COMMENTS AND RESPONSE TO COMMENTS ON OEL: PROPOSAL AND JUSTIFICATION

All comments and attachments including confidential information received during the consultation have been provided in full to the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the consultation and are also published together with the opinion (after adoption) on ECHA's website. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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Substance name: 2,3-epoxypropyl methacrylate (glycidyl methacrylate)
EC number: 203-441-9
CAS number: 106-91-2

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
28.03.2023	Switzerland	<confidential>	Company Manufacturer	1
Comment received				
Higher Methacrylates Reach Task Force comments on the ECHA scientific report for evaluation of limit values for 2,3-epoxypropyl methacrylate We the Higher methacrylate REACH task force (HMRTF), representing co-registrant manufacturers of Glycidyl Methacrylate (GMA), welcome the ability to comment on the ECHA scientific report for evaluation of limit values for 2,3-epoxypropyl methacrylate. In general, we have identified a number of concerns with the proposed approach which we believe leads to an overly conservative limit value being derived particularly relating to the following points: 1) General use of the T25 approach 2) Selection of the appropriate point of departure for derivation of the OEL 3) Likely Mode-of-action of the carcinogenicity of GMA & demonstrable species differences in carboxylesterase activity 4) Current approach for DNEL derivation In addition to the above points, we provide further information on the current analytical detection techniques used for monitoring of GMA in the workplace and practicable levels considered achievable from an Industrial hygiene perspective. 1) General use of the T25 approach The T25 approach is defined as the dose rate in mg/kg bw per day, which will give 25% of the animals tumours at a specific tissue site, after correction for spontaneous incidence, within the standard life time of that species. This approach is a simplified method not requiring complicated statistical analyses and is specifically used in regulatory settings when a ranking according to carcinogenic potency is deemed necessary for classification of carcinogens. However, the simplicity of the T25 approach has led to several concerns amongst which are that estimates based on simple proportional linear extrapolation from the T25 should not be used to predict absolute cancer risk because of unverifiable assumptions used in their calculation. Furthermore, the estimate is based on unproven and perhaps flawed methodology and species differences and mechanistic data not being taken into account (ECETOC 2002), that in the case of MMA are significant and would lead to a different conclusion. In addition, there have been several literature reports where a comparison of the T25 approach with BMD methodologies indicates that				

the T25 method underestimates the true T25 dose (and overestimates the carcinogenic potency (Landingham et al. 2001, Benford et al, 2010). In summary, the use of the T25 approach for derivation of the OEL for GMA is likely to be significantly over-conservative and lead to an OEL estimate that is practically unachievable with current detection technologies.

2) Selection of the appropriate point of departure
In general, for estimating the T25 (in mg/kg bw per day), the lowest tumour incidence data showing a statistically significant response are used (EFSA, 2005) and the tumour type selected should be of relevance to humans.
In the proposed approach, the point of departure chosen is a LOAEC of 0.6ppm based upon olfactory epithelium metaplasia observed in the chronic mouse study (JBRC, 2015 as reported by IARC 2020). Changes in olfactory epithelium are common in rodent studies involving forced inhalation of concentrated, irritant test materials. Indeed, metaplasia can occur in response to hormonal or growth factor alterations or as part of an adaptive response to protect against chronic irritation with examples of irritants known to induce hyperplasia, metaplasia and keratinization being formaldehyde or acetaldehyde.
GMA is classified as a respiratory irritant and metaplastic changes in the nasal epithelia should not necessarily be considered preneoplastic & subsequently leading to tumour development, but merely an adaptive response to repeated tissue injury and repair as a result of local irritation. It should be recognised that metaplasia of nasal epithelia may lead to the promotion of pre-neoplastic events but that in itself is irritant induced and therefore concentration dependent event i.e. it is a threshold mediated step.
In general, the rodent studies demonstrated increased tumour incidence in the nasal cavity and lung only at the top-dose tested of 10ppm. However, the tumours observed in the study may be considered not suitable for identification as the POD for OEL derivation on the basis of lack of human relevance. For example, the hemangioma and hemangiosarcomas observed in the mouse study with GMA at the highest dose tested can be considered of questionable relevance to humans (Weiss and Goldblum 2008, Edler et. al 2014).
In summary, we therefore consider the LOAEC chosen as POD for T25 derivation to be too conservative since no tumour incidence of statistical significance occurred at this dose level and the tumour type is considered non-relevant for humans.

3) Likely MOA and metabolism to glycidol
The metabolism of glycidyl methacrylate in mammals is hypothesized to proceed by at least two different and competing enzyme systems, epoxide hydratase and non-specific carboxylesterases. Metabolism of GMA by carboxylesterase results in formation of glycidol and methacrylic acid, while initial metabolism by epoxide hydrolase results in the formation of glycerol methacrylate.
Metabolism studies in vitro using liver homogenate and nasal epithelial tissues from humans, rats and rabbits have revealed significant species differences in metabolism that call into question the assertion of a quantitative correlation between effect observed in rodents and humans. In vitro incubations of 14C GMA with tissue preparations from human, rat and rabbit resulted in the formation of only one metabolite, tentatively identified as glycidol. The half-lives of GMA hydrolysis were faster in incubations with rat and rabbit tissue versus humans indicating that for these species the pathway of metabolism is predominantly via carboxylesterase enzymes (IARC 2020, Shi et. al 1988). This correlates with the known and significant species differences in carboxylesterase activity in the nasal tissues demonstrated with other esters like vinyl acetate and methyl methacrylate and perhaps helps to explain why there is a good correlation of toxicity between GMA and glycidol. To summarise, basing the T25 calculation on 2-year carcinogenicity studies with glycidol will be sufficiently protective for GMA due the significant differences in metabolism (i.e., metabolism with the preferential production of

glycidol) associated in the more sensitive rodent species as compared with humans.

4) Current approach to DNEL derivation
According to CLP, glycidol has a harmonized classification as Cat 1.b carcinogen, Cat 2. Germ cell mutagen and Cat 1.b reprodevelopmental toxicant. Given the metabolism of GMA to glycidol is significantly greater in rodents, the current conservative approach described by ECHA in the OEL proposal has been to apply the T25 approach to an appropriate POD, such as that derived from a 2-year carcinogenicity study, with additional, appropriate, safety factors.
In summary, for the calculation of the T25 for the parent study on glycidol, female rat mammary gland adenocarcinomas were considered as an appropriate POD since 1) these have a high relevance for human carcinogenicity and 2) these were statistically significantly increased at both 37.5 and 75.0 mg/kg bw/d.
The dose of 37.5 mg/kg/d was corrected for 5 days dosing/wk instead of 7 days (factor 5/7), for 103 weeks dosing instead of 104 (factor 103/104) and for the purity of the glycidol used (94% instead of 100%: factor 94/100).
The percentage of this type of cancer at 37.5 mg/kg/d was 11 rats out of 48 rats or 23%, while the percentage at 0 mg/kg/d was 1 rat out of 50 rats or 2%. The net percentage increase was thus 21%.
This leads to a T25 for glycidol of 37.5x5/7x103/104x94/100*25/21= 29.7 mg/kg/d
This number can be corrected to a T25 for GMA for molecular weight differences: 29.7 x 142.17/74.08 = 57 mg/kg/day (Chemical Safety Report – GMA).

Practicability considerations and current Industrial Hygiene (IH) monitoring considerations
From an IH monitoring perspective, current methodologies for the detection of GMA in the workplace enable a limit of detection (LOD) of 0.01 ppm when monitoring against the shift average i.e., 8-hr TWA, and 0.017 ppm for when monitoring against the short-term exposure limit or STEL. These values are significantly higher than any of the proposed values in the table and raise concerns over compliance measurement and enforceability. Via method extension i.e. further development and validation, it may be possible to lower the LOD to below the 0.008 ppm limit mentioned in table 12 (e.g. by lowering Reporting Limit, convert to GS/MS and increasing the maximum collection volume). However, getting to a much lower level is probably not feasible based upon current technologies. This means that if the OEL is set at the lower end of the range of levels mentioned in Table 12 of the report, or down to 0.00002 ppm, then IH monitoring to verify compliance would be impossible and enforcement unpracticable.

References
Benford et. al. (2010), Application of the Margin of Exposure (MOE) approach to substances in food that are genotoxic and carcinogenic. Food and Chemical Toxicology Vol. 48. S2-S24

Opinion of the Scientific Committee on a request from EFSA related to A Harmonised Approach for Risk Assessment of Substances Which are both Genotoxic and Carcinogenic (Request No EFSA-Q-2004-020) (ADOPTED ON 18 OCTOBER 2005)
IARC 2020. IARC Monographs on the Identification of Carcinogenic Hazards to Humans. Volume 125. Some Industrial Chemical Intermediates and Solvents.
IUCLID dissemination tool https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/15212/7/1ion Dossier - ECHA (europa.eu)
Lutz Edler, Andy Hart, Peter Greaves, Philip Carthew, Myriam Coulet, Alan Boobis, Gary M. Williams, Benjamin Smith (2014), Selection of appropriate tumour data sets for Benchmark Dose Modelling (BMD) and derivation of a Margin of Exposure (MoE) for substances that are genotoxic and carcinogenic: Considerations of biological relevance of tumour type, data quality and uncertainty assessment. Food and Chemical Toxicology,

Vol.70, pp 264-289
Shi T, Zhang BZ, , Yu TJ (1988). [Toxicokinetics of glycidyl methacrylate]. Zhongguo Yaolixue Yu Dulixue Zazhi/Chinese Journal of pharmacology and toxicology. 2:226–31. [Chinese]
The Use of T25 Estimates and Alternative Methods in the Regulatory Risk Assessment of Non-Threshold Carcinogens in the European Union. ECETOC TR. No 83, 2002.
Weiss, S. W., and Goldblum, J. R. (2008). Malignant vascular tumors. In Enzinger and Weiss's Soft Tissue Tumors, 5th ed. (S. W. Weis and J. R. Goldblum, Eds.), pp. 703–732. Mosley Elsevier, China

ECHA note – An attachment was submitted with the comment above. Refer to public attachment HMRTF Comments on GMA OEL proposal - finalized.docx

ECHA/RAC Response

Thank you for the comments you provided to improve and support the RAC in its opinion-making.
Re. 1) the T25 approach has been a scientific approach recognised and agreed with the European Commission to support their setting of an EU binding OEL.
Note that the ECHA Guidance on OEL derivation states that the BMD10 or the T25 may be used as a point of departure, and contains a reference to the SCOEL guidance of 2017: f1d45aca-193b-a7f5-55ce-032b3a13f9d8 (europa.eu)
Other considerations are then being discussed during the legislative process.

Re. 2) For the cancer risk assessment, RAC considered the relevance of the different mice and rat turmours, and derived T25s for different tumour types. The mesothelioma in the peritoneum in male rats was found to result in the lowest T25. The Annex 1 was amended accordingly.
Next to derivation of an ERR for cancer, an 8h TWA levelwas derived based on the local irritant effects.

Re. 3) and 4) the 2-year inhalation studies in mice and rats (JBRC, 2015) were identified as key information, because they are performed with GMA itself, with the correct duration, and via the relevant exposure route.

Re. 4) ECHA and RAC have provided their consideration regarding the current monitoring techniques and the corresponding LoD. This will be taken further in the legislative process discussions.

Date	Country	Organisation	Type of Organisation	Comment number
27.03.2023	Germany	Federal Institute for Occupational Safety and Health (BAuA)	National Authority	2

Comment received

The Federal Institute for Occupational safety and health - division 4 for Hazardous Chemicals and Biological Agents would like to comment on the OEL report for glycidyl methacrylate as follows:
Page 47: In the ECHA scientific report for glycidyl methacrylate the 2-year inhalation studies in mice and rats were identified as key information for cancer risk assessment (JBRC, 2015). It is stated that pre-neoplastic pathological changes in olfactory and respiratory epithelia of mice occured at or above 0.6 ppm and significant dose-response relationships for mesothe-lioma of peritoneum in rats appeared at or above 3.2 ppm. The pre-neoplastic effects in mice were considered as the most sensitive endpoint. Since the dose-response relationship was not considered suitable for benchmark dose modelling, the T25 approach was used to identify the point-of-departure for olfactory epithelium metaplasia findings in male mice (LOAEC 0.6 ppm; lowest concentration tested) and a

T25 of 0.575 ppm was calculated. The T25 was then adjusted to worker exposure conditions ((*75/40 years) * (52/48 weeks) * (6/8 h) * (6.7/10 m3)) which results in a T25 (worker) of 0.59 ppm. From that an exposure-risk relationship was derived and additional lifetime cancer risks were calculated according to a linearised approach. For example an exposure concentration of 0.00002 ppm (0.00014 mg/m3) corresponds to a risk of 1*10-5.

ECHA is asked why carcinogenicity data from animal experiments were not taken into account for deriving additional lifetime cancer risks for workers. Usually, for derivation of an exposure-risk relationship (ERR) data on carcinogenic effects (tumour incidences) are taken into account. Instead, ECHA uses olfactory epithelium metaplasia findings in male mice (LOAEC 0.6 ppm) for the ERR. These data on non-carcinogenic effects (respiratory toxicity) should have been used for dering a hypothetical health-based OEL (as it was calculated for fertility effects, page 48).

Page 38/39: Please note that in Table 11 (column "Remarks") for male mice it is stated "The increased nasal and forestomach tumour incidences were deemed “clear evidence of carcinogenicity” by the authors". However, on closer examination at column "Results”, it is noticeable that the values given for the forestomach and the harderian gland are not statistically significant. Besides, it is stated for female mice (column "Remarks") "The increased nasal, lung and uterus tumour incidences were deemed “clear evidence of carcinogenicity” by the authors". However, the values (column "Results") for the uterus and haderian gland are also not statistically significant.

ECHA/RAC Response

Thank you for your constructive comments.

ECHA and RAC have taken the carcinogenicity data into account for the derivation of the ERR, and amended the Annex 1 report accordingly. See the final opinion and Annex 1, sections 9.1.2 and 9.2.2
Also section 7.7.2 was re-structured for increased clarity.

Date	Country	Organisation	Type of Organisation	Comment number
27.03.2023	Sweden	Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG)	International NGO	3

Comment received

See attachment for comments

ECHA note – An attachment was submitted with the comment above. Refer to public attachment NEG comments ECHA glycidyl methacrylate 27 March 2023.pdf

ECHA/RAC Response

Thank you very much for your detailed and constructive comments.

Typographical errors and suggestions have been taken into account, although some of your comments were not taken into account as they are departing from our internal policy agreements (eg hazard codes, bold font or not).

Inconsistencies and re-structuring have been addressed and more details were provided where identified as relevant.

Date	Country	Organisation	Type of Organisation	Comment number
29.01.2023	Netherlands		Individual	4

Comment received

Without wanting to go into the details of the report, I would like to emphasize that the REACH Registration dossier as disseminated on the ECHA website, and furthermore in particular the CSR, contain carefully calculated DNELs based on the carcinogenic character and other toxicological properties of the substance.
But I must assume that the report has already taken this into consideration. Kind regards, Dr. Peter Ruifrok, Stadex Nederland BV, Lead Registrant

ECHA/RAC Response

Thank you for your comment. Indeed our scientific assessment takes into account the existing information into account and particularly the content of registration dossiers. We note that deriving a DNEL and an OEL do not have the same prupose and may follow different approaches – you may refer to our R8 guidance:
(https://echa.europa.eu/documents/10162/17224/information_requirements_r8_en.pdf/e153243a-03f0-44c5-8808-88af66223258?t=1353935239897)

Further, the 2-year inhalation studies in mice and rats (JBRC, 2015) were identified as key information, because they are performed with GMA itself, with the correct duration, and via the relevant exposure route.

PUBLIC ATTACHMENTS
1. HMRTF Comments on GMA OEL proposal - finalized.docx [Please refer to comment No. 1]
2. NEG comments ECHA glycidyl methacrylate 27 March 2023.pdf [Please refer to comment No. 3]