Epoxidised cycloaliphatic olefins: Human health tier II assessment

01 July 2016

- Chemicals in this assessment
- Preface
- Grouping Rationale
- Import, Manufacture and Use
- Restrictions
- Existing Worker Health and Safety Controls
- Health Hazard Information
- Risk Characterisation
- NICNAS Recommendation
- References

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
7-Oxabicyclo[4.1.0]heptane, 3-oxiranyl-	106-87-6
7-Oxabicyclo[4.1.0]heptane-3-carboxylic acid, 7-oxabicyclo[4.1.0]hept-3-ylmethyl ester	2386-87-0

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 epoxidised cycloaliphatic compounds with an extra epoxy group either as an oxirane pendant (vinyl cyclohexene diepoxide (VCHD); CAS No. 106-87-6) or an epoxidised cycloaliphatic ester (3,4-epoxycyclohexylmethyl 3,4-epoxycyclohexanecarboxylate (ECHM-ECHC); CAS No. 2386-87-0). Given their diepoxy functionality, consequent reactivity and their comparatively low molecular weights, these chemicals have similar use as reactive diluents and thus 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 International Agency for Research in Cancer (IARC);
- the European Union (EU) Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) dossiers; and
- National Toxicology Program (NTP) Technical Report Series No. 362.

The chemicals in this group have reported commercial use as reactive diluents for other diepoxides and for epoxy resins derived from bisphenol A and epichlorohydrin.

The chemicals in this group have reported site-limited uses including in:

- producing epoxy resins for coatings, adhesives and inks; and
- formulating encapsulants for various electrical applications.

Restrictions

Australian

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

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

No international restrictions have been identified.

Existing Worker Health and Safety Controls

Hazard Classification

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

- T; R23/24/25 (Toxic by inhalation, in contact with skin and if swallowed)
- Carc. Cat. 3; R40 (Limited evidence of a carcinogenic effect)

Exposure Standards

Australian

The chemical VCHD has an exposure standard of 57 mg/m^3 (10 ppm) time weighted average (TWA) (Safe Work Australia).

International

The chemical VCHD has an exposure limit of 57–60 mg/m^3 (0.1–10 ppm) TWA in different countries such as the United States of America (USA) (Hawaii, Minnesota), Canada (Quebec), Spain and Taiwan (Galleria Chemica).

Health Hazard Information

Toxicokinetics

Studies in rodents show that VCHD can be absorbed orally and by inhalation as well as by rapid dermal absorption (NTP, 1989). The metabolism of VCHD occurs through epoxide group hydrolysis to the respective glycols (which is catalysed by epoxy hydrolase), forming a tetrol, or conjugation with glutathione. Elimination occurs mainly via the urine with the tetrol form and polar conjugates being the major metabolites in rats and mice, respectively (NTP, 1989; IARC, 1994).

Acute Toxicity

Oral

The chemical VCHD is classified as hazardous with the risk phrase 'Toxic if swallowed' (T; R25) in the HSIS (Safe Work Australia). Although the limited information available for the chemicals in the group does not support this classification, in the absence of more comprehensive information, there is insufficient evidence to amend the current classification of VCHD. The available data for ECHM-ECHC do not support a classification for this particular endpoint.

In a study conducted on Fischer 344 (F344) rats (five animals/sex/dose), single doses of VCHD (in corn oil) were administered by gavage at doses of 187.5, 375, 750, 1500 or 3000 mg/kg bw. All of the animals in the 3000 mg/kg bw group and one female in the 1500 mg/kg bw group died before the end of the study. Observed clinical signs in the 1500 and 3000 mg/kg bw groups included rapid respiration, staggering gait, increased eye blinking and half-closed eyelids; in the 750 mg/kg bw group burrowing activity and half-closed eyelids. Lesions were not observed at necropsy. The acute median lethal dose (LD50) value was calculated to be 1847 mg/kg bw (NTP, 1989).

In a study conducted on B6C3F1 mice (five animals/sex/dose), single doses of VCHD (in corn oil) were administered by gavage at doses of 375, 750, 1500, 3000 or 6000 mg/kg bw. Mortalities occurred before the end of the study as follows:

- all the animals in the 6000 mg/kg bw group;
- 4/5 males and 3/5 females in the 3000 mg/kg bw group;
- 2/5 males in the 1500 mg/kg bw group; and
- 1/5 female in the 750 mg/kg bw group.

Clinical signs observed in the 1500 mg/kg bw group and higher included staggering gait, rough hair, and rapid respiration. The LD50 values were calculated to be 1862 mg/kg bw for males and 2358 mg/kg bw for females (NTP, 1989).

In a study conducted in Crl:CD rat (10 animals/sex/dose), a single dose of ECHM-ECHC was administered by gavage at 2959 or 5000 mg/kg. Mortalities occurred only in the 5000 mg/kg bw group (three males and two females). The observed gastric abnormalities in these five animals were localised in the stomach and included dark red contents and/or distension. Clinical signs in the surviving animals included discoloration due to discharges and/or excretions, hypoactivity, and impaired muscle coordination. Effects in the animals in the high dose group included: decreased defacation, decreased urination, laboured respiration and/or convulsions. In this study, the LD50 value was determined to be approximately 5000 mg/kg bw (REACH).

Dermal

The chemical VCHD is classified as hazardous with the risk phrase 'Toxic in contact with skin' (T; R24) in the HSIS (Safe Work Australia). Although the limited information available for the chemicals in the group does not support this classification, in the absence of more comprehensive information, there is insufficient evidence to amend the current classification of VCHD. The available data for ECHM-ECHC do not support a classification for this particular endpoint.

In a study conducted on F344 rats (five animals/sex/dose), a single dermal application of VCHD (in acetone) was administered at doses of 198, 388, 773, 1568, and (neat only) 3074 mg/kg. No mortalities occurred in any dose groups. A treatment-related

decrease in physical activity was observed in the 773 mg/kg and higher dose groups. No lesions were reported at necropsy (NTP, 1989).

In a study conducted on B6C3F1 mice (five animals/sex/dose), a single dermal application of VCHD (in acetone) was administered at doses of 338.3, 671.6, 1378, 2741 or (neat only) 5487 mg/kg. One female died in each of the 671.6 mg/kg and the 2741 mg/kg dose groups. Clinical signs observed included decreased activity, rapid respiration, and skin irritation on the application site. No lesions were reported at necropsy (NTP, 1989).

In a limited-dose study conducted in Wistar rats (five animals/sex/dose), a single dermal application of ECHM-ECHC 2000 mg/kg dose was administered. No deaths occurred and no abnormal dermal changes were observed. No macroscopic changes were observed at necropsy. The LD50 value was reported to be >2000 mg/kg (REACH).

Inhalation

The chemical VCHD is classified as hazardous with the risk phrase ‘Toxic by inhalation’ (T; R23) in the HSIS (Safe Work Australia). Although the limited information available for the chemicals in the group does not support this classification, in the absence of more comprehensive information, there is insufficient evidence to amend the current classification of VCHD. The available data for ECHM-ECHC do not support a classification for this particular endpoint.

The acute median lethal concentration (LC50) value of 800 ppm (vapour concentration equivalent to 4.58 mg/L) for four hours was reported for VCHD (NTP, 1989).

In a limited range-finding study, six female rats (strain not specified) were exposed to aerosols of the chemical product EP-221 (concentration of ECHM-ECHC not reported) for eight hours. Only one animal died and necropsy revealed 70 % to 80% lung haemorrhage in this animal. Increased body weight was observed in the survivors. No other gross changes were observed (IUCLID, 2005).

Corrosion / Irritation

Respiratory Irritation

No data are available for the chemicals in the group.

Skin Irritation

Based on the available information, the chemicals are slightly irritating to skin.

No data are available for VCHD. The chemical is reported to irritate skin in chronic animal studies (refer to **Repeat dose toxicity: Dermal** and **Carcinogenicity** sections). Observations of treatment-related skin lesions included redness, scabs and ulcers at the application site; diffuse hyperplasia of the sebaceous gland and/or acanthosis; and hyperkeratosis of the stratified squamous epithelium (NTP, 1989).

In a study conducted in New Zealand White rabbits (three animals/sex), 0.5 mL of ECHM-ECHC was applied to shaved skin occlusively for four hours. Minor erythema (all the animals) and minor transient oedema (3/6 animals) was observed during the study. All the changes resolved within 14 days. The modified primary irritation score was reported to be 1.35 (average of one and 24 hours). The mean score for erythema and oedema was 0.83 and 0.17, respectively (mean score for 24, 48 and 72 hours) (IUCLID, 2005; REACH).

Eye Irritation

Based on the limited information available, the chemicals have the potential to irritate the eyes, although the data are insufficient to determine a hazard classification.

The chemical VCHD was found to be irritating to the eyes based on corneal injury studies in rabbits (NTP, 1989).

No information is available for ECHM-ECHC.

Sensitisation

Respiratory Sensitisation

No data are available for the chemicals in the group.

Skin Sensitisation

No data are available for the chemicals in the group.

Observation in humans

In a case study, a female electron microscopist reported allergic contact dermatitis three months after using VCHD. It was found that VCHD could permeate disposable and polyvinyl chloride gloves (IARC, 1994).

Repeated Dose Toxicity

Oral

In a 13-week study in F344/N rats and B6C3F1 mice (10 animals/sex/dose), VCHD (in corn oil) was administered by gavage at doses of 0, 62.5, 125, 250, 500 or 1000 mg/kg bw/day for five days per week (NTP, 1989).

In the rat study, a total of 30 animals died before the end of the study. Nine from the 1000 mg/kg bw group died from the test substance administration (3/10 males; 6/10 females); the remaining deaths were from all groups, including controls, and were not related to the chemical. Clinical signs observed in the 500 and 1000 mg/kg groups included burrowing behaviour and closed eyes. Excessive salivation was observed in the 250, 500, and 1000 mg/kg bw groups. In the 500 and 1000 mg/kg bw group, the relative weights of the kidneys, liver, heart, brain, lung and testis were increased. All rats in the 125, 250, 500 and 1000 mg/kg bw groups exhibited diffuse hyperplasia and hyperkeratosis in the stratified squamous epithelium of the forestomach. Regeneration of the tubular epithelium of the testes was observed in the 250, 500 and 1000 mg/kg group (NTP, 1989).

In the mouse study, a total of 13 animals died, mostly due to gavage errors. Decreased body weights were observed in the 500 and 1000 mg/kg bw groups compared with controls. Lung and liver weights were significantly greater in the 1000 mg/kg bw group compared with controls. Treatment-related effects included diffuse hyperplasia and/or hyperkeratosis involving the stratified squamous epithelium of the forestomach in all dose groups; multifocal and diffuse testicular degeneration in males in the 250, 500 and 1000 mg/kg bw groups; uterine atrophy in females in the 1000 mg/kg bw group; and diffuse ovarian atrophy in females from the 250, 500, and 1000 mg/kg bw groups. The report also noted that a total of nine females from different dose groups gave birth during week four of the study (not part of the study design; the mice escaped from the cages as the study started) (NTP, 1989). Therefore, in this study, only a limited interpretation on the effects of VCHD in mice from repeated oral exposure can be made.

The no observed adverse effect level (NOAEL) value was not determined in either study.

In a 90-day study conducted in Crl:CD rats (20–25 animals/sex/dose), ECHM-ECHC (in corn oil) was administered daily by gavage at doses of 5, 50, and 500 mg/kg bw/d. No mortalities occurred in any dose group. Increased salivation and yellow material on various body surfaces (urogenital area, anogenital area, hindlimbs and ventral neck/trunk) were observed in the 500 mg/kg bw group. Mean body weight and body weight gain was reduced in males from the 500 mg/kg bw group compared with controls. Rats in the 50 and 500 mg/kg bw groups exhibited higher mean liver and kidney weights compared with controls, as

well as degeneration of the olfactory epithelium in the nasal tissues. Pale livers were observed in 3/15 males from the 500 mg/kg bw group. Based on this study, the no observed effect level (NOEL) value was determined to be 5 mg/kg bw/d (IUCLID, 2005; REACH).

Dermal

Extensive dermal studies have been conducted to assess the carcinogenicity potential of VCHD (see **Carcinogenicity** section) (NTP, 1989).

In 13-week dermal studies conducted in F344/N rats and B6C3F1 mice (10 animals/sex/dose), VCHD in acetone was applied to the clipped dorsal interscapular region at doses of 0, 3.75, 7.5, 15, 30 or 60 mg/kg (for rats) or 0, 0.625, 1.25, 2.5, 5 or 10 mg/kg (for mice).

In the rat study, no mortalities occurred in any of the dosed groups. In the 60 mg/kg group, observed clinical signs and effects included: redness, scabbing and ulceration on the back at the application site; burrowing behaviour; skin ulcers in males; and acute to chronic inflammation of the epidermis at the application site. Thymus weights in males in the 30 and 60 mg/kg groups were significantly lower compared with controls. Yellowing scabs and thickened skin at the nape of the neck was observed in the 60 mg/kg group. Diffuse hyperplasia of the sebaceous gland and/or acanthosis and hyperkeratosis of the stratified squamous epithelium were observed in the 15, 30 and 60 mg/kg groups.

In the mouse study, no mortalities occurred in any of the dosed groups. Acanthosis and hyperkeratosis of the stratified squamous epithelium was observed in the 5 and 10 mg/kg group. Diffuse ovarian atrophy and uterine atrophy was observed in females in the 10 mg/kg group (NTP, 1989).

In a two-year study conducted in F344/N rats and B6C3F1 mice (60 animals/sex/dose), VCHD in acetone was applied to the clipped dorsal interscapular region at doses of 0, 15, or 30 mg/kg (for rats) or 0, 2.5, 5 or 10 mg/kg (for mice) for five days per week (NTP, 1989).

In the rat study, the female survival rate in all dose groups was lower compared with controls, while no significant differences were observed in males. However, the survival of all the animals at the end of the study, including controls, was very low. In the high dose group, the mean body weights were lower compared with controls. Hair at the application site was discoloured. A single small papilloma of the transitional cell epithelium was present in a female from the low dose group. Hyperplasia of the transitional epithelium was observed in females in all dose groups. No proliferative lesions were observed in the urinary bladder of the vehicle control or exposed male rats (NTP, 1989).

In the mouse study, all the animals in the 10 mg/kg group died before the end of the study (all males by week 83; all females by week 85). The mean body weights of the 5 and 10 mg/kg groups were reduced compared with controls. At the site of application, crusts, scales and ulcers were observed. Ovarian follicular atrophy and tubular hyperplasia were observed in all dosed females. Subacute inflammation of the epididymis was observed in males from the 5 and 10 mg/kg groups (NTP, 1989).

Inhalation

No data are available for the chemicals in the group.

Observation in humans

No data are available for the chemicals in the group.

Genotoxicity

The chemicals in the group were reported to induce genotoxic effects based on various tests.

In vitro

Positive results were reported for VCHD in the following tests:

- an Ames assay conducted in *Salmonella typhimurium* strains TA98, TA100 and TA1535, with and without metabolic activation (NTP, 1989; IARC, 1994);
- a gene conversion assay in *Saccharomyces cerevisiae* D4 and D7 without metabolic activation (IARC, 1994);
- in both the hprt and tk loci in cultured mammalian cells (IARC, 1994);
- in mouse L5178Y/TK cells without exogenous metabolic activation (NTP, 1989) where resistance to trifluorothymidine was induced;
- in sister chromatid exchange and chromosomal aberrations in Chinese hamster ovary (CHO) cells in the presence and absence of exogenous metabolic activation (NTP, 1989).

Positive results were reported for ECHM-ECHC in the following tests:

- an Ames assay conducted in *S. typhimurium* strains TA100 and TA1535 and in *Escherichia coli* WP2, with metabolic activation (REACH);
- a gene mutation assay in mouse L5178Y cells with and without metabolic activation (REACH); and
- in sister chromatid exchange in CHO cells without metabolic activation (REACH).

In vivo

No in vivo genotoxicity data are available for VCHD.

ECHM-ECHC tested negative in an unscheduled DNA synthesis (UDS) test in Sprague Dawley (SD) rats at doses up to 2000 mg/kg bw, and did not induce micronuclei in bone marrow erythrocytes of mice at doses of up to 2.25 g/kg (REACH).

Carcinogenicity

The chemical VCHD 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 chemical VCHD was also classified as 'possibly carcinogenic to humans (Group 2B)' by IARC (IARC, 1994). The information below supports the current classification for VCHD. The available information for ECHM-ECHC, as well as read across from VCHD, indicates that this chemical should also be considered a possible carcinogen.

A two-year study was conducted in F344/N rats and B6C3F1 mice (60 animals/sex/dose) using dermal application of VCHD in acetone (see **Repeat dose toxicity: dermal** section for study details).

In the rat study, increased incidences of skin neoplasms including basal cell adenomas and carcinomas, squamous cell papillomas and carcinomas, and sebaceous gland hypertrophy were observed at the application site in all dose groups. The carcinomas in some animals metastasised to the lung and/or other organs.

In the mice study, incidences of squamous cell carcinomas in all dose groups were significantly higher than controls. Malignant carcinomas, which consisted of highly anaplastic cells, metastisised to lymph nodes or visceral organs in many animals from all dose groups. Females dosed with 5 mg/kg bw/d of VCHD had an increased incidence of alveolar/bronchiolar adenomas and/or carcinomas than controls (NTP, 1989).

In a limited study conducted in male mice, dermal application of undiluted ECHM-ECHC caused tumours at the application site (IUCLID, 2005).

Reproductive and Developmental Toxicity

Reproductive toxicity

The chemical VCHD was demonstrated to be toxic to ovarian follicles, based on results from several studies.

Ovarian follicles, or primordial follicles, are formed during foetal development. Destruction of the primordial follicles or primary follicles results in ovarian failure (early menopause) (Hoyer et al., 2001). Based on a study conducted in female F344 rats, repeated oral exposure to VCHD (in sesame oil) caused significant reduction in follicle counts compared with controls, without oxidative stress or alterations in glutathione levels (Devine et al., 2001). Experiments in Nrf2 mice also exhibited this ovotoxic effect upon intraperitoneal (i.p.) administration of VCHD, where apoptosis was noted to be the possible mechanism for follicular loss (Hu et al., 2006). In a separate study in female SD rats, it was concluded that follicular reduction, a decrease in the number of implanted embryos, and a reduced rate of implantation occurred at repeated i.p. doses of up to 80 mg/kg (Ito et al., 2009; Kodama et al., 2009). In vitro studies in rat ovaries showed that VCHD specifically destroys primordial and primary follicles through direct inhibition of KIT receptor autophosphorylation in the oocytes (Mark-Kappeler et al., 2011).

In a 90-day gavage study conducted in SD rats (25 animals/sex/dose), ECHM-ECHC did not cause any mortalities nor any treatment-related reproductive effects in both sexes at doses of up to 500 mg/kg bw/d (IUCLID, 2005). Effects on ovarian follicles were not reported in this study.

Developmental toxicity

No data are available for VCHD.

In a study conducted in female SD rats (25 animals/dose), ECHM-ECHC was administered daily by gavage at doses of 0, 5, 25, 125 and 500 mg/kg during gestation days (GD) 6–19. No mortalities occurred in any of the dose groups. No effects were observed in the 5 or 25 mg/kg groups. Effects that were observed in the 125 and 500 mg/kg group included decreased body weight and increased mean kidney weight. Additional effects that were observed in the 500 mg/kg group included reduced mean foetal weight, increased skeletal developmental variations and increased litter proportions of unossified sternebrae. The NOAELs for maternal and developmental toxicity were 25 and 125 mg/kg bw/d, respectively (IUCLID, 2005). These results indicate that developmental effects are likely to be secondary to maternal toxicity.

Based on the studies reported above under reproductive toxicity, there is clear evidence of ovotoxicity upon exposure to VCHD through various mechanisms. The effect of ECHM-ECHC on ovarian follicles is currently unknown and the available information does not specifically study this effect.

Therefore, based on ovarian follicle effects, it is recommended that VCHD should be classified as hazardous, a Category 3 substance toxic to reproduction, with the risk phrase 'Possible risk of impaired fertility' (Xn; R62) in the HSIS. As this effect involves distribution of VCHD to the ovaries and this cannot be assumed to also occur for ECHM-ECHC, in the absence of specific information, it is not proposed that this classification be extended to ECHM-ECHC.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (carcinogenicity, mutagenicity and reproductive toxicity) for the chemicals in this group and systemic acute effects (acute toxicity from oral, dermal and inhalation exposure) for VCHD.

Public Risk Characterisation

Given the uses identified for these chemicals, it is unlikely that the public will be exposed except on a small-scale incidental basis. Hence, the public risk from these chemicals is not considered to be unreasonable.

Occupational Risk Characterisation

During product formulation, dermal 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.

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

NICNAS Recommendation

Assessment of these chemicals are 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 (see **Note** below). This assessment does not consider classification of physical and environmental hazards.

Note: The classification for acute toxicity from all routes of exposure and reproductive toxicity applies only to VCHD. In the absence of more comprehensive information, classification for acute toxicity and reproductive toxicity is not recommended for ECHM-ECHC.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Toxic if swallowed (T; R25)* Toxic in contact with skin (T; R24)* Toxic by inhalation (T; R23)*	Toxic if swallowed - Cat. 3 (H301) Toxic in contact with skin - Cat. 3 (H311) Toxic if inhaled - Cat. 3 (H331)
Carcinogenicity	Carc. Cat 3 - Limited evidence of a carcinogenic effect (Xn; R40)	Suspected of causing cancer - Cat. 2 (H351)
Reproductive and Developmental Toxicity	Repro. Cat 3 - Possible risk of impaired fertility (Xn; R62)	Suspected of damaging fertility - Cat. 2 (H361f)

[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 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 which 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;
- 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 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.

References

Devine PJ, Sipes IG, Hoyer PB 2001. Effect of 4-Vinylcyclohexene Diepoxide Dosing in Rats on GSH Levels in Liver and Ovaries. Toxicol. Sci. 62(2) pp. 315-320.

Galleria Chemica. Accessed April 2015 at **http://jr.chemwatch.net/galeria/**

Hoyer PB, Devine PJ, Hu X, Thompson KE, Sipes IG 2001. Ovarian toxicity of 4-vinylcyclohexene diepoxide: a mechanistic model. Toxicol Pathol. 29(1) pp.91-9.

Hu X, Roberts JR, Apopa PL, Kan YW, Ma Q 2006. Accelerated ovarian failure induced by 4-vinyl cyclohexene diepoxide in Nrf2 null mice. Mol Cell Biol. 26(3) pp. 940-54.

International Agency for Research on Cancer (IARC) 1994. IARC monographs on the evaluation of carcinogenic risks to humans, Volume 60. Some Industrial Chemicals. Accessed April 2015 at **http://monographs.iarc.fr/ENG/Monographs/vol60/mono60-14.pdf**

International Uniform Chemical Information Database (IUCLID) Dataset 2005. 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate (CAS No. 2386-87-0). Accessed April 2015 at **http://www.epa.gov/chemrtk/pubs/summaries/cycloerl/c14963rr.pdf**

Ito A, Mafune N, Kimura T 2009. Collaborative work on evaluation of ovarian toxicity. 4) Two- or four-week repeated dose study of 4-vinylcyclohexene diepoxide in female rats. J Toxicol Sci. 34 Suppl 1 SP53-8.

Kodama T, Yoshida J, Miwa T, Hasegawa D, Masuyama T. Collaborative work on evaluation of ovarian toxicity. 4) Effects of fertility study of 4-vinylcyclohexene diepoxide in female rats. J Toxicol Sci.34 Suppl 1:SP59-63.

Mark-Kappeler CJ, Sen N, Lukefahr A, McKee L, Sipes IG, Konhilas J, Hoyer PB 2011. Inhibition of ovarian KIT phosphorylation by the ovotoxicant 4-vinylcyclohexene diepoxide in rats. Biol Reprod. 85(4) pp. 755-62.

National Toxicology Program (NTP) 1989. Toxicology and Carcinogenesis Studies of 4-Vinyl-1-Cyclohexene Diepoxide (CAS No. 106-87-6) in F344/N Rats and B6C3F1 Mice. Technical Report Series No. 362. Accessed on April 2015 at **https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr362.pdf**

Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Dossier. 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate (CAS No. 2386-87-0). Accessed April 2015 at **http://apps.echa.europa.eu/registered/data/dossiers/DISS-a212d721-c5dc-4b33-e044-00144f67d031/AGGR-a18da1d1-8913-4394-a25f-80a2e8757587_DISS-a212d721-c5dc-4b33-e044-00144f67d031.html#AGGR-a18da1d1-8913-4394-a25f-80a2e8757587**

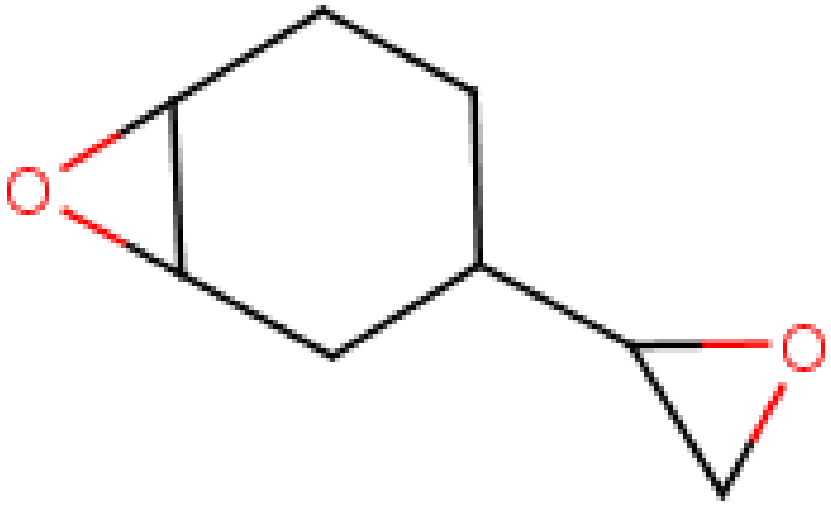
Safe Work Australia (SWA). Hazardous Substances Information System (HSIS). Accessed April 2015 at **http://hsis.safeworkaustralia.gov.au/HazardousSubstance**.

The Poisons Standard (the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)) 2015.Accessed April 2015 at **http://www.comlaw.gov.au/Details/F2015L00128**

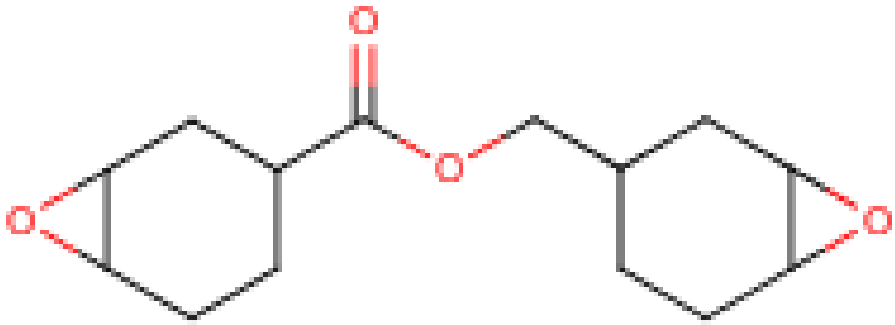
Last Update 01 July 2016

Chemical Identities

Chemical Name in the Inventory and Synonyms	**7-Oxabicyclo[4.1.0]heptane, 3-oxiranyl-** 4-vinylcyclohexene diepoxide vinyl cyclohexene dioxide VCHD
CAS Number	106-87-6
Structural Formula	

	
Molecular Formula	C8H12O2
Molecular Weight	140.18

Chemical Name in the Inventory and Synonyms	**7-Oxabicyclo[4.1.0]heptane-3-carboxylic acid, 7-oxabicyclo[4.1.0]hept-3-ylmethyl ester** 3,4-Epoxycyclohexylmethyl 3,4-epoxycyclohexanecarboxylate ERL-4221 ECHM-ECHC
CAS Number	2386-87-0
Structural Formula	

	
Molecular Formula	C14H20O4
Molecular Weight	252.31

Share this page