5.19 PROPYLENE OXIDE (250)

TOXICOLOGY

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 ºC) 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.

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 1.48; 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. This conversion assumed standard breathing rates and volumes, a body weight (bw) 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 bw per day in rats and 80 mg/kg bw per day in mice. This is likely to be a conservative estimate for systemic propylene oxide exposures via the oral route.

Toxicological data

The acute toxicity of propylene oxide has been investigated orally (median lethal doses [LD_{50}s] 300–1000 mg/kg bw), dermally (LD_{50}s 950–1250 mg/kg bw) and by inhalation (median lethal concentration [LC_{50}] 1–9.5 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 14 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 no-observed-adverse-effect level (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 no-observed-adverse-effect concentration (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 is 200 ppm (~160 mg/kg bw per day orally), based on the nasal tumours seen at 400 ppm (~320 mg/kg bw per day orally). The NOAEC for systemic toxicity is 200 ppm (~160 mg/kg bw per day orally), based on reduced body weight gain at 400 ppm (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 due to 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 range. A NOAEC for systemic effects was 100 ppm (~40 mg/kg bw per day orally), based on body weight gain reductions at 300 ppm (~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 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 is 200 ppm (~80 mg/kg bw per day orally), based on the increase in papillary adenomas of the nasal cavity at 400 ppm (~160 mg/kg bw per day orally). The NOAEC for chronic site of contact toxicity is less than 200 ppm (~80 mg/kg bw per day orally), based on nasal cavity inflammation. For systemic toxicity, the NOAEC is 200 ppm (~80 mg/kg bw per day orally), based on reduced body weight gain at 400 ppm (~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/m^3), 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 deoxyribonucleic acid (DNA) adducts (primarily N^7G, plus N^3A, N^3C and N^1A) in respiratory mucosa and liver of exposed rats, and 1-hydroxypropyl-adenine 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 (~120 mg/kg bw per day orally), the highest dose tested. The NOAEC for parental and pup toxicity was 100 ppm (~40 mg/kg bw per day orally), based on reduced body weight gain at 300 ppm (~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 (~260 mg/kg bw per day orally)[15]. 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 (~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 corpora lutea, 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; ~200 mg/kg bw per day orally) is a NOAEC for teratogenicity and a lowest-observed-adverse-effect concentration (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; ~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-Hydroxypropyl-adenine 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 LD_{50} 200–250 mg/kg bw), the dermal route (rabbit LD_{50} 500 mg/kg bw) and inhalation (LC_{50} > 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

[15] Different conversion rate, as exposures occurred every day as opposed to 5 days/week.

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) and pancreatic degeneration/acinar cell changes were seen at 1000 mg/L (equal to 100 mg/kg bw per day). A NOAEL could not be determined due to 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 the Joint FAO/WHO Expert Committee on Food Additives in 2002,[16] when an acceptable daily intake (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.

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[16] *Evaluation of certain food additives and contaminants* (Fifty-seventh report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 909, 2002.

Propylene chlorohydrin

The Meeting could not establish an ADI or ARfD for propylene chlorohydrin due to 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 due to 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.

A toxicological monograph was prepared.

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]
	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	500 ppm (~260 mg/kg bw per day

Species	Study	Effect	NOAEL/C	LOAEL/C
			day orally)[e]	orally)[e]
		Embryo and fetal toxicity	300 ppm	500 ppm
			(~160 mg/kg bw per day orally)[e]	(~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] Assuming 100 ppm = 240 mg/m^3; 100% absorption; 250 g body weight; standard breathing rates and volumes; exposures for 6 hours/day, 5 days/week.

[c] Limited examination.

[d] Highest concentration tested.

[e] Assuming 100 ppm = 240 mg/m^3; 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[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[17].

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)

[17] *Principles and methods for the risk assessment of chemicals in food.* A joint publication of the Food and Agriculture Organization of the United Nations and the World Health Organization. Geneva, World Health Organization, 2009 (Environmental Health Criteria 240).

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
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

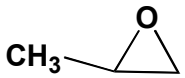
	Value	Study	Safety factor
ADI	None established		
ARfD	None established		

RESIDUE AND ANALYTICAL ASPECTS

Propylene oxide is used in agriculture as an insecticidal fumigant and sterilant to control bacteria contamination, mould contamination, insect infestations, and microbial spoilage of food products as well as to control insects in non-food products. Propylene oxide is also a commercially important industrial chemical finding application as an intermediate for a wide array of products. At the Forty-second Session of the CCPR (2010), it was scheduled for evaluation as a new compound by 2011 JMPR.

Residue studies were submitted by the manufacturers for support of the following commodities: cereal grains (maize, wheat), tree nuts, cocoa, herbs and spices, dried vegetables (onion and garlic) and dried fruit (raisins, figs and prunes).

Propylene oxide is methyloxirane.



The following abbreviations are used for the metabolites discussed below:

PPO = propylene oxide

PCH = propylene chlorohydrin, (1-chloro-2-propanol and 2-chloro-1-propanol)

PBH = propylene bromohydrin, (1-bromo-2-propanol and 2-bromo-1-propanol)

PPG = 1,2 propanediol

Animal metabolism

No data for livestock are available on the absorption following oral dosing with propylene oxide. However, data from rats on other routes of administration enable conclusions on the metabolism of PPO to be made. Two metabolic pathways are suggested: 1) conjugation with glutathione via glutathione epoxide transferase; 2) hydrolysis by epoxide hydrolase to 1,2-propanediol (propylene glycol, PPG). PPG can be excreted as such or metabolized to lactic and pyruvic acid. Propylene oxide is a direct alkylating agent that forms DNA (N-2-hydroxypropyl-guanosine, N-2-hydroxypropyl-guanosine) and protein adducts (hemoglobin alkylation at the cysteine, histidine or valine) residues. Assuming a 100% alveolar absorption and first-order kinetics, a half-life of 40 minutes was estimated for the elimination of PPO in rats. Under *in vitro* conditions, the half-life of PPO in human gastric juice (pH 1.46 and 37 °C) is approximately 1.9 minutes while in rat gastric juice (pH 4.8) it is 347 minutes.

Plant metabolism

Limited data were available of the metabolism of propylene oxide in plants and fumigated plant-based commodities. The Meeting concluded, based on the similarity in reactions and chemistry between ethylene oxide and propylene oxide and reported degradates from studies with unlabelled PPO, that in addition to PPO residues of PPG (free and conjugated), PCH and PBH are formed upon and after postharvest fumigation of plant-based commodities. In commodities that contain salt the PPO will react with chloride ions to form PCH. Similarly, bromide ions present react with PPO to form PBH. Reaction with water present in fumigated samples can produce PPG. In addition, PPO may react with exposed -COOH, $-NH_2$, -OH and -SH groups present in natural constituents to give the corresponding hydroxy-propyl compounds.

Environmental fate

Propylene oxide is a post-harvest fumigant and sterilant and is not expected to be released into the environment such that significant levels will be found in soil and water. In addition, PPO is hydrolysed in water at 25 °C with a half-life of 10.7 to 14.6 days. The rate of hydrolysis is increased in the presence of acid or base. Propylene oxide is not expected to be present or persist in the environment.

Analytical methods

Methods are available for the analysis of PPO and PCH in plant commodities. Samples are ground under cryogenic conditions (liquid nitrogen), transferred to a vial, the vial sealed and the PPO residues desorbed by heating. Powdered samples do not need the grinding step and can be added directly to the vial. The volatilized PPO equilibrates in the headspace of the vial which is then sampled by an automated headspace sampler and injected onto a GC-FID system. Quantitation was achieved by comparison with a calibration curve consisting of fortified matrix samples. It was reported that headspace analysis should occur within 1 hour of sample preparation for nuts or 2 hours for cocoa, herbs and spices. An LOQ of 0.1 mg/kg was attained for most matrices.

Residues of PCH (1-chloro-2-propanol and 2-chloro-1-propanol) and PBH (1-bromo-2-propanol and 2-bromo-1-propanol) are extracted with acetone and quantitated via gas chromatography with electrolytic conductivity detection (GC-ELCD). Detector response is not linear over the fortification range and a quadratic model was used for the standard curve. An LOQ of 1 mg/kg has been demonstrated for most commodities.

Stability of pesticide residues in stored analytical samples

No data were provided on the stability of residues of PPO, PCH, PBH or PPG when samples were stored frozen. In most of the supervised residue trials samples were analysed on the day of collection or soon after, in which case the samples were stored at 2 °C or -20 °C until analysis.

Definition of the residue

Following fumigation, the major components of the residue observed in trials are PPO, PCH, PBH and PPG. In nuts and cocoa PCH and PBH were present at levels that are about 10% of the PPO level while PCH levels were the same or much greater that PPO in spices and dried fruit. Levels of PPG were about the same as those of PPO in nuts but much greater than PPO in cocoa and spices. PBH residues were similar in magnitude relative to PCH residues in almonds, pecans, walnuts and cocoa powder but much lower in herbs and spices.

The Meeting considered that although PPG was often present at the highest concentration, PPG is much less toxic than PPO and PCH and is not required to be included in the residue for dietary risk assessment. The residues of concern for dietary risk assessment are PPO, PCH and PBH. Based on differences in toxicological effects, PPO and PCH/PBH are assessed separately and the residues are not combined for estimation of dietary risk exposure.

The Meeting recommended that the residue definition for plant and animal commodities, for compliance with MRLs should be propylene oxide.

The Meeting recommended that the residue definition for plant and animal commodities, for dietary risk assessment should be propylene oxide, propylene chlorohydrins and propylene

bromohydrin. Propylene chlorohydrin and propylene bromohydrin to be considered separately from propylene oxide.

The log K_{ow} of propylene oxide (log K_{ow} 2.9, pH 7) suggests that PPO is likely to be borderline fat soluble however, the predicted distribution of residues in the rat study suggested the residues are not fat soluble[18].

Definition of the residue (for compliance with MRL): *propylene oxide*.

Definition of the residue (for estimation of dietary intake): *propylene oxide, propylene chlorohydrin and propylene bromohydrin. Propylene chlorohydrin and propylene bromohydrin to be considered separately from propylene oxide.*

The residue is not considered fat soluble.

Results of supervised trials on crops

Residue trials, including data from published scientific papers, were available for the use of PPO on: cereal grains, tree nuts, spices and herbs, dried garlic, dried onion, cocoa beans and dried fruit. No GAP was available to assess trials on cereal grains and these trials are not considered further.

Residues are reported below for PPO with corresponding values for PCH reported in brackets. During fumigation almost all the PPO is absorbed by the commodity being fumigated, at least for initial fumigation chamber PPO concentrations in the range 0.0125 to 0.1 g ai/L. The load ratio (volume occupied by material for fumigation to total chamber volume) may have an influence on the final residues. In the residue trials the load was generally 50% capacity. Factors important in determining residues of the related fumigant ethylene oxide are also likely to be relevant to propylene oxide. Important factors include: the total amount and concentration of propylene oxide, the composition of the treatment mixture, temperature, the type of commodity and its moisture content, pH, permeability, and particle size, and the method of packaging as well as aeration and storage conditions after treatment.

Tree nuts

Data were available from supervised trials on almonds, pecans and walnuts in the USA. The GAP of the USA is for fumigation of tree nuts at 2 g ai/L for up to six hours and a post fumigation interval (PFI) of 28 days if off-gasing at 25 °C otherwise the product can be released if residues have declined to below 300 mg/kg. Residues in tree nuts from trials in the USA matching GAP were: 273 (PCH 3.0) for shelled almonds, 37 (PCH 8.2) mg/kg for pecan pieces and 209 (PCH 7.4) mg/kg for walnut pieces.

To be able to estimate a maximum residue level according to the use pattern, sufficient trials are required to estimate a maximum level or to be confident that residues remain below 300 mg/kg at 28 days or more of off-gasing at 25 °C. The number of trials that comply with maximum GAP are too few to estimate a maximum residue level. The Meeting also noted that data from commercial fumigations where shelled almond nuts were fumigated at a lower rate suggest PPO residues in almonds decline rapidly during the first 15 days of off-gasing and only slowly thereafter. If

[18] Csanády GA, Filser JG (2009) A Physiological Toxicokinetic Model for Inhaled Propylene Oxide in Rat and Human with Special Emphasis on the Nose. Toxicology Sciences 95: 37–62. (tissue:blood partitionratios; fat:blood 1.06, muscle:blood 0.84)

proportionality were to apply to fumigation, the commercial results also suggest residues of PPO may be higher than 300 mg/kg at PFIs of greater than 28 days. The Meeting considered the data inadequate to estimate maximum residue levels for PPO and PCH in tree nuts.

Dried fruit

Data were available from supervised trials on dried fruit in the USA.

The GAP of the USA is for fumigation of figs, prunes and raisins at 0.2 g ai/L for up to 48 hours and off-gasing at ≥25 °C for 48 hours prior to shipment. No trials complied with GAP.

Herbs and Spices

Data were available from supervised trials on a variety of dried herbs, spices as well as dried vegetables in the USA. The GAP of the USA is for fumigation of processed spices at 2 g ai/L for up to 12 hours and off-gasing at≥ 25 °C for 48 hours prior to shipment with earlier release possible if residues of PPO are less than 300 mg/kg. Clarification was sought from the US EPA regarding the commodities covered by processed spices in the US. The term processed spices is applied to herbs and spices as well as dried onions and dried garlic. Residues in black pepper complying with GAP were 93 (PCH not reported) mg/kg while those in onion powder were 15.2 (PCH not reported) mg/kg. Residues of PPO in an additional trial on celery seed sampled at 4 rather than 2 days after fumigation were 69 (PCH not reported) mg/kg while day 0 residues in the same trial were 126 (PCH 474) mg/kg. Residues in dried basil sampled at day 4 rather than day 2 after fumigation were 164 (PCH not reported) mg/kg and on day zero 372 (PCH 6670) mg/kg.

To be able to estimate a maximum residue level according to the use pattern, sufficient trials are required or to be confident that residues remain below 300 mg/kg after off-gasing at 25 °C for 48 hours. The Meeting considered whether or not the available data provided confidence that residues at a post fumigation interval of 48 hours would be below 300 mg/kg. Account was taken of trials conducted in 1995 that were not adequate to resolve questions over their use for estimation of maximum residue levels but did show a large variation in residues of PPO in treated spices, dried vegetables and dried herbs and that residues at 48 hours after fumigation may exceed 300 mg/kg. The Meeting concluded the small number of supervised residue trials that comply with GAP were not sufficient to estimate a maximum residue level for herbs and spices, for dried garlic and dried onion or for dried chili powder.

Cocoa Powder

The GAP of the USA is for fumigation of cocoa beans and cocoa powder at 2 g ai/L for up to 4 hours and off-gasing at≥ 25 °C for 48 hours prior to shipment with earlier release if residues of PPO are less than 300 mg/kg. The residues of PPO for supervised trials conducted on cocoa powder that complied with GAP of the USA are: 71.8 (PCH 11.6) and 136 (PCH 12.5) mg/kg. The Meeting considered two trials as insufficient for the purposes of estimating maximum residue levels.

Animal feedstuffs

No animal feed items were considered by the current Meeting.

Fate of residues during processing

No data is available on the effect of processing on the nature of residues.

Residues in animal commodities

No animal feed commodities were considered at by the current Meeting. No data were supplied for the transfer of residues from feed to foods of animal origin. Propylene oxide is degraded to PPG in the stomach such that should livestock be exposed, no residues are anticipated to transfer from feed to tissues, milk or eggs.

FURTHER WORK OR INFORMATION

Desirable

Additional trials conducted according to GAP to support estimation of maximum residue levels.