Oxirane: Human health tier II assessment

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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

Chemical Identity

Synonyms	ethylene oxide oxacyclopropane epoxyethane or 1,2-epoxyethane dimethylene oxide dihydrooxirene
Structural Formula	
Molecular Formula	C2H4O
Molecular Weight (g/mol)	44.05
Appearance and Odour (where available)	Colourless, sweet smelling gas
SMILES	C1CO1

Import, Manufacture and Use

Australian

The following industrial uses were identified in the National Pollutant Inventory (NPI).

The chemical has reported site-limited use including in chemical manufacturing such as in the production of ethylene glycol (used in automotive antifreeze/coolant) and polyester.

The following non-industrial uses have been identified in Australia:

- to control pests in stored agricultural products; and
- to sterilise equipment in hospitals and veterinary institutions.

International

The following international uses have been identified through European Union Registration, Evaluation, Authorisation and Restriction of Chemicals (EU REACH) dossiers; the Organisation for Economic Cooperation and Development Screening Information Dataset Initial Assessment Report (OECD SIAR); Galleria Chemica; Substances and Preparations in the Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) dictionary; and eChemPortal: OECD High Production Volume chemical program (OECD HPV), the US Environmental Protection Agency's Aggregated Computational Toxicology Resource (ACToR), and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical has reported site-limited uses including:

- as a rocket propellant and fuel additive;
- in manufacturing polymers;
- in manufacturing surfactants;
- as an intermediate in some chemical manufacturing;
- in rocket motor production;
- in coatings and sealants; and
- as a laboratory reagent.

The following non-industrial uses have been identified internationally:

- to sterilise heat and irradiation-sensitive surgical instruments; and
- as a fumigant.

The chemical is reported to occur as a contaminant in skin care products containing commercial preparations of polyglycol ethers at residues up to 1 ppm (0.08–1.5 mg/L) (Filser JG et al., 1994).

The chemical is a component of mainstream tobacco smoke, at 7 µg/cigarette (IARC, 2012).

Restrictions

Australian

The chemical (as ethylene oxide) is listed in the Poisons Standard (Standard for the Uniform Scheduling of Medicines and Poison—SUSMP) in Schedule 7.

Schedule 7 chemicals are labelled with 'Dangerous poison'. These are 'substances with a high potential for causing harm at low exposure and which required special precautions during manufacture, handling or use. These poisons should be available only to specialised or authorised users who have the skills necessary to handle them safely. Special regulations restricting their availability, possession, storage or use may apply' (SUSMP, 2013).

International

The chemical is listed on the following (Galleria Chemica):

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

Existing Work Health and Safety Controls

Hazard Classification

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

- T; R23 (acute toxicity)

- Xi; R36/37/38 (irritant)
- Muta. Cat. 2; R46 (mutagen)
- Carc. Cat. 2; R45 (carcinogen)

Exposure Standards

Australian

The chemical has an exposure standard of 1.8 mg/m³ (1 ppm) time weighted average (TWA).

International

The following exposure standards are identified (Galleria Chemica).

A TWA of:

- 0.84 mg/m³ in the Netherlands;
- 1.8 mg/m³ in different countries such as the USA, Canada (Alberta and Ontario), Norway, Denmark, Finland, Hungary, Iceland, Indonesia, Italy, Japan, Korea and New Zealand;
- 2 mg/m³ in Mexico;
- 9.2 mg/m³ (5 ppm) in the UK;
- 10 mg/m³ in Greece and Ireland;
- 20 mg/m³ in Canada (NW territories) and Egypt; and
- 90 mg/m³ in Argentina.

Health Hazard Information

Toxicokinetics

The chemical is a gas at room temperature (boiling point 10.5 °C). When inhaled, the chemical is rapidly taken up via the lungs, distributed, and then metabolised by enzymatic and non-enzymatic hydrolysis to ethylene glycol, or by conjugation with glutathione (GSH). Subsequent conversion produces oxalic acid, formic acid, and carbon dioxide (IARC, 2008; HSDB).

Absorption can occur though the skin from the gas phase or from aqueous solutions, leading to uniform distribution throughout the body. The chemical is a direct alkylating agent and forms protein and DNA adducts (HSDB).

Species-related differences in the metabolic disposition were observed among rats, mice and rabbits, when administered the chemical intravenously or exposed via inhalation (HSDB). Rats eliminated 37 % of the chemical as 2-hydroxyethylmercapturic acid (31 %) and ethylene glycol (6 %); mice eliminated 19.3 % of the chemical as 2-hydroxyethylmercapturic acid (8.3 %), S-2-hydroxyethyl-L-cysteine (5.8 %), S-carboxymethyl-L-cysteine (1.9 %), and ethylene glycol (3.3 %). The rabbits excreted only 2 % of the chemical, primarily as ethylene glycol. In rats, larger amounts of 2-hydroxyethylmercapturic acid were excreted in the 6–24 hour period, and larger amounts of ethylene glycol were excreted in the 0–6 hour period. In mice, equal amounts of 3-hydroxyethylmercapturic acid were excreted in the two collection periods (0–6 hour and 6–24 hour) and larger amounts of ethylene glycol were excreted in the 6–24 hour period (HSDB).

Acute Toxicity

Oral

The chemical had moderate acute toxicity in animal tests following oral exposure, warranting a hazard classification.

The median lethal dose (LD50) was 330 mg/kg bw in male Wistar rats after a single oral gavage dose (REACHa). Observed sublethal effects included sluggish and depressed functioning.

The LD50 in mice was 280 mg/kg bw after a single oral gavage dose (eChemPortal).

Dermal

No data are available.

Inhalation

The chemical is classified as hazardous with the risk phrase ‘Toxic by inhalation’ (T; R23) in HSIS (Safe Work Australia). The available data support this classification.

The median lethal concentration (LC50) in male Sprague Dawley (SD) rats was 2.63 mg/L/4 hour (REACH). Observed sublethal effects included frequent movement and preening, a clear nasal discharge, lacrimation, diarrhoea, gasping and occasionally salivation. Gasping increased in intensity during exposure.

In other acute inhalation toxicity studies in rats, the LC50 values were reported as 3.13 mg/L/4 hour (REACH) and 1.44 mg/L/4 hour (HSDB).

The LC50 was 1.73 and 1.19 mg/L/4 hour in dogs and female mice, respectively (REACHa).

Observation in humans

A 43-year-old female nurse accidentally broke an ampule containing 17 g of the chemical while sterilising heat-sensitive medical items. The exposure was estimated to have been of 2–3 minutes duration and did not exceed 500 ppm. She experienced nausea and stomach spasms, became pale and lightheaded, and passed out for approximately 3–4 minutes. Convulsive movements of her arms and legs were noted during a one-minute period of apnoea (pause in breathing). She was given oxygen, began breathing, and awoke instantly without confusion or nausea. Approximately three minutes later she again felt nausea, stomach spasms, and lightheadedness and became apnoeic and passed out. Twitching of the extremities occurred and she was given oxygen again. During the 24 hours following discharge she continued to complain of random muscle twitches, nausea, and malaise (HSDB).

Corrosion / Irritation

Corrosivity

The chemical is classified as hazardous with the risk phrases 'Irritating to skin' (Xi; R38), 'Irritating to eyes' (Xi; R36) and 'Irritating to respiratory system' (Xi; R37) in HSIS (Safe Work Australia). The available data indicate the need for a higher classification for these hazards.

Skin

Skin irritation with hyperaemia, oedema, and scar formation was observed (irritation scores not available) from six minutes after the chemical was applied using pads of cotton, moistened with solutions containing the chemical at 10 % or 50 % w/v in water, on the shaved, intact skin of rabbits, under a plastic cover (IPCS; REACHa; SYKE).

In another patch test, the undiluted chemical (0.5 mL) was applied to the shaved, intact skin of New Zealand White rabbits (n=6) for four hours (occlusive) (non-guideline study). The study authors reported a skin irritation score of 7.8/8 and described the chemical as corrosive, irreversibly changing or destroying the structure of tissue at the site of contact (REACH). Subdermal haemorrhage was noted in all animals following the four-hour exposure, with irreversible chemical burns observed after 24 hours (Celanese Chemical, 1983).

Eye

In a Draize test (non-guideline study), 1 % of the chemical (0.05 mL) applied into the conjunctival sac of New Zealand White rabbits (n=6) at 10-minute intervals for six hours caused reversible changes in conjunctivae such as hyperaemia and swelling, and irreversible opacity, both in the cornea and in the lens (Draize score for cornea was 0.9/1.8) (REACHa). At a concentration of 20 %, damage to the lens and retina was observed, along with irreversible opacity of the cornea (HSDB).

It has been noted that 'exposure to high levels of the gas may cause corneal burns and cataracts' (ATSDR). No further details were provided.

In Draize test conducted with two possible metabolites of the chemical, 2-chloroethanol and 1,2-ethanediol were found to be less irritating to the rabbit eye (REACHa; SYKE).

Respiratory tract

Acute inhalation toxicity studies in rats showed irritation in the upper respiratory tract in post-mortem examinations. Secretion around the eyes and nose were also observed (REACHa).

Observation in humans

Exposure to high concentrations of vapour/gas or eye splashes of concentrated solutions can cause eye irritation, inflammation of the eye membrane and corneal injury. Exposure to the chemical has also been linked to the development of cataracts. Aqueous solutions of the chemical, or solutions formed when the undiluted chemical comes in contact with moist skin, are irritating and may lead to severe dermatitis with blisters and burns (HSDB).

Sensitisation

Respiratory Sensitisation

No case reports of respiratory sensitisation were found.

Skin Sensitisation

The chemical was not a skin sensitiser in guinea pigs. The chemical has produced allergic skin reactions in humans (see **Observation in humans**).

The chemical was not sensitising in a skin sensitisation study (guideline not stated) with male Hartley guinea pigs (n=10). The chemical (0.5 mL) was applied dermally for six hours/day, three times per week for three weeks. The animals were then challenged with an intracutaneous injection (0.1 mL) two weeks after the last dermal application. No skin sensitisation reactions were observed (REACHa).

Observation in humans

The chemical is considered to be a skin sensitiser in humans, warranting a hazard classification.

The chemical induced dermal sensitisation in a human patch test (similar to OECD TG 406). The chemical was applied to the skin of 12 subjects at 100 mg/kg bw (in polyvinyl chloride). A positive skin reaction was observed in 1/12 subjects (REACHb).

In a human skin test, eight subjects were exposed to the concentrated chemical and various aqueous dilutions (details not available). Skin sensitisation was reported in 3/8 subjects, 19–20 days after the first exposure and 5–9 days after the last exposure (REACHa).

Repeated Dose Toxicity

Oral

Based on the limited data available, the chemical is not expected to cause serious damage to health from repeated oral exposure.

Groups of Wistar rats (n=5/group) received 22 doses of the chemical at concentrations of 0, 3, 10 or 30 mg/kg bw/day in olive oil for 30 days, or 15 doses of 100 mg/kg bw/day in olive oil for 21 days. A lowest observed adverse effect level (LOAEL) of 100 mg/kg bw/day was reported based on decreased body weight, gastric irritation and slight liver damage observed at this dose level. No mortalities or toxic effects were reported at the lower doses of 3–30 mg/kg bw/day (IPCS).

Dermal

No data are available.

Inhalation

Based on the data available (a 10-week study indicating a no observed adverse effect concentation (NOAEC) of 0.018 mg/L in mice), the chemical is considered to cause serious damage to health from repeated inhalation exposure, warranting a hazard classification.

In a 10-week repeated dose inhalation toxicity study, B6C3F1 mice (n=30/sex/group) were exposed to the chemical at concentrations of 0, 18, 90, 180 or 450 mg/m³ (0, 10, 50, 100 or 250 ppm), six hours/day for five days/week. Mortality rates did not differ from controls. Statistically significant toxic symptoms observed in the 450 mg/m³ group included decreased body weight gain (in the last week of the study), increased liver weights and decreased testicular and spleen weights (also noted in the 180 mg/m³ group). Neuromuscular function, including reflex and locomotor activity, were also affected in the 90–450 mg/m³ dose groups. Statistically significant decreases in body weight gain were observed in male mice from 18 mg/m³ (NTP). The NOAEC for the chemical was reported to be 18 mg/m³ (0.018 mg/L) based on the neuromuscular function changes (abnormal gait and abnormal locomotor activity) observed at 90 mg/m³ (REACHa).

In a 14-week inhalation toxicity study, B6C3F1 mice were exposed to the chemical at 0, 50, 100, 200, 400 or 600 ppm. Histopathologic examinations revealed dose-related increases in the incidence and severity of nasal (at 200, 400 and 600 ppm), thymic (at 600 ppm), and renal (at 100, 200 and 400

ppm) lesions. At the two higher doses, all mice died with severe clinical signs. Mean body weights were comparable in mice at 50, l00, 200 ppm and the control groups (NTP, 1987).

In an eight-week repeated dose inhalation study (range finding), Fischer 344 rats were exposed to the chemical at 0, 90, 180 or 270 mg/m³ (0, 50, 100 or 150 ppm). Statistically significant decreases in body weight gain were observed at 180 and 270 mg/m³ (-16 % and -29 % at 270 mg/m³ in males and females, respectively, compared with controls) and differences in haemoglobin concentration and kidney weights were observed at 270 mg/m³ (Celanese Chemical, 1983).

In a seven-week inhalation study, high mortality rates were observed in Fischer 344 rats and CD1 and CF1 mice at 450 ppm, due to vascular damage. Several clinical chemistry parameters were affected and thymus atrophy was also observed in rats at 450 ppm (UCC).

Neurological effects were also reported in animals and humans exposed to the chemical (see **Other health effects**).

Genotoxicity

The chemical is classified as hazardous—Category 2 mutagenic substance—with the risk phrase ‘May cause heritable genetic damage’ (T; R46) in HSIS (Safe Work Australia). The data available support this classification.

The chemical showed positive results for gene mutation and clastogenicity in several in vitro tests (REACHa) in a:

- bacterial reverse mutation assay (Ames test) with two strain of *Salmonella typhimurium* (TA 100 and TA1535), without metabolic activation;
- mammalian cell gene mutation assay using Chinese hamster lung fibroblasts (V79), without metabolic activation, at concentrations of 1.125–13.5 mg/L;
- mammalian cell transformation assay using mouse embryo fibroblasts (C3H/10T1/2), without metabolic activation, at concentrations up to 7.5 mM; and
- sister chromatid exchange assay in human peripheral hepatocytes, without metabolic activation, at concentrations up to 120 mM.

The chemical showed positive results in several in vivo genotoxicity tests, including in germ cells (REACHa):

- Dominant lethal mutations were observed in a chromosome aberration assay in Long Evans rats exposed to the chemical at a concentration of 1000 ppm for four hours. A decreased fertility index and post-implantational losses were also observed.
- A dose-related increase in dominant lethal mutations was observed in a chromosome aberration assay in male (C3Hx101)F1 mice exposed to the chemical up to 3.24 mg/L by inhalation for six hours/day over four consecutive days.
- Reciprocal translocations were observed in somatic and germ cells of male B6C3F1 mice exposed to the chemical by inhalation at concentrations of 25, 50, 100 or 200 ppm for six hours/day, five days/week for 48 weeks. Reciprocal translocations in spermatogonial stem cells showed significant increases (but not dose-related) in translocation frequencies at all concentrations.
- Clastogenic effects in a dominant lethal chromosome aberration assay in male (C3Hx101)F1 mice exposed to the chemical by inhalation at concentrations up to 0.54 mg/L for six hours/day, five days/week for 8.5 weeks.

Mutagenic effects in humans exposed to the chemical were investigated using workers at hospitals or factories involved in sterilising equipment using the chemical, and also in workers in manufacturing and processing plants (IARC, 2012). Results included:

- Sister chromatid exchange (SCE) frequencies varied with the level and frequency of exposure to the chemical. In two studies, increased SCE frequencies persisted for at least 6 months following cessation of exposure.
- Frequencies in chromosomal aberrations correlated with exposure concentration and duration of exposure. Workers exposed to the chemical at 0.02–366 mg/m³ showed significant increases in chromosomal aberrations.
- Workers exposed to the chemical at 1.83–732 mg/m³ showed increased frequencies of micronucleated lymphocytes.
- Workers exposed to the chemical below 0.7 mg/m³ TWA had significant increases in micronucleus frequency in nasal mucosa cells, but not in exfoliated buccal cells.
- A T-cell cloning assay measured HPRT (hypoxanthine phosphoribosyltransferase) mutant frequencies in peripheral blood lymphocytes in nine hospital workers exposed to the chemical at 36.6–45.8 mg/m³ or 40.3–131.8 mg/m³, and in 15 factory workers exposed to an average ambient concentration of the chemical at ~31 mg/m³. Both groups had similarly elevated average HPRT mutant frequencies, compared with their respective control groups (increase of 55 % and 60 %, respectively). However, the increase was significant only in the factory workers.
- In a follow-up study with workers in a chemical manufacturing plant, a T-cell cloning assay measured HPRT mutant frequencies in three exposed groups and one unexposed group (n=7/group). No significant differences were observed in mutant frequencies in any of the groups, implying that incidental exposure to high levels of the chemical (52–785 mg/m³), or long-term exposure to low concentrations of the chemical (<0.01–0.04 mg/m³) did not cause permanent gene mutations in lymphocytes.

IARC (2012) concluded that the chemical 'acts as a mutagen and clastogen at all phylogenic levels, it induces heritable translocations in the germ cells of exposed rodents, and a dose-related increase in the frequency of sister chromatid exchange, chromosomal aberrations and micronucleus formation in the lymphocytes of exposed workers'.

Carcinogenicity

The chemical is currently classified as hazardous as a Category 2 carcinogen with the risk phrase ‘May cause cancer’ (T; R45) in HSIS (Safe Work Australia). The data available support this classification.

This is a different category with the International Agency for Research on Cancer (IARC) classification which is Group 1, (known human carcinogen), principally due to differences in the carcinogen classification criteria and also consideration of the weight of evidence.

According to the Approved Criteria, there should be 'sufficient evidence to establish a causal association between human exposure to a substance and the development of cancer' on the basis of epidemiological data to classify a chemical as a Category 1 carcinogen. Although IARC has classified the chemical as ‘carcinogenic to humans’ (Group 1), based on limited evidence for carcinogenicity in humans, but sufficient evidence for carcinogenicity based on animal testing (IARC, 2012), limited data on humans support a Category 2 carcinogen classification for the chemical according to the Approved Criteria. The IARC upgraded the carcinogenicity classification to Group 1 in 1994 (from Group 2A; IARC, 1985, 1987, 1994) based on mechanistic and other relevant data, 'and relied heavily on the compelling data in support of the genotoxic mechanism' (IARC, 2012).

There is only limited evidence in humans for a causal association of the chemical with lymphatic and haematopoietic cancers and breast cancer (IARC, 2012). IARC also concluded that, 'There is strong evidence that the carcinogenicity of ethylene oxide, a direct-acting alkylating agent, operates by a genotoxic mechanism. A dose-related increase in the frequency of ethylene oxide-derived haemoglobin adducts has been observed in exposed humans and rodents, and a dose-related increase in the frequency of ethylene oxide-derived DNA adducts has been demonstrated in exposed rodents' (IARC, 2012).

Several long-term animal carcinogenicity studies are available, using oral, dermal and inhalation routes of exposure (IARC, 2008; IARC 2012; IPCS; REACHa).

A 110-week oral gavage study in female SD rats (n=50), reported an increased incidence of squamous cell carcinomas of the forestomach at 7.5 and 30 mg/kg bw/day (8/50 and 29/50, respectively compared with none in the control group). Increased hyperplasia, hyperkeratosis and papillomas of the forestomach were also observed in both dose groups. Invasive growth and metastases (10/50) and fibrosarcomas (2/50) were observed at 30 mg/kg bw/day (IARC, 2012; IPCS).

In a lifetime dermal toxicity study, female Swiss Millerton mice (n=30) showed no skin tumours when exposed to a 10 % solution (in acetone) of the chemical (approximately 100 mg), three times per week for 493 days. The dose applied on the clipped dorsal skin may have been reduced due to the volatility of the chemical (IPCS).

In a number of two-year inhalation toxicity studies in Fischer 344 (F344) rats, dose-related increases in the prevalence of mononuclear cell leukaemia (a tumour common in aged F344 rats), peritoneal mesothelioma, mixed cell gliomas and gliosis, increased primary brain tumours and pituitary adenoma were observed from 10–100 ppm (18–180 mg/m^3) (IARC, 2012; REACHa).

In a two-year inhalation study in B6C3F1 mice (n=50/sex/group), neoplasms were observed at both treatment groups of 90 and 180 mg/m³. These included alveolar and bronchiolar carcinomas, papillary cystadenoma of the Harderian gland, malignant lymphomas (only in females at 180 mg/m³, 22/49 compared with 9/49 for controls), uterine adenocarcinoma (0/49, 2/47 and 5/49 at 0, 90 and 180 mg/m³, respectively) and mammary gland adenocarcinoma (1/49, 8/48 and 6/49 at 0, 90 and 180 mg/m³, respectively) (IARC, 2008; REACHa).

In a number of epidemiological studies in humans, 'a significant positive trend in risk with the increasing cumulative exposure to ethylene oxide was observed for all neoplasms of the lymphatic and haematopoetic tissues' (IARC, 2012). Dose-related increases in the frequency of sister chromatid exchange, chromosomal aberrations and micronucleus formation in the lymphocytes in workers indicated a genotoxic mechanism to induce carcinogenicity (IARC, 2012).

An epidemiological cohort study in New York, USA, reported a borderline significantly increased risk of about 60% for the incidence of breast cancer in 1132 workers employed (1974–80) at a sterilising plant that used the chemical. Leaks of the chemical had been documented on several occasions, and the 8-hour TWA exposures of steriliser operators were estimated to be 90–360 mg/m³ (IARC, 2008). A cohort study conducted by the National Institute for Occupational Safety and Health (NIOSH) of 7576 women who worked at 13 chemical plants for more than one year, found excess risk for breast cancer (IARC, 2008).

Reproductive and Developmental Toxicity

Based on the data available, the chemical is not expected to have specific developmental toxicity. The available studies in rats and rabbits reported similar NOAECs for both maternal and foetal/developmental toxicity, indicating that any foetal effects may have occurred due to maternal toxicity. Although the fertility effects are fairly significant, details available on maternal systemic toxicity effects are not sufficient to eliminate the likelihood that the reproductive toxicity effects were not secondary to systemic toxicity. Therefore, a hazard classification for reproductive toxicity was not recommended.

In a reproductive toxicity study (OECD TG 415), F344 rats (n=30/sex/group) were exposed to the chemical at concentrations of 0, 18, 54 or 180 mg/m³ for 12 weeks before mating, during mating, during gestation days (GD) 0 to 19 (females) and from 5 to 21 days after the birth. A NOAEC of 54 mg/m³ was established for both the P (parent) and F1 generations. Females in the 180 mg/m³ exposure group had longer gestation periods compared with the control group (7/14 pregnancies were longer than 22 days gestation), fewer pups per litter (four versus 9–10 in the control group) and fewer implantation sites (six versus 10–11 in the control group). The ratio of the number of live foetuses to the number of implantation sites for each female rat was also reduced in this group (57 % versus 92–100 % in the control group) and the fertility indices were also affected in both male and female rats (REACHa).

In a two-generation reproductive toxicity study in CD rats (n=28/sex/group), a no observed effect concentration (NOEC) of 10 ppm was established for both parental and reproductive toxicity. At 33 and 100 ppm (0.054 and 0.18 mg/L), decreased body weight gain in P and F1 male rats (exposed to the chemical for 10 weeks before mating), increased postimplantation loss in F0 dams and reduced weight gain in F1 and F2 pups were observed (US EPA 2008; CDPR).

In a prenatal developmental toxicity study (OECD TG 414), female F344 rats (n=22/dose) were exposed to the chemical at concentrations of 0, 18, 54 or 180 mg/m³ for six hours/day during GD 6–15. A NOAEC of 180 mg/m³ was established for both maternal toxicity and teratogenicity. Depressed foetal body weights and several skeletal abnormalities and visceral alterations (including either split or poorly ossified sternebrae, bilobed distal thoracic vertebral centra and renal pelvic dilatation—bilateral or unilateral—with renal papilla) were observed at 180 mg/m³. However, these abnormalities were reported as not statistically significant compared with the controls (REACHa).

In a prenatal developmental toxicity study, New Zealand White rabbits (n=30 females/dose) were exposed to the chemical at 0 or 270 mg/m³ for seven hours/day during GD 1–19 or GD 7–19. A NOAEC of 270 mg/m³ was established for both maternal toxicity and teratogenicity (REACHa).

Other Health Effects

Neurotoxicity

Neurological effects have been reported in animals and humans repeatedly exposed to the chemical.

Animals exposed to the chemical at 200–375 ppm for 6–7 months showed hind leg paralysis and atrophy, abnormal knee and extensor reflexes, and diminished pain perception. In mice, an exposure level of 50 ppm for l0–11 weeks resulted in hunched posture, reduced locomotion, and abnormal righting reflexes. In rats, a 9-month exposure to 250 ppm resulted in distal axonal degeneration of myelinated fibres in both sural nerves and gracile fascicles. Chronic exposure to 500 ppm resulted in brain lesions in rats. Chronic exposure at 100 ppm resulted in slight demyelination in monkeys' brains (ATSDR, 1990).

Neurological effects are frequently reported following occupational exposure to the chemical. In several case studies of workers exposed to the chemical for various durations, peripheral neuropathy, impaired hand-eye coordination and memory loss have been reported at estimated average exposure levels as low as 3 ppm (with possible short-term peaks as high as 700 ppm). During sural nerve biopsies, two of these studies indicated axonal degeneration and regeneration (ATSDR, 1990).

Four steriliser operators, who were exposed to the chemical for up to two months on an intermittent basis at levels of approximately 700 ppm (based on the odour threshold for vapours emitted from a leaking apparatus), reported headaches, nausea, vomiting, clumsiness, blunting of the senses, lethargy, numbness and weakness in their extremities. In one operator, recurrent major motor seizures at 20–30 minute intervals near the end of the work shift were reported. Nerve conduction studies indicated sensorimotor neuropathy (ATSDR, 1990).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (carcinogenicity, mutagenicity and neurotoxicity), systemic acute effects (acute toxicity from oral and inhalation exposure) and local effects (skin sensitisation and corrosivity). The chemical can also cause toxic effects, following repeated inhalation exposure.

Reproductive toxicity of the chemical could also be a concern, although the chemical is not classified for fertility effects. However, the protective measures required, based on other severe hazards, are expected to protect workers from any reproductive toxicity effects.

Public Risk Characterisation

The chemical is listed on Schedule 7 of the SUSMP and will be available to specialised or authorised users only. Considering the uses identified, no public exposure is expected.

Occupational Risk Characterisation

Given the critical health effects (carcinogenicity; mutagenicity; skin sensitisation; acute oral and inhalation toxicity; repeated dose inhalation toxicity and corrosivity), the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and inhalation exposure to the chemical 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 appropriate controls.

The data available support an amendment to the hazard classification in HSIS (refer to **Recommendation section**).

NICNAS Recommendation

Assessment of the chemical 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. No further assessment is required.

Regulatory Control

Work Health and Safety

The chemical is recommended for classification and labelling under the current approved criteria and adopted GHS as below. This assessment does not consider classification of physical hazards and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful if swallowed (Xn; R22) Toxic by inhalation (T; R23)*	Harmful if swallowed - Cat. 4 (H302) Toxic if inhaled - Cat. 3 (H331)
Irritation / Corrosivity	Causes burns (C; R34)	Causes severe skin burns and eye damage - Cat. 1B (H314)
Sensitisation	May cause sensitisation by skin contact (Xi; R43)	May cause an allergic skin reaction - Cat. 1 (H317)
Repeat Dose Toxicity	Toxic: danger of serious damage to health by prolonged exposure through inhalation (T; R48/23)	Causes damage to organs through prolonged or repeated exposure through inhalation - Cat. 1 (H372)
Genotoxicity	Muta. Cat 2 - May cause heritable genetic damage (T; R46)*	May cause genetic defects - Cat. 1B (H340)
Carcinogenicity	Carc. Cat 2 - May cause cancer (T; R45)*	May cause cancer - Cat. 1B (H350)

[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 industry

Control measures

Control measures to minimise the risk from oral, dermal, ocular and inhalation exposure to the chemical 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 chemical is used. Examples of control measures which can minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- health monitoring for any worker who is at risk of exposure to the chemical if valid techniques are available to monitor the effect on the worker's health;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- 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 chemical.

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 assist with meeting 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 chemical 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 the chemical has not been undertaken as part of this assessment.

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