Short-chain alkyl oxiranes: Human health tier II assessment

01 September 2015

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Oxirane, ethyl-	106-88-7
Oxirane, propyl-	1003-14-1
Oxirane, butyl-	1436-34-6

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

For more detail on this program please visit:**www.nicnas.gov.au**

Disclaimer

ACRONYMS & ABBREVIATIONS

Grouping Rationale

The chemicals in this group are composed of linear hydrocarbon molecules with carbon lengths from C4–C6 with an a-oxirane functional group. Given the similar reactive oxirane moiety, these chemicals are expected to have similar toxicological profiles and qualify to be assessed as a group.

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacturing information has been identified.

International

The following international uses have been identified through the European Union (EU) Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) dossiers; the Organisation for Economic Co-operation and Development Screening information data set International Assessment Report (OECD SIAR); Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; the OECD High Production Volume chemical program (OECD HPV); the US Household Products Database; the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR); the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); US Household Products Database; and various international assessments including National Toxicology Program (NTP, 1999); Screening assessment by Environment and Health Canada (2008); International Agency for Research on Cancer (IARC, 1999) and National Occupational Health and Safety Commission (NOHSC:3016 (1992)).

Ethyloxirane has reported domestic use in aerosol foam cleaner.

Ethyloxirane has reported domestic use in the SPIN database. However, it should be noted that SPIN does not distinguish between direct use of the chemical or using the materials that are produced from its chemical reactions. The US Household Products Database states a concentration of 0.5 % (aerosol) for use in arts and crafts products, consistent with the SPIN entry.

Ethyloxirane has reported commercial uses including as a:

- stabiliser in organic solvents;
- surface-active agent;
- monomer in a polymerisation process;
- corrosion inhibitor; and
- gasoline additive.

Propyloxirane has reported site-limited uses as:

- an intermediate in the manufacture of cosmetic and domestic products; and
- a monomer in the polymerisation reaction.

The chemicals in this group have reported non-industrial use in the production of pharmaceuticals.

Restrictions

Australian

These chemicals are listed in the *Poisons standard—the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)*–Schedule 5 under '*Epoxy resins, Liquid*' (SUSMP, 2015).

Schedule 5 chemicals are described as 'Substances with a low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with simple warnings and safety directions on the label.' Schedule 5 chemicals are labelled with 'Caution' (SUSMP, 2015).

International

The chemicals in this group are listed on the following (Galleria Chemica):

- EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products;
- ASEAN Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products;
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain; and
- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient ‘Hotlist’).

Existing Worker Health and Safety Controls

Hazard Classification

The chemical, ethyloxirane is classified as hazardous, with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

- Xn; R20/21/22 (acute toxicity)
- Xi; R36/37/38 (irritation)
- C; R40 Carc. Cat 3 (carcinogenicity).

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards are identified for ethyloxirane (Galleria Chemica).

An exposure limit of 40 ppm time weighted average (TWA) and 2 ppm workplace environmental exposure limit (WEEL) in different countries such as the USA (Alaska, Hawaii), Austria, Canada, Germany and Denmark.

Temporary Emergency Exposure Limits (TEELs) defined by the US Department of Energy (DOE) for ethyloxirane (1,2-epoxybutane) are reported as protective action criteria (PAC):

PAC-1 = 72 ppm;

PAC-2 = 140 ppm; and

PAC-3 = 330 ppm.

Health Hazard Information

The chemicals in this group are volatile liquids with boiling points of 63.4°C (ethyloxirane), 91.02°C (propyloxirane) and 117.1°C (butyloxirane). For consideration of the mechanism of action in regards to the carcinogenic potential, the chemicals in this group are compared to phenyl- and methyl oxirane (NICNASa & b).

Toxicokinetics

Ethyloxirane is readily absorbed following oral and inhalation exposure in Fischer 344 (F344) male rats. Radiolabelled chemical is extensively metabolised and, within 36 hours, 80-90 % of the administered dose is excreted as carbon dioxide or urinary metabolites. Around 44-53 % of the total administered dose is excreted as urinary metabolites and around 3 % of the administered dose is found in liver. Detoxification of the epoxides in vivo occurs by hydrolysis and conjugation with glutathione (NTP, 1999; OECD SIDS, 2001; HSDB; REACHa; REACHb).

Acute Toxicity

Oral

Ethyloxirane is classified as hazardous with the risk phrase ‘Harmful if swallowed’ (Xn; R22) in the HSIS (Safe Work Australia). The available data (median lethal dose (LD50) range—900-1327 mg/kg bw) for ethyl and propyloxirane support this classification (REACHa; REACHb). Reported signs of toxicity include slight apathy, partial staggering, dyspnoea, exsiccosis (dehydration), abdominal and lateral position, atonia, diarrhoea, and loss of pain and corneal reflexes.

In an acute toxicity study, ethyloxirane was administered to Sprague Dawley (SD) rats (five animals/sex/dose) as an emulsion in 0.5 % aqueous carboxymethyl cellulose solution once by gavage at doses of 0, 100, 464, 681, 1000, 1210, 1470, 1780, 2150, 4640 or 10000 µL/kg. The LD50 was calculated to be 900 mg/kg bw (equivalent to 1100 µL/kg). Pathological examination showed acute heart dilatation, acute congestive hyperaemia, intra-abdominal adhesions of the stomach, thickened wall of the forestomach and partially formed diverticulum (REACHa).

In an acute toxicity study conducted according to OECD Test Guideline (TG) 401, propyloxirane was administered in Wistar rats (five animals/sex/dose) in 0.5 % aqueous carboxymethyl cellulose solution once by gavage at doses of 0, 1000, 1470, 2150 or 3160 mg/kg bw. All animals in 3160 mg/kg bw dose group, 9/10 animals in the 2150 mg/kg bw group and 5/10 animals in the 1470 mg/kg bw dose group died within one day after application. The LD50 was calculated to be 1327 mg/kg bw (REACHb).

Based on the similarity of the results for propyloxirane and ethyloxirane, particularly on a molar basis, it is expected that butyloxirane would also warrant classification.

Dermal

Ethyloxirane is classified as hazardous with the risk phrase ‘Harmful in contact with skin’ (Xn; R21) in the HSIS (Safe Work Australia). The available data (median lethal dose (LD50) range—1255-2546 mg/kg bw) support this classification (REACHa; REACHb). Reported signs of toxicity observed after prolonged exposure include marked erythema and necrosis with scab formation. While it is possible that propyl- and butyloxirane may have moderate dermal toxicity, the lower irritancy reported for propyloxirane compared with ethyloxirane (see **Irritation** section) and the indicators that the dermal toxicity of ethyloxirane may be due to local effects, it is not possible to draw conclusions for the other chemicals in this group.

In an acute dermal toxicity study, ethyloxirane was applied to the skins of male New Zealand White rabbits (four animals/dose) under occlusive conditions at doses of 1.25 or 2.5 mL/kg bw/day for 24 hours. Three of the four animals in the 2.5 mL/kg bw/day group and one of the four in the 1.25 mL/kg bw/day died. Marked erythema and necrosis of the skin were observed at the covered application site. Gross pathology examination revealed petechial haemorrhages in the lungs, pale or mottled livers and pale kidneys and stomachs of the treated animals. The LD50 for rabbits was 1.77 mL/kg bw(REACHa).

Ethyloxirane was applied to the skins of male New Zealand White rabbits (four animals/dose) under occlusive conditions for 24 hours. The LD50 was reported to be in the range of 1500 to 2950 mg/kg bw (REACHb).

Inhalation

Ethyloxirane is classified as hazardous with the risk phrase ‘Harmful by inhalation’ (Xn; R20) in the HSIS (Safe Work Australia). The available data (median lethal concentration (LC50) of 18.1 mg/L) support this classification (REACHa; REACHb). Observed sub-lethal effects included respiratory sounds, reddish nasal discharge, eye discharge, high-stepping gait, deteriorated general state and salivation.

In an acute toxicity inhalation study, ethyloxirane was tested in SD rats (10 animals/sex/dose) by whole body inhalation exposure to the vapours of the chemicals for a 4 hour duration at 6.3 mg/L concentration. No mortalities and no symptoms of toxicity were reported. The median lethal concentration (LC50) was reported to be >6.3 mg/L for 4 hour exposure (REACHa).

In another study, rats (unknown strain) (six animals/dose) were exposed to vapours of ethyloxirane at 4000 or 8000 ppm for up to 6 hours. All animals exposed to 8000 ppm died in the exposure chamber or within one hour after a 4 hour exposure period. One animal in the 4000 ppm dose group died after a 4 hour inhalation period (REACHa).

In other study, female rats (strains unknown) were exposed to vapours of ethyloxirane (99.9 % pure) for 6, 12 or 30 minute exposures. Five animals were exposed for 12 and 30 minutes and three animals were exposed for six minutes. All five animals exposed to the chemical vapours for 12 and 30 minutes were unconscious and died by the end of the day, while all three animals in the six minute exposure group survived and appeared normal after a few hours. Necropsy examination revealed lung congestion in animals with six minute exposure to the chemical (REACHa).

In a study conducted according to OECD TG 403, Wistar rats (five animals/sex/dose) were exposed to propyloxirane (90 %) as vapour at concentrations of 0, 5.3, 10.6 or 21.3 mg/L for four hours. Eight out of ten animals exposed to 21.3 mg/L of the chemical vapour died either on the day of exposure or one day after exposure. Clinical signs observed included accelerated respiration, eyelid closure, ruffled fur, wiping of snouts, restlessness, abdominal position, staggering gaits, reddish nasal discharge, eye discharge, salivation, deteriorated general state and lethality. Gross pathology examination revealed general congestion, focal hyperaemia with oedema and areas of emphysema in the lungs and slight hydrothorax. The LC50 was calculated to be 18 mg/L (REACHb).

Based on this study, propyloxirane should be classified as harmful by inhalation, as the LC50 results for ethyloxirane and propyloxirane, and it is probable that butyloxirane should also be classified by extrapolation.

Corrosion / Irritation

Respiratory Irritation

Ethyloxirane is classified as hazardous with the risk phrase 'Irritating to respiratory system' (Xi; R37) in the HSIS (Safe Work Australia). The available data support this classification (see **Repeated dose toxicity-Inhalation** section).

Skin Irritation

Ethyloxirane is classified as hazardous with the risk phrase 'Irritating to skin' (Xi; R38) in HSIS (Safe Work Australia). While the available data provided some support for this classification for ethyloxirane, data on propyloxirane indicate the chemical is less irritating. The data for propyloxirane relate to semi-occlusive conditions, and ethyloxirane was also less irritating under these conditions, possibly due to evaporation.

Ethyloxirane (0.5 mL) was found to be corrosive when applied to shaved intact skin of four Vienna White rabbits for one hour under occlusive application. Erythema, oedema, scale formation and marked necrosis were observed at one hour, 1 day, 2 days and 8 days. The chemical was reported to not be irritating after semi-occlusive application. Due to the high volatility of the chemical, loss of chemical under semi-occlusive conditions may have occurred. (REACHa).

In a skin irritation study conducted in Vienna White rabbits (two animals), ethyloxirane (unknown concentration) was applied to shaved skin under occlusive conditions for a 20 hour exposure. The chemical was found to be irritating to the rabbit skin (REACHa).

In a study conducted according to OECD TG 404, 0.5 mL of undiluted propyloxirane was applied to skins of three Vienna White rabbits for four hours under semi-occlusive conditions. Slight erythema and oedema were observed, which were fully reversed within 24 to 48 hours. The chemical was not irritating under these conditions (REACHb).

Eye Irritation

Ethyloxirane is classified as hazardous with the risk phrase 'Irritating to eyes' (Xi; R36) in HSIS (Safe Work Australia). While the available data provided some support for this classification for ethyloxirane, data on propyloxirane indicate the chemical is not irritating.

In an eye irritation study in rabbits, ethyloxirane was found to be irritating with slight reddening, slight oedema and cloudiness with smeary stratification in the eyes observed at 1 and 24 hours application (REACHa). Effects were reversible within the observation period of 8 days.

In another study, ethyloxirane at concentrations of 0.005 or 0.02 mL was instilled in the eyes of rabbits. Moderate corneal damage was seen at 0.005 mL and marked eye damage was observed at 0.02 mL (REACHa).

Propyloxirane (0.1 mL) instilled in the eyes of three Vienna White rabbits, according to OECD TG405, was found to be slightly irritating to the eyes with the irritation scores for corneal effects, iris, conjunctival redness and chemosis being 0.69, 1.59 and 0.33 respectively. All the irritation effects were fully reversed by 72 hours to 8 days (REACHb).

Sensitisation

Skin Sensitisation

The negative results observed for ethyloxirane in several skin sensitisation animal studies (guinea pig maximisation tests (GPMT)) support a conclusion that the chemicals are not skin sensitisers.

In a guinea pig maximisation test, ethyloxirane (0.1 mL; undiluted) was applied epicutaneously under occlusive conditions on male Pirbright-Hartley guinea pigs (10 animals/dose), followed by a challenge intradermal dose of 0.2 mL of Freund's Adjuvant. No signs of sensitisation were observed in the treated animals (REACHa; REACHb).

Repeated Dose Toxicity

Oral

No data are available.

Dermal

No data are available.

Inhalation

Based on the available data, a hazard classification is not warranted for repeated dose toxicity via the inhalation route.

In a 90-day repeated dose inhalation toxicity study conducted similarly to OECD TG 413 in male and female Fischer 344 (F344) rats, ethyloxirane (> 99 % purity) was administered (15 animals/sex/dose) by inhalation (vapour) at concentrations of 0, 75, 150 or 600 ppm (0, 225, 450 or 1800 mg/m^3) for 6 hours/day for 5 days/week. Significant reduction in the mean body weights in female rats in the 600 ppm group was observed in the last few weeks of the study. Decreased amounts of abdominal adipose tissue and thymus size and mediastinal fat were seen in pathological examination in the rats in the 600 ppm group. There were no treatment related pathological observations in the 75 or 150 ppm dose groups. The highest dose group (600 ppm) of rats showed changes in the nasal mucosa attributed to upper respiratory tract irritation. Microscopic examination revealed minimal changes to the nasal turbinates and flattening of the olfactory and respiratory epithelia. An increased number of inflammatory cells in the nasal mucosa and within the lumen of the nasal cavity with some focal thickening of the respiratory epithelium was observed. Female rats in the 150 ppm group showed significantly higher mean haemoglobin values and mean red blood cell count than the controls. There were no other changes in the animals in the 75 and 150 ppm dose group. The lowest observed adverse effect concentration (LOAEC) was 600 ppm (1800 mg/m^3) (OECD SIDS, 2001; REACHa; REACHb).

In two separate 90-day inhalation studies, rats and mice (10 animals/sex/dose, respectively) were exposed to ethyloxirane at concentrations of 0, 150, 300, 600, 1200 or 2400 mg/m^3 for 6 hours/day and 5 days/week. No mortalities were noted in rats. Rats (both sexes) in the highest dose group (2400 mg/m^3) showed decreased body weight gain and inflammation of the mucosa of the nasal turbinates and the septum, and olfactory and respiratory epithelia. Two male mice in the 150 mg/m^3 dose group and all mice of the highest dose group (2400 mg/m^3) died within 10 weeks of the treatment. No dose-dependent changes in the body weight were observed. Inflammation with necrosis of the renal tubules and inflammation of nasal turbinates were observed in the 600 mg/m^3 dose group and higher in mice and at 2400 mg/m^3 in rats. These effects were dose-dependent in mice. Mice in the 300, 600 and 1200 mg/m^3 showed nasal inflammation. Mice had a LOAEC of 300 mg/m^3 based on nasal effects (OECD SIDS, 2001; REACHa; REACHb).

Ethyloxirane was tested for inhalation toxicity in B6C3F1 mice (10 animals/sex/dose) at concentrations of 0, 50, 100, 200, 400 or 800 ppm for 6 hours/day and 5 days/week for 90 days. All animals in the 800 ppm dose group and two males in the 50 ppm group died within 10 weeks. Clinical signs included listlessness and renal tubular necrosis (6/10 males and 8/10 females) in the animals in the highest dose (800 ppm) group. Inflammation of nasal turbinates was observed in all animals in the 100, 200 and 400 ppm dose groups. Gross pathological examination revealed red discolouration of the lungs in 4/10 males and all females of the 800 ppm group and in 1/10 males in the 400 ppm group, distension of the gastrointestinal tract and paleness of spleen in the 800 ppm dose group. Thymic necrosis, thymic atrophy, splenic atrophy and splenic necrosis were observed in the histological examination of the mice in the 800 ppm group. The NOAEC was 50 ppm and the LOAEC was 100 ppm (OECD SIDS, 2001; REACHa; REACHb).

Genotoxicity

Based on the weight of evidence from the available in vitro and in vivo genotoxicity studies, the chemicals in this group are not considered to be genotoxic. While some in vitro genotoxicity tests were positive, all in vivo tests, including in germ cells, were negative.

In vitro studies

In an Ames test conducted according to OECD TG471, *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 were exposed to ethyloxirane at concentrations up to 7500 µg/plate. The chemical gave weakly positive responses in TA1535 and TA100 with and without metabolic activation (OECD SIDS, 2001; REACHa; REACHb).

In another Ames test, *S.typhimurium* strains TA98, TA100, TA1535 and TA1537 were exposed to ethyloxirane at concentrations up to 10000 µg/plate. Positive results were found in TA100 and TA1535 with and without activation at concentrations of 1000 µg/plate and higher (OECD SIDS, 2001; REACHa; REACHb).

Ethyloxirane at concentrations of 16-500 µg/mL gave positive mutagenic activity in a chromosome aberration test in Chinese hamster ovary cells (CHO) without activation at 500 µg/mL and equivocal results with metabolic activation (OECD SIDS, 2001; REACHa; REACHb).

In a gene mutation assay, ethyloxirane in concentrations up to 800 µg/mL was tested in mouse lymphoma L5178Y cells. The chemical was positive for mutagenicity both in the presence and absence of metabolic activation (OECD SIDS, 2001; REACHa; REACHb).

In vivo studies

In a micronucleus assay conducted similarly to OECD TG 475, ethyloxirane was tested in male and females SD rats (10 animals/sex/dose) by inhalation at concentrations of 250 or 1000 ppm for either a single exposure for 7 hours or a 7 hour exposure on five consecutive days. The chemical did not induce micronuclei in this assay (OECD SIDS, 2001; REACHa; REACHb).

In a dominant lethal assay conducted according to OECD TG 478, ethyloxirane was tested in male SD rats (10 animals/sex/dose) at concentrations of 250 or 1000 ppm. The chemical did not cause dominant lethal mutations in germ cells of rats (OECD SIDS, 2001; REACHa; REACHb).

Carcinogenicity

The chemical ethyloxirane is classified as hazardous—Category 3 carcinogenic substance—with the risk phrase ‘Limited evidence of carcinogenic effect’ (Xn; R40 in the HSIS (Safe Work Australia). The International Agency for Research on Cancer (IARC) has classified ethyloxirane as 'possibly carcinogenic to humans' (Group 2B) (IARC, 1989).

In a 2-year carcinogenicity study, ethyloxirane was tested in F344 rats (50 animals/sex/dose) at concentrations of 200 or 400 ppm (590 or 1180 mg/m^3) by inhalation exposure for 6 hours/day for 5 days/week. Body weights of male rats in the 400 ppm group decreased by 4-8 % after week 86 and in females the body weights for the high dose group decreased by 5-10 % after week 22. Papillary adenomas of the nasal cavity were seen in 7/50 high dose males and 2/50 high dose females. Alveolar and/or bronchiolar carcinomas were seen in 4/49 high dose males and 1/50 high dose females. Non-neoplastic effects including inflammation, epithelial hyperplasia, squamous metaplasia, hyperostosis of the nasal turbinate bone and atrophy of the olfactory epithelium observed at both treatment doses were all considered treatment-related. The no observed adverse effect concentration (NOAEC) for tumour induction was 200 ppm (US EPA IRIS, 1992; OECD SIDS, 2001; REACHa; REACHb).

In B6C3F1 mice (50 animals/sex/dose), ethyloxirane was administered by inhalation at doses of 50 or 100 ppm, 6 hours/day for 5 days/week for 2 years. One male at 100 ppm had a single squamous-cell papilloma in the nasal cavity. Other treatment-related and non-neoplastic changes at both doses included inflammation, emphysema, erosion, regeneration, hyperplasia and inflammation of the nasolacrimal duct. No effects were seen on the body weights. A decrease in survival rate for females seen in low and high-dose groups was considered to be associated with suppurative inflammation of the ovary and uterus, but was not treatment-related. The LOAEC was 100 ppm (US EPA IRIS, 1992; OECD SIDS, 2001; REACHa; REACHb).

Based on the available data on the carcinogenic potential of the reactive oxirane groups such as phenyl oxirane and its isomers (NICNASa) and methyl oxirane (NICNASb) at the site of contact, and the available data for ethyl oxirane (OECD SIDS, 2001), other chemicals in this group are expected to have carcinogenic potential. The available data support the classification of ethyloxirane and the extension of this classification to other chemicals of this group.

Reproductive and Developmental Toxicity

The chemicals do not show specific reproductive or developmental toxicity. Any reproductive and developmental effects were only observed secondary to maternal toxicity.

In a reproductive toxicity study conducted according to OECD TG 414, and ethyloxirane was administered by inhalation exposure to female Wistar rats (groups of 38-45 animals/dose) at doses of 0, 250 or 1000 ppm for 7 hours/day for 5 days/week on gestation days 1-19 or for a combination exposure of pregestational (21 days premating) and gestational days (up to day 21 post-caesarian section). Significant reduction was observed in the body weights of the rats of the 1000 ppm group with pregestational exposure. No significant changes in the food consumption, lung weights and liver weights were observed. No significant effect on the weight or lengths of foetuses was observed. The NOAECs for both maternal toxicity and teratogenicity were determined to be >1000 ppm based on the overall effects (US EPA IRIS, 1992; OECD SIDS, 2001; REACHa; REACHb).

In a developmental toxicity study conducted according to OECD TG 414, New Zealand White rabbits (24 animals/sex/dose) were administered ethyloxirane at doses of 250 or 1000 ppm by inhalation exposure for 7 hours/day and 5 days/week during day 1-24 of gestation. In the 1000 ppm group, 14 of the 24 animals died during exposure. Necropsy examination showed suppurative pneumonia (formation of pus and destruction of pulmonary tissue) in the dead animals. No major treatment related effects were observed on lung weights, kidney weights or the placental weights in surviving maternal animals. Reduction in the percentage of sperm-positive rabbits seen at sacrifice was considered to be due to preimplantation mortality in the females at 1000 ppm. No significant effect on the weight or length of the foetuses was seen. Two litters of the high dose group females showed a decrease in number of live foetuses per litter and an increase in the frequency of resorptions. The NOAEC for both maternal and foetal toxicity was 250 ppm based on maternal mortality, the decrease in the number of live foetuses per litter and an increase in resorption at 1000 ppm (US EPA IRIS, 1992; OECD SIDS, 2001; REACHa; REACHb).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (carcinogenicity) and systemic acute effects (acute toxicity from oral, dermal and inhalation exposure). The chemicals may also cause respiratory, skin and eye irritation.

Public Risk Characterisation

Although the chemicals are known to be used as intermediates in the manufacture of cosmetics chemicals, there are no reports to suggest these chemicals are being used as cosmetic ingredients overseas. The use of the chemicals in domestic products in Australia is not known. However, ethyloxirane is reported to be used in a domestic product overseas at a concentrations of 0.5 % in an art and craft product as an aerosol. Considering the low concentration used in the product, the risk to public health is not considered to be unreasonable. Furthermore, similar potential products are adequately risk managed in Australia as the chemicals in this group are currently listed on Schedule 5 of the *Poisons Standard* under '*Epoxy resins, Liquid*'.

Occupational Risk Characterisation

During product formulation, dermal, ocular and inhalation exposure may occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemicals at lower concentrations could also occur while using formulated products containing the chemicals. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic long-term, systemic acute and local health effects, the chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and inhalation exposure are implemented. The chemicals should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine the appropriate controls.

The data available support an amendment to the hazard classification in the Hazardous Substances Information System (HSIS) (Safe Work Australia) (refer to **Recommendation** section).

NICNAS Recommendation

Assessment of these chemicals is considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Work Health and Safety

The chemicals are recommended for classification and labelling under the current approved criteria and adopted GHS as below. No change in classification has been recommended for ethyloxirane (CAS No. 106-88-7). Classification for acute dermal toxicity (Xn; R21) and irritation (R36/37/38) only applies to ethyloxirane. This assessment does not consider classification of physical and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful if swallowed (Xn; R22)* Harmful in contact with skin (Xn; R21)* Harmful by inhalation (Xn; R20)*	Harmful if swallowed - Cat. 4 (H302) Harmful in contact with skin - Cat. 4 (H312) Harmful if inhaled - Cat. 4 (H332)
Irritation / Corrosivity	Irritating to eyes (Xi; R36)* Irritating to skin (Xi; R38)* Irritating to respiratory system (Xi; R37)*	Causes serious eye irritation - Cat. 2A (H319) Causes skin irritation - Cat. 2 (H315) May cause respiratory irritation - Specific target organ tox, single exp Cat. 3 (H335)
Carcinogenicity	Carc. Cat 3 - Limited evidence of a carcinogenic effect (Xn; R40)*	Suspected of causing cancer - Cat. 2 (H351)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

[*] Existing Hazard Classification. No change recommended to this classification

Advice for consumers

Products containing the chemicals should be used according to the instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from oral, dermal and inhalation exposure to the chemicals should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate, or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemicals are used. Examples of control measures that could minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemicals from entering the breathing zone of any worker;

- health monitoring for any worker who is at risk of exposure to the chemicals, if valid techniques are available to monitor the effect on the worker's health;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemicals.

Guidance on managing risks from hazardous chemicals are provided in the *Managing risks of hazardous chemicals in the workplace—Code of practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to help meet obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((M)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemicals are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (M)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals—Code of practice* and *Labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of these chemicals has not been undertaken as part of this assessment.

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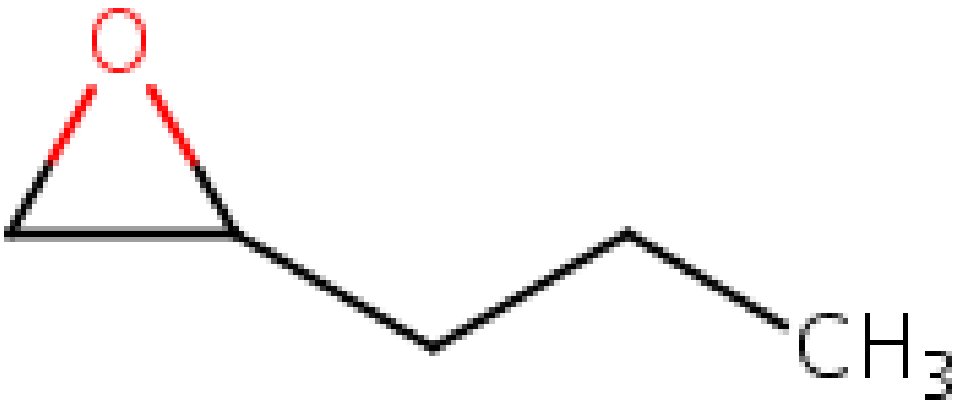
Last Update 01 September 2015

Chemical Identities

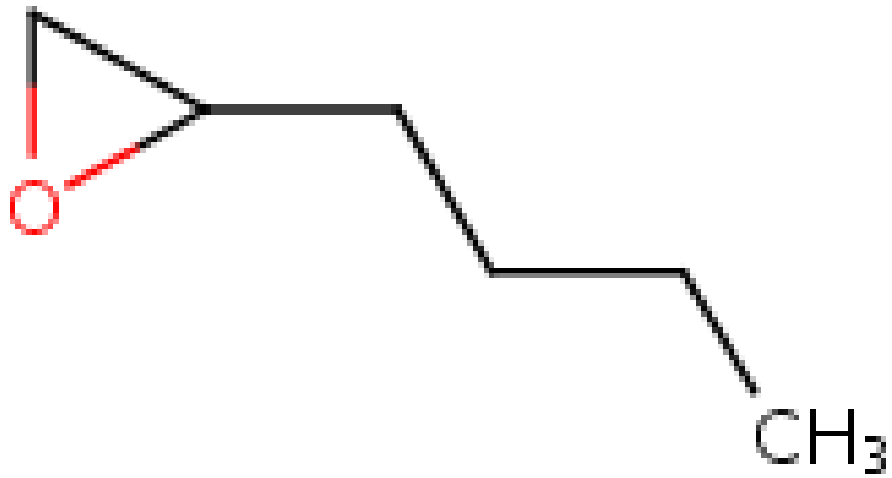
Chemical Name in the Inventory and Synonyms	**Oxirane, ethyl-** ethyloxirane ethylene oxide, ethyl- 2-ethyloxirane 1,2-epoxybutane 1,2-butene oxide
CAS Number	106-88-7

Structural Formula	
Molecular Formula	C4H8O
Molecular Weight	72.1

Chemical Name in the Inventory and Synonyms	**Oxirane, propyl-** propyloxirane 1-pentene oxide 1,2-epoxypentane
CAS Number	1003-14-1
Structural Formula	

	
Molecular Formula	C5H10O
Molecular Weight	86.1

Chemical Name in the Inventory and Synonyms	**Oxirane, butyl-** butyloxirane 1-hexene oxide epoxy-n-hexane 1,2-epoxyhexane
CAS Number	1436-34-6
Structural Formula	

	
Molecular Formula	C6H12O
Molecular Weight	100.1

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