Workplace Exposure Standard (WES) review

ALLYL GLYCIDYL ETHER
(CAS NO: 106-92-3)

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New Zealand Government

WORKSAFE
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1.0
Introduction

This WorkSafe New Zealand (WorkSafe) review considers whether the **WES** for allyl glycidyl ether should be changed.

The WES review considers the potential for exposures to allyl glycidyl ether in New Zealand, the health effects and risks, exposure standards from other jurisdictions around the world, and the practicability of measuring exposures.

The review includes a recommendation to change the WorkSafe WES for to allyl glycidyl ether, which is currently set at a **WES-TWA** of 5ppm [23**mg/m³**] for **inhalable fraction** and **WES-STEL** of 10ppm [47mg/m³] with a skin notation, as published in the special guide *Workplace Exposure Standards and Biological Exposure Indices*, 11th Ed., November 2019 (WorkSafe, 2019).

Terms that are **bold** (first occurrence only) are further defined in the Glossary. Synonyms: AGE; Oxirane, [(2-propenyloxy)methyl]- ; Allyl 2,3-epoxypropyl ether; 1-Allyloxy-2,3-epoxypropane; Glycidyl allyl ether; 1,2-Epoxy-3-allyloxypropane.

2.0 Chemical and physical properties

Allyl glycidyl ether is a colourless, flammable liquid at room temperature with a characteristic aldehyde-like odour (**NIH** PubChem, 2019; **ACGIH**®, 2001).

Allyl glycidyl ether is reported to have an odour threshold at 44mg/m^3 [9ppm] in air (ACGIH®, 2001).

Chemical and physical properties allyl glycidyl ether include:

Molecular weight	114.11g/mol
Formula	$C_6H_{10}O_2$
Specific gravity	0.9698 at 20°C
Melting point	-100°C
Boiling point	154°C
Vapour pressure	2.6hPa at 20°C; 16hPa at 50°C
Relative vapour density [air = 1]	3.94
Flash point	Closed cup: 45°C; Open cup: 57.22°C
Auto-ignition	264°C
Log KOW	0.46
Solubility	Water: 50g/L
Decomposition products	Peroxides
Hazardous chemical reactions	Can react dangerously with: strong oxidising agents; bases; strong acids; amines; alkalies
Conversion factors	1mg/m^3 = 0.2ppm 1ppm = 4.74mg/m^3

NIH PubChem, 2019; **DGUV-IFA**, 2019; ACGIH®, 2001

TABLE 1: Physicochemical properties of allyl glycidyl ether

Health-related hazard classifications for allyl glycidyl ether:

	HSNO CLASSIFICATION
Substance	Allyl 2,3-epoxypropyl ether
CAS No.	106-92-3
Classification	6.1D (All); 6.1D (O); 6.1D (I); 6.3A; 6.5B; 6.6B; 6.7B; 6.8B 8.3A

TABLE 2:
HSNO health-related hazard classifications of allyl 2,3-epoxypropyl ether (**EPA**, 2019)

For a full listing of all HSNO health-related hazardous substances classification codes and their descriptions, see Appendix 2.

[All] Overall classification for that endpoint.
[O] Oral exposure route.
[D] Dermal exposure route.
[I] Inhalation exposure route.

3.0
Uses

Allyl glycidyl ether is predominantly used as a reactive intermediate; resin intermediate; and, a stabiliser of chlorinated compounds, vinyl resins and rubber (**NICNAS**, 2015; ACGIH®, 2001).

Occupational exposure to allyl glycidyl ether can occur during production, storage, transportation and end-use.

Workers can be exposed to allyl glycidyl ether aerosols and/or vapour via inhalation and eye or dermal contact (NICNAS, 2015; ACGIH®, 2001).

The number of workers exposed or potentially exposed to allyl glycidyl ether in New Zealand workplaces is unknown.

Statistics New Zealand 2019 data indicate that 12,840 New Zealand workers were working in the areas of:

- basic polymer manufacturing
- basic organic chemical manufacturing
- polymer product and rubber product manufacturing (NZ.Stat, 2019).

4.0
Health effects

IN THIS SECTION:

Allyl glycidyl ether shares similar toxicological profiles with other glycidyl ethers, such as phenyl glycidyl ether [CAS No.: 122-60-1] and *n*-butyl glycidyl ether [CAS No.: 2426-08-6] (NICNAS, 2015).

4.1 Non-cancer

Humans

The available toxicological information on effects of allyl glycidyl ether on exposed workers is limited.

The **NLM HSDB** included the following excerpts:

> "Allyl glycidyl ether is a **CNS** depressant and also causes acute pulmonary edema. It is classified as slightly toxic after oral administration and percutaneous application, appreciably irritating and injurious to the eyes and skin, capable of causing skin sensitization in human subjects ..."
>
> "Short-term (acute): Exposure to **AGE** can cause moderate irritation of the skin and severe irritation of the eyes and respiratory tract. Long-term (chronic): Exposure to AGE can cause dermatitis with itching, swelling, and blisters. Skin sensitization to AGE and cross sensitization with other epoxy agents can also occur."
>
> "Dermal contact is the usual mode of exposure, but droplets in mist can also attack the eyes and respiratory tract." (NLM HSDB, 2019).

The New Zealand EPA classifies allyl glycidyl ether as a 6.1D, 6.3A and 8.3A substance – a substance that is acutely toxic, irritating to the skin, and corrosive to ocular tissue, respectively (EPA, 2019).

The NIOSH Skin Notation Profile for allyl glycidyl ether noted:

> "Limited occupational exposure data were identified. Dermatitis, consisting of tenderness, itching, swelling, and blister formation, and whitish macules, were observed in 10 of 20 workers dermally exposed to AGE vapor and/or liquid [Hine *et al*., 1956]." (Reference cited in NIOSH, 2014).

The NIOSH Skin Notation Profile for allyl glycidyl ether summarised the sensitisation potential in exposed humans:

> "A limited number of studies were identified that evaluated the potential of AGE to cause skin sensitization in both humans and animals. Hine *et al*. [1956] provided data that indicated that occupational exposure to AGE resulted in skin sensitization. Occupational exposure to a resin composed of epoxy resin and ortho-cresyl glycidyl ether produced contact dermatitis and airborne contact dermatitis in 10 of 22 workers after 20 days to 2 months of exposure [Angelini *et al*. 1996]. All 10 reacted to the diluent ortho-cresyl glycidyl ether (**CGE**), while only one of the 22 showed allergic reactions to AGE [Angelini *et al*. 1996]. Dooms-Goossens *et al*. [1995] also reported a case study in which a worker in the plastics industry who presented with dermatitis on his hands and forearms reacted positively to AGE after patch testing. Fregert and Rorsman [1964] conducted patch tests on people that presented with contact allergies to resins of diglycidyl ethers of bisphenol A. In this study, 2 of 20 subjects were sensitized to AGE." (References cited in NIOSH, 2014).

The New Zealand EPA classifies allyl glycidyl ether as a 6.5B substance – a substance that is a contact sensitiser (EPA, 2019).

Animals

The NICNAS review of allyl glycidyl ether summarised the acute toxicity in experimental animals:

> "Male Sprague-Dawley (SD) rats (six animals/dose) were exposed to AGE for 7h 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 1.18mg/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 1.46mg/L— to be 2.56mg/L (**REACH**)." (References cited NICNAS, 2015).
>
> "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 500mg/kg) or overnight (at a dose of 1000mg/kg) (MAK, 2013)." (References cited NICNAS, 2015).
>
> "It was reported that the oral median lethal dose (LD50) of AGE was 390mg/kg and 1600mg/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 1600mg/kg bw (REACH)." (References cited NICNAS, 2015).

The NIOSH Skin Notation Profile for allyl glycidyl ether summarised the skin irritation/corrosion potential in experimental animals:

> "In rabbits, a single application of 0.5 milliliter (mL) of undiluted AGE to the clipped skin for 24 hours, according to the Draize protocol, resulted in moderate skin irritation on intact skin and moderate to severe irritation on abraded skin [Hine *et al*. 1956; Dow Chemical Company 1957]. The structure activity relationship model, Deductive Estimation of Risk from Existing Knowledge (***DEREK***), predicted AGE to be a skin irritant." (References cited in NIOSH, 2014).

The NICNAS review of allyl glycidyl ether summarised the eye irritation/corrosion potential in experimental animals:

> "In a study conducted in three New Zealand White rabbits, undiluted AGE (0.1mL) was applied to one eye with an observation period of up to 48h. 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 1–48h and 24–48h, respectively;
> – overall irritation score for all animals: 72 (1, 24 and 48h readings)." (Reference cited in NICNAS, 2014).

The NIOSH Skin Notation Profile for allyl glycidyl ether summarised the sensitisation potential in experimental animals:

> "No predictive tests [guinea pig maximization test (**GPMT**), Buehler test, local lymph node assays (**LLNA**), mouse ear swelling test (**MEST**) etc] were identified. *DEREK* predicted AGE to be a skin sensitizer." (References cited in NIOSH, 2014).

The NICNAS review of allyl glycidyl ether summarised the repeated dose toxicity in experimental animals:

> "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 200ppm (equivalent to 0, 0.019, 0.047, 0.140, 0.467, or 0.933mg/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 200ppm 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 4ppm (or 0.019mg/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 30ppm (equivalent to 0, 0.005, 0.019, 0.047, 0.140mg/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 1ppm (or 0.005mg/L) (NTP, 1990; REACH)." (References cited in NICNAS, 2015).

The NICNAS review of allyl glycidyl ether summarised the reproductive/ developmental toxicity in experimental animals:

> "In an eight-week study, Osborne-Mendel rats (20 animals/sex/dose) were exposed to AGE at vapour concentrations of 0, 30, 100 or 200ppm (equivalent to 0.140, 0.467, and 0.933mg/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 eight-week inhalation study conducted in Osborne-Mendel rats and B6C3F1 mice exposed to AGE at concentrations of 0, 30, 100 or 200ppm (equivalent to 0.140, 0.467, and 0.933mg/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)." (References cited in NICNAS, 2014).

The NTP toxicological summary for *n*-butyl glycidyl ether noted that:

> "In rats given an **i.m.** injection of AGE (400mg/kg) for three nonconsecutive days, testicular degeneration was observed but was not statistically significant. In one of the three surviving rats, focal necrosis of the testis was also seen (Gardiner *et al*., 1992). When rats were administered AGE vapor (300ppm) via inhalation for seven hours per day, five days per week for a total of 50 exposures, testicular atrophy occurred in five of ten rats, and small testes was found in one of ten rats (Gardiner *et al*., 1993)." (References cited in NTP, 2004).

The **OECD SIDS** review of allyl glycidyl ether summarised the genotoxic potential in experimental animals and *in vitro* test systems:

> "Allyl glycidyl ether is found to be mutagenic/genotoxic in all *in vitro* tests conducted (Ames, sister chromatid exchange assay and chromosome aberration test) with and without metabolic activation. Allyl glycidyl ether was positive in an *in vivo* mouse micronucleus test as well as *in vivo* drosophila sex-linked recessive lethal test. It is shown *in vitro* as well as *in vivo* that allyl glycidyl ether may form adducts to proteins. In addition, allyl glycidyl ether is capable of producing adducts of **DNA** *in vitro* and *in vivo* (**N**-7-guanine, N-1-adenine, N-3-adenine and N-3-cytosine, N-3-uracil) after dermal application and **i.p.** administration in mice. Based on these results, allyl glycidyl ether is an *in vitro* and *in vivo* genotoxicant." (References cited in OECD SIDS, 2007).

4.2 Cancer

The International Agency for Research on Cancer [**IARC**] evaluation of some glycidyl ethers came to no conclusion on the potential carcinogenicity of allyl glycidyl ether (IARC, 1989).

The National Toxicology Program [NTP] evaluation of allyl glycidyl ether by inhalation bioassays concluded that:

> There was *equivocal evidence of carcinogenic activity* in male Osborne-Mendel rats; *no evidence of carcinogenic activity* in female rats; *some evidence of carcinogenic activity* in male B6C3F$_1$ mice; and equivocal *evidence of carcinogenic activity* in female mice (NTP, 1990).

The US National Toxicology Program [NTP] Report on Carcinogens [**RoC**], Fourteenth Edition has no evaluation on the carcinogenic potential of allyl glycidyl ether (NTP RoC, 2019).

The New Zealand EPA classifies allyl glycidyl ether as 6.7B – a substance suspected to be a human carcinogen (EPA, 2019).

Humans

No data were available from studies in humans on the carcinogenicity of allyl glycidyl ether.

Animals

The NTP evaluation of allyl glycidyl ether by inhalation bioassays summarised the carcinogenicity data in experimental animals:

> "In male rats exposed to 10ppm allyl glycidyl ether, three apparently unrelated neoplasms of the nasal passage were found. Two neoplasms, a papillary adenoma and a squamous cell carcinoma, appeared to arise from different cell types in the respiratory epithelium. One poorly differentiated adenocarcinoma in the olfactory region was also found. One papillary adenoma of respiratory epithelial origin was found in a female rat exposed to 5ppm. Exposure-related nonneoplastic lesions of the nasal passages in rats included inflammation, squamous metaplasia, respiratory metaplasia (replacement of olfactory epithelium by ciliated epithelium), hyperplasia of the respiratory epithelium, and degeneration of the olfactory epithelium.

> In male mice exposed to 10ppm allyl glycidyl ether, a hemangioma and three papillary adenomas were present in the nasal passage. In female mice exposed to 10ppm, a hemangioma and an adenoma were found in the nasal passage. Nonneoplastic lesions of the nasal passages in mice included inflammation, squamous metaplasia, hyperplasia, basal cell hyperplasia, dysplasia of the respiratory epithelium, and metaplasia of the olfactory epithelium. In male mice, there was an exposure-related decrease in the incidences of hepatocellular neoplasms; in female mice, there was a decrease [sic] in the incidences of pituitary gland adenomas." (NTP, 1990).

The ACGIH® review of allyl glycidyl ether noted:

> "Even at 5ppm, 92% to 98% of the male and female mice and 18% to 90% of the male and female rats developed epithelial degeneration/metaplasia/hyperplasia in the respiratory tract. A no-observed-adverse-effect level for inhaled AGE could not be identified." (ACGIH®, 2001).

The OECD SIDS assessment of allyl glycidyl ether noted:

> "The biological significance of three neoplasms observed in the respiratory tract in male rats could not be assessed due to the lack of historical control data in this strain. The number of tumors in mice is limited, but the rarity of the neoplasms seen in this species and the presence of preneoplastic lesions at the site of the tumors suggests carcinogenic potential. Based on these studies and the demonstrated *in vitro* and *in vivo* genotoxicity allyl glycidyl ether is considered to have a carcinogenic potential." (OECD SIDS, 2007).

The Health Canada review of *n*-butyl glycidyl ether noted:

> "In order to further inform the database with respect to the potential carcinogenicity of *n*-butyl glycidyl ether, **QSAR** models were used to predict its toxicity and that of the related substances considered here. In general, the predictions for all substances were similar, as **CASETOX** (2008), DEREK (2008) and **TOPKAT** (2004) indicated that genotoxicity was probable/plausible for *n*-butyl glycidyl ether and its analogues, due to the presence of the glycidyl (ether) moiety, consistent with available empirical data. With respect to predictions for carcinogenicity, DEREK (2008) predicted that *n*-butyl glycidyl ether and its analogues were plausible carcinogens, CASETOX (2008) predictions were mostly positive and TOPKAT (2004) predictions were negative. Although different models may provide varying results for a substance (likely principally due to the different model assumptions and supporting datasets), it is the similarity in predictions of each model across this group of compounds that provides support for the consideration of information on allyl glycidyl ether, glycidol, phenyl glycidyl ether and **BADGE** in the assessment of the carcinogenic potential of *n*-butyl glycidyl ether.
>
> "Although a mode of action for tumour induction by analogues of *n*-butyl glycidyl ether has not been elucidated, the potential of the epoxy ring contained in the glycidyl group to interact with DNA suggests a genotoxic mechanism of carcinogenicity. The possibility that *n*-butyl glycidyl ether could act as a direct carcinogen is supported by the available genotoxicity data." (References cited in Health Canada, 2010).

The Health Canada review of *n*-butyl glycidyl ether concluded that the structural analogue allyl glycidyl ether should also be considered carcinogenic via a mode of action potentially involving direct interaction with genetic material:

> "Based principally on the weight of evidence assessment of the European Commission, a critical effect for characterization of risk to human health for *n*-butyl glycidyl ether is carcinogenicity. Although *n*-butyl glycidyl ether has not been tested in a long-term cancer bioassay, exposure to analogous substances via inhalation, topical application or ingestion increased the incidence of tumours in various organs in rodents.
>
> "*n*-Butyl glycidyl ether was also genotoxic in a range of *in vivo* and *in vitro* assays; likewise, the structural analogues allyl glycidyl ether and glycidol also tested positive for various endpoints in both *in vivo* and *in vitro* genotoxicity assays. Considering that the glycidyl ether functional group is present in each of the analogues, that the epoxide moiety contained therein is known to alkylate DNA, that all analogues have tested positive in several *in vitro* genotoxicity assays and some have tested positive in *in vivo* assays, that all show some evidence for carcinogenicity and that similar health effects were observed for other endpoints (irritation, sensitization and reproductive toxicity), it can be reasonably concluded that *n*-butyl glycidyl ether and the selected analogues cause similar health effects and that the use of such analogues is appropriate to better inform understanding of the hazards associated with exposure to *n*-butyl glycidyl ether. Therefore, in light of the genotoxicity of *n*-butyl glycidyl ether and the carcinogenicity and genotoxicity of structurally similar compounds, it cannot be precluded that *n*-butyl glycidyl ether would induce tumours via a mode of action involving direct interaction with genetic material." (Health Canada, 2010).

4.3 Absorption, distribution, metabolism and excretion

The NICNAS review of allyl glycidyl ether summarised the **ADME**:

> "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)." (Reference cited in NICNAS, 2015).

The Health Canada review of *n*-butyl glycidyl ether noted that although a mode of action for tumour induction by analogues of *n*-butyl glycidyl ether, such as allyl glycidyl ether, has not been elucidated, the potential of the epoxy ring contained in the glycidyl group to interact with DNA suggests a genotoxic mechanism of carcinogenicity (Health Canada, 2010).

The New Zealand EPA classifies allyl glycidyl ether as a 6.6B substance – a substance that is a suspected human mutagen.

5.0 Exposure standards

IN THIS SECTION:

5.1 Other exposure standards

Table 3 below shows allyl glycidyl ether exposure standards from around the world, as published by the Institute for Occupational Safety and Health of the German Social Accident Insurance (**IFA**, 2019).

JURISDICTION OR ADVISORY BODY	8-HOUR LIMIT VALUE		SHORT-TERM LIMIT VALUE	
	ppm	mg/m³	ppm	mg/m³
Australia	5	23	10	47
Belgium	1	4.7		
Canada – Ontario	1			
Canada – Québec	5	23	10	47
Denmark	5	22	5	22
Finland	1		5[1]	
France	5	22		
Ireland	5	22	10[2]	44[2]
New Zealand	5	23	10	47
Poland		6		12
Singapore	5	23	10	47
South Korea	1	4.7		
Spain[3]	1	4.7		
Switzerland	5	22		
USA – NIOSH	5	22	10[1]	44[1]
USA – OSHA			10	45
UK[4]	5	24	10	47

TABLE 3: Exposure standards for allyl, 2,3-epoxypropyl ether from around the world

It is noted that the only organisations from whom we obtained information as to how and why they set occupational exposures standards on allyl glycidyl ether were ACGIH®, DFG and Safe Work Australia.

5.2 ACGIH®

The American Conference of Governmental Industrial Hygienists [ACGIH®] review recommended a **TLV-TWA** of 1ppm [4.7mg/m³] for occupational exposure to allyl glycidyl ether to minimise the potential for ocular, dermal, and upper respiratory tract irritation and contact dermatitis (ACGIH®, 2001).

[1] 15 minutes average value.

[2] 15 minutes reference period.

[3] **sen**.

[4] Health may not be adequately protected because of doubts that the limit was not soundly-based. These **OEL**s were included in the published UK 2002 list and its 2003 supplement, but are omitted from the published 2005 list.

The rationale for their conclusions included:

> "AGE is an acute irritant in rodents after single (Hine *et al*., 1956) or repeated exposures (Hine *et al*., 1956; NTP, 1990), producing squamous metaplasia, inflammation, respiratory epithelial and basal cell hyperplasia, olfactory epithelial degeneration, and dysplasia after repeated exposures at 5ppm (NTP, 1990). It is the physiology of the rodent upper airway which dictates high, local, delivered dose of reactive, volatile chemicals to those sites (Gardiner *et al*., 1993), and it has been demonstrated that the human oncogenic hazard based on delivered dose for such agents is substantially less than what would be predicted, based on nominal exposure concentration (administered dose) (Casanova *et al*., 1991). Based on the results of the rodent irritation (Gagnaire *et al*., 1987; Schaper, 1993) and chronic inhalation bioassays (NTP, 1990), the human ocular and upper respiratory tract irritation (Hine *et al*., 1956; NIOSH, 1978; Gardiner *et al*., 1993), contact dermatitis, skin irritation, and allergy/sensitization, a TLV-TWA of 1ppm is believed to be sufficiently low to prevent primary irritation. The TLV-TWA, however, may not be so low as to prevent contact sensitization in all workers. Unlike the related glycidyl ethers which are testicular toxins and nasal carcinogens in rats (for example, phenyl glycidyl ether), the effects seen after AGE do not occur at the same level. Given the allergic sensitization reported for AGE (Fregert and Rorsman, 1964; NIOSH, 1978; Gardiner *et al*., 1993), the (**SEN**) notation is under review.
>
> "In that no epidemiological studies were located on AGE and that lifetime rodent inhalation bioassays were judged equivocal (showing no to at best little evidence for carcinogenic activity) (NTP, 1990), the A4, Not Classifiable as a Human Carcinogen, category is appropriate.
>
> "Sufficient data were not available to recommend a Skin notation or a **TLV-STEL**." (References cited in ACGIH®, 2001).

The ACGIH® also noted that:

> "It is recognized that the recommended TLV-TWA may not necessarily protect susceptible workers from possible sensitization or an allergic reaction in previously sensitized individuals. Accordingly, exposures to AGE should be kept as low as possible below the recommended **TLV**." (ACGIH®, 2001).

5.3 DFG

The Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) review of allyl glycidyl ether recommended no MAK value; no Peak limitation; Skin notation, "**H**"; Sensitisation notation, "**Sh**"; **Carcinogenicity Category**, 2; no Pregnancy Risk or Germ cell mutation classifications (DFG, 1992, 2013, 2018).

The rationale for their conclusions included:

> "For allyl glycidyl ether, there are no data available for effects on workers exposed for longer periods to monitored concentrations of the substance. The available animal studies have not revealed a concentration which had no effects (the lowest concentration tested was 1ml/m³). The MAK value of 10ml/m³ which was valid until 1992 is thus certainly too high. In long-term studies in rats and mice, allyl glycidyl ether was shown to have weak carcinogenic effects. The highest concentration tested, 10ml/m³, was below

the maximal tolerated concentration so that higher levels of the substance would be expected to produce a more marked carcinogenic effect. That the substance is clearly genotoxic supports this assessment as does a consideration of structural analogy with other glycidyl ethers. Allyl glycidyl ether is therefore classified in category IIIA2 in the "List of MAK and **BAT** Values". A MAK value cannot be established. The designation "**S**" is retained because recent studies (Jolanki *et al*. 1990, Jolanki 1991) also confirm the skin sensitizing properties of allyl glycidyl ether." (References cited in DFG, 1992).

"Exposure to allyl glycidyl ether leads to sensitization of the skin and to the formation of DNA adducts in skin cells. In addition, the lowest dermal lethal dose is given as 500mg/kg body weight. The absorption of relevant amounts by the skin has therefore been demonstrated. The substance is a known genotoxic carcinogen, for which no tolerable level of exposure can be deduced. It must be assumed, therefore, that even after the percutaneous absorption of small amounts the carcinogenic risk is increased. The substance is therefore designated with an "H"." (DFG, 2013).

5.4 Safe Work Australia

Safe Work Australia proposed an interim 8-h TWA of 0.1ppm to protect for cancers in exposed workers. This TWA is also expected to minimise the potential for ocular, dermal and upper respiratory tract irritation and contact dermatitis in exposed workers.

In their review, they say, "AGE is characterised as a non-threshold based genotoxic carcinogen. Currently (DFG, 2003). [sic] No suitable exposure-response functions are available to derive a risk-based value in relation to carcinogenicity. Therefore, an interim TWA of 0.1ppm (0.5mg/m^3) has been recommended. The interim TWA is derived from a sub-chronic inhalation study in mice that reported upper respiratory tract irritation at 1ppm and an interspecies uncertainty factor of 10." (Safe Work Australia, 2019).

6.0 Analytical methods for the assessment of airborne allyl glycidyl ether

A common method to measure allyl glycidyl ether exposure is using NIOSH Method 2545, Issue 1 (NIOSH, 1994).

Using this method an air sample of 1.5 to 8 litres is collected onto a sampling train consisting of a Tenax GC solid sorbent tube, with the sampling train set at a flow rate of 0.01 to 0.2 litres per minute. Following desorption of the analyte using diethyl ether, the sample is analysed using gas chromatography with flame ionisation detection.

This method can achieve a detection limit of 10µg per sample. This would allow quantitation of samples at an airborne concentration of 0.3ppm for an 8 litre air sample over 8 hours, or 0.7ppm for a 3 litre sample over 15 minutes.

It is acknowledged that determination of the airborne concentration of allyl glycidyl ether for comparison with the proposed WES-TWA or WES-STEL cannot be achieved using this method.

7.0
Discussion

WorkSafe's WES for allyl glycidyl ether has been unchanged since adoption in 1994.

The toxicological database reviewed above indicates allyl glycidyl ether is locally and systemically toxic to humans, causing skin, eye and respiratory tract irritation/corrosion, and dermal sensitisation; and locally and systemically toxic to laboratory species causing skin, eye and respiratory tract irritation/corrosion, dermal sensitisation, testicular damage, and nasal tumours in rodents.

Based on the aforementioned documentation, informed by the conclusions of the ACGIH®, Safe Work Australia and DFG reviews, and in particular the findings listed below, WorkSafe considers its current WES-TWA of 5ppm [23mg/m^3] and WES-STEL of 10ppm [47mg/m^3] for inhalable fraction of allyl glycidyl ether to be inadequate to manage health risks from possible workplace exposure:

- Allyl glycidyl ether has the potential to induce respiratory tract, skin and eye irritation/corrosion, and skin sensitisation in exposed workers (NLM HSDB, 2019; ACGIH®, 2001).
- Allyl glycidyl ether has the potential to induce respiratory tract, skin and eye irritation/corrosion, skin sensitisation, and male reproductive toxicity in experimental animals (NICNAS, 2015).
- Allyl glycidyl ether has the potential to induce nasal cavity tumours in male and female B6C3F$_1$ mice, and in male Osborne-Mendel rats, with a **NOAEL** of 5ppm, **LOAEL** = 10ppm with concurrent non-neoplastic lesions, including: inflammation, squamous metaplasia, hyperplasia, basal cell hyperplasia, dysplasia of the respiratory epithelium, and metaplasia of the olfactory epithelium (NTP, 1990; DFG, 1992).
- Allyl glycidyl ether was mutagenic/genotoxic in all *in vitro* tests reported with and without metabolic activation; positive in an *in vivo* mouse micronucleus test, *in vivo* drosophila sex-linked recessive lethal test; and can form adducts to proteins and DNA *in vitro* and *in vivo* (OECD SIDS, 2007).
- The mechanism(s) by which allyl glycidyl ether induces cancer in rodents has not been elucidated, but the potential of the epoxy ring in the glycidyl group to interact with DNA suggests genotoxic involvement cannot be discounted (Health Canada, 2010).
- No robust human studies examining possible adverse health effects after workplace exposures to allyl glycidyl ether that could be used to establish lifetime no-effect levels have been reported (DFG, 1992).
- The DFG review of allyl glycidyl ether concluded that the substance, similarly to other glycidyl ethers, was genotoxic and no MAK Value could be set (DFG, 1992, 2013, 2017).
- The ACGIH® proposed an OEL for allyl glycidyl ether at 1ppm [4.7mg/m^3], based on the results of the rodent irritation and chronic inhalation bioassays, human dermal, ocular and upper respiratory tract irritation, contact dermatitis, and allergy/sensitisation (ACGIH®, 2001).

- In 2016 the **JSOH** recommended an **OEL-M** of 0.25ppm [1.3mg/m^3] for the structurally related *n*-butyl glycidyl ether, that was based reports of nasal cavity tumours in mice from a 2-year inhalation study (JSOH, 2016).
- In 2018 WorkSafe recommended a WES-TWA of 0.1ppm [0.6mg/m^3] for the structurally related phenyl glycidyl ether, based on a similar toxicological profile (WorkSafe, 2019b).
- The WES-TWA for allyl glycidyl ether is recommended in the same range of 0.1–0.25ppm as the structural analogues [for example, phenyl glycidyl ether and *n*-butyl glycidyl ether] to adequately protect against respiratory tract irritation and any possible (carcinogenic) sequelae.
- A WES-STEL is justified for allyl glycidyl ether because respiratory tract irritation/corrosion is a critical, acute, endpoint with the potential for genotoxic activity, so peak concentrations should be limited to also help prevent eye irritation and contact sensitisation.
- A *skin notation* is justified for allyl glycidyl ether, based on potential exposure contribution, reported systemic toxicity after dermal administration, and the potential for genotoxic activity (DFG, 2013).
- Available information indicates that while allyl glycidyl ether is a dermal sensitiser, there is insufficient evidence about respiratory sensitisation, so an ***rsen*** *notation* is not warranted but a ***dsen*** *notation* is recommended (DFG, 2013; ACGIH®, 2001).
- Allergic sensitisation is considered an irreversible change (OECD, 2012), and while threshold levels exist for allergic sensitisation by allergenic substances (OECD, 2012), the data for allyl glycidyl ether from human experience or animal studies was inadequate to quantitatively derive such a threshold.

8.0 Recommendations

WorkSafe considers its current WES-TWA of 5ppm [23mg/m^3] and WES-STEL of 10ppm [47mg/m^3] for inhalable fraction of allyl glycidyl ether with a *skin notation* to be inadequate to protect workers exposed in the workplace, based on current knowledge.

It is proposed that WorkSafe:

1. adopt a WES-TWA for allyl glycidyl ether of 0.25ppm [1.2mg/m^3, inhalable fraction];
2. adopt a WES-STEL for allyl glycidyl ether of 0.5ppm [2.4mg/m^3, inhalable fraction];
3. adopt a *dsen notation* for allyl glycidyl ether; and
4. retain the *skin notation* for allyl glycidyl ether.

Noting that the recommended WES-TWA of 0.25ppm and WES-STEL of 0.5ppm for allyl glycidyl ether may not eliminate all risk, due to the genotoxic potential of allyl glycidyl ether, the impact of dermal absorption, and the potential for dermal sensitisation, so exposures should be eliminated ideally, or minimised, particularly with regard to individuals who may already be sensitised to allyl glycidyl ether or other glycidyl ethers.

It is acknowledged that currently there are no available analytical methods that would allow determination of airborne levels of allyl glycidyl ether at the proposed WES-TWA or the WES-STEL. WorkSafe recommends substituting alternative substances so far as is reasonably practicable.

Appendices

IN THIS SECTION:

Appendix 1: Glossary

TERM	MEANING
ACGIH®	The American Conference of Governmental Industrial Hygienists (ACGIH®) is a member-based organisation, established in 1938, that advances occupational and environmental health. Examples of this include their annual edition of the TLVs® and BEIs® book and work practice guides. Store at: www.acgih.org/store
ADME	Absorption, Distribution, Metabolism and Excretion.
AGE	Allyl glycidyl ether [CAS No.: 106-92-3].
BADGE	Bisphenol A diglycidyl ether.
BAT	Biologische Arbeitsstoff-Toleranzwerte [Biological Tolerance Value], a DFG term.
Carcinogen category 2	DFG MAK designation: Substances that are considered to be carcinogenic for man because sufficient data from long-term animal studies or limited evidence from animal studies substantiated by evidence from epidemiological studies indicate that they can contribute to cancer risk. Limited data from animal studies can be supported by evidence that the substance causes cancer by a mode of action that is relevant to man and by results of *in vitro* tests and short-term animal studies.
CASETOX	A statistically driven substructure/fragment-based genotoxicity prediction program.
CGE	o-Cresyl glycidyl ether [CAS No.: 2210-79-9].
CNS	Central nervous system.
DEREK	Deductive Estimation of Risk from Existing Knowledge software modelling structure activity relationships.
DFG	Deutsche Forschungsgemeinschaft (German Research Foundation), the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Federal Republic of Germany. The science-based MAK values are recommended to the German Minister of Labour and Social Affairs for possible adoption under the German Hazardous Substances Ordinance.
DGUV-IFA	Deutschen Gesetzlichen Unfallversicherung ([German Social Accident Insurance] – Institut für Arbeitsschutz [Institute for Occupational Safety and Health].
DNA	Deoxyribonucleic acid.
dsen	A substance that can 'sensitise' the skin, inducing a state of hypersensitivity to it, so that on subsequent exposures, an allergic reaction can occur (which would not develop in non-sensitised individuals). It is uncommon to become sensitised to a compound after just a single reaction to it. A WorkSafe term.
EPA	The New Zealand Environmental Protection Authority.
GPMT	Guinea pig maximization test.
"H"	DFG MAK designation: *danger of percutaneous absorption*. Equivalent to the 'skin' notation in the WorkSafe WES Special Guide.
HSDB	Hazardous Substances Data Bank, administered by the US National Library of Medicine.
HSNO	Hazardous Substances and New Organisms Act 1996, New Zealand.
IARC	International Agency for Research on Cancer, World Health Organization.
IFA	Institut für Arbeitsschutz der Deutschen Gestzlichen Unfallversicherung [Institute for Occupational Safety and Health of the German Social Accident Insurance].
i.m.	Intramuscular.
Inhalable fraction	Inhalable particulate fraction is that fraction of dust that can be breathed into the nose or mouth. Particulate size: mostly <100µm, 50% cut point. For sampling purposes the inhalable dust is to be collected according to the method set out in AS 3640-2009: Workplace Atmospheres – Method for Sampling and Gravimetric Determination of Inhalable Dust (Standards Australia, 2009b). (*cf.* Respirable fraction) (Also referred to as: inhalable aerosol; inhalable particulate matter)
i.p.	Intraperitoneal.
JBRC	Japan Bioassay Research Center.

TERM	MEANING
JSOH	Japan Society for Occupational Health.
LC_{50}	Lethal Concentration for 50% of the test population.
LD_{50}	Lethal Dose for 50% of the test population.
LLNA	Local lymph node assay.
LOAEC	Lowest Observed Adverse Effect Concentration.
LOAEL	Lowest Observed Adverse Effect Level.
MAK	Maximale Arbeitsplatz-Konzentration, (maximum workplace concentration) is defined as the maximum concentration of a chemical substance (as gas, vapour or particulate matter) in the workplace air which generally does not have known adverse effects on the health of the employee nor cause unreasonable annoyance (for example, by a nauseous odour) even when the person is repeatedly exposed during long periods, usually for 8 hours daily but assuming on average a 40-hour working week. A value set by the DFG.
MEST	Mouse-ear swelling test.
mg/kg	Milligrams per kilogram.
mg/kg b.w./ mg/kg bw	Milligram of substance per kilogram body weight.
mg/L	Milligram of substance per litre.
mg/m^3	Milligrams of substance per cubic metre of air.
N	Nitrogen [Number suffixes indicate position in associated molecule].
NICNAS	National Industrial Chemicals Notification and Assessment Scheme is the Australian government's regulatory body for industrial chemicals.
NIH	National Institutes of Health, United States federal agency.
NIOSH	The National Institute for Occupational Safety and Health is the United States federal agency responsible for conducting research and making recommendations for the prevention of work-related injury and illness.
NLM	National Library of Medicine, administered by the US National Institutes of Health.
NOAEL	No Observed Adverse Effect Level.
NTP	National Toxicology Program, US Department of Health and Human Services.
OECD	Organisation for Economic Co-operation and Development.
OEL	Occupational Exposure Limit (equivalent to a WES).
OEL-M	Occupational Exposure Limit-Mean: the reference value to the mean exposure concentration at or below which adverse health effects caused by the sub-stance do not appear in most workers working for 8 hours a day, 40 hours a week under a moderate work-load. A JSOH term.
OSHA	Occupational Safety and Health Administration, US Department of Labor.
ppm	Parts of vapour or gas per million parts of air.
QSAR	Quantitative structure-activity relationship.
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals. An EU program and regulation.
RoC/ROC	Report on Carcinogens.
rsen	A substance that can 'sensitise' the respiratory system, inducing a state of hypersensitivity to it, so that on subsequent exposures, an allergic reaction can occur (which would not develop in non-sensitised individuals). It is uncommon to become sensitised to a compound after just a single reaction to it. A WorkSafe term.
"S"	DFG MAK designation: *danger of sensitisation of the skin*.

TERM	MEANING
SEN	A notation indicating the substance is a sensitiser. DSEN and RSEN are used in place of SEN when specific evidence of sensitisation by the dermal or respiratory route, respectively, is confirmed by human or animal data. An ACGIH® term.
"Sh"	DFG MAK designation: *danger of sensitisation of the skin*.
SIDS	Screening Information DataSet [OECD].
skin	Skin absorption – applicable to a substance that is capable of being significantly absorbed into the body through contact with the skin. A WorkSafe term.
Skin	A notation indicating the potential for significant contribution to the overall exposure, by the cutaneous route, including mucous membranes and the eyes, by contact with vapours, liquids and solids. An ACGIH® term.
STEL	Short-Term Exposure Limit. The STEL is a limit value above which exposure should not occur and usually relates to a 15-minute reference period.
TLV®	Threshold Limit Value (see TLV-STEL and TLV-TWA below). An ACGIH® term. Please see the Statement of Position Regarding the TLVs® and BEIs® and Policy Statement on the Uses of TLVs® and BEIs®
TLV-STEL	TLV-Short-Term Exposure Limit; a 15 minute TWA exposure that should not be exceeded at any time during a work day, even if the 8-hour TWA is within the TLV-TWA. An ACGIH® term.
TLV-TWA	TLV – Time-Weighted Average; the TWA concentration for a conventional 8-hour workday and a 40-hour workweek, to which it is believed that nearly all workers may be repeatedly exposed to, day after day, for a working lifetime without adverse effect. An ACGIH® term.
TOPKAT	Toxicity Prediction by Komputer Assisted Technology.
WES	Workplace Exposure Standard – WESs are values that refer to the airborne concentration of substances, at which it is believed that nearly all workers can be repeatedly exposed to, day after day, without coming to harm. The values are normally calculated on work schedules of five shifts of eight hours duration over a 40 hour week. A WorkSafe term.
WES-STEL	The 15-minute time-weighted average exposure standard. Applies to any 15-minute period in the working day and is designed to protect the worker against adverse effects of irritation, chronic or irreversible tissue change, or narcosis that may increase the likelihood of accidents. The WES-STEL is not an alternative to the WES-TWA; both the short-term and time-weighted average exposures apply. Exposures at concentrations between the WES-TWA and the WES-STEL should be less than 15 minutes, should occur no more than four times per day, and there should be at least 60 minutes between successive exposures in this range. A WorkSafe term.
WES-TWA	The average airborne concentration of a substance calculated over an eight-hour working day. A WorkSafe term.

Appendix 2: HSNO health-related hazardous substance classifications

This is the full list of all health-related hazardous substances classifications that are listed by the NZ EPA, including those that apply to this substance.

CLASSIFICATION CODE	MEANING
Acutely toxic	
6.1A	Substances that are acutely toxic – Fatal
6.1B	Substances that are acutely toxic – Fatal
6.1C	Substances that are acutely toxic – Toxic
6.1D	Substances that are acutely toxic – Harmful
6.1E	Substances that are acutely toxic – May be harmful, aspiration hazard
Skin irritant	
6.3A	Substances that are irritating to the skin
6.3B	Substances that are mildly irritating to the skin
Eye irritant	
6.4A	Substances that are irritating to the eye
Sensitisation	
6.5A	Substances that are respiratory sensitisers
6.5B	Substances that are contact sensitisers
Mutagens	
6.6A	Substances that are known or presumed human mutagens
6.6B	Substances that are suspected human mutagens
Carcinogens	
6.7A	Substances that are known or presumed human carcinogens
6.7B	Substances that are suspected human carcinogens
Reproductive/developmental toxicants	
6.8A	Substances that are known or presumed human reproductive or developmental toxicants
6.8B	Substances that are suspected human reproductive or developmental toxicants
6.8C	Substances that produce toxic human reproductive or developmental effects on or via lactation
Target organ toxicants	
6.9A	Substances that are toxic to human target organs or systems
6.9B	Substances that are harmful to human target organs or systems
Skin corrosive	
8.2A	Substances that are corrosive to dermal tissue (UN PGI)
8.2B	Substances that are corrosive to dermal tissue (UN PGII)
8.2C	Substances that are corrosive to dermal tissue (UN PGIII)
Eye corrosive	
8.3A	Substances that are corrosive to ocular tissue

Source: www.epa.govt.nz/industry-areas/hazardous-substances/rules-for-hazardous-substances/hazardous-substances-classification-codes

Appendix 3: References

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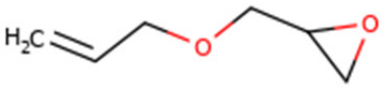
Appendix 4: Structures of allyl glycidyl ether and some analogues

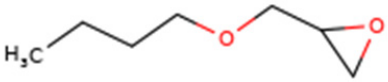
Allyl glycidyl ether [AGE, CAS No.: 106-92-3]

https://chem.nlm.nih.gov/chemidplus/rn/106-92-3



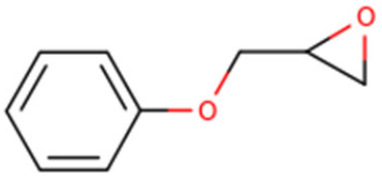
n-Butyl 2,3-epoxypropyl ether [BGE, CAS No.: 2426-08-6]

https://chem.nlm.nih.gov/chemidplus/rn/2426-08-6



Phenyl glycidyl ether [PGE, CAS No.: 122-60-1]

https://chem.nlm.nih.gov/chemidplus/rn/122-60-1



Notes

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