Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

2,3-epoxypropyl methacrylate; glycidyl methacrylate

EC Number: 203-441-9
CAS Number: 106-91-2

CLH-O-0000001412-86-96/F

Adopted

4 December 2015

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 2,3-EPOXYPROPYL METHACRYLATE; GLYCIDYL METHACRYLATE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

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Substance name: 2,3-epoxypropyl methacrylate; glycidyl methacrylate
CAS number: 106-91-2
EC number: 203-441-9
Dossier submitter: The Netherlands

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
22.06.2015	Germany		MemberState	1

Comment received

In the IUCLID dossier as well as in the report the CAS name is stated as "glycidyl methacrylate" and should be corrected into "2-propenoic acid, 2-methyl-, 2-oxiranylmethyl ester".
Please add CAS number 556-52-5 to glycidol in Section 4.1.3 p. 32.
In chapter 4.1 "toxicokinetics" two possible metabolic routes for GMA are described. First, metabolism of GMA by caboxylesterase would result in the formation of glycidol and methacrylic acid as metabolites. Secondly, metabolism by epoxid hydrolase would result in the formation of glycerol methacrylate. The dossier submitter concluded that the primary metabolite of GMA in humans is glycidol. In our opinion this statement, why the epoxide hydrolysis is not a major route of metabolism for GMA has to be justified in more detail.

Please check references in Section 4.4.2.4 (p. 45) "according to chapter 3.2.3 of CLP" (Does reference refer to chapter 3.3.2.3 in Annex 1 of CLP?) and in Section 4.8.2 (p.60) "… see also sections 4.4.3.3 and 4.4.3.5".

Dossier Submitter's Response

We thank you for the comments.

We agree with the proposed CAS name.

Agreed, the CAS numbers for the metabolites glyclidol (556-52-5) and methacrylic acid (79-41-4) might be useful additions to section 4.1.3 in p.32.

In chapter 4.1, Domoradzki et al. (2004) have hypothesized that the metabolism of GMA by mammals potentially proceeds via at least three different enzyme systems, carboxylesterase, glutathione conjugation and epoxide hydrolase based on data from on ethyl acrylate. Epoxide hydrolyses is considered a *possible* mechanism from a theoretical

point of view due to the presence of an epoxide group in GMA and the presence of epoxide hydrolase in several tissues as indicated in the supportive studies. Although the *in vitro* biotransformation was faster in rats and rabbits cellular fractions as compared to human cellular fractions, under all circumstances only one metabolite appeared which was tentatively identified as glycidol (EINECS 209 -128 -3), thereby supporting the premise that the primary metabolite of GMA in humans is glycidol. This further supported by the *in vivo* study in rabbits were a carboxylester inhibitor resulted in a 90% reduction of the only metabolite detected and the observation of comparable effects of GMA and glycidol in the available studies on sexual function and fertility. Agreed, we have made typing errors in the references: In Section 4.4.2.4 (p.45), reference should be 'chapter 3.3.2.3 in Annex I of CLP' and in Section 4.8.2 (p.60), reference should be 'section 4.3.3 and 4.4.3.3 of CLH Report'.
RAC's response
RAC notes that metabolism by epoxide hydrolase that would result in the formation of glycerol methacrylate has been identified as a possible theoretical pathway but the available experimental data do not support the existence of such a pathway.

Date	Country	Organisation	Type of Organisation	Comment number
18.05.2015	Netherlands	Stadex Nederland BV	Company-Importer	2
Comment received				
The Lead Registrant dossier / the REACH registration does NOT support PROC4, although this is mentioned on page 24 of the CLH report. PROC4 must be taken out since there are no RMMs/OCs available under which the RCR is below 1.				
Dossier Submitter's Response				
We do not agree as PROC 4 is still claimed for GMA by one of the registrants according to the public dissimination site of ECHA.				
RAC's response				
Noted.				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
22.06.2015	Germany		MemberState	3
Comment received				
Assuming that the primary metabolite of GMA is glycidol (see comment to chapter 4.1 "toxicokinetics") the German CA supports the proposed classification Carc. 1B, H350 based on read across to glycidol.				
Dossier Submitter's Response				
Thanks to Germany.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
17.06.2015	France		MemberState	4
Comment received				
p78: FR does support the NL proposal to classify GMA as Carc. 1B H350				
Dossier Submitter's Response				
Thanks to France.				
RAC's response				
Noted.				

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
22.06.2015	Germany		MemberState	5
Comment received				
The German CA supports the proposed classification Muta 2, H341 based on a positive in vivo micronucleus assay.				
Dossier Submitter's Response				
Thanks to Germany.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
17.06.2015	France		MemberState	6
Comment received				
P74: According to FR, mutagenicity effects on germ cells can be anticipated from sperm abnormality tests in mice in which increased abnormal cells and decreased sperm count were reported. Therefore, there is an indication that GMA is able to reach germ cells and interact with genetic material. Furthermore, in the UDS test performed in mice, it cannot be concluded that an inverse U curve is followed by GMA considering the standard deviations, but rather that the severity of the effect is similar in all the tested groups. In conclusion, a category 1B for mutagenicity may be appropriate for GMA based on the in vivo and in vitro data on somatic cells and on the above arguments.				
Dossier Submitter's Response				
We disagree because eventhough GMA increased unscheduled DNA synthesis in germ cell of male mice, this effect was very slight (~25% above controls for all doses administered) and not considered dose-related (Xie et al.: 1990b) [p. 71-72 CLH Report]. The results of this supporting study were ambiguous (Table 21a, p. 68). Also, the effects on sperm cells in the sperm abnormality test were performed using ip exposure which may not reflect testes exposure through normal routes of exposure as it avoids first contact with sites relevant for metabolism. In addition, it only could be used as support for the fact that the substance (or its metabolite) reaches the germ cells, but it does not provide direct evidence of interaction of the substance or its metabolite with the genetic material of the germ cells. Although we agree that the observed mutagenic effects and effects on fertility are indicating an ability to induce germ cell mutagencity, the available evidence is in our opinion currently too limited				

to justify classification as Muta 1B and therefore classification as Muta 2 (H341) is in our view appropriate.
RAC's response
RAC agrees that although there are some indications that GMA induces germ cell mutagenicity in sperm cells (infertility in an oral study, slight increase in UDS and effect on sperm count and sperm abnormality by the IP route), it does not provide direct evidence of an interaction of the substance or its metabolite with the genetic material of the germ cells and the available evidence is not sufficient to justify a classification Muta 1B.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
22.06.2015	Germany		MemberState	7
Comment received				
The German CA supports the proposed classification Repr. 1B, H360F based on a decrease in fertility index in rats, presumably due to the low sperm motility. Supporting studies in mice dosed i.p. showed an increase in the percentage of abnormal sperm and decrease in sperm counts. Furthermore, the proposed metabolite of GMA glycidol also leads to an impairment of male fertility.				
Dossier Submitter's Response				
Thank-you Germany.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
17.06.2015	France		MemberState	8
Comment received				
p.92: FR does support the NL proposal to classify GMA as Repro. 1B H360F				
Dossier Submitter's Response				
Thank you France.				
RAC's response				
Noted.				

RESPIRATORY SENSITISATION

Date	Country	Organisation	Type of Organisation	Comment number
17.06.2015	France		MemberState	9
Comment received				
p. 50: Concerning the possible respiratory sensitisation induced by GMA, it has to be noted that asthma is a common finding associated with an exposure to methacrylates. Additionally, FR recognized that no study design is available to assess this hazard, and that when a substance is corrosive it is difficult to discriminate between effects due to corrosion and effects due to sensitisation. Nevertheless, it is sometimes possible to find human cases for who a reaction appears sometimes after people have been exposed. Are there some potential cases that have been identified for GMA?				

Dossier Submitter's Response
To the best of our knowledge we could not find any human cases with exposure to GMA which would lead to suspicion for respiratory sensitisation.
RAC's response
Noted.

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
22.06.2015	Germany		MemberState	10
Comment received				
Oral: Acute Tox. 4 (H302) It is stated (in Section 4.2.3, p. 36) that "all available acute studies (…) have limitations (…) in the conduct of the study (score 3)". However, one study (Zdravko, 1985; Guinea pig) has been regarded as reliable with restrictions (score 2) (Table 12a). Please clarify this point. Dermal: Acute Tox. 3 (H311) The classification proposal is based on a study (Smyth, 1969) considered as not assignable. However, this study, at the same time, is regarded as key study which is considered inconsistent. Please provide some further evidence or justification. Please give some more detailed reasons why "it is likely that this study was the basis for the current harmonized classification" (Section 4.2.1.3, p. 36). Please change Smith 1969 (Section 4.2.4, p. 37) to Smyth 1969. Inhalation: (No classification) Please correct concentration value 310 mg/m3 to 610 mg/m3 in Table 12b (study: Nitschke, 1990, p.34). Please clarify if exposure concentration was 255 ppm or 259 ppm (see Section 4.2.1.2, p. 35; study: Nitschke, 1990 and Section 4.2.1.2 Table 12b, p.34).				
Dossier Submitter's Response				
Oral: Acute Tox. 4 (H302) The study considered reliable with restrictions (score 2 by Zdravko et al.: 1985) was a study that the OECD used for derivation of an oral LD50 value for GMA of 597 mg/kg bw for rat. Although the available studies are only limitedly reported, all studies provide the same range of LD50 values of 390 – 1050 mg/kg bw. Therefore, overall the level of evidence is considered sufficient to allow classification for acute oral toxicity. Dermal: Acute Tox. 3 (H311) The available information on the only available acute dermal study is very limited and would normally not be usable for classification. However, there is already a harmonised minimum classification of GMA for acute dermal toxicity. It is likely that this study was the basis for the current harmonised classification although we have no access to the original classification proposal. Therefore, this study can be used to adapt the current minimum classification. The dermal LD50 for rabbits in this study was 480 mg/kg bw (Smyth et al.: 1969). We agree that Smith should be changed to Smyth.				

Inhalation: (No classification) The value of 610 mg/m^3 should be changed. The exposure concentration should be 269 ppm.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
17.06.2015	France		MemberState	11
Comment received				
p35: FR questioned if acute inhalation data are sufficiently reliable to remove the current classification of GMA as Acute Tox 4 – H332.				
Dossier Submitter's Response				
As mentioned in Table 12b and in the description of the Nitschke (1990) study (p. 35), 412 ppm (2394 mg/m^3) was the maximum practically attainable vapour concentration and no mortalities were reported at this concentration. This is supported by the results of the 2-weeks inhalation study (Landry, 1991), which was not lethal within 4 days after exposure for 3 days during 6 hours/day to 931 mg/m^3 although the observed effects indicate that the lethal dose is not so much higher. In our opinion, this is sufficient to remove the current classification of GMA as Acute Tox 4 (H332).				
RAC's response				
RAC agrees that none of the available data, including a guideline-compliant study, provide evidence that a classification is justified. No classification is therefore warranted.				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
17.06.2015	France		MemberState	12
Comment received				
p.45: Just a short remark, according to the CLP guidance it has to be noted that: "A skin corrosive substance is considered to also cause serious eye damage which is indicated in the hazard statement for skin corrosion (H 314: Causes severe skin burns and eye damage). Thus, in this case both classifications (Skin Corr. 1 and Eye Dam. 1) are required but the hazard statement H318 'Causes serious eye damage' is not indicated on the label because of redundancy (CLP Article 27)."				
Dossier Submitter's Response				
Thank-you for the remark. We agree.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
22.06.2015	Germany		MemberState	13
Comment received				
The classification as STOT SE 1 H370 is not supported.				

Justification: According to the Guidance on the Application of the CLP Criteria (Version 4.0, 2013, Section 3.8.2.5) a classification as corrosive is considered to cover and communicate the specific toxicological effects adequately and an additional classification as specific target organ toxicant (single exposure, Category 1 or 2) is not indicated if the severe toxicological effect is the consequence of the corrosive mode of action. GMA is proposed to be classified as corrosive (Skin Corr. 1C H314 and Eye Dam. 1 H318). In the CLH report it is stated (Section 4.3.2, p. 40) that STOT SE effects "are due to local irritation". Hence, the additional classification as STOT SE is not indicated for GMA.
A classification as STOT SE 3 (respiratory tract irritation) instead of STOT SE 1 should be assessed for GMA as labored breathing was induced in rats by acute inhalation exposure to GMA vapour for 4 hours at 1.56 mg/l (Nitschke et al., 1990, considered as reliable, Table 12b). This observation is supported by the detected changes in lungs, thorax, respiration, etc. in rats, rabbits, guinea pigs and dogs by Haag, 1953 (score 3) considered as supporting studies. However, these changes should be described in more detail.

Dossier Submitter's Response

We agree that several options for clasification based on the corrosive effect on the lungs after single and repeated exposure could be considered. In our opinion only one such classification should be sufficient as the corrosive effect seems to be determinative. As the substance is not classified for acute inhalation toxicity, the possibility of the additional labelling with EUH071 is not possible. The observed effects on the upper and lower respiratory tract especially after 4 days in the rat study (Landry et al., 1991) are considered more severe than required for STOT SE 3. Therefore, STOT SE 3 is not possible (CLP Annex I 3.8.2.2.1). As the lung effects were already observed after exposure to the vapour, specifying the effects after a single inhalation is considered very relevant. Therefore, STOT SE 1 is proposed.
The CLP Guidance concentration value for single dose exposures for placing a substance in Category 1 is C ≤ 10 mg/l/4h for vapours (rat). The experimental value found for GMA in an acute inhalation toxicity study was at 1.563 mg/l/4h (laboured breathing was observed at this concentration of 269 ppm or 1.563 mg/l/4h by Nitschke et al. (1990) and thus this substance must be classified in STOT SE Category 1 (damage to the respiratory tract after inhalation). This classification is also justified because of the ***severe multifocal necroses*** and ***inflammation of the lung*** after 4 days of exposure to 0.931 mg/L for 6 hours. Although the exposure was repeated for 4 days and the exposure period per day was somewhat longer, the exposure concentration was clearly below the guidance value of 10 mg/L for category 1. In addition, changes in the lungs, thorax and respiration were reported by Haag (1953) in the acute toxicity studies (Table 12b, p. 34), eventhough no further details on the severity of these changes were reported. It remains unclear whether a corrosive mode of action is solely responsible for the changes observed in these studies.

RAC's response

It is not known whether the effects after a single exposure are as severe as the effects in the respiratory tract reported after a 4-day exposure and therefore classification as STOT SE 1 is not justified.
However, the observation of laboured breathing and changes in the respiratory tract after single exposure taken together justify classification as STOT SE 3 – H335.

Date	Country	Organisation	Type of Organisation	Comment number
17.06.2015	France		MemberState	14

Comment received

p40: For Classification of GMA as STOT SE, please note that according to CLP guidance (p362), "an additional classification as specific target organ toxicant (single exposure, cat 1

or 2) is not indicated if the severe toxicological effect is the consequence of the local (i.e corrosive) mode of action". Therefore, the proposal to classify GMA as STOT SE 1 seems not to be appropriate.

Instead, a classification STOT RE 1 should be discussed based on respiratory effects (in particular, necrosis, ulcer, degeneration…) observed at concentrations from 29 mg/m3 in rabbits. Indeed, in the CLP guidance (p 490), "if the dose is more than half an order of magnitude lower than that mediating the evident acute toxicity (corrosivity) then it could be considered to be a repeated-dose effect distinct from the acute toxicity". This is the case for GMA where acute effects were reported at 1400 mg/m3 (Haag et al. , 1953) and repeated effects from 29 mg/m3 (Cieszlak et al., 1996).

Dossier Submitter's Response

Regarding STOT SE classification see our reply to comment 13.

We disagree given that these effects are already covered by the STOT SE 1 (H370) classification. In addition, the rabbit study by Haag (1953) only tested one concentration of 1400 mg/m^3 (saturated concentration). Therefore, it is unknown whether single exposure to a lower concentration would induce comparable effects. Therefore, it is unclear whether there is a large difference between single and repeated exposure in rabbits.

RAC's response

It is not known whether the effects after a single exposure are as severe as the effects in the respiratory tract reported after a 4-day exposure and therefore classification as STOT SE 1 is not justified.
However, the observation of laboured breathing and changes in the respiratory tract after single exposure taken together justify a classification as STOT SE 3 – H335.

See response to comment 15 on STOT RE.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
22.06.2015	Germany		MemberState	15

Comment received

Related to the shown repeated dose toxicity data (inhalation route) a classification as STOT RE 1 (H372) is proposed.
Justification: Six repeated dose inhalation studies with GMA (vapour) are reported and are considered as reliable with restrictions (score 2) (Section 4.7.1.2, Table 19c). In a sub-chronic (13 weeks) inhalation study in rats hyperplasia of the respiratory epithelium of the nasal tissues at a concentration of 0.087 mg/L has been observed (Landry, 1996; considered as key study). This value is below the guidance value for inhalation (rat, vapour) of 0.2 mg/L to assist in Category 1 classification (see Section 3.9.2.9.6 and Table 3.9.2 in Annex 1 of CLP). These findings are supported by three sub-acute studies in rats and rabbits (Landry, 1991; Du Pont, 1977; Cieszlak, 1996) in which slight multifocal necrosis of respiratory epithelial cells at 0.058 mg/L (rat, two weeks), respiratory symptoms at 0.204 mg/L (rat, two weeks) and olfactory epithelial degeneration at 0.0116 mg/L (rabbits, 13 days) have been observed. Moreover, in two 26 weeks studies (Ouyang Guoshun, 1990) using rats and rabbits lesions in the central nervous system, cardiovascular system, liver and kidney, and other degenerative changes in brain and coverings were observed at the low exposure concentration of 0.0153 mg/L. The observed effects are considered to support classification for specific target organ toxicity following repeated exposure as described in

Section 3.9.2.7 in Annex 1 of CLP. Hence, due to the observed effects at low exposure concentrations (related to Table 3.9.2 in Annex 1 of CLP) a classification of GMA as STOT RE 1 (H372) is warranted.
Note: Related to the comments in Table 19c (Section 4.7.1.2): The studies by Ouyang Guoshun, 1990 were considered as reliable with restrictions and as long as impurities have not been described in more detail, the studies should be taken into account for the assessment of GMA.

Dossier Submitter's Response

We agree that the observed effects on the respiratory tract in the repeated dose inhalation studies fulfill the criteria for STOT RE 1. However, comparable effects were also observed in the single dose inhalation study (Nitschke, 1990). As described in the CLP guidance (chapter 3.9.2.5.1 page 490) it should be considered for corrosive substances like GMA whether the severe effect is a reflection of the true repeated exposure or whether it is in fact just acute toxicity. The suggested way to distinguish between these possibilities is to consider the dose level which causes toxicity. If the dose is more than half an order of magnitude lower than that mediating the evident acute toxicity (corrosivity) then it could be considered to be a repeated-dose effect distinct from the acute toxcity. In the main rat repeated dose toxicity studies, the LOAEC for histopathological effects on the respiratory tract were:
Landry (1996) (13 weeks, 5 days/week, 6 h/day): 87 mg/m^3
Landry (1991) (2 weeks, 5 days/week, 6 h/day): 58 mg/m^3

The comparable effects at the same dose level in a 2 and 13 week study suggests that the exposure duration is less relevant for the induction of the histopathological in the respiratory tract. In the available acute inhalation study (Nitschke, 1999), inhalation levels of 1563 and 2394 mg/m^3 lung irritation was observed clinically in the form of laboured breathing. At 610 mg/m^3, no such effects were reported. Histopathology of the respiratory tract is not normally performed in an acute study therefore comparison with the repeated dose studies is difficult. Comparison of the available data suggest that the factor between the lowest dose inducing effect on the respiratory tract after acute and repeated exposure (58 mg/m^3 / 1563 mg/m^3 = 27) is clearly above half an order of magnitude. However, when taking into account the absence of histopathological data from the acute studies and the absence of a duration effect between 2 and 13 weeks of exposure, this factor is likely to be an overestimate of the real magnitude. Overall, we agree that STOT RE could be considered but prefer not to classify for STOT RE because of the classification with STOT SE 1 (H370).

In our opinion, the 26-week inhalation study by Ouyang Guoshun et al (1990) is of doubtfull relevance for GMA because of the described higher vapour pressure and the difference of the effects observed with the other inhalation studies.

RAC's response

RAC agrees that the study by Ouyang Guoshun *et al*. (1990) is inconsistent with the other studies available and considering also the uncertainties raised by the study author on the purity of the test item, the systemic effects observed in this study are not considered as sufficient evidence to classify GMA for STOT RE.

At doses relevant for classification as STOT RE 1, multifocal necrosis and inflammation of the nasal epithelium were observed after 2 weeks of exposure in rats and rabbits. These effects are consistent with the corrosive effects of GMA. The corrosive effects of GMA on the respiratory tract are also responsible for the agreed classification as STOT SE 3 for respiratory irritation after acute exposure. However, RAC considers that significant local effects occur in repeated dose toxicity studies at doses lower than the effective doses after

acute exposure: effective doses of 1.4 to 2.4 mg/L were reported after a single exposure and of 0.9 mg/L after a 4-day exposure compared to effective doses of 0.23 and 0.029 mg/L in two-week studies in rats and rabbits, respectively. On this basis, classification as STOT RE 1 (respiratory tract) (inhalation) is justified.

OTHER HAZARDS AND ENDPOINTS – Physical Hazards

Date	Country	Organisation	Type of Organisation	Comment number
17.06.2015	France		MemberState	16
Comment received				
P23 (1.3 physico-chemical properties) Please note that there is an inconsistency in the CLH report between the result of the flash point and the flammability reported in the table. The flash-point is higher than 60°C therefore the substance is not flammable. However in the flammability, it is reported "flammable" and that "With a flashpoint of 76 (closed cup) – 84 (open cup) deg C and a low volatility (vapour pressure of 4.2 x 100 Pa @ 25 deg C) a separate flammability test is not needed. GMA is a combustible liquid class IIIA and should be kept away from heat, sparks, flame and any source of ignition".				
Dossier Submitter's Response				
We agree that there is an error. GMA is not flammable and the sentence 'GMA is a combustible liquid class IIIA and should be kept away from heat, sparks, flame and any source of ignition" should be removed.				
RAC's response				
Noted.				