischer 344 rats were exposed to propylene oxide at 0, 100, 300 or 500 ppm for 6 hours/day on days 6–15 of gestation. Dams were killed and caesarean sections performed on day 20 of gestation. Fetuses were removed and examined for external, skeletal and visceral abnormalities.

There were no adverse effects on survival, appearance or behaviour. Maternal body weight gain was reduced at 500 ppm. There was no increase in malformations, and the NOAEC for teratogenicity was 500 ppm. There were no effects on litter size, post-implantation losses, fetal viability or litter size. The only significant developmental finding was an increase in accessory cervical ribs at 500 ppm.

The NOAEC for developmental effects was 500 ppm (1200 mg/m³), and the NOAEC for maternal effects was 300 ppm (720 mg/m³) (Harris et al., 1989).

Mated female SD rats (32–45 per group) were exposed to propylene oxide (> 99% pure) via inhalation at 500 ppm for 7 hours/day. Groups of animals were exposed on days 7–16 of gestation, on days 1–16 of gestation or from 3 weeks pre-mating until day 16 of gestation, although it is not clear which dosing regimen applied to which results. On day 21 of gestation, dams were sacrificed, uterine contents removed and fetuses examined for external, visceral and skeletal abnormalities.

There were no deaths. Body weight gain was reduced in treated animals, whereas kidney, liver, lung and spleen weights were increased. There were decreases reported in numbers of corpora lutea and implantation sites and live fetus weights, length and numbers in the group exposed pre-mating and during gestation. Increased incidences of wavy ribs and reduced ossification of the ribs and vertebrae were reported for the exposed groups, possibly secondary to maternal toxicity. There were no increases in malformations.

The single air concentration tested (500 ppm; 1200 mg/m³) was the NOAEC for teratogenicity, but a lowest-observed-adverse-effect concentration (LOAEC) for fetotoxicity and maternal toxicity (Hardin et al., 1983b).

Rabbits

Mated female New Zealand White rabbits (23–30 per group) were exposed to propylene oxide (> 99% pure) via inhalation at 500 ppm for 7 hours/day. Groups of animals were exposed on days 7–19 of gestation or days 1–19 of gestation. On day 30 of gestation, dams were sacrificed, uterine contents removed and fetuses examined for size, weight, viability and external, visceral and skeletal abnormalities.

There were reductions reported in maternal body weight gain, histopathological changes to a number of organs and increases in resorptions and minor skeletal abnormalities. There were no reported increases in malformations.

The single air concentration tested (500 ppm; 1200 mg/m³) was a NOAEC for teratogenicity, but a NOAEC could not be determined for maternal toxicity and fetotoxicity (Hardin et al., 1983b).

2.6 Special studies

(a) Adduct formation

A review by ECB (2002) cited a number of studies reporting that inhaled propylene oxide gives rise to DNA or haemoglobin adducts in a range of tissues and species, including humans. The predominant reactions are the hydroxypropylation of adenosine and guanosine bases and of histidine. In F344 rats exposed to propylene oxide (500 ppm, 6 hours/day, 5 days/week, for 4 weeks), increased levels of *N*⁷-(2-hydroxypropyl) guanine were recorded (using gas chromatography–mass spectrometry) in respiratory mucosa (835 pmol/μg) and liver (35 pmol/μg) on the day of the last exposure; 3 days after the last exposure, levels were 593 and 23 pmol/g in respiratory mucosa and liver, respectively.

(b) Stability in gastric juice

The relative stability of propylene oxide in synthetic human and rat gastric juices was determined by Thilagar, Patil & Todhunter (2000). Propylene oxide (99% pure; batch No. I4621JS) and [¹⁴C]-propylene oxide (batch No. 990119; final activity 185 kBq/ml) were incubated at 37 °C in rat or human gastric juices and analysed by high-performance liquid chromatography for the presence of propylene oxide or propylene glycol. Samples were taken at regular intervals between 10 seconds and 2 hours. The human gastric juice had a pH of 1.46, and the rat forestomach juice had a pH of 4.8. The results showed that in human gastric juice, approximately 15% of the propylene oxide had hydrolysed to propylene glycol in the first 10 seconds, and over 90% of the propylene oxide had hydrolysed within 1 hour. In contrast, in rat gastric juice, less than 5% of the propylene oxide had hydrolysed in the first minute, and less than 20% had hydrolysed in 90 minutes. These results indicate that exposures to propylene oxide, as opposed to its hydrolysis products, are likely to be significantly more prolonged in the rat stomach than in the human stomach.

(c) Studies on propylene chlorohydrin

A number of studies have been performed on the propylene oxide plant metabolite propylene chlorohydrin (chloropropanol), which are summarized in NTP (1998). The material tested in the NTP studies was batch No. B15, containing approximately 75% 1-chloro-2-propanol and 25% 2-chloro-1-propanol.

Absorption, distribution, metabolism and excretion

Following oral administration of 1-chloro-2-propanol (purity unknown) to rabbits at 140 mg/kg bw, 11% of the dose was excreted in urine as its glucuronide conjugate. In rats, 2-hydroxypropyl-mercapturic acid was identified as a urinary metabolite of orally administered 1-chloro-2-propanol.

Table 7. Acute toxicity studies with propylene chlorohydrin

Species	Strain	Sex	Route	LD ₅₀ (mg/kg bw)	LC ₅₀ (mg/l)	Purity (%); batch	Vehicle	Reference
Rat	Carworth-Wistar	—	Oral	200–250	—	—	Not stated	Smyth, Seaton & Fischer (1941); Smyth et al. (1969)
Guinea-pig	—	—	Oral	720	—	—	Not stated	
Dog	—	—	Oral	~200	—	—	Not stated	FAO (1974)
Rabbit	New Zealand White	—	Dermal	500	—	—	Not stated	Smyth et al. (1969)
Rat	—	—	Inhalation 6 h	—	> 3.8 (1000 ppm)	—	None	Gage (1970)

LC₅₀, median lethal concentration; LD₅₀, median lethal dose

Rats dosed orally for 4 days with 1-chloro-2-propanol (100 mg/kg bw per day) had *N*-acetyl-*S*-(2-hydroxypropyl)-cysteine and β -chlorolactate as major urinary metabolites. Cysteine conjugates were also identified after inhalation exposures (cited in NTP, 1998).

Lethal doses

Propylene chlorohydrin (chloropropanol) was of moderate acute toxicity via the oral and dermal routes and of moderate acute toxicity via the inhalation route (Table 7).

Dermal and ocular irritation and dermal sensitization

Propylene chlorohydrin is not irritating to the skin of rabbits (Smyth et al., 1969), but it is reported to be severely irritating to the eyes of rabbits (Carpenter & Smyth, 1946).

Short-term studies of toxicity

Groups of B6C3F1 mice (10 of each sex per dose) received 1-chloro-2-propanol (batch No. B15) in drinking-water at 0, 100, 330, 1000, 3300 or 10 000 mg/l for 14 days. All animals were necropsied and major organs weighed. An extensive range of tissues from control and top-dose animals and liver, pancreas, spleen and thymus from selected groups were examined histopathologically. Achieved doses were not reported.

One male from the 10 000 mg/l group died. Mice in the top-dose groups lost weight and had an approximately 70% reduction in water consumption. At 3300 mg/l, body weight gain was similar to that of controls, with water consumption reduced by 20–40%. Atrophy of the spleen was present in top-dose groups. Pancreatic acinar cell alterations together with pancreatic degeneration and bone marrow atrophy were present in both sexes at and above 3300 mg/l. Hepatocyte vacuolation (mainly periportal) incidence was increased significantly at 1000 mg/l and above, with non-significant increases at 330 mg/l and in males at 100 mg/l.

A NOAEL of 330 mg/l (approximately 100 mg/kg bw per day, based on the values for the 14-week study) can be determined, based on the statistically significant increase in hepatocyte vacuolation in both sexes at 1000 mg/l (NTP, 1998).

Groups of B6C3F1 mice (10 of each sex per dose) received 1-chloro-2-propanol (batch No. B15) in drinking-water at 0, 33, 100, 330, 1000 or 3300 mg/l for 14 weeks. Achieved doses were reported to be 0, 5, 15, 50, 170 and 340 mg/kg bw per day in males and 0, 7, 20, 70, 260 and 340 mg/kg bw per day in females. All animals were necropsied and major organs weighed. A sample for haematology was taken at study termination. An extensive range of tissues from control and top-dose animals

Table 8. Findings in a 14-week mouse study with propylene chlorohydrin in drinking-water

	0 mg/l		33 mg/l		100 mg/l		330 mg/l		1000 mg/l		3300 mg/l	
	M	F	M	F	M	F	M	F	M	F	M	F
Water consumption, week 13 (g/day)	4.1	6.0	5.0	5.8	4.6	6.3	4.4	5.6	4.2	5.1	3.1*	3.4*
Haemoglobin (g/dl)	17.6	18.6	17.6	18.2	17.5	17.8	17.7	18.4	17.1*	17.3*	15.9*	18.0
Erythrocytes (10 ⁶ /μl)	10.5	9.6	10.5	10.3	10.3	10.2	10.5	10.4	10.2	10.0	9.5*	10.5*
Reticulocytes (10 ⁶ /μl)	0.23	0.20	0.26	0.18	0.19	0.17	0.22	0.19	0.24	0.18	0.25	0.24
Pancreas acinar cell degeneration (n = 10)	0	0	0	0	0	0	0	0	2	0	10*	9*
Pancreas fatty change (n = 10)	0	0	0	0	0	0	0	1	2	0	9*	4
Hepatocyte vacuolation (n = 10)	0	0	0	7*	0	10*	0	7*	0	9*	0	10*
Epididymis weight (g)	0.053	—	0.049	—	—	—	0.048	—	—	—	0.059*	—
Abnormal sperm (%)	1.4	—	1.8	—	—	—	1.6	—	—	—	1.7	—

From NTP (1998)

F, female; M, male; * $P < 0.05$

and pancreas, liver and kidneys from all groups were examined histopathologically. An extensive examination of sperm morphology, numbers and motility was performed on all male animals from the control, 33, 330 and 3300 mg/l groups. Estrous cycling was examined in all females.

One male from the 330 mg/l group died during the study. Mice in the top-dose groups had significant reductions (20–40%) in water consumption. Erythrocyte parameters indicative of mild anaemia were present in males at and above 1000 mg/l (Table 8). Pancreatic acinar cell alterations together with pancreatic fatty change were present in both sexes at 3300 mg/l. Vacuolation of hepatocytes (primarily centrilobular) was significantly increased in all female groups, but not in males (Table 8). The severity of renal tubule vacuolation was increased in males at and above 1000 mg/l. Epididymal weights were increased at 3300 mg/l, but there were no adverse effects on measured sperm parameters (Table 8).

No NOAEL could be determined because of the high incidences of hepatocyte vacuolation in all treated female groups (NTP, 1998).

Groups of F344/N rats (10 of each sex per dose) received 1-chloro-2-propanol (batch No. B15) in drinking-water at 0, 100, 330, 1000, 3300 or 10 000 mg/l for 14 days. All animals were necropsied and major organs weighed. An extensive range of tissues from control and top-dose animals and pancreas, spleen, bone marrow and uterus from selected groups were examined histopathologically. Achieved doses were not reported.

Two females from the 10 000 mg/l group died. Rats in the top-dose groups lost weight and had an 80% reduction in water consumption. At 3300 mg/l, body weight gain was reduced by approximately 30%, with water consumption reduced by 40–50%. Haematopoiesis was present in the spleen of the 3300 mg/l groups. Pancreatic acinar cell alterations together with pancreatic degeneration and bone marrow atrophy were present in both sexes at and above 3300 mg/l and in females at 1000 mg/l.

A NOAEL was not determined in females, as the pancreas was not examined at doses below 1000 mg/l (approximately 200 mg/kg bw per day, based on the values for the 14-week study) (NTP, 1998).

Groups of F344/N rats (10 of each sex per dose) received 1-chloro-2-propanol (batch No. B15) in drinking-water at 0, 33, 100, 330, 1000 or 3300 mg/l for 14 weeks. Achieved doses were reported

Table 9. Findings in a 14-week rat study with propylene chlorohydrin in drinking-water

	0 mg/l		33 mg/l		100 mg/l		330 mg/l		1000 mg/l		3300 mg/l	
	M	F	M	F	M	F	M	F	M	F	M ^a	F
Body weight gain (g)	267	108	257	106	254	109	260	104	258	100	196*	82*
Water consumption, week 13 (g/day)	22	18	21	17	23	17	22	19	20	17	14*	9*
Haemoglobin (g/dl)	16.4	16.9	16.7	16.3*	16.5	16.7	16.7	16.7	16.4	15.9*	15.7*	16.0*
Erythrocytes (10 ⁶ /μl)	8.7	8.3	8.9	8.1	8.7	8.3	9.1	8.3	8.9	7.9*	8.6	7.6*
Reticulocytes (10 ⁶ /μl)	0.26	0.15	0.22	0.20*	0.21	0.19	0.22	0.18	0.22	0.18	0.27	0.33*
Pancreas acinar cell degeneration (n = 10)	0	0	0	0	0	0	0	0	10*	10*	9*	10*
Pancreas fatty change (n = 10)	0	0	0	0	0	0	0	1	10*	10*	9*	10*
Hepatocyte vacuolation (n = 10)	0	—	1	—	6*	—	2	—	7*	—	10*	—
Cauda epididymis weight (g)	0.15	—	0.14	—	—	—	0.14	—	—	—	0.12*	—
Epididymis weight (g)	0.47	—	0.45	—	—	—	0.47	—	—	—	0.42*	—
Abnormal sperm (%)	0.78	—	0.90	—	—	—	0.86	—	—	—	1.5*	—

From NTP (1998)

F, female; M, male; * $P < 0.05$ ^a $n = 9$.

to be 0, 5, 10, 35, 100 and 220 mg/kg bw per day. All animals were necropsied and major organs weighed. Blood samples for clinical chemistry were taken on days 3, 15 and 45 and at study termination. Urinalysis was performed on day 14 and at study termination. A sample for haematology was taken at study termination. An extensive range of tissues from control and top-dose animals and pancreas (both sexes) and liver (males) from all groups were examined histopathologically. An extensive examination of sperm morphology, numbers and motility was performed on all male animals from the control, 33, 330 and 3300 mg/l groups. Estrous cycling was examined in all females.

There were no deaths during the study and no notable effects on estrous cycling or clinical chemistry. Rats in the top-dose groups had significant reductions in body weight gain (20–25%) and in water consumption (40–50%). Urinalysis results were consistent with the reduced water intake, showing a reduction in volume and an increase in specific gravity at the top dose level. Erythrocyte parameters indicative of mild anaemia were present in both sexes at 3300 mg/l and in females dosed at 1000 mg/l (Table 9). Pancreatic acinar cell alterations together with pancreatic fatty change were present in both sexes at and above 1000 mg/l. Vacuolation of hepatocytes (primarily centrilobular) was significantly increased in males from the 100, 1000 and 3300 mg/l groups, but not at 330 mg/l (Table 9); the finding at 100 mg/l is not considered as adverse, as it was not seen at 330 mg/l, and the NTP (1998) report indicated that the change is considered to be of minimal biological significance. Epididymal weights were reduced and abnormal sperm numbers were increased at 3300 mg/l (Table 9).

A NOAEL of 330 mg/l (equal to 35 mg/kg bw per day) was determined, based on the range of findings at 1000 mg/l (NTP, 1998).

Long-term studies of toxicity and carcinogenicity

Groups of B6C3F1 mice (50 of each sex per dose) received 1-chloro-2-propanol (batch No. B15) in drinking-water at 0, 250, 500 or 1000 mg/l for 2 years. All animals were necropsied, and an extensive range of tissues from all animals were examined histopathologically. Achieved doses were 0, 45, 75 and 150 mg/kg bw per day in males and 0, 25, 50 and 100 mg/kg bw per day in females.

Survival was good (> 60% at termination) and similar across treated and control groups. There were no effects on body weight, water consumption or histopathology findings. Tumour incidences and patterns were similar in treated and control groups.

The NOAEL for general toxicity and carcinogenicity was 1000 ppm (equal to 100 mg/kg bw per day), the highest dose tested (NTP, 1998).

Groups of F344/N rats (50 of each sex per dose) received 1-chloro-2-propanol (batch No. B15) in drinking-water at 0, 150, 325 or 650 mg/l for 2 years. All animals were necropsied, and an extensive range of tissues from all animals were examined histopathologically. Achieved doses were 0, 8, 17 or 34 mg/kg bw per day.

Survival was acceptable in treated groups (> 45% in males and > 60% in females at termination) and similar across treated and control groups. There were no effects on body weight, water consumption or histopathology findings. Tumour incidences and patterns were similar in treated and control groups.

The NOAEL for general toxicity and carcinogenicity was 650 ppm (equal to 34 mg/kg bw per day), the highest dose tested (NTP, 1998).

Genotoxicity

Testing of the genotoxicity of propylene chlorohydrin has been performed in a range of assays. The overall database is considered adequate to conclude that propylene chlorohydrin is an in vitro genotoxin. The response in the chromosomal aberration assay in the presence of S9 was very high, with 75% or more aberrant cells compared with 4% in controls. The weight of evidence is that propylene chlorohydrin is not genotoxic in vivo.

Key data on the genotoxicity of propylene chlorohydrin are summarized in [Table 10](#).

Reproductive and developmental toxicity

In a continuous-breeding protocol, groups of Sprague-Dawley rats (VAF CrI:CD BR) received 1-chloro-2-propanol (batch No. B15) in the drinking-water at 0, 300, 650 or 1300 mg/l. There were 40 control pairs and 20 treated pairs per dose level. Exposure was for 112 days for both sexes, plus 21 days in females for delivery of the final litter. Parameters examined included pregnancy index, litters per pair, litter size, pup viability and pup body weight. Pups from the final litters (20 of each sex) from the control and 1300 mg/l groups were allowed to mature and mated to produce the F₂ litters. At necropsy of the final litter (F₁ parents), epididymal sperm data were collected from control and top-dose animals, and reproductive organs were weighed and examined histopathologically.

Maternal body weights were reduced at 650 and 1300 mg/l. There were no significant or consistent changes to reproductive parameters over the five litters produced. The only effects seen in the final F₁ litters were reduced body weights of pups at 650 (~10%) and 1300 mg/l (~20%). In the mating for the F₂ litter (control and 1300 mg/l only), the mean weight of dams at delivery was reduced (~20%), and there was an increase in abnormal epididymal sperm (2.4% versus 0.8% in controls) in male parents; the estrous cycle was slightly extended (4.6 days versus 4.2 days in controls), but this was not statistically significant. These effects had no impact on reproductive outcome, as there were no effects on any reproductive parameters or pup viability.

The NOAEL for reproductive toxicity was 1300 ppm (equal to 130 mg/kg bw per day), the highest dose tested. The NOAELs for offspring and parental toxicity were 300 ppm (equal to 30 mg/kg bw per day), based on deficits in body weight at 650 ppm (NTP, 1998).

Groups of female rats (five per group) received propylene chlorohydrin by gavage at a dose of 0, 8, 20, 50 or 125 mg/kg bw per day on days 6–15 of gestation. Fetuses were examined only for gross external abnormalities.

Maternal body weight gain was reduced at the top dose level of 125 mg/kg bw per day. There were no treatment-related increases in external findings and no effects on viable fetal numbers.

Table 10. Results of studies of genotoxicity with propylene chlorohydrin (1-chloro-2-propanol)

Vehicle	End-point	Test object	Concentration	Purity (%); supplier	Result	Reference
In vitro						
—	Reverse mutation	<i>Salmonella typhimurium</i> strains TA97, TA98, TA100, TA1535, TA1537	100–10 000 µg/plate, with and without S9 mix	Not specified; Radian Corp., Austin, TX, USA	Positive with TA1535 (±S9), equivocal with TA100; negative with other strains	NTP (1998)
—	Chromosomal aberrations	Chinese hamster ovary cells	3000, 4000 or 5000 µg/ml, with and without S9 mix	Not specified; Radian Corp., Austin, TX, USA	Positive (±S9)	NTP (1998)
—	Sister chromatid exchanges	Chinese hamster ovary cells	167–4000 µl/plate without S9 mix; 167–1700 µl/plate with S9 mix	Not specified; Radian Corp., Austin, TX, USA	Positive (±S9)	NTP (1998)
Acetone	Reverse mutation	<i>S. typhimurium</i> strains TA98, TA100, TA1535, TA1537	Up to 120 µmol/plate without S9	99; Merck-Schusardt	Positive with TA100 and TA1535; less potent (~10-fold) than propylene oxide	Pfeiffer & Dunkelberg (1980)
In vivo						
—	Sex-linked recessive mutation	<i>Drosophila melanogaster</i> (feed)	200 mg/kg for 3 days	Not specified; Radian Corp., Austin, TX, USA	Negative	NTP (1998)
Saline	Sex-linked recessive mutation	<i>D. melanogaster</i> (injection into abdomen)	1000 mg/l	Not specified; Radian Corp., Austin, TX, USA	Positive	NTP (1998)
Saline	Reciprocal chromosome translocations	<i>D. melanogaster</i> (injection into abdomen)	1000 mg/l	Not specified; Radian Corp., Austin, TX, USA	Negative	NTP (1998)
Drinking-water	Micronucleus assay	B6C3F1 mouse peripheral blood	0, 33, 100, 330, 1000, 3300 mg/l for 14 weeks	Not specified; Radian Corp., Austin, TX, USA	Negative	NTP (1998)

This study is inadequate, in terms of group size and extent of investigations, to permit identification of a NOAEL for developmental toxicity (Phillips, 1980).

(d) Studies on propylene bromohydrin

Propylene bromohydrin (1-bromo-2-propanol; 2-bromo-1-propanol) is a plant metabolite formed following the use of propylene oxide. No in vivo toxicity data were available for evaluation. Genotoxicity data show that propylene bromohydrin is genotoxic in vitro. Comparative data indicate that in some bacterial mutagenicity tests, the bromopropanol derivatives are more potent mutagens than the equivalent chloro- compounds (NTP, 1985).

(e) *Studies on propylene glycol*

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) established an acceptable daily intake (ADI) of 0–25 mg/kg bw per day for propylene glycol (1,2-propanediol), last evaluated in 2002 (FAO/WHO, 2002).

3. Observations in humans

3.1 Workplace monitoring

(a) *Propylene oxide*

Haemoglobin adducts (hydroxypropylvaline) were increased significantly in a starch alkylation factory, from 20 pmol/g haemoglobin in controls to 230–3500 pmol/g haemoglobin in exposed workers. In a Chinese factory, a group of eight workers exposed to propylene oxide had hydroxypropylvaline levels of 0.13–4.9 nmol/g haemoglobin compared with a control level of less than 0.01 nmol/g haemoglobin (Czene et al., 2002). 1-Hydroxypropyladenine was reported in the leukocytes of a group of workers at a Chinese propylene oxide production plant (Czene et al., 2002). Epidemiological studies of workers exposed to propylene oxide as well as other chemicals have been inconclusive. A number of cohort studies have been performed covering workers exposed to ethylene oxide and propylene oxide. IARC (1994, 2010) concluded that there were limitations to the studies, in particular relating to exposure characterization and correction for confounders such as smoking, and that further epidemiological investigations of propylene oxide-exposed cohorts should be performed.

(b) *Propylene chlorohydrin*

An epidemiological study, published in 1990, of workers at a plant producing both ethylene chlorohydrin and propylene chlorohydrin reported an excess of mortality due to pancreatic cancer (odds ratio 4.2) and leukaemia (odds ratio 7.5) in operators working in the chlorohydrin unit for over 2 years. Nine of the 10 decedents had worked in the plant between 1935 and 1945. There were significant trends with duration of employment in the chlorohydrin plant and both cancers. Although no data are available on exposures to chlorohydrins or related chemicals, the authors concluded that the pancreatic cancers and leukaemias were associated with the production of ethylene chlorohydrin and/or propylene chlorohydrin (Greenberg, Ott & Shore, 1990). A second study at the plant confirmed increased risks for pancreatic cancer and leukaemia and identified increased risks with increasing duration of employment for total cancers and all lymphatic and haematopoietic cancers. The authors suggested that exposure to high concentrations of ethylene dichloride, possibly with other chlorinated hydrocarbons, was the most likely causative agent (Benson & Teta, 1993).

Comments

Biochemical aspects

There are no reliable in vivo data on the kinetics or biotransformation of propylene oxide. By analogy with ethylene oxide, it is likely that propylene oxide is rapidly and extensively absorbed via the inhalation route. Oral exposure to propylene oxide is likely to result in hydrolysis to propylene glycol in the stomach. In vitro work has shown that propylene oxide hydrolyses significantly more rapidly in human synthetic gastric juice (pH 1.46; half-life ~2 minutes) than in rat synthetic gastric juice (pH 4.8; half-life > 2 hours). Absorbed propylene oxide is likely to be hydrolysed to propylene glycol by epoxide hydrolase or bind to non-protein sulfhydryl groups, such as glutathione. There are no data that permit comparison of systemic exposures to propylene oxide by the inhalation and oral

routes. It is expected that inhalation exposures to propylene oxide will result in greater systemic levels than equivalent oral exposures when account is taken of the likely hydrolysis rates in the human stomach combined with kinetic data on propylene oxide levels in blood following inhalation exposure and a physiologically based pharmacokinetic model for inhalation exposures to propylene oxide.

For the purposes of this assessment, a simplistic conversion between inhalation exposures and oral dosing has been performed. For rats, this conversion assumed standard breathing rates and volumes, a body weight of 250 g and 100% absorption via each exposure route. The conversion resulted in an atmospheric concentration of 100 ppm (240 mg/m³) inhaled for 6 hours/day, 5 days/week, being approximately equivalent to an oral dose of 40 mg/kg bw per day in rats. The corresponding value for mice is considered to be approximately double that for rats, giving 100 ppm equivalent to 80 mg/kg bw per day. These are likely to be conservative estimates for systemic propylene oxide exposures via the oral route.

Toxicological data

The acute toxicity of propylene oxide has been investigated orally (mouse and rat LD₅₀s 300–1000 mg/kg bw), dermally (rabbit LD₅₀s 950–1250 mg/kg bw) and by inhalation (mouse and rat LC₅₀s 1.0–9.5 mg/l). Propylene oxide is an irritant to skin, respiratory tract and eyes. There are no data on its sensitizing potential.

Short-term studies of toxicity with propylene oxide have been performed in mice and rats, mainly via the inhalation route, in which no systemic effects other than body weight deficits were evident. No effects on the nasal cavity were reported in rats or mice exposed for 13 weeks (6 hours/day, 5 days/week) at up to 500 ppm. In a gavage study in rats dosed 18 times in 24 days, reduced body weight gain, gastric irritation and hepatotoxicity were reported at 300 mg/kg bw per day, with a NOAEL of 200 mg/kg bw per day.

In a chronic toxicity and carcinogenicity study in mice exposed via inhalation at 200 or 400 ppm for 6 hours/day, 5 days/week, survival was reduced at both concentrations. Body weights were significantly lower in the 400 ppm groups during the second half of the study. Inflammation of the nasal epithelia was seen in all treated groups. Low incidences of squamous cell carcinoma and adenocarcinoma of the nasal epithelia were present in high-dose animals. There was also an increase in haemangiosarcoma and haemangioma of the vascular plexus below the nasal epithelium. An increase in mammary gland adenocarcinoma was seen in females, which was statistically significant in the high-dose group when corrected for survival; the incidences are within the historical control range and considered to be not clearly treatment related. A NOAEC for site of contact toxicity cannot be derived for this study due to the inflammation of the nasal epithelia seen at both concentrations. The NOAEC for carcinogenicity was 200 ppm (equivalent to approximately 160 mg/kg bw per day orally), based on the nasal tumours seen at 400 ppm (equivalent to approximately 320 mg/kg bw per day orally). The NOAEC for systemic toxicity was 200 ppm (equivalent to approximately 160 mg/kg bw per day orally), based on reduced body weight gain at 400 ppm (equivalent to approximately 320 mg/kg bw per day orally).

In a published 150-week study, female rats were exposed to propylene oxide by gavage twice a week at 15 or 60 mg/kg bw per administration (equal to 4.3 or 17 mg/kg bw per day). The extent of the tissues examined and level of reporting are less than those carried out in a normal regulatory study, with minimal or no reporting of body weights, clinical signs or non-neoplastic lesions. Within the limitations of the investigative procedure, the only organ with an increased incidence of non-neoplastic lesions (hyperkeratosis) or tumours was the stomach/forestomach (data not presented separately). The incidence of squamous cell carcinoma in the stomach/forestomach showed a clear dose–response relationship. The lowest dose level gave a slight increase in squamous cell carcinoma of the stomach/forestomach. The NOAEL for carcinogenicity was less than 4.3 mg/kg bw per day.

The study did not demonstrate a NOAEL for chronic toxicity because of the presence of hyperkeratosis at 4.3 mg/kg bw per day, the lowest dose tested.

In a 28-month inhalation study in rats, survival was reduced in the 300 ppm groups and in 100 ppm females at the end of the study (after week 115). Body weights were reduced in the 300 ppm groups. Increases in relative liver weights (10–15%) were statistically significant at 300 ppm in males sacrificed at 24 and 28 months and in females sacrificed at 24 months. Local effects on the basal mucosa, nasal turbinates and olfactory epithelium were seen at 300 ppm and occasionally at 100 ppm from 12 months onwards. Non-neoplastic findings were seen in the heart, liver, lung and kidneys at 300 ppm; the effects at 100 and 30 ppm are unclear because of the limited number of tissues examined. There were no increases in tumour incidence in the nose or respiratory tract. Increased incidences of mammary gland fibroadenomas and thyroid tumours (follicular cell adenoma and parafollicular cell adenoma) were recorded in the 300 ppm groups. The incidences of multiple mammary gland tumours were increased in all treated female groups but were reported to be within the historical control range. A NOAEC for systemic effects was 100 ppm (equivalent to approximately 40 mg/kg bw per day orally), based on body weight gain reductions at 300 ppm (equivalent to approximately 120 mg/kg bw per day orally). The increased mortality at 100 ppm at week 115 is not considered relevant, as this is beyond the normal lifespan of laboratory rats.

In a second chronic inhalation study, rats were exposed to propylene oxide at 0, 200 or 400 ppm for 6 hours/day, 5 days/week, for 2 years. Body weights were slightly lower (< 10%) in the 400 ppm groups than in controls. Inflammation of the nasal cavity was increased at 400 ppm and in males at 200 ppm. Tumours of the nasal cavity (papillary adenoma) were increased in both sexes at 400 ppm, outside the historical control range. Other tumours showing increased incidences were mammary gland, uterus and thyroid tumours in females. The uterine stromal sarcoma incidences were above the historical control range at both concentrations of propylene oxide, but did not exhibit a dose–response relationship. The thyroid gland C-cell tumours were at the upper end of the historical control range, and as there was no related increase in hyperplasia, the relationship to propylene oxide is considered equivocal. The mammary gland tumours were not increased statistically significantly and were within the historical control range, but are consistent with results in other studies, and their relationship to propylene oxide is equivocal. The NOAEC for tumours was 200 ppm (equivalent to approximately 80 mg/kg bw per day orally), based on the increase in papillary adenomas of the nasal cavity at 400 ppm (equivalent to approximately 160 mg/kg bw per day orally). The NOAEC for chronic site of contact toxicity was less than 200 ppm (equivalent to approximately 80 mg/kg bw per day orally), based on nasal cavity inflammation. For systemic toxicity, the NOAEC was 200 ppm (equivalent to approximately 80 mg/kg bw per day orally), based on reduced body weight gain at 400 ppm (equivalent to approximately 160 mg/kg bw per day orally).

Evidence of carcinogenicity was seen in long-term studies of toxicity and carcinogenicity with propylene oxide in rats via both oral (stomach/forestomach) and inhalation routes (nasal cavity and mammary tumours) and in mice via inhalation (nasal cavity and mammary tumours). The relevance of these tumours to human exposures to relatively low levels of propylene oxide via the diet is equivocal. In vitro work has shown that propylene oxide hydrolyses significantly more rapidly in human synthetic gastric juice than in rat synthetic gastric juice. This indicates that the stomach tumours seen in the rat gavage study might be associated with a much more prolonged exposure to propylene oxide than would occur in humans.

Similarly, for the nasal cavity tumours seen in the inhalation studies with rats and mice, these could be associated with chronic irritation of the epithelial cells and depletion of sulfhydryl groups and not relevant to oral exposures. However, there have been no specific mechanistic investigations to demonstrate that site of contact mutagenic effects do not occur. A threshold concentration for nasal tumours in chronic studies appears to be 300 ppm (720 mg/m³), which is consistent with data on non-protein sulfhydryl group depletion in nasal mucosa.

In mice and rats exposed to propylene oxide by inhalation, increases in mammary tumours were noted, but these were reported to be within the historical control ranges.

The Meeting concluded that there was no convincing evidence that propylene oxide caused systemic tumorigenicity in mice and rats.

The potential genotoxicity of propylene oxide has been investigated in an adequate battery of tests *in vitro* and *in vivo*. Positive results were seen in a range of *in vitro* assays. *In vivo* assays (for micronuclei and dominant lethal mutations) using oral administration were negative; positive results were seen following high-dose intraperitoneal administration in mice and a high-concentration inhalation study in fruit flies. There are no *in vivo* data from tissues directly exposed to propylene oxide rather than its metabolites. Propylene oxide produces DNA adducts (primarily *N*⁷G, plus *N*³A, *N*³C and *N*¹A) in respiratory mucosa and liver of exposed rats, and 1-hydroxypropyladenine was reported in the leukocytes of a group of propylene oxide production plant workers.

The Meeting concluded that propylene oxide is genotoxic *in vitro* but is unlikely to be genotoxic via the oral route due to hydrolysis to propylene glycol in the stomach.

The Meeting concluded that propylene oxide is carcinogenic to experimental animals at the site of initial contact, but because of the likely rapid hydrolysis to propylene glycol in the human stomach and negative genotoxicity *in vivo* via oral administration, it is unlikely to be carcinogenic to humans following exposure via the oral route to propylene oxide residues in the diet.

No oral studies of reproductive toxicity or developmental toxicity are available. In a rat reproductive toxicity study using inhalation exposure, there were no effects reported on mating performance, fertility, litter size, pup survival or development at the highest concentration tested (300 ppm, 6 hours/day, 5 days/week). Reduced body weight gain was seen in parental animals and pups at 300 ppm. The NOAEC for reproductive toxicity was 300 ppm (equivalent to approximately 120 mg/kg bw per day orally), the highest dose tested. The NOAEC for parental and pup toxicity was 100 ppm (equivalent to approximately 40 mg/kg bw per day orally), based on reduced body weight gain at 300 ppm (equivalent to approximately 120 mg/kg bw per day orally).

The Meeting concluded that propylene oxide does not adversely affect reproduction via the inhalation route at exposure concentrations producing parental toxicity.

In a well-reported developmental toxicity study, rats were exposed to propylene oxide at 0, 100, 300 or 500 ppm for 6 hours/day on days 6–15 of gestation. Maternal body weight gain was reduced at 500 ppm. There was no increase in malformations, and the NOAEC for teratogenicity was 500 ppm (equivalent to approximately 260 mg/kg bw per day orally).¹ There were no effects on litter size, post-implantation losses, fetal viability or litter size. The only significant developmental finding was an increase in accessory cervical ribs at 500 ppm. The NOAECs for maternal and developmental effects were both 300 ppm (equivalent to approximately 160 mg/kg bw per day orally). In a limited developmental toxicity study, rats were exposed by inhalation to a single concentration of propylene oxide (500 ppm) for 7 hours/day during various phases of gestation. Body weight gain was reduced in treated animals, whereas kidney, liver, lung and spleen weights were increased. There were decreases reported in numbers of corpora lutea and implantation sites and live fetus weights, length and numbers. The only visceral, skeletal or external alterations were increased incidences of wavy ribs and reduced ossification of the ribs and vertebrae in the exposed groups. The single air concentration tested (500 ppm; equivalent to approximately 200 mg/kg bw per day orally) is a NOAEC for teratogenicity and a LOAEC for maternal and developmental toxicity. In an almost identical study in rabbits, there were reductions reported in maternal body weight gain, histopathological changes in a number of organs and increases in resorptions and minor skeletal abnormalities. There were no reported increases in malformations. The single concentration tested (500 ppm; equivalent

¹ A different conversion rate was used, as exposures occurred every day as opposed to 5 days/week.

to approximately 75 mg/kg bw per day orally) is reported to be a NOAEC for teratogenicity and a LOAEC for maternal and developmental toxicity in rabbits.

The Meeting concluded that propylene oxide produced developmental toxicity via the inhalation route, but the available evidence indicated that it was not teratogenic.

Hydroxypropylvaline adducts of haemoglobin have been detected in workers in industrial facilities using or producing propylene oxide. 1-Hydroxypropyladenine was reported in the leukocytes of a group of propylene oxide production plant workers. Epidemiological studies of workers exposed to propylene oxide as well as other chemicals have been inconclusive.

Biochemical and toxicological data on propylene chlorohydrin

Propylene chlorohydrin (1-chloro-2-propanol, 2-chloro-1-propanol) is a plant metabolite formed following the use of propylene oxide. Data have been generated on a 3:1 mixture of 1-chloro-2-propanol and 2-chloro-1-propanol.

Biochemical aspects

Limited, qualitative data indicate that propylene chlorohydrin is absorbed following oral administration, conjugated to glucuronic acid or glutathione and excreted in the urine.

Toxicological data

The acute toxicity of propylene chlorohydrin has been investigated via the oral route (rat LD₅₀ 200–250 mg/kg bw), the dermal route (rabbit LD₅₀ 500 mg/kg bw) and inhalation (rat LC₅₀ > 3.8 mg/l). Propylene chlorohydrin is not irritating to rabbit skin but is a severe eye irritant. There are no data on its skin sensitizing potential.

In a 14-day drinking-water study in mice, reductions in body weight were seen at the top dose level (10 000 mg/l). Alterations in pancreatic acinar cells and pancreatic degeneration and hepatocyte vacuolation were reported at 3300 mg/l and above. The NOAEL was 330 mg/l (equivalent to 33 mg/kg bw per day), based on hepatocyte vacuolation at 1000 mg/l (equivalent to 100 mg/kg bw per day). In a subsequent 14-week study, findings were similar (including pancreatic acinar cell degeneration and fatty change of the pancreas), but it was not possible to identify a NOAEL due to hepatocyte vacuolation at the lowest dose tested, 33 mg/l (equal to 7 mg/kg bw per day).

In a 14-day drinking-water study in rats, reduced body weight was seen at high dose levels. Indications of red cell effects (splenic haematopoiesis, bone marrow atrophy) were present at 3300 mg/l and above, and pancreatic degeneration/acinar cell changes were seen at 3300 mg/l and above in males and at 1000 mg/l and above in females. A NOAEL could not be determined because of the limited investigations at dose levels below 1000 mg/l (equal to 100 mg/kg bw per day). In an equivalent 14-week study, body weight, erythrocyte, pancreas and liver effects were seen at 1000 mg/l, with a NOAEL of 330 mg/l (equal to 35 mg/kg bw per day).

Chronic toxicity and carcinogenicity studies have been performed in mice and rats exposed to propylene chlorohydrin in the drinking-water for 2 years. In both of the studies, there were no indications of carcinogenicity or general toxicity, including of the pancreas and liver. Haematological and clinical chemistry examinations were not performed. The NOAELs were the highest concentrations tested, 1000 mg/l (equal to 100 mg/kg bw per day) in mice and 650 mg/l (equal to 34 mg/kg bw per day) in rats.

The potential genotoxicity of propylene chlorohydrin has been investigated in an adequate battery of tests in vitro and in vivo. Positive results were seen in a range of in vitro assays. Negative results were seen in vivo with oral administration, although a mutation assay in *Drosophila* using injection administration was positive.

The Meeting concluded that propylene chlorohydrin is genotoxic in vitro but unlikely to be genotoxic in vivo.

Taking note of the absence of genotoxicity in vivo in mammals and the absence of carcinogenicity in rats and mice, the Meeting concluded that propylene chlorohydrin is unlikely to be carcinogenic to humans.

In a continuous breeding reproductive toxicity study, rats were exposed to propylene chlorohydrin in drinking-water over two generations. Reduced body weight gain was seen in dams and pups at 650 mg/l. There were no adverse effects on reproduction or pup viability at any dose level. An increase in numbers of abnormal sperm and slightly extended estrus were reported in parental animals at 1300 mg/l, but these were without any reproductive consequence and are considered not to be adverse. The reproductive NOAEL was 1300 mg/l (equal to 130 mg/kg bw per day), the highest dose tested. The NOAEL for parental toxicity was 300 mg/l (equal to 30 mg/kg bw per day), based on reduced body weights at 650 mg/l (equal to 65 mg/kg bw per day). The NOAEL for offspring toxicity was 300 mg/l (equal to 30 mg/kg bw per day), based on reduced body weight gain at 650 mg/l (equal to 65 mg/kg bw per day).

The Meeting concluded that propylene chlorohydrin is not toxic to reproduction.

In a limited developmental toxicity study, propylene chlorohydrin was administered to five pregnant rats per group. Fetuses were examined only for gross external abnormalities. Maternal body weight gain was reduced at the top dose level of 125 mg/kg bw per day. There were no treatment-related increases in external findings and no effects on viable fetal numbers. This study is inadequate, with respect to group size and extent of investigations, to permit identification of a NOAEL for developmental toxicity.

Epidemiological studies of workers in plants producing propylene chlorohydrin and other chlorinated hydrocarbons identified an excess of mortality due to pancreatic cancer, leukaemia, and all lymphatic and haematopoietic cancers. The involvement, if any, of propylene chlorohydrin in these effects is unclear.

Toxicological data on propylene bromohydrin

Propylene bromohydrin (1-bromo-2-propanol; 2-bromo-1-propanol) is a plant metabolite formed following the use of propylene oxide. No in vivo toxicity data were available for evaluation. Genotoxicity data show that propylene bromohydrin is genotoxic in vitro. Comparative data indicate that in some bacterial mutagenicity tests, the bromopropanol derivatives are more potent mutagens than the equivalent chloro- compounds.

Toxicological data on propylene glycol

Propylene glycol (1,2-propanediol) is a plant metabolite formed following the use of propylene oxide. It is also an approved food additive (e.g. E1520). It was reviewed by JECFA in 2002, when an ADI of 0–25 mg/kg bw was derived.

The Meeting concluded that the existing database on propylene oxide was adequate to characterize the potential hazards to fetuses, infants and children by the inhalation route. Taking account of the likely hydrolysis to propylene glycol following oral exposure, the inhalation studies are considered to provide adequate reassurance for potential risks to fetuses, infants and children via the oral route.

The Meeting concluded that the existing database on propylene chlorohydrin was adequate to characterize the potential hazards to infants and children, but not to fetuses.

Toxicological evaluation

Propylene oxide

The Meeting established an ADI of 0–0.04 mg/kg bw derived from the NOAEC for systemic effects (reduced body weight gain) in the chronic inhalation studies in rats of 100 ppm (equivalent to approximately 40 mg/kg bw per day orally), supported by the NOAEC of 100 ppm (equivalent to approximately 40 mg/kg bw per day orally) for offspring and parental toxicity (reduced body weight gain) in the reproductive toxicity study in rats. Kinetic and metabolic data indicate that there is likely to be greater systemic exposure to propylene oxide following inhalation exposures relative to equivalent oral exposures; thus, the extrapolation is likely to be conservative. A safety factor of 1000 was applied. An additional factor of 10 was applied to the default safety factor of 100 to address the limitations in the database. The 150-week oral study in rats was not used in the establishment of the ADI, as there was limited investigation of non-neoplastic systemic effects and the critical findings reported were local effects in the rat stomach that are considered not relevant to human exposures to propylene oxide residues in the diet.

The Meeting established an acute reference dose (ARfD) of 0.04 mg/kg bw on the same basis as the ADI. The Meeting concluded that there was inadequate information to support the derivation of a value based on specific acute effects.

Propylene chlorohydrin

The Meeting could not establish an ADI or ARfD for propylene chlorohydrin because of the absence of any reliable data to characterize the hazards to fetuses. The chemical properties and toxicity profile of propylene chlorohydrin are different from those of propylene oxide, and it is not possible to read across between the two compounds.

Propylene bromohydrin

The Meeting could not establish an ADI or ARfD for propylene bromohydrin because of the absence of any in vivo data. The chemical properties of propylene bromohydrin are different from those of propylene oxide, and it is not possible to read across between the two compounds.

Levels relevant to risk assessment of propylene oxide

Species	Study	Effect	NOAEL/C	LOAEL/C
Mouse	Two-year study of toxicity and carcinogenicity ^a	Systemic toxicity	200 ppm (~160 mg/kg bw per day orally) ^b	400 ppm (~320 mg/kg bw per day orally) ^b
		Carcinogenicity	200 ppm (~160 mg/kg bw per day orally) ^b	400 ppm (~320 mg/kg bw per day orally) ^b
Rat	Twenty-eight-month study of toxicity and carcinogenicity ^a	Systemic toxicity	100 ppm ^c (~40 mg/kg bw per day orally) ^b	300 ppm (~120 mg/kg bw per day orally) ^b
		Carcinogenicity	300 ppm ^d (~120 mg/kg bw per day orally) ^b	—
	Two-year study of toxicity and carcinogenicity ^a	Systemic toxicity	200 ppm (~80 mg/kg bw per day orally) ^b	400 ppm (~160 mg/kg bw per day orally) ^b
		Carcinogenicity	200 ppm (~80 mg/kg bw per day orally) ^b	400 ppm (~160 mg/kg bw per day orally) ^b

Species	Study	Effect	NOAEL/C	LOAEL/C
	Multigeneration study of reproductive toxicity ^a	Reproductive toxicity	300 ppm ^d (~120 mg/kg bw per day orally) ^b	—
		Parental toxicity	100 ppm (~40 mg/kg bw per day orally) ^b	300 ppm (~120 mg/kg bw per day orally) ^b
		Offspring toxicity	100 ppm (~40 mg/kg bw per day orally) ^b	300 ppm (~120 mg/kg bw per day orally) ^b
	Developmental toxicity study ^a	Maternal toxicity	300 ppm (~160 mg/kg bw per day orally) ^e	500 ppm (~260 mg/kg bw per day orally) ^e
		Embryo and fetal toxicity	300 ppm (~160 mg/kg bw per day orally) ^e	500 ppm (~260 mg/kg bw per day orally) ^e
Rabbit	Developmental toxicity study ^a	Maternal toxicity	—	500 ppm ^f (~75 mg/kg bw per day orally)
		Embryo and fetal toxicity	—	500 ppm ^f (~75 mg/kg bw per day orally)

^a Inhalation exposure.

^b Conversion of 100 ppm equivalent to 40 mg/kg bw per day in rats, assuming 100 ppm = 240 mg/m³; 100% absorption; 250 g body weight; standard breathing rates and volumes; exposures for 6 hours/day, 5 days/week. For mice, the corresponding value is double that for rats: 100 ppm equivalent to 80 mg/kg bw per day.

^c Limited examination.

^d Highest concentration tested.

^e Conversion of 100 ppm equivalent to 40 mg/kg bw per day in rats, assuming 100 ppm = 240 mg/m³; 100% absorption; 250 g body weight; standard breathing rates and volumes; exposures for 6 hours/day on gestation days 6–15.

^f Lowest concentration tested.

Levels relevant to risk assessment of propylene chlorohydrin

Species	Study	Effect	NOAEL	LOAEL
Mouse	Fourteen-week toxicity study ^a	Toxicity	—	7 mg/kg bw per day ^b
	Two-year study of toxicity and carcinogenicity ^a	Toxicity	100 mg/kg bw per day ^c	—
		Carcinogenicity	100 mg/kg bw per day ^c	—
Rat	Two-year study of toxicity and carcinogenicity ^a	Toxicity	34 mg/kg bw per day ^c	—
		Carcinogenicity	34 mg/kg bw per day ^c	—
	Multigeneration study of reproductive toxicity ^a	Reproductive toxicity	130 mg/kg bw per day ^c	—
		Parental toxicity	30 mg/kg bw per day	65 mg/kg bw per day
		Offspring toxicity	30 mg/kg bw per day	65 mg/kg bw per day

^a Drinking-water administration.

^b Lowest dose tested.

^c Highest dose tested.

Estimate of acceptable daily intake for humans

0–0.04 mg/kg bw for propylene oxide

No ADI could be established for propylene chlorohydrin or propylene bromohydrin.

Estimate of acute reference dose

0.04 mg/kg bw for propylene oxide

No ARfD could be established for propylene chlorohydrin or propylene bromohydrin.

Information that would be useful for the continued evaluation of the compound

- Results from epidemiological, occupational health and other such observational studies of human exposure

- Developmental toxicity data via the oral route for propylene chlorohydrin
- Sufficient information to evaluate the potential toxicity of propylene bromohydrin residues in the diet

For further information, see Environmental Health Criteria 240 (FAO/WHO, 2009).

Critical end-points for setting guidance values for exposure to propylene oxide

Absorption, distribution, excretion and metabolism in mammals

Rate and extent of oral absorption	No data
Dermal absorption (human skin in vitro)	No data
Distribution	No data
Potential for accumulation	Unlikely
Rate and extent of excretion	No data
Metabolism in animals	Hydrolysed to propylene glycol or conjugated
Toxicologically significant compounds (animals, plants and the environment)	Propylene oxide, propylene chlorohydrin, propylene bromohydrin

Acute toxicity

Rat, LD ₅₀ , oral	300–1000 mg/kg bw
Rat, LD ₅₀ , dermal	950 mg/kg bw
Rat, LC ₅₀ , inhalation	3.2–3.4 mg/l (4 h, nose only)
Rabbit, dermal irritation	Severe
Rabbit, ocular irritation	Moderate to severe
Dermal sensitization	No data

Short-term studies of toxicity

Target/critical effect	Body weight gain
Lowest relevant oral NOAEL	200 mg/kg bw per day (rats)
Lowest relevant dermal NOAEL	No data
Lowest relevant inhalation NOAEC	250 ppm (600 mg/m ³) (mice and rats)

Genotoxicity

Genotoxic in vitro; unlikely to be genotoxic in humans at dietary exposure levels

Long-term studies of toxicity and carcinogenicity

Target/critical effect	Site of contact irritation (nasal cavity inflammation; stomach hyperkeratosis); systemic toxicity (reduced body weight gain)
Lowest relevant LOAEL	4.3 mg/kg bw per day (lowest dose tested) (rat)
Lowest relevant NOAEC (systemic toxicity)	100 ppm (rat) (~40 mg/kg bw per day oral)
Carcinogenicity	Site of contact tumours (nasal cavity; stomach)

Reproductive toxicity

Reproduction target/critical effect	None
Lowest relevant reproductive NOAEC	300 ppm (rat) (~120 mg/kg bw per day oral)
Developmental target/critical effect	Accessory cervical ribs (rat)
Lowest relevant developmental NOAEC	300 ppm (rat) (~120 mg/kg bw per day oral)

Neurotoxicity/delayed neurotoxicity

No data

*Other toxicological studies*DNA and haemoglobin adduct formation in rats and humans;
depletion of non-protein sulfhydryl groups*Medical data*

Epidemiological studies of production plant workers inconclusive

Critical end-points for setting guidance values for exposure to propylene chlorohydrin*Absorption, distribution, excretion and metabolism in mammals*

Rate and extent of oral absorption	> 11% (limited information)
Dermal absorption (human skin in vitro)	No data
Distribution	No data
Potential for accumulation	Unlikely
Rate and extent of excretion	> 11% (urine, rabbit)
Metabolism in animals	Glucuronide and glutathione conjugates
Toxicologically significant compounds (animals, plants and the environment)	Propylene chlorohydrin

Acute toxicity

Rat, LD ₅₀ , oral	200–250 mg/kg bw
Rat, LD ₅₀ , dermal	500 mg/kg bw
Rat, LC ₅₀ , inhalation	> 3.8 mg/l (6 h)
Rabbit, dermal irritation	Not irritating
Rabbit, ocular irritation	Severe
Dermal sensitization	No data

Short-term studies of toxicity

Target/critical effect	Liver (hepatocyte vacuolation); pancreas (acinar cell alterations)
Lowest relevant oral NOAEL	35 mg/kg bw per day (rat)
Lowest relevant dermal NOAEL	No data
Lowest relevant inhalation NOAEC	No data

Genotoxicity

Genotoxic in vitro; unlikely to be genotoxic in vivo

Long-term studies of toxicity and carcinogenicity

Target/critical effect	None
Lowest relevant NOAEL	34 mg/kg bw per day (highest dose tested) (rat) 100 mg/kg bw per day (highest dose tested) (mouse)
Carcinogenicity	Not carcinogenic

Reproductive toxicity

Reproduction target/critical effect	None
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Lowest relevant reproductive NOAEL	130 mg/kg bw per day (highest dose tested)
Developmental target/critical effect	Inadequate data
Lowest relevant developmental NOAEC	Inadequate data

Neurotoxicity/delayed neurotoxicity

No data

Other toxicological studies

No data

Medical data

Epidemiological studies of production plant workers inconclusive

Summary for propylene oxide

	Value	Study	Safety factor
ADI	0–0.04 mg/kg bw	Rat chronic inhalation	1000
ARfD	0.04 mg/kg bw	Same basis as ADI; insufficient data to establish a value for specific acute effects	1000

Summary for propylene chlorohydrin

	Value	Study	Safety factor
ADI	None established		
ARfD	None established		

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