Aliphatic and allyl glycidyl ethers: Human health tier II assessment

03 July 2015

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Oxirane, [(2-propenyloxy)methyl]-	106-92-3
Oxirane, (butoxymethyl)-	2426-08-6
Oxirane, [(1,1-dimethylethoxy)methyl]-	7665-72-7

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 oxirane ethers of small aliphatic or allylic hydrocarbon molecules. These epoxy resins contain a glycidyl ether moiety which confers their similar reactivity and uses. The glycidyl ether moiety is also known to be responsible for the sensitising potential for these group of chemicals. It is expected that these chemicals 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, Authorisation 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 US National Library of Medicine's Hazardous Substances Data Bank (HSDB); and

- Handbook of Fillers, Extenders and Diluents.

The chemicals have reported commercial uses including as:

- reactive diluents and/or viscosity reducers for epoxy resins, laminate, flooring and encapsulants;
- modifiers for elastomers, adhesives and fibres;
- additives in epoxy chemicals used for food contact articles.

The chemicals have reported site-limited uses including as:

- reactive intermediates in electrical product coatings; and
- stabilisers for chlorinated compounds.

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

Allyl glycidyl ether (AGE; CAS No 106-92-3) and butyl glycidyl ether (n-BGE; CAS No. 2426-08-6) are listed on the following (Galleria Chemica):

- EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products; and
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain.

Existing Worker Health and Safety Controls

Hazard Classification

The chemicals in this group are classified as hazardous, with the following risk phrases for human health in the Hazardous Substances Information System (HSIS):

Allyl glycidyl ether (AGE; CAS No 106-92-3):

- Carc. Cat. 3; R40 (Limited evidence of a carcinogenic effect);
- Muta. Cat. 3; R68 (Possible risk or irreversible effects);
- Repr. Cat. 3; R62 (Possible risk of impaired fertility);
- Xn; R20/22 (Harmful by inhalation and if swallowed);
- Xi; R37/38-41 (Irritating to respiratory system and skin and risk of serious eye damage); and

- R43 (May cause sensitisation by skin contact)

Butyl glycidyl ether (n-BGE; CAS No. 2426-08-6):

- Carc. Cat. 3; R40 (Limited evidence of a carcinogenic effect);
- Muta. Cat. 3; R68 (Possible risk or irreversible effects);
- Xn; R20/22 (Harmful by inhalation and if swallowed);
- Xi; R37 (Irritating to respiratory system); and
- R43 (May cause sensitisation by skin contact)

The chemical tert-butyl glycidyl ether (t-BGE; CAS No. 7665-72-7) is not listed in HSIS.

Exposure Standards

Australian

The chemicals in this group have exposure standards as follows (Safe Work Australia):

The chemical AGE (CAS No. 106-92-3) has an exposure standard of 23 mg/m^3 (5 ppm) time weighted average (TWA) and 47 mg/m^3 (10 ppm) short-term exposure limit (STEL).

The chemical n-BGE (CAS No. 2426-08-6) has an exposure standard of 133 mg/m^3 (25 ppm) time weighted average (TWA).

These chemicals are known to be sensitisers and are designated with a 'Sen' notation. Caution should be exercised in the industrial use of these substances.

International

The following exposure standards are identified for AGE (CAS No. 106-92-3) (Galleria Chemica):

An exposure limit of 4.7–45 mg/m^3 (1–10 ppm) time weighted average (TWA) and 22–44 mg/m^3 (5–10 ppm) short-term exposure limit (STEL) in various countries such as the United States of America (USA) (California, Hawaii, Minnesota and Vermont), Canada (Alberta, Saskatchewan, Yukon and Quebec), Iceland, Poland, Russia, Singapore, Norway and Switzerland.

The following exposure standards are identified for n-BGE (CAS No. 2426-08-6)(Galleria Chemica):

An exposure limit of 16–270 mg/m^3 (3–50 ppm) time weighted average (TWA) and 80–400 mg/m^3 (15–75 ppm) short-term exposure limit (STEL) in different countries such as the USA (California, Hawaii, Minnesota and Vermont), Canada (Alberta, Yukon and Quebec), Philippines, Singapore, Spain, Norway and Switzerland.

Health Hazard Information

Toxicokinetics

Allyl glycidyl ether (AGE; CAS No 106-92-3)

There are limited toxicokinetic studies available for AGE. Intraperitoneal (i.p.) injections in mice showed that metabolism of AGE occurs either through epoxidation of the alkene moiety and/or hydrolysis of the oxirane ring to the diol form (OECD, 2007).

Butyl glycidyl ether (n-BGE; CAS No 2426-08-6)

Studies have shown that orally administered n-BGE is rapidly absorbed and metabolised (NTP, 2004; MAK, 1992). It was also reported that n-BGE is readily absorbed through the skin (MAK, 1992). Excretion of n-BGE occurs mainly as urinary metabolites with up to 91.5% of the absorbed dose being excreted after 96 hours (NTP, 2004).

Acute Toxicity

Oral

The chemicals AGE and n-BGE are classified as hazardous with the risk phrase 'Harmful if swallowed' (Xn; R22) in the Hazardous Substances Information System (HSIS). The available information for AGE and n-BGE supports the current classification.

It was reported that the oral median lethal dose (LD50) of AGE was 390 mg/kg and 1600 mg/kg in mice and rats, respectively. Mortalities occurred between 4 hours and 5 days post administration. The main reported adverse effects included central nervous system (CNS) depression, dyspnoea, reduced tonus in the digestive tract and occasional focal necrosis in the liver (MAK, 1996). In a study conducted in male Long-Evans rats (six animals/dose), a single dose of AGE (50% in propylene glycol) was administered by gavage at doses of 1300, 1600, 1900 or 2300 mg/kg bw (REACH). Mortalities occurred in treated animals except in the low dose group. The following clinical signs were observed: slight lacrimation, mussed fur, restlessness, unsteadiness, depression, and dyspnoea. Gross pathology on the deceased animals showed: diffuse inflammation of the lungs; irritation of the gastrointestinal tract; haemorrhage in the stomach; and pale and discoloured spleen and kidneys. Pathological examination of the survivors showed hypotonicity (muscle weakness) of the enteric tract and extensive adhesions of the stomach walls to adjacent tissues. The LD50 value was determined to be 1600 mg/kg bw (REACH).

It was reported that the LD50 value of n-BGE was 2050-2500 mg/kg bw in rats and 1530 mg/kg bw in mice (NTP, 2004; MAK, 1992). Intragastric administration of n-BGE caused CNS depression, uncoordinated movement, ataxia, agitation, delirium and death (MAK, 1992). No other study details were available.

For t-BGE, LD50 values of 1530 mg/kg and >2000 mg/kg was reported for mice and rats, respectively. Rats administered with a dose of 1000 mg/kg bw via gastric intubation had slight accumulation of darkened material around the nares and slight oedema on the mucosal surface of the stomach (NTP, 2004). Given the similarity in chemical structure and reactivity of AGE and n-BGE with t-BGE, it is recommended that the current acute oral toxicity classification of AGE and n-BGE be used for t-BGE.

Dermal

The dermal LD50 value of AGE in rabbits was reported to be 2550 mg/kg (MAK, 1996). It was also reported that application of AGE to intact rabbit skin for 24 hours killed all the dosed animals within a week (at a dose of 500 mg/kg) or overnight (at a dose of 1000 mg/kg) (MAK, 2013).

It was reported that the dermal LD50 value of n-BGE in rabbits was 2520 mg/kg (MAK, 1992). No other study details were provided.

No information is available for t-BGE.

The available information for the chemicals in this group is very limited and is insufficient to support the classification for acute dermal toxicity applying to these chemicals.

Inhalation

The chemicals AGE and n-BGE are classified as hazardous with the risk phrase ‘Harmful by inhalation’ (Xn; R20) in the HSIS. The available information for AGE and n-BGE supports the current classification.

Male Sprague-Dawley (SD) rats (six animals/dose) were exposed to AGE for 7 h at vapour concentrations of 0.47, 1.18, 1.42, 1.78, 2.37, 3.32, 5.57 or 12.31 mg/L. Mortalities occurred in exposed animals except in the 0.47 and 1.18 mg/L dose groups. Examination of the deceased animals exhibited the following signs: distended stomach; hyperaemic nasal turbinates; dark and congested lungs; congested livers; hydrothorax; and paleness of the cortex of the kidneys with an accentuated corticomedullary junction. In the lowest dose group, slight nasal irritation and gasping was observed. The 4-h median lethal concentration (LC50) was calculated—from the 7-h LC50 value of 1.46 mg/L— to be 2.56 mg/L (REACH).

Inhalation studies using n-BGE gave a 4-h LC50 value in mice of >3500 ppm (equivalent to 18.62 mg/L) and an 8-h LC50 value in rats of 1030 ppm (equivalent to 5.48 mg/L) (NTP, 2004). Reported effects from vapour exposure to n-BGE included delirium, depression, dyspnoea, lacrimation, salivation, nasal discharge, and aerophagia (excessive air swallowing which goes to the stomach).

Limited information indicated that exposure to t-BGE vapours up to seven hours did not cause any signs of toxicity in female rats at concentrations of up to 3333 ppm (equivalent to 17.73 mg/L). However, exposure to t-BGE at a concentration of 16 180 ppm (equivalent to 86.09 mg/L) caused deaths of 80% of the dose group (NTP, 2004).

In the absence of more comprehensive information for t-BGE, there is insufficient evidence to support the current classification of AGE and n-BGE to be adopted for t-BGE.

Corrosion / Irritation

Respiratory Irritation

AGE and n-BGE are classified as hazardous with the risk phrase ‘Irritating to respiratory system’ (Xi; R37) in the HSIS.

Available respiratory irritation studies for AGE and n-BGE reported respiratory effects (see **Repeat dose Toxicity–Inhalation** section), which supports the current classification.

Similarly, respiratory effects were also observed in inhalation studies for t-BGE in various experimental animals (see **Repeat dose Toxicity–Inhalation** section).

There is enough evidence to suggest that t-BGE is irritating via inhalation exposure. There is also sufficient evidence to warrant the current classification of AGE and n-BGE to be adopted for t-BGE.

Skin Irritation

The chemical AGE is classified as hazardous with the risk phrase 'Irritating to skin' (Xi; R38) in the HSIS. The available information for AGE supports the current classification.

In a study conducted in three New Zealand White rabbits, undiluted AGE (0.5 mL) was applied by occlusive patch to intact skin for 24 h. Skin effects were evaluated according to the Draize method. The mean erythema scores (24–72 h) for all dosed animals were 1.0–1.5. The mean oedema scores (24–72 h) for all dosed animals were 2.5–3.0. No other study details were provided (REACH).

It was reported that n-BGE was a skin irritant based on various occlusive studies (MAK, 1992). Experimental studies on the skin of New Zealand White rabbits caused mild irritation (score of 2.8 on the Draize scale) after 24 and 48 hour occlusive treatments. Moderate irritation (score of five on the Draize scale) was observed when n-BGE (0.01 mL undiluted) was applied to covered abdominal skin of rabbits after 24 hours. In another study, application of 500 mg of t-BGE caused moderate irritation (MAK, 1992).

It was reported that t-BGE produced blanching with severe erythema, oedema, and necrosis (NTP, 2004).

There is enough evidence to suggest that the chemicals in this group are irritating to skin. There is also sufficient evidence, including in humans, to warrant the current classification of AGE to be adopted for n-BGE and t-BGE.

Eye Irritation

The chemical AGE is classified as hazardous with the risk phrase 'Risk of serious damage to eyes' (Xi; R41) in the HSIS. The available information for AGE supports the current classification.

In a study conducted in three New Zealand White rabbits, undiluted AGE (0.1 mL) was applied to one eye with an observation period of up to 48 h. After evaluating the effects according to the Draize method, it was reported that severe ocular injury occurred without blindness or adverse effects on the cornea, lens, or iris. The following scores were reported (REACH):

- mean irritation scores of 72 and 73.5 for 1–48 h and 24–48 h, respectively;
- overall irritation score for all animals: 72 (1, 24 and 48 h readings).

Several eye irritation studies have reported that undiluted n-BGE caused eye irritation at doses ranging from 0.005 mL to 0.1 mL (MAK, 1992). Application of t-BGE in rabbit eyes produced reversible effects including slight conjunctival inflammation, slight corneal injury and iritis (NTP, 2004).

Based on the available information for n-BGE and t-BGE, and taking into account the effects from AGE, there is sufficient evidence to recommend that both chemicals be classified as hazardous with risk phrase 'Irritating to eyes' (Xi; R36) in HSIS.

Observation in humans

Patch tests on humans exposed to undiluted n-BGE showed severe dose-dependent irritation effects such as erythema, oedema, vesiculation, and superficial ulceration (MAK, 1992).

Sensitisation

Skin Sensitisation

The chemicals AGE and n-BGE are classified as hazardous with the risk phrase ‘May cause sensitisation by skin contact’ (R43) in the HSIS.

There are no available animal sensitisation studies for AGE. However, human case reports indicate that AGE has a potential for causing skin sensitisation (see **Sensitisation – Observation in humans** section) (OECD, 2007).

Based on experiments conducted in guinea pigs, intracutaneous and topical application of n-BGE was demonstrated to cause sensitisation in >50% of the dosed animals (MAK, 1992).

No information available for t-BGE for this particular endpoint.

While limited information is available for these specific chemicals, glycidyl ethers are known to be irritants and sensitising agents (HSDB). Based on the similarity of the chemical structure and as this group of chemicals are glycidyl ethers, it is recommended that the current skin sensitisation classification of AGE and n-BGE be adopted for t-BGE.

Observation in humans

In a study conducted in patients exposed to epoxy resin compounds, patch testing with AGE (25% (w/w) in petrolatum) showed allergic reactions in 12.9% of the tested patients (Jolanki et al., 1990). Similar cases in the plastic and marble industry demonstrated skin sensitisation from AGE exposure (Angelini et al., 1996; Dooms-Goossens et al., 1995).

In a human patch test, five out of 25 volunteers exposed to 1.25% of n-BGE tested positive for sensitisation effects. This result was also evident in another study where 19 out of 24 volunteers tested positive for sensitisation to n-BGE (1 mL of a 10% solution) (MAK, 1992).

No information for t-BGE is available for this particular endpoint.

Repeated Dose Toxicity

Oral

No data are available for any chemicals in the group.

Dermal

No data are available for AGE and t-BGE.

A limited study conducted in five rabbits reported small, white lesions in the liver following dermal application of n-BGE five times per week, for four weeks (NTP, 2004).

Inhalation

Based on the available data, the chemicals in this group are considered not to cause serious systemic effects following repeated exposure through inhalation.

In a 13-week study, Osborne-Mendel rats and B6C3F1 mice (10 animals/sex/dose) were exposed to AGE at vapour concentrations of 0, 4, 10, 30, 100 or 200 ppm (equivalent to 0, 0.019, 0.047, 0.140, 0.467, or 0.933 mg/L) for six hours per day, five days per week. No deaths occurred in any dose groups. Dose-dependent reductions in the final mean body weights of all dose groups were observed. All dosed animals exhibited nasal lesions including inflammation, epithelial hyperplasia, and squamous metaplasia. In the 300, 100, and 200 ppm groups, minimal hyperostosis of the nasal turbinate bone (which consists of mucosal fibrosis with slight bone remodelling and sclerosis) was also observed. Except for the animals in the low dose group, exposed animals exhibited metaplasia of the larynx, trachea, and bronchi. Focal fibrosis of the anterior dorsal part of the nasal passage was also seen in the highest dose group. The lowest observed adverse effect concentration (LOAEC) value for rats was determined to be 4 ppm (or 0.019 mg/L) (NTP, 1990; REACH).

In a 13-week study, B6C3F1 mice (10 animals/sex/dose) were exposed to AGE at vapour concentrations of 0, 1, 4, 10 or 30 ppm (equivalent to 0, 0.005, 0.019, 0.047, 0.140 mg/L) for six hours per day, five days per week for 13 weeks. Since mortality occurred only in the low dose group (three males and two females), this observation was not considered to be treatment-related. Reduction in the final body weights in all dose groups was observed. Similar to the rat study, all dose groups exhibited lesions in the nasal passage including squamous metaplasia of the respiratory and olfactory epithelium as well as chronic inflammation of the mucosa. Epithelial erosion was also seen in the highest dose group. The LOAEC value for mice was determined to be 1 ppm (or 0.005 mg/L) (NTP, 1990; REACH).

In a study conducted in male rats exposed to n-BGE vapours for seven hours per day, five days per week for ten weeks, a dose of 300 ppm (equivalent to 1.60 mg/L) caused an increase in mortality (50%), emaciation, liver necrosis, rough appearance, and significant increases in kidney:body weight and lung:body weight ratios. Growth retardation was observed in the 150 ppm group (equivalent to 0.80 mg/L). In another rat study, exposure to n-BGE vapours at concentrations from 0.5 to 1.0 mg/L caused degeneration of the olfactory mucosa and metaplasia of the ciliated respiratory epithelium (NTP, 2004). No NOAEC values were determined in these studies.

In a two-week inhalation study, mice, rats and rabbits were exposed to vapours of t-BGE at doses of up to 1000 ppm (equivalent to 5.32 mg/L) for six hours per day, five days per week (NTP, 2004). In the high dose group, all rabbits and most of the female mice died. Rhinitis, lethargy and gait changes were reported in all exposed animals. The NOAEC value for this study was determined to be 100 ppm (equivalent to 0.53 mg/L) (NTP, 2004).

In a 13-week vapour inhalation study, mice, rats and rabbits were exposed to t-BGE at doses of 25, 75, or 225 ppm (equivalent to 0.13, 0.39, or 1.19 mg/L) for six hours per day, five days per week (NTP, 2004). No deaths occurred in any dose groups. Reported effects in the high dose group included: decrease in body weight gain, inflammation of the nasal mucosa, hyperplasia of the nasal respiratory system. Rabbits exposed to ≥75 ppm (equivalent to ≥0.40 mg/L) had collapsed lungs (atelectasis). The NOAEC value was determined to be 25 ppm (equivalent to 0.13 mg/L) (NTP, 2004).

Genotoxicity

The chemicals AGE and n-BGE are classified as hazardous—Category 3 mutagenic substance—with the risk phrase 'Possible risk of irreversible effects' (Xn; R68) in the HSIS (Safe Work Australia). The available data support this classification.

In vitro

The chemical AGE gave positive results for mutagenicity based on the following tests:

- Ames assay in *Salmonella typhimurium* strains TA100 and TA 1535, with and without metabolic activation (MAK, 2013; NTP, 1990; REACH);
- in *Escherichia coli WP2uvrA* and in *Klebsiella pneumoniae* without metabolic activation (MAK, 2013);
- SOS chromotest in *E. coli* PQ37 (MAK, 2013); and
- sister chromatid exchange and chromosomal aberration assay in Chinese hamster ovary (CHO) cells with and without metabolic activation (NTP, 1990).

The chemical n-BGE tested positive for mutagenicity based on the following tests:

- Ames assay in *S. typhimurium* strains TA100 and TA 1535, with and without metabolic activation (NTP, 2004);
- unscheduled DNA synthesis (UDS) assay in mouse lymphoma cells and in human erythrocytes (MAK, 1992);
- SOS chromotest in *E. coli* PQ37 (NTP, 2004);
- sister chromatid exchange assay in CHO cells (NTP, 2004);
- dominant lethal assay in rats (Government of Canada, 2010).

The chemical t-BGE tested positive for mutagenicity based on the following tests:

- Ames assay in *Salmonella typhimurium* strains TA100 and TA 1535, with and without metabolic activation (NTP, 2004);
- SOS chromotest in *E. coli* PQ37 (NTP, 2004);
- sister chromatid exchange assay in Chinese hamster lung V79 cells (NTP, 2004);
- UDS assay in human peripheral blood lymphocytes (MAK, 1992);

In vivo

The chemical AGE tested positive for genotoxicity based on the following tests:

- micronucleus assay in male mice where AGE (at doses of up to 200 mg/kg bw) was administered through i.p. injections (REACH);
- sex-linked recessive lethal mutations and loss of ring X-chromosome in *Drosophila melanogaster* (MAK, 2013; NTP, 1990).

The chemical n-BGE produced positive results in a dominant lethal test in rats with increased foetal mortality, reduced number of pregnancies and possible implantation losses. Positive results were also observed in a micronucleus test. However, results of a host-mediated assay, testing mouse urine in *S. typhimurium* were negative (MAK, 1992).

The chemical t-BGE gave negative results in a micronucleus test and a dominant lethal assay (NTP, 2004). However, urine analysis of mice fed with t-BGE gave positive results in *S. typhimurium* TA1535 and TA98, only after the addition of β-glucuronidase (MAK, 1992).

There are very limited *in vivo* studies available for t-BGE. Based on the similarity in chemical structure and reactivity of t-BGE with AGE and n-BGE, it is recommended that the current classification for genotoxicity of AGE and n-BGE be adopted for t-BGE.

Carcinogenicity

The chemicals AGE and n-BGE are 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 available data support the current classification of AGE. While there are no available carcinogenicity studies for n-BGE and t-BGE, it is expected that both chemicals behave similarly to AGE. Data from AGE, which have similar chemical structure and toxicity profile with n-BGE and t-BGE are provided as read across.

In a two-year inhalation study conducted in Osborne-Mendel rats and B6C3F1 mice (50 animals/sex/dose), AGE (at concentrations of up to 100 ppm (equivalent to 0.467 mg/L)) caused tumours in the nasal passages of both species which includes epithelial adenocarcinomas, papillary adenomas, harderian gland adenomas, and squamous cell carcinomas. No deaths occurred in either rat or mouse study. There were also no significant differences in body weight gain between the exposed groups and the control group (NTP, 1990).

There are no available carcinogenicity studies for n-BGE and t-BGE. However, in the case of n-BGE, the induction of mutagenic effects (see **Genotoxicity** section) and similarity to AGE, which is a carcinogenic substance, supports the current classification. This approach is also applicable to t-BGE.

Based on the similarity in chemical structure, reactivity and toxicity profile amongst these chemicals, it is recommended that the current classification for carcinogenicity of AGE and n-BGE be adopted for t-BGE.

Reproductive and Developmental Toxicity

Reproductive Toxicity

The chemical AGE is classified as hazardous—Category 3 substance toxic to reproduction—with the risk phrase 'Possible risk of impaired fertility' (Xn; R62) in the HSIS (Safe Work Australia). The available data support this classification. While there are no available reproductive studies for t-BGE, it is expected that t-BGE will behave similarly to AGE and n-BGE. Data from AGE and n-BGE, which have similar chemical structure and toxicity profile to t-BGE are provided as read across.

In an eight-week study, Osborne-Mendel rats (20 animals/sex/dose) were exposed to AGE at vapour concentrations of 0, 30, 100 or 200 ppm (equivalent to 0.140, 0.467, and 0.933 mg/L) for six hours per day, five days per week. Mating occurred two days after the eight-week exposure period. Mortalities occurred in the high dose groups before the end of the eight-week exposure period (two out of 20 males). It was reported that the reproductive performance of males was impaired in the highest dose group. There were a significant reduction in the number of implantation sites per dam, and live foetuses per litter in dams mated with exposed males. These reductions were not observed in exposed females mated with unexposed males. At the highest dose, females mated with exposed males did not become pregnant and implantation sites were missing. The number of live pups sired by any exposed male groups was significantly lower compared to those sired by the control males. However, exposure to AGE did not have an effect on sperm motility or sperm count recovered from the cauda epididymis in exposed males (NTP, 1990).

In a similar eight-week inhalation study conducted in B6C3F1 mice, exposure to AGE vapours did not affect the reproductive performance of males or females (NTP, 1990).

In an inhalation study conducted in rats exposed to n-BGE vapours, testicular atrophy was observed at concentrations of 400 mg/m^3 (equivalent to 0.4 mg/L) and above.

There were no reproductive toxicity studies available for t-BGE.

Based on the similarity in chemical structure, reactivity and toxicity profile amongst these chemicals, it is recommended that the current reproductive toxicity classification of AGE be adopted for n-BGE and t-BGE.

Developmental toxicity

In an eight-week inhalation study conducted in Osborne-Mendel rats and B6C3F1 mice exposed to AGE at concentrations of 0, 30, 100 or 200 ppm (equivalent to 0.140, 0.467, and 0.933 mg/L), there were no deficiencies in the foetal or postnatal development of the offspring. Although few foetal malformations in the offspring of exposed dams in the rat study were reported, these effects were not considered to be related to chemical exposure (NTP, 1990).

No developmental toxicity studies are available for n-BGE and t-BGE.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (carcinogenicity, mutagenicity, and reproductive toxicity), systemic acute effects (acute toxicity from oral and inhalation exposure) and local effects (skin sensitisation, skin and respiratory irritation, and possibly serious eye damage).

Public Risk Characterisation

Given the uses identified for the chemicals, it is unlikely that the public will be exposed. Although the public could come into contact with articles/coated surfaces containing the chemicals, it is expected that the chemicals will be reacted within the article/coated surface and hence will not be bioavailable. Therefore, the chemicals are not considered to pose an unreasonable risk to public health.

Occupational Risk Characterisation

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 oral, dermal, ocular, and inhalational 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.

NICNAS Recommendation

Assessment of these chemical 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

Public Health

Products containing these chemicals should be labelled in accordance with state and territory legislation (SUSMP, 2015).

Work Health and Safety

The chemicals in this group are recommended for classification and labelling under the current approved criteria and adopted GHS as below (see **Notes** below). This assessment does not consider classification of physical and environmental hazards.

Note 1: The classification for acute inhalation toxicity applies to AGE and n-BGE only. In the absence of more comprehensive information, classification for acute inhalation toxicity is not recommended for t-BGE.

Note 2: The available information on AGE supports the current 'Xi; R41' classification. However, n-BGE and t-BGE are recommended with the 'Xi; R36' classification.

Note 3: Classification for carcinogenicity, genotoxicity, and reproductive toxicity as well as acute oral toxicity, skin and respiratory irritation, and sensitisation by skin contact are recommended for all chemicals in this group.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful if swallowed (Xn; R22) Harmful by inhalation (Xn; R20)*	Harmful if swallowed - Cat. 4 (H302) Harmful if inhaled - Cat. 4 (H332)
Irritation / Corrosivity	Irritating to eyes (Xi; R36) Risk of serious eye damage (Xi; R41)* Irritating to skin (Xi; R38) Irritating to respiratory system (Xi; R37)	Causes serious eye irritation - Cat. 2A (H319) Causes serious eye damage - Cat. 1 (H318) Causes skin irritation - Cat. 2 (H315) May cause respiratory irritation - Specific target organ tox, single exp Cat. 3 (H335)
Sensitisation	May cause sensitisation by skin contact (Xi; R43)	May cause an allergic skin reaction - Cat. 1 (H317)
Genotoxicity	Muta. Cat 3 - Possible risk of irreversible effects (Xn; R68)	Suspected of causing genetic defects - Cat. 2 (H341)
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 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, ocular, and inhalational 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;
- 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.

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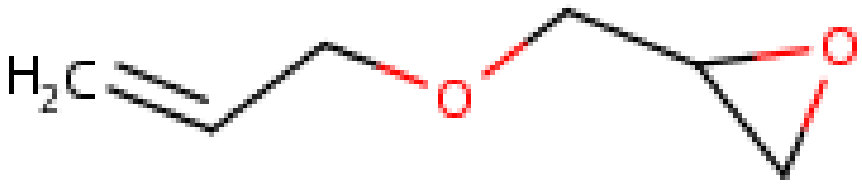
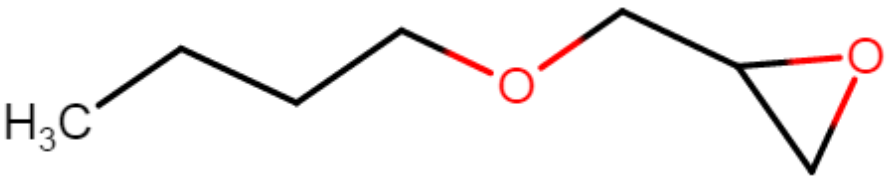
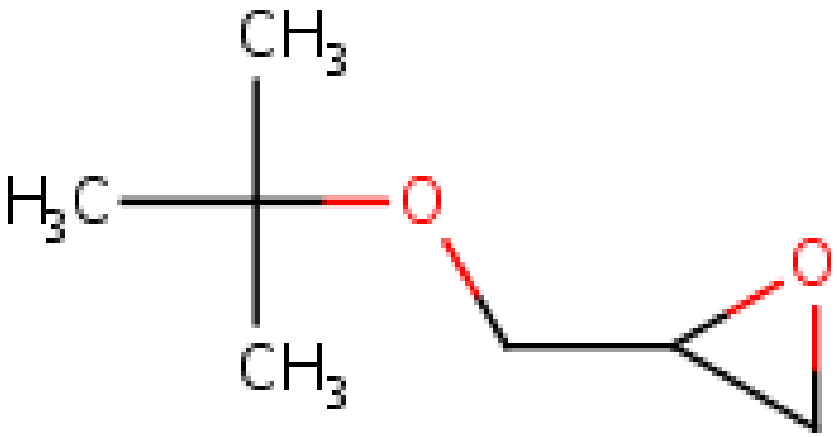
Last Update 03 July 2015

Chemical Identities

Chemical Name in the Inventory and Synonyms	**Oxirane, [(2-propenyloxy)methyl]-** allyl glycidyl ether (AGE) allyl-2,3-epoxypropyl ether 1,2-epoxy-3-allyloxypropane 1-allyloxy-2,3-epoxypropane
CAS Number	106-92-3
Structural Formula	

	
Molecular Formula	C6H10O2
Molecular Weight	114.14

Chemical Name in the Inventory and Synonyms	**Oxirane, (butoxymethyl)-** butyl glycidyl ether n-BGE
CAS Number	2426-08-6
Structural Formula	
Molecular Formula	C7H14O2
Molecular Weight	130.18

Chemical Name in the Inventory and Synonyms	**Oxirane, [(1,1-dimethylethoxy)methyl]-** tert-butyl glycidyl ether t-butyl glycidyl ether t-BGE
CAS Number	7665-72-7
Structural Formula	
Molecular Formula	C7H14O2
Molecular Weight	130.19

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