ECHA Scientific report

for evaluation of limit values for 2,3-epoxypropyl methacrylate (glycidyl methacrylate) at the workplace

Prepared by the European Chemicals Agency

8 June 2023

Preamble

The Commission, in view of the preparation of the proposals for amendment of Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens, mutagens or reprotoxic substances at work (CMRD), and in line with the 2017 Commission Communication '*Safer and Healthier Work for All*' - *Modernisation of the EU Occupational Safety and Health Legislation and Policy*[1], asked the advice of RAC to assess the scientific relevance of occupational exposure limits

Therefore, the Commission made a request on 23 February 2022 to ECHA in accordance with the Service Level Agreement (SLA) (Ares(2022)711149), to evaluate, in accordance with the Directive 2004/37/EC, the following substances: 2,3-epoxypropyl methacrylate (glycidyl methacrylate or GMA).

In support of the Commission's request, ECHA has prepared a scientific report concerning occupational limit values for 2,3-epoxypropyl methacrylate (EC number 203-441-9) at the workplace.

In the preparatory phase of making this report, a call for evidence was started on 05 May 2022 to invite interested parties to submit comments and evidence by 01 August 2022.

This scientific report was made available at: Occupational exposure limits-Consultations on OEL recommendation on **26 January 2023** and interested parties were invited to submit comments by **28 March 2023**.

The Committee for Risk Assessment (RAC) will develop its opinion on the basis of the scientific report submitted by ECHA.

---

[1] http://ec.europa.eu/social/main.jsp?langId=en&catId=148&newsId=2709&furtherNews=yes

Table of Contents

Figures

Tables

List of abbreviations

Abbreviation	Definition
ADME	Absorption, distribution, metabolism and excretion
AGS	Ausschuss für Gefahrstoffe (German Committee on Hazardous Substances)
ANSES	Agence Nationale de Sécurité Sanitaire de l'alimentation, de l'environnement et du travail (French Agency for Food, Environmental and Occupational Health & Safety)
ATSDR	Agency for Toxic Substances and Disease Registry, Atlanta, Georgia (USA)
BAuA	Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (German Federal Institute for Occupational Safety and Health)
BGV	Biological Guidance Value
BisGMA	Bisphenol A-glycidyl methacrylate
BLV	Biological Limit Value
BOEL(s)	Binding Occupational Exposure Limit(s)
bw	Body weight
CAD	Chemical Agents Directive 98/24/EC
CAS RN	CAS Registry Number (unique identifier providing an unambiguous means to distinguish chemical substances or molecular structures when there are many possible systematic, generic, proprietary or otherwise trivial names).
CLP	Regulation EC No 1272/2008 on the Classification, Labelling and Packaging of substances and mixtures (CLP Regulation)
CMD / CMRD	Carcinogens and Mutagens Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work.
	The amendment of the CMD, Directive 2022/431/EU also brought reprotoxic substances within the scope of the directive, changing the original title on the protection of workers from the risks related to exposure to carcinogens or mutagens at work to the protection of workers from the risks related to exposure to carcinogens, mutagens or reprotoxic substances at work (CMRD).
CMR	Carcinogens, Mutagens or substances toxic to Reproduction
DEGDA	Diethylene glycol diacrylate
DFG	Deutsche Forschungsgemeinschaft (German Research Foundation)
EC	European Commission
ECHA	European Chemicals Agency
EEA	European Economic Area
EFSA	European Food Safety Authority
EGDMA	Ethylene glycol dimethacrylate
EPA	Environmental Protection Agency
ERR	Exposure-risk relationship
EU	European Union
GC-FID	Gas chromatography with flame ionization detection
GESTIS Substance Database	GEfahrSToffInformationsSystem (German information system for the safe handling of hazardous substances and other chemical substances at work)
GLP	Good Laboratory Practice

Abbreviation	Definition
GMA	2,3-Epoxypropyl methacrylate or glycidyl methacrylate
2-HEMA	2-Hydroxyethyl methacrylate
2-HPMA	2-Hydroxypropyl methacrylate
IARC	International Agency for Research on Cancer (World Health Organization)
IOELV(s)	Indicative Occupational Exposure Limit Value(s)
JBRC	Japan Bioassay Research Centre
JSOH	Japan Society for Occupational Health
LOAEC	Lowest observed adverse effect concentration
LOD	Limit of Detection
LOQ	Limit of Quantification
MCI/MI	Methylchloroisothiazolinone/methylisothiazolinone
MoA	Mode of Action
MRLs	Maximum Residue Levels
NAC	N-Acetyl Cysteine
NIOSH	National Institute for Occupational Safety and Health (USA)
NOAEC	No observed adverse effect concentration
NOAEL	No observed adverse effect level
NTP	National Toxicology Program (USA)
OECD	Organisation for Economic Co-operation and Development
OECD TG	OECD Guidelines for the Testing of Chemicals
OEL(s)	Occupational exposure limit(s)
PFGE	Pulsed Field Gel Electrophoresis
RAC	Committee for Risk Assessment
REACH	Regulation (EC) No 1907/2006 of the European Union concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals
SCE	Sister Chromatid Exchange
SLA	Service Level Agreement
SML	Specific Migration Limit
STEL	Short Term Exposure Limit
TEGDA	Triethyleneglycoldiacrylate
TEGDMA	Triethylene glycol-dimethacrylate
TRGS	Technische Regeln für Gefahrstoffe (German Technical regulations for hazardous substances)
TWA	Time-Weighted-Average
USA	United States of America

Literature search

This report is based on international assessments such as OECD (2000), DFG (2015), ECHA (2015), JSOH (2018), IARC (2020), Australian Government review (2022). A literature search of published papers from the last ten years completed the source of information (date of last literature search: 12/2022).[2]

Databases used were last accessed: 12/2022.

ECHA evaluation and recommendation

The tables below present the outcome of the scientific evaluation to derive limit values for GMA.

Outcome of the scientific evaluation

Derived Limit Values	Value
OEL as 8-hour TWA	None proposed
STEL	Recommended – none proposed before the legislative process**
BLV	None proposed
BGV	None proposed

Notations	Value
Skin notation	Proposed
Skin sensitisation	Proposed

Cancer exposure-risk relationship*

GMA concentration in air (mg/m³)	GMA concentration in air(ppm)	Excess life-time cancer risk (Cases per 100 000 exposed)
0.0063	0.0011	4
0.063	0.011	40
0.63	0.11	400
6.3	1.1	4000

* Assuming an 8-hour exposure per day and 5 days per week, over a 40-year working life
** see t section 9.2.3

In the future, the European Commission and its relevant stakeholders will aim to set limit values for non-threshold substances between the predetermined "upper risk level" and the "lower risk level". It is agreed that the upper risk is 4:1 000 (corresponding to 4 predicted cancer cases in 1 000 employees) and the lower risk level is 4:100 000. This assumes exposure occurs over 8 hours per day, 5 days a week over a 40-year working life period (ACSH, 2022).

---

[2] All references are listed at the end of the report.

1. Chemical Agent Identification and Physico-Chemical Properties

GMA is a liquid substance with high water solubility, low vapour pressure and is flammable.

The chemical identifiers and main physico-chemical properties of GMA are listed in Table 1 and Table 2.

Table 1: Chemical Identification

Identifier	
IUPAC Name	2,3-epoxypropyl methacrylate
Synonyms	glycidyl methacrylate (GMA) oxiran-2-ylmethyl 2-methylprop-2-enoate
EC/ List No	203-441-9
CAS RN	106-91-2
Chemical structure	
Chemical formula	$C_7H_{10}O_3$
Molecular weight	142.15 g/mol

Table 2: Physico-chemical properties[3]

Property	
Appearance	liquid
Boiling point	189ºC at 101,3 kPa
Melting point	-41.5 °C
Density	1.07 at 20ºC
Vapour pressure*	420 Pa at 25ºC
Partition coefficient (log Pow)*	0.96 at 25ºC
Water solubility*	50 g/L at 25ºC
Viscosity	5.481 mPa · s (dynamic) at 20ºC
Conversion factor	1 ppm = 5.91 mg/m³ (at 20°C)[4] 1 mg/m³ = 0.17 ppm (at 20°C)

---

[3] Values obtained from registration data published on www.echa.europa.eu

[4] $concentration\left[\frac{mg}{m^3}\right] = 142.15\ \frac{g}{mol} \cdot \frac{1.013 \cdot 10^5 Pa \cdot 1m^3}{8.314 \cdot \frac{Pa \cdot m^3}{mol \cdot K} 293.15K} \cdot 10^{-3} \cdot concentration[ppm]$

2. EU Harmonised Classification and Labelling - CLP (EC) 1272/2008

The harmonisation classification of GMA is presented in Table 3.

Table 3: EU classification: summary of existing classifications

Index No	International chemical ID	EC number	CAS RN	Annex VI of CLP hazard class and category	Hazard statement code
607-123-00-4	2,3-epoxypropyl methacrylate (glycidyl methacrylate)	203-441-9	106-91-2	Acute Tox. 4 Acute Tox. 3 Eye Dam. 1 Skin Corr. 1C Skin Sens. 1 STOT SE 3 STOT RE 1 Muta. 2 Carc. 1B Repr. 1B	H302 (oral) H311 (dermal) H318 H314 H317 H335 (resp tract) H372 (resp tract) (inhalation) H341 H350 H360F

The Commission Regulation (EU) 2017/776 (10th adaptation to technical and scientific progress) of 4 May 2017 added to the classification of 2,3-epoxypropyl methacrylate (glycidyl methacrylate) as Carc. 1B, Muta. 2 and Repr 1B.
The classification has applied since 1 December 2018.

3. Chemical Agent and Scope of Legislation - Regulated uses in the EU

3.1 Directive 98/24/EC and Directive 2004/37/EC

There is currently no binding or indicative occupational exposure limit value for 2,3-epoxypropyl methacrylate under Directives 98/24/EC[5] or 2004/37/EC [6].

3.2 REACH Registrations

Table 4: REACH Registrations and tonnage

Substance(s) Name	EC number	Tonnage (tonnes/annum Full registration	intermediate use
2,3-epoxypropyl methacrylate (glycidyl methacrylate)	203-441-9	> 1000 tpa (33 active registrants)	Industrial use of process regulators for polymerisation processes in production of resins, rubbers, polymers

3.3 Authorised uses under Annex XIV of REACH

2,3-Epoxypropyl methacrylate (glycidyl methacrylate) is not currently listed in Annex XIV of REACH ("Authorisation List").

3.4 Restricted uses under Annex XVII of REACH

2,3-Epoxypropyl methacrylate (glycidyl methacrylate) is not currently listed in Annex XVII of REACH.

3.5 Plant Protection Products Regulation (EC) 1107/2009

There are no plant protection products authorised under Regulation (EC) No 1107/2009[7] which are based on or include 2,3-epoxypropyl methacrylate (glycidyl methacrylate). 2,3-epoxypropyl methacrylate (glycidyl methacrylate) is not listed as an active substance in the Annex of Commission Implementing Regulation (EU) No 540/2011[8].

3.6 Human and Veterinary Medicinal Products Directives 2001/83/EC and 2004/28/EC respectively

2,3-Epoxypropyl methacrylate (glycidyl methacrylate) is not listed among authorised medicines contained in the Article 57 of Regulation (EC) No 726/2004[9]. It is also not subject to maximum residue levels (MRLs) and are therefore not included in Annex II of Council Regulation (EEC) No 2377/90[10], in accordance with Directive 2004/28/EC.

3.7 Biocidal Products Regulation (EU) 528/2012

There are no biocidal products authorised on the EU/EEA market which are based on or include 2,3-epoxypropyl methacrylate (glycidyl methacrylate) which is also not listed as an active substance under Regulation (EC) No 528/2012[11] or Directive 98/8/EC[12].

3.8 Other legislations

2,3-Epoxypropyl methacrylate (glycidyl methacrylate) is listed in the Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food with a specific migration limit (SML) of 0.02 mg/kg food[13].

4. Existing Occupational Exposure Limits

None of the EU Member States have established OEL values for GMA.

In Germany, Glycidyl methacrylate is listed in the "List of MAK and BAT values" in Section IIa ('List of allergens'): GMA is classified as substance which can cause allergic reactions of the skin and the mucosa close to the skin (skin-sensitizing substances)[14].

Table 5 presents values established in China and Japan. No BLV or BGV have been found. The list should not be considered as exhaustive.

---

[7] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02009R1107-20210327
[8] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32011R0540
[9] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32004R0726
[10] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A01990R2377-20080816
[11] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32012R0528
[12] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A31998L0008
[13] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02011R0010-20200923
[14] German "List of MAK and BAT values" (DFG, 2021- rapport 57) designates GMA as "Sh". "Sh" designates substances which can cause allergic reactions of the skin and the mucosa close to the skin (skin-sensitizing substances) characterized according to the criteria in Section IV a) or IV b) as belonging in Categories 1) or 2).

Table 5: Existing Occupational Exposure Limits (OELs) indicated as 8-h Time-Weighted Average (TWA) for 2,3-epoxypropyl methacrylate (glycidyl methacrylate)

Country	TWA (8 hrs)		STEL (15 min)		Remarks
	ppm	mg/m^3	ppm	mg/m^3	
China				5 (1)	(1) Ceiling Limit value
Japan (JSOH)[1]	0.01 (1)	0.06 (1)			(1) Skin

[1] JSOH, Japan Society for Occupational Health.
Source: GESTIS - https://www.dguv.de/ifa/gestis/gestis-internationale-grenzwerte-fuer-chemische-substanzen-limit-values-for-chemical-agents/index-2.jsp (accessed September 2022; searched for '2,3-epoxypropyl methacrylate (glycidyl methacrylate)')

5. Occurrence, Use and Occupational Exposure

5.1 Occurrence

2,3-Epoxypropyl methacrylate (glycidyl methacrylate – GMA) is not known to occur naturally in the environment. There are few data on the environmental occurrence of this chemical.

GMA 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 TG 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 GMA 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%) (OECD, 2000).

5.2 Production and Use Information

5.2.1 Production

GMA is listed as a High Production Volume chemical in the Screening Information Data Set of the Organisation for Economic Co-operation and Development. GMA is produced by the esterification of methacrylic acid with either glycidol or epichlorohydrin (HSDB 2003, cited in IARC 2020). Currently, the majority of manufacturing sites are located in the USA and Europe, with fewer sites being situated in Asia ((Chem Sources, 2019) as cited in (IARC, 2020)).
The European Chemicals Agency (ECHA) reported that 1000–10000 tonnes of GMA per year are currently manufactured and/or imported in the European Economic Area. The aggregate production volume in the USA in 2014 and 2015 has been reported to be between 4500 and 23 000 tonnes ((US EPA, 2016) as cited in (IARC, 2020)). The production volume in Japan for GMA in 1995 was approximately 3000 tonnes (OECD, 2000).

5.2.2 Uses

The following international uses have been identified through EFSA Scientific opinions, REACH (ECHA, 2022), ECHA CLP report (ECHA, 2015), ChemWatch and United States Environmental Protection Agency (US EPA, 2016) documents as cited in (IARC, 2020) and (OECD, 2000).

GMA has site-limited use as a monomer. The reactive polymers and pre-polymers manufactured from GMA have reported uses in the following industrial products:
• powder and metal coatings
• paints and coating products

• adhesive products
• two-part resins
• printing inks
• rubber and plastic products
• food contact materials.

GMA is reported to have non-industrial site limited uses in the manufacture of polymers and pre-polymers used in medical applications such as:
• dental sealants and bone composite materials
• hydrogel lenses (Australian Government, 2022)

GMA 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). BisGMA and triethylene glycol-dimethacrylate are used as dental sealants.
GMA is also used as an adhesion promotion/ crosslinking co-monomer in the manufacture of vinyl and acrylic resins. These resins are used as industrial powder and metal coatings for household appliances, facades, and automotives. GMA, as an acrylic copolymer, has also been classified as a food contact material substance by the US Food and Drug Agency for aqueous and fatty foods, and for components of paper and paperboard in contact with dry food. GMA 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 (IARC, 2020).

In the European Economic Area, ECHA (2022) reported that GMA has active registrations under 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 tabletting, compression, extrusion, or pelletization. Specifically, the industrial GMA 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, GMA-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 registered in the European Union containing the bound monomer (expected to be GMA). There are therefore no identified uses in the EU for the bound monomer in the polymer substance.

5.3 Occupational exposure

Worker exposure is through inhalation, dermal exposure and oral exposure due to hand to mouth contact.

GMA 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 GMA can also be used in food contact material.

GMA is manufactured in a closed system under well-controlled conditions, so air release is unlikely (OECD, 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, 2022).
The only sampling for occupational exposure available for GMA was for Japan (OECD, 2000): GMA was produced in a closed system, and 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/m^3 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 which was 2.3 mg/m^3. Generally, dermal exposure, although the duration of activity was short (5 minutes/day), was estimated to be 0.04 or 0.22mg/kg body weight (bw) per day (OECD, 2000).

GMA is also used in the preparation of TEGDMA and Bis-GMA (dental and bone composite materials). Dental workers are known to be exposed to bis-GMA and other methacrylated prepolymers (Pemberton and Kimber, 2022). The Working Group of IARC 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.*" It can be assumed that workers preparing these materials can also be potentially exposed to GMA:

- Specifically, some release of unreacted GMA has been shown from a bone composite in an experimental setting, but the amount was not reported;
- Another study assessing dental-care personnel reported occupational exposure for respirable dust containing Bis-GMA and TEGDMA polymers, formed by reaction from bisphenol A and GMA. The particles ranged in diameter from 6 nm to 5 μm and consisted of resin matrix. Bis-GMA and TEGDMA monomers were released from the polymer by the grinding process. GMA itself was not measured. [The Working Group noted that the GMA monomer is not likely to be released from the grinding process.] (several references, as cited in (IARC, 2020)).
- 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 GMA via compounded emulsions

5.4 General population

General population exposure is through inhalation, dermal exposure and oral exposure via drinking water and food as well as exposure due to hand to mouth following dermal exposure.

GMA is expected to be readily absorbed following oral, dermal and inhalation exposure.

Exposure to GMA in the general population has not been well documented but is not expected from use of the polymerized. GMA has a low vapour pressure but inhalation may still be possible.

Although GMA is readily biodegradable and low bioaccumulative, the exposure to the general population via the environment is possible through drinking water processed from surface water and through fish which may accumulate this chemical. Estimates of consumption of GMA via drinking-water and fish for locations near to chemical-manufacturing plants that produce or use this chemical have been calculated.

The concentration in drinking water is estimated to be equal to 8.9 x 10^{-3} mg/l.
The daily intake through drinking water (average for Japan) is calculated as: 2.97 x 10^{-4} mg/kg/day (2 l/day, 60 kg bw).

Using the bioconcentration factor of 1.0 estimated from log$_{Pow}$ (0.96), the concentration of this chemical in fish can be calculated as follows:

$$PEC_{fish} = 8.9 \times 10^{-3} \times 1.0 = 8.90 \times 10^{-6} \text{ mg/g-wet.}$$

As a daily intake of fish in Japan is estimated to be 90 g for 60 kg body weight person, a daily intake of GMA will be 1.34×10^{-5} mg/kg/day.

GMA produced in Japan is used as monomer unit of paint resin and as intermediate of chemical products. As the detailed information could not be given in Japan, one report indicates it is used as paints in the product concentrations of 1 to 5% and the other shows it is mainly used as car coating paints in car industry. Therefore consumer exposure might be low (OECD, 2000).

Patients, including young children, receive dental and bone composite materials containing TEGDMA and BisGMA. (Bationo et al., 2016) reported use of monomers containing 3–5% GMA to make an adhesive resin for orthodontic mineral fillers. (IARC, 2020).

6. Monitoring Exposure

6.1 External exposure

There are no validated methods particularly for measuring 2,3-epoxypropyl methacrylate (glycidyl methacrylate – GMA). However methods for volatile organic compounds in air including the analysis of ethyl acrylate and methyl methacrylate can possibly be adapted to the determination of GMA.

For a purpose of assessing occupational exposure, airborne GMA has been measured accordingly: an XAD2 sorbent was used for personal air sampling at a flow rate of 1 L/minute, butyl acetate for desorption, and gas chromatography with flame ionization detection (GC-FID) for detection of GMA. However, the limit of detection (LOD) with this method was high being 2.3 mg/m^3 (0.4 ppm) for 3-L sample (OECD, 2000).
(Ling et al., 2017) have developed a sensitive method for measuring GMA in workplace air by using sorbent tube filled with carbon aerogel adsorbent, desorbed with solution of 50% (V/V) dimethylformamide-carbon disulfide, and analysed by GC-FID. The limit of quantification (LOQ) was 0.07 mg/m^3 (0.01 ppm) for 3-L sample (Ling et al., 2017).

There are two NIOSH methods which most probably can be validated for GMA:

- The first one is the NIOSH 'method 2537' for methyl and ethyl methacrylate and it consists of solid sorbent tube (XAD-2) for sampling and gas chromatography with flame ionization detection (GC-FID). The working range for methyl methacrylate is 0.07 to 670 ppm (0.30 to 2747 mg/m^3) and for ethyl methacrylate 0.11 to 19.7 ppm (0.50 to 91.7 mg/m^3) for a 3-L air sample. The air sample volume can be increased to 8 l (NIOSH, 2003).
- The other method is the NIOSH 'method 3900' for volatile organic compounds (C1 to C10) using canister method for sampling and GC-MS for detection. This method is very sensitive when selected ion monitoring is applied. The method has been validated for methyl methacrylate. The LOD for methyl methacrylate is 0.2 ppm and it can be lowered to 0.5 ppb by using selected ion monitoring mode (NIOSH, 2018). Most probably the method can be adapted for GMA, however, the LOD could be higher for GMA than for methyl methacrylate since methyl methacrylate has a lower molecular weight (100.12 g/mol) and boiling point (100.5°C) than GMA.

Currently, the methods available for GMA can be used to monitor exposure levels above 0.01 ppm. However, it may be possible to lower the LOD in some extent by increasing sample volume and using GC-MS for detection. The available methods for GMA and similar substances (methyl and ethyl methacrylate) are presented in the Table 6.

Table 6: Overview of sampling and analytical methods for air monitoring at the workplace

Method	Analytical technique	LOQ/ LOD, sampling volume and time	Reference
XAD2 tube Desorption with butyl acetate	GC-FID	LOD 2.3 mg/m^3 (0.4 ppm), flow rate 1 l/min; air volume 3 l;	(OECD, 2000), Initial assessment Report for 10th SIAM (Japan) UNEP Publications;)
Sorbent tube (carbon aerogel); desorption with 50% (v/v) DMF-CS$_2$ -solution	GC-FID	LOQ 0.07 mg/m3 (0.01 ppm) with 3 l air volume	(Ling et al., 2017) abstract in English
NIOSH 'method 2537' XAD-2 (400/200 mg) Desorption with CS$_2$	GC-FID	LOQs for methyl and ethyl methacrylates are 0.07 and 0.11 ppm with 3 l air volume; flow rate 0.01-0.05 l/min;	(NIOSH, 2003)
NIOSH 'method 3900' Canister method for volatile organics	GC-MS	LOD for methyl methacrylate is 0.2 ppm and it can be lowered to 0.5 ppb; sampler is a fused-silica lined stainless steel canister, 6 L, 450, or 400 ml; flow rate 0.06 to 50 ml/min; method is not validated for GMA	(NIOSH, 2018)

LOD: Limit of detection; DMF=dimethylformamide, CS$_2$=carbon disulfide

6.2 Biomonitoring of exposure (internal exposure)

No analytical methods for biological monitoring of GMA in biological materials such as blood or urine samples from exposed individuals are available. However, 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 GMA (IARC, 2020, Honda et al., 2014).

7. Health Effects

7.1 Toxicokinetics (Absorption, distribution, metabolism and excretion - ADME)

7.1.1 Human data

There are no human data on 2,3-Epoxypropyl methacrylate (glycidyl methacrylate – GMA). It is expected to be readily absorbed following oral, dermal and inhalation exposure. See also section 7.1.3 below.

7.1.2 Animal data

7.1.2.1 Absorption - distribution

GMA is expected to be readily absorbed following oral, dermal and inhalation exposure.

Shi Tao et al. (1988) (as cited in (IARC, 2020) investigated the toxicokinetics of GMA in male rabbits. After an intravenous injection of 200 mg/kg, the concentration-time curve could fit the two-compartment open model,. Following subcutaneous injection of 800 mg/kg, the toxicokinetics appeared to a first-order absorption one-compartment open model. A subcutaneous co-administration of tri-o-cresyl-phosphate, a carboxylesterase inhibitor, resulted in a 10-fold increase in the maximum blood concentrations of GMA, compared to the animals dosed with GMA alone.

7.1.2.2 Metabolism - excretion

GMA is metabolised by first-order process in incubation with whole blood, plasma, erythrocyte suspension and homogenates of brain, heart, liver, lung, spleen, kidney, small intestine and muscle. The highest rate of elimination was found in blood and liver homogenate. In male rabbits the elimination of more than 95% of GMA from the rabbit blood occurred within 10 minutes Shi Tao et al. (1988) (as cited in (IARC, 2020).

(Bogdanffy et al., 1987) studied the activity and cellular distribution of carboxylesterase in the nasal passages of rats and mice. This is because inhalation exposure of rats and mice to acrylate esters, cause degeneration of the olfactory epithelium but not of the respiratory epithelium, and are metabolised via carboxylesterase to acids that are toxic to the olfactory epithelium. The author found that the olfactory mucosa of rats and mice hydrolyse carboxylesters more efficiently than the respiratory mucosae. Furthermore, all cell types of the respiratory epithelium had some carboxylesterase activity, with varying intensities between individual cell populations.
Together, these data quantitate carboxylesterase activity in nasal mucosal homogenates and localize the enzyme in individual cell types. The data suggest that olfactory mucosa may metabolise carboxylesters to acids more readily than respiratory mucosa.

(Dahl et al., 1987) and (Mattes and Mattes, 1992) also concluded that carboxylesterase activity is high in the nasal ethmoturbinates and that the rat nasal mucosa plays an important role in the response to certain toxic inhaled esters.

7.1.3 In vitro data

Domoradzki et al. (2004) investigated the metabolism of GMA *in vitro*, using tissues from humans, rats and rabbits. Differences in carboxylesterase and epoxide hydrolase activities in tissues from these species may result in differences in formation of glycidol, methacrylic acid, GMA-diol and glycerol.
This may provide a basis to judge the relative sensitivity of humans to rabbits and rats for the generation of toxic effects with GMA. Radiolabelled GMA [^{14}C 1,3-glycidyl] was used in this study and was 92% radio chemically pure.
In vitro incubation of GMA (2mM) with nasal tissue preparations and liver homogenate from human, rat (Fischer 344) and rabbit (New Zealand) resulted in the formation of only one metabolite, tentatively identified as glycidol (EC number 209-128-3; based on similar retention time with ^{14}C-glycidol).
Since no other metabolite (GMA-diol and glycerol) was formed, it appears that epoxide hydrolysis is not a major *in vitro* route of metabolism for GMA using rat, rabbit and human tissue preparations (as cited in (ECHA, 2015)).

At an initial concentration of 2 mM of GMA, the half-live of GMA (via hydrolysis) was shorter in incubations with rat and rabbit tissues as compared to human tissues (biotransformation of GMA in liver homogenates was completed within approximately 30 minutes versus 2 hours, respectively).This indicates that carboxylesterase activity is lower in humans than in rats and rabbits.

7.1.4 Summary

In general, glycidyl esters are expected to be primarily hydrolysed through chemical and enzymatic hydrolysis on the ester bond, thereby releasing glycidol.

Limited toxicokinetic and metabolism data are available for GMA.

The metabolism of GMA in mammals was hypothesized to proceed by at least two different and competing enzyme systems, epoxide hydrolase and non-specific carboxylesterases (see Figure 1).

Methacrylic acid   Glycidol   Glycerol methacrylate
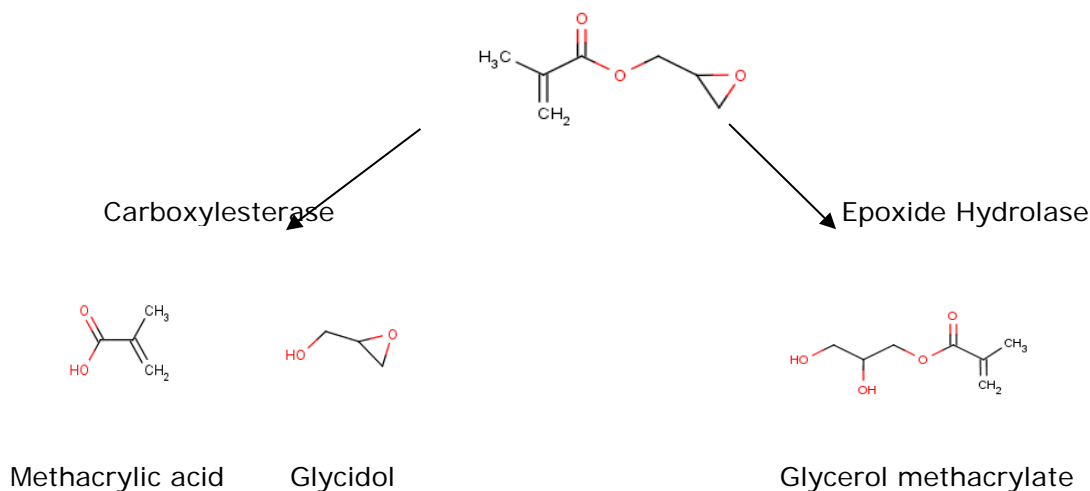
Figure 1: Hypothesised metabolism of GMA in mammals

Metabolism of GMA by carboxylesterase would result in the formation of glycidol and methacrylic acid as metabolites, while initial metabolism by epoxide hydrolase would result in the formation of glycerol methacrylate. The relative speed at which the two competing metabolic reactions occur in different tissues and species is believed to be important for understanding the toxicity of GMA.

(OECD, 2000) concluded that "*the metabolism of glycidyl methacrylate in mammals will likely proceed by at least two different and competing enzyme systems (epoxide hydratase and non-specific carboxylesterases*". Species differences in the activity of these enzymes suggest that the carboxylesterase route of metabolism may predominate in the nasal tissue of rabbits (yielding glycidol and methacrylic acid) while the epoxide hydrolase route was hypothesized to predominate in rats and humans (producing glycerol methacrylate, then glycerol and methacrylic acid by carboxylesterase) (Bogdanffy et al., 1987, Dahl et al., 1987, Mattes and Mattes, 1992).

Overall, the available studies show that GMA is metabolised into glycidol. Metabolism of GMA to glycidol has ramifications for hazard identification. Glycidol has a harmonised classification according to CLP as carcinogenic (category 1B), germ cell mutagenic (category 2) and toxic to reproduction (category 1B).

7.2 Acute toxicity

7.2.1 Human data

No relevant information is available.

7.2.2 Animal data

7.2.2.1 Acute oral toxicity

Glycidyl methacrylate has an entry in Annex VI of the CLP regulation as an Acute Tox 4 (oral) substance.

All available acute oral studies are old and have limitations either in reporting (score 4 as per Klimisch et al., 1997) or in the conduct of the study (score 3 as per Klimisch et al., 1997). The OECD has chosen an oral LD50 value for GMA of 597 mg/kg bw for rat

((Zdravko et al. (1985) as cited in (OECD, 2000)). All other acute oral studies resulted in LD50 values in the same range.

7.2.2.2 Acute dermal toxicity

Glycidyl methacrylate has an entry in Annex VI of the CLP regulation as an Acute Tox 3 (dermal) substance.
Dermal LD50 for rabbits was 480 mg/kg bw (Smyth et al., 1969) as cited in (OECD, 2000).

7.2.2.3 Acute inhalation toxicity

Nitschke et al. (1990) (as cited in (OECD, 2000) (ECHA, 2022)) reported results of rats (5 males and 5 females) exposed to saturated vapours of GMA (105, 269 and 412 ppm, equivalent to 610, 1563 and 2394 mg/m^3) for 4 hours (OECD TG 403).
All animals survived the exposure and 14-day post-exposure observation period:
- at 412 ppm, at the end of the exposure period, laboured breathing and up to 15% decrease in body weight were observed;
- at 269 ppm, similar but less severe effects were observed;
- at 105 ppm a very slight transitory body weight loss of 3% was noted on the day following the end of exposure.

Eye irritation and corneal opacities were considered moderate at 412 ppm and slight at 269 ppm and were not reversible within 14 days post-exposure. Corneal opacity was also observed at 105 ppm.

In another inhalation toxicity study (reliability 4; Smyth et al., 1969, as cited in (ECHA, 2022)), acute exposure of rats with saturated vapour resulted in a maximum survival time of 2 hours. It was reported that saturated vapour of GMA at 20°C was 474 ppm (2754 mg/m^3) (as cited in (OECD, 2000)).

7.2.3 Summary

All available acute oral studies are old and have limitations either in reporting or in the conduct of the study. The OECD adopted an oral LD50$_{rat}$ value for GMA of 597 mg/kg bw, while all other studies provide the same range of LD50 values of 390–1050 mg/kg bw.

By inhalation (OECD TG 403; key study), no mortality was observed in rats exposed for 4 hours at 2394 mg/m^3, the highest practically attainable vapour concentration.
Overall, higher concentrations including the testing of aerosols were not performed.

Table 7: Summary of acute toxicity studies via three different routes of exposure

Route	Strain / Type	Value	Reference*
Oral	Rat /LD50	597 mg/kg	Zdravko, 1985
	Rat/ LD50	About 700 mg/kg	Olson, 1960; Smyth, 1969
	Rat/ LD 50	451 mg/kg	EPA, 1992
	Rat/ LD 50 Mouse/ LD 50	390 mg/kg	Zdravko, 1985
	Mouse/ LD 50	1050 mg/kg	Smyth, 1969
	Guinea pig/ LD 50	697 mg/kg	Zdravko, 1985
Inhalation	Rat/ LC 0	2394 mg/m^3/ 4hr	Nitschke, 1990
	Rat/ LCL0	1400 mg/m^3/ 6hr	Haag,1953
	Rabbit/ LCL 0	1400 mg/m^3/ 6hr	Haag,1953
	Guinea pig/ LCL 0	14000 mg/m^3/ 6hr	Haag,1953
	Dog/ LCL 0	1400 mg/m^3/ 6hr	Haag,1953
	Rat/ LCL 0	2754 mg/m^3/ 2hr	Smyth, 1969
Dermal	Rabbit/ LD 50	480 mg/kg	Smyth, 1969

LC0 (lethal concentration 0%), concentration which causes no death. LCL 0 (lethal concentration low): lowest concentration in air which causes death. * References are taken from (OECD, 2000) and (ECHA, 2022)

The existing harmonised minimum classification of GMA for acute dermal toxicity is likely to be based on the dermal LD50 for rabbits at 480 mg/kg bw from the Smyth et al. (1969) study.

7.3 Specific target organ toxicity/Repeated dose toxicity

Glycidyl methacrylate has an entry in Annex VI of the CLP regulation as a STOT SE3 (resp. tract) and STOT RE 1 (resp. tract).

7.3.1 Human data

No relevant information is available on GMA.

7.3.2 Animal data

7.3.2.1 Oral route

Ministry of Health and Welfare, MHWJ, (1997) as cited in (OECD, 2000, ECHA, 2022, ECHA, 2015) performed an oral repeated-dose toxicity study of GMA in Crj:CD rats (n=12) according to the OECD TG 422 (combined repeated dose and reproductive/developmental toxicity screening test), using doses of 10, 30 and 100 mg/kg/day (gavage) for 45 days in males and from 14 days before mating to day 3 of lactation in females.
The results on reproductive toxicity are presented in sections 7.8.2.1 and 7.8.2.2.
In males, salivation was observed at 30 mg/kg (5/12) and 100 mg/kg (12/12); there was an increase in absolute and relative kidney and adrenal weights at 100 mg/kg; there was an increase in total protein and albumin (in blood chemistry). These changes were not considered as adverse effects.
Furthermore, some histological changes were considered to be due to the irritation of GMA: squamous hyperplasia in forestomach was observed at 30 and 100 mg/kg in males and cellular infiltration in forestomach at 100 mg/kg in females.
Note: Salivation and increased serum protein in males was not considered as adverse effects. Histological change observed in forestomach was considered to be due to irritation of this chemical.

The NOAEL (including local effects) for oral repeated dose toxicity was considered to be 10 mg/kg/day for males and 30 mg/kg/day for females. The NOAEL for oral repeated dose toxicity (systemic effects) was considered to be 30 mg/kg/day (both sexes).

Two other studies were performed with little information on protocol or data analysis:
- A one-year study (Hadidian et al., 1968) was performed on rats dosed 5 days/ week at 0.1 mg/kg (3 males and 3 females) and at 0.3 mg/kg (15 males and 15 females). The authors concluded that there were treatment-related effects on tissue.
- A 15-day study ((Ou-Yang et al. (1988) was performed with rabbits (n= 10) dosed at 50 mg/kg/day: two animals died and others showed slow reactions, head shaking, and prostration. There were several haematological and pathological changes including bleeding, necrosis in the heart, lungs, kidney and stomach. No NOAEL was identified (ECHA, 2015).

7.3.2.2 Dermal route

No relevant information is available on GMA.

7.3.2.3 Inhalation route

Sub-acute and a sub-chronic inhalation toxicity studies were performed in rats and rabbits (see Table 8).

Landry et al. (1996) performed a sub-chronic inhalation toxicity study in rats at concentrations of 2.9, 12 or 87 mg/m^3 (equivalent to approximately 0.5, 2 and 15 ppm, respectively) for 13 weeks (6 hours/day, 5 days/week) (ECHA, 2015, ECHA, 2022). There were no treatment-related in-life observations, and no significant treatment-related effects on body weight, urinalysis, clinical chemistry or haematology parameters, as well as gross pathologic changes or organ weights at any exposure level. Treatment-related effects were limited to hyperplasia of respiratory epithelium of the nasal tissues in all animals at 87 mg/m^3. In all affected animals, the hyperplastic respiratory epithelium was approximately two to three times as thick as in control animals, and was located in the anterior portions of the nasal passages, involving the tips of the turbinates and the lateral walls of the nasal passages. These changes were considered to have resulted from respiratory irritation. Therefore, the NOAEC was considered to be 12 mg/m^3 (2 ppm) for both sexes.

Landry et al. (1991) exposed rats to GMA at concentrations of 58.2, 233 or 931 mg/m^3 (equivalent to 10, 40 and 160 ppm respectively) for 2 weeks (6 hours/day, 5 days/week. A decrease in body weight was observed at the top two doses (ECHA, 2015, ECHA, 2022). The respiratory tract was the primary target organ. At the highest dose, general debilitation with noisy and difficult (mouth) breathing, eye irritation, corneal clouding and distended abdomen (day 4) were observed, so the animals were terminated on day 4 because of the severity of the respiratory and ocular effects. Microscopically, severe multifocal necrosis and inflammation of the olfactory epithelium in the nasal cavity were noted. Animals of the other 2 groups were also terminated earlier (day 9). At the mid-dose, there were slight to moderate multifocal necrosis, and inflammation of the respiratory and olfactory nasal epithelium. At the lowest dose, microscopic observation showed a very slight multifocal necrosis of individual respiratory epithelial cells in 3/5 males and in 2/5 females. These changes (effects on the nasal cavity) in respiratory tract were considered to be due to irritation of GMA. There were no histopathological changes in any other tissues. Although a NOAEC was not determined in this study, 10 ppm caused relatively mild effects. Therefore, 58.2 mg/m^3 (10 ppm) was considered to be the LOAEC because of tissue damages in respiratory tract.

Table 8: Summary of repeated dose toxicity studies performed by inhalation

Strain / Type	Duration	Doses	Effects observed	NOAEC / LOAEC (mg/m³)	Reference*
F344 rats M/F N= 10/sex/dose	13 weeks; 6 hr/d, 5 d/wk)	2.9, 12 or 87 mg/m³	Treatment-related effects were limited to hyperplasia of respiratory epithelium of the nasal tissues in all animals at top dose; hyperplastic respiratory epithelium was located in the anterior portions of the nasal passages, involving the tips of the turbinates and the lateral walls of the nasal passages	NOAEC= 12 mg/m³ (2 ppm)	Landry et al. (1996) in (ECHA, 2015, ECHA, 2022)
F344 rats M/F N= 5/sex/dose	2 weeks; 6 hr/d, 5 d/wk)	58.2, 233 or 931 mg/m³	Decrease in body weight was observed at the top 2 doses; respiratory tract was the primary target organ; D4: termination of the top dose group, due to general debilitation with noisy & difficult breathing, eye irritation, corneal clouding and distended abdomen + microscopically, severe multifocal necrosis and inflammation of the olfactory epithelium in the nasal cavity; D9: termination of the 2 other dose groups, due multifocal necrosis, and inflammation of the respiratory and olfactory nasal epithelium; no histopathological changes in any other tissues.	No NOAEC determined; LOAEC= 58.2 mg/m³ (10 ppm) because of tissue damages in respiratory tract.	Landry et al. (1991) in (ECHA, 2015, ECHA, 2022)
Rats and rabbits	6 months; 6 hr/d, 6 d/wk	15.3 and 206 mg/m³	In the high-dose group, multiple effects were observed, including on the CNS, heart, liver and kidney; condition of the animals worsened during the 1-month post exposure period; In the low-dose group, no abnormalities were observed except for a few signs in a minority of the animals;	LOAEC= 15 mg/m³ (2.6 ppm) Note: suspicion that test material contained other components than GMA which may have contributed to the toxicity observed	(Guoshun et al. (1990); in (ECHA, 2022).
Rats	2 weeks; 6 hr/d, 5 d/wk	204 mg/m³	No histopathological effects were observed, although the rats had reduced body weight gain, respiratory	No NOAEC defined	(Dupont,1982) in (ECHA, 2015, OECD, 2000)

			symptoms and higher red blood cell counts. After 2 weeks post-exposure, no remaining effects we observed		
B6D2F 1/Crlj mice M/F N=50/ sex/ dose	104 weeks; 6 hr/d, 5 d/wk	3.5, 15 and 59 mg/m^3	Significantly increased incidences of non-neoplastic lesions, mostly slightly to moderately severe, were mainly observed in the nasal cavity, both in the respiratory and olfactory epithelia; also effects in the transitional epithelium, respiratory metaplasia, and the nasopharynx	LOAEC = 3.5 mg/m^3 (0.6 ppm)	(JBRC, 2015) and cited in (IARC, 2020)
F344/D uCrlCrlj rats M/F N=50/ sex/ dose	104 weeks; 6 hr/d, 5 d/wk	19, 47 and 118 mg/m^3	Significantly increased incidences of non-neoplastic lesions, slightly to markedly severe, were observed in the nasal cavity of exposed rats and included squamous cell hyperplasia, effects in respiratory, olfactory and transitional epithelia; Apart from the nasal mucosa, other sites were significantly affected	LOAEC = 19 mg/m^3 (3.2 ppm)	(JBRC, 2015) and cited in (IARC, 2020)
Rabbits F	13 days; 6 hr/d,	11.6, 29.1, 58.2 mg/m^3	Treatment-related degeneration of the nasal olfactory epithelium was observed as of low dose (changes reversible); At the two highest doses, olfactory epithelial degeneration was observed as well as hyperplasia, erosions, ulcers and inflammation of the nasal epithelium; all changes were reversible except for olfactory epithelial degeneration which showed only partial reversibility	LOAEC= 11.6 mg/m^3 (2 ppm)	Cieszlak et al. (1996) in (ECHA, 2015, ECHA, 2022)
Rabbits F	13 days (GD7 to GD19); 7 hr/d	2.9, 11.6, 58.2 mg/m^3	Treatment-related effects consisted of erosions and/or ulcers of the olfactory and respiratory epitheliums, hyperplasia of the respiratory epithelium, and an increased incidence of subacute to chronic inflammation of the respiratory epithelium	No NOAEC determined	(Vedula et al., 1996) in (ECHA, 2015, ECHA, 2022)

A chronic study ((Guoshun et al. (1990); summarised in the Landry et al, 1996 study report)) was conducted in rats and rabbits exposed to 15.3 and 206 mg/m^3 (equivalent to

2.6 and 35 ppm respectively) for 6 hours/ days, 6 days/ week, for 6 months (ECHA, 2022). In the high-dose group, multiple effects were observed, including on the central nervous system, heart, liver and kidney. The condition of the animals was reported to worsen during the one-month post exposure period. In the low-dose group, no abnormalities were observed except for a few signs in a minority of the animals. Hence, 15.3 mg/m^3 was considered to be the LOAEC. Note that because of the higher vapor pressure and lower purity, the authors suggested that the test material used in this study contained components other than glycidyl methacrylate, which may have contributed to the toxicity observed.

In another two-week study (Dupont,1982), rats were exposed to 204 mg/m^3 (35 ppm) for 6h/ day, 5days/ week. No histopathological effects were observed, although the rats had reduced body weight gain, respiratory symptoms and higher red blood cell counts. After 2 weeks post-exposure, no remaining effects were observed (ECHA, 2015, OECD, 2000).

In a two-year inhalation study conducted by the Japan Bioassay Research Centre (JBRC, 2015) and cited in (IARC, 2020), B6D2F1/Crlj mice were exposed to 0, 0.6, 2.5, 10 ppm (equivalent to 0, 3.5, 15 and 59 mg/m^3 respectively), 6 hours/day, 5 days/week for 104 weeks (see also section 7.7.2; Table 12). Significantly increased incidences of non-neoplastic lesions, mostly slightly to moderately severe, were observed mainly in the nasal cavity of exposed mice and included:

- in the respiratory epithelium:
  eosinophilic change: 10 ppm in M: (29/50 vs 7/50 in controls); ≥ 0.6 ppm in F: (47/50 vs 35/50, at 0.6 ppm),
  inflammation: 10 ppm in M: (12/50 vs 0/50 in controls)
  squamous cell metaplasia: 10 ppm in M/F; M: (7/50 vs 0/50 in controls), F: (14/50 vs 0/50)
  regeneration: 10 ppm in M: (14/50 vs 0/50 in controls); ≥ 2.5 ppm in F: (7/50 vs 0/50, at 2.5 ppm)
- in the olfactory epithelium:
  eosinophilic change: 10 ppm in M/F; M: (15/50 vs 3/50 in controls) F: (37/50 vs 11/50)
  respiratory metaplasia: ≥ 0.6 ppm in M/F); M: (16/50 vs 4/50 in controls, at 0.6 ppm), F: (41/50 vs 0/50, at 0.6 ppm)
  necrosis:10 ppm in F: (6/50 vs 0/50 in controls)
- in the transitional epithelium
  hyperplasia: 10 ppm M/F; M: (20/50 vs 0/50 in controls), F: (6/50 vs 0/50)
- respiratory metaplasia: gland (nasal cavity): ≥ 0.6 ppm in M/F; M: (22/50 vs 12/50 in controls, at 0.6 ppm), F: (47/50 vs 16/50, at 0.6 ppm)
- angiectasis: 10 ppm in F: (7/50 vs 0/50 in controls).

Other sites/organs affected included the nasopharynx, presenting a significant increase in eosinophilic change (10 ppm in M: (15/50 vs 2/50 in controls); ≥ 0.6 ppm in F: (14/50 vs 4/50 in controls, at 0.6 ppm).
These changes, attributed to injury were considered exposure-related with some age-related ones further enhanced by exposure.

JBRC also conducted a chronic study in F344/DuCrlCrlj rats, exposed to 0, 3.2, 8, 20 ppm GMA (equivalent to 0, 19, 47 and 118 mg/m^3 respectively), 6 hours/day, 5 days/week for 104 weeks (cited in (IARC, 2020); see section 7.7.2; Table 12 for study design).

Significantly increased incidences of non-neoplastic lesions, slightly to markedly severe, were observed in the nasal cavity of exposed rats and included:

- squamous cell hyperplasia with atypia: 20 ppm in M/F); M: (27/50 vs 0/50 in controls), F: (13/50 vs 0/50)
- in the respiratory epithelium:
  squamous cell metaplasia: ≥ 8 ppm in M: (8/50 vs 0/50 in controls, at 8 ppm); ≥ 3.2 ppm in F: (6/50 vs 0/50 at 3.2 ppm),
  squamous cell metaplasia with atypia: ≥ 8 ppm in M: (25/50 vs 0/50, at 8 ppm); 20 ppm in F: (18/50 vs 0/50)
  inflammation: ≥ 8 ppm in F: (22/50 vs 7/50 in controls)
- in the olfactory epithelium:
  atrophy: ≥ 8 ppm in M/F; M: (14/50 vs 2/50 in controls, at 8 ppm), F: (10/50 vs 0/50, at 8 ppm),
  respiratory metaplasia: ≥ 8 ppm in M (7/50 vs 0/50 in controls, at 8 ppm); 20 ppm in F: (15/50 vs 0/50)
  necrosis: 8 ppm in M: (7/50 vs 0/50 in controls)
  regeneration: 20 ppm in F: (10/50 vs 0/50)
- in the transitional epithelium:
  hyperplasia: 3.2 and 8 ppm in M (16/50 vs 0/50 and 35/50 vs 0/50, respectively); ≥ 3.2 ppm in F: (8/50 vs 0/50 at 3.2 ppm)

Apart from the nasal mucosa, other sites significantly affected by exposure to GMA, were the:
- forestomach, displaying hyperplasia at 20 ppm in females,
- bone marrow, where increasingly marked haematopoiesis was observed (8 ppm in M (31/50 vs 13/50 in controls); 20 ppm in F (12/50 vs 6/50),
- spleen (extramedullary), at ≥ 3.2 ppm in M (23/50 vs 21/50 in controls at 3.2 ppm); 20 ppm in F (26/50 vs 32/50[15]),
- eyes of males, which had significant increases in the incidence of keratitis and corneal ulceration at 20 ppm (21/50 vs 2/50 and 10/50 vs 1/50, respectively).

Cieszlak et al. (1996) exposed female rabbits to GMA at 11.6, 29.1, 58.2 mg/m³ (equivalent to 2, 5, 10 ppm respectively) 6 hours/day, daily for 13 consecutive days (ECHA, 2015, ECHA, 2022).
Treatment-related degeneration of the nasal olfactory epithelium was observed as of 11.6 mg/m³. At the two highest doses, olfactory epithelial degeneration was observed as well as hyperplasia, erosions, ulcers and inflammation of the nasal epithelium.
After a 4-week recovery period: at 29.1 and 58.2 mg/m³, there was complete reversibility of all changes (hyperplasia, erosions and/ or ulcers and inflammation of the nasal respiratory epithelium) except for olfactory epithelial degeneration which showed only partial reversibility, while at 11.6 mg/m³, nasal tissue was indistinguishable from controls. The authors concluded that treatment-related degeneration of the nasal olfactory epithelium was completely reversible in rabbits exposed to 2 ppm followed by a 4-week recovery period while rabbits exposed to 5 and 10 ppm had only partial reversal of the treatment-related effects. Poor reporting leaving several uncertainties related to the study, including unclear reporting of the test material is noted. The LOAEC is 2 ppm.

(Vedula et al., 1996) exposed, via inhalation, female rabbits during day 7 to day 19 of gestation to GMA at concentrations of 2.9, 11.6 and 58.2 mg/m³ (or 0.5, 2, 10 ppm, respectively) 7 hours/day (found in (ECHA, 2015)). Treatment-related alterations consisted of erosions and/or ulcers of the olfactory and respiratory epitheliums, hyperplasia of the respiratory epithelium, and an increased incidence of subacute to chronic inflammation of the respiratory epithelium.

---

[15] An increase in the grade of severity among the reported incidences with increasing concentration was noted (e.g. at 20 ppm there were 9/5- occurrences of marked severity vs 1/50 in the controls)

Note: Mattsson et al. (1996) exposed Fischer 344 rats by inhalation to GMA at 0.5, 2 or 15 ppm (2.9, 12, 89 mg/m^3), 6 hours/day, 5 days/ week for 13 weeks (ECHA, 2022) The animals were weighted and clinically examined weekly. A functional observation battery (FOB) and motor activity (MA) were conducted pre-exposure and at the end of each month of exposure. In addition, the post-exposure neurotoxicity evaluation focused on evoked potential testing of the visual (FEP), auditory (ABR), somatosensory system (SEP), and caudal nerves (CNAP), and a comprehensive neuropathological examination.

At week 4, there was a low incidence of nasal discharge and enlarged nostrils at 0.5 and 2 ppm. There were no treatment-related effects in any of the other measures. Hence there was no evidence of neurotoxic effects at any exposure level. Thus, the neurotoxicity NOEL was 15 ppm.

7.3.3 Summary

The major toxic effect of GMA was tissue damage at the first exposure sites such as the forestomach after oral administration and the respiratory tract after inhalation exposure, due to its irritation properties.

Consequently, a NOAEL and a NOAEC were determined to be 10 mg/kg/day for male rat after oral dosing (42 to 63 days of exposure) and 12 mg/m^3 (2 ppm) for rat after inhalation dosing (90-day exposure) respectively. The neurotoxicity NOEL was 15 ppm (13-week exposure).

Furthermore, LOAECs were estimated at 2.6 ppm in rats and rabbits (6-month exposure), 0.6 ppm in mice (2-year exposure), 3.2 ppm in rats (2-year exposure), and also 2 ppm in female rabbits (13 days exposure).

7.3.4 Additional relevant toxicity data — Glycidol, principal metabolite

As per Figure 1 (section 7.1.4), glycidol is the main metabolite during the metabolisation of GMA.

7.3.4.1 Oral and inhalation route

Several oral and inhalation studies were available for glycidol. No dermal study for glycidol was available.

The details presented here are available from the C&L proposal on glycidol; two oral dose-range finding studies (14 days) in F344/N rats and B6C3F1 mice were followed by two oral 13-week repeated dose toxicity studies in the same species (NTP, 1990) as cited in (ECHA, 2015):

- Rat, oral, 91-day study (25, 50, 100, 200 and 400 mg/kg of glycidol)
  All rats that received 400 mg/kg died by week 2; three males and one female that received 200 mg/kg died during weeks 11-12.
  Sperm count and sperm motility were reduced in male rats that received 100 or 200 mg/kg. Necrosis of the cerebellum, demyelination in the medulla of the brain, tubular degeneration and/or necrosis of the kidney, lymphoid necrosis of the thymus, and testicular atrophy and/or degeneration occurred in rats that received 400 mg/kg.
- Mouse, oral, 91-day study (19, 38, 75, 150 and 300 mg/kg of glycidol)
  All mice that received 300 mg/kg died by week 2; deaths of mice that received 150 mg/kg occurred during weeks 4-8 for males and weeks 1-5 for females.
  Sperm count and sperm motility were reduced in dosed male mice. Compound-related histopathologic lesions included demyelination of the brain in males and females that received 150 or 300 mg/kg, testicular atrophy in males at all doses, and renal tubular cell degeneration in male mice that received 300 mg/kg.

Also, an inhalation study was performed in Long-Evans rats exposed to glycidol for 50 days, at one concentration: 1.2 mg/L ((Hine et al. (1956) as cited in (ECHA, 2015)):

- One rat died of bronchopneumonia between days 49 and 50, without any other deaths. Very slight irritation of the eyes, with slight lacrimation and encrustation of the eyelids and slight respiratory distress were observed following the first few exposures to glycidol. These signs of toxicity did not increase in severity with subsequent exposures. Necropsy at the end of dosing revealed no significant gross or microscopic lesions.

7.3.4.2 Comparative findings

The observed effects in the available oral and inhalation repeated dose studies indicate mainly local effects of GMA at the port of entry. The RAC (ECHA, 2015) considered that these effects were likely concentration-dependent and would occur already after a single exposure at concentrations not so different from the dose levels at which these effects were actually observed in the repeated dose study. The local effects are due to the irritating/ corrosive properties of GMA. Systemic effects were absent or limited. Partially different toxicity effects were observed with repeated dose toxicity studies with glycidol probably because glycidol is an irritant (and not corrosive as GMA).

GMA induced more severe local effects at lower doses/concentrations (oral: squamous hyperplasia in forestomach; inhalation: hyperplasia of respiratory epithelium of the nasal tissues), in comparison to glycidol (oral: no reported local effects; inhalation: very slight irritation of the eyes, slight lacrimation and encrustation of the eyelids and slight respiratory distress). Both GMA and glycidol induced systemic effects on the kidney and male reproductive system: reduction in sperm motility for GMA and testicular atrophy for glycidol, at comparable doses. However, glycidol induced effects on the brain (demyelination and other) which were not observed with GMA, at an external dose level that was (or could) not be tested with GMA (ECHA, 2015).

7.4 Irritancy and corrosivity

Glycidyl methacrylate has an entry in Annex VI of the CLP regulation as a Skin Corr. 1C and Eye Dam. 1.

7.4.1 Human data

Shimizu et al. (2008) described a case of severe irritant contact dermatitis in a 21 year-old female chemistry undergraduate student who accidentally spilled GMA on her hands and right foot. She immediately washed her hands and no symptoms occurred later on the hands. However, she did not wash her right foot until she went home, 6 hours later. An erythema appeared on her foot the next morning and a topical corticosteroid was prescribed. Large painful blisters appeared a few days later and a clinical examination showed several tense blisters surrounded by macerated skin. Because the patient declined patch testing, skin sensitisation cannot be excluded.

7.4.2 Animal data

7.4.2.1 Skin irritation and corrosion

In an OECD TG 404 study (Lockwood, 1991), New Zeeland White rabbits were examined 4, 24 and 48 hours after a 4-hour exposure to 0.5 ml of GMA under occlusive conditions (ECHA, 2015, ECHA, 2022).
When exposed for 1 hour, slight erythema and moderate erythema were observed in some animals. Oedema and/or erythema were further observed at all time points in all rabbits. They were accompanied by moderate necrosis (score 4) in 2/6 animals at the last observation point of 48 h after exposure. Necrosis was also identified in another animal at 48 hours and described as very slight (score 2) and in 2 animals at 24 hours and described as superficial (score 3).
Reversibility or worsening of the lesions in this study could not be further assessed as no data was available later than 48 h after exposure.

Two other studies found in (ECHA, 2015, ECHA, 2022) were considered despite their limitations:

- In a poorly reported study (Olson, 1960), a single covered topical application (10% aqueous solution of GMA) to the skin of an albino rabbit for 4 hours induced moderate to severe skin irritation including necrosis with slight to moderate oedema and mortality.
- (Ou-Yang et al., 1988) also reported high irritation and necrosis after skin exposure to GMA (0.1 ml/ 100 mg neat GMA, 5-day exposure). The tested area showed as red, swelled and blistered after one or two days, with subdermal bleeding and ulcers developing after three days, and hard, thicker, cracked, pigmentation after five days. The pathological changes were degeneration and necrosis of surface skin cells, disappearance of cellular boundaries, displaying pink staining material, bleeding in the corium cells and lymph cell infiltration with accompanying formation of abscesses.

7.4.2.2 Eye irritation

In the Nitschke et al. (1990) study reported earlier (see section 7.2.2.3) (OECD TG 403), rats were exposed to vapours of GMA (105, 269 and 412 ppm, equivalent to 610, 1563, 2394 mg/m^3) for 4 hours and exhibited eye irritation and corneal opacity. These changes were not reversible within 14 days post-exposure.

In Olson (1960), direct instillation of undiluted GMA was applied to both eyes of albino rabbits. Within 30 seconds, one eye was washed with tap water for two minutes. GMA was allowed to remain in the other eye.
Results showed that (i) slight to moderate conjunctivitis was observed in the unwashed eye where slight corneal injury cleared in one week; (ii) slight conjunctivitis was observed in the washed eye, which cleared in one hour.
Corneal damage did not heal within 7 days post-dosing. This ocular damage was prevented by washing with water within 30 seconds (Olson, 1960; Smyth, 1969).
In a solution of 10% GMA in propylene glycol, slight conjunctivitis was observed in the unwashed eye, which cleared after 48 hours, and slight conjunctivitis was observed in the washed eye, which cleared within 24 hours.

In a subacute study (Landry et al., 1991) as cited in (ECHA, 2015, ECHA, 2022), rats were exposed at 58.2, 223 and 931 mg/m^3 (equivalent to 10, 40 and 160 ppm respectively), 6 hours/day, 5 days/week for 2 weeks. As a result, eye irritation and corneal clouding were observed at 931 mg/m^3.

(Vedula et al., 1995) exposed, via inhalation, female rabbits during day 7 to day 19 of gestation to GMA at concentrations of 29.1, 58.2 and 291 mg/m^3 (or 5, 10, 50 ppm; daily intake is calculated as 2.6, 5.2 and 26.2 mg/kg/day, respectively), 6 hours/day, found in (ECHA, 2015). At 58.2 mg/m^3 (10 ppm), there were signs of ocular and respiratory irritation consisting of reddened eyes, wet muzzle and sneezing after exposure were observed.
(Vedula et al., 1996) exposed, via inhalation, female rabbits during day 7 to day 19 of gestation to GMA at concentrations of 2.9, 11.6 and 58.2 mg/m^3 (or 0.5, 2, 10 ppm, respectively) 7 hours/day (found in (ECHA, 2015)).
Treatment-related in-life observations included excessive sneezing after exposure, reddened eyes, facial soiling and dorsal extension of the during exposure at high dose (10 ppm).

7.4.2.3 Respiratory irritation

In Nitschke et al. (1990), laboured breathing was induced in rats after acute inhalation exposure for 4 hours at 1563 mg/m^3 and 2394 mg/m^3 of GMA (OECD, 2000, ECHA, 2022).

In another acute inhalation study (Haag, 1953), exposure at 1,400 mg/m^3 (equivalent to 237 ppm respectively) GMA for 6 hours, induced changes in the lungs, thorax, respiration, etc. in rats, rabbits, guinea pigs and dogs. These changes are suspected to result from respiratory irritation (OECD, 2000, ECHA, 2022).

In the inhalation repeated dose toxicity studies (see section 7.3.2.3), there were also many changes in the respiratory tract, such as noisy and difficult respiration (mouth breathing), and hyperplasia, necrosis and inflammation in nasal tissues, with LOAEC 15 ppm (NOAEC 2 ppm) in the 13-week study by Laundry et al. (1996), and LOAEC 10 ppm (lowest dose tested) in the 2-week study by Laundry et al. (1991) (both in (ECHA, 2015, ECHA, 2022)).

In one subacute toxicity study (Cieszlak et al., 1996) (as cited in (ECHA, 2015, ECHA, 2022), rabbits were exposed at 2.9, 11.6, 29.1, 58.2 mg/m^3 (equivalent to 0.5, 2.0, 5.0 and 10 ppm respectively), 6 hours/day, daily for 13 (consecutive) days.
- Treatment-related degeneration of the nasal olfactory epithelium was observed at 11.6 mg/m^3. Nonetheless, nasal tissue was indistinguishable from controls at one month post-exposure.
- At 29.1 and 58.2 mg/m^3, there were olfactory epithelial degeneration, and hyperplasia, erosions, ulcers and inflammation of the nasal epithelium. After 4-week recovery period, there was complete reversibility of these changes except for olfactory epithelial degeneration, which showed only partial reversibility.

7.4.3 Summary

Based on these data, GMA is considered irritant to the skin, eyes and respiratory tract. Because the irritation occurs at the site of first contact, the irritation is expected to be stronger via inhalation route.

7.5 Sensitisation

Glycidyl methacrylate has an entry in Annex VI of the CLP regulation as a Skin Sens. 1.

7.5.1 Human data

7.5.1.1 Respiratory sensitisation

There are no data on respiratory sensitisation of GMA.

7.5.1.2 Skin sensitisation

(Dempsey, 1982) described three cases of allergic contact dermatitis of the hands in workers exposed to GMA employed in anaerobic industrial sealants. Both closed and open patch testing with 1% GMA solution in petrolatum was positive in all three cases. Positive patch test results were also seen to ethyl methacrylate, methyl methacrylate and polyurethane dimethacrylate. For three patients a 2+ reaction (a strong edematous or vesicular reaction according to recommendations of the International Contact Dermatitis Research Group).

Note: the concurrent exposure to other acrylates is frequent in this industry. Hence, an exposure to a single acrylate is rarely seen in practice

Matura et al. (1995) described a case of contact sensitivity to GMA and ethoxyethyl acrylate in a 31-year-old non-atopic female chemist. She compounded emulsions used to impregnate paper and textile materials to make them oil and water resistant. For six months she was in contact with acrylate derivatives, isocyanates and other chemicals. She then developed a recurrent acute vesiculo-papular hand dermatitis, accompanied by severe itching and burning (appeared mainly on the fingertips, palmar and dorsal aspects of the fingers, and both palms). It improved on holidays and on treatment with a topical corticosteroid. Patch testing with the European standard series and (meth)acrylate series

(Chemotechnique) showed positive reactions to nickel (relevant to jewellery intolerance) and two of her own materials: GMA (0.1% and 0.05% in acetone) and ethoxyethyl acrylate (both positive down to 0.05% and 0.1% in acetone).

(Gruvberger et al., 1998) described an investigation of occupational dermatoses, based on questionnaire, clinical examination and patch testing, among 85 present and 17 former workers of a Swedish plant producing binders for paints and glues. Commonly used acrylates included methyl methacrylate, butyl acrylate and 2-ethylhexyl acrylate. Workers were also exposed to vinyl chloride, styrene, dibutyl maleate and methylchloroisothiazolinone/methylisothiazolinone (MCI/MI). Occupational contact allergies were detected in 13 present and 3 former employees. Patch testing was performed with various substances, including to GMA in 0.2% petrolatum.
Contact allergy to GMA, 2-(acetoacetoxy)ethyl methacrylate, N-isobutoxymethylacrylamide and 2-hydroxyethyl methacrylate was demonstrated in one production worker.

(Sanchez-Perez et al., 2008) described a case of occupational allergic contact dermatitis in a 26-year old women who worked for a company manufacturing lenses and spectacles. There GMA was used for coating lenses in spectacles. For the last two years, her work consisted of refilling injectors with a mixture of various chemical substances containing (meth)acrylates. She was diagnosed with itchy vesicles that appeared in the first and second fingertips of her right hand that later spread to the rest of her fingertips, the dorsum of the fingers and the rest of both hands. The lesions disappeared after one month of treatment with topical corticosteroids, coinciding with her vacation period. Similar lesions reappeared just one day after returning to work only to disappear again after three weeks during her sick leave. Patch tests to GMA were positive to 0.5% and 0.05% in acetone. Patch test were also positive to 2-hydroxyethyl methacrylate (2-HEMA), ethylene glycol dimethacrylate (EGDMA), 2-hydroxypropyl methacrylate (2-HPMA), diethylene glycol diacrylate (DEGDA), triethyleneglycoldiacrylate (TEGDA) and epoxi cycloaliphatic resin.

Vogel et al. (2014) described a case of occupational bullous allergic contact dermatitis in a 50-year old man working for three years as a process operator who controlled production processes and manually added ammonium persulfate and different liquid acrylates in a semi-closed process. According to safety data sheets these liquid acrylates included GMA and 1,6- hexanediol diacrylate. Patch testing with the European baseline series and an additional national series was performed. Positive patch test results were observed for the (meth)acrylates series and the dilution series of the patient's own industrial acrylates GMA and 1,6- hexanediol diacrylate. The severity of reaction increased with a level of exposure to GMA: 0.01% pet. (no reaction), 0.03% petrolatum (questionable reaction), 0.1% petrolatum (+/++), 0.3% petrolatum and 1% petrolatum (+++).

(Aalto-Korte et al., 2009) reviewed the 1994–2008 patch test files at the Finnish Institute of Occupational Health between 1994–2008 for reactions to the five epoxy (meth)acrylates. Among 24 patients had an allergic reaction to at least one of the studied epoxy (meth)acrylates. Nine patients developed a positive patch test reaction [16] to GMA 0.1% in petrolatum: dentist (+), manicurist (+), plumber (+), machinist-assembler (+), warehouse-worker (+), assembler in a foundry (++), two bricklayers (+/++) and renovation worker (+). Several of these cases had been also reported in (Aalto-Korte et al., 2008, Aalto-Korte et al., 2010).

---

[16] Reactions are graded on a spectrum as: negative, +/- doubtful, + weak positive, ++ moderate reaction, +++ strong reaction.

(Aalto-Korte et al., 2008) studied the patterns of allergic patch test reactions to acrylic monomers in relation to exposure in patients sensitized from glues. Authors observed three cases of positive patch test results to GMA 0.1% in petrolatum (+) among 10 patients who had contact allergy to methacrylates or acrylates and had used acrylic glues at work. These workers worked as sewing-machine mechanics and assemblers in a foundry.

(Aalto-Korte et al., 2007) aimed to analyse patch test reactivity to 36 acrylic monomers in Finnish dental personnel and found out that among 15 dental nurses GMA yielded a negative reaction or was not tested.

Several authors questioned whether contact sensitisation to acrylates is concomitant, a cross-reaction or a reaction to the impurities in preparations which use all these compounds (Sanchez-Perez et al., 2008, Aalto-Korte et al., 2009, Aalto-Korte et al., 2010). It is known that in an industrial setting most acrylates contain up to 20% contamination with other acrylates (Rustemeyer et al., 2001, Kanerva, 2001).

7.5.2 Animal data

7.5.2.1 Respiratory sensitisation

No respiratory sensitisation was observed in any of the acute or sub-acute inhalation studies.

7.5.2.2 Skin sensitisation

In the key study (Dow, 1990) as found in (ECHA, 2015, ECHA, 2022), guinea pigs received three topical applications with 0.4 ml of 10 % (third application) or 25 % (first and second application) GMA in dipropylene glycol monomethyl ether during the three-week induction phase. The single challenge application with 1% GMA induced slight erythema in these animals (7/10). The concentrations were lowered for the challenge application due to the erythema observed after the third induction, Also necrosis was observed on four animals treated with GMA.
The authors concludes that GMA caused delayed contact hypersensitivity. This study deviates from the OECD TG 406 as no control animals (only exposed to the solvent during induction and exposed to the same GMA concentration during the challenge) were included.

Other studies provided similar supportive results:
- the Bibra study (1988), only informed that there was an induced positive reaction in first reading in 6 out of 6 guinea pigs (ECHA, 2015).
- Ou-Yang et al. (1988) (as cited in (ECHA, 2015)) reported on delayed and rapid allergy reaction tests in guinea pigs:
  - In delayed allergy reaction test, the induction was performed with localized smear applications or intradermal injection with 0.1 ml of 1% GMA in acetone for 10 days and the challenge with an unknown concentration. The authors observed induced hyperaemia, oedema, scleroma and necrosis (these changes reached a peak on the fourth day), which belong to the strong allergenic category.
  - In rapid allergic reaction test, two tests by active and passive stimulation were conducted: (i) In the active stimulation, 0.5 % GMA with homologous serum albumin was injected intradermally and the challenge was conducted intravenously. Breathing difficulties, wheezing, increased mouth and nose secretions, spasms and death were observed, belonging to the strong allergic category; (ii) In the passive stimulation, firstly, the diluted serum given from the sensitized guinea pig was injected subcutaneously to other animals and one hour later, 0.5 ml of 0.1% GMA with homologous serum albumin was injected intravenously to the same animals. Blue circles or spots observed belonged to the strong allergic category.

- o Using the evaluation standards of rating the intensity of delayed reactions, the skin smear allergic intensity was 14 and the intradermal injection intensity was 13, both belonging to the strong allergenic category. The author reported that it may be due to the fact that the epoxy radical of GMA may easily combine with proteins.

7.5.3 Summary

In several case reports, positive epicutaneous tests with GMA in eczema patients, from which a sensitising effect in humans can be inferred. Some of these reactions may result from a cross-reaction after previous sensitisation by structurally related acrylates, methacrylates or aliphatic glycidyl compounds. The findings in humans are supported by positive results from an animal experiment, without the use of adjuvants.
A contact-sensitising effect of GMA is also plausible from a structural point of view. Data on a sensitising effect on the respiratory tract are not available (DFG, 2015).

The key study (Dow, 1990) showed erythema in 7 out of 10 guinea pigs dermally induced with 25% GMA (reduced to 10% for the third induction) and dermally challenged with 1% GMA. The method used resembles the Buehler method. However, a negative control group was missing. The induction dose of 10% induced also some local effects.
Because of the strong reduction in concentration of the challenge dose it is expected that the observed effects are sensitisation and not irritation. The key study is supported by some other test with (very) limited study information or using a different, non-standard, approach. Although the predictive value of these studies is not known, the results were considered positive.

Based on these data, GMA is considered to be a skin sensitizer.

7.6 Genotoxicity

Glycidyl methacrylate has an entry in Annex VI of the CLP regulation as a Muta. 2 substance.

7.6.1 Human data

No data from exposed humans are available.

7.6.2 Animal data (*in vivo*)

A number of *in vivo* genotoxicity studies have been reported and are summarised below in Table 9.

Repeated oral administration of GMA to F344 rats caused a concentration-dependent increase in the frequency of micronucleated reticulocytes and *Pig-a* mutant red blood cells and reticulocytes as a result of DNA damage identified in liver, kidney and bone marrow cells (all assays performed per OECD Test Guidelines).

Based on these findings, GMA was deemed by the authors to be a systemic genotoxin and mutagen in rats (Dobrovolsky et al., 2016). Administration of GMA by gavage yielded positive results in mice and rats in the micronucleus assay, with DNA damage and specific adducts detected in a number of tissues in rats. Administration by i.p produced mixed outcomes in the micronucleus assay and induced unscheduled DNA synthesis in germ cells in mice.

Table 9: Summary of *in vivo* genotoxicity studies

Species (test system)	Dose levels/ route/ duration	Study endpoints	Results	References
Transgenic BigBlue Fischer 344 rats, M (n=15/group)	1, 10 and 25 ppm (5.82, 58.2, and 145.5 mg/m^3) (calculated daily doses: 0.71, 7.08, 17.70 mg/kg/day); 6 h/day, 5 days/wk for 4 weeks	*Lacl* locus, gene mutations	negative in olfactory and respiratory epithelium at the highest dose	Gollapudi et al 1999 as cited in (OECD, 2000, ECHA, 2022, ECHA, 2015)
Rat, Fischer 344, M (n=6); RBCs and RETs in peripheral blood	0, 50, 100 and 150 mg/kg/day up to 29 days; gavage	*Pig-a* assay; mutagenicity; induction of CD59-deficient *Pig-a* mutant RBCs and RETs	**positive** dose-dependent increase in frequency of mutant RBCs (at all doses, on days 29 and 56) and RETs (at 100 and 150 mg/kg/day doses, as early as day 15)	(Dobrovolsky et al., 2016)
Mice	42.2., 133, 422, and 464 mg/kg, i.p	Micronucleus assay	negative	INBIFO 1979 as cited in (OECD, 2000)
Mice, M; PCE	up to 300 mg/kg, i.p; 2x, 24 h interval	Micronucleus assay	**positive** slight increase in micronucleated cells (at 25 mg/kg bw/day), with an inverse dose-response	Ouyang et al 1988 as cited in (IARC, 2020)
Mice, CD-1, (n=5/sex/ group/sacrifice time); PCE	75, 150, 300 mg/kg, i.p	Micronucleus assay	negative	Lick et al., 1995 as cited in (OECD, 2000)
Mice, Crj:BDF1; M+F (n=5/sex/ group)	M: 188, 375 and 750 mg/kg; F: 250, 500, 1000 mg/kg; gavage	Micronucleus assay	**positive** significantly at the highest dose in both sexes	MHW 1997 as cited in (OECD, 2000)
Rat, Fischer 344, M (n=6); peripheral blood RETs	0, 50, 100 and 150 mg/kg/day up to 29 days; gavage	Micronucleus assay	**positive** dose-dependent increase, significant at 150 mg/kg/day	(Dobrovolsky et al., 2016)
Mice, Kunming hybrid strain, M, 5 groups (n=5/group)	25, 50, 100 mg/kg, single i.p injection	Unscheduled DNA synthesis in germ cells	**positive** slight increase (25 mg/kg bw per day), not dose-dependent	(Xie et al., 1990b)
Wistar rats, M, 5 groups; liver, kidney, white blood cells, testis	31.25, 62.5, 125, 250 mg/kg for 14 days, gavage	DNA adducts (RP-HPLC and nuclease P1 mediated ^{32}P-postlabelling method	**positive** several GMA-DNA adducts were formed in various organs (in white blood cells, 4 types, liver and kidney, 3 types and testis 1 type); adducts levels: kidney > liver > white blood cells > testis; plateaued at 125	Tan et al., 1999 and Fang et al. 1999, as cited in (IARC, 2020)

Species (test system)	Dose levels/ route/ duration	Study endpoints	Results	References
			mg/kg N3-methacrylate-2-hdroxypropyl-deoxycytidine monophosphate detected in kidney, liver and white blood cells	
Rat, Fischer 344, M (n=3-6); liver, bone marrow and kidneys	0, 50, 100 and 150 mg/kg/day up to 29 days; gavage or 250 mg/kg/day for 3 days	DNA damage; alkaline comet assay	**positive** 29 d: in bone marrow and liver cells (≥100 mg/kg/day) 3 d: all tested tissues	(Dobrovolsky et al., 2016)

PCE: polychromatic erythrocytes; RBC: red blood cells; RET: reticulocytes
Note: Positive outcomes are always presented in bold

7.6.3 *In vitro* data

The mutagenic potential of glycidyl methacrylate in *Salmonella typhimurium* has been confirmed in tester strains TA97, TA100, TA1535, TA102, in the presence and absence of microsomal S9 fraction (metabolic activation). GMA was also mutagenic in *Klebsiella pneumoniae* and in *Escherichia coli*. Relevant studies in bacterial test systems are presented in Table 10.

Table 10: Summary of *in vitro* genotoxicity studies in bacterial test systems

Species (test system)	Dose levels	Study endpoints	Results		References
			With metabolic activation	Without metabolic activation	
Salmonella typhimurium TA100 TA1535 TA1537 TA98	32, 100, 320, 1000 mg/ plate	Bacterial reverse mutation	**positive** negative	**positive** negative	Goodyear 1981 as cited in (OECD, 2000)
Salmonella typhimurium TA100 TA1535 TA97 TA98	10, 33, 100, 333, 1000 mg/ plate	Bacterial reverse mutation	**positive** negative	**positive** negative	Dorothy et al., 1986 as cited in (OECD, 2000)
Salmonella typhimurium TA100 TA1535 TA97	10 mg/ plate - 1 mg/ plate	Bacterial reverse mutation	**positive** ≥33 mg/plate **positive**	**positive** ≥33 mg/plate **positive**	(Canter et al., 1986)

Species (test system)	Dose levels	Study endpoints	Results		References
			With metabolic activation	Without metabolic activation	
TA98			negative	negative	
Salmonella typhimurium *TA100* *TA95* *TA98*	112, 224, 448, 896 mg/ plate	Bacterial reverse mutation	**positive** all doses negative	**positive** all doses negative	OuYang et al, 1988 as cited in (IARC, 2020)
Salmonella typhimurium *TA97a* *TA98* *TA100* *TA102*	0.25, 0.5, 1.25, 5.0, 12.5 mg/ plate	Bacterial reverse mutation	weakly **positive** 0.25 mg/plate negative **positive** 0.25 mg/plate weakly **positive** 0.25 mg/plate	weakly **positive** 0.25 mg/plate negative **positive** 0.25 mg/plate weakly **positive** 0.5 mg/plate	(Schweikl et al., 1998)
Klebsiella pneumoniae	0.05, 0.1, 02., 0.5, and 1 mmoles/l	Mutagenicity	-	**positive** ≥0.2 mmoles/l	Voogd et al., 1981, as cited by (IARC, 2020)
Escherichia coli HB101	0.1, 0,3 and 1.0 mmol/l	Transformation mutations, (restriction enzyme mapping)	-	**positive** reduced for GMA-modified plasmid DNA (pBR322); mutations in transformants	(Xie et al., 1990a)
Escherichia coli PQ37	0.1, 0.3, 1.0 mmol/l 0.3 mM (43 mg/plate)	SOS-Chromotest – DNA damage repair induction (b-galactosidase induction)	-	**positive**	(von der Hude et al., 1990)

-: Not reported/not tested
Note: Positive outcomes are always presented in bold

In mammalian systems, GMA consistently exerted mutagenic activity in Chinese hamster, mouse and human cells and induced malignant transformation in Syrian Hamster embryo (SHE) cells and human lung fibroblasts. GMA was positive in all the reported cytogenetic assays (i.e induction of micronucleated cells, sister-chromatid exchange, chromosomal aberrations) and produced DNA damage (single and double-strand breaks), as shown in Table 11.

Most of the GMA effects were concentration-dependent and the majority of the *in vitro* studies were conducted/reported without metabolic activation. GMA-mediated DNA breakage, confirmed as oxidative DNA damage by the modified comet assay was significantly reduced in the presence of antioxidant NAC, supporting a role of oxidative stress and ROS in the observed genotoxicity (Lee et al., 2006, Styllou et al., 2015, Styllou et al., 2017, Poplawski et al., 2009).

Table 11: Summary of *in vitro* genotoxicity studies in mammalian cells

Species (test system)	Dose levels	Study endpoints	Results		References
			With metabolic activation	**Without metabolic activation**	
Mouse, embryonic fibroblasts, BALB/c 3T3 cells		Mutation	-	**positive** 64 mg/ml	Lei et al 1998 as cited in (IARC, 2020)
Chinese hamster ovary (CHO) cells	+S9: 25-600 mg/ml -S9: 5-80 mg/ml	CHO/HGPRT forward gene mutation assay	**positive** ≥ 500 mg/ml	negative ≥ 50 mg/ml	Linscombe and Engle, 1995 as cited in
Chinese hamster (V79) cells	0, 0.1, 0.2 mM (-S9) 0, 0.2, 0.3 mM (+/- S9)	*Hprt* locus forward gene mutation assay	negative	**positive** ≥0.1 mM, dose-dependent	(Schweikl et al., 1998)
Human lung fibroblast (2BS) cells		*Hprt* locus forward gene mutation assay	-	**positive** 1.0 µg /ml concentration-dependent	Yin et al, 2003 as cited in (IARC, 2020)
Human bronchial epithelial (16HBE) cells		Mutation of DNA repair genes (*XRCC1, hMSH2, XPD, XRCC3*)	-	**positive** 8 µg/ml only for the hMSH2 gene	Dong et al, 2009 as cited by (IARC, 2020)
Human embryonic lung fibroblasts (cell line)		Mutation of *TP53* gene	negative	**positive** 8 µg/ml exon 9 altered	Tan et al., 1996, Tan et al., 1997 as cited in (IARC, 2020)
Golden Syrian hamster embryonic stem cells (SHE)	0.9-14.2 mg/l	Transformation	-	**positive**	Yang et al., 1996 as cited in (OECD, 2000)
Human embryonic lung fibroblasts		Transformation		**positive**	Tan et al., 1999 as cited by (IARC, 2020)
Syrian hamster embryonic (SHE) stem cells		Transformation	-	**positive**	Xie et al., 1992 as cited in (OECD, 2000)

Species (test system)	Dose levels	Study endpoints	Results		References
			With metabolic activation	**Without metabolic activation**	
Human lung fibroblast (2BS) cells		Transformation	-	**positive**	Yin et al., 2003 as cited in (IARC, 2020)
Human bronchial epithelial (16HBE) cells	0, 1, 2, 4, 8 mg/ml	Transformation	-	**positive** ≥1 mg/ml 8 mg/ml; methylation pattern of a number of gene promoters changed	Yang et al., 2009 Wang et al., 2014, as cited in (IARC, 2020)
Human embryonic lung fibroblasts		Transformation		**positive** early stage methylation of P16 gene promoter methylation of the opioid binding protein/cell adhesion molecule-like (OPCML) gene promoter	Hu et al., 2012, as cited in (IARC, 2020) Liu et al., 2015 (as cited in (IARC, 2020)
Chinese hamster (V79) cells	-S9; 24 h: 0, 100, 150, 200 mmol/l +S9; 4 h:0, 100, 200, 300, 400, 500 mmol/l)	Micronucleus assay	negative negative	**positive** ≥100 mmol/l **positive** ≥200 mmol/l, dose-dependent	(Schweikl et al., 2001)
Chinese hamster (V79) cells	0, 0.1, 0.15, 0.2 mM	Micronucleus assay	-	**positive** ≥ 0.1 mM/14 mg/ml dose-dependent; effect reduced by NAC	(Lee et al., 2006)
Chinese hamster (V79) cells	0.02, 0.039, 0.078, 0.16, 0.31 mM	SCE exchange	-	**positive** 0.078 mM/11 mg/ml	(von der Hude et al., 1991)
Chinese hamster lung (CHL/IU) cells	-S9, continuous: 0.0063, 0.013, 0.025, 0.050 mg/ml -S9, short-term: 0.011, 0.022, 0.044, 0.088 mg/ml	Chromosomal aberration	**positive** clasto-genicity ambiguous for polyploidy	**positive** clastogenicity, polyploidy	MHW, Japan 1997 as cited in (OECD, 2000)

Species (test system)	Dose levels	Study endpoints	Results		References
			With metabolic activation	Without metabolic activation	
	+S9 (short-term): 0.044, 0.088, 0.18, 0.35 mg/ml				
Human embryonic lung fibroblasts		Chromosomal aberration		**positive**	Tan et al., 1998 as cited in (IARC, 2020)
Human Bronchial epithelial (16HBE) cells	4, 8, 12, 16 and 20 mg/ml (1-3 times)	Chromosomal aberration		**positive** dose-dependent	Wang et al., 2011 as cited in (IARC, 2020)
Human/rat lymphocytes	-	Unscheduled DNA synthesis	-	(weakly) **positive**	(Xie et al., 1990b)
Human/rat lymphocytes		Non-reverse type inhibition of DNA replication		**positive**	Xie et al., 1989 as cited in (OECD, 2000)
Human lung fibroblast (2BS) cells		DNA breaks; alkaline comet assay, DNA fragmentation (ladder assay)	-	**positive** 0.5 µg/ml dose-dependent	Ying et al, 2003 – as cited by (IARC, 2020)
Rat clonal pulp (RPC-C2A) cells; isolated DNA	0, 300 mM	DNA fragmentation	-	**positive** reduced by NAC	(Lee et al., 2006)
Human peripheral blood lymphocytes	0.3-5 mM	Oxidative damage, DNA strand breaks and DNA repair (double, total); alkaline/neutral comet assay +/- Endo III and Fpg	-	**positive** ≥0.3 mM dose-dependent	(Poplawski et al., 2009)
Human peripheral blood lymphocytes	0.3-5 mM	DNA double strand breaks (PFGE)	-	**positive** 1.2-5 mM	(Poplawski et al., 2009)
Human gingival fibroblasts (HGFs)	0, 0.012, 0.03, 0.1, 0.3 mM	DNA strand breaks, immuno-fluorescence; γ-H2AX/53BP1 foci; chromatin condensation	-	**positive** ≥0.012 mM dose-dependent; effect reduced by NAC	(Styllou et al., 2015) and (Styllou et al., 2017)

-: Not reported/not tested; SCE: Sister Chromatid Exchange; PFGE: Pulsed Field Gel Electrophoresis; NAC: N-Acetyl Cysteine

Note: Positive outcomes are always presented in bold

Glycidyl methacrylate has been shown to covalently bind to plasmid DNA (pBR322) by spectrophotometric methods. GMA-modified pBR322 exhibited reduced transformation efficiency in *Escherichia coli HB101* and induced stable and heritable mutations in the

ampicillin or tetracycline resistant genes regions in the transformants, suggesting that GMA interaction with DNA produces premutagenic lesions that can be converted in cells into point mutations (Xie et al., 1990a) (Fang, 1991) (Gao et al., 1994). Further sequence analysis revealed that GMA-induced mutations occur predominantly at C-G runs and at the 5'-CNCCN-3' sequence (Gao et al., 1994).

GMA was also shown to bind strongly (covalently) to calf thymus DNA, based on a shift and a decrease in the DNA absorption spectrum (Xie et al., 1990b). The *in vitro* interaction of GMA with calf thymus DNA and dAMP, dCMP, dGMP, dTMP was further analysed by HPLC, UV and mass spectrometry. The results confirmed the sequence specific covalent DNA binding at the N6-adenine and N3-cytosine positions with the main GMA-calf thymus DNA adduct identified as N3-methacrylate-2-hydroxypropyl-dCMP (Fude et al., 1999). However, GMA failed to introduce any strand breaks to plasmid DNA (pUC19), as assessed by a plasmid relaxation assay, up to concentrations of 5 mM (Poplawski et al., 2009). GMA-induced DNA damage was detected in bone marrow, liver and kidney cells of orally exposed F344 rats while the major adduct: N3-methacrylate-2-hydroxypropyl-deoxycytidine monophosphate was found in kidney, liver and white blood cells ((Dobrovolsky et al., 2016) and (Tan et al., 1999; Fang et al., 1999 as cited in (IARC, 2020)).

Also GMA induced specific epigenetic changes at different stages of the malignant transformation of treated human bronchial epithelial cells or embryonic fibroblasts (Table 11). The changes in the methylation pattern of a number of gene promoters including P16 and POCML were considered as specific biomarkers of the transformation process (Wang et al., 2014; Hu et al., 2012; Liu et al., 2015 as cited in (IARC, 2020).

Glycidol (metabolite of GMA; a reactive epoxide that has been demonstrated to alkylate DNA in several studies) has been shown to induce chromosomal aberrations and unscheduled DNA synthesis in human cells and has consistently yielded positive results (e.g. mutagenicity, micronuclei induction, chromosomal aberrations, sister-chromatid exchange, DNA damage) in mammalian cells. Additionally, glycidol has consistently displayed mutagenic activity in bacteria (reviewed by (IARC, 2020), references found therein).

7.6.4 Summary

No data for exposed humans are available. Glycidyl methacrylate is mutagenic in a number of *Salmonella typhimurium* tester strains, with or without metabolic activation. It has also exhibited mutagenic activity and has yielded uniformly positive results in cytogenetic assays in mammalian cells including primary human cells.
In animals, GMA has produced predominantly positive results, with more recent, OECD test guidelines-compliant oral studies suggesting that it is a systemic genotoxicant and mutagen in rats. DNA damage has been evident in naked DNA, DNA isolated from treated cells and genomic DNA from exposed animals. GMA-mediated DNA damage is reduced by concomitant antioxidant treatment implicating oxidative stress and ROS in the observed genotoxicity. GMA has also been shown to produce epigenetic changes, with the methylation of specific gene promoters occurring at the early stages of malignant transformation.

7.7 Carcinogenicity

Glycidyl methacrylate has an entry in Annex VI of the CLP regulation as a Carc. 1B substance.
IARC (2020) concluded that glycidyl methacrylate is *probably carcinogenic to humans (Group 2A)*. This conclusion was based on *inadequate evidence* in humans and *sufficient evidence* in experimental animals for the carcinogenicity of glycidyl methacrylate.

The IARC rationale was summarised as follows: "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."

7.7.1 Human data

IARC (2020) did not identify any human data regarding carcinogenicity of GMA. No human carcinogenicity data were identified since IARC (2020) evaluation.

7.7.2 Animal data

Two-year inhalation carcinogenicity studies in mice and rats have been conducted and reported by the Japan Bioassay Research Centre (JBRC, 2015) as cited by (IARC, 2020). The main findings of these GLP-compliant studies are summarised in Table 12. (Note: the preneoplastic findings are presented in section 7.3.2.3).

In the mouse study, B6D2F1/Crlj mice were exposed by whole-body inhalation to GMA vapours. At the end of the study, the survival rates of males exposed to 2.5 and 10 ppm (30% and 28%) and of females in the 0.6 and 10 ppm groups (30% and 18%) were significantly lower than those of concurrent controls (52% and 54% in males and females, respectively). There was no significant effect on the body weight of exposed males and females.
The mean body weights of males and females in the 10 ppm group remained slightly lower than those of the control groups, throughout the dosing period.
Significant reductions in the relative weights of the lungs at 0.6 and 2.5 ppm and of the brain in the 10 ppm dose group, were noted in female mice only.

At the highest dose of 10 ppm, GMA caused, compared to controls, significant increases in the incidences of:
- in males and females: hemangioma and hemangioma or hemangiosarcoma (combined) in the nasal cavity; a positive trend in the incidence of Harderian gland adenomas was noted.
- in males only: hemangiosarcoma; positive trends in the incidences of nasal adenoma and squamous cell papilloma in the forestomach were noted.
- in females only: bronchioalveolar carcinoma; a positive trend in the incidence of histiocytic sarcoma in the uterus was noted.

Table 12: Incidences of tumours in rats and mice after inhalation exposure to GMA for 104 weeks (JBRC, 2015)

GLP study, covering most of lifespan; multiple-doses	0	0.6	2.5	10	0	0.6	2.5	10
	Female				Male			
MICE								
Nasal cavity								
- Haemangioma	0/50[a]	0/50	3/50	7/50**	0/50	0/50	3/50	8/50**
- Haemangiosarcoma	0/50	0/50	1/50	4/50	0/50	0/50	1/50	10/50**
- Combined	0/50	0/50	4/50	11/50**	0/50	0/50	4/50	16/50**
- Adenoma[1]	0/50	0/50	3/50	7/50**	0/50	0/50	0/50	3/50
Forestomach - Squamous cell papilloma[1]					0/50	1/50	0/50	3/50
Harderian gland - Adenoma	1/50	1/50	2/50	4/50	1/50	1/50	5/50	5/50
Lung- Bronchioalveolar carcinoma	0/50	2/50	0/50	5/50*				
Uterus - Histiocytic sarcoma[1]	11/50	10/50	12/50	18/50				
GLP study, covering most of lifespan; multiple-doses	0	3.2	8	20	0	3.2	8	20
	Female				Male			
RATS								
Nasal cavity								
- Squamous cell carcinoma	0/50	0/50	0/50	10/50*	0/50	0/50	0/50	29/50**
- Neuroepithelial carcinoma					0/50	0/50	0/50	7/50**
- Adenoma	0/50	3/50	3/50	1/50	0/50	7/50**	9/50**	0/50
Peritoneum - Mesothelioma					1/50	7/50*	16/50***	14/50***
Skin								
- Basal cell epithelioma					0/50	1/50	1/50	4/50
- Basal cell epithelioma and carcinoma					0/50	1/50	2/50	5/50*
- Keratoacanthoma					0/50	4/50	3/50	3/50
Subcutis - Fibroma	0/50	2/50	2/50	3/50	5/50	4/50	4/50	13/50*
Uterus - Endometrial stroma sarcoma[1]	1/50	1/50	1/50	5/50				
Mammary gland - Fibroadenoma	7/50	14/50	14/50	23/50**				
Thyroid - C-cell adenoma	1/50	1/50	3/50	4/50				
Clitoral gland - Adenoma	0/50	0/50	3/50	4/50				

[a] overall rates: number of tumour-bearing animals/No of animals examined at the sites
*p<0.05 **p<0.01 ***p<0.001 (Fisher exact test)

[1] HCD: historical control data
Female mice: uterus histocytic sarcoma (534/2545; 21%, 10-34%)
Male mice: nasal cavity adenoma (2/2345; 0.1%, 0-2%); forestomach squamous cell papilloma (7/2545; 0.3%, 0-2%)
Female rats: endometrial stromal sarcoma (54/2846; 1.9%, 0-8%)

In the rat study, F344/DuCrlCrlj rats were exposed by whole-body inhalation to GMA vapours. Survival rates of both males and females exposed to 20 ppm were significantly lower than concurrent controls (week 104: 18% vs 82% in males; 58% vs 78% in females) (see Table 13).

Table 13: Survival rates of rats and mice after exposure by inhalation to GMA for 104 weeks, with 50 animals at the start (JBRC, 2015)

	0	0.6	2.5	10	0	0.6	2.5	10
	Female				Male			
MICE								
Number of animals at week 105	27	15	19	9	26	26	15	14
Survival rate (%)	54	30	38	18	52	52	30	28
	0	3.2	8	20	0	3.2	8	20
RATS								
Number of animals at week 104	39	39	35	29	41	44	39	9
Survival rate (%)	78	78	70	58	82	88	78	18

Significant decreases in body weight were noted in males at 20 ppm throughout the dosing period, and in females exposed to 8 ppm and 20 ppm from weeks 82 and 54 onwards. Significant increases were reported in the relative weights of the heart, lungs, adrenals, kidneys, liver and brain in males and females exposed to ≥ 8 ppm GMA, possibly due to the lower animal body weights at these doses. Additionally, the relative weights of the spleen and the ovaries were significantly increased in males at 8 ppm and in females at 20 ppm, respectively.

At the highest dose of 20 ppm, GMA caused, compared to controls, significant increases in the incidences of:
- in males and females: squamous cell carcinoma in the nasal cavity; squamous cell carcinoma is an extremely rare tumour with no occurrence in the historical control data; a significant positive trend in the occurrence of fibroma in the subcutis was also noted
- in male rats: nasal esthesioneuroepithelioma (neuroepithelial carcinoma), basal cell epithelioma and carcinoma of the skin and subcutaneous fibroma
- in female rats: mammary gland fibroadenoma and a positive trend in endometrial stroma sarcoma in the uterus.

A significant increase in the incidence of mesothelioma of the peritoneum was observed in male rats at all doses. Nasal adenomas were significantly increased in the lowest and intermediate doses in males; 3 occurrences in the same doses and one at 20 ppm were also observed in females. Positive trends in the incidences of C-cell adenoma of the thyroid and clitoral gland adenoma in female rats were within the range of the centre's historical data and were therefore not considered to be exposure-related.

Collectively, the increased incidences of the neoplastic lesions described in the JBRC studies above, exceeded – unless stated otherwise - the incidence range of the historical control data and were deemed by the authors as "clear evidence for carcinogenicity" in mice and rats.

In an earlier inhalation study, three groups of Wistar rats (n=20/sex) were exposed to GMA at concentrations of 0, 15.3 or 206 mg/m^3 (equivalent to 2.6, and 35 ppm respectively) for 6 hours per day, 6 days per week, for 6 months. Two rats (unspecified sex) died before the end of the study in the high dose groups. No significant increases in the incidence of any tumour type at any site were reported (Oyang et al, 1990 as cited in (IARC, 2020).

The sites of carcinogenicity and the tumour types observed in the above inhalation studies in mice and rats, mirror to a large extent the findings of the respective JBRC carcinogenicity bioassays with glycidol (JBRC, 2003, as cited in (IARC, 2020)). Similar to GMA, inhalation of glycidol induced significant, dose-dependent increases in the incidence of nasal cavity malignant tumours (hemangioma/ hemangiosarcoma and adenoma/ adenocarcinoma) in both male and female BDF1 mice. The incidence of Harderian gland adenomas was also increased in both sexes. Nasal squamous cell carcinomas, uterine (histiocytic sarcomas) and mammary gland (adenocarcinomas) malignant tumours were also observed in female mice. In exposed F344 rats, glycidol induced malignant tumours of the nasal cavity (adenoma /adenocarcinoma and squamous cell carcinoma) and mammary gland (fibroadenomas) in males and females, peritoneum (mesothelioma) and skin (squamous cell papillomas) in males, and uterus (endometrial stromal sarcoma) in females.

Oral administration of GMA to Fischer rats (n=3/sex/group) at doses ranging from 0.001 to 0.3 mg, given five times per week, for 52 weeks, and similar treatment to an additional group (n=15/sex) with 0.1 mg GMA yielded negative results at the end of the study, which included an additional six-month observation period, as reported by Hadidian et al, 1968 (cited in (IARC, 2020)).

7.7.3 Summary

No human carcinogenicity data are available. The carcinogenic potential of GMA in experimental animals was demonstrated in 2-year inhalation studies (JBRC, 2015), in B6D2F1/Crlj mice and F344 rats, exposed up to 10 ppm and 20 ppm respectively.

In mice, significant increases, compared to controls, were observed at 10 ppm GMA in the incidences of hemangioma and hemangiosarcoma in the nasal cavity of males and females. Bronchiolar carcinomas were significantly increased at this dose in females only.
Significant positive trends were noted in the incidences of:
- in males and females: adenoma of the Harderian gland
- in male mice: nasal adenoma and squamous cell papilloma of the forestomach
- in female mice: uterine histiocytic sarcoma.

In rats, significant increases at 20 ppm GMA, compared to controls, were observed in the incidences of :
- in males and females: squamous cell carcinoma in the nasal cavity
- in male rats: nasal ethesioneuroepithelioma, skin basal cell epithelioma and carcinoma and subcutaneous fibroma
- in female rats: mammary gland fibroadenoma

In male rats, peritoneal mesothelioma occurred at a significant rate, at all the doses tested (≥3.2 ppm). In female rats a positive trend was noted for endometrial stromal sarcoma.

The above observations in mice and rats exceeded the occurrence of historical controls. A shorter inhalation and a gavage study in rats did not report an increase in any neoplastic incidences in exposed animals over controls.

7.8 Reproductive toxicity

7.8.1 Human data

No relevant information is available on GMA.

7.8.2 Animal data

7.8.2.1 Fertility

Glycidyl methacrylate has an entry in Annex VI of the CLP regulation as a Repr. 1B (fertility) substance.

(MHWJ, 1997) as cited in (OECD, 2000, ECHA, 2022, ECHA, 2015) performed an oral OECD TG 422 toxicity study in Crj:CD rats (combined repeat dose and reproductive/ developmental toxicity screening test) (n= 12/sex/dose). Administration was conducted by gavage at doses of 10, 30 and 100 mg/kg/day (in corn oil) from 14 days before mating to 14 days after mating in males and from 14 days before mating to day 3 of lactation in females (ie total of 40 to 47 days).

Maternal toxicity was mainly limited to effects on the stomach at all dose levels due to the local irritating/corrosive properties of GMA (see section 7.3.2.1).

In the 100 mg/kg group (males and females), many animals seemed infertile (ie. fertility was significantly decreased), although no morphological abnormalities were observed in the epididymis, seminal vesicles, prostate, uterus, or pituitary gland.
- Moreover, histopathological analysis of the gonads showed that, in all treatment groups, no significant effect was considered to cause infertility. No change in the number of gonocyte per Sertoli cell was observed in epithelium of seminiferous tubule (stage VIII) in the testes of all survival males, that could be attributed to GMA exposure. Consequently the fertility index (number of delivered animals/ number of mated animals) decreased significantly presumably due to the low sperm mobility.
  No sperm analysis was performed in the original investigation. Secondary investigations showed reduced motility in sperm but no further details were provided in the report.
- No effects on the estrous cycle, copulation index, gestation length or parturition were noted. Slight decreases in the numbers of corpora lutea, implants, pups born and live pups as well as the implantation and delivery indices were observed. However, clear effects attributable to the administration of GMA could not be concluded due to the few cases.
  There were no significant differences in gestation index, live birth index or viability index on day 4. No abnormalities attributable to GMA were noted in body weights of live pups or on necropsy of pups in any GMA-treated group.
  Therefore, NOAEL for reproductive performance of parents (males and females) was considered to be 30 mg/kg/day, respectively

Two 5-day studies were performed to evaluate the potential effects of GMA on spermatogenesis:
- (Xie et al., 1990) (as cited in (ECHA, 2015)), 3 doses (25, 50 or 100 mg/kg/day) daily by intraperitoneal route administered to 5 male (Kunming hybrid) mice for 5 days. Results showed an increase in sperm abnormality frequency, and a decrease in the number of sperm cells. The results were confirmed in a subsequent study.

- (Vedula, 1994) found in (ECHA, 2022) administered 4 doses (1, 5, 25 or 100 mg/kg) daily by intraperitoneal route to 5 male (CD-1) mice for 5 days. The aim if the study was to evaluate the potential of GMA to affect epididymal sperm count and sperm morphology and to determine a NOEL for alterations in these parameters. Also the results of the study were used to determine whether the results from Xie et al. (1990) were reproducible. On day 36, complete necropsy was performed.

There were no treatment-related changes in behaviour or in clinical observations at any dose level. Also feed consumption, bw and bw gains, gross pathology remained unaffected. Treatment-related decreases in caudal epididymal sperm count and perm count per gram of caudal epididymis occurred in mice treated with 25 and 100 mg/kg/day. Treatment-related increases in percent abnormal sperm were also noted in the same 2 dose-groups.

At 100 mg/kg, mice had decreased caudal epididymal weights and slightly lower testicular weights, decreased sperm counts and increased abnormal sperm. Mice given 25 mg/kg/day showed decreased sperm counts and increased abnormal sperm. The NOEL for spermatoxicity (as evaluated by epididymal sperm counts and morphology) was 5 mg/kg/day.

7.8.2.2 Developmental toxicity

(OuYang et al., 1988) administered GMA by oral gavage to female Wistar rats during day 5 to day 15 of gestation at doses of 5.4, 10.8, 21.5 and 108.0 mg/kg/day (n= 14 to 18 females per dose group). The dams were sacrificed on day 19 of pregnancy (as cited in (ECHA, 2015)).

At 108.0 mg/kg, the body weight gain was significantly decreased as sign of maternal toxicity; also there was a statistically significant increase in the fetal resorption rate and a non-dose-related increase in fetal resorptions in the presence of maternal toxicity.

Neither birth defects nor fetal abnormalities (ie teratogenic effects) were noted in rats treated with GMA. There was also no significant difference in fetal body weight from the control.

The percentage of pups stillborn was somewhat higher than control at all dose levels (0% for control, and 1.35%, 7.58%, 1.26% and 6.03% for treated group at 5.4, 10.8 21.5 and 108.0 mg/kg/day, respectively). However, because this change was not dose-dependent and statistically significant change only at the 10.8 mg/kg dose, this was not considered to be chemical-related change.

Therefore, NOAELs were considered to be 21.5 mg/kg/day for maternal toxicity and 108.0 mg/kg/day for teratogenicity.

From (MHWJ, 1997) detailed above (see section 7.8.2.1), the oral (gavage) OECD TG 422 study was performed in Crj:CD rats at doses of 10, 30 and 100 mg/kg/day from 14 days before mating to 14 days after mating in males (n= 12/sex/dose) and from 14 days before mating to day 3 of lactation in females (ie for 40 to 47 days). No abnormalities attributable to the administration of GMA were noted in the body weights of live pups or on necropsy of pups in any treated group. Therefore, no teratogenic effects were induced by GMA in rats with a NOAEL for F1 offspring of 100 mg/kg/day.

A further two inhalation tests on developmental toxicity were performed in rabbits:
- (Vedula et al., 1995) exposed, via inhalation, New Zealand White female rabbits during day 7 to day 19 of gestation to GMA at concentrations of 29.1, 58.2 and 291 mg/m^3 (or 5, 10, 50 ppm; daily intake is calculated as 2.6, 5.2 and 26.2 mg/kg/day, respectively), 6 hours/day, found in (ECHA, 2015). Respiratory distress and decrease in feed consumption was observed at 291 mg/m^3. Therefore rabbit dams were removed early from study (after the third exposure). Consequently the evaluation of reproductive and embryonal/fetal parameter was precluded. Nonetheless GMA did not adversely affect any of the embryonal/ fetal or reproductive parameters at 5 or 10 ppm:
At 29.1 and 58.2 mg/m^3 no adverse effects on any reproductive and embryo/fetal parameter were noted.
In addition, treatment-related histopathologic alterations of the nasal tissues (hyperplasia, necrosis, etc.) were present in all animals treated with GMA. Hence the nasal tissue was identified as the main target organ.
The LOAEC for maternal toxicity was 29.1 mg/m^3 (5 ppm) and NOAEC for teratogenicity was 58.2 mg/m^3 (10 ppm) (or developmental NOAEC > 10 ppm as the top dose was not further investigated).

- (Vedula et al., 1996) exposed, via inhalation, New Zealand White female rabbits during day 7 to day 19 of gestation to GMA at concentrations of 2.9, 11.6 and 58.2 mg/m^3 (or 0.5, 2, 10 ppm, respectively) 7 hours/day (found in (ECHA, 2015)). No significant effects were noted at any exposure level. The principal indication of maternal toxicity was inflammation/ degeneration of the nasal olfactory and respiratory epithelium at the 11.6 and 58.2 mg/m^3 dose-groups without any adverse effect on any reproductive and embryo/ fetal parameter at any doses. Therefore, NOAEC for maternal toxicity was 2.91 mg/m^3 (0.5 ppm) and NOAEC for teratogenicity was 58.2 mg/m^3 (10 ppm).

7.8.3 Relevant information – Glycidol, principal metabolite

As shown in section 7.1.4, GMA is metabolised into glycidol. Glycidol has a harmonised classification for reproductive toxicity in category 1B with H360F indicating an effect on fertility.

Summaries of the main studies showing effects of glycidol on fertility are provided below and were copied from the C&L proposal of glycidol (ECBI-92/95-add.3). In addition, a summary of the 13-week study by the NTP in rats and mice is also summarized below.

In a 13-week study (NTP, 1990) (as cited in (ECHA, 2015), glycidol was administered to rats (10/ group) at doses from 25 to 400 mg/kg, and to mice (10/ group) at doses from 19 to 300 mg/kg (vehicle control groups received distilled water).
- All rats that received 400 mg/kg died by week 2. Three males and one female that received 200 mg/kg died during weeks 11-12.
  Final mean body weights of male rats that received 50, 100, or 200 mg/kg were 96%-85% that of vehicle controls. Final mean body weights of female rats receiving the same doses were 94%-89% that of vehicle controls.
  Sperm count and sperm motility were reduced in male rats that received 100 or 200 mg/kg. Necrosis of the cerebellum, demyelination in the medulla of the brain, tubular degeneration and/or necrosis of the kidney, lymphoid necrosis of the thymus, and testicular atrophy and or degeneration occurred in rats that received 400 mg/kg.
- All mice that received 300 mg/kg died by week 2; deaths of mice that received 150 mg/kg occurred during weeks 4-8 for males and weeks 1-5 for females.
- Mean body weights of mice surviving to the end of the studies were generally 90%-94% those of vehicle controls.
- Sperm count and sperm motility were reduced in dosed male mice. Compound-related histopathologic lesions included demyelination of the brain in males and females that received 150 or 300 mg/kg, testicular atrophy in males at all doses, and renal tubular cell degeneration in male mice that received 300 mg/kg.

The effects observed with glycidol resemble the effects observed in the combined repeated dose toxicity and reproductive screening study in that effects were observed on the fertility without clear effects on the reproductive organs.

7.8.4 Summary

In the OECD TG 422 (oral route), the NOAEL for reproductive toxicity was considered to be 30 mg/kg/day, based on a decrease in the fertility index (number of delivered animals/ number of mated animals) at 100 mg/kg. No effects on the reproductive organs were observed. Comparable effects on the fertility were observed for glycidol, a metabolite of GMA, supporting the relevance of the effect in the screening study. The effects on fertility were observed in the presence of maternal toxicity which was limited to local irritation of the forestomach. The mechanism by which GMA induces the reduced pregnancy is not clear as no effects were observed on the reproductive organs in the male and female rats. The reduction in fertility was observed in studies in which only males were exposed confirming that this was an effect on fertility. The observed effects with glycidol confirm the effects on fertility without effects on the reproductive organs for GMA

As three reliable developmental studies by two different routes, oral and inhalation, and the screening study indicated no teratogenicity even at the highest doses which showed maternal toxicity, GMA is not considered to induce developmental toxicity.

8. Other considerations

8.1 Mode of action (MoA) considerations

There is consistent evidence that GMA is genotoxic in bacterial and mammalian cells (including human primary cells) and in exposed animals and consequently carcinogenic in rodents.
GMA-induced DNA modifications have been shown in a number of studies (see section 7.6.3). GMA binds covalently to plasmid and calf thymus DNA at the N6-adenine and N3-cytosine positions, suggesting that it is electrophilic. GMA-DNA adducts, including the main lesion N3-methacrylate-2-hdroxypropyl-deoxycytidine monophosphate, formed dose-dependently and were identified in several tissues of exposed rats (Tan et al., 1999, Fang, 1991). As a result, GMA was positive on several genotoxic endpoints in treated mammalian cells, producing mostly dose-related DNA strand breaks, chromosomal aberrations, sister chromatid exchange and induction of micronuclei (Table 11).
In isolated human lymphocytes and fibroblasts, a GMA dose-dependent induction of DNA strand breaks was detected by the comet assay including a modified version of the assay using lesion-specific endonucleases, specifically detecting oxidative DNA damage (Poplawski et al., 2009). The evidence for oxidative DNA damage was further enhanced by the observation of GMA-mediated effects in treated cells, being markedly reduced or prevented by co-treatment with NAC (Lee et al., 2006, Styllou et al., 2015, Styllou et al., 2017). Additionally, antioxidant treatment ameliorated the nuclear chromatin condensation observed in treated human gingival fibroblasts, suggesting that these effects are at least partly mediated by radical species. The induction of colocalised g-H2Ax/53BP1 nuclear foci, an established surrogate marker for DNA double-strand breaks (DSBs), in treated human cells indicates that GMA produces these highly deleterious DNA lesions. DSBs were additionally detected by pulsed field electrophoresis of DNA isolated from human lymphocytes (Poplawski et al., 2009). In animals, orally-delivered GMA was reported as active in cytogenetic assays, producing DNA strand breaks in liver, kidney and bone marrow cells, and micronucleated reticulocytes (Dobrovolsky et al., 2016).

GMA was consistently mutagenic in bacterial strains containing base-pair substitutions and in mutation assays in mouse, hamster and human cells (Table 10 and Table 11). In addition, GMA induced malignant cell transformation and epigenetic alterations such as the methylation of gene promoter regions in cultured human bronchial epithelial cells. Transformed cells could subsequently form subcutaneous tumours (squamous cell carcinoma) in nude mice (Yang et al., 2009). In chronic inhalation studies in mice and rats, GMA induced dose-related increases in the incidences of transitional cell hyperplasia, in mice and rats of both sexes and squamous cell hyperplasia/metaplasia with atypia in rats, exhibiting the capacity to alter cell proliferation. Increased incidence of malignant neoplasms in the nasal cavity in rats and mice of both sexes, along with a spectrum of tumours at other sex and species-specific sites were reported. Collectively, IARC deemed the evidence regarding cancer in experimental animals as "sufficient".

The mechanistic evidence suggests that GMA belongs to a class of reactive glycidyl epoxides, bearing structural similarity and concordance in terms of genotoxicity and site-specific carcinogenicity to glycidol. As a result, IARC concluded that GMA is probably carcinogenic in humans (Group 2A). Collectively, GMA displays a number of properties i.e. is reactive with DNA and potentially electrophilic, is genotoxic, alters cell proliferation, induces epigenetic alterations and oxidative stress, which have been identified as key mechanistic characteristics pertinent to carcinogenicity (Smith et al., 2016) .

In conclusion, there is insufficient information available to conclude on a threshold MoA for the carcinogenic action of GMA and therefore a non-threshold MoA is assumed.

8.2 Groups at Extra Risk

No groups at extra risk were identified.

9. Evaluation and recommendations

9.1 Cancer risk assessment

9.1.1 Published approach for cancer risk assessment

The Committee for Recommendation of Occupational Exposure Limits of the Japan Society for Occupational Health (JSOH) classifies the occupational carcinogens based primarily on the epidemiological evidence, but the results of the animal experiments and their extrapolation to human are also considered (JSOH and Health, 2018). The classification is made by strength of the evidence but does not reflect the carcinogenic potency. JSOH considers that the classification of occupational carcinogens proposed by IARC is appropriate in principle.

According to JSOH, GMA was classified as a group 2A carcinogen (probably carcinogenic to humans), class 2 skin sensitiser (substance which probably induce allergic reactions in humans) and class 3 reproductive toxicant (substance suspected to cause reproductive effects in humans, limited evidence has been demonstrated).
It is noted that according to the JSOH methodology (JSOH and Health, 2018), "Only when scientifically reasonable information is available, JSOH will estimate a reference value corresponding to an individual excess lifetime risk of cancer due to exposure to a Group I carcinogen (carcinogenic to humans)".

Despite acknowledging a non-threshold MoA of GMA, JSOH (Araki et al., 2018) derived an OEL rather than exposure-response relationship (ERR) (see Section 9.2.1).

9.1.2 Cancer risk assessment

Multiple site tumours are found in rats and mice, after inhalation and oral exposure to GMA. There is not sufficient information to conclude on a threshold MoA, therefore a non-threshold carcinogenic action is assumed.

The 2-year inhalation studies in mice and rats were identified as key information (JBRC, 2015), because they are performed with GMA itself, with the correct duration, and via the relevant exposure route (inhalation). Dose ranges tested in mice (0.6-10 ppm; corresponding to 3.5-59 mg/m^3) were lower compared to rats (3.2-20 ppm; corresponding to 19-118 mg/m^3). However some tumours are already found at the low or mid dose in the rat study.

With regard to survival rates, the survival in the mouse study is around 80% at 18 months, although decreased to 18-52% at the end of the study (24 months/105 weeks). In the rat study, the survival at 18 months is between 70-100%, and was decreased to around 80% at the end of the study (104 weeks), except in the high dose group. Survival rates were decrease to 18% in male rats and 58% in female rats.

T25 can be defined as "*the chronic dose rate which will give 25% of the animals tumours at a specific tissue site, after correction for spontaneous incidence, within the standard life-time of that species*" (Sanner et al., 2001).

Calculations, based on the incidences presented in Table 14, included the following steps:

1) T25 was calculated as:

T25 = C*(reference incidence (0.25) / (incidence at C – control incidence) * (1- control incidence) / 1

where C is the lowest dose with a statistically significant increased frequency (with a P<0.01)[17].

Table 14: Several calculations for T25 depending on species, sex and tumour observed

Animal	Sex	Tumour observed	Significant dose (ppm)	Incidence at C	Incidence control	T25
Mice	M	Nasal cavity hemangioma & aemangiocarcinoma	10	16/50	0/50	7.81
	F	Nasal cavity hemangioma & hemangiocarcinoma	10	11/50	0/50	11.36
Rats	M	Nasal cavity neuroepithelial carcinoma	20	7/50	0/50	35.71
	M	Nasal squamous cell carcinoma	20	29/50	0/50	8.62
	M	Peritoneal mesothelioma	3.2	7/50	1/50	6.53

For the most relevant tumour, the peritoneal mesothioloma in male rats, statistically significantly increased incidences are reported in all dose groups. Hence the incidences were used for T25 derivation.

2) The lowest derived T25 of 6.53 ppm needs to be adjusted to correspond to worker exposure conditions (40 years, 48 weeks/year, 8 h/day, and correction for the inhalation volume for workers at light physical activity. No allometric scaling was needed for inhalation exposure:

T25 (worker)=6.53 ppm x (75/40 years) x (52/48 weeks) x (6/8 h) x (6.7/10 m^3) = **6.67 ppm**

Using the conversion factor for 1 ppm = 5.91 mg/m^3, the T25 worker is **39.4 mg/m³**.

3) Additional lifetime cancer risks were calculated as follows according to a linearised approach (high to low dose extrapolation)[17].

Exposure concentration representing a 1*10^{-5} risk: 6.53 ppm/25 000=0.00027 ppm (corresponding to 0.0016 mg/m^3).

Assuming linearity, excess life-time cancer risks were calculated and are presented in Table 15.

---

[17] As per R8 guidance (ECHA, 2012) – https://echa.europa.eu/documents/10162/17224/information_requirements_r8_en.pdf/e153243a-03f0-44c5-8808-88af66223258?t=1353935239897

Table 15: Cancer exposure-risk relationship (pathological changes in olfactory and respiratory epithelia in the nasal cavity) after a working life exposure to a given 8-hour air concentration of GMA for five days a week over a 40-year working life period

GMA concentration in air (mg/m^3)	GMA concentration in air(ppm)	Excess life-time cancer risk (Cases per 100 000 exposed)
0.0063	0.0011	4
0.063	0.011	40
0.63	0.11	400
6.3	1.1	4000

* Assuming an 8-hour exposure per day and 5 days per week, over a 40-year working life

A quantitative cancer risk assessment based on human data was not considered feasible because human cancer studies lack exposure data.

9.2 Derived Occupational Exposure Limit (OEL) Values

There is insufficient information available to conclude on a threshold MoA for the carcinogenic action of GMA. Therefore a non-threshold MoA is assumed. For that reason, it is not possible to derive a health-based OEL, and exposure-risk relationships (ERR) were calculated from animal data (see section 9.1.2).

9.2.1 Published approach to establishing OELs

The Committee for Recommendation of Occupational Exposure Limits of the Japan Society for Occupational Health (JSOH) recently proposed an OEL-M (OEL Mean) of 0.01 ppm (0.06 mg/m^3) for GMA (Araki et al., 2018). JSOH considered a LOAEC of 0.6 ppm in mice based on non-carcinogenic pathological changes: pathological changes in olfactory and respiratory epithelia in the nasal cavity at or above 0.6 ppm observed in a 2-year inhalation study of B6D2F1/Crlj mice (0.6-10 ppm) ((JBRC, 2015) as cited by (IARC, 2020). An uncertainty factor of 10 was applied to allow for extrapolation from LOAEC to NOAEC, and an uncertainty factor of 5 for the severity of carcinogenic effects.

The JSOH evaluation of carcinogenicity and genotoxicity studies indicated a possible non-threshold carcinogen for rodents. In addition, it was taken into account that GMA is mutagenic in a wide range of *in vivo* and *in vitro* test systems. Due to scarce data on carcinogenicity of GMA in humans, JSOH admitted large uncertainty and decided not to establish an ERR.

The OEL Mean is defined "as the reference value to the mean exposure concentration at or below which adverse health effects caused by the substance do not appear in most workers working for 8 hours a day, 40 hours a week under a moderate work-load." (JSOH and Health, 2018)

9.2.2 8h TWA for non-cancer effects

In addition to being carcinogenic, GMA showed local irritative effects at low doses in repeated dose toxicity studies. Further, GMA has a harmonised classification for reproductive toxicity (category 1B, for fertility effects).

Cancer risk values set in the future should be compared to a health-based **limit value** which would protect from relevant hazard endpoints other than carcinogenicity.

9.2.2.1 Repeated dose/ chronic toxicity

If an 8h TWA level for non-cancer effects was to be derived from data on threshold effects, the pre-neoplastic pathological findings in olfactory and respiratory epithelia could be used as the starting point. Other studies had higher NOAEC/LOAEC values (see section 7.3.2):

- The major toxic effect of GMA found in animal studies is tissue damage at the first site of contact, such as the forestomach after oral administration and respiratory tract after inhalation exposure. The lowest LOAEC was observed for pre-neoplastic pathological changes, ie metaplasia in the olfactory epithelium and respiratory gland and appeared in mice at or above 0.6 ppm (equivalent to 3.5 mg/m^3) in the 2-year inhalation study (inhalation exposure 6 h /day, 5 days/week) (JBRC, 2015; cited in IARC, 2020).
- In a 90-day inhalation study in rats (Landry et al., 1996; cited in ECHA, 2015), a NOAEC of 2 ppm was established based on thickened hyperplastic respiratory epithelium.

Based on these results, the lowest chronic LOAEC is 0.6 ppm (equivalent to 3.5 mg/m^3) for repeated dose (chronic) toxicity.

It is not deemed necessary to adjust the starting point with respect to differences in human and experimental exposure conditions, as the toxic effect (local irritation) is driven by the concentration.

Assessment factors to be applied include a factor of 3 for LOAEC to NOAEC extrapolation, a factor of 2.5 to cover interspecies differences, and 5 for worker intraspecies differences.

Application of these factors would lead to a **limit value based on chronic toxicity**:

8h TWA: 0.6 ppm / 3 x 2.5 x 5 ≈ 0.016 ppm (0.094 mg/m^3)

At this exposure level the excess life-time cancer risk would be above 4:10 000 (see section 9.1.2). This would correspond to an excess life cancer risk of about 57 cases per 100.000 exposed workers.

9.2.2.2 Reproduction toxicity

If an 8h-TWA level for non-cancer effects were to be derived for reproduction toxicity, the NOAEL of 30 mg/kg bw/day, based on decreased fertility indexes, as identified in a combined repeated dose and reproductive/developmental toxicity screening test in rats (OECD TG 422; MHWJ, 1997), could be used as the point-of-departure.
This NOAEL can be converted using route-to-route extrapolation into a NOAEC for workers, following the steps below:

1) Conversion of the oral rat dose to the corresponding air concentration using the standard breathing volume for the rat (0.384 m^3/kg), correction for exposure regime (days/ week) and correction for the inhalation volume of workers (rats in rest versus worker at light activity) using default values[17]:

30 mg/kg/d * (1/0.384 m^3/kg/day) * 7/5 * 6.7/10 mg/m^3 = 73.3 mg/m^3 (corresponding to 12.4 ppm).

2) Assessment factors proposed to be applied include: a factor of 2.5 to cover interspecies differences, and a factor of 5 for intraspecies differences (worker):
8h TWA: 73.3 mg/m^3 /2.5*5 = 5.9 mg/m^3 (corresponding to 1 ppm).

At this exposure level the excess life-time cancer risk would be above 4:10 000 (see section 9.1.2). This would correspond to an excess life cancer risk of about 3700 cases per 100.000 exposed workers.

9.2.2.3 Summary

When comparing the 8h TWA limit which would be protective for the pre-neoplastic effects in olfactory and respiratory epithelia, a concentration of 0.094 mg/m^3 (0.016 ppm) would correspond to an excess cancer risk of about 60 cases per 100 000 exposed workers.

Furthermore, when comparing the 8h TWA limit which would protect from reproductive effects with the ERR for cancer, a concentration of 5.9 mg/m^3 (1 ppm) would correspond to an excess cancer risk of about 3700 cases per 100 000 exposed workers.

Consequently, the BOEL based on cancer risk will also protect from non-cancer effects, such as effects at the site of first contact (nose, respiratory tract) as well as reproductive toxicity effects, provided that the value does not exceed 0.094 mg/m^3 (0.016 ppm).

9.2.3 Short Term Exposure Limits (STELs)

GMA has a harmonised classification for respiratory after short term exposure (STOT SE 3), as well as for eye damage (category 1) and skin corrosion (category 1C). The potential of such local effects is influenced by both cumulative and peak exposures. However it is not possible to identify a threshold (or exposure-response) for induction of respiratory irritation/corrosivity by peak exposures, based on available animal data.

No STEL is currently proposed. However, and considering the above, a STEL is required, because inhalation exposure to GMA results in respiratory irritation. Furthermore, GMA is a corrosive substance and a skin sensitizer.
It is not possible to derive a specific 15-minute value based on the available (animal) data. Derivation of a STEL based on a BOEL is also not possible, as the BOEL is not yet established.
Note: a STEL set at the level of the BOEL would achieve adequate protection.

9.2.4 Biological Limit Value (BLV)

There is no information available on biomonitoring of GMA exposure and no limit value is proposed.

9.2.5 Biological Guidance Value (BGV)

There is no information available on biomonitoring of GMA exposure and no limit value is proposed. No Biological Guidance Value (BGV) is proposed due to lack of suitable biomarkers.

9.3 Notations

GMA is acutely toxic in contact with skin (harmonised classification Acute tox. 3), indicating systemic uptake via the dermal route. Therefore a 'skin' notation is proposed.

GMA has a harmonised classification as skin sensitiser and a 'skin sensitisation' notation is proposed.

REFERENCES

AALTO-KORTE, K., ALANKO, K., KUULIALA, O. & JOLANKI, R. 2007. Methacrylate and acrylate allergy in dental personnel. *Contact Dermatitis,* 57**,** 324-330.

AALTO-KORTE, K., ALANKO, K., KUULIALA, O. & JOLANKI, R. 2008. Occupational methacrylate and acrylate allergy from glues. *Contact Dermatitis,* 58**,** 340-6.

AALTO-KORTE, K., HENRIKS-ECKERMAN, M.-L., KUULIALA, O. & JOLANKI, R. 2010. Occupational methacrylate and acrylate allergy – cross-reactions and possible screening allergens. *Contact Dermatitis,* 63**,** 301-312.

AALTO-KORTE, K., JUNGEWELTER, S., HENRIKS-ECKERMAN, M. L., KUULIALA, O. & JOLANKI, R. 2009. Contact allergy to epoxy (meth)acrylates. *Contact Dermatitis,* 61**,** 9-21.

ACSH 2022. Opinion on limit value setting for non-threshold carcinogens, a Risk-Based Approach. Advisory Committee on Safety and Health at Work. Reference Doc. 005-22, adopted on 30/11/2022 https://circabc.europa.eu/ui/group/cb9293be-4563-4f19-89cf-4c4588bd6541/library/78479925-4a39-46fd-b2dc-085a244db2d6/details.

ARAKI, A., AZUMA, K., ENDO, G., ENDO, Y., FUKUSHIMA, T., HARA, K., HORI, H., HORIE, S., HORIGUCHI, H., ICHIBA, M., ICHIHARA, G., IKEDA, M., ISHITAKE, T., ITO, A., ITO, Y., IWASAWA, S., KAKUMU, T., KAMIJIMA, M., KARITA, K., KATOH, T., KAWAI, T., KAWAMOTO, T., KUMAGAI, S., KUSAKA, Y., MATSUMOTO, A., MIYAGAWA, M., MIYAUCHI, H., MORIMOTO, Y., NAGANO, K., NAITO, H., NAKAJIMA, T., NAKANO, M., NOMIYAMA, T., OKUDA, H., OKUDA, M., OMAE, K., SAKURAI, H., SATO, K., SOBUE, T., SUWAZONO, Y., TAKEBAYASHI, T., TAKESHITA, T., TAKEUCHI, A., TAKEUCHI, A., TANAKA, M., TANAKA, S., TSUKAHARA, T., TSUNODA, M., UENO, S., UEYAMA, J., UMEDA, Y., YAMAMOTO, K., YAMANO, Y., YAMAUCHI, T. & YANO, E. 2018. Occupational Exposure Limits for ethylidene norbornene, ethyleneimine, benomyl, and 2,3-epoxypropyl methacrylate, and classifications on carcinogenicity. *J Occup Health,* 60**,** 333-335.

AUSTRALIAN GOVERNMENT, D. O. H., AUSTRALIAN INDUSTRIAL CHEMICALS INTRODUCTION SCHEME 2022. Glycidyl acrylate and glycidyl methacrylate, Evaluation statement 30 June 2022. *In:* DEPARTMENT OF HEALTH, A. I. C. I. S. (ed.).

BATIONO, R., JORDANA, F., BOILEAU, M. J. & COLAT-PARROS, J. 2016. Release of monomers from orthodontic adhesives. *Am J Orthod Dentofacial Orthop,* 150**,** 491-8.

BOGDANFFY, M. S., RANDALL, H. W. & MORGAN, K. T. 1987. Biochemical quantitation and histochemical localization of carboxylesterase in the nasal passages of the Fischer-344 rat and B6C3F1 mouse. *Toxicol Appl Pharmacol,* 88**,** 183-94.

CANTER, D. A., ZEIGER, E., HAWORTH, S., LAWLOR, T., MORTELMANS, K. & SPECK, W. 1986. Comparative mutagenicity of aliphatic epoxides in Salmonella. *Mutation Research/Genetic Toxicology,* 172**,** 105-138.

DAHL, A. R., MILLER, S. C. & PETRIDOU-FISCHER, J. 1987. Carboxylesterases in the respiratory tracts of rabbits, rats and Syrian hamsters. *Toxicol Lett,* 36**,** 129-36.

DEMPSEY, K. J. 1982. Hypersensitivity to Sta-Lok and Loctite anaerobic sealants. *J Am Acad Dermatol,* 7**,** 779-84.

DFG 2015. Glycidylmethacrylat MAK, 58. Lieferung, 2015.

DOBROVOLSKY, V. N., PACHECO-MARTINEZ, M. M., MCDANIEL, L. P., PEARCE, M. G. & DING, W. 2016. In vivo genotoxicity assessment of acrylamide and glycidyl methacrylate. *Food and Chemical Toxicology,* 87**,** 120-127.

ECHA 2015. The registry of classification and labelling (CLH) intentions until outcome https://echa.europa.eu/registry-of-clh-intentions-until-outcome

European Chemicals Agency.

ECHA 2022. *Registered substances dissemination site.* *https://echa.europa.eu/information-on-chemicals/registered-substances* (last visited 10.2022). *European Chemicals Agency.*

FANG, F. 1991. [Plasmid pBR322 drug-resistance gene changes induced by glycidyl methacrylate]. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao,* 13**,** 309-12.

FUDE, F., JIN, Z., HAIXIN, L. & MINGJIA, T. 1999. Study on GMA-DNA adducts. *Chin Med Sci J,* 14**,** 1-6.

GAO, H., ZUO, J., XIE, D. & FANG, F. 1994. Molecular mutagenesis induced by glycidyl methacrylate. *Chin Med Sci J,* 9**,** 1-7.

GRUVBERGER, B., BRUZE, M. & ALMGREN, G. 1998. Occupational dermatoses in a plant producing binders for paints and glues. *Contact Dermatitis,* 38**,** 71-7.

HADIDIAN, Z., FREDRICKSON, T. N., WEISBURGER, E. K., WEISBURGER, J. H., GLASS, R. M. & MANTEL, N. 1968. Tests for chemical carcinogens. Report on the activity of derivatives of aromatic amines, nitrosamines, quinolines, nitroalkanes, amides, epoxides, aziridines, and purine antimetabolites. *J Natl Cancer Inst,* 41**,** 985-1036.

HONDA, H., TÖRNQVIST, M., NISHIYAMA, N. & KASAMATSU, T. 2014. Characterization of glycidol-hemoglobin adducts as biomarkers of exposure and in vivo dose. *Toxicology and Applied Pharmacology,* 275**,** 213-220.

IARC 2020. *IARC Monographs on the Identification of Carcinigenic Hazards to Humans. Volume 125. Some Industrial Chemical Intermediates and Solvents.*

JSOH & HEALTH, J. S. F. O. 2018. Recommendation of Occupational Exposure Limits (2018-2019). *J Occup Health,* 60**,** 419-542.

KANERVA, L. 2001. Cross-reactions of multifunctional methacrylates and acrylates. *Acta Odontol Scand,* 59**,** 320-9.

LEE, D. H., LIM, B.-S., LEE, Y.-K., AHN, S.-J. & YANG, H.-C. 2006. Involvement of oxidative stress in mutagenicity and apoptosis caused by dental resin monomers in cell cultures. *Dental Materials,* 22**,** 1086-1092.

LING, W., RONG, W., RUAN, X., HU, J., MENG, R. & LIU, Y. 2017. Determination of glycidyl methacrylate in the air of workplace captured adsorbent tube by gas chromatography (article in Chinese; abstract in English). *Chinese Journal of Industrial Hygiene and Occupational Diseases,* 35.

MATTES, P. M. & MATTES, W. B. 1992. alpha-Naphthyl butyrate carboxylesterase activity in human and rat nasal tissue. *Toxicol Appl Pharmacol,* 114**,** 71-6.

MATURA, M., POESEN, N., DE MOOR, A., KERRE, S. & DOOMS-GOOSSENS, A. 1995. Glycidyl methacrylate and ethoxyethyl acrylate: new allergens in emulsions used to impregnate paper and textile materials. *Contact Dermatitis,* 33**,** 123-4.

NIOSH 2003. Method No 2537. Methyl and Ethyl Methacrylate.

NIOSH 2018. Volatile Organic Compounds, C1 to C10, Canister Method: METHOD 3900. *NIOSH Manual of Analytical Methods (NMAM), Fifth Edition.*

OECD 2000. SIDS Initial Assessment Report for 10th SIAM. Glycidyl methacrylate. UNEP Publications.

PEMBERTON, M. A. & KIMBER, I. 2022. Methyl methacrylate and respiratory sensitisation: a comprehensive review. *Crit Rev Toxicol,* 52**,** 139-166.

POPLAWSKI, T., PAWLOWSKA, E., WISNIEWSKA-JAROSINSKA, M., KSIAZEK, D., WOZNIAK, K., SZCZEPANSKA, J. & BLASIAK, J. 2009. Cytotoxicity and genotoxicity of glycidyl methacrylate. *Chemico-Biological Interactions,* 180**,** 69-78.

RUSTEMEYER, T., DE GROOT, J., VON BLOMBERG, B. M., FROSCH, P. J. & SCHEPER, R. J. 2001. Induction of tolerance and cross-tolerance to methacrylate contact sensitizers. *Toxicol Appl Pharmacol,* 176, 195-202.

SANCHEZ-PEREZ, J., GONZALEZ-ARRIBA, A., GOIRIZ, R. & GARCIA-DIEZ, A. 2008. Occupational allergic contact dermatitis to acrylates and methacrylates. *Contact Dermatitis,* 58, 252-4.

SANNER, T., DYBING, E., WILLEMS, M. I. & KROESE, E. D. 2001. A simple method for quantitative risk assessment of non-threshold carcinogens based on the dose descriptor T25. *Pharmacol Toxicol,* 88, 331-41.

SCHWEIKL, H., SCHMALZ, G. & RACKEBRANDT, K. 1998. The mutagenic activity of unpolymerized resin monomers in Salmonella typhimurium and V79 cells. *Mutation Research/Genetic Toxicology and Environmental Mutagenesis,* 415, 119-130.

SCHWEIKL, H., SCHMALZ, G. & SPRUSS, T. 2001. The Induction of Micronuclei in vitro by Unpolymerized Resin Monomers. *Journal of Dental Research,* 80, 1615-1620.

SHIMIZU, A., KAMADA, N., KAMBE, N. & MATSUE, H. 2008. Chemical burn caused by glycidyl methacrylate. *Contact Dermatitis,* 59, 316-7.

SMITH, M. T., GUYTON, K. Z., GIBBONS, C. F., FRITZ, J. M., PORTIER, C. J., RUSYN, I., DEMARINI, D. M., CALDWELL, J. C., KAVLOCK, R. J., LAMBERT, P. F., HECHT, S. S., BUCHER, J. R., STEWART, B. W., BAAN, R. A., COGLIANO, V. J. & STRAIF, K. 2016. Key Characteristics of Carcinogens as a Basis for Organizing Data on Mechanisms of Carcinogenesis. *Environ Health Perspect,* 124, 713-21.

STYLLOU, M., REICHL, F.-X., STYLLOU, P., URCAN, E., ROTHMUND, L., HICKEL, R., HÖGG, C. & SCHERTHAN, H. 2015. Dental composite components induce DNA-damage and altered nuclear morphology in gingiva fibroblasts. *Dental Materials,* 31, 1335-1344.

STYLLOU, P., STYLLOU, M., HICKEL, R., HÖGG, C., REICHL, F. X. & SCHERTHAN, H. 2017. NAC ameliorates dental composite-induced DNA double-strand breaks and chromatin condensation. *Dent Mater J,* 36, 638-646.

TAN, M., XU, J., LI, Z., LEI, H. & ZUO, J. 1999. [Study on GMA-DNA adducts in vivo]. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao,* 21, 444-9.

VOGEL, T. A., CHRISTOFFERS, W. A., ENGFELDT, M., BRUZE, M., COENRAADS, P. J. & SCHUTTELAAR, M. L. 2014. Severe bullous allergic contact dermatitis caused by glycidyl methacrylate and other acrylates. *Contact Dermatitis,* 71, 247-9.

VON DER HUDE, W., CARSTENSEN, S. & OBE, G. 1991. Structure-activity relationships of epoxides: induction of sister-chromatid exchanges in Chinese hamster V79 cells. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis,* 249, 55-70.

VON DER HUDE, W., SEELBACH, A. & BASLER, A. 1990. Epoxides: comparison of the induction of SOS repair in Escherichia coli PQ37 and the bacterial mutagenicity in the Ames test. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis,* 231, 205-218.

XIE, D. Y., GAO, H. L., ZUO, J., ZHANG, W., LI, Z. S., YANG, H. F. & FANG, F. D. 1990a. Analysis of the phenotype and the restriction enzyme mapping level of mutations induced by the new mutagen glycidyl methacrylate. *Biomed Environ Sci,* 3, 146-55.

XIE, D. Y., ZHANG, W., CAO, L. F., SUN, W. Q., LI, Z. S., GAO, Q., WU, Y. L., GAO, H. L., YANG, H. F., ZUO, J. & ET AL. 1990b. Studies of the genotoxicity of glycidyl methacrylate (GMA). *Biomed Environ Sci,* 3, 281-9.

YANG, M., XU, J. N., WANG, Q. K., LI, Y., SUN, J. X., LI, J. Y., XIE, G. Y. & WANG, J. 2009. [Study on malignant transformation of human bronchial epithelial cells induced by glycidyl methacrylate]. *Zhonghua Yu Fang Yi Xue Za Zhi,* 43, 187-92.