Committee for Risk Assessment

RAC

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

3 June 2016

CLH-O-0000001412-86-117/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37(4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: **isobutyl methacrylate**

EC Number: **202-613-0**

CAS Number: **97-86-9**

The proposal was submitted by **Germany** and received by RAC on **4 September 2015.**

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

Germany has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **27 October 2015**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **11 December 2015**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Radu Branisteanu**

Co-Rapporteur, appointed by RAC: **Žilvinas Užomeckas**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on **3 June 2016** by **consensus**.

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling				
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)	Specific Conc. Limits, M-factors	Notes
Current Annex VI entry	607-113-00-X	isobutyl methacrylate	202-613-0	97-86-9	Flam. Liq. 3 STOT SE 3 Skin Irrit. 2 Eye Irrit. 2 Skin Sens. 1 Aquatic Acute 1	H226 H335 H315 H319 H317 H400	GHS02 GHS07 GHS09 Wng	H226 H335 H315 H319 H317 H400	-	-	D
Dossier submitters proposal	607-113-00-X	isobutyl methacrylate	202-613-0	97-86-9	**Modify** Skin Sens. 1B **Remove** Eye Irrit. 2 Aquatic Acute 1	**Retain** H317 **Remove** H319 H400	**Retain** GHS07 Wng **Remove** GHS09	**Retain** H317 **Remove** H319 H400	-	-	**Retain** D
RAC opinion	607-113-00-X	isobutyl methacrylate	202-613-0	97-86-9	**Modify** Skin Sens. 1B **Remove** Eye Irrit. 2 Aquatic Acute 1	**Retain** H317 **Remove** H319 H400	**Retain** GHS07 Wng **Remove** GHS09	**Retain** H317 **Remove** H319 H400	-	-	**Retain** D
Resulting Annex VI entry if agreed by COM	607-113-00-X	isobutyl methacrylate	202-613-0	97-86-9	Flam. Liq. 3 STOT SE 3 Skin Irrit. 2 Skin Sens. 1B	H226 H335 H315 H317	GHS02 GHS07 Wng	H226 H335 H315 H317	-	-	D

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

Based on data from the REACH registration dossiers, the present proposal was for removal of the Eye Irrit. 2 and Aquatic Acute 1 classifications for isobutyl methacrylate (i-BMA) from the existing entry in Annex VI to the CLP Regulation. In addition, classification for Skin sensitisation was proposed to be changed from Skin Sens. 1 to Skin Sens. 1B.

The classifications as Skin Irrit. 2; H315 and STOT SE 3; H335 for respiratory irritation were not evaluated by the dossier submitter (DS); the information regarding these endpoints in the CLH dossier was given for information only. Consequently, RAC did not assess these endpoints.

The presented data included studies performed with the structural analogue butyl methacrylate (n-BMA); the justification included closely related molecular structure, identical metabolic pathways with common or similar metabolites and half-lives (Jones, 2002) as well as similar physicochemical properties (i-BMA/n-BMA - molecular weight: 142.2/142.2 g/mol; boiling point: 155/163 °C; vapour pressure: 2.11/2.1 hPa; water solubility: 0.47 g/L @ 20 °C/0.36 g/L @ 25 °C; log P_{ow}: 2.95/3.0). However, the findings from the studies performed with n-BMA were considered as supportive only and no formal read across was conducted.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of serious eye damage/irritation

Summary of the Dossier Submitter's proposal

The assessment of eye irritation was based on two studies with isobutyl methacrylate; additional information from two studies with butyl methacrylate was also provided.

Studies with isobutyl methacrylate

In an OECD TG 405 guideline compliant study (Schreiber, 1988; reliability 1) using undiluted i-BMA (0.1 mL), one out of the three New Zeeland White (NZW) rabbits exhibited slight conjunctival redness, chemosis and discharge one hour after dosing. Only erythema persisted for 24h. At 48h following dosing all signs of irritation had resolved. The remaining animal showed no signs of irritation at any time during the test (mean conjunctival erythema score over a period of 24, 48 and 72h: 0-0.33). At the end of the 8-day observation period, no signs of cornea, iris or conjunctival irritation could be observed; consequently based on this study i-BMA was considered not irritating to eyes.

In a study which was not OECD compliant but followed an FDA guideline -Draize protocol (Poole, 1980, reliability 2), undiluted i-BMA (0.1 mL) showed signs of slight to moderate erythema and chemosis of the conjunctiva in all 6 NZW rabbits tested. While the chemosis had almost completely resolved by 72h the erythema had improved but was not completely reversible at that time. In this study i-BMA is considered as slightly irritating to eyes (mean erythema scores over a period of 24, 48 and 72h: 0.33-2.0, mean chemosis scores: 0-1.33).

Studies with butyl methacrylate

In an OECD TG 405 study (Schreiber and Wodtke, 1988, reliability 1) 0.1 ml undiluted n-BMA, two out of the three NZW rabbits exhibited slight conjunctival redness, chemosis and discharge, after one hour after dosing which persisted for 24h in one animal. The second animal also exhibited conjunctival erythema at 24h after dosing. At 48h following dosing, all signs of irritation had resolved. The remaining animal showed no signs of irritation at any time during the test (mean conjunctival redness scores and oedema scores over a period of 24, 48 and 72h: 0-0.33). In summary, at the end of the observational period of 8 days, no signs of cornea, iris or conjunctival irritation could be observed; consequently in this study n-BMA is considered to be not irritating to eyes.

In a non OECD compliant study (FDA Draize test, Poole, 1980, reliability 2), 0.1 mL undiluted n-BMA was applied into the conjunctival sac of one eye of six NZW rabbits. The ocular reactions were observed at 24, 48 and 72h after instillation. Slight to well defined redness of the conjunctivae was observed in four of six animals. There were no signs of damage to the iris or cornea (scores: 0). Mean scores over 24, 48 and 72h were 0-1.67 for erythema and 0-1.33 for chemosis. Consequently, in this study n-BMA is considered to be slightly irritant to the eyes.

Comments received during public consultation

Three comments were received during public consultation and all agreed with no classification of isobutyl methacrylate for eye irritation. In addition, one comment considered that the read across from other methacrylates was not adequately justified. In particular, these substances are small but very reactive molecules and even the smallest change in chemical structure can have an impact upon the effects.

Assessment and comparison with the classification criteria

Two studies with i-BMA were been presented for assessment. In the OECD compliant test, no sign of eye irritation was noticed after an 8 day observation period. In the OECD non-compliant test, the highest score for erythema was 2 (seen in 1/6 animals) and the highest score for oedema was 1.33 (also seen in 1/6 animals); both were observed after 72 hours. No effects on the cornea or iris were present in either study. The results are similar to those obtained with n-BMA.

Based on this, the severity of the effects was considered to be low. The eye irritation was completely reversible within 8 days in the OECD compliant study. In the non-compliant study, the conjunctival erythema persisted beyond 72h but the scores were below 2 in 5 out of 6 animals.

The CLP criteria for Category 2 specifies that, based on an OECD compliant study, a substance should be classified for eye irritation if a conjunctival erythema and/or oedema score ≥ 2 is produced in 2 out of 3 tested animals (or in 4 out of 6 rabbits in experiments with 6 animals).

RAC notes that these conditions are not fulfilled and agrees with the DS that isobutyl methacrylate should **not be classified for serious eye damage/irritation** according to the CLP.

Consequently RAC agrees with the DS proposal to delete the existing classification.

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

The assessment of skin sensitisation was based on a study with isobutyl methacrylate; additional information from a study with butyl methacrylate was provided.

Study with isobutyl methacrylate

In a guideline-compliant mouse local lymph node assay - LLNA, OECD TG 429 (Harlan CCR, 2013) i-BMA, formulated in acetone/olive oil (4+1 v/v), was assessed for its possible skin sensitising potential using test item concentrations of 25, 50 and 100%. All treated animals survived the scheduled study period and no signs of systemic toxicity were observed. On day 4, the animals treated with the test material at a concentration of 100% showed erythema of the ear skin (Score 1). Stimulation Indices (S.I.) of 1.78, 3.64 and 5.13 were determined with i-BMA at concentrations of 25, 50 and 100%. A clear dose response relationship was observed. The test material i-BMA was found to be a skin sensitiser but with weak potency, due to the derived EC3 value of 41.4% (w/v).

Study with butyl methacrylate

The isomer n-BMA was investigated in a delayed contact hypersensitivity test in Guinea pigs similar to OECD TG 406 (Guinea pig maximisation test; GPMT) with a reduced number of animals (CIT, 2008). In conclusion, when very high concentrations of n-BMA were used for intradermal induction (> 1%; CLP Guidance, Table *3.4.2-g Potency on basis of the Guinea Pig Maximisation test)*, delayed contact hypersensitivity was observed in 4/5 (80%) guinea pigs.

Comments received during public consultation

Three comments were received during public consultation and all agreed with the re-classification of isobutyl methacrylate as Skins Sensitiser Category 1B.

Assessment and comparison with the classification criteria

One LLNA test was presented for the assessment of skin sensitisation. The results showed a positive response. The test data included a study from which an EC3 of 41.4% was derived, thus enabling the sensitising potency to be assessed. According to the CLP Guidance, Table 3.4.2-f, a value of EC3 > 2 is associated with a moderate potency corresponding to sub-category 1B. The same category is consistent with the findings from a GPMT study in which a very high concentration of n-BMA was used for induction.

RAC considers that there are sufficient data for sub-categorisation of the substance and agrees with the proposal of the DS to re-classify isobutyl methacrylate as **Skin Sensitiser Category 1B**.

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

Isobutyl methacrylate (i-BMA) is currently listed in Annex VI of CLP. The current classification as Aquatic Acute 1 is based on a study on algae toxicity conducted according to OECD TG 201 and which resulted in an E_rC_{50} (96h) of > 0.74 mg/L and a NOEC growth rate of 0.047 mg/L (Hoberg, 1995). The DS proposed to revise the existing classification as they considered that this result is not consistent with algae toxicity observed with several other lower weight methacrylates and could not be reproduced in three further tests that were performed according to OECD TG 201 with i-BMA in a different test laboratory as well as in the same laboratory by the same study director. After re-evaluation of existing data and evaluation of new data, the DS came to the conclusion that the current classification for the hazards to the aquatic environment is no longer consistent with the criteria for classification and labelling as presented in Annex I of the CLP Regulation (1972/2008/EC).

Degradation

The DS considered that i-BMA is hydrolytically stable under normal environmental conditions based on its similarity to n-BMA (Staples, 1996) and hydrolysis appears not to be an important aqueous degradation process for this substance.

The ready biodegradation of isobutyl methacrylate was investigated by a screening test (Thiébaud and Moncel, 1995) (OECD TG 301D, GLP). According to the test results, i-BMA degraded with no lag time and no inhibition. In less than 2 days, 10% biodegradation was achieved, 61.4% was biodegraded after 7 days (10-day window achieved), 74.1% after 14 days and 74.3% after 28 days. Degradation products were not measured. The DS concluded that i-BMA achieved the criteria for readily biodegradability in an OECD TG 301D screening test and passed the 10-day window (> 60% after 10 days). Therefore, the DS concluded that i-BMA is rapidly degradable according to CLP criteria.

Aquatic Bioaccumulation

Based on an experimentally determined logK_{OW} of 2.95 and estimated BCF of 64, the DS concluded that i-BMA has a low bioaccumulation potential according to CLP criteria. Therefore, the DS proposed not to consider the isobutyl methacrylate as bioaccumulative.

Aquatic Toxicity

The results from ecotoxicological tests for i-BMA from available acute and chronic studies are summarised in the following table.

Test organism / guideline, test method	Short-term result (endpoint)	Long-term result (endpoint)	Reference
Rainbow trout (*Oncorhynchus mykiss*) / OECD TG 203	96h LC_{50} = 20 mg/L	-	Sousa (1995)
Daphnia magna / OECD TG 202	48h EC_{50} = >29 mg/L	-	Putt (1995)
Invertebrate toxicity / QSAR	-	**21 day NOEC = 2.1 mg/L**	Staples *et al.* (2009)
Selenastrum capricornutum (*Pseudokirchneriella subcapitata*) / OECD TG 201	72h EC_{50} = 44 mg/L	72h NOEC = 9.5 mg/L	Smyth & Long (1999)
Selenastrum capricornutum (*Pseudokirchneriella subcapitata*) / OECD TG 201, EPA OPPTS 850.5400	96h EC_{50} = 14 mg/L (cell density) 72h EC_{50} = 8.3 mg/L (biomass) **72h EC_{50} = 16 mg/L (growth rate)**	96h NOEC = 5.8 mg/L (cell density) 72h NOEC = 2.1 mg/L (biomass) **72h NOEC = 5.8 mg/L (growth rate)**	Hoberg (2002b)
Selenastrum capricornutum (*Pseudokirchneriella subcapitata*) / equivalent or similar to OECD TG 201	96h EC_{50} = 0.29 mg/L (cell density) 96h EC_{50} ≥ 0.74 mg/L (growth rate)	72h NOEC = 0.047 mg/L (cell density) 72h NOEC = 0.047 mg/L (growth rate)	Hoberg (1995)
Selenastrum capricornutum (*Pseudokirchneriella subcapitata*) / OECD TG 201	96h EC_{50} (deionized water) = 10-100 mg/L (cell density) 96 EC_{50} (distilled water) = 10-100 mg/L (cell density)	**-**	Hoberg (2001)

The DS pointed out that there are no data for i-BMA with marine species, but studies with methacrylic acid (MAA), which is the common metabolite of the lower methacrylates (methyl-, ethyl- n-butyl, isobutyl and ethylhexyl methacrylate), indicated that marine species are not expected to be more sensitive to methacrylates than freshwater species. The marine ecotoxicity of MAA was investigated in a series of experiments with marine fish, invertebrates and algae. There was no evidence that MAA was more toxic to marine species.

The DS concluded that the study on algae toxicity which has been performed according to OECD TG 201 and resulted in an E_rC_{50} (96h) of > 0.74 mg/L and a NOEC growth rate of 0.047 mg/L (Hoberg, 1995) should be considered as invalid based on the three further studies performed according to OECD TG 201 with i-BMA in a different test laboratory, as well as in the same

laboratory by the same study director in order to clarify the large differences between the E_rC_{50} value of the Hoberg study (1995) and those with the other lower methacrylates. In order to clarify if the result of the Hoberg study was reproducible itself, the study was repeated first in a different laboratory (Smyth and Long 1999) and after this twice in the same laboratory by the same study director (Hoberg, 2001 and Hoberg, 2002b). These studies were also conducted with *Pseudokirchneriella subcapitata*.

The DS identified algae *(Pseudokirchneriella subcapitata)* as the most sensitive trophic group in aquatic acute toxicity relevant studies and based the non-classification proposal on the 72h EC_{50} = 16 mg/L (based on growth rate) for the algae. The acute toxicity to the fresh water organisms was based on measured concentrations, each with one reliable study with fish and daphnia: LC_{50} (96h) fish: 20 mg/L, EC_{50} (48h) daphnia: > 29 mg/L.

No data was provided for the chronic toxicity studies with fish. The chronic toxicity to fresh water organisms is based on QSAR estimation using data of five lower alkyl methacrylates with $logK_{OW}$ in the range of 1.32 and 5.59. The most sensitive species in relevant chronic aquatic toxicity studies are aquatic invertebrates (*Daphnia magna*) with a 21d NOEC of 2.1 mg/L (based on reproduction). The NOEC for algae *(Pseudokirchneriella subcapitata)* is based on the most sensitive value of the two reliable studies 72h NOEC = 5.8 mg/L (based on growth rate).

Based on the data presented above, the DS concluded that i-BMA does not meet the criteria for classification as acute/chronically toxic to aquatic organisms.

Comments received during public consultation

Four MSCAs and one Industry Association submitted comments on the environmental part of the DS's proposal. One of the commenting MSCAs and the Industry Association agreed with the DS proposal not to classify i-BMA for aquatic toxicity. The Industry Association pointed out that according to UN-GHS rev. 4 (2011) the substance is classified in category 3 for acute aquatic toxicity (a category which has not been included in CLP).

Two MSCAs disagreed with the DS proposal to not classify i-BMA as toxic to the aquatic environment. They noted that the current aquatic classification is based on the algae study (Hoberg, 1995), which has been evaluated and accepted previously by the US EPA, as well as in the OECD SIDS process. They pointed out that the reliability of the later studies cannot be evaluated due to the deficiencies identified and the short study descriptions in the DS proposal.

- In Smyth and Long (1999), test conditions were not sufficiently well described to be certain that it is a repeated study. It is not a GLP-compliant test and the concentrations used were not clearly described ('measured (not specified)' or 'median effective concentration').
- In Hoberg (2001b), it was not clear if the endpoints were expressed in measured initial concentrations or mean measured concentrations. Furthermore, the test conditions were also not the same as in the initial test of Hoberg (1995), preventing a reliable comparison (pseudo closed conditions compared to closed test system).
- Hoberg (2002b) was based only on initial measured concentrations, even though the study has been performed under pseudo closed conditions and the substance is considered highly volatile (2.11 hPa at 20 °C).

Commenting MSCAs noted that the read-across from other lower methacrylates was not sufficiently justified and the study descriptions of the tests conducted with the primary metabolite methacrylic acid should also have been presented.

In conclusion, they were of the opinion that in the absence of robust data on i-BMA, the current classification Aquatic Acute 1 (H400) should not be removed.

Another MSCA pointed out that the original Hoberg (1995) algal study gave a 'greater than' E_rC_{50} value (*i.e.* > 0.74 mg/L) so the actual algal E_rC_{50} may well also be > 1 mg/L as indicated in the newer algal studies (Smyth & Long, 1999 and Hoberg, 2002b).

In response to all these comments, the DS replied that the read-across with other methacrylates was only presented in the dossier as additional information. The classification proposal was not based on this read-across data. Furthermore the DS specified that indeed, all concentrations described with "measured (not specified)" are "mean measured concentrations". The DS pointed out that in the text in the CLH report chapter 5.4.3 there was a mistake: for the Hoberg (1995) study the nominal concentrations were stated instead of mean measured concentrations. They also added that the test (Hoberg, 1995) is not valid because the mean coefficient of variation for section-by-section growth rates in the control cultures exceeded the test validity criterion (≤ 35%). Therefore the reliability of the study (Hoberg, 1995) is 3 according to Klimisch (1997). The DS agreed that Hoberg (1995), Smyth and Long (1999) and Hoberg (2001) are not GLP compliant tests, but remarked that in Hoberg (2002b), a GLP study, the concentrations are "initial measured concentrations" and the text in chapter 5.4.3 is misleading. Concerning the partly closed conditions, the DS replied that there was an analytical confirmation. To better compare the data from Hoberg (2002b) with the results of other algae studies, the DS recalculated the effect concentrations (from initial measured to mean measured). The resulting NOE_rC based on mean measured concentrations was 2.9 mg/L and the E_rC_{50} was 10.45 mg/L. Although these values were the lowest ones obtained for algae, i-BMA does not fulfil the criteria for classification as Aquatic Acute 1.

Assessment and comparison with the classification criteria

Degradation

RAC agrees that isobutyl methacrylate is rapidly degradable, based on screening test results (< 2 days 10%, 61.4% after 7 days (10-day window achieved), 74.1% after 14 days, 74.3% after 28 days) (Thiébaud and Moncel, 1995). Therefore, RAC considers that the isobutyl methacrylate is rapidly degradable.

Bioaccumulation

RAC agrees that isobutyl methacrylate does not meet the CLP criteria for bioaccumulation, based on an experimentally determined log K_{OW} of 2.95 which is less than the CLP trigger value of ≥ 4. Therefore, RAC considers that the isobutyl methacrylate is not bioaccumulative.

Aquatic Toxicity

RAC notes that there are no data available on isobutyl methacrylate chronic aquatic toxicity for fish and that according to the surrogate approach, the potential classification derived from the other chronic data should be compared with that made using the acute toxicity data for the other trophic levels and the most stringent classification of the two selected.

RAC agrees that the reliability of the original Hoberg (1995) study according to Klimisch is 3 (not reliable) because the mean coefficient of variation for section-by-section growth rates in the control cultures exceeded the test protocol validity criterion (≤ 35%). RAC considers that isobutyl methacrylate is rapidly degradable and does not fulfil the criteria for bioaccumulation. The Hoberg (1995) study on algae toxicity is recognised as invalid as proposed by the DS and therefore i-BMA should no longer be classified as Aquatic Acute 1 based on the following:

- the lowest acute endpoints for the algae *Pseudokirchneriella subcapitata* 72 hour initial measured E_rC_{50} = 16 mg/L (or recalculated the effect concentrations from initial measured to mean measured E_rC_{50} = 10.45 mg/L)

- the lowest chronic endpoints for the aquatic invertebrates 21 day NOEC = 2.1 mg/L (QSAR) based on reproduction.

This is in line with the lowest result for algae *Pseudokirchneriella subcapitata* at 72 hours, with an initially measured NOE_rC = 5.8 mg/L that is based on growth rate (or the recalculated effect concentrations from initial measured to mean measured NOE_rC = 2.9 mg/L).

RAC considered the following data as key in determining the acute and chronic aquatic classification of isobutyl methacrylate:

Fish:

- LC50 (96 h) = 20 mg/L
- NOEC not available

Invertebrates:

- EC_{50} (48 h) > 29 mg/L
- NOEC (21d) = **2.1 mg/L (QSAR)**

Algae:

- E_rC50 (72 h) = 16 mg/L (**10.45 mg/L**)
- NOE_rC (72 h) = 5.8 mg/L (**2.9 mg/L**)

In conclusion, RAC considers in line with the DS that isobutyl methacrylate **does not meet the criteria for acute or chronic aquatic toxicity**.

ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).