Australian Government
Department of Health and Aged Care
Australian Industrial Chemicals Introduction Scheme

Glycidyl neodecanoate and glycidyl tert-decanoate

Evaluation statement

25 September 2023

Draft

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AICIS evaluation statement

Subject of the evaluation

Glycidyl neodecanoate and glycidyl tert-decanoate

Chemicals in this evaluation

Name	CAS registry number
Neodecanoic acid, oxiranylmethyl ester	26761-45-5
tert-Decanoic acid, oxiranylmethyl ester	71206-09-2

Reason for the evaluation

Evaluation Selection Analysis indicated a potential human health risk.

Parameters of evaluation

The chemicals in this evaluation are a group of glycidyl esters of neo- (glycidyl neodecanoate; CAS No. 26761-45-5) and tert-decanoic acid (glycidyl tert-decanoate; CAS No. 71206-09-2) that are listed on the Australian Inventory of Industrial Chemicals (the Inventory). This evaluation is a human health risk assessment for all identified industrial uses of these chemicals. These chemicals are expected to have similar critical health effects driven by either direct reactions of the epoxide group or the metabolite glycidol.

Summary of evaluation

Summary of introduction, use and end use

There is currently no specific information about the introduction, use and end use of these chemicals in Australia.

Based on international use information, these chemicals are used in a range of commercial applications including in paints and varnishes, adhesives and sealants, and plastic and construction materials. Although some of these products may be available to consumers, available data indicates that any domestic use is not widespread. Glycidyl neodecanoate also has reported use as an intermediate in manufacturing other chemicals including the manufacture of plastic and rubber products, toys and childcare articles.

Human health

Summary of health hazards

Limited data are available for glycidyl tert-decanoate. Given the close structural similarity to glycidyl neodecanoate and the common metabolite glycidol (CAS No. 556-52-5), data for

glycidyl neodecanoate and glycidol are used to draw conclusions on health hazards of glycidyl tert-decanoate.

Based on the available data, these chemicals:

- have low acute and dermal toxicity
- are slight skin and eye irritants
- are not expected to cause serious systemic health effects following repeated oral or dermal exposure.

Available in vitro data indicate limited dermal absorption of these chemicals. Available in vitro studies indicate that glycidyl neodecanoate is metabolised into glycidol and neodecanoic acid via carboxylesterase-mediated hydrolysis. Although no toxicokinetic data are available for glycidyl tert-decanoate, it is expected to have a similar toxicokinetic profile as glycidyl neodecanoate based on its structural similarity. Therefore, glycidyl tert-decanoate is expected to be metabolised to glycidol.

Based on the available data these chemicals are considered to be skin sensitisers. Positive results were reported for glycidyl neodecanoate in 4 in vivo skin sensitisation studies (guinea pig maximisation test (GPMT). Based on 65% sensitisation rate observed following induction at 0.05%, glycidyl neodecanoate is considered to have extreme potency.

Based on the weight of evidence from the available in vitro and in vivo data for glycidyl neodecanoate and the metabolite glycidol, as well as in silico data, these chemicals are considered to have genotoxic and carcinogenic potential. Glycidyl neodecanoate was positive in several bacterial reverse mutation assays but negative in in vitro chromosome aberration assays and in an in vitro gene mutation assay. Although mixed results were reported in in vivo studies, glycidyl neodecanoate was positive in an in vivo transgenic rodent assay. In a study with MutaMouse, repeated exposure to glycidyl neodecanoate resulted in increased mutation frequency in liver, kidney and bone marrow but not in sperm cells. The potential for genotoxicity of these chemicals is supported by in silico analysis.

There are no carcinogenicity data available for chemicals in this group. The metabolite glycidol is classified for Carcinogenicity – Category 1B, and Germ cell mutagenicity – Category 1B. Based on the available information on the potential genotoxicity of glycidyl neodecanoate and the metabolite glycidol, supported by in silico data, chemicals in this group have been shown to have carcinogenic potential. Although the mechanism of action for carcinogenicity is not completely understood, both genotoxic and non-genotoxic mechanisms are considered plausible. In the absence of more comprehensive information, no classification is recommended. A review may be required should further information become available.

No reproductive and developmental toxicity data are available for glycidyl tert-decanoate and limited data are available for glycidyl neodecanoate. Based on data for the metabolite, glycidol, these chemicals have potential to cause effects on male fertility. No inhalation data are available. Based on the low volatility limited inhalation exposure is expected unless chemical is aerosolised.

For further details of the health hazard information see **Supporting information**.

Hazard classifications relevant for worker health and safety

These chemicals satisfy the criteria for classification according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) (UNECE 2017) for hazard classes relevant for work health and safety as follows. This does not consider classification of physical hazards and environmental hazards.

Health hazards	Hazard category	Hazard statement
Skin Sensitisation	Skin Sens. 1A	H317: May cause an allergic skin reaction
Germ cell mutagenicity	Muta. 2	H341: Suspected of causing genetic defects

Summary of health risk

Public

Based on the available use information, it is unlikely that the public will be significantly exposed to these chemicals.

There may be exposure to the chemical if present in domestic products such as paints and coatings. However, this use is not expected to be widespread. In addition, exposure to do it yourself (DIY) products is incidental and normal precautions to avoid prolonged contact are expected. Exposure will be also limited by the expected limited dermal absorption and inhalation exposure potential.

Although the public could come into contact with articles manufactured with these chemicals, they will be fully reacted with other components and bound to the matrix of the substrates. Therefore, they will not be expected to be bioavailable.

Overall, there are no identified risks to the public that require risk management.

Workers

During product formulation and packaging, dermal, ocular and inhalation exposure might 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 these chemicals at lower concentrations could also occur while using formulated products containing these chemicals. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic and local effects, these chemicals could pose a risk to workers. Control measures to minimise dermal, ocular and inhalation exposure are needed to manage the risk to workers (see **Proposed means for managing risk** section). Control measures implemented due to the mutagenicity and sensitisation classification are expected to be sufficient to protect workers from any potential reproductive and carcinogenic effects.

Proposed means for managing risk

Workers

Recommendation to Safe Work Australia

It is recommended that Safe Work Australia (SWA) update the Hazardous Chemical Information System (HCIS) to include classifications relevant to work health and safety.

A specific concentration limit for glycidyl neodecanoate (CAS No. 26761-45-5) of 0.001% is recommended based on the potency observed in animal studies.

Information relating to safe introduction and use

The information in this statement including recommended hazard classifications, should be used by a person conducting a business or undertaking at a workplace (such as an employer) to determine the appropriate controls under the relevant jurisdiction Work Health and Safety laws.

Control measures that could be implemented to manage the risk arising from oral, dermal and inhalation exposure to these chemicals include, but are not limited to:

- using closed systems or isolating operations
- minimising manual processes and work tasks through automating processes
- adopting work procedures that minimise splashes and spills
- cleaning equipment and work areas regularly
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with these chemicals.

Measures required to eliminate or manage risk arising from storing, handling and using these hazardous chemicals depend on the physical form and how these chemicals are used.

These control measures may need to be supplemented with:

- conducting health monitoring for any worker who is at significant risk of exposure to these chemicals, if valid techniques are available to monitor the effect on the worker's health.

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.

Model codes of practice, available from the Safe Work Australia website, provide information on how to manage the risks of hazardous chemicals in the workplace, prepare an SDS and label containers of hazardous chemicals. Your Work Health and Safety regulator should be contacted for information on Work Health and Safety laws and relevant Codes of Practice in your jurisdiction.

Conclusions

The conclusions of this evaluation are based on the information described in this statement.

Considering the proposed means of managing risks, the Executive Director proposes to be satisfied that the identified human health risks can be managed within existing risk management frameworks. This is provided that all requirements are met under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory, and the proposed means of managing the risks identified during this evaluation are implemented.

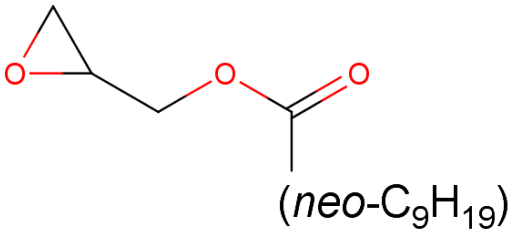
Note: Obligations to report additional information about hazards under *Section 100 of the Industrial Chemicals Act 2019* apply.

Supporting information

Grouping rationale

The chemicals in this group are glycidyl esters of neo-decanoic acid (CAS No. 26761-45-5) or tert-decanoic acid (CAS No. 71206-09-2). They have similar uses and bioavailability and are expected to metabolise to glycidol (CAS No. 556-52-5) which is likely to drive systemic toxicity. Glycidol has been previously assessed under our former scheme, the National Industrial Chemicals Notification and Assessment Scheme (NICNAS 2014). Findings from that assessment will be used to support toxicological endpoints of the chemicals where information is not available.

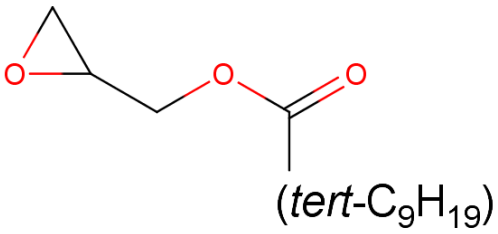
Chemical identity

Chemical name	Neodecanoic acid, oxiranylmethyl ester
CAS No.	26761-45-5
Synonyms	glycidyl neodecanoate, neodecanoic acid, 2,3-epoxypropyl ester, 2,3-epoxypropyl neodecanoate
Molecular formula	C13H24O3
Molecular weight (g/mol)	228.33
SMILES (canonical)	unspecified
Chemical description	UVCB
Structural formula:	

(*neo*-C_9H_{19})

Chemical name	tert-Decanoic acid, oxiranylmethyl ester
CAS No.	71206-09-2
Synonyms	glycidyl tert-decanoate
Molecular formula	C13H24O3
Molecular weight (g/mol)	228.33
SMILES (canonical)	unspecified
Chemical description	UVCB

Structural formula:



Relevant physical and chemical properties

Measured physical and chemical property data for the chemical were identified from the European Union Registration, Evaluation and Authorisation of Chemicals dossiers (REACH n.d.) the ECHA CLH opinion (ECHA 2021) and the EPI Suite experimental database (Danish QSAR).

Chemical	glycidyl neodecanoate	glycidyl tert-decanoate
Physical form	clear yellow liquid	-
Boiling point	269–272 °C	272 °C
Vapour pressure	1.5 Pa at 25 °C	0.68 Pa at 20 °C
Water solubility	70 mg/L at 20 °C	-
log K_{ow}	4.4	3.73

Introduction and use

Australia

No information is available on the introduction, use and end use of these chemicals in Australia.

International

The following international uses have been identified through the:

- Galleria Chemica (ChemWatch)
- Substances in Preparations in Nordic Countries (SPIN) database
- European Union (EU) Registration, Evaluation and Authorisation of Chemicals (REACH) dossier
- European Chemicals Agency (ECHA) Annex VI, Part 2 – Proposal for Harmonised Classification and Labelling CLH report (ECHA 2021)
- United States Environmental Protection Agency Chemical Data Reporting (CDR) (US EPA 2016; US EPA 2020)
- Canada Domestic Substance List (DSL) 2017 Inventory Update (Government of Canada n.d.).

These chemicals have reported commercial uses in:

- paints, lacquers, and varnishes including automotive resins
- building and construction materials
- fillers.

In addition, glycidyl neodecanoate has reported commercial uses including:

- adhesives and sealants and for epoxy flooring (concentration 20%)
- electrical and electronic products
- hydraulic fluids and additives
- heat stabilisers
- solvents and viscosity adjustors.

Some of the commercial uses may also be considered domestic. There were no identified products containing these chemicals in North American consumer product databases (DeLima Associates). The REACH registration dossier for glycidyl neodecanoate identified uses by professional users only. Consumer uses were reported in the US Chemical Data Reporting (CDR) under the Toxic Substances Control Act (US EPA 2016) for glycidyl neodecanoate including paints and coatings and construction materials. The reported concentration was <1%. For glycidyl tert-decanoate the SPIN database did not include any consumer preparations. The industrial use of these chemicals was by automotive repair shops and construction. Consumer preparations were included in SPIN for glycidyl neodecanoate However, it should be noted that the SPIN database does not include any distinction between direct use of the chemical and use of the materials that are produced from chemical reactions involving the chemical. Information provided for the Canadian Inventory update indicated use of glycidyl neodecanoate as a paint additive without use in consumer activities.

Glycidyl neodecanoate has reported site limited uses as an intermediate in product formulation and chemical synthesis including the manufacture of plastic and rubber product and toys, playground, and sporting equipment.

Existing Australian regulatory controls

AICIS

No specific controls are currently available for these chemicals.

Public

No specific controls are currently available for these chemicals.

Workers

These chemicals are not listed on the HCIS (Safe Work Australia, SWA).

No exposure standards are available for these chemicals in Australia (SWA).

International regulatory status

Exposure standards

The following exposure standards were identified for glycidyl neodecanoate:

Time weighted average (TWA): 10 mg/m^3 — Russia.

Health hazard information

Toxicokinetics

In in vitro metabolism studies in cell-free tissue preparations from human, rat and mouse, liver, lung and skin, glycidyl neodecanoate was rapidly metabolised by carboxylesterase hydrolysis and epoxide hydrolase, and to a lesser extent via glutathione conjugation (ECHA 2021, REACH). Estimation of in vivo clearance based on the in vitro kinetic data and scaling suggested that the human detoxication rate was approximately an order of magnitude slower relative to rodents.

In an in vitro study conducted using diffusion cell technology with skin samples from rats, mice and humans, the data showed that the radiolabelled glycidyl neodecanoate isomer was metabolised to the corresponding diol and ester hydrolysis product. Human skin samples were approximately an order of magnitude less permeable to the chemical than rodent skin. The mean percent penetration in human skin samples was 0.24 +/- 0.06% (ECHA 2021; REACH).

No specific toxicokinetic data are available for glycidyl tert-decanoate. Based on the close chemical structure and physico-chemical properties, the metabolic pathway is expected to be similar to that of glycidyl neodecanoate with metabolism likely by carboxylesterase to glycidol and decanoic acid. This is supported by the metabolite profiles predicted using the skin metabolism simulator of the OECD Quantitative Structure Activity Relationship (QSAR) Toolbox v4.4 (OECD 2020) and the expert rule based metabolism prediction tool, Meteor Nexus Phase I metabolism (Lhasa Limited n.d.).

Acute toxicity

Oral

Based on the available data, chemicals in this group are considered to have low acute toxicity following oral exposure.

In a GLP compliant acute oral toxicity study conducted in accordance with OECD Test Guideline (TG) 420, Crl:CD (Sprague Dawley (SD)) rats (5/sex/dose) were administered a single dose of glycidyl neodecanoate at 2000 mg/kg bw via oral gavage. The reported median lethal dose (LD50) was >2000 mg/kg bw. Reported clinical signs of toxicity included piloerection, anogenital soiling and stained fur (REACH n.d.).

LD50 values of >10000 mg/kg bw were reported in rats and mice for both glycidyl neodecanoate and glycidyl tert-decanoate. Reported clinical signs of toxicity for glycidyl neodecanoate following acute oral exposure in rats included ataxia and decreased weight gain (CCOHS 2023).

Dermal

Based on the available data, chemicals in this group are considered to have low acute toxicity following dermal exposure.

In a GLP compliant acute dermal toxicity study conducted in accordance with OECD TG 402, Crl:CD SD rats (5/sex/dose) were applied (semi-occlusive) a single dose of 2000 mg/kg bw of glycidyl neodecanoate. The reported median LD50 was >2000 mg/kg bw. Reported clinical signs of toxicity included chromodacryorrhoea (increased tear secretion) and anogenital soiling (REACH n.d.).

In an acute dermal toxicity study in Wistar rats (4/sex/dose), the reported LD50 was >39000 mg/kg bw for glycidyl neodecanoate. No signs of toxicity were reported other than irritation of the dorsal skin (REACH n.d.).

Corrosion/Irritation

Skin irritation

No data are available for glycidyl tert-decanoate. Based on the limited available data for glycidyl neodecanoate, chemicals in this group are potential skin irritants. However, there is insufficient evidence to warrant classification. In a guideline study only slight irritant effects were observed.

In a GLP compliant skin irritation study conducted in accordance with OECD TG 404, the skin of 3 New Zealand White (NZW) rabbits (sex not specified) was applied with undiluted glycidyl neodecanoate (0.5 mL) under semi-occlusive conditions for 4 hours. Observations were recorded at 24, 48 and 72 hours, and at 8 and 15 days after patch removal. An erythema score of 1 was reported for 2 animals at 72 hours and an oedema score of 1 was reported for one animal at 24 hours (maximum score 0 of 4). Skin irritation effects were reversible in all animals within 15 days (REACH n.d.)

Undiluted glycidyl neodecanoate (0.5 mL) was applied to the intact and abraded skin of NZW rabbits (4/sex) under semi-occlusive conditions for 24 hours. These animals were observed for up to 7 days. Moderate skin irritation was observed in test animals with mean scores of 2.4 for erythema and 1.8 for oedema (calculated from mean primary dermal irritation index = 2.7) at 24 hours. The mean score of 1.1 for erythema and 1 for oedema was reported after 7 days (REACH n.d.). No further details are available.

Application of 0.5 mL of glycidyl neodecanoate to the skin of rabbits resulted in moderate irritation (CCOHS 2023). No further details are available.

Eye irritation

No data are available for glycidyl tert-decanoate. Based on the available data for glycidyl neodecanoate, chemicals in this group are expected to be, at most, slightly irritating to the eye.

In a GLP compliant eye irritation study conducted in accordance with OECD TG 405, 0.1 mL of glycidyl neodecanoate (undiluted) was instilled into the conjunctival sac of one eye for each of 3 NZW rabbits. Observations were recorded at 1, 4 and 24 hours. The following group mean scores were reported at 1 and 4 hours: conjunctival redness 0.7 and chemosis 0.3, respectively. The irritation effects were reversible in all animals within 2 days. No iridial or corneal changes were reported (REACH n.d.).

In a non-guideline eye irritation study, 0.2 mL of glycidyl neodecanoate (undiluted) was instilled into the conjunctival sac of one eye for each of 4 NZW rabbits. Observations were recorded at 1–2 hours and at 1, 2, 3 and 7 days. A mean conjunctival redness score of 0.6 was reported at 1–2 hours for the group. No other signs of eye irritation were observed. Irritation effects were reversible in all animals within 24 hours (REACH n.d.).

In another non-guideline eye irritation study, 0.2 mL of glycidyl neodecanoate (undiluted) was instilled into the conjunctival sac of one eye each of 4 NZW rabbits. Observations were recorded at 1–2 hours and at 1, 2, 3 and 7 days. A mean conjunctiva redness score of 1 was reported at 1–2 hours for the group. No other signs of eye irritation were observed. Irritation effects were reversible in all animals within 7 days (REACH n.d.).

Sensitisation

Skin sensitisation

No data are available for glycidyl tert-decanoate. Based on the available data for glycidyl neodecanoate, chemicals in this group have the potential to cause skin sensitisation, warranting classification. Based on a 65% sensitisation rate observed following induction at 0.05%, glycidyl neodecanoate is considered to have extreme potency supporting sub-categorisation and a specific concentration limit of 0.001% (ECHA 2022).

In a GLP compliant guinea pig maximisation test (GPMT) conducted according to OECD TG 406, Dunkin Hartley guinea pigs (20 females) received intradermal injection of 25% glycidyl neodecanoate in Alembicol D and topical application of 100% chemical under occlusive condition. The animals were challenged with topical application of the chemical at 25 and 50% in Alembicol D and dermal reactions were observed at 24 and 48 hours after removal of the patch. Positive reactions were reported in 45% (9/20) and 20% (4/20) of the animals challenged with 50% and 25% of the chemical, respectively. The chemical was reported to cause skin sensitisation (ECHA 2021; REACH n.d.).

In a GPMT conducted similarly to OECD TG 406, guinea pigs (20 females; strain unspecified) received intradermal injection of 5% glycidyl neodecanoate in Drakeol 19 and topical application of 100% glycidyl neodecanoate. The animals were challenged with topical application of 50% glycidyl neodecanoate in Drakeol 19 under occlusive condition and examined at 24 and 48 hours after removal of the dressing. Positive reactions were reported in 85% (17/20) of the animals at 24 hours observation period. The chemical was reported to cause skin sensitisation (ECHA 2021; REACH n.d.).

In an in vivo skin sensitisation study described as being a GPMT, “P” strain guinea pigs (10/sex) received intradermal injection of 0.5% (w/v) glycidyl neodecanoate in corn oil and topical application of 100% glycidyl neodecanoate. Topical challenge under occlusive dressing with the chemical at 50% (w/v) in corn oil resulted in erythema or severe erythema in 95% (19/20) of the animals. The chemical was reported to cause skin sensitisation (ECHA 2021; REACH n.d.).

In an in vivo skin sensitisation study described as being a GPMT, “P” strain guinea pigs (10/sex) received intradermal injection of 0.05% (w/v) glycidyl neodecanoate in corn oil and topical application of 50% (w/v) glycidyl neodecanoate. Topical challenge under occlusive conditions with the chemical at 50% (w/v) in corn oil showed positive results in 13/20 and 7/20 animals at 24 and 48 hours after patch removal, respectively (REACH n.d.).

Observation in humans

Cases of allergic contact hypersensitivity were reported in 3 separate human case studies following occupational exposure to epoxy resins. The studies reported positive results in patch tests to glycidyl neodecanoate (0.01 to 0.25%) in 2 out of 9 workers (ECHA 2021).

In 2 human patch tests, glycidyl neodecanoate at 0.25 or 1% was applied to 341 individuals with contact dermatitis. No sensitisation was observed (ECHA 2021).

Repeat dose toxicity

Oral

No data are available for glycidyl tert-decanoate. Based on the available data for glycidyl neodecanoate, chemicals in this group are not expected to cause serious damage to health following repeated oral exposure. The severity of the adverse effects or doses at which effects were observed in the liver and kidneys is not sufficient to warrant hazard classification.

In a GLP-compliant sub-acute repeated dose study conducted in accordance with OECD TG 407, Wistar rats (10/sex/dose) were fed glycidyl neodecanoate at 0, 100, 500, 1000, 5000 or 10,000 ppm daily for 5 weeks. No mortality or treatment related clinical signs of toxicity were reported. A significant reduction in red blood cell (RBC) count was reported in males at the highest dose. At 5000 or 10000 ppm, decreased blood glucose levels and increased plasma urea, sodium and potassium ion concentrations in males, and decreased plasma alkaline phosphatase (AP) activity and increased plasma protein in females were reported. Liver and kidney weights (absolute and relative) were also increased in both sexes. Histopathological findings showed nephrotoxic effects including degenerative, occlusive and regenerative lesions in the proximal tubules of the kidneys in males and, to a lesser extent, in females at the highest dose. The no observed adverse effect level (NOAEL) was determined to be 1000 ppm (equivalent to approximately 90 mg/kg bw/day) for both sexes based on the haematological as well as liver and kidney effects (REACH n.d.).

In a repeated dose study conducted in accordance with OECD TG 408, Wistar rats (10/sex/dose) were administered glycidyl neodecanoate by gavage at 0, 100, 300 or 1000 mg/kg bw/day daily for 90 days. No treatment related mortality was reported. At 1000 mg/kg bw/day, statistically significant reduction in haemoglobin, RBC count and haematocrit, as well as an increase in AP activity and bile acid level were reported in males. Increase in liver weights with hepatocellular hypertrophy and hypertrophy of the follicular epithelium in both sexes were also reported at the highest dose. The effects in thyroid glands are considered to be related to the changes in the liver, where hypertrophy of the follicular cells compensates for the increased hepatic clearance of thyroid hormones. Absolute and relative kidney weights were increased in both sexes at 300 and 1000 mg/kg bw/day. Histopathological findings showed adverse effects in kidneys (hyaline droplets, granular casts, multifocal basophilic tubules or nephropathy) in males at 300 or 1000 mg/kg bw/day (REACH n.d.). The NOAEL value was determined to be 300 mg/kg bw/day based on liver effects in both sexes, in addition to haematology effects seen in males at the highest dose tested.

Genotoxicity

No data are available for glycidyl tert-decanoate. Based on the available data for glycidyl neodecanoate, the metabolite glycidol and in silico data, chemicals in this group are considered to be genotoxic. Glycidyl neodecanoate was reported to be positive in bacterial reverse mutation assays but negative in chromosome aberration assays and a gene

mutation assay. Glycidyl neodecanoate result was reported to be positive in an in vivo transgenic rodent assay with increased mutation frequencies reported in the liver, kidney and bone marrow but not in sperm cells. Based on in silico data, glycidyl neodecanoate and glycidyl tert-decanoate have the same potential genotoxic mode of action. Overall, the weight of evidence is sufficient for this group of chemicals to be classified for their potential genotoxicity.

These chemicals are expected to be metabolised to glycidol. The genotoxicity potential of glycidol should also be considered when determining the genotoxic potential of these chemicals. Glycidol is classified as hazardous (Category 1B; H340 – May cause genetic defects) in the HCIS (Safe Work Australia).

In vitro

The following results were reported for glycidyl neodecanoate:

- positive with metabolic activation (S9) and negative without metabolic activation in a bacterial reverse mutation assay (OECD TG 471) in *Salmonella typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537 at concentrations of 0–5000 µg/plate (ECHA 2021, REACH n.d.)
- positive with metabolic activation and negative without metabolic activation in a bacterial reverse mutation assay (OECD TG 471) in *S. typhimurium* TA 98, TA 100, TA 1535 and TA 1537 and *Escherichia coli* strains WP2 and WP2 uvrA at concentrations of 1–1000 µg/plate (ECHA 2021, REACH n.d.)
- positive without metabolic activation in a bacterial reverse mutation assay (OECD TG 471) in *S. typhimurium* TA 98, TA 100, TA 1535 and TA 1537 with and without metabolic activation at concentrations of 1–1000 µg/plate (ECHA 2021, REACH n.d.)
- positive with metabolic activation and negative without metabolic activation in a bacterial reverse mutation assay (OECD TG 471) in *S. typhimurium* strains TA 100 and TA 1535; and negative in TA 97, TA 98 and TA 1537 with and without metabolic activation at concentrations of 1–1000 µg/plate (NTP)
- negative in a chromosome recombination assay (OECD TG 481) in *Saccharomyces cerevisiae* (yeast) JD1 with and without metabolic activation at concentrations of up to 5000 µg/mL (REACH n.d.)
- negative or ambiguous in two mammalian chromosome aberration assays in rat liver epithelial cell line RL1 or Chinese hamster ovary (CHO) cells with and without metabolic activation at concentrations up to 50 µg/mL (ECHA 2021, REACH n.d.)
- negative in a mammalian cell transformation assay in Syrian hamster fibroblast kidney (BHK) cells with metabolic activation at concentrations of 0–350 µg/mL (ECHA 2021, REACH n.d.).

In vivo

In a GLP-compliant transgenic rodent assay conducted in accordance with OECD TG 488, MutaMouse (number of animals not reported) were administered glycidyl neodecanoate by gavage at 0, 250, 500 or 1000 mg/kg bw/day daily for 42 days followed by three days of recovery. The mutation frequency in the liver, kidney and bone marrow was reported to be significantly increased but not in developing sperm cells (ECHA 2021, REACH n.d.).

In a GLP compliant transgenic rodent assay conducted in accordance with OECD TG 488, male MutaMouse (n=10) were administered glycidyl neodecanoate by gavage at 1000 mg/kg bw/day daily for 28 days followed by 50 days of recovery. The mutation frequency in mature sperm cells was reported not to be significantly increased (ECHA 2021, REACH n.d.).

In a GLP compliant unscheduled DNA synthesis test conducted in accordance with OECD TG 486, glycidyl neodecanoate was administered as a single dose by gavage to male SD rats (4/dose) at 0, 500, 1000 or 2000 mg/kg bw. There were no signs reported of DNA damage in liver cells at all doses tested (ECHA 2021, REACH n.d.).

In a GLP compliant mammalian DNA damage and/or repair study, glycidyl neodecanoate was administered as a single dose by gavage to Wistar rats (2/sex/dose) at approximately 4850 mg/kg bw. There were no signs reported of DNA damage in liver cells at the dose tested (ECHA 2021, REACH n.d.).

In silico (QSAR)

Chemicals in this group present alerts for mutagenicity based on the molecular structure as profiled by the OECD QSAR Toolbox v4.4 (OECD 2020) and OASIS-TIMES (optimized approach based on structural indices set–tissue metabolism simulator) (OASIS LMC n.d). Both glycidyl neodecanoate and glycidyl tert-decanoate have structural alerts as epoxides and aziridines for in vitro mutagenicity (Ames tests) and in vivo mutagenicity (micronucleus). These chemicals contain epoxides and aziridines and have potential to react with nucleophilic centres of DNA molecules through alkylation or cross linking, causing toxic and mutagenic effects. The OASIS TIMES prediction for both chemicals were within the applicability domain of the model. The expert rule based system, DEREK (Deductive Estimation of Risk from Existing Knowledge) Nexus (Lhasa Limited n.d.) identified alerting groups (glycidyl ether, amine, ester or amide) indicating that the epoxide ring of glycidyl derivatives have the potential to alkylate DNA nucleophilic centres leading to potentially mutagenic and carcinogenic effects.

Carcinogenicity

No data are available for chemicals in this group. The metabolite glycidol is classified as hazardous (Category 1B; H350 – May cause cancer) in the HCIS (Safe Work Australia). Based on the available information on the potential genotoxicity of glycidyl neodecanoate, and data for the metabolite glycidol, supported by in silico data, chemicals in this group may have carcinogenic potential. The mechanism of action for carcinogenicity of these chemicals is not completely understood. In the absence of more comprehensive information, carcinogenicity classification is not warranted. However, the carcinogenic potential of these chemicals cannot be ruled out and should be reviewed if further information becomes available.

There are several alerts for mutagenicity and carcinogenicity for chemicals in this group as profiled by the OECD QSAR Toolbox v4.4 (OECD 2020). Both glycidyl neodecanoate and glycidyl tert-decanoate have structural alerts for carcinogenicity (genotoxic and non-genotoxic), which suggests carcinogenic potential is considered plausible through genotoxic and non-genotoxic mechanisms.

Reproductive and development toxicity

No data are available for glycidyl tert-decanoate and limited data are available for glycidyl neodecanoate. The metabolite, glycidol, is classified as a reproductive toxicant in the HCIS; however, in the absence of more comprehensive information, reproductive and developmental toxicity classification for these chemicals is not warranted. The potential for reproductive and developmental toxicity should be reviewed if further information becomes available.

In a GLP compliant prenatal developmental toxicity study conducted in accordance with OECD TG 414, pregnant SD rats (24/dose) were administered glycidyl neodecanoate by gavage in arachis oil once daily at 0, 100, 300 or 1000 mg/kg bw/day on gestation days (GD) 3–9. Dams

were sacrificed on GD 20 and the foetuses examined. No mortality or significant treatment related effects on reproduction, gestation or development were observed. Marginal reduction in maternal body weight gains was reported at 300 and 1000 mg/kg bw/day. Based on these observations, NOAEL values were determined to be 100 mg/kg bw/day for maternal toxicity and 1000 mg/kg bw/day for developmental toxicity (REACH n.d.).

These chemicals are expected to be metabolised to glycidol. Glycidol has been classified by Safe Work Australia and the former NICNAS as 'May damage fertility – Cat 1B (H360F)'. Studies investigating fertility showed that glycidol induced male infertility (ECHA 2015b; NICNAS 2014a).

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