5.30 PROPYLENE OXIDE (250)

TOXICOLOGY

Propylene oxide (PPO) is the International Organization for Standardization (ISO)–approved name for methyloxirane (International Union of Pure and Applied Chemistry [IUPAC]) with the Chemical Abstracts Service (CAS) number 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 (JMPR) in 2011 when an acceptable daily intake (ADI) of 0–0.04 mg/kg body weight (bw) and an acute reference dose (ARfD) of 0.04 mg/kg bw were established. The 2011 Meeting was unable to establish ADIs or ARfDs for propylene chlorohydrin or propylene bromohydrin due to shortcomings in the databases.

PPO was re-reviewed at the 2017 Meeting at the request of the Codex Committee on Pesticide Residues (CCPR). Additional data has been made available on propylene oxide, propylene chlorohydrin and propylene bromohydrin. The new data have been summarized in the toxicological addendum.

The original 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 (GLP). The new studies contain GLP compliance statements and meet the requirements of national or international test guidelines.

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 to propylene oxide and oral dosing has been performed. This conversion assumed standard breathing rates and volumes, a rat body weight of 250 g and 100% absorption via each exposure route. The conversion resulted in an atmospheric concentration of 100 parts per million (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, in a volume of 1 mL, (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 inside 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 N7G, plus N3A, N3C and N1A) 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 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.

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 gestation days 6–15. 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)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 (~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 to 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 toxicity and developmental toxicity in rabbits.

In an oral developmental toxicity study, rabbits were exposed to propylene oxide at 0, 75, 150 or 300 mg/kg bw per day by gavage on gestation days 7–28. Maternal deaths and reductions in maternal and fetal body weights were reported at 300 mg/kg bw per day. There were no reported increases in malformations or fetal anomalies/variations. The NOAELs for maternal toxicity and embryo/fetal effects were 150 mg/kg bw per day.

The Meeting concluded that propylene oxide is not teratogenic.

Toxicological data on metabolites and/or degradates

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 mg/kg bw), the dermal route (rabbit LD_{50}: 500 mg/kg bw) and by 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 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 haematopoeisis, bone marrow atrophy) and pancreatic degeneration/acinar cell changes were seen at 1000 mg/L (equal to 100 mg/kg bw per day). An 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 recognized that there was a negative in vivo assay.

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 is 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 is 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.

In a study of developmental toxicity, propylene chlorohydrin was administered to pregnant rats by gavage at 0, 10, 30 or 100 mg/kg bw per day on gestation days 6–19. Maternal body weight gain was reduced at 100 mg/kg bw per day throughout the dosing period, with body weight loss at the start of the dosing period. Fetal weights in the 100 mg/kg bw per day group were lower than controls. There were no reported increases in malformations or fetal anomalies. A reduced level of ossification was reported in the 100 mg/kg bw per day group. The NOAELs for maternal toxicity and embryo/fetal toxicity are 30 mg/kg bw per day.

In a study of developmental toxicity, propylene chlorohydrin was administered to pregnant rabbits by gavage at 0, 10, 50 or 175 mg/kg bw per day on gestation days 7–29. Maternal body weight gain was reduced at 175 mg/kg bw per day throughout the dosing period. Fetal weights in the 175 mg/kg bw per day group were lower than controls. There were no treatment-related increases in

malformations or fetal anomalies or changes in ossification. The NOAELs for maternal toxicity and embryo/fetal toxicity are 50 mg/kg bw per day.

The Meeting concluded that propylene chlorohydrin is not teratogenic.

In a study of acute neurotoxicity, rats were administered a single dose of propylene chlorohydrin by gavage at 0, 25, 75 or 200 mg/kg bw. There were no deaths or changes in clinical signs and no notable changes in functional observational battery (FOB) parameters other than motor activity counts. There were no effects on brain weight or morphology or on nervous system tissues. Transient body weight loss and reductions in motor activity counts were reported in the 200 mg/kg bw groups. Reduced motor activity counts were seen in males at 75 mg/kg bw. The NOAEL was 25 mg/kg bw.

The Meeting concluded that propylene chlorohydrin is not neurotoxic.

Propylene bromohydrin

Propylene bromohydrin (1-bromo-2-propanol; 2-bromo-1-propanol) is a plant metabolite formed following the use of propylene oxide.

The acute toxicity of propylene bromohydrin has been investigated via the oral route (LD_{50} = 175 mg/kg bw).

In a 28-day study of toxicity, rats were administered propylene bromohydrin by gavage at 0, 10, 30 or 80 mg/kg bw per day. The NOAEL was 30 mg/kg bw per day based on liver inflammation in females at 80 mg/kg bw per day.

Genotoxicity data show that propylene bromohydrin is genotoxic in vitro, but negative results were obtained in an in vivo micronucleus assay. Comparative data in the published literature indicate that in some bacterial mutagenicity tests, bromopropanol derivatives are more potent mutagens than the equivalent chloro- compounds.

The Meeting concluded that propylene bromohydrin is genotoxic in vitro but recognized that there was a negative in vivo assay.

A comparison of the toxicity of propylene oxide, propylene chlorohydrin and propylene bromohydrin identified a consistent pattern of genotoxicity. The limited in vivo toxicity data on propylene bromohydrin indicate it is qualitatively similar but more potent than propylene chlorohydrin by a factor of approximately 3.

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 (TRS 913-JECFA 59/112), when an ADI of 0–25 mg/kg bw was derived.

Human data

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.

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.

The Meeting concluded that the existing database on propylene oxide was adequate to characterize the potential hazards to the general population, fetuses, infants and children by the inhalation route.

Most of the database on propylene oxide consists of studies by the inhalation route. Taking account of the likely hydrolysis to propylene glycol following oral exposure, the Meeting concluded that the overall database of inhalation studies supplemented by an oral developmental toxicity study in rabbits, was adequate to provide sufficient information to assess the risks to the general population 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 the general population, fetuses, infants and children.

The Meeting concluded that the existing database on propylene bromohydrin, in combination with the database on the structurally very similar compound propylene chlorohydrin, was adequate to provide sufficient information to assess the risks to the general population, fetuses, infants and children.

Toxicological evaluation

Propylene oxide

The Meeting re-affirmed the 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 maintain a margin of 100 to the lowest-observed-adverse-effect level (LOAEL) of 4.3 mg/kg bw per day for findings at the site of contact in the 150 week gavage carcinogenicity study for which a mode of action had not been conclusively determined. 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 re-affirmed the 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 from dietary exposure.

Propylene chlorohydrin

The Meeting established an ADI of 0–0.3 mg/kg bw based on the NOAEL of 25 mg/kg bw per day in the acute neurotoxicity study in rats based on reduced motor activity in males at 75 mg/kg bw per day, and using a 100-fold safety factor. This is supported by NOAELs of 30 mg/kg bw per day for maternal toxicity and embryo/fetal toxicity in the developmental toxicity study in rats and for parental and offspring toxicity in the multigeneration reproductive toxicity study in rats.

The Meeting established an ARfD of 0.3 mg/kg bw based on the NOAEL of 25 mg/kg bw per day in the acute neurotoxicity study in rats based on reduced motor activity at 75 mg/kg bw per day, and using a 100-fold safety factor. This is supported by the NOAEL in the rat developmental toxicity study based on body weight loss at the start of the dosing period.

Propylene bromohydrin

The Meeting established an ADI of 0–0.03 mg/kg bw based on read across from the ADI for propylene chlorohydrin with an additional factor of 10. The Meeting concluded that based on the closely related chemical structure and a comparison of the available toxicity data, propylene bromohydrin was likely to have similar toxicity to propylene chlorohydrin. However, there were uncertainties in the read across as not all end-points had been tested, there were no single studies which used both compounds and there was evidence propylene bromohydrin was of greater potency

than propylene chlorohydrin. The Meeting concluded that these uncertainties could be addressed by the application of an extra 10 fold factor.

The Meeting established an ARfD of 0.03 mg/kg bw on the same basis as the ADI, as the ADI was based on some effects seen after single dose.

An addendum to the toxicological monograph was prepared.

Levels relevant to risk assessment of Propylene Oxide

Species	Study	Effect	NOAEL	LOAEL
Mouse	Two-year study of toxicity and carcinogenicity[a]	Toxicity	200 ppm (~160 mg/kg bw per day orally)[b]	400 ppm (~320 mg/kg bw per day orally)
		Carcinogenicity	200 ppm (~160 mg/kg bw per day orally)	400 ppm (~320 mg/kg bw per day orally)
Rat				
	Two-year study of toxicity and carcinogenicity[c]	Toxicity	—	4.3 mg/kg bw per day[d]
		Carcinogenicity	—	4.3 mg/kg bw per day[d]
	Twenty eight month study of toxicity and carcinogenicity[a,]	Toxicity	100 ppm[e] (~40 mg/kg bw per day orally)[b]	300 ppm (~120 mg/kg bw per day orally)
		Carcinogenicity	300 ppm[f] (~120 mg/kg bw per day orally)[b]	—
	Multigeneration study of reproductive toxicity[a]	Reproductive toxicity	300 ppm[f] (~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)[g]	500 ppm (~260 mg/kg bw per day orally) [g]
		Embryo and fetal toxicity	300 ppm (~160 mg/kg bw per day orally)[g]	500 ppm (~260 mg/kg bw per day orally) [g]
Rabbit	Developmental toxicity study[c]	Maternal toxicity	150 mg/kg bw per day	300 mg/kg bw per day
		Embryo and fetal toxicity	150 mg/kg bw per day	300 mg/kg bw per day

[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] Gavage dosing

[d] Lowest concentration / dose tested.

[e] Limited examination.

[f] Highest concentration tested.

[g] 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.

Estimate of acceptable daily intake (ADI)

0–0.04 mg/kg bw

Estimate of acute reference dose (ARfD)

0.04 mg/kg bw

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.

Further information to establish the mode of action underlying the stomach tumours seen following gavage administration of propylene oxide.

Levels relevant to risk assessment of Propylene chlorohydrin

Species	Study	Effect	NOAEL	LOAEL
Mouse	Two-year study of toxicity and carcinogenicity[a]	Toxicity	100 mg/kg bw per day[b]	—
		Carcinogenicity	100 mg/kg bw per day[b]	—
Rat	Study of acute neurotoxicity[d]	Toxicity	25 mg/kg bw	75 mg/kg bw
	Two-year study of toxicity and carcinogenicity[a]	Toxicity	34 mg/kg bw per day[b]	—
		Carcinogenicity	34 mg/kg bw per day[b]	—
	Multigeneration study of reproductive toxicity[a]	Reproductive toxicity	130 mg/kg bw per day[b]	—
		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
	Developmental toxicity study[c]	Maternal toxicity	30 mg/kg bw per day	100 mg/kg bw per day
		Embryo/fetal toxicity	30 mg/kg bw per day	100 mg/kg bw per day
Rabbit	Developmental toxicity study[c]	Maternal toxicity	50 mg/kg bw per day	175 mg/kg bw per day
		Embryo/fetal toxicity	50 mg/kg bw per day	175 mg/kg bw per day

[a] Drinking-water administration.

[b] Highest dose tested.

[c] Gavage administration

Estimate of acceptable daily intake (ADI)

0–0.3 mg/kg bw

Estimate of acute reference dose (ARfD)

0.3 mg/kg bw

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.

Levels relevant to risk assessment of Propylene bromohydrin

Species	Study	Effect	NOAEL	LOAEL
Rat	28 day study of toxicity[a]	Toxicity	25 mg/kg bw	75 mg/kg bw

[a] Gavage administration

Estimate of acceptable daily intake (ADI)

0–0.03 mg/kg bw

Estimate of acute reference dose (ARfD)

0.03 mg/kg bw

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.

Additional information on the toxicity of propylene bromohydrin to permit a more robust comparison with the toxicity of propylene chlorohydrin.

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	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 in animals and plants	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
Guinea-pig, 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)
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	100 ppm (rat) (~40 mg/kg bw per day oral)
Carcinogenicity	Site of contact tumours (nasal cavity; stomach)[a]
Genotoxicity	
	Genotoxic in vitro; unlikely to be genotoxic in humans at dietary exposure levels [a]
Reproductive toxicity	
Target/critical effect	None
Lowest relevant parental NOAEC	100 ppm (rat) (~40 mg/kg bw per day oral)
Lowest relevant offspring NOAEC	100 ppm (rat) (~40 mg/kg bw per day oral)
Lowest relevant reproductive NOAEC	300 ppm (rat) (~120 mg/kg bw per day oral)
Developmental toxicity	
Target/critical effect	Reduced fetal weight
Lowest relevant maternal NOAEL	150 mg/kg bw per day (rat)
Lowest relevant embryo/fetal NOAEL	150 mg/kg bw per day (rat)
Neurotoxicity	
Acute neurotoxicity NOAEL	No data
Subchronic neurotoxicity NOAEL	No data
Developmental neurotoxicity NOAEL	No data
Other toxicological studies	
Immunotoxicity	No data
	DNA and haemoglobin adduct formation in rats and humans; depletion of non-protein sulfhydryl groups
Studies on toxicologically relevant metabolites	
[Metabolite name]	See below

Human data	
	Epidemiological studies of production plant workers inconclusive

[a] Unlikely to pose a carcinogenic risk to humans via exposure from the diet.

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	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 in animals and plants	Propylene chlorohydrin
Acute toxicity	
Rat, LD_{50}, oral	532 mg/kg bw
Rat, LD_{50}, dermal	500 mg/kg bw
Rat, LC_{50}, inhalation	> 3.8 mg/L (6 hours)
Rabbit, dermal irritation	Not irritating
Rabbit, ocular irritation	Severe
Guinea-pig, 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
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[a]
Genotoxicity	
	Genotoxic in vitro; negative in an in vivo assay[a]
Reproductive toxicity	
Target/critical effect	None
Lowest relevant parental NOAEL	30 mg/kg bw per day (rat)
Lowest relevant offspring NOAEL	30 mg/kg bw per day (rat)
Lowest relevant reproductive NOAEL	130 mg/kg bw per day (rat)

Developmental toxicity	
Target/critical effect	Reduced fetal weight and reduced ossification
Lowest relevant maternal NOAEL	30 mg/kg bw per day (rat)
Lowest relevant embryo/fetal NOAEL	30 mg/kg bw per day (rat)
Neurotoxicity	
Acute neurotoxicity NOAEL	25 mg/kg bw per day (rat)
Subchronic neurotoxicity NOAEL	No data
Developmental neurotoxicity NOAEL	No data
Other toxicological studies	
Immunotoxicity	No data
Studies on toxicologically relevant metabolites	
	See below
Human data	
	Epidemiological studies of production plant workers inconclusive

Critical end-points for setting guidance values for exposure to Propylene bromohydrin to support the read across to propylene chlorohydrin

Acute toxicity	
Rat, LD_{50}, oral	175 mg/kg bw
Short-term studies of toxicity	
Target/critical effect	Liver inflammation
Lowest relevant oral NOAEL	30 mg/kg bw per day (rat)
Genotoxicity	
	Genotoxic in vitro; negative in an in vivo assay [a]

Summary

	Value	Study	Safety factor
Propylene oxide			
ADI	0–04 mg/kg bw	Rat chronic inhalation	1000
ARfD	0.04 mg/kg bw	Rat chronic inhalation	1000
Propylene chlorohydrin			
ADI	0–0.3 mg/kg bw	Rat acute neurotoxicity; rat developmental toxicity; rat multigeneration	100
ARfD	0.3 mg/kg bw	Rat acute neurotoxicity; rat developmental toxicity	100
Propylene bromohydrin			

ADI	0–0.03 mg/kg bw	Rat acute neurotoxicity; rat developmental toxicity; rat multigeneration with propylene chlorohydrin	1000
ARfD	0.03 mg/kg bw	Rat acute neurotoxicity; rat developmental toxicity; rat with propylene chlorohydrin	1000

RESIDUE AND ANALYTICAL ASPECTS

Propylene oxide is used in agriculture as an insecticidal fumigant and sterilant, to control bacterial 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. It was first evaluated by JMPR in 2011. Residue definitions established by the 2011 JMPR are:

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

Definition of the residue (for estimation of dietary intake) for plant commodities: *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.

Propylene oxide was scheduled at the 48th Session of the CCPR for the evaluation of additional MRLs by the 2017 JMPR.

Residue studies were submitted for tree nuts.

Methods of analysis

Descriptions of analytical methods together with validation data for residues of propylene oxide (PPO), the two isomers of propylene chlorohydrin (PCH) (1-chloropropan-2-ol (PCH-1), 2-chloropropan-1-ol (PCH-2)) and the two isomers of propylene bromohydrin (PBH) (1-bromopropan-2-ol (PBH-1) and 2-bromopropan-1-ol (PBH-2)) in tree nuts were made available to the Meeting.

Residues of PPO, PCH, and PBH were measured using GC-MS. Gas chromatographic retention time and/or mass spectrometry were used for confirmation of chemical identity. Respective GC-EIMS LOQs for PPO, PCH-1 and PCH-2, in non-concentrated MTBE extracts based on the lowest fortification level for which satisfactory recoveries were obtained are 1, 2 and 2 mg/kg for PPO, PCH-1 and PCH-2 respectively in almonds and walnuts.

GC-ECD: With a 10-fold concentration of the MTBE extract, LOQs for PBH-1 and PBH-2 were 0.08 mg/kg for almonds and walnuts and for a 20-fold concentration were 0.04 mg/kg. PPO is not amenable to analysis by GC-ECD.

Stability of residues in stored analytical samples

PPO is particularly volatile. In the supervised residue trials samples were extracted on the day of collection.

Results of supervised residue trials on crops

The Meeting received information on supervised field trials on post-harvest fumigation of almonds (shelled) and walnuts (in-shell and shelled).

The critical GAP in the USA for post-harvest treatment of tree nuts (includes almonds and walnuts) is fumigation at 2 g ai/L in a sealed chamber and at temperatures of less than 52 °C for up to 6 hours. This is followed by four flushes of the chamber with air or an inert gas and storage for a post-fumigation interval of 28 days at 25° or 35 °C or until the residues of propylene oxide decline to below 300 mg/kg.

It was observed that although residues in nuts fumigated at 2 g ai/L chamber for 4.5 hours were greater than those fumigated at 1.5 g ai/L for 6 hours at the first sampling time, 0 hours after fumigation, at ≥ 7 days off-gassing there was no statistical difference in residue levels. It was proposed that since air is nearly saturated with propylene oxide on fumigation at 2 g ai/L and at ~600 mmHg, that propylene oxide sorption to the nutmeat surface exceeds monolayer coverage for the two applied doses. Propylene oxide sorbed to the adsorption layer, which is reflected in the levels immediately after fumigation, is no longer present in samples during off-gassing at ≥ 7 days. The Meeting agreed the results for fumigation conducted at 1.5 and 2 g ai/L could be considered to approximate critical GAP and the results could be combined for the purposes of estimating maximum residue levels.

However, the Meeting also noted issues with the residue data. The laboratory sample for analysis was a 25 g subsample for almonds and a 15 g subsample of nutmeat for walnuts. The laboratory sample sizes do not correspond to the generally accepted prescribed sample size of 1 kg for tree nuts, see the "*FAO manual on the submission and evaluation of pesticide residues data for the estimation of maximum residue levels in food and feed*, 3rd edition" (2016), p 168. There is a concern that variability in residues, even for post-harvest fumigation, is such that the results may not adequately represent the average residue in the lot sampled. While the Meeting noted the difficulties presented by the analysis of a volatile fumigant such as PPO the small sample size was considered unacceptable.

In addition, clarification is required as to the calculation of residue values in the analytical method.

In summary, the trials approximating cGAP for almonds and walnuts were not considered valid as the sample analysed was too small (2×15+–25 g). Additionally clarification regarding the calculations of residue levels is required.