Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

isobutyl methacrylate

EC Number: 202-613-0
CAS Number: 97-86-9

CLH-O-0000001412-86-117/F

Adopted

3 June 2016

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: isobutyl methacrylate
EC number: 202-613-0
CAS number: 97-86-9
Dossier submitter: Germany

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
11.12.2015	France		MemberState	1
Comment received				
Although we agree with the proposed classifications for irritation (skin, eye and respiratory) and skin sensitisation endpoints, we consider the read-across with other methacrylates not sufficiently justified based on the data included in the CLH report. In particular, these substances are small molecules with very reactive functions. In this context, it is considered that even the smallest change in chemical structure can have an impact on the reactivity of the molecule, and the effects it will lead to. In addition, there is enough data on i-BMA itself to conclude on classification on dermal and eye irritation and on skin sensitisation. For respiratory irritation, we agree that in a precautionary principle and in the absence of robust data with i-BMA, the current classification should not be deleted.				
Dossier Submitter's Response				
Thank you for the support of the proposed amendments regarding the toxicological classification of isobutyl methacrylate.				
RAC's response				
Noted. Regarding the comparison with other methacrylates, RAC agrees with the comment but notes that no formal read across is proposed.				

Date	Country	Organisation	Type of Organisation	Comment number
03.11.2015	United Kingdom		Industry or Trade Association	2
Comment received				
Comments for Classification proposal on iBMA (EC 202-613-0) The potential future registrant supports the new proposed classification of isobutyl methacrylate by the lead registrant. The potential future registrant is a member of the lower methacrylates REACH task force, which reviews endpoint studies and data used for				

the registration of lower methacrylates (including isobutyl methacrylate). The data made available within the ECHA dissemination website, indicates that isobutyl methacrylate is readily biodegradable, and has low potential for bio-accumulation. Additionally isobutyl methacrylate is moderately toxic to aquatic organisms but does not meet the criteria of classification according to CLP criteria (1272/2008/EC). According to UN-GHS rev. 4 (2011) the substance is classified in category 3 for acute aquatic toxicity. The eye irritation within the disseminated data also supports the classification of no eye hazards for isobutyl methacrylate as it is considered not irritating to eyes in one key study and slightly irritating in another study , but not meeting the criteria for classification. The substance is analogues to n-butyl methacrylate, and has the potential for Skin Sensitization effects, therefore without substance specific data the classification of skin sensitisation should remain, and be re-defined as Skin Sens 1B.
Dossier Submitter's Response
Thank you for the support of the proposed amendments regarding the toxicological classification of isobutyl methacrylate.
RAC's response
Noted. Regarding the analogy with other methacrylates please see response to comment #1.

RESPIRATORY SENSITISATION

Date	Country	Organisation	Type of Organisation	Comment number
11.12.2015	France		MemberState	3
Comment received				
We do not agree that there is "no evidence that i-BMA causes respiratory sensitisation" (page 36) since there is no data with i-BMA and respiratory sensitisation has already been reported with other methacrylates. Therefore, we consider this endpoint not conclusive for classification.				
Dossier Submitter's Response				
Thank you for your comment. We agree to the conclusion that the toxicological endpoint respiratory sensitisation is not conclusive for classification due to the lack of data with isobutyl methacrylate.				
RAC's response				
Noted. The respiratory sensitisation was not assessed by RAC.				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
11.12.2015	Finland		MemberState	4
Comment received				
The Finnish CA supports the proposed removal of the current classification Eye Irrit. 2; H319.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
11.12.2015	Finland		MemberState	5
Comment received				
The Finnish CA supports the proposed classification of isobutyl methacrylate as Skin Sens. 1B; H317. In a guideline LLNA study with i-BMA the result EC3 value of 41.4 % meets the criteria for sub-category 1B. One GPMT was negative for i-BMA but the study cannot be considered as acceptable due to deficiencies in the reporting. A GPMT with a structurally similar isomer n-BMA gave positive result. However, there were only 5 animals in the test group and therefore the study cannot be taken into consideration in the classification of i-BMA.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted. RAC agrees with the comment regarding the GPMT study.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
11.12.2015	Sweden		MemberState	6
Comment received				
The Swedish CA supports the declassification of Isobutyl methacrylate as specified in the proposal. The current classification Aquatic Acute 1(H400) is not required since isobutyl methacrylate is rapidly degradable and has a low bioaccumulation, the values for the acute aquatic toxicity are > 1 mg/l and the NOECs for chronic toxicity are > 1 mg/l.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
11.12.2015	France		MemberState	7
Comment received				
We disagree to withdraw the current classification. The three studies used to justify that the current classification is not deemed necessary are not sufficiently detailed; some discrepancies in the Table 17 and in the text (section 5.4.3.) are noted. In the 1st study, the test conditions are not sufficiently described to be sure that it is a repeated study, it is not a GLP test and the type of concentrations used is not clear ('measured (not specified)' or 'median effective concentration', Table 17). In the Horberg test (2001b), it is not clear if the endpoints are expressed in measured initial concentrations or mean measured concentrations. Furthermore, the test conditions are also not the same as the initial test of Hoberg (1995) preventing a reliable comparison (pseudo closed conditions compared to closed test system). In the initial test Hoberg (1995), the endpoints are indicated as nominal concentrations whereas in the Table 17, they are presented as 'measured (not specified)'. It is concluded that the two reliable studies were performed in closed vessels but it is not clearly demonstrated;				

The read-across with other methacrylates is not sufficiently justified. It could be specified why the 2-EHMA is considered as a lower alkyl methacrylates compared to i-BMA.

The 3 repeated algae growth inhibition tests cannot be compared based on the available information in the CLH report; it is not possible to conclude on their reliability and then, to withdraw the current classification of i-BMA using those data.

In the absence of robust data on i-BMA, the current classification Aquatic Acute 1 (H400) should not be deleted.

Dossier Submitter's Response

Thank you for your points concerning the algae studies.

Concerning the read-across with other methacrylates: This was only presented in the dossier as additional information. The classification is based on this read-across data. Indeed all concentrations described with "measured (not specified)" in the Table 17 are "mean measured concentrations".
In the text in chapter 5.4.3 Hoberg (1995) there was a mistake in this context because there nominal concentrations were stated instead of mean measured concentrations. We would like to add also that this test is not valid because the mean coefficient of variation for section-by-section growth rates in the control cultures exceeds the validity criterion (≤ 35%). Therefore the reliability is 3 according to Klimisch (1997).
It is correct that Hoberg (1995) is a not a GLP test as well as Smyth and Long (1999) and Hoberg (2001). Sverdrup et al. (2001) is a GLP test with *Skeletonema costatum* but not for the other tested algae.
For Hoberg (2002b), a GLP study, the concentrations are "initial measured concentrations" and the text in chapter 5.4.3 is misleading. For a better possibility to compare the data from Hoberg (2002b) with the other algae studies results we recalculated the effect concentrations (from initial measured to mean measured). The resulting NOE_rC based on mean measured concentrations is 2.9 mg/L and the E_rC_{50} is 10.45 mg/L based on mean measured concentrations. These results are the lowest ones for algae but also with them i-BMA has not to be classified with Aquatic Acute 1.

RAC's response

Noted. The validity and reliability of all relevant studies on the aquatic toxicity of isobutyl methacrylate have been addressed in the opinion.

Date	Country	Organisation	Type of Organisation	Comment number
11.12.2015	United Kingdom		MemberState	8

Comment received

1. With regards to acute aquatic classification, i-BMA appears to be of low acute toxicity to fish and invertebrates (L/EC50s >1 mg/L). The original Hoberg (1995) algal study gave a 'greater than' ErC50 value (i.e. >0.74 mg/L) so the actual algal ErC50 may well also be >1 mg/L as indicated in the newer algal studies (Smyth & Long, 1999 and Hoberg, 2002b). However, Table 17 and a number of subsequent study summaries appear unclear/inconsistent about whether acute endpoints in these later studies were indeed based on mean measured concentrations or not (e.g. 'initial' or 'not specified' is given in Table 17). Please clarify.

2. With regards to the chronic aquatic classification, we note that the substance does appear to be 'rapidly degradable' and also to have a low enough bioaccumulation potential. However, we request clarification on some issues that are unclear from the CLH Report..:

i) There is no chronic NOEC for fish, and so a complete chronic data set is not available. We have not considered the reliability of the chronic QSAR for invertebrates in detail - but were there no data to also run a QSAR for fish?. Fish do not appear to be significantly less acutely sensitive (≥10x) than either invertebrates or algae. Although this may not be such an issue if the substance is 'rapidly degradable' - this is not discussed further.. Can a case be made why the lack of chronic fish data does not affect the proposed classification?
ii) As with the acute endpoints, there appears to be an inconsistency between Table 17 where some chronic endpoints are given as 'not specified' or 'initial' in relation to analyses, yet 'mean measured' in subsequent text and tables. Please clarify.
iii) For all studies considered 'reliable without restriction' in Table 17 please clarify whether they were to GLP or why that doesn't necessarily affect their reliability.
iv) We note the original algal study (Hoberg, 1995) and NOErC of 0.047 mg/L is based on nominals, however a mean measured value might have been even lower. Without further detail and clarification of the reliability or not of this study, as well as the analytics performed in the newer algal studies - we are currently unclear why this original endpoint should be discounted as completely invalid. Other 1995 studies on fish and daphnia (not all to GLP or with clear analytics) are, in contrast, considered fully reliable. Saying that the wrong substance might have been tested seems unlikely.

Dossier Submitter's Response

Thank you for your remarks concerning the algae studies and please see the response to comment number 7 for clarifications.

2.i) When there is not a complete chronic data set then the surrogate system has to be used for chronic classification. As you stated i-BMA is "rapidly degradable" and has a low bioaccumulation potential therefore no chronic classification is justified.

ii+iii) please see the response to comment 7.

iv) We agree with your assumption that the wrong substance might have been tested seems unlikely. The study does not fulfil the validitiy criterion of OECD 201 because the mean coefficient of variation for section-by-section growth rates in the control cultures exceeds the validity criterion (≤ 35%). Therefore the reliability is 3 according to Klimisch (1997). Please see also the response to comment 7.

RAC's response

Noted. The validity and reliability of all relevant studies on the aquatic toxicity of isobutyl methacrylate have been addressed in the opinion.

Date	Country	Organisation	Type of Organisation	Comment number
11.12.2015	Finland		MemberState	9

Comment received

Finnish CA does not support the proposed deletion of Aquatic Acute 1, H400 classification for Isobutyl methacrylate.

The current harmonised aquatic acute classification is based on the algae study (Hoberg, 1995), which has been evaluated and accepted before by the USA EPA (1996) as well as in the OECD SIDS process (2004). According to the dossier submitter the deletion of current classification is justified based on the differing test results gained from the later studies presented in the CLH proposal.

The reliability of the later studies cannot be evaluated due to identified deficiencies and

short study descriptions in the proposal: e.g. a clear description of the test substance is not always present, it is not clear whether validity criteria of OECD 201 test guideline is met, how the sampling has been performed or how the measured concentrations have been calculated. In addition, the results from the later Hoberg study (2002b) are based only on initial measured concentration even though the study has been performed under pseudo closed conditions and the substance is considered highly volatile (2.11 hPa at 20 °C). The study descriptions of the tests conducted with the primary metabolite methacrylic acid should also be presented. On the page 44 it is mentioned that the results from the original algae study (Hoberg, 1995) are based on nominal concentrations. However, in the Table 17 it is said that the results are based on the measured concentrations. Could you please clarify? Due to the above mentioned concerns the Finnish CA considers that it is not possible to decide based upon the available information whether the previous algae study by Hoberg (1995) is relevant for the classification of Isobutyl methacrylate (i-BMA) or not. In order to make the definite conclusion on the proposed deletion of aquatic acute classification more information is needed especially on studies conducted with i-BMA.
Dossier Submitter's Response
Thank you for your remarks concerning the algae studies and please see the response to comment number 7 for clarifications. Concerning the pseudo closed conditions: there was an analytical confirmation. Even with recalculated results basing on mean measured instead of initial measured concentrations i-BMA has not to be classified. (The resulting NOE_rC based on mean measured concentrations is 2.9 mg/L and the E_rC_{50} is 10.45 mg/L based on mean measured concentrations.) The detailed description of the test substance can be found in the technical dossier (IUCLID).
RAC's response
Noted. The validity and reliability of all relevant studies on the aquatic toxicity of isobutyl methacrylate have been addressed in the opinion.