Committee for Risk Assessment

RAC

Opinion on scientific evaluation of occupational exposure limits for 2,3-epoxypropyl methacrylate (glycidyl methacrylate)

ECHA/RAC/A77-D-0000007302-83-01/F

Adopted

8 June 2023

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OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON THE EVALUATION OF THE OCCUPATIONAL EXPOSURE LIMITS (OELs) FOR GLYCIDYL METHACRYLATE

Commission request

The Commission asked the advice of RAC to assess the scientific relevance of occupational exposure limits for some carcinogenic chemical substances, in support of the preparation of 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)[1].

I PROCESS FOR ADOPTION OF THE OPINION

Following the above request from the European Commission RAC is requested to draw up an opinion on the evaluation of the scientific relevance of occupational exposure limits (OELs) for 2,3-epoxypropyl methacrylate with a deadline of 22 February 2024.

Chemical name(s): 2,3-epoxypropyl methacrylate (EC number 203-441-9, CAS RN 106-91-2)

In support of the Commission's request, ECHA prepared a scientific report concerning occupational limit values at the workplace. This scientific report was made available at: Occupational exposure limits-Consultations on OEL recommendation on **26 January 2023** and interested parties were invited to submit comments by **28 March 2023**.

RAC developed its opinion on the basis of the scientific report submitted by ECHA. During the preparation of the opinion, the scientific report was further developed as an Annex to the RAC opinion to ensure alignment.

The RAC opinion includes a recommendation to the Advisory Committee on Safety and Health at Work (ACSH) in line with the relevant Occupational Safety and Health legislative procedures.

II ADOPTION OF THE OPINION OF THE RAC

Rapporteurs, appointed by RAC: **Gerlienke Schuur** and **Susana Viegas**.

The opinion was adopted by **consensus** on **8 June 2023.**

RAC Opinion on the assessment of the scientific relevance of OELs for glycidyl methacrylate

RECOMMENDATION

The draft opinion of RAC on the assessment of the scientific relevance of Occupational Exposure Limits (OELs) for 2,3-epoxypropyl methacrylate or glycidyl methacrylate (GMA) (EC number 203-441-9, CAS RN 106-91-2) is set out in the tables below and in the following summary, supported by Annex 1.

GMA is considered to be a non-thresholded carcinogen. Consequently, no health-based OEL nor a Short-Term Exposure Limit (STEL) can be identified. Instead, RAC derived an exposure-risk-relationship (ERR) expressing the excess cancer risk as a function of the air concentration of GMA.

SUMMARY TABLE

The tables present the outcome of the RAC evaluation to derive limit values for the inhalation route, for dermal exposure and a skin notation.

Derived Limit Values[1]

OEL as 8-hour TWA:	See Exposure-Risk-Relationship below
STEL:	None*
BLV:	None
BGV:	None

* Please see text in the STEL section

Notations

Notations:	Skin Sensitisation, Skin

Cancer exposure-risk relationships (ERR)*

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

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

[1] The naming conventions of limit values and notations used here follow the 'Methodology for the Derivation of Occupational Exposure Limits' (SCOEL 2013; version 7) and the Joint ECHA/RAC – SCOEL Task Force report (2017b). [https://echa.europa.eu/documents/10162/13579/jtf_opinion_task_2_en.pdf/db8a9a3a-4aa7-601b-bb53-81a5eef93145].

RAC notes that, in the future, the European Commission and its relevant stakeholders will aim to set limit values for non-threshold substances between the predetermined "upper risk level" and the "lower risk level". (ACSH, 2022) opinion[2] agreed that the upper risk level is 4:1 000 (corresponding to 4 predicted cancer cases in 1 000 employees) and the lower risk level is 4:100 000, assuming exposure over 8 hours per day, 5 days a week over a 40-year working life period.

In addition, 8h TWA levels were derived for reproductive toxicity (5.9 mg/m³; 1 ppm) as well as for local effects in the nasal cavity (0.094 mg/m^3; 0.016 ppm).
The binding OEL (BOEL) based on cancer risk would also protect from non-cancer effects, provided that the chosen value will not exceed 0.094 mg/m^3 (0.016 ppm).

RAC OPINION

Background

This draft opinion concerns **glycidyl methacrylate** (GMA) or 2,3-epoxypropyl methacrylate (see section 1 of Annex 1).

This evaluation takes previous reviews into account, in particular:

- The hazard assessment performed in the SIDS program by OECD (2000);
- The CLH report and RAC CLH opinion on 2,3-epoxypropyl methacrylate (2015);
- The evaluation by DFG (Deutsche Forschungsgemeinschaft) in the framework of the MAK evaluation (on skin sensitisation) (2015);
- The evaluation by the Committee for Recommendation of Occupational Exposure Limits of the Japan Society for Occupational Health (JSOH) on GMA;
- The evaluation by IARC (International Agency for Research on Cancer) on some industrial chemical intermediates and solvents (IARC, Monograph 125, 2020);
- The evaluation by AICIS (Australian Industrial Chemicals Introduction Scheme) on glycidyl acrylate and glycidyl methacrylate (2022).

A literature search of published papers from the last ten years completed the source of information (date of last literature search: 12/2022).[3]

Key conclusions of the evaluation

- GMA is a colourless liquid, mainly used as a (co-)monomer in the production of epoxy polymers and vinyl and acrylic resins. Exposure is expected in occupational settings, and is via the inhalation, dermal and oral (hand-to-mouth contact) routes.
- GMA is classified as:
    - Acute Tox 4- H302 harmful if swallowed,
    - Acute Tox 3 - H311 toxic in contact with skin,
    - Skin Corr 1C- H314 causes sever skin burns,
    - Eye Dam. 1 - H318 causes serious eye damage,
    - Skin Sens 1 - H317 may cause an allergic skin reaction,

[2] https://circabc.europa.eu/ui/group/cb9293be-4563-4f19-89cf-4c4588bd6541/library/78479925-4a39-46fd-b2dc-085a244db2d6/details

[3] All references are listed at the end of the Annex.

  - STOT SE3 - H335 may cause respiratory irritation,
  - Muta 2 - H341 suspected of causing genetic defects,
  - Carc 1B - H350 may cause cancer,
  - STOT RE1 - H371 may cause damage to organs (respiratory tract; inhalation),
  - Repr 1B - H360F may damage fertility.

- GMA is expected to be readily absorbed through inhalation, dermal and oral exposure routes. *In vitro* (in animals and human tissues) and *in vivo* studies indicate carboxylesterase-mediated hydrolysis of GMA to glycidol and methacrylic acid.
- No data on humans after exposure to GMA are available, except for several cases with regard to skin sensitisation.
- GMA is carcinogenic; exposure results in tumours in multiple organs in rats and mice of both sexes.
- GMA is mutagenic, based on positive effects in mutagenicity tests *in vivo* (oral micronucleus test), as well as positive effects in several *in vitro* genotoxicity assays. Further, the metabolite glycidol is considered a mutagen.
- GMA exposure results in effects on the fertility index, showing a reduced number of pregnancies in a rat study.
- GMA is a known skin sensitiser. This is based on a positive Buhler assay, as well as several human case reports.
- GMA exerts tissue damage at the first site of contact in animal studies after repeated exposure. After inhalation exposure, respiratory tract irritation is noted in almost all studies.
- GMA is corrosive to skin, induces serious eye damage and causes irritation to the respiratory tract. These local effects are influenced by both cumulative and peak exposures.
- Only two existing OELs are available, namely in Japan (TWA-8 hrs of 0.01 ppm or 0.06 mg/m^3) and China (STEL of 5 mg/m^3).
- No validated methods are available to measure GMA specifically. Methods available for ethyl acrylate or methyl methacrylate can possibly be adapted to measure GMA. The Limit of Detection (LoD) noted by Industry is 0.01 ppm in air sampled for 8 hours. A method might be further developed to a lower LoD of 0.008 ppm.
- No analytical methods for biological monitoring of GMA are available.

Carcinogenicity and mode of action (see section 7.7 of Annex 1 for full discussion)

GMA has an entry in Annex VI of the CLP Regulation as a Carc 1B substance (ATP 10). GMA was also concluded to be *probably carcinogenic to humans* (group 2A) by IARC (2020).

No human data with regard to carcinogenicity of GMA are identified.

Animal studies - inhalation

In animals, two 2-year studies, in mice and rats are available (JBRC, 2015; cited in IARC, 2020).

- Mice were exposed to 0, 0.6, 2.5 or 10 ppm (vapour) for 6 h/day, 5 days/week (50 animals per group). It should be noted that in all groups, including the control, fifty percent or more survived. Incidences of haemangioma and haemangiosarcomas in the

nasal cavity were statistically significantly increased in both sexes. There was also a statistically significant increase in the incidence of bronchioloalveolar carcinomas in females. Furthermore, an increase in incidence was seen in harderian gland adenomas in both sexes (not statistically significant) and in bronchioalveolar carcinomas and uterine histiocytic sarcoma in the females.

- Rats were exposed to 0, 3.2, 8 and 20 ppm (vapour) for 6 h/day, 5 days/week (50 animals per group). Survival rates were significantly lower, especially in males in the high dose group. Squamous cell carcinomas were found in the high dose group in both females and males (statistically significant increase). Other increases in tumour incidences found were in mammary gland fibroadenoma (females), mesothelioma in the peritoneum (males) and fibroma in the subcutis (males).

Animal studies - oral

Oral administration of GMA in rats at doses ranging from 0.001 to 0.3 mg/kg bw for one year with an additional 6-month observation period (Hadidian et al., 1968; cited in IARC, 2020/ ECHA, 2015) did not result in any tumours.

The registrant (see ECHA, 2022) uses an oral carcinogenicity study with 2,3-epoxypropan-1-ol (glycidol) for DMEL derivation (Irwin et al. 1990; NTP report; cited in ECHA, 2015/2022), based on a read-across approach that identified glycidol as the common metabolite.

Rats were dosed with 0, 37.5 and 75 mg/kg bw for 5 days a week for 103 weeks. Mice were dosed with 0, 25 or 50 mg/kg bw for 5 days a week for 103 weeks. Multiple tumours were reported, some of them showed a dose-dependent increase in incidences. Amongst them: mesotheliomas of the *tunica vaginalis*/peritoneum (males), mammary fibro-adenoma and adenocarcinoma (males and females), papilloma in the oral mucosa and forestomach, brain gliomas, and harderian gland adenoma/adenocarcionma (females).

Mode of action (MoA; see section 8.1 of Annex 1)

There is consistent evidence that GMA is genotoxic in bacterial and mammalian cells and in exposed animals. Mechanistic evidence suggests that glycidyl methacrylate is electrophylic, based on the formation of DNA adducts in exposed rats. Furthermore, the metabolite glycidol is a reactive epoxide that alkylates DNA. Induction of oxidative stress or induction of cell proliferation might also be added to the list of potential relevant properties causing cancer.

In conclusion, although insufficient evidence on the exact MoA is available, the information available is sufficient to conclude on a non-threshold MoA for the carcinogenic action of GMA.

Cancer Risk Assessment (see section 9.1 of of Annex 1 for full discussion)

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

The two 2-year inhalation studies in mice and rats are identified as the key studies, because they are performed with GMA itself, with the correct duration, and via the relevant exposure route (inhalation). Doses in mice are lower compared to rats. However some tumours are already found at the low or mid dose in the rat study.

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

Statistically significantly increased incidences are reported in all dose groups for the most relevant tumour, the peritoneal mesothioloma in male rats. Therefore it is used for T25 derivation.

T25 is derived using the following equation:

C × (Reference incidence 0.25)/(incidence at C – control incidence) × (1-control incidence)/1

In which C = the lowest dose with a statistically significant increased frequency (with a P<0.01 or 0.05) (ECHA R8 guidance, 2012).

Calculation:
T25 (based on male rats – peritoneal mesothelioma)
= 3.2 ppm × (0.25/(7/50 – 1/50) × (1-1/50) /1 = 3.2 × (0.25 / (0.14-0.02) × (1-0.02)/1 = **6.53 ppm**

T25 was calculated for several tumour types in each species and sex (see Table below):

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

The lowest derived T25 of 6.53 pp needs to be adjusted with regard to worker exposure conditions (40 years, 48 weeks/year, 8 h/day and correction for inhalation volume at light physical activity):
T25 (worker)= 6.53 ppm × (75/40 years) × (52/48 weeks) × (6/8 h) × (6.7/10 m^3)
= **6.67 ppm**
Using the conversion factor for 1 ppm = 5.91 mg/m^3, the T25 worker is **39.4 mg/m^3**.

Additional lifetime cancer risks were calculated as follows according to the linearised approach[4]. In the case of using a T25, 2.5 is used.

Exposure concentration representing a 1×10^{-5} risk: 6.67 ppm/25 000 = 0.00027 ppm (corresponding to 0.0016 mg/m^3).

Assuming linearity, excess life-time cancer risks were calculated and are presented below (see section 'Derived Limit Values').

[4] As per R8 guidance (ECHA, 2012) - https://echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf/e153243a-03f0-44c5-8808-88af66223258

8h TWA for non-cancer effects

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

Repeated dose/chronic toxicity

There are no human data on chronic toxicity of GMA.

The major toxic effect of GMA found in animal studies is tissue damage at the first site of contact, such as the forestomach after oral administration and respiratory tract after inhalation exposure.

In a 90-day inhalation study in rats (Landry et al., 1996; cited in ECHA, 2015), a NOAEC of 2 ppm was established based on thickened hyperplastic respiratory epithelium. In a 2-year inhalation study in mice (JBRC, 2015; cited in IARC, 2020), the LOAEC was 0.6 ppm based on metaplasia in the olfactory epithelium and respiratory gland.

Taking the LOAEC of 0.6 ppm as PoD for an 8h-TWA derivation for these nasal effects, it is not deemed necessary to adjust the starting point with respect to differences in human and experimental exposure conditions, as the toxic effect (local irritation) is driven by the concentration.

Applying relevant default AFs, this results in an 8h-TWA of 0.016 ppm (0.094 mg/m³) (see Table below).

Point of departure for 8h-TWA for repeated dose toxicity – local effects	
2-year inhalation study in mice with GMA (MWH Japan, 1997)	
LOAEC	**0.6 ppm (3.5 mg/m³)**
Assessment Factors	
LOAEC to NOAEC	3
Interspecies, allometric scaling (not for inhalation)	-
Interspecies, remaining differences	2.5
Intraspecies	5
Exposure duration	1
Quality of whole database	1
Overall assessment factors	37.5
8 hr TWA – local effects	**0.016 ppm (0.094 mg/m³)**

This would correspond to an excess life cancer risk of about 57 cases per 100 000 exposed workers. As a consequence, the OEL based on cancer risk will also protect from non-cancer effects, provided that the value will not exceed 0.016 ppm (0.094 mg/m³).

Reproductive toxicity

In developmental toxicity studies, no adverse effects on embryo or fetal parameters were reported. In two inhalation rabbit studies, NOAECs of >10 ppm (59.1 µg/m³) were derived.

No inhalation studies with regards to reproductive toxicity (fertility) are available. In an oral combi repro study in rats (OECD TG 422) (MHW Japan, 1997; cited in ECHA, 2015), a NOAEL of 30 mg/kg bw/day was derived, based on decreased fertility index.

This NOAEL can be converted using route-to-route extrapolation into a NOAEC for workers. Using relevant assessment factors, this leads to 5.9 mg/m³ (1 ppm) (see Table below).

Point of departure for 8h-TWA for reproductive toxicity	
Oral OECD TG 422 screening study in rats with GMA via gavage (MWH Japan, 1997; cited in ECHA, 2015)	
NOAEL (mg/kg bw/day)	**30**
Inhalation absorption (%)	100
Oral absorption (%)	100
INHALATION	
Adjustment oral to inhalation	1 / 0.384
Correction for exposure regime (day/week)	7 / 5
Absorption percentage rat oral / human inhalation (%)	100 / 100
Breathing rate for workers light activity vs rest	6.7 / 10
Corrected NOAEC (mg/m^3)	73.3
Assessment Factors	
Interspecies, allometric scaling (not for inhalation)	-
Interspecies, remaining differences	2.5
Intraspecies	5
Exposure duration	1
Quality of whole database	1
Overall assessment factors	12.5
8h-TWA – reproductive toxicity	**5.9 mg/m³ (1 ppm)**

Summarizing 8h TWA limits for non-cancer effects

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

Furthermore, when comparing the 8h TWA for reproductive effects with the ERR for cancer (section 9.1.2), a concentration of 5.9 mg/m^3 (1 ppm) would correspond to an excess cancer risk of about 3700 cases per 100 000 exposed workers.

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

Derived Limit Values (see section 9.2 of of Annex 1 for full discussion)

OEL - 8h-TWA

GMA is considered to be an non-threshold carcinogen. Consequently, no health-based OEL nor a STEL can be identified. Instead, an exposure-risk-relationship has been established, as described above.

Cancer exposure-risk relationship (based on peritoneal mesotheliomas in male rats)*

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

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

Short term limit value (STEL)

RAC is of the opinion that a STEL is required, because inhalation exposure to GMA results in respiratory irritation. Furthermore, GMA is a corrosive substance and a skin sensitizer. It is not possible to derive a specific 15-minute value based on the available (animal) data. Derivation of a STEL based on a BOEL is also not possible, as the BOEL is not yet established.
RAC notes that the STEL set at the level of the BOEL would achieve adequate protection.

Biological guidance and limit values

Biomarkers of exposure specific for GMA or its metabolites have not been established. Also no information is available with regards to the biomonitoring of GMA exposure.

No Biological Limit Value (BLV) is proposed, as GMA is considered a non-threshold carcinogen. No Biological Guidance Value (BGV) is proposed due to lack of suitable biomarkers.

Notations

GMA is classified under CLP as a skin sensitiser. A notation for Skin Sensitisation is therefore proposed.

GMA causes acute toxicity in the same concentration range via the dermal route, as via oral route, indicating significant absorption through the skin. A skin notation is therefore proposed.

ATTACHMENTS:

The Annex (Annex 1) gives the detailed scientific grounds for the opinion.

RCOM (Annex 2): Comments received on the ECHA scientific report, and responses provided by ECHA and RAC (excluding confidential information).