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

Prepared by the European Chemicals Agency

26 January 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, 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 02 May 2022 to invite interested parties to submit comments and evidence by 01 August 2022.

This scientific report is 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
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADME</td>
<td>Absorption, distribution, metabolism and excretion</td>
</tr>
<tr>
<td>AGS</td>
<td>Ausschuss für Gefahrstoffe (German Committee on Hazardous Substances)</td>
</tr>
<tr>
<td>ANSES</td>
<td>Agence Nationale de Sécurité Sanitaire de l'alimentation, de l'environnement et du travail (French Agency for Food, Environmental and Occupational Health &amp; Safety)</td>
</tr>
<tr>
<td>ATSDR</td>
<td>Agency for Toxic Substances and Disease Registry, Atlanta, Georgia (USA)</td>
</tr>
<tr>
<td>BAuA</td>
<td>Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (German Federal Institute for Occupational Safety and Health)</td>
</tr>
<tr>
<td>BGV</td>
<td>Biological Guidance Value</td>
</tr>
<tr>
<td>BisGMA</td>
<td>Bisphenol A-glycidyl methacrylate</td>
</tr>
<tr>
<td>BLV</td>
<td>Biological Limit Value</td>
</tr>
<tr>
<td>BOEL(s)</td>
<td>Binding Occupational Exposure Limit(s)</td>
</tr>
<tr>
<td>bw</td>
<td>Body weight</td>
</tr>
<tr>
<td>CAD</td>
<td>Chemical Agents Directive 98/24/EC</td>
</tr>
<tr>
<td>CAS RN</td>
<td>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).</td>
</tr>
<tr>
<td>CLP</td>
<td>Regulation EC No 1272/2008 on the Classification, Labelling and Packaging of substances and mixtures (CLP Regulation)</td>
</tr>
<tr>
<td>CMD / CMRD</td>
<td>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).</td>
</tr>
<tr>
<td>CMR</td>
<td>Carcinogens, Mutagens or substances toxic to Reproduction</td>
</tr>
<tr>
<td>DEGDA</td>
<td>Diethylene glycol diacrylate</td>
</tr>
<tr>
<td>DFG</td>
<td>Deutsche Forschungsgemeinschaft (German Research Foundation)</td>
</tr>
<tr>
<td>EC</td>
<td>European Commission</td>
</tr>
<tr>
<td>ECHA</td>
<td>European Chemicals Agency</td>
</tr>
<tr>
<td>EEA</td>
<td>European Economic Area</td>
</tr>
<tr>
<td>EFSA</td>
<td>European Food Safety Authority</td>
</tr>
<tr>
<td>EGDMA</td>
<td>Ethylene glycol dimethacrylate</td>
</tr>
<tr>
<td>EPA</td>
<td>Environmental Protection Agency</td>
</tr>
<tr>
<td>ERR</td>
<td>Exposure-risk relationship</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>GC-FID</td>
<td>Gas chromatography with flame ionization detection</td>
</tr>
<tr>
<td>GESTIS Substance Database</td>
<td>GEfahrStoffInformationsSystem (German information system for the safe handling of hazardous substances and other chemical substances at work)</td>
</tr>
<tr>
<td>GLP</td>
<td>Good Laboratory Practice</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>GMA</td>
<td>2,3-Epoxypropyl methacrylate or glycidyl methacrylate</td>
</tr>
<tr>
<td>2-HEMA</td>
<td>2-Hydroxyethyl methacrylate</td>
</tr>
<tr>
<td>2-HPMA</td>
<td>2-Hydroxypropyl methacrylate</td>
</tr>
<tr>
<td>IARC</td>
<td>International Agency for Research on Cancer (World Health Organization)</td>
</tr>
<tr>
<td>IOELV(s)</td>
<td>Indicative Occupational Exposure Limit Value(s)</td>
</tr>
<tr>
<td>JBRC</td>
<td>Japan Bioassay Research Centre</td>
</tr>
<tr>
<td>JSOH</td>
<td>Japan Society for Occupational Health</td>
</tr>
<tr>
<td>LOAEL</td>
<td>Lowest observed adverse effect concentration</td>
</tr>
<tr>
<td>LOD</td>
<td>Limit of Detection</td>
</tr>
<tr>
<td>LOQ</td>
<td>Limit of Quantification</td>
</tr>
<tr>
<td>MCI/MI</td>
<td>Methylchloroisothiazolinone/methylisothiazolinone</td>
</tr>
<tr>
<td>MoA</td>
<td>Mode of Action</td>
</tr>
<tr>
<td>MRLs</td>
<td>Maximum Residue Levels</td>
</tr>
<tr>
<td>NAC</td>
<td>N-Acetyl Cysteine</td>
</tr>
<tr>
<td>NIOSH</td>
<td>National Institute for Occupational Safety and Health (USA)</td>
</tr>
<tr>
<td>NOAEC</td>
<td>No observed adverse effect concentration</td>
</tr>
<tr>
<td>NOAEL</td>
<td>No observed adverse effect level</td>
</tr>
<tr>
<td>OECD</td>
<td>Organisation for Economic Co-operation and Development</td>
</tr>
<tr>
<td>OECD TG</td>
<td>OECD Guidelines for the Testing of Chemicals</td>
</tr>
<tr>
<td>OEL(s)</td>
<td>Occupational exposure limit(s)</td>
</tr>
<tr>
<td>PFGE</td>
<td>Pulsed Field Gel Electrophoresis</td>
</tr>
<tr>
<td>RAC</td>
<td>Committee for Risk Assessment</td>
</tr>
<tr>
<td>REACH</td>
<td>Regulation (EC) No 1907/2006 of the European Union concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals</td>
</tr>
<tr>
<td>SCE</td>
<td>Sister Chromatid Exchange</td>
</tr>
<tr>
<td>SLA</td>
<td>Service Level Agreement</td>
</tr>
<tr>
<td>SML</td>
<td>Specific Migration Limit</td>
</tr>
<tr>
<td>STEL</td>
<td>Short Term Exposure Limit</td>
</tr>
<tr>
<td>TEGDA</td>
<td>Triethyleneglycoldiacrylate</td>
</tr>
<tr>
<td>TEGDMA</td>
<td>Triethylene glycol-dimethacrylate</td>
</tr>
<tr>
<td>TRGS</td>
<td>Technische Regeln für Gefahrstoffe (German Technical regulations for hazardous substances)</td>
</tr>
<tr>
<td>TWA</td>
<td>Time-Weighted-Average</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Derived Limit Values</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OEL as 8-hour TWA</td>
<td>None proposed</td>
</tr>
<tr>
<td>STEL</td>
<td>Recommended – none proposed before the legislative process</td>
</tr>
<tr>
<td>BLV</td>
<td>None proposed</td>
</tr>
<tr>
<td>BGV</td>
<td>None proposed</td>
</tr>
</tbody>
</table>

Notations

<table>
<thead>
<tr>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin notation</td>
</tr>
<tr>
<td>Skin sensitisation</td>
</tr>
</tbody>
</table>

Cancer exposure-risk relationship*

<table>
<thead>
<tr>
<th>Air concentration of GMA (mg/m³)</th>
<th>Air concentration of GMA (ppm)</th>
<th>Excess life-time cancer risk (Cases per 100 000 exposed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00014</td>
<td>0.00002</td>
<td>1</td>
</tr>
<tr>
<td>0.00056</td>
<td>0.00008</td>
<td>4</td>
</tr>
<tr>
<td>0.0014</td>
<td>0.0002</td>
<td>10</td>
</tr>
<tr>
<td>0.0056</td>
<td>0.0008</td>
<td>40</td>
</tr>
<tr>
<td>0.014</td>
<td>0.002</td>
<td>100</td>
</tr>
<tr>
<td>0.056</td>
<td>0.008</td>
<td>400</td>
</tr>
</tbody>
</table>

* Assuming exposure 8 hours per day and 5 days per week, over a 40-year working life period. The air concentration values refer to inhalable particles.

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

<table>
<thead>
<tr>
<th>Identifier</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IUPAC Name</td>
<td>2,3-epoxypropyl methacrylate</td>
</tr>
<tr>
<td>Synonyms</td>
<td>glycidyl methacrylate (GMA)</td>
</tr>
<tr>
<td>EC/ List No</td>
<td>203-441-9</td>
</tr>
<tr>
<td>CAS RN</td>
<td>106-91-2</td>
</tr>
<tr>
<td>Chemical structure</td>
<td><img src="image" alt="Chemical structure" /></td>
</tr>
<tr>
<td>Chemical formula</td>
<td>C(<em>{7})H(</em>{10})O(_{3})</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>142.15 g/mol</td>
</tr>
</tbody>
</table>

Table 2: Physico-chemical properties

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>liquid</td>
</tr>
<tr>
<td>Boiling point</td>
<td>189°C at 101.3 kPa</td>
</tr>
<tr>
<td>Density</td>
<td>1.07 at 20°C</td>
</tr>
<tr>
<td>Vapour pressure*</td>
<td>420 Pa at 25°C</td>
</tr>
<tr>
<td>Partition coefficient (log Pow)*</td>
<td>0.96 at 25°C</td>
</tr>
<tr>
<td>Water solubility*</td>
<td>50 g/L at 25°C</td>
</tr>
<tr>
<td>Viscosity</td>
<td>5.481 mPa · s (dynamic) at 20°C</td>
</tr>
<tr>
<td>Conversion factor</td>
<td>1 ppm = 5.91 mg/m(^3) (at 20°C)(^4)</td>
</tr>
<tr>
<td></td>
<td>1 mg/m(^3) = 0.17 ppm (at 20°C)</td>
</tr>
</tbody>
</table>

---

3 Values obtained from registration data published on [www.echa.europa.eu](http://www.echa.europa.eu)

4 concentration [PPM] = 142.15 \(\frac{g}{mol}\) \* 1.013 \(10^{6}\) Pa \(1\) m\(^3\) \* \(293.15K\) \* \(10^{-3}\) \(\text{concentration[ppm]}\)
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

<table>
<thead>
<tr>
<th>Index No</th>
<th>International chemical ID</th>
<th>EC number</th>
<th>CAS RN</th>
<th>Annex VI of CLP hazard class and category</th>
<th>Hazard statement code</th>
</tr>
</thead>
<tbody>
<tr>
<td>607-123-00-4</td>
<td>2,3-epoxypropyl methacrylate (glycidyl methacrylate)</td>
<td>203-441-9</td>
<td>106-91-2</td>
<td>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</td>
<td>H302 (oral), H311 (dermal), H314, H317, H335 (resp tract), H372 (resp tract) (inhalation), H341, H350, H360F</td>
</tr>
</tbody>
</table>

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


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

3.2 REACH Registrations

Table 4: REACH Registrations and tonnage

<table>
<thead>
<tr>
<th>Substance(s) Name</th>
<th>EC number</th>
<th>Tonnage (tonnes/annum Full registration)</th>
<th>Intermediate use</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,3-epoxypropyl methacrylate (glycidyl methacrylate)</td>
<td>203-441-9</td>
<td>&gt; 1000 tpa (329 active registrants)</td>
<td>Industrial use of process regulators for polymerisation processes in production of resins, rubbers, polymers</td>
</tr>
</tbody>
</table>

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").

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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.


\(^14\) 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)

<table>
<thead>
<tr>
<th>Country</th>
<th>TWA (8 hrs) ppm</th>
<th>STEL (15 min) ppm</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>0.01</td>
<td>5 (1)</td>
<td>(1) Ceiling Limit value</td>
</tr>
<tr>
<td>Japan (JSOH)¹</td>
<td>0.06 (1)</td>
<td></td>
<td>(1) Skin</td>
</tr>
</tbody>
</table>

¹ JSOH, Japan Society for Occupational Health.

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.

On the basis of its low vapour pressure, GMA is not expected to aerosolize readily (OECD, 2000). 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

GMA is listed as a High Production Volume chemical in the Screening Information Data Set of the Organisation for Economic Co-operation and Development (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).

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. However GMA as such is not present as it is cross-linked with the backbone of the polymer.

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 automobiles. 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 product registered in the European Union that can contain the monomer in or on the article.

5.3 Occupational exposure

GMA is a High Production Volume chemical that is mainly used as an intermediate in the production of epoxy polymers and vinyl and acrylic resins. These polymers are used in dental sealants, composites and adhesives; bone composite materials; powder coatings; and hydrogel lenses. There are emerging applications for the polymers in medical imaging and targeting drug delivery. Polymers formed of 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/m³ for filtration that was conducted three times per day and can filling that was conducted once every 7 days. For the other tasks, concentrations were below the limit of detection which was 2.3 mg/m³. Generally, dermal exposure, although the duration of activity was short (5 minutes/day), was estimated to be 0.04 or 0.22 mg/kg body weight (bw) per day (OECD, 2000).
GMA is also used in the preparation of TEGDMA and BisGMA (dental and bone composite materials). 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 BisGMA 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. BisGMA 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.] 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 Routes of exposure and uptake

Worker exposure is through inhalation, dermal exposure and oral exposure due to hand to mouth contact. Further details are provided in section 5.4.1.

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. Further details are provided in section 5.4.2.

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

5.4.1 General population

Exposure to GMA in the general population has not been well documented but is not expected from use of the polymerized products (IARC, 2020). 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 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 logPow (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 x 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. The polymerization reaction for the dental resin occurs before the material is used in the patient, but often requires a
blue visible light for a short time period to allow photo- or co-initiators to start the polymerization reaction. Curing time varies depending on the polymer, with some taking 20 seconds, while others, such as root canal sealer, taking 24 hours to set and 7 days to completely polymerize GMA, and bone composites taking as long as 10 days. Release of bisphenol A, BisGMA, and TEDGMA was reported in many studies, but GMA was not measured (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/m³/0.4 ppm (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/m³ 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/m³) and for ethyl methacrylate 0.11 to 19.7 ppm (0.50 to 91.7 mg/m³) 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.

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

<table>
<thead>
<tr>
<th>Method</th>
<th>Analytical technique</th>
<th>LOQ, sampling volume and time</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>XAD2 tube</td>
<td>Desorption with butyl acetate</td>
<td>GC-FID</td>
<td>LOD 2.3 mg/m³ (0.4 ppm), flow rate 1 l/min; air volume 3 l; (OECD, 2000), Initial assessment Report for 10th SIAM (Japan) UNEP Publications;</td>
</tr>
<tr>
<td>Sorbent tube (carbon aerogel); desorption with 50% (V/V) DMF-CS₂ solution</td>
<td>GC-FID</td>
<td>LOQ 0.07 mg/m³ with 3 L air volume</td>
<td>(Ling et al., 2017) abstract in English</td>
</tr>
</tbody>
</table>
Method | Analytical technique | LOQ, sampling volume and time | Reference
---|---|---|---
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

##### 7.1.1.1 Absorption- distribution

2,3-Epoxypropyl methacrylate (glycidyl methacrylate – GMA) is expected to be readily absorbed following oral, dermal and inhalation exposure.

##### 7.1.1.2 Metabolism - excretion

See section 7.1.3 below.

#### 7.1.2 Animal data

Shi Tao et al. (1988) (as cited in (IARC, 2020) investigated the toxicokinetics of GMA in rabbits:

- After an intravenous injection of 200 mg/kg, the concentration-time curve could fit the two-compartment open model, and over 95% of the parent compound had disappeared from the blood within 10 minutes.
- After a subcutaneous injection of 800 mg/kg, the toxicokinetics appeared to a first-order absorption one-compartment open model.

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.

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.

##### 7.1.2.1 Absorption - distribution
GMA is expected to be readily absorbed following oral, dermal and inhalation exposure.

### 7.1.2.2 Metabolism - excretion

(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. However, such metabolism does not occur in the target cell population, the olfactory sensory neurons, raising the possibility of intercellular migration of toxic acid metabolites.

(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 esterase 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}\text{C}\ 1,3\text{-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 \(^{14}\text{C}\)-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)).

Half-lives of GMA hydrolysis were faster in incubations with rat and rabbit tissue as compared to humans (completed within 30 minutes versus 2 hours), which indicates carboxylesterase activity to be 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).
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 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 a category Acute Tox 4 (oral).

All available acute oral studies are old and have limitations either in reporting (score 4) or in the conduct of the study (score 3). 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 a category Acute Tox 3 (dermal).

Dermal LD50 for rabbits was 480 mg/kg b.w. (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/m³) 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, acute exposure of rats with saturated vapour resulted in a maximum survival time of 2 hours Smyth et al., 1969, as cited in (ECHA, 2022). It was reported that saturated vapour of glycidyl methacrylate at 20°C was 474 ppm (2,754 mg/m³) (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/m³, the highest practically attainable vapour concentration. In another inhalation toxicity study, acute exposure to rats with saturated vapour for 2 hours at 2754 mg/m³ (474 ppm) resulted in no deaths (Smyth et al., 1969). Overall, higher concentrations including the testing of aerosols were not performed.

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

<table>
<thead>
<tr>
<th>Route</th>
<th>Strain / Type</th>
<th>Value</th>
<th>Reference *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Rat /LD50</td>
<td>597 mg/kg</td>
<td>Zdravko, 1985</td>
</tr>
<tr>
<td></td>
<td>Rat/ LD50</td>
<td>About 700 mg/kg</td>
<td>Olson, 1960; Smyth, 1969</td>
</tr>
<tr>
<td></td>
<td>Rat/ LD 50</td>
<td>451 mg/kg</td>
<td>EPA, 1992</td>
</tr>
<tr>
<td></td>
<td>Rat/ LD 50</td>
<td>390 mg/kg</td>
<td>Zdravko, 1985</td>
</tr>
<tr>
<td></td>
<td>Mouse/ LD 50</td>
<td>1050 mg/kg</td>
<td>Smyth, 1969</td>
</tr>
<tr>
<td></td>
<td>Guinea pig/ LD 50</td>
<td>697 mg/kg</td>
<td>Zdravko, 1985</td>
</tr>
<tr>
<td>Inhalation</td>
<td>Rat/ LC 0</td>
<td>2394 mg/m³/ 4hr</td>
<td>Nitschke, 1990</td>
</tr>
<tr>
<td></td>
<td>Rat/ LCL0</td>
<td>1400 mg/m³/ 6hr</td>
<td>Haag, 1953</td>
</tr>
<tr>
<td></td>
<td>Rabbit/ LCL 0</td>
<td>1400 mg/m³/ 6hr</td>
<td>Haag, 1953</td>
</tr>
<tr>
<td></td>
<td>Guinea pig/ LCL 0</td>
<td>14000 mg/m³/ 6hr</td>
<td>Haag, 1953</td>
</tr>
<tr>
<td></td>
<td>Dog/ LCL 0</td>
<td>1400 mg/m³/ 6hr</td>
<td>Haag, 1953</td>
</tr>
<tr>
<td></td>
<td>Rat/ LCL 0</td>
<td>2754 mg/m³/ 2hr</td>
<td>Smyth, 1969</td>
</tr>
<tr>
<td>Dermal</td>
<td>Rabbit/ LD 50</td>
<td>480 mg/kg</td>
<td>Smyth, 1969</td>
</tr>
</tbody>
</table>

LC0: lethal concentration 0%, at which no death is expected. 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.

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 (in blood chemistry) an increase in total protein and albumin. 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.

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 on rabbits doses 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 (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.

Landry et al. (1996) performed a sub-chronic inhalation toxicity study in rats at concentrations of 2.9, 12 or 87 mg/m³ (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/m³. 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) (ECHA, 2015, ECHA, 2022). A decrease in body weight was observed at the top two doses. 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 NOAEL 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 LOAEL because of tissue damages in respiratory tract.

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 we observed (ECHA, 2015, OECD, 2000).

Cieszlak et al. (1996) exposed female rabbits to GMA at 11.6, 29.1, 58.2 mg/m\(^3\) (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/m\(^3\). 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/m\(^3\), 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/m\(^3\), 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.

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 LOAE. 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 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 GMA (equivalent to 0, 3.5, 15 and 59 mg/m³ respectively), 6 hours/day, 5 days/week for 104 weeks (see section 7.7.2; Table 11). Significantly increased incidences of non-neoplastic lesions, mostly slightly to moderately severe, were mainly observed in the nasal cavity of exposed mice and included:

- in the respiratory epithelium:
  - eosinophilic change (10 ppm in M; 0.6 ppm in F),
  - inflammation (10 ppm in M),
  - squamous cell metaplasia (10 ppm in M/F), and
  - regeneration (10 ppm in M; ≥ 2.5 ppm in F)
- in the olfactory epithelium:
  - eosinophilic change (10 ppm in M/F),
  - metaplasia (≥ 0.6 ppm in M/F), and
  - necrosis (10 ppm in F)
- in the transitional epithelium
  - hyperplasia (10 ppm M/F),
- respiratory metaplasia: gland (nasal cavity) (≥ 0.6 ppm in M/F, reaching marked severity)
- angiectasis (10 ppm in F).

Other sites/organs affected included the nasopharynx, presenting a significant increase in eosinophilic change (10 ppm in M; ≥ 0.6 ppm in F).

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/DuCrICrIj rats, exposed to 0, 3.2, 8, 20 ppm GMA (equivalent to 0, 19, 47 and 118 mg/m³ respectively), 6 hours/day, 5 days/week for 104 weeks (cited in (IARC, 2020)).

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 (at 20 ppm in M/F);
- in the respiratory epithelium:
  - squamous cell metaplasia (≥ 8 ppm in M; ≥ 3.2 ppm in F),
  - squamous cell metaplasia with atypia (≥ 8 ppm in M; 20 ppm in F) and,
  - inflammation (≥ 8 ppm in F)
- in the olfactory epithelium:
  - atrophy (≥ 8 ppm in M/F),
  - metaplasia (≥ 8 ppm in M; 20 ppm in F)
  - necrosis (8 ppm in M) and,
  - regeneration (20 ppm in F)
- in the transitional epithelium:
  - hyperplasia (3.2 and 8 ppm in M, ≥ 3.2 ppm in F)

Apart from the nasal mucosa, other sites significantly affected by exposure to GMA, were the forestomach displaying hyperplasia at 20 ppm in females, while increasingly marked haematopoiesis was observed in the bone marrow (8 ppm in M; 20 ppm in F) and extramedullary in the spleen (≥ 3.2 ppm in M; 20 ppm in F). Significant increases in the incidence of keratitis and corneal ulceration were noted in the eyes of males at 20 ppm.

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/m³), 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, NOAELs were determined to be 10 mg/kg/day for male rat after oral dosing (42 to 63 days of exposure) and 12 mg/m³ (2 ppm) for rat after inhalation dosing (90-day exposure). The neurotoxicity NOEL was 15 ppm (13-week exposure).

Furthermore, LOAECs were estimated at 2 ppm in female rabbits (13 days exposure), 0.6 ppm in mice (2-year exposure) and 3.2 ppm in rats (2-year exposure), and also 2.5 ppm in rats and rabbits (6-month 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 metabolism 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)**
  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)**
  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 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.

7.4 Irritancy and corrosivity

Glycidyl methacrylate has an entry in Annex VI of the CLP regulation as a category 1C for skin corrosion.
Glycidyl methacrylate has an entry in Annex VI of the CLP regulation as a category 1 for eye damage.

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), 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, 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) in rats exposed to saturated vapoours of GMA (105, 269 and 412 ppm, equivalent to 610, 1563, 2394 mg/m\(^3\)) for 4 hours, eye irritation and corneal opacity were also induced. These changes were not reversed 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\(^3\).

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.

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/m³, 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 category 1 for skin sensitisation.

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 woman 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 epoxycycloaliphatic 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% petrolatum (no reaction), 0.03% petrolatum (questionable reaction), 0.1% petrolatum (+/+), 0.3% petrolatum and 1% petrolatum (+++).

(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., 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 15 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).

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.” (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

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

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 study resembles the Buehler study. However, a negative control group was missing. The induction dose of 10% induced some local effects. However, 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.

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).

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 category 2 mutagen.

#### 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 8. 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>
<thead>
<tr>
<th>Species system</th>
<th>Dose levels/route/duration</th>
<th>Study endpoints</th>
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<tr>
<td>Transgenic BigBlue Fischer 344 rats, M (n=15/group)</td>
<td>1, 10 and 25 ppm (5.82, 58.2, and 145.5 mg/m³) (calculated daily doses: 0.71, 7.08, 17.70 mg/kg/day); 6 h/day, 5 days/wk for 4 weeks</td>
<td>LacI locus, gene mutations</td>
<td>negative in olfactory and respiratory epithelium at the highest dose</td>
<td>Gollapudi et al 1999 as cited in (OECD, 2000, ECHA, 2022, ECHA, 2015)</td>
</tr>
<tr>
<td>Rat, Fischer 344, M (n=6); RBCs and RETs in peripheral blood</td>
<td>0, 50, 100 and 150 mg/kg/day up to 29 days; gavage</td>
<td>Pig-a assay; mutagenicity; induction of CD59-deficient Pig-a mutant RBCs and RETs</td>
<td>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)</td>
<td>(Dobrovolsky et al., 2016)</td>
</tr>
<tr>
<td>Mice</td>
<td>42.2, 133, 422, and 464</td>
<td>Micronucleus assay</td>
<td>negative</td>
<td>INBIFO 1979 as cited in</td>
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<tr>
<td>Species system</td>
<td>Dose levels/route/duration</td>
<td>Study endpoints</td>
<td>Results</td>
<td>References</td>
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<tr>
<td>Mice, M; PCE</td>
<td>up to 300 mg/kg, i.p; 2x, 24 h interval</td>
<td>Micronucleus assay</td>
<td>positive</td>
<td>slight increase in micronucleated cells (at 25 mg/kg bw/day), with an inverse dose-response</td>
</tr>
<tr>
<td>Mice, CD-1, (n=5/sex/group/sacrifice time); PCE</td>
<td>75, 150, 300 mg/kg, i.p</td>
<td>Micronucleus assay</td>
<td>negative</td>
<td>Lick et al., 1995 as cited in (OECD, 2000)</td>
</tr>
<tr>
<td>Mice, Crj:BDF1; M+F (n=5/sex/group)</td>
<td>M:188, 375 and 750 mg/kg; F: 250, 500, 1000 mg/kg; gavage</td>
<td>Micronucleus assay</td>
<td>positive</td>
<td>significantly at the highest dose in both sexes</td>
</tr>
<tr>
<td>Rat, Fischer 344, M (n=6); peripheral blood RETs</td>
<td>0, 50, 100 and 150 mg/kg/day up to 29 days; gavage</td>
<td>Micronucleus assay</td>
<td>positive</td>
<td>dose-dependent increase, significant at 150 mg/kg/day</td>
</tr>
<tr>
<td>Mice, Kunming hybrid strain, M, 5 groups (n=5/group)</td>
<td>25, 50, 100 mg/kg, single i.p injection</td>
<td>Unscheduled DNA synthesis in germ cells</td>
<td>positive</td>
<td>slight increase (25 mg/kg bw per day), not dose-dependent</td>
</tr>
<tr>
<td>Wistar rats, M, 5 groups; liver, kidney, white blood cells, testis</td>
<td>31.25, 62.5, 125, 250 mg/kg for 14 days, gavage</td>
<td>DNA adducts (RP-HPLC and nuclease P1 mediated 32P-postlabelling method)</td>
<td>positive</td>
<td>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 &gt; liver &gt; white blood cells &gt; testis; plateaued at 125 mg/kg N3-methacrylate-2-hydroxypropyl-deoxycytidine monophosphate detected in kidney, liver and white blood cells</td>
</tr>
<tr>
<td>Rat, Fischer 344, M (n=3-6); liver, bone marrow and kidneys</td>
<td>0, 50, 100 and 150 mg/kg/day up to 29 days; gavage or 250 mg/kg/day for 3 days</td>
<td>DNA damage; alkaline comet assay</td>
<td>positive</td>
<td>29 d: in bone marrow and liver cells (≥100 mg/kg/day) 3 d: all tested tissues</td>
</tr>
</tbody>
</table>

PCE: polychromatic erythrocytes; RBC: red blood cells; RET: reticulocytes

### 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 9.

**Table 9: Summary of in vitro genotoxicity studies in bacterial test systems**

<table>
<thead>
<tr>
<th>Species (test system)</th>
<th>Dose levels</th>
<th>Study endpoints</th>
<th>Results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Salmonella typhimurium</em> TA100 TA1535 TA1537</td>
<td>32, 100, 320, 1000 µg/plate</td>
<td>Bacterial reverse mutation</td>
<td>positive</td>
<td>Goodyear 1981 as cited in (OECD, 2000)</td>
</tr>
<tr>
<td><em>Salmonella typhimurium</em> TA98</td>
<td>10, 33, 100, 333, 1000 µg/plate</td>
<td>Bacterial reverse mutation</td>
<td>positive</td>
<td>Dorothy et al., 1986 as cited in (OECD, 2000)</td>
</tr>
<tr>
<td><em>Salmonella typhimurium</em> TA98</td>
<td>10 µg/plate - 1 mg/plate</td>
<td>Bacterial reverse mutation</td>
<td>≤33 µg/plate positive</td>
<td>(Canter et al., 1986)</td>
</tr>
<tr>
<td><em>Salmonella typhimurium</em> TA100 TA1535 TA97</td>
<td>112, 224, 448, 896 µg/plate</td>
<td>Bacterial reverse mutation</td>
<td>positive all doses</td>
<td>OuYang et al, 1988 as cited in (IARC, 2020)</td>
</tr>
<tr>
<td><em>Salmonella typhimurium</em> TA98</td>
<td>0.25, 0.5, 1.25, 5.0, 12.5 µg/plate</td>
<td>Bacterial reverse mutation</td>
<td>weakly positive 0.25 µg/plate</td>
<td>(Schweikl et al., 1998)</td>
</tr>
</tbody>
</table>
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 10.

Most of the GMA effects were concentration-dependent and were more pronounced if not exclusively occurring without metabolic activation. GMA-mediated DNA breakage, confirmed as oxidative DNA damage by the modified comet assay (with the inclusion of the DNA repair enzymes endonuclease III (Endo III) and formamidopyrimidine-DNA glycosylase (Fpg)), 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 10: Summary of in vitro genotoxicity studies in mammalian cells
<table>
<thead>
<tr>
<th>Species (test system)</th>
<th>Dose levels</th>
<th>Study endpoints</th>
<th>Results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human lung fibroblast (2BS) cells</td>
<td>0.9-14.2 mg/l</td>
<td>Transformation</td>
<td>positive</td>
<td>Yang et al., 1996, Tan et al., 1997 as cited in (IARC, 2020)</td>
</tr>
<tr>
<td>Human bronchial epithelial (16HBE) cells</td>
<td>0, 1, 2, 4, 8 μg/ml</td>
<td>Transformation</td>
<td>positive</td>
<td>Wang et al., 2014, as cited in (IARC, 2020)</td>
</tr>
<tr>
<td>Human embryonic lung fibroblasts</td>
<td></td>
<td>Transformation</td>
<td>positive</td>
<td>Hu et al., 2012, as cited in (IARC, 2020)</td>
</tr>
</tbody>
</table>

- **Hprt locus forward gene mutation assay**: positive 1.0 μg/ml concentration-dependent (Yin et al., 2003 as cited in (IARC, 2020))
- **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))
- **Mutation of TP53 gene**: positive 8 μg/ml exon 9 altered (Tan et al., 1996, Tan et al., 1997 as cited in (IARC, 2020))
- **Transformation**: positive (Tan et al., 1999 as cited by (IARC, 2020))
- **Transformation**: positive (Xie et al., 1992 as cited in (OECD, 2000))
- **Transformation**: positive (Yin et al., 2003 as cited in (IARC, 2020))

- **Early stage methylation of P16 gene promoter and methylation of the opioid binding protein/cell**: positive 8 μg/ml; methylation pattern of a number of gene promoters changed (Yang et al., 2009, as cited in (IARC, 2020))

- **Methylation pattern of a number of gene promoters changed**: positive 1.0 μg/ml (Yang et al., 2009, as cited in (IARC, 2020))
<table>
<thead>
<tr>
<th>Species (test system)</th>
<th>Dose levels</th>
<th>Study endpoints</th>
<th>Results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>With metabolic activation</strong></td>
<td><strong>Without metabolic activation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chinese hamster (V79) cells</strong></td>
<td>-S9; 24 h: 0, 100, 150, 200 μmol/l</td>
<td>Micronucleus assay</td>
<td>negative</td>
<td>positive ≥100 μmol/l</td>
</tr>
<tr>
<td></td>
<td>+S9; 4 h:0, 100, 200, 300, 400, 500 μmol/l</td>
<td></td>
<td>negative</td>
<td>positive ≥200 μmol/l, dose-dependent</td>
</tr>
<tr>
<td><strong>Chinese hamster (V79) cells</strong></td>
<td>0, 0.1, 0.15, 0.2 mM</td>
<td>Micronucleus assay</td>
<td>-</td>
<td>positive ≥ 0.1 mM/14 μg/ml dose-dependent; effect reduced by NAC</td>
</tr>
<tr>
<td><strong>Chinese hamster lung (CHL/IU) cells</strong></td>
<td>0.02, 0.039, 0.078, 0.16, 0.31 mM</td>
<td>SCE exchange</td>
<td>-</td>
<td>positive 0.078 mM/11 μg/ml clastogenicity, clastogenicity, polyploidy</td>
</tr>
<tr>
<td><strong>Chinese hamster lung (CHL/IU) cells</strong></td>
<td>-S9, continuous: 0.0063, 0.013, 0.025, 0.050 mg/ml</td>
<td>Chromosomal aberration</td>
<td>positive</td>
<td>ambiguous for polyploidy</td>
</tr>
<tr>
<td><strong>Chinese hamster lung (CHL/IU) cells</strong></td>
<td>-S9, short-term: 0.011, 0.022, 0.044, 0.088 mg/ml</td>
<td>Chromosomal aberration</td>
<td>positive</td>
<td></td>
</tr>
<tr>
<td><strong>Chinese hamster lung (CHL/IU) cells</strong></td>
<td>+S9 (short-term): 0.044, 0.088, 0.18, 0.35 mg/ml</td>
<td>Chromosomal aberration</td>
<td>positive</td>
<td></td>
</tr>
<tr>
<td><strong>Human embryonic lung fibroblasts</strong></td>
<td>0.5 μg/ml</td>
<td>Chromosomal aberration</td>
<td>positive</td>
<td></td>
</tr>
<tr>
<td><strong>Human Bronchial epithelial (16HBE) cells</strong></td>
<td>4, 8, 12, 16 and 20 μg/ml (1-3 times)</td>
<td>Chromosomal aberration</td>
<td>positive dose-dependent</td>
<td></td>
</tr>
<tr>
<td><strong>Human/rat lymphocytes</strong></td>
<td>-</td>
<td>Unscheduled DNA synthesis</td>
<td>(weakly) positive</td>
<td>positive</td>
</tr>
<tr>
<td><strong>Human/rat lymphocytes</strong></td>
<td>-</td>
<td>Non-reverse type inhibition of DNA replication</td>
<td>positive</td>
<td>0.5 μg/ml</td>
</tr>
<tr>
<td><strong>Human lung fibroblast (2BS) cells</strong></td>
<td>DNA breaks; alkaline comet assay, DNA</td>
<td>-</td>
<td>positive</td>
<td>Ying et al, 2003 – as cited by</td>
</tr>
</tbody>
</table>
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, immunofluorescence; 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

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)).

Glycidyl methacrylate induced specific epigenetic changes at different stages of the malignant transformation of treated human bronchial epithelial cells or embryonic fibroblasts (Table 10). 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 and 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 category 1B carcinogen.

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 and the study design details of these GLP-compliant studies are summarised in Table 11.

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 11: Carcinogenicity studies in mice and rats exposed to GMA by inhalation

<table>
<thead>
<tr>
<th>Species, strain, sex, No/group</th>
<th>Doses, route, duration of exposure</th>
<th>Results</th>
<th>Remarks</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mouse, B6D2F1/Crlj (M), n=50</strong></td>
<td>0, 0.6, 2.5, 10 ppm (vapour), inhalation, whole body, 6 hours/day, 5 days/wk; 104 wk</td>
<td>No of survivors (wk 105)/Starting No of animals: 26/50, 26/50, 15/50, 14/50</td>
<td>GLP study covering most of lifespan; multiple-doses</td>
<td>JBRC (2015) (study 0795) as cited in (IARC, 2020)</td>
</tr>
<tr>
<td><strong>Nasal cavity:</strong></td>
<td></td>
<td>haemangioma 0/50*, 0/50, 3/50, 8/50** hemangiosarcoma 0/50, 0/50, 1/50, 10/50** hemangioma or hemangiosarcoma (combined) 0/50, 0/50, 4/50, 16/50*** adenoma 0/50, 0/50, 0/50, 3/50</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Foregut:</strong></td>
<td></td>
<td>squamous cell papilloma 0/50, 1/50, 0/50, 3/50</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Harderian gland:</strong></td>
<td></td>
<td>adenoma 1/50, 1/50, 5/50, 5/50</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mouse, B6D2F1/Crlj (F), 0, 0.6, 2.5, 10 ppm</strong></td>
<td>1/50/50**</td>
<td>No of survivors at wk 105/Starting No of</td>
<td>GLP study covering most of</td>
<td>JBRC (2015) (study 0795)</td>
</tr>
<tr>
<td>Species, strain, sex, No/group</td>
<td>Doses, route, duration of exposure</td>
<td>Results</td>
<td>Remarks</td>
<td>References</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------------------------------</td>
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<td>---------</td>
<td>------------</td>
</tr>
<tr>
<td>n=50</td>
<td>(vapour), inhalation, 6 h/day, 5 days/wk; 104 wk</td>
<td>animals: 27/50, 15/50, 19/50, 9/50</td>
<td>lifespan; multiple-doses</td>
<td>as cited in (IARC, 2020)</td>
</tr>
<tr>
<td><strong>Nasal cavity:</strong></td>
<td>haemangioma 0/50, 0/50, 3/50, 7/50**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>hemangiosarcoma 0/50, 0/50, 1/50, 4/50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>hemangioma or hemangiosarcoma (combined) 0/50, 0/50, 4/50, 11/50**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lung:</strong></td>
<td>bronchioalveolar carcinoma 0/50, 2/50, 0/50, 5/50*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Uterus:</strong></td>
<td>histiocytic sarcoma 11/50, 10/50, 12/50, 18/50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Harderian gland:</strong></td>
<td>adenoma 1/50, 1/50, 2/50, 4/50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0, 3.2, 8, 20 ppm (vapour), inhalation, 6 h/day, 5 days/wk; 104 wk</td>
<td>No of survivors at wk 104/Starting No of animals: 41/50, 44/50, 39/50, 9/50</td>
<td>GLP study, covering most of lifespan; multiple-doses</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nasal cavity:</strong></td>
<td>squamous cell carcinoma 0/50, 0/50, 0/50, 29/50***</td>
<td></td>
<td>The increased nasal, lung and uterus tumour incidences were deemed “clear evidence of carcinogenicity” by the authors</td>
<td></td>
</tr>
<tr>
<td></td>
<td>esthesioneuroepithelioma (neuroepithelial carcinoma) 0/50, 0/50, 0/50, 7/50**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>adenoma 0/50, 7/50**, 9/50**, 0/50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Peritoneum:</strong></td>
<td>mesothelioma 1/50, 7/50*, 16/50***, 14/50***</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Skin:</strong></td>
<td>basal cell epithelioma 0/50, 1/50, 1/50, 4/50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Species, strain, sex, No/group</td>
<td>Doses, route, duration of exposure</td>
<td>Results</td>
<td>Remarks</td>
<td>References</td>
</tr>
<tr>
<td>-------------------------------</td>
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<td>---------</td>
<td>---------</td>
<td>------------</td>
</tr>
<tr>
<td>Rat, F344/DuCrIrf (F) n=50</td>
<td>0, 3.2, 8, 20 ppm (vapour), inhalation, 6 h/day, 5 days/wk; 104 wk</td>
<td><strong>Subcutis:</strong> fibroma 5/50, 4/50, 4/50, 13/50* No of survivors at wk 104/Starting No of animals: 39/50, 39/50, 35/50, 29/50 <strong>Nasal cavity:</strong> squamous cell carcinoma 0/50, 0/50, 0/50, 10/50*** adenoma 0/50, 3/50, 3/50, 1/50 <strong>Uterus:</strong> endometrial stromal sarcoma 1/50, 1/50, 1/50, 5/50 <strong>Mammary gland:</strong> fibroadenoma 7/50, 14/50, 14/50, 23/50*** <strong>Subcutis:</strong> fibroma 0/50, 2/50, 2/50, 3/50 <strong>Thyroid:</strong> C-cell adenoma 1/50, 1/50, 3/50, 4/50 <strong>Clitoral gland:</strong> adenoma 0/50, 0/50, 3/50, 4/50</td>
<td>“not exposure-related” GLP study, covering most of lifespan; multiple-doses The increased tumour incidences were deemed “clear evidence of carcinogenicity” by the authors</td>
<td>JBRC (2015) (study 0794) as cited in (IARC, 2020)</td>
</tr>
<tr>
<td>Rat, Wistar (M+F) combined (n=20/sex/group)</td>
<td>0, 15.3, 206 mg/m³ 6 h/day, 6 days/wk, 6 months</td>
<td>No of survivors at the end of study/Starting No of animals: 40/40, 40/40, 38/40 negative; no significant increase in the incidence of tumours at any site</td>
<td>Short duration of study, limited experimental details</td>
<td>Oyang et al, 1990 as cited in (IARC, 2020)</td>
</tr>
</tbody>
</table>

*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)

In the rat study, F344/DuCrIrf 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).

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/m³ (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 and were ultimately deemed as "clear evidence of carcinogenicity". 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 category 1B reproductive toxicant (fertility).

(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). 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 no significant effect considered to cause infertility in all treatment groups. No change in the number of gonocyte per Sertoli cell was observed in epithelium of seminiferous tubule (stage VIII) in the testes of all 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, liver birth index or viability index on day 4. No abnormalities attributable to GMA were noted in body weights of
Two short 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 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 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. 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 rats at doses of 10, 30 and 100 mg/kg/day 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 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, 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 58.2 mg/m$^3$ (10 ppm), less severe signs of ocular and respiratory irritation consisting of reddened eyes, wet muzzle and sneezing after exposure were observed.

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 LOAEL for maternal toxicity was 29.1 mg/m$^3$ (5 ppm) and NOAEL for teratogenicity was 58.2 mg/m$^3$ (10 ppm) (or developmental NOAEL > 10 ppm as the top dose was not further investigated).

• (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); in addition 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. No other 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, NOAEL for maternal toxicity was 2.91 mg/m$^3$ (0.5 ppm) and NOAEL 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, 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-hydroxpropyl-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 10). 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 γ-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 9 and Table 10). 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 approaches for cancer risk assessment

9.1.1.1 JSOH

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. 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

The 2-year inhalation studies in mice and rats were identified as key information (JBRC, 2015).

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$^3$). Significant pre-neoplastic pathological changes in olfactory and respiratory epithelia appeared in mice at or above 0.6 ppm (3.5 mg/m$^3$). Significant dose-response relationships for the mesothelioma of peritoneum in rats appeared at or above 3.2 ppm (19 mg/m$^3$).

Pre-neoplastic pathological changes in olfactory and respiratory epithelia of mice were considered as the most sensitive endpoint. The dose-response relationship reported was not suitable for benchmark dose modelling.

Therefore, the T25$^{16}$ approach in male mice was used to identify the point-of-departure for olfactory epithelium metaplasia findings (LOAEC of 0.6 ppm; corresponding to 3.5 mg/m$^3$).

Calculations included the following steps:

1) T25 was calculated as:

\[
T25 = C \times \left( \frac{\text{reference incidence} (0.25)}{\text{incidence at C - control incidence}} \right) \times (1 - \text{control incidence}) / 1
\]

\[
= 0.6 \text{ ppm} \times \left( \frac{0.25/(16/50 - 4/50)}{1 - 4/50} \right) \times (1 - 4/50)/1 = 0.575 \text{ ppm (corresponding to 3.4 mg/m}^3) \text{ GMA}
\]

2) The T25 value was 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:

\[
T25(\text{worker}) = 0.575 \text{ ppm} \times (75/40 \text{ years}) \times (52/48 \text{ weeks}) \times (6/8 \text{ h}) \times (6.7/10 \text{ m}^3) = 0.59 \text{ ppm (corresponding to 3.5 mg/m}^3)
\]

3) Additional lifetime cancer risks were calculated as follows according to a linearised approach (high to low dose extrapolation)$^{16}$.

Exposure concentration representing a 1*10-5 risk: 0.59 ppm / 25 000 = 0.00002 ppm (corresponding to 0.00014 mg/m$^3$).

Assuming linearity, excess life-time cancer risks were calculated and are presented in Table 12.

---


T25 is the “chronic dose rate that 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. It is a value calculated from a single observed dose-response and based upon the assumption of a linear dose-response relationship over the entire dose-range”.
Table 12: 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

<table>
<thead>
<tr>
<th>GMA (mg/m³)</th>
<th>GMA (ppm)</th>
<th>Excess lifetime cancer risk (Cases per 100 000 exposed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00014</td>
<td>0.00002</td>
<td>1</td>
</tr>
<tr>
<td>0.00056</td>
<td>0.00008</td>
<td>4</td>
</tr>
<tr>
<td>0.0014</td>
<td>0.0002</td>
<td>10</td>
</tr>
<tr>
<td>0.0056</td>
<td>0.0008</td>
<td>40</td>
</tr>
<tr>
<td>0.014</td>
<td>0.002</td>
<td>100</td>
</tr>
<tr>
<td>0.056</td>
<td>0.008</td>
<td>400</td>
</tr>
</tbody>
</table>

9.2 Derived Occupational Exposure Limit (OEL) Values

9.2.1 Published approaches to establishing OELs

9.2.1.1 JSOH

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 (0.06mg/m³) for GMA (Araki et al., 2018). JSOH considered a LOAEL 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 LOAEL to NOAEL, 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 Occupational Exposure Limits (OELs) - 8h TWA

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

In addition to being carcinogenic, GMA has a harmonised classification for reproductive toxicity (category 1B, for fertility effects). If a hypothetical OEL was derived from threshold fertility effects, the NOAEC of 30 mg/kg bw/day, as identified in a combined repeated dose and reproductive/developmental toxicity screening test in rats (MHWJ, 1997), could be used as the point-of-departure.
For the derivation of a limit, we first need to correct the point-of-departure to correspond to worker inhalation exposure conditions:

\[ 30 \text{ mg/kg/d} \times \left( \frac{1}{0.38 \text{ m}^3/\text{kg/day}} \right) \times 6.7/10 \text{ mg/m}^3 = 52.9 \text{ mg/m}^3 \text{ (corresponding to 9.0 ppm).} \]

We then need to apply assessment factors: factor of 6 for extrapolation from sub-acute to chronic exposure, factor 2.5 to cover interspecies differences, and factor 5 for intraspecies differences (worker):

\[ \text{OEL (8h TWA)}: 
\frac{52.9 \text{ mg/m}^3}{6\times2\times2.5} = 1.8 \text{ mg/m}^3 \text{ (corresponding to 0.3 ppm).} \]

When comparing with the ERR for cancer (section 9.1.2), a concentration of 1.8 mg/m³ is very high. ECHA considers that if an OEL is set for carcinogenicity on the basis of the ERR, it will also ensure the protection of workers from reproductive toxicity effects.

### 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 caused by GMA is influenced by both cumulative and peak exposures. It is not possible to identify a threshold or exposure-response for induction of respiratory irritation/corrosivity by peak exposures.

We therefore recommend that, when using the exposure-responses described in Section 9.1.2 to establish a binding OEL (8-hour TWA), a 15-min STEL is defined as to not be more than 5 times higher than that OEL value. This will ensure the protection of the workers from local irritation occurring at short exposure durations.

### 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.

### 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


ECHA SCIENTIFIC REPORT on 2,3-epoxypropyl methacrylate (glycidyl methacrylate) EC No 203-441-9


