



**SOME INDUSTRIAL
CHEMICAL INTERMEDIATES
AND SOLVENTS**

VOLUME 125

This publication represents the views and expert opinions of an IARC Working Group on the Identification of Carcinogenic Hazards to Humans, which met in Lyon, 5–11 November 2019

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**IARC MONOGRAPHS
ON THE IDENTIFICATION
OF CARCINOGENIC HAZARDS
TO HUMANS**

GLYCIDYL METHACRYLATE

1. Exposure Characterization

1.1 Identification of the agent

1.1.1 Nomenclature

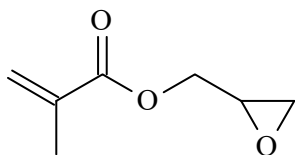
Chem. Abstr. Serv. Reg. No.: 106-91-2

Chem. Abstr. Serv. name: 2,3-epoxypropylmethacrylate

IUPAC systematic name: (oxiran-2-yl)methyl 2-methylprop-2-enoate

Synonyms: glycidyl methacrylate; (*RS*)-2,3-epoxypropylmethacrylate; (\pm)-2,3-epoxypropylmethacrylate; 2-((methacryloxy)methyl)oxirane; 2-oxiranylmethyl ester; methacrylic acid-2,3-epoxypropylester; 2-propenoic acid, 2-methyl-; 1-propanol, 2,3-epoxy-methacrylate.

1.1.2 Structural and molecular formula, and relative molecular mass



Molecular formula: C₇H₁₀O₃

Relative molecular mass: 142.15

1.1.3 Chemical and physical properties of the pure substance

Description: colourless, combustible liquid substance with a sweetish or fruity odour, which tends to polymerize spontaneously ([HSDB, 2003](#))

Boiling point: 189 °C ([HSDB, 2003](#))

Melting point: -41.5 °C ([HSDB, 2003](#))

Density: 1.04–1.07 g/cm³ (20 °C) ([ECHA, 2019](#); [IFA, 2019](#))

Solubility: < 10–50 g/L (in water at 20–25 °C) ([ECHA, 2019](#); [IFA, 2019](#)), very soluble in benzene, ethyl ether, and ethyl alcohol ([HSDB, 2003](#))

Vapour pressure: 4.2 hPa (25 °C) ([ECHA, 2019](#))

Flash point: 76–84 °C at 101.3 kPa ([ECHA, 2019](#))

Auto-ignition temperature: 389 °C at 101.3 kPa ([ECHA, 2019](#))

Vapour density: 4.91 (air = 1) ([IFA, 2019](#))

Octanol/water partition coefficient (P): log K_{ow} = 0.96 ([ILO, 2006](#))

Conversion factor: 1 ppm = 5.91 mg/m³ (at 20 °C and 101.3 kPa).

1.1.4 Technical grade and impurities

The purity of technical-grade glycidyl methacrylate is 92% ([HSDB, 2003](#)). Known potential impurities of the technical product can be epichlorohydrin (0.02%) and polymerization inhibitors such as monomethyl ether hydroquinone ($\leq 0.01\%$) ([HSDB, 2003](#); [Dobrovolsky et al., 2016](#)).

1.2 Production and use

1.2.1 Production process

Glycidyl methacrylate belongs to the group of substituted epoxides or substituted carboxylic acid esters and is produced by the esterification of methacrylic acid with either glycidol or epichlorohydrin ([HSDB, 2003](#)).

1.2.2 Production volume

Glycidyl methacrylate is listed as a High Production Volume chemical in the Screening Information Data Set (SIDS) of the Organisation for Economic Co-operation and Development ([OECD, 2009](#)). Currently, the majority of manufacturing sites are located in the USA and Europe, with fewer sites being situated in Asia ([Chem Sources, 2019](#)). The European Chemicals Agency (ECHA) reported that 1000–10 000 tonnes of glycidyl methacrylate per year are currently manufactured and/or imported in the European Economic Area ([ECHA, 2019](#)). The aggregate production volume in the USA in 2014 and 2015 has been reported to be between 10 000 000 and 50 000 000 lb [between approximately 4500 and 23 000 tonnes] ([US EPA, 2016](#)). The production volume in Japan for glycidyl methacrylate in 1995 was approximately 3000 tonnes ([OECD-SIDS, 2000](#)).

1.2.3 Uses

Glycidyl methacrylate is mainly used as co-monomer for the production of various composite materials and epoxy polymers, such as bisphenol A-glycidyl methacrylate (BisGMA) and triethylene glycol-dimethacrylate (TEGDMA). These are used as dental sealants ([Pulgar et al., 2000](#); [Gioka et al., 2005](#); [Vervliet et al., 2018](#)), or bone adhesives and tissue ([Palussière et al., 2005](#); [Middleton et al., 2008](#); [Sanus et al., 2008](#); [Monmaturapoj et al., 2017](#)). Glycidyl methacrylate is also used as an adhesion promotion/crosslinking co-monomer in the manufacture of vinyl and acrylic resins ([HSDB, 2003](#)). These resins are used as industrial powder and metal coatings for household appliances, facades, and automotives ([Pietschmann, 2010](#)). Glycidyl methacrylate, as an acrylic copolymer, has also been classified as a food contact material substance by the United States Food and Drug Agency ([US FDA, 2018a](#)) for aqueous and fatty foods ([US FDA, 2018b](#)), and for components of paper and paperboard in contact with dry food ([US FDA, 2018b](#)). Glycidyl methacrylate is also used for the manufacture of epoxy polymers, which are increasingly proposed for new medical applications such as hydrogel contact lenses, medical imaging, 3D-printing biomaterials and targeted drug delivery ([Hagit et al., 2010](#); [Hardy et al., 2015](#); [Li et al., 2015](#); [Abbadessa et al., 2016](#); [Musgrave & Fang, 2019](#); [Pei et al., 2019](#)).

In the European Economic Area, the ECHA reported that glycidyl methacrylate has active registrations under the regulations of Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) and is used in articles, in formulation or re-packing, at industrial sites, and in manufacturing. Similarly, use as monomer in polymer synthesis has also been registered outside the European Union. The substance is used for the production of mixtures or articles by tableting, compression, extrusion, or pelletization. Specifically, the industrial

use of monomers occurs in the manufacture of thermoplastics and as a process regulator for polymerization processes in the production of resins, rubbers, and polymers. Consequently, glycidyl methacrylate-based polymers can be found in products with plastic materials, such as food packaging and storage devices, toys, and mobile phones. In addition, there is an imported polymer product registered in the European Union that can contain the monomer in or on the article ([ECHA, 2019](#)).

1.3 Methods of measurement and analysis

For personal air sampling of glycidyl methacrylate and its analysis, the use of an XAD2 sorbent tube at a flow rate of 1 L/minute for sample collection, butyl acetate for desorption, and gas chromatography with flame ionization detection (GC-FID) has been used previously ([OECD-SIDS, 2000](#)). [The Working Group noted that no further methodological details were mentioned in this report; however, the United States Environmental Protection Agency (US EPA) Compendium Method TO-15 for the analysis of volatile organic compounds in air, including the analysis of ethyl acrylate and methyl methacrylate, or the United States National Institute for Occupational Safety and Health (NIOSH) method 1614 for the analysis of ethylene oxide could possibly be adapted to the determination of glycidyl methacrylate.]

No methods have been published for the measurement of glycidyl methacrylate in other environmental media such as water, soil or waste matrices.

No analytical methods for biological monitoring of glycidyl methacrylate in biological materials such as blood or urine samples from exposed individuals were available [The Working Group noted that previously published methods on the determination of epoxides such as ethylene oxide,

i.e. measuring haemoglobin adducts in blood or mercapturic acids in urine, could possibly be adapted for glycidyl methacrylate.]

1.4 Exposure and occurrence

1.4.1 Environmental occurrence

Glycidyl methacrylate is not known to occur naturally in the environment. There are few data on the environmental occurrence of this chemical. On the basis of its low vapour pressure, glycidyl methacrylate is not expected to aerosolize readily ([OECD-SIDS, 2000](#)).

Glycidyl methacrylate can occur in the environment after release into waste water from chemical manufacturing; the amount released into air is negligible. It has been reported to be 100% biodegradable after 28 days using OECD 301C protocol and has a half-life of 3.66 days at pH 7 in water. On the basis of its low octanol/water partition coefficient, bioaccumulation of glycidyl methacrylate is expected to be low. It was reported that 99.1% will be distributed into the water phase when discharged into water; the remainder will be distributed between soil (0.4%) and air (0.4%). In Japan, approximately 3.3 tonnes per year were reported to be released into rivers by one manufacturer, and 1.62 tonnes per year by a second manufacturer, while release into air was negligible. The higher of the two releases resulted in a local predicted environmental concentration (PEC_{local}) of 8.9×10^{-3} mg/L as a worst-case scenario for water ([OECD-SIDS, 2000](#)).

1.4.2 Occupational exposure

Glycidyl methacrylate is manufactured in a closed system under well-controlled conditions, so air release is unlikely ([OECD-SIDS, 2000](#)). Some direct handling is required, such as during transfer at dedicated facilities and into small

containers, or laboratory work, when exposure can take place ([ECHA, 2019](#)).

The only sampling for occupational exposure available for glycidyl methacrylate was for Japan ([OECD-SIDS, 2000](#)). Glycidyl methacrylate was produced in a closed system. Sampling was conducted at two chemical-production sites for workers who were directly handling resin materials during sampling, maintaining, can filling, filtering, analysing, and removing sludge. The tasks that did not involve direct handling were transferring and treating waste. The highest personal air concentration was 2.3 mg/m³ for filtration that was conducted three times per day and can filling that was conducted once every 7 days. For the other tasks, concentrations were below the limit of detection. Generally, dermal exposure, although short (5 minutes per day), was estimated to be 0.04 or 0.22 mg/kg body weight (bw) per day ([OECD-SIDS, 2000](#)).

Because glycidyl methacrylate is also used in the preparation of TEGDMA and BisGMA it can be assumed that workers preparing these dental and bone composite materials can also be potentially exposed ([Olea et al., 1996](#)). Specifically, some release of unreacted glycidyl methacrylate has been shown from a bone composite in an experimental setting, but the amount was not reported ([Monmaturapoj et al., 2017](#)). [The Working Group noted that short-term exposure to unreacted glycidyl methacrylate monomer might occur for workers during the preparation of dental and bone composite materials. Once the polymer is completely hardened, no exposure to glycidyl methacrylate is expected to occur. Hardening can take from a few minutes up to several days for some bone composites.]

Another study assessing dental-care personnel reported occupational exposure for respirable dust containing BisGMA and TEGDMA polymers, formed by reaction from bisphenol A and glycidyl methacrylate. The particles ranged in diameter from 6 nm to 5 µm and consisted of resin matrix. BisGMA

and TEGDMA monomers were released from the polymer by the grinding process. Glycidyl methacrylate itself was not measured ([Cokic et al., 2017](#)). [The Working Group noted that the glycidyl methacrylate monomer is not likely to be released from the grinding process.]

Additionally, an occupation of potential concern is work in a chemical laboratory. [Matura et al. \(1995\)](#) reported a case study of a female laboratory worker with confirmed allergic contact dermatitis after exposure to glycidyl methacrylate via compounded emulsions.

1.4.3 Exposure of the general population

Exposure for the general population has not been well documented. Glycidyl methacrylate has a low vapour pressure but inhalation may still be possible. Estimates of consumption of glycidyl methacrylate via drinking-water and fish for locations near to chemical-manufacturing plants that produce or use this chemical are 2.97×10^{-4} mg/kg bw per day and 1.34×10^{-5} mg/kg bw per day, respectively, for an adult consuming 2 L per day of drinking-water or 90 g of fish, with a body weight of 60 kg ([OECD-SIDS, 2000](#)).

Patients, including young children, receive dental and bone composite materials containing TEGDMA and BisGMA ([Olea et al., 1996](#); [Nathanson et al., 1997](#); [Pulgar et al., 2000](#); [Gioka et al., 2005](#); [Zimmerman-Downs et al., 2010](#); [Vervliet et al., 2018](#)). [Bationo et al. \(2016\)](#) reported use of monomers containing 3–5% glycidyl methacrylate to make an adhesive resin for orthodontic mineral fillers. The polymerization reaction for the dental resin occurs before the material is used in the patient, but often requires a blue visible light for a short time period to allow photo- or co-initiators to start the polymerization reaction. Curing time varies depending on the polymer, with some taking 20 seconds, while others, such as root canal sealer, taking 24 hours to set and 7 days to completely polymerize

([Vervliet et al., 2018](#)), and bone composites taking as long as 10 days ([Monmaturapoj et al., 2017](#)). Release of bisphenol A, BisGMA, and TEDGMA was reported in many studies, but glycidyl methacrylate was not measured ([Mair, 1994](#); [Schmalz et al., 1999](#); [Hagio et al., 2006](#); [Lin et al., 2007](#)).

[The Working Group noted that short-term exposure to unreacted glycidyl methacrylate monomer might occur for patients receiving these dental and bone composite materials while the polymerization process occurs. Once the polymer is completely hardened, no exposure to glycidyl methacrylate is expected to occur. Hardening can take few minutes up to several days for some bone composites.]

1.5 Regulations and guidelines

Glycidyl methacrylate has been listed by the ECHA as a carcinogen (Category 1B) and as a germ cell mutagen (Category 2) ([ECHA, 2015a](#)). An occupational exposure limit of 0.01 ppm [0.06 mg/m³] has been recommended by the Japan Society for Occupational Health ([JSOH, 2018](#)), whereas a short-term limit value of 5 mg/m³ is recommended in the People's Republic of China ([IFA, 2019](#)).

2. Cancer in Humans

No data were available to the Working Group.

3. Cancer in Experimental Animals

See [Table 3.1](#).

3.1 Mouse

Inhalation

In a study that complied with good laboratory practice (GLP), groups of 50 male and 50 female B6D2F₁/CrIj [Crj:BDF₁] mice (age, 5 weeks) were exposed by whole-body inhalation to clean air (control) or 2,3-epoxypropyl methacrylate [glycidyl methacrylate] (purity, > 99.7%) vapours at a concentration of 0.6, 2.5, or 10 ppm (v/v) for 6 hours per day, 5 days per week, for 104 weeks ([JBRC, 2015a, b](#)). The mice were observed daily for clinical signs and mortality. Survival rates of males at 2.5 and 10 ppm and of females at 0.6, 2.5, and 10 ppm were significantly lower than those of their respective controls (males, 26/50 controls, 26/50, 15/50, 14/50; females, 27/50 controls, 15/50, 19/50, 9/50). There was no significant effect on body weight in exposed males and females. All mice underwent complete necropsy and histopathological examination.

In male and female mice, glycidyl methacrylate caused a significant increase in the incidence and/or a positive trend in the incidence of haemangiosarcoma of the nasal cavity in males (0/50 controls, 0/50, 1/50, 10/50; $P < 0.01$ at the highest dose, Fisher exact test; $P < 0.01$, Cochran–Armitage and Peto trend tests) and females (0/50 controls, 0/50, 1/50, 4/50; $P < 0.01$, Cochran–Armitage and Peto trend tests), and of haemangioma of the nasal cavity in males (0/50 controls, 0/50, 3/50, 8/50; $P < 0.01$ at the highest dose, Fisher exact test; $P < 0.01$, Cochran–Armitage and Peto trend tests) and females (0/50 controls, 0/50, 3/50, 7/50; $P < 0.01$ at high dose, Fisher exact test; $P < 0.01$, Cochran–Armitage and Peto trend tests). There was a significant increase in the incidence at the highest dose, and a positive trend in the incidence of haemangioma or haemangiosarcoma (combined) of the nasal cavity in male and female mice.

There was a significant positive trend in the incidence of adenoma of the Harderian gland

Table 3.1 Studies of carcinogenicity with glycidyl methacrylate in mice and rats exposed by inhalation (whole-body exposure)

Species, strain (sex) Age at start Duration Reference	Purity (vehicle) Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments	
Mouse, B6D2F ₁ /Crlj (M) Age, 5 wk 104 wk JBRC (2015a, b)	Purity, > 99.7% (clean air) 0, 0.6, 2.5, 10 ppm (vapour) 6 h/day, 5 days/wk 50, 50, 50, 50 26, 26, 15, 14	<i>Nasal cavity</i>		Principal strengths: multiple-dose study; males and females used, GLP study, covered most of lifespan Other comments: survival rates of males exposed at 2.5 and 10 ppm significantly decreased; incidence in historical controls for laboratory: nasal cavity adenoma, 2/2545 (range, 0.1%, 0–2%); and forestomach squamous cell papilloma, 7/2545 (range, 0.3%, 0–2%)	
		Haemangioma	0/50, 0/50, 3/50, 8/50*		$P < 0.01$ (Cochran–Armitage and Peto trend tests), * $P < 0.01$ (Fisher exact test)
		Haemangiosarcoma	0/50, 0/50, 1/50, 10/50*		$P < 0.01$ (Cochran–Armitage and Peto trend tests), * $P < 0.01$ (Fisher exact test)
		Haemangioma or haemangiosarcoma (combined)	0/50, 0/50, 4/50, 16/50*		$P < 0.01$ (Cochran–Armitage and Peto trend tests), * $P < 0.01$ (Fisher exact test)
		Adenoma	0/50, 0/50, 0/50, 3/50 (6%)		$P < 0.01$ (Cochran–Armitage and Peto trend tests)
		<i>Forestomach</i> : squamous cell papilloma	0/50, 1/50, 0/50, 3/50 (6%)		$P < 0.05$ (Cochran–Armitage trend test), $P < 0.01$ (Peto trend test)
Mouse, B6D2F ₁ /Crlj (F) Age, 5 wk 104 wk JBRC (2015a, b)	Purity, > 99.7% (clean air) 0, 0.6, 2.5, 10 ppm (vapour) 6 h/day, 5 days/wk 50, 50, 50, 50 27, 15, 19, 9	<i>Nasal cavity</i>		Principal strengths: multiple-dose study, males and females used, GLP study, covered most of lifespan Other comments: survival rates of all three groups of treated females significantly decreased; incidence in historical controls for the laboratory, histiocytic sarcoma of the uterus, 534/2545 (21.0%, 10–34%)	
		Haemangioma	0/50, 0/50, 3/50, 7/50*		$P < 0.01$ (Cochran–Armitage and Peto trend tests), * $P < 0.01$ (Fisher exact test)
		Haemangiosarcoma	0/50, 0/50, 1/50, 4/50		$P < 0.01$ (Cochran–Armitage and Peto trend tests)
		Haemangioma or haemangiosarcoma (combined)	0/50, 0/50, 4/50, 11/50*		$P < 0.01$ (Cochran–Armitage and Peto trend tests), * $P < 0.01$ (Fisher exact test)
		<i>Harderian gland</i> : adenoma	1/50, 1/50, 5/50, 5/50	$P < 0.05$ (Peto trend test)	

Table 3.1 (continued)

Species, strain (sex) Age at start Duration Reference	Purity (vehicle) Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Mouse, B6D2F1/Crlj (F) Age, 5 wk 104 wk JBRC (2015a, b) (cont.)		<i>Lung</i> : bronchioloalveolar carcinoma 0/50, 2/50, 0/50, 5/50*	$P < 0.01$ (Cochran–Armitage and Peto trend tests), * $P < 0.05$ (Fisher exact test)	
		<i>Uterus</i> : histiocytic sarcoma 11/50, 10/50, 12/50, 18/50	$P < 0.05$ (Cochran–Armitage trend test), $P < 0.01$ (Peto trend test)	
		<i>Harderian gland</i> : adenoma 1/50, 1/50, 2/50, 4/50	$P < 0.05$ (Peto trend test)	
Rat, Wistar (M+F, combined) NR (weight, 200 ± 20 g) Age, 6 months Ouyang et al. (1990)	Purity, NR (air) 0, 15.3, 206 mg/m ³ 6 h/day, 6 days/wk 40, 40, 40 40, 40, 38	<i>All sites</i> No significant increase in the incidence of tumour		Principal strengths: males and females used Principal limitations: limited experimental details, short duration of the study Other comments: groups of 20 males and 20 females at start
Rat, F344/DuCrlCrlj (M) Age, 5 wk 104 wk JBRC (2015c, d)	Purity, > 99.7% (clean air) 0, 3.2, 8, 20 ppm (vapour) 6 h/day, 5 days/wk 50, 50, 50, 50 41, 44, 39, 9	<i>Nasal cavity</i> Squamous cell carcinoma 0/50, 0/50, 0/50, 29/50*	$P < 0.01$ (Cochran–Armitage and Peto trend tests), * $P < 0.01$ (Fisher exact test)	Principal strengths: males and females used, multiple-dose study, GLP study, study covered most of lifespan Other comments: survival rates of males at the highest dose significantly decreased
		Esthesioneuroepithelioma [neuroepithelial carcinoma] 0/50, 0/50, 0/50, 7/50*	$P < 0.01$ (Cochran–Armitage and Peto trend tests), * $P < 0.01$ (Fisher exact test)	
		Adenoma 0/50, 7/50*, 9/50*, 0/50	* $P < 0.01$ (Fisher exact test)	
		<i>Peritoneum</i> : mesothelioma 1/50, 7/50*, 16/50**, 14/50**	$P < 0.01$ (Cochran–Armitage and Peto trend tests); * $P < 0.05$, ** $P < 0.01$ (Fisher exact test)	

Table 3.1 (continued)

Species, strain (sex) Age at start Duration Reference	Purity (vehicle) Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Rat, F344/DuCr1Cr1j (M) Age, 5 wk 104 wk JBRC (2015c, d) (cont.)		<i>Skin</i> Basal cell epithelioma 0/50, 1/50, 1/50, 4/50 Keratoacanthoma 0/50, 4/50, 3/50, 3/50 <i>Subcutis</i> : fibroma 5/50, 4/50, 4/50, 13/50*	$P < 0.05$ (Cochran–Armitage trend test), $P < 0.01$ (Peto trend test) $P < 0.05$ (Peto trend test) $P < 0.01$ (Cochran–Armitage and Peto trend tests), * $P < 0.05$ (Fisher exact test)	
Rat, F344/DuCr1Cr1j (F) Age, 5 wk 104 wk JBRC (2015c, d)	Purity, > 99.7% (clean air) 0, 3.2, 8, 20 ppm (vapour) 6 h/day, 5 days/wk 50, 50, 50, 50 39, 39, 35, 29	<i>Nasal cavity</i> : squamous cell carcinoma 0/50, 0/50, 0/50, 10/50* <i>Uterus</i> : endometrial stromal sarcoma 1/50, 1/50, 1/50, 5/50 (10%) <i>Mammary gland</i> : fibroadenoma 7/50, 14/50, 14/50, 23/50* <i>Subcutis</i> : fibroma 0/50, 2/50, 2/50, 3/50 <i>Thyroid</i> : C-cell adenoma 1/50, 1/50, 3/50, 4/50 <i>Clitoral gland</i> : adenoma 0/50, 0/50, 3/50, 4/50	$P < 0.01$ (Cochran–Armitage and Peto trend tests), * $P < 0.01$ (Fisher exact test) $P < 0.05$ (Cochran–Armitage trend test), $P < 0.01$ (Peto trend test) $P < 0.01$ (Cochran–Armitage and Peto trend tests), * $P < 0.01$ (Fisher exact test) $P < 0.05$ (Peto trend test) $P < 0.05$ (Peto trend test) $P < 0.05$ (Peto trend test)	Principal strengths: males and females used, multiple-dose study, GLP study, covered most of lifespan Other comments: survival rates of females at the highest dose significantly decreased; incidence in historical controls for the laboratory, endometrial stromal sarcoma, 54/2846 (1.9%, 0–8%)

F, female; GLP, good laboratory practice; h, hour; M, male; NR, not reported; ppm, parts per million; wk, week.

in male and female mice ($P < 0.05$, Peto trend test). In male mice, glycidyl methacrylate caused a significant positive trend in the incidence of adenoma of the nasal cavity (0/50 controls, 0/50, 0/50, 3/50; $P < 0.01$, Cochran–Armitage and Peto trend tests; with a historical control rate of 0.1% of 2545 male mice, range, 0–2%), and of squamous cell papilloma of the forestomach (0/50 controls, 1/50, 0/50, 3/50; $P < 0.05$, Cochran–Armitage trend test; $P < 0.01$, Peto trend test; with a historical control rate of 0.3% of 2545 male mice, range, 0–2%).

In female mice, glycidyl methacrylate caused a significant increase in the incidence at the highest dose ($P < 0.05$, Fisher exact test) and a positive trend in the incidence of bronchioloalveolar carcinoma ($P < 0.01$, Cochran–Armitage and Peto trend tests), and a positive trend in the incidence of histiocytic sarcoma in the uterus ($P < 0.05$, Cochran–Armitage trend test; $P < 0.01$, Peto trend test).

Regarding non-neoplastic lesions, transitional cell hyperplasia of the nasal cavity was observed in males and females exposed at 10 ppm and angiectasis of the nasal cavity was observed in females at 10 ppm (JBRC, 2015a, b). [The Working Group noted the strengths of this GLP study: the use of multiple doses and both males and females, while covering most of the lifespan.]

3.2 Rat

3.2.1 Inhalation

Three groups of 20 male and 20 female Wistar rats [age not reported; weight, 200 ± 20 g] were exposed to glycidyl methacrylate [purity not reported] at a concentration of 0 (control), 15.3, or 206 mg/m³ for 6 hours per day, 6 days per week, for 6 months. Two rats [sex unspecified] in the group at the highest dose died before the end of the study at 6 months. There was no significant increase in the incidence of

any tumour type in exposed rats (Ouyang et al., 1990). [The Working Group noted the limited experimental details and short duration of the study.]

In a study that complied with GLP, groups of 50 male and 50 female F344/DuCr1Cr1j (Fischer) rats (age, 5 weeks) were exposed by whole-body inhalation to clean air (control) or 2,3-epoxypropyl methacrylate [glycidyl methacrylate] (purity, > 99.7%) vapours at a dose of 3.2, 8, or 20 ppm (v/v) for 6 hours per day, 5 days per week, for 104 weeks (JBRC, 2015c, d). The rats were observed daily for clinical signs and mortality. Survival rates of males and females exposed at 20 ppm were significantly lower than their respective controls (males, 41/50 controls, 44/50, 39/50, 9/50; females, 39/50 controls, 39/50, 35/50, 29/50). Body weights were significantly decreased in males at 20 ppm throughout the 2-year exposure period, and in females at 20 ppm during the last half (from 54 weeks) of the 2-year exposure period and females at 8 ppm during the late period (from 82 weeks) of the exposure, compared with their respective controls. All rats underwent complete necropsy and histopathological examination.

In male and female rats, glycidyl methacrylate caused a significant increase in the incidence at the highest dose ($P < 0.01$, Fisher exact test), and a positive trend in the incidence of squamous cell carcinoma of the nasal cavity ($P < 0.01$, Cochran–Armitage and Peto trend tests).

In male rats, glycidyl methacrylate caused a significant increase in the incidence and a positive trend in the incidence of esthesioneuroepithelioma [neuroepithelial carcinoma] of the nasal cavity (0/50 controls, 0/50, 0/50, 7/50; $P < 0.01$ at the highest dose, Fisher exact test; $P < 0.01$, Cochran–Armitage and Peto trend tests), mesothelioma of the peritoneum (1/50 controls, 7/50, 16/50, 14/50; $P < 0.05$ at the lowest dose, $P < 0.01$ at the intermediate and highest doses, Fisher exact test; $P < 0.01$, Cochran–Armitage and Peto trend tests), subcutis fibroma (5/50 controls,

4/50, 4/50, 13/50; $P < 0.05$ at the highest dose, Fisher exact test; $P < 0.01$ Cochran–Armitage and Peto trend tests), and a significant positive trend in the incidence of basal cell epithelioma of the skin ($P < 0.05$, Cochran–Armitage trend test; $P < 0.01$, Peto trend test). There was also a significant increase ($P < 0.01$, Fisher exact test) in the incidence of adenoma of the nasal cavity in the groups at the lowest and intermediate doses, and a significant positive trend ($P < 0.05$, Peto trend test) in the incidence of skin keratoacanthoma.

In female rats, glycidyl methacrylate caused a significant positive trend in the incidence of endometrial stromal sarcoma of the uterus ($P < 0.05$, Cochran–Armitage trend test; $P < 0.01$, Peto trend test), and a significant increase in the incidence at the highest dose ($P < 0.01$, Fisher exact test) and a positive trend in the incidence of fibroadenoma of the mammary gland ($P < 0.01$, Cochran–Armitage and Peto trend tests). There was also a significant positive trend ($P < 0.05$, Peto trend test) in the incidence of subcutis fibroma, thyroid C-cell adenoma, and adenoma of the clitoral gland.

Regarding non-neoplastic lesions in the nasal cavity, squamous cell hyperplasia with atypia in males and females at 20 ppm, squamous cell metaplasia in the respiratory epithelium in females at 3.2 ppm and in males and females at 8 and 20 ppm, squamous cell metaplasia with atypia in males at 8 ppm and in males and females at 20 ppm, and transitional epithelium hyperplasia in males and females at 3.5 and 8 ppm and in females at 20 ppm, were observed in exposed groups (JBRC, 2015c, d). [The Working Group noted the strengths of this GLP study: the use of multiple doses and both males and females, while covering most of the lifespan.]

3.2.2 Oral administration (gavage)

In the study by Hadidian et al. (1968), five groups of three male and three female Fischer rats [age not reported, weanling] were given

glycidyl methacrylate by gavage at a dose of 0.001, 0.003, 0.01, 0.03, or 0.3 mg (in 0.5 mL steroid) per rat, five times per week for a total of 260 individual doses, for 52 weeks. A sixth group of 15 male and 15 female Fischer rats underwent similar treatment with doses of 0.1 mg per rat. Two groups of 30 male and 30 female Fischer rats served as vehicle or untreated concurrent controls. The rats were observed for six additional months after treatment. At the end of the experiment (up to 600 days), full histopathology was performed. The pattern of tumour incidence observed with glycidyl methacrylate was similar to that observed in controls. [The Working Group noted the small number of animals per treated groups, the limited experimental details, the lack of statistics, and the limited reporting of results for controls. The Working Group judged the study inadequate for the evaluation.]

[The Working Group noted that the tumour site profile of glycidyl methacrylate in these studies is similar to that reported in carcinogenicity bioassays with glycidol. Specifically, in both male and female BDF₁ mice exposed by inhalation, glycidol induced significant increases in the incidence of malignant tumours (haemangiosarcoma, and adenoma/adenocarcinoma) of the nasal cavity (JBRC, 2003a, b). In these female mice, squamous cell carcinoma of the nasal cavity, and malignant tumours of the uterus (histiocytic sarcoma) and mammary gland (adenocarcinoma) were also reported. In F344 rats exposed by inhalation, glycidol induced malignant tumours of the nasal cavity (adenoma or adenocarcinoma in males and females, and squamous cell carcinoma in males), peritoneum (mesothelioma in males), and uterus (endometrial stromal sarcoma in females); other reported tumours in the rat were thyroid follicular cell carcinoma in males and splenic mononuclear cell leukaemia in females. In F344 rats treated with glycidol by gavage (IARC, 2000), there was an increased incidence of malignant tumours including of the peritoneum (males), mammary

gland (females), apocrine glands (males), brain (males and females), and gastrointestinal tract (males). In B6C3F₁ mice treated with glycidol by gavage, there was an increased incidence of malignant tumours including of the uterus (female), Harderian gland (males and females), and mammary gland (females).]

4. Mechanistic Evidence

4.1 Absorption, distribution, metabolism, and excretion

4.1.1 Humans

(a) Exposed humans

No data were available to the Working Group.

(b) Human tissues *in vitro*

The metabolism of ¹⁴C-labelled glycidyl methacrylate (2 mM) was investigated in human liver homogenates over a 6-hour period (ECHA, 2015b). In the course of this study, the concentration of a single metabolite that was formed was mass balanced with the concentration of glycidyl methacrylate. This metabolite was identified as glycidol based on retention time match with [¹⁴C] glycidol. [The Working Group considered such identification to be reasonable, taking also into account that maximum blood levels of glycidyl methacrylate were increased by 10-fold in rabbits in the presence of a carboxylesterase inhibitor (Shi et al., 1988); formation of both glycidol and methacrylic acid during ester cleavage remains to be definitely confirmed.]

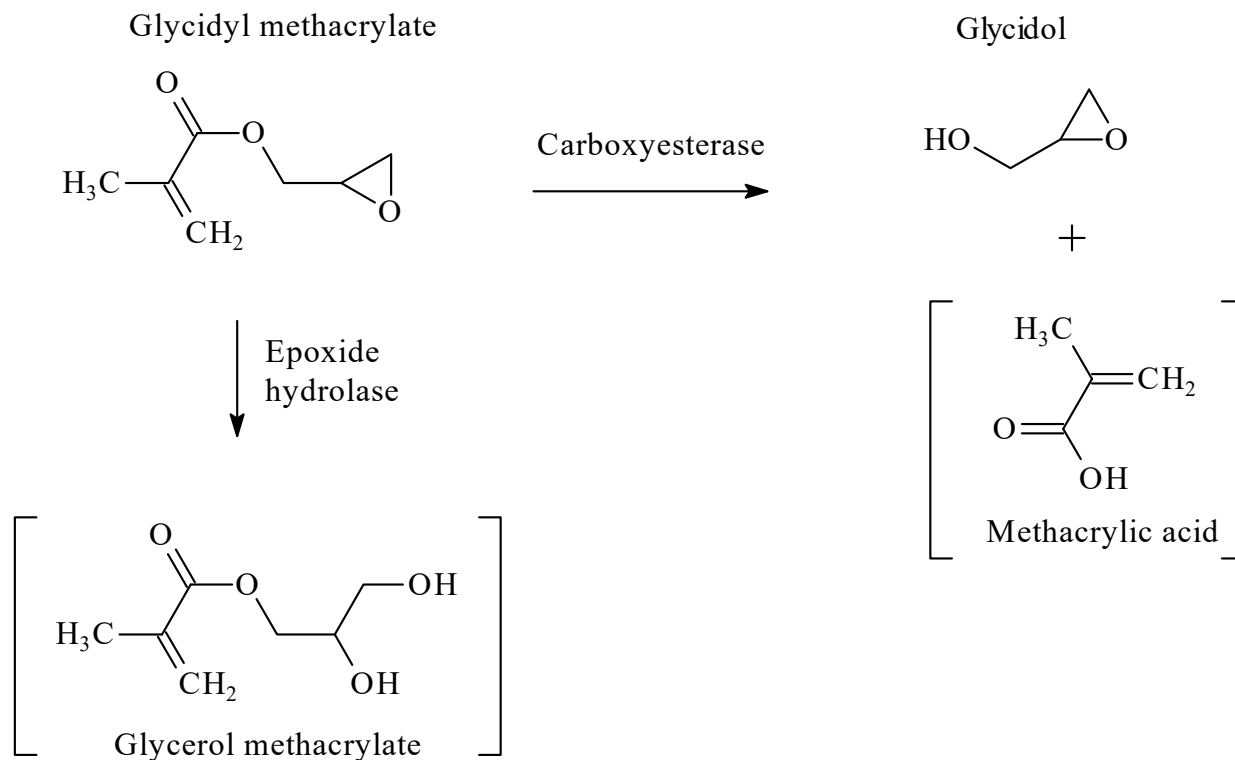
4.1.2 Experimental systems

The intravenous administration of glycidyl methacrylate (200 mg/kg bw) in male rabbits resulted in the elimination of more than 95% of the compound from the rabbit blood within 10 minutes [The Working Group noted the lack

of experimental detail on sample collection]. In male rabbits treated with both glycidyl methacrylate (800 mg/kg bw, subcutaneously) and the carboxylesterase inhibitor tri-*ortho*-cresyl phosphate (100 µg/kg bw), maximum blood levels of glycidyl methacrylate were increased by 10-fold compared with administration of glycidyl methacrylate alone, indicating that glycidyl methacrylate was most probably metabolized by carboxylesterase (Shi et al., 1988). [The Working Group noted that this study reported on first-order kinetics of the parent compound; no metabolites were specifically measured.]

First-order elimination of glycidyl methacrylate occurred in rabbit blood, plasma, and tissue homogenates, with half-lives of 4.6–22.2 minutes. Liver homogenate eliminated glycidyl methacrylate most effectively. Co-incubation of blood and plasma with glycidyl methacrylate and tri-*ortho*-cresyl phosphate (0.1 mM) decreased the elimination rate of glycidyl methacrylate by several fold. The microsomal fraction of the rabbit liver homogenate eliminated glycidyl methacrylate faster than the mitochondrial and supernatant fractions. Co-incubation with tri-*ortho*-cresyl phosphate decreased the glycidyl methacrylate elimination rate in the supernatant, but not in the microsomes, indicating the role of microsomal oxidases in the biotransformation of glycidyl methacrylate (Shi et al., 1988).

The metabolism of [¹⁴C]glycidyl methacrylate (2 mM) was investigated using liver homogenates and nasal epithelial tissues from Fischer 344 (F344) rats and New Zealand rabbits (ECHA, 2015b). The half-life of glycidyl methacrylate hydrolysis in liver homogenates was faster in tissues from rats and rabbits (30 minutes) than in those from humans (2 hours). In the course of this study, the concentration of a single metabolite that was formed was mass balanced with the concentration of glycidyl methacrylate. This metabolite was identified as glycidol based on retention time match with [¹⁴C]glycidol

Fig. 4.1 Proposed metabolic pathways for glycidyl methacrylate in mammals

Two metabolic pathways have been proposed, one mediated by carboxyesterase and a second mediated by epoxide hydrolase. [The Working Group noted that metabolites other than glycidol (see Working Group comment in Section 4.1.1) are putative.] Adapted with permission from [ECHA \(2015a\)](#). CLH report proposal for 2,3-epoxypropyl methacrylate (glycidyl methacrylate, GMA).

[see Working Group comment above, Section 4.1.1(b)].

Glycidyl methacrylate is likely to penetrate the skin *in vivo* given that the median lethal dose (LD₅₀) values for dermal exposure (480 mg/kg bw in rabbits) are in the same range as the LD₅₀ values for oral and intraperitoneal administration (290–1050 mg/kg bw in various studies in mice, rats, and guinea-pigs) ([ECHA, 2015a](#)).

A proposed metabolic scheme for glycidyl methacrylate is presented in [Fig. 4.1](#).

4.2 Evidence relevant to key characteristics of carcinogens

This section summarizes the evidence for the key characteristics of carcinogens ([Smith et al., 2016](#)), including whether glycidyl methacrylate is electrophilic or can be metabolically activated to an electrophile; is genotoxic; alters cell proliferation, cell death, or nutrient supply; induces epigenetic alterations; induces oxidative stress; or causes immortalization. Insufficient data were available for the evaluation of other key characteristics of carcinogens.

4.2.1 Is electrophilic or can be metabolically activated to an electrophile

No data on DNA adducts in humans or human systems were available.

Glycidyl methacrylate-specific DNA adducts were detected in the kidney, liver, testis and blood of rats treated with glycidyl methacrylate at a dose of 125 or 250 mg/kg bw using a nuclease P1-mediated ³²P-postlabelling method (Fang et al., 1999a; Tan et al., 1999).

Glycidyl methacrylate (62.2 μM) induced a shift in the calf thymus DNA absorbance spectrum, indicating binding of glycidyl methacrylate to DNA (Xie et al., 1990a, 1992). After reaction of glycidyl methacrylate with deoxyadenosine monophosphate (dAMP), deoxycytidine monophosphate (dCMP), deoxyguanosine monophosphate (dGMP), thymidine monophosphate (dTMP), and calf thymus DNA, covalent binding to all except dTMP at N⁶ of adenine or N³ of cytosine was observed, and a main DNA adduct in the reaction of glycidyl methacrylate with calf thymus DNA was N³-methacrylate-2-hydroxypropyl-dCMP (Fang et al., 1999b).

Glycidol, a metabolite of glycidyl methacrylate that has been identified with reasonable certainty, is a reactive epoxide that has been demonstrated to alkylate DNA in several studies in vitro (Hemminki, 1979; Hemminki et al., 1980; Hemminki, 1983; Djurič & Sinsheimer, 1984a, b; Djurič et al., 1986; Segal et al., 1990).

4.2.2 Is genotoxic

Studies on glycidyl methacrylate have been carried out in human cells in vitro, in non-human mammalian cells in vivo, in non-human mammalian cells in vitro, and in non-mammalian systems, as summarized in Table 4.1, Table 4.2, Table 4.3, and Table 4.4, respectively.

(a) Glycidyl methacrylate

(i) Humans

See Table 4.1.

No studies in exposed humans were available to the Working Group.

In several studies in primary human cells in vitro, induction of DNA strand breaks was reported after exposure to glycidyl methacrylate (Xie et al., 1990a; Poplawski et al., 2009; Styllou et al., 2015, 2017). Glycidyl methacrylate induced concentration-dependent increases in DNA double-strand breaks and single-strand breaks in human primary peripheral blood lymphocytes as assessed using neutral and alkaline comet assays (Poplawski et al., 2009). A concentration-dependent increase in the number of foci containing both gamma-H2A histone family member X and tumour protein p53 binding protein 1 (γ-H2AX/53BP1) was seen in primary human gingival fibroblasts (Styllou et al., 2015). This effect was reduced by the antioxidant N-acetylcysteine (Styllou et al., 2017). Glycidyl methacrylate induced unscheduled DNA synthesis in lymphocytes (Xie et al., 1990a).

In cultured human lung fibroblast 2BS cells, glycidyl methacrylate induced a significant, concentration-dependent increase in DNA single-strand breaks, as measured by the alkaline comet assay Yin et al. (2003). The highest tested concentration of glycidyl methacrylate (5 μg/mL [35 μM]) induced significant DNA damage after as little as 1 hour. Glycidyl methacrylate induced a significant and concentration-dependent increase in mutant frequencies in the hypoxanthine-guanine phosphoribosyltransferase (HPRT) gene in the absence of metabolic activation in cultured human lung fibroblasts (Yin et al., 2003). In transformed lung fibroblasts, mutations were observed in the TP53 gene (Tan et al., 1996) and the migration of the TP53 exon 8 amplicons was altered in the absence, but not presence, of metabolic activation (Tan et al., 1997). Glycidyl methacrylate induced phenotype

Table 4.1 Genetic and related effects of glycidyl methacrylate in human cells in vitro

End-point	Tissue, cell line	Results ^a		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
Unscheduled DNA synthesis	Human lymphocytes (primary)	+	NT	5.2 mM [739 µg/mL] GMA and hydroxyurea	Purity is described as refractive index, $n_D^{30} = 1.4494$	Xie et al. (1990a)
DNA strand breaks (alkaline or neutral comet assay)	Lymphocytes (primary)	+	NT	0.3 mM [42.5 µg/mL]	Purity, NR	Poplawski et al. (2009)
DNA strand breaks (pulse- field electrophoresis)	Lymphocytes (primary)	+	NT	1.2 mM [224 µg/mL]	Purity, NR	Poplawski et al. (2009)
DNA strand breaks, γ-H2AX/53BP1 foci)	Gingival fibroblasts (primary)	+	NT	0.012 mM [1.7 µg/mL]	Purity, NR	Styllou et al. (2015)
DNA strand breaks (alkaline comet assay)	Lung fibroblast	+	NT	0.5 µg/mL [0.0035 mM]		Yin et al. (2003)
Gene mutation, <i>HPRT</i> locus	Lung fibroblast	+	NT	1.0 µg /mL [0.007 mM]		Yin et al. (2003)
Mutation of DNA repair genes (<i>XRCC1</i> , <i>hMSH2</i> , <i>XPB</i> , <i>XRCC3</i>)	Human bronchial epithelial cells, 16HBE	+	NT	8 µg/mL [0.06 mM]	Single dose tested Cytotoxicity, NR	Dong et al. (2009)
Mutation of <i>TP53</i> gene	Human embryonic lung fibroblasts (cell line)	+	NT	8 µg/mL [0.06 mM]	Purity, NR Single dose tested Cytotoxicity, NR	Tan et al. (1996)
Chromosomal aberrations	Human embryonic lung fibroblasts (cell line)	+	NT	1 µg/mL [0.007 mM]	Purity, NR Cytotoxicity, NR	Tan et al. (1998)
Chromosomal aberrations	Human bronchial epithelial cell line, 16HBE	+	NT	Single exposure: 16 µg/mL [0.11 mM]		Wang et al. (2011)
		+	NT	Three rounds of exposure, 8 µg/mL		

53BP1, P53 binding protein 1; GMA, glycidyl methacrylate; γ-H2AX, gamma-histone 2AX; HIC, highest ineffective concentration; *HPRT*, hypoxanthine-guanine phosphoribosyltransferase; LEC, lowest effective concentration; NR, not reported; NT, not tested.

^a +, positive.

Table 4.2 Genetic and related effects of glycidyl methacrylate in non-human mammals in vivo

End-point	Species, strain, (sex)	Tissue	Results ^a	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
Glycidyl methacrylate -DNA adducts	Rat, Wistar (M)	Kidney, liver, leukocytes, and testis	+	31.25 mg/kg bw per day	Gavage, 2 wk, 4× doses	Source and purity, NR	Tan et al. (1999) ; Fang et al. (1999a)
Unscheduled DNA synthesis	Mouse, Kunming hybrid strain (M)	Sperm cells	+	25 mg/kg bw per day	Intraperitoneal injection, 1×, killed 35 days after treatment	Purity is described as refractive index $n_D^{30} = 1.4494$ Magnitude of effect did not increase with increasing dose	Xie et al. (1990a)
DNA strand breaks, alkaline elution assay	Rat, Fischer 344 (M)	Liver, kidney, bone marrow	+	LED, 100 mg/kg bw per day (29 days, bone marrow and liver); HID, 150 mg/kg per day (29 days, kidney); LED, 250 mg/kg bw per day (3 days, bone marrow, liver, and kidney)	Gavage, 29 days or 3 days		Dobrovolsky et al. (2016)
Gene mutations by <i>Pig-a</i> assay	Rat, Fischer 344 (M)	Peripheral blood cells, reticulocytes	+	100 mg/kg bw per day (erythrocytes, 56 days), 150 mg/kg bw per day (reticulocytes, 15, 29, and 56 days)	Gavage, 15 or 29 days		Dobrovolsky et al. (2016)
Micronucleus formation	Rat, Fischer 344 (M)	Peripheral blood cells, reticulocytes	+	150 mg/kg bw per day	Gavage, 4 days		Dobrovolsky et al. (2016)
Micronucleus formation	Mouse, Kunming strain (M)	Polychromatic erythrocytes in bone marrow	+	25 mg/kg bw per day	Intraperitoneal injection; 2×, 24 h interval	Statistical test did not correct for multiple comparisons	Ouyang et al. (1988)

bw, body weight; h, hour; HID, highest ineffective dose; LED, lowest effective dose; M, male; NR, not reported; *Pig-a*, glycosylphosphatidyl inositol class A gene; wk, week.

^a+, positive.

Table 4.3 Genetic and related effects of glycidyl methacrylate in non-human mammals in vitro

End-point	Species, tissue, cell line	Results ^a		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
Unscheduled DNA synthesis	Rat (strain and sex, NR), lymphocytes	+	NT	1300 µM [185 µg/mL]	Purity is described as refractive index $n_D^{30} = 1.4494$ Cytotoxicity, NR	Xie et al. (1990a)
Gene mutation, <i>Hprt</i> locus	Chinese hamster lung fibroblast cells, V79	+	-	-S9: 100 µM [14 µg/mL] (24 h), 200 µM [28 µg/mL] (4 h) +S9: 300 µM [42.5 µg/mL] (4 h)	Purity, NR	Schweikl et al. (1998)
Mutation frequency	Mouse, embryonic fibroblasts, BALB/c 3T3 cells	+	NT	64 µg/mL	Purity, NR Cytotoxicity, NR	Lei et al. (1998c)
Micronucleus formation	Chinese hamster lung fibroblast cells, V79	+	-	-S9: 200 µM [28 µg/mL] (4 h), 100 µM [14 µg/mL] (24 h) +S9: 500 µM [71 µg/mL] (4 h)		Schweikl et al. (2001)
Micronucleus formation	Chinese hamster lung fibroblast cells, V79	+	NT	100 µM [14 µg/mL]		Lee et al. (2006)
Sister-chromatid exchange	Chinese hamster lung fibroblast cells, V79	+	NT	78 µM [11 µg/mL]		von der Hude et al. (1991)

h, hour; HIC, highest ineffective concentration; LEC, lowest effective concentration; NR, not reported; NT, not tested; S9, 9000 × g supernatant.

^a +, positive; -, negative.

Table 4.4 Genetic and related effects of glycidyl methacrylate in non-mammalian systems

Test system (species, strain)	End-point	Results ^a		Concentration (LEC or HIC)	Comments on study quality	Reference
		Without metabolic activation	With metabolic activation			
<i>Salmonella typhimurium</i> TA100	Reverse mutation	+	+	250 µg/plate	Purity, NR	Schweikl et al. (1998)
<i>Salmonella typhimurium</i> TA100	Reverse mutation	+	+	112 µg/plate	Source, NR Purity, 92% Cytotoxicity, NR	Ouyang et al. (1988)
<i>Salmonella typhimurium</i> TA98	Reverse mutation	-	-	5000 µg/plate	Purity, NR	Schweikl et al. (1998)
<i>Salmonella typhimurium</i> TA98	Reverse mutation	-	-	NR		Canter et al. (1986)
<i>Salmonella typhimurium</i> TA98	Reverse mutation	-	-	896 µg/plate	Source, NR Purity, 92% Cytotoxicity, NR	Ouyang et al. (1988)
<i>Salmonella typhimurium</i> TA97a, TA102	Reverse mutation	+/-	+/-	250 µg/plate (TA97a) 500 µg/plate (TA102)	Purity, NR	Schweikl et al. (1998)
<i>Salmonella typhimurium</i> TA97, 100, 1535	Reverse mutation	+	+	33 µg/plate for TA100 and TA1535 NR for TA97		Canter et al. (1986)
<i>Klebsiella pneumoniae</i>	Mutation	+	NT	1 mM [142 µg/plate]	Purity, 92% Cytotoxicity, NR	Voogd et al. (1981)
<i>Escherichia coli</i> PQ37 SOS chromotest	DNA damage	+	NT	0.3 mM [43 µg/plate]	Purity, 97%	von der Hude et al. (1990)

HIC, highest ineffective concentration; LEC, lowest effective concentration; NR, not reported; NT, not tested.

^a +, positive; -, negative; +/-, equivocal.

transformation and chromosomal aberrations in cultured embryonic lung fibroblasts ([Tan et al., 1998](#)). Chromosomal aberrations were detected in cultured bronchial epithelial cells treated with glycidyl methacrylate ([Wang et al., 2011](#)).

(ii) *Experimental systems*

Non-human mammals in vivo

See [Table 4.2](#).

In male F344 rats, oral exposure to glycidyl methacrylate induced a dose-dependent increase in the percentage of tail DNA in bone marrow, liver, and kidney cells, as measured by the alkaline comet assay, and in gene mutation in erythrocytes and reticulocytes as measured by *Pig-a* assay ([Dobrovolsky et al., 2016](#)). Glycidyl methacrylate increased micronucleus formation in erythrocytes from peripheral blood in male F344 rats treated orally with a dose of 150 mg/kg bw per day for 4 days, and in polychromatic erythrocytes in bone marrow of male Kunming hybrid mice exposed to glycidyl methacrylate as two doses of 25 mg/kg bw per day by intraperitoneal injection at an interval of 24 hours ([Ouyang et al., 1988](#); [Dobrovolsky et al., 2016](#)).

Unscheduled DNA synthesis was increased in the sperm of male Kunming hybrid mice 35 days after being exposed to glycidyl methacrylate at a dose of 25 mg/kg bw per day or higher as a single intraperitoneal injection ([Xie et al., 1990a](#)). [The Working Group noted that the magnitude of the effect did not increase with increasing dose.]

Non-human mammalian cells in vitro

See [Table 4.3](#).

Glycidyl methacrylate induced unscheduled DNA synthesis and semi-conservative DNA replication in rat lymphocytes ([Xie et al., 1990a](#)). Glycidyl methacrylate induced a concentration-dependent increase in hypoxanthine-guanine phosphoribosyltransferase (*Hprt*) mutation in V79 Chinese hamster lung fibroblast cells, an effect completely abolished by the addition of rat liver S9 microsomal fraction ([Schweikl et al.,](#)

[1998](#)). Glycidyl methacrylate induced a concentration-dependent increase in the frequencies of sister-chromatid exchange in Chinese hamster V79 cells ([von der Hude et al., 1991](#)). [Schweikl et al. \(2001\)](#) reported a dose-related increase in the frequencies of micronucleus formation in V79 Chinese hamster lung fibroblast cells exposed to glycidyl methacrylate (for 24 hours at 100, 150, or 200 μ M or for 4 hours at 200, 300, 400, or 500 μ M). The 24-hour exposure effects were reproduced by [Lee et al. \(2006\)](#). The effects disappeared in the presence of rat liver S9 microsomal fraction (only 4-hour exposure tested) ([Schweikl et al., 2001](#)).

Non-mammalian experimental systems

See [Table 4.4](#).

Glycidyl methacrylate induced reverse mutations in *Salmonella typhimurium* strains TA97, TA100, TA1535, and TA102, but not TA98, both in the presence and in the absence of a rat liver S9 microsomal fraction ([Canter et al., 1986](#); [Ouyang et al., 1988](#); [Schweikl et al., 1998](#)). Glycidyl methacrylate was also mutagenic in *Klebsiella pneumoniae* ([Voogd et al., 1981](#)). Glycidyl methacrylate induced DNA damage in the SOS chromotest using *Escherichia coli* PQ37 ([von der Hude et al., 1990](#)).

Acellular systems

Glycidyl methacrylate did not introduce DNA breaks to isolated DNA, as assessed by the plasmid relaxation assay using pUC19 plasmids isolated from *E. coli* ([Poplawski et al., 2009](#)). *E. coli* HB101 transfected with glycidyl methacrylate-bound pBR322 was transformed to two stable and heritable mutants, from one of which deletion and insertion were detected in hot-spot regions ([Xie et al., 1990b](#); [Fang, 1991](#); [Zuo et al., 1991](#); [Zuo, 1991](#); [Gao et al., 1994a, b](#)).

(b) *Glycidol*

See [Table 4.5](#), [Table 4.6](#), [Table 4.7](#), and [Table 4.8](#).

Table 4.5 Genetic and related effects of glycidol in human cells in vitro

End-point	Tissue, cell line	Results ^a		Concentration (LEC or HIC)	Reference
		Without metabolic activation	With metabolic activation		
Unscheduled DNA synthesis	WI-38 cells	–	+	0.33 µg/mL	Thompson et al. (1981)
Chromosomal aberrations	Lymphocytes (primary)	+	NT	29.6 µg/mL	Norppa et al. (1981)
Sister-chromatid exchange	Lymphocytes (primary)	+	NT	3.7 µg/mL	Norppa et al. (1981)

HID, highest ineffective dose; LED, lowest effective dose; NT, not tested.

^a +, positive; –, negative.

Table 4.6 Genetic and related effects of glycidol in non-human mammals in vivo

End-point	Species, strain (sex)	Tissue	Results ^a	Dose (LED or HID)	Route, duration, dosing regimen	Reference
Chromosomal aberrations	Rats, Sprague-Dawley (F)	Bone marrow	–	226 mg/kg bw per day	Oral × 5	Thompson & Hiles (1981)
Chromosomal aberrations	Rats, Sprague-Dawley (F)	Bone marrow	–	145 mg/kg bw per day	Intraperitoneal × 5	Thompson & Hiles (1981)
Micronucleus formation	Mouse, B6C3F ₁ (M)	Polychromatic erythrocytes	+	37.5 mg/kg bw per day	Intraperitoneal × 2	NTP (1990)
Micronucleus frequency	Mouse, BalbC (M)	Polychromatic erythrocytes	+	120 mg/kg bw	Intraperitoneal × 1	Aasa et al. (2017)

bw, body weight; F, female; HID, highest ineffective dose; LED, lowest effective dose; M, male.

^a +, positive; –, negative.

Table 4.7 Genetic and related effects of glycidol in non-human mammals in vitro

End-point	Species, tissue, cell line	Results ^a		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
DNA damage (alkaline comet assay)	Chinese hamster ovary cells	+	NT	20 µg/mL	Purity, NR	El Ramy et al. (2007)
Gene mutation, <i>Tk</i> locus	L5178Y mouse, lymphoma cells	+	+	8 µg/mL		Thompson et al. (1981)
Gene mutation, <i>Tk</i> locus	L5178Y mouse, lymphoma cells	+	NT	1.43 µg/mL		NTP (1990)
Gene mutation, <i>Hprt</i> locus	Chinese hamster ovary cells	+	NT	50 mM ^b [3.7 µg/mL]		Aasa et al. (2016)
Gene mutation, 6-thioguanine resistance	Chinese hamster lung V79 cells	+	NT	0.15 µg/mL		Smith et al. (1990)
Chromosomal aberrations	Chinese hamster cells	+	+	12.5 µg/mL		NTP (1990)
Sister-chromatid exchange	Chinese hamster cells	+	+	1.11 µg/mL		NTP (1990)
Sister-chromatid exchange	Chinese hamster V79 cells	+	NT	92.6 µg/mL		von der Hude et al. (1991)

HIC, highest ineffective concentration; LEC, lowest effective concentration; NR, not reported; NT, not tested.

^a +, positive.

^b Value of LEC was not provided by the authors, but was estimated from the relevant figure in the publication.

Table 4.8 Genetic and related effects of glycidol in non-mammalian systems

Test system (species, strain)	End-point	Results ^a		Concentration (LEC or HIC)	Reference
		Without metabolic activation	With metabolic activation		
<i>Drosophila melanogaster</i>	Sex-linked recessive lethal mutations, heritable translocation test	+	NA	1230 ppm in feed	Fouremant et al. (1994)
<i>Neurospora crassa</i>	Reverse mutation	+	NT	37 000 ^b µg/mL (15 min)	Kølmark & Giles (1955)
<i>Schizosaccharomyces pombe</i>	Forward mutation	+	+	74 µg/mL	Migliore et al. (1982)
<i>Klebsiella pneumoniae</i>	Forward mutation	+	NT	14.8 µg/mL	Voogd et al. (1981)
<i>Salmonella typhimurium</i> TA1535	Reverse mutation	+	+	20.6 µg/plate	Thompson et al. (1981)
<i>Salmonella typhimurium</i> TA1535	Reverse mutation	+	+	500 µg/plate	Mamber et al. (1984)
<i>Salmonella typhimurium</i> TA1535	Reverse mutation	+	+	3 µg/plate	Canter et al. (1986)
<i>Salmonella typhimurium</i> TA1535	Reverse mutation	+	+	1 µg/plate	NTP (1990)
<i>Salmonella typhimurium</i> TA100	Reverse mutation	+	NT	100 µg/plate	Wade et al. (1979)
<i>Salmonella typhimurium</i> TA100	Reverse mutation	+	+	61.7 µg/plate	Thompson et al. (1981)
<i>Salmonella typhimurium</i> TA100	Reverse mutation	+	+	33 µg/plate	Canter et al. (1986)
<i>Salmonella typhimurium</i> TA100	Reverse mutation	+	NT	25 µg/plate	Claxton et al. (1991)
<i>Salmonella typhimurium</i> TA100	Reverse mutation	+	+	125 µg/plate	De Flora (1979)
<i>Salmonella typhimurium</i> TA100	Reverse mutation	+	+	100 µg/plate	NTP (1990)
<i>Salmonella typhimurium</i> TA98	Reverse mutation (spot test)	-	NT	10 000 µg/plate	Wade et al. (1979)
<i>Salmonella typhimurium</i> TA98	Reverse mutation	+	+	3333 µg/plate	NTP (1990)
<i>Salmonella typhimurium</i> TA1537	Reverse mutation	+ ^w	+	1670 µg/plate	NTP (1990)
<i>Salmonella typhimurium</i> TA97	Reverse mutation	+	+	NR	Canter et al. (1986)

Table 4.8 (continued)

Test system (species, strain)	End-point	Results ^a		Concentration (LEC or HIC)	Reference
		Without metabolic activation	With metabolic activation		
<i>Salmonella typhimurium</i> TA97	Reverse mutation	+	+	1000 µg/plate	NTP (1990)
<i>Escherichia coli</i> (Sd-4)	Reverse mutation	+	NT	740 µg/mL	Hussain & Osterman-Golkar (1984)
<i>Escherichia coli</i> PQ37 SOS chromotest	DNA strand breaks, cross-links or related damage	+	NT	244.5 µg/mL	von der Hude et al. (1990)
<i>Escherichia coli</i> , rec assay	Differential toxicity	+	NT	NR	Mamber et al. (1984)
Prophage induction, SOS repair test	DNA strand breaks, cross-links or related damage	-	NT	500 µg/plate	Mamber et al. (1984)

HIC, highest ineffective concentration; LEC, lowest effective concentration; NA, not applicable; NT, not tested.

^a +, positive; -, negative; +^w, weakly positive.

^b One dose tested; time-dependent response.

(i) Humans

No data on exposed humans were available to the Working Group.

Glycidol induced chromosomal aberrations and sister-chromatid exchange in primary human lymphocytes in the absence of metabolic activation ([Norppa et al., 1981](#)), while unscheduled DNA synthesis was induced in human fibroblast WI-38 cells only in the presence of metabolic activation ([Thompson et al., 1981](#)).

(ii) Experimental systems

Glycidol induced the formation of micronuclei in male mice B6C3F₁ and BalbC mice after intraperitoneal administration ([NTP, 1990](#); [Aasa et al., 2017](#)). It was without effect on chromosomal aberrations in rats after oral or intraperitoneal treatment ([Thompson & Hiles, 1981](#)).

Tests performed in experimental systems in vitro gave consistently positive results. Glycidol induced DNA damage in the alkaline comet assay in Chinese hamster ovary cells ([El Ramy et al., 2007](#)). Glycidol induced *Tk* gene mutation in mouse lymphoma L5178Y cells ([Thompson et al., 1981](#); [NTP, 1990](#)), *Hprt* gene mutation in Chinese hamster ovary cells ([Aasa et al., 2016](#)), and gave positive results in the 6-thioguanine resistance test in Chinese hamster lung V79 cells ([Smith et al., 1990](#)). Glycidol also induced chromosomal aberrations and sister-chromatid exchange in Chinese hamster cells ([NTP, 1990](#); [von der Hude et al., 1991](#)).

Glycidol gave uniformly positive results in several assays for reverse mutation in *S. typhimurium* ([De Flora, 1979](#); [Wade et al., 1979](#); [Thompson et al., 1981](#); [Mamber et al., 1984](#); [Canter et al., 1986](#); [NTP, 1990](#); [Claxton et al., 1991](#)) and in two assays for mutation in fungi ([Kølmær & Giles, 1955](#); [Migliore et al., 1982](#)). Glycidol was also mutagenic in *K. pneumoniae* ([Voogd et al., 1981](#)) and in *E. coli* ([Hussain & Osterman-Golkar, 1984](#)). Glycidol gave positive results in the assay for sex-linked recessive lethal mutation and in the heritable translocation test

in *Drosophila melanogaster* ([Fouremant et al., 1994](#)). Glycidol gave positive results in the *E. coli* PQ37 SOS chromotest, and negative results in the prophage-induction SOS repair test ([Mamber et al., 1984](#); [von der Hude et al., 1990](#)).

4.2.3 Alters cell proliferation, cell death, or nutrient supply

In B6D2F₁/Crlj mice exposed to glycidyl methacrylate by inhalation for 104 weeks, increases in transitional cell hyperplasia of the nasal cavity were reported in males and females ([JBRC, 2015a](#)).

In F344/DuCrjCrlj rats exposed to glycidyl methacrylate by inhalation for 104 weeks, non-neoplastic lesions in the nasal cavity (squamous cell hyperplasia with atypia, squamous cell metaplasia in respiratory epithelium, and squamous cell metaplasia with atypia) and transitional cell hyperplasia were reported in males and females ([JBRC, 2015b](#)).

Gap-junctional intercellular communication, as measured by the scrape-loading/dye-transfer technique, was significantly inhibited in transformed human lung fibroblast cells treated with glycidyl methacrylate (2.5 or 5 µg/mL) ([Yin et al., 2003](#)).

4.2.4 Induces oxidative stress

Glycidyl methacrylate induced oxidative damage to DNA in primary human lymphocytes as assessed with the alkaline comet assay using the DNA repair enzymes endonuclease III (Endo III) and formamidopyrimidine-DNA glycosylase (Fpg) ([Poplawski et al., 2009](#)). The antioxidant *N*-acetylcysteine reduced the glycidyl methacrylate-induced double-strand breaks and nuclear chromatin condensation in primary human gingiva fibroblasts ([Styllou et al., 2017](#)). *N*-acetylcysteine reduced the frequency of micronucleus formation induced by glycidyl methacrylate in Chinese hamster lung fibroblast

V79 cells ([Lee et al., 2006](#)) (see Section 4.2.2(a) (ii)).

4.2.5 Evidence on other key characteristics of carcinogens

Glycidyl methacrylate (8.0 µg/mL [0.06 mM]) induced cell transformation of human lung fibroblasts ([Yin et al., 2003](#)). In addition, glycidyl methacrylate induced cell transformation of BALB/c mouse embryonic fibroblasts 3T3 cells or Golden Syrian hamster embryonic SHE cells in several studies ([Xu et al., 1994](#); [Yang et al., 1996](#); [Zhang et al., 1996](#); [Lei et al., 1998a, b](#)).

In a series of studies, glycidyl methacrylate induced malignant transformation and methylation of the promoter regions or overexpression of several genes in human bronchial epithelial cells or embryonic lung fibroblast ([Tan et al., 1998](#); [Xu et al., 2001](#); [Dong et al., 2009](#); [Yang et al., 2009](#); [Dong et al., 2010](#); [Hu et al., 2012](#)). Glycidyl methacrylate (8 µg/mL) induced changes in DNA methylation in stages of malignant transformation, as detected by a CpG (cytosine–phosphate–guanine) promoter methylation microarray ([Wang et al., 2014](#)), including of the opioid binding protein/cell adhesion molecule-like (*OPCML*) gene ([Liu et al., 2015](#)) in cultured human bronchial epithelial cells (16HBE).

Methylation of the *P16* [*CDKN2A*] gene promoter was detected at the early stage and prophase stage in the process of malignant transformation of human bronchial epithelial cells exposed to glycidyl methacrylate ([Hu et al., 2012](#)).

4.3 Data relevant to comparisons across agents and end-points

The analysis of the bioactivity in vitro of the agents reviewed in *IARC Monographs* Volume 125 was informed by data from high-throughput screening assays generated by the Toxicity Testing in the 21st Century (Tox21) and Toxicity

Forecaster (ToxCast) research programmes of the Government of the USA ([Thomas et al., 2018](#)). Glycidyl methacrylate was one of thousands of chemicals tested across the large assay battery of the Tox21 and ToxCast research programmes as of 1 September 2019 ([US EPA, 2019a](#)). Detailed information about the chemicals tested, assays used, and associated procedures for data analysis is publicly available ([US EPA, 2019a](#)). [The Working Group noted that the metabolic capacity of the cell-based assays is variable, and generally limited, as acknowledged in [Kavlock et al. \(2012\)](#).]

Among the 402 assays in which glycidyl methacrylate (at concentrations up to 100 µM) was tested, it was found to be inactive in almost all assays. Active responses were observed in 8 assays ([US EPA, 2019a](#)). Effect on upregulation of nuclear factor erythroid 2-related factor 2 (NRF2) was reported at a half-maximal activity concentration (AC_{50}) of 38 µM. For nuclear receptors, borderline activity (potency of > 50% or activity observed only at the highest concentration tested) was found for the mouse embryonic cell-based assay (SSH_3T3_GLI3) at an AC_{50} of 82 µM. For cell viability, glycidyl methacrylate was shown to be cytotoxic only in human T47D, HEK293, and HEPG2 cells at AC_{50} s of 0.45–83 µM.

Glycidol was also tested (at concentrations up to 100 µM) in 673 assays and found to be inactive in almost all assays. Active responses were observed in 16 assays ([US EPA, 2019b](#)). Effects were observed in the form of TIMP metalloproteinase inhibitor 1 downregulation, retinoid X receptor α agonism and androgen receptor antagonism at concentrations between 10 and 38.9 µM. These were noted as borderline effects (< 50% efficacy, only highest concentration above baseline). For cell viability, glycidol was shown to be cytotoxic only in human HEK293 and HEPG2 cells at AC_{50} s of 33.6–65.5 µM.

5. Summary of Data Reported

5.1 Exposure characterization

Glycidyl methacrylate is a High Production Volume chemical that is mainly used as an intermediate in the production of epoxy polymers and vinyl and acrylic resins. These polymers are used in dental sealants, composites and adhesives; bone composite materials; powder coatings; and hydrogel lenses. There are emerging applications for the polymers in medical imaging and targeting drug delivery. Polymers formed of glycidyl methacrylate can also be used in food contact material. Occupational exposures by inhalation and dermal contact have been reported for chemical-production workers in a single study. Occupational exposure when preparing the dental and bone materials or exposure to patients receiving these materials may potentially occur, but has not been targeted for measurement. Exposure in the general population is not expected from use of the polymerized products.

5.2 Cancer in humans

No data were available to the Working Group.

5.3 Cancer in experimental animals

Glycidyl methacrylate was tested for carcinogenicity in one strain of male and female mice in one inhalation study, and in two different strains of male and female rats, respectively, in two inhalation studies, and one gavage study.

The inhalation study in mice was well-conducted under good laboratory practice, and resulted in a significant positive trend and increase in the incidence of haemangioma of the nasal cavity and of haemangioma or haemangiosarcoma (combined) of the nasal cavity in males and females, and of nasal cavity

haemangiosarcoma in males and females (positive trend only for females). In female mice, there was a significant positive trend and increase in the incidence of bronchioalveolar carcinoma. There was also a significant positive trend in the incidence of uterine histiocytic sarcoma, and adenoma of the Harderian gland in female mice. There was a significant positive trend in the incidence of adenoma of the nasal cavity, squamous cell papilloma of the forestomach, and adenoma of the Harderian gland in male mice.

One inhalation study in male and female rats was well-conducted under good laboratory practice. In male and female rats, exposure to glycidyl methacrylate resulted in a significant positive trend and increase in the incidence of squamous cell carcinoma of the nasal cavity. In male rats, there was a significant positive trend and increase in the incidence of esthesioneuroepithelioma (neuroepithelial carcinoma) of the nasal cavity, and a significant increase in the incidence of adenoma of the nasal cavity. In male rats, there was also a significant positive trend and increase in the incidence of peritoneal mesothelioma and subcutis fibroma; significant positive trends in the incidence of skin basal cell epithelioma and skin keratoacanthoma were also observed. In female rats, exposure to glycidyl methacrylate resulted in a significant positive trend and increase in the incidence of fibroadenoma of the mammary gland; significant positive trends in the incidence of uterine endometrial stromal sarcoma, subcutis fibroma, thyroid C-cell adenoma, and adenoma of the clitoral gland were also observed.

The other inhalation study in rats gave negative results.

The study in male and female rats treated by gavage was inadequate for the evaluation of the carcinogenicity of glycidyl methacrylate in experimental animals.

5.4 Mechanistic evidence

No data on the absorption, distribution, metabolism or excretion of glycidyl methacrylate in exposed humans were available. No direct data on the absorption or excretion of glycidyl methacrylate were available from mammalian species. Indirect evidence of dermal and oral absorption is provided by tests for acute toxicity in various rodent species, which suggest that dermal absorption of glycidyl methacrylate is likely to be as efficient as oral absorption. In one study in rabbits, a carboxyesterase inhibitor markedly reduced the decline of glycidyl methacrylate in the blood. Studies *in vitro* in human, rabbit, and rat tissue homogenates showed the formation over time of a metabolite that was reasonably identified as glycidol.

There is consistent and coherent evidence that glycidyl methacrylate exhibits key characteristics of carcinogens (is genotoxic) in human primary cells. In all available studies in human primary cells, glycidyl methacrylate induced DNA damage, including double-strand breaks and unscheduled DNA synthesis. In different cultured human cell lines, consistent findings of various types of damage to DNA, including DNA strand breaks, gene mutations, and chromosomal aberrations were seen. In two studies in orally exposed rats, glycidyl methacrylate induced various types of damage to DNA, including strand breaks, gene mutations, and micronucleus formation. After intraperitoneal administration in mice, glycidyl methacrylate induced micronucleus formation and unscheduled DNA synthesis in two studies. In several studies in rodent cells *in vitro*, glycidyl methacrylate induced *Hprt* gene mutation, micronucleus formation, sister-chromatid exchanges, and unscheduled DNA synthesis; the effects were abolished by metabolic activation in the available tests. In addition, glycidyl methacrylate gave generally positive results in tests for base-pair substitution mutation in bacteria, both in

the presence and in the absence of metabolic activation. Glycidyl methacrylate–DNA lesions in plasmid DNA yielded stable and heritable mutations.

Glycidol caused DNA damage, chromosomal aberrations, and sister-chromatid exchange in one study in human primary cells *in vitro*, and increased micronucleus formation in mice after intraperitoneal administration, but not chromosomal aberrations in rats after intraperitoneal or oral administration. Glycidol gave consistently positive results in a substantial number of genotoxicity assays *in vitro*. Glycidol gave positive results both in rodent cells, covering a range of end-points such as DNA damage, gene mutation and chromosomal aberrations, and in mutation tests in bacteria.

In experimental systems, there were consistent and coherent findings in male and female rats and mice exposed chronically by inhalation that glycidyl methacrylate alters cell proliferation, cell death, or nutrient supply. Glycidyl methacrylate induced a dose-related increase in the incidence of transitional cell hyperplasia of the nasal cavity in both sexes of mice and rats, and in squamous cell hyperplasia with atypia, squamous cell metaplasia in respiratory epithelium, and squamous cell metaplasia with atypia in male and female rats.

There is suggestive evidence that glycidyl methacrylate is electrophilic, based on the formation of DNA adducts in tissues of exposed rats and when glycidyl methacrylate was added to DNA or DNA bases, in the few available studies. In addition, glycidol is electrophilic. Glycidol is a reactive epoxide that alkylates DNA *in vitro*. There is also suggestive evidence from a narrow range of experiments in human and mammalian cells *in vitro* that glycidyl methacrylate induces oxidative stress or causes immortalization. Glycidyl methacrylate induced oxidative damage to DNA, and the antioxidant *N*-acetylcysteine reduced the effect of glycidyl methacrylate on several genotoxic end-points in human and

rodent cells. Glycidyl methacrylate also induced cell transformation in human and rodent cells in vitro.

Glycidyl methacrylate and glycidol were found to be mostly without effects in the assay battery of the Toxicity Testing in the 21st Century (Tox21) and Toxicity Forecaster (ToxCast) research programmes.

Overall, the mechanistic evidence is consistent and coherent that glycidyl methacrylate belongs, on the basis of mechanistic considerations, to a class of reactive glycidyl epoxides, for which one member has been classified as probably carcinogenic to humans. Glycidyl methacrylate bears structural similarity to other glycidyl epoxides, and there is close concordance with glycidol with respect to the genotoxicity profile as well as the tumour-site profile in chronic animal bioassays.

6. Evaluation and Rationale

6.1 Cancer in humans

There is *inadequate evidence* in humans regarding the carcinogenicity of glycidyl methacrylate.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of glycidyl methacrylate.

6.3 Mechanistic evidence

There is *strong evidence* that glycidyl methacrylate belongs, on the basis of mechanistic considerations, to a class of reactive glycidyl epoxides for which one member, glycidol, has been classified as *probably carcinogenic to humans (Group 2A)*. There is also *strong evidence*

in human primary cells that glycidyl methacrylate exhibits key characteristics of carcinogens.

6.4 Overall evaluation

Glycidyl methacrylate is *probably carcinogenic to humans (Group 2A)*.

6.5 Rationale

The Group 2A evaluation for glycidyl methacrylate is based on *sufficient evidence* of cancer in experimental animals and *strong* mechanistic evidence. The evidence regarding cancer in humans was *inadequate* as no data were available. The *sufficient evidence* of carcinogenicity in experimental animals is based on the induction of malignant neoplasms in two species.

There was *strong* mechanistic evidence, based on two distinct topics. There is *strong evidence* that glycidyl methacrylate belongs, based on mechanistic considerations, to a class of reactive glycidyl epoxides for which one member, glycidol, has been classified as *probably carcinogenic to humans*. Glycidyl methacrylate bears structural similarity to other members of this class, and there is close concordance with respect to the genotoxicity profile, and the target organs of carcinogenicity in chronic animal bioassays. There is also *strong evidence* in primary human cells that glycidyl methacrylate exhibits key characteristics of carcinogens; glycidyl methacrylate is genotoxic in all available tests in human primary cells, supported by consistent findings across several different test systems in various species. It also alters cell proliferation, cell death, or nutrient supply in experimental systems.

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