Committee for Risk Assessment

RAC

Annex 1
Background document
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

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to public consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

3 June 2016

CLH report

Proposal for Harmonised Classification and Labelling

**Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2**

Substance Name: Isobutyl methacrylate

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

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

Index Number: **607-113-00-X**

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Industry in accordance with Article 37(6) of CLP Regulation

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Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	Isobutyl methacrylate
EC number:	202-613-0
CAS number:	97-86-9
Annex VI Index number:	607-113-00-X
Degree of purity:	> 98 %
Impurities:	ca. 0.5 % (w/w) methyl methacrylate (CAS 80-62-6) ca. 0.4 % (w/w) 2-methylpropan-1-ol (CAS 78-83-1) ca. 0.1 % (w/w) butyl methacrylate (CAS 97-88-1) <= 0.02 % (w/w) water (CAS 7732-187-5) < 0.005 % (w/w) methacrylic acid (CAS 79-41-4)
Additives	ca. 0.01 % mequinol (CAS 150-76-5) ca. 0.01 % (w/w) hydroquinone (CAS 123-31-9) ca. 0.01 % (w/w) 6-tert-butyl-2,4-xylenol (CAS 1879-09-0)

1.2 Harmonised classification and labelling proposal

Table 2: The current Annex VI entry and the proposed harmonised classification

	CLP Regulation
Current entry in Annex VI, CLP Regulation	Flam. Liq. 3, H226 Eye Irrit. 2, H319 STOT SE 3, H335 Skin Irrit. 2, H315 Skin Sens. 1, H317 Aquatic Acute 1, H400
Current proposal for consideration by RAC	**Deletion of:** Eye Irrit. 2, H319 and Aquatic Acute 1, H400 **Revised entry:** Skin Sens. 1B, H317
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Flam. Liq. 3, H226 STOT SE 3, H335 Skin Irrit. 2, H315 Skin Sens. 1B, H317

1.3 Proposed harmonised classification and labelling based on CLP Regulation

Table 3: Proposed classification according to the CLP Regulation

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	Explosives				
2.2.	Flammable gases				
2.3.	Flammable aerosols				
2.4.	Oxidising gases				
2.5.	Gases under pressure				
2.6.	Flammable liquids	Flam. Liq. 3 H226		Flam. Liq. 3 H226	
2.7.	Flammable solids				
2.8.	Self-reactive substances and mixtures				
2.9.	Pyrophoric liquids				
2.10.	Pyrophoric solids				
2.11.	Self-heating substances and mixtures				
2.12.	Substances and mixtures which in contact with water emit flammable gases				
2.13.	Oxidising liquids				
2.14.	Oxidising solids				
2.15.	Organic peroxides				
2.16.	Substance and mixtures corrosive to metals				
3.1.	Acute toxicity - oral				
	Acute toxicity - dermal				
	Acute toxicity - inhalation				
3.2.	Skin corrosion / irritation	Skin Irrit. 2 H315		Skin Irrit. 2 H315	
3.3.	Serious eye damage / eye irritation	none		Eye Irrit. 2 H319	
3.4.	Respiratory sensitisation				
3.4.	Skin sensitisation	Skin Sens. 1B H317		Skin Sens. 1 H317	
3.5.	Germ cell mutagenicity				
3.6.	Carcinogenicity				
3.7.	Reproductive toxicity				
3.8.	Specific target organ toxicity –single exposure	STOT SE 3 H335		STOT SE 3 H335	
3.9.	Specific target organ toxicity – repeated exposure				
3.10.	Aspiration hazard				
4.1.	Hazardous to the aquatic environment	none		Aquatic Acute 1 H400	
5.1.	Hazardous to the ozone layer				

[1)] Including specific concentration limits (SCLs) and M-factors
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Table 4: Proposed labelling based according to the CLP Regulation

	Labelling	Wording
Pictograms	GHS02, GHS07	
Signal Word	Warning	
Hazard statements	H226 H315 H317 H335	Flammable liquid and vapour May cause skin irritation May cause an allergic skin reaction May cause respiratory irritation.
Suppl. Hazard statements		

Proposed notes assigned to an entry: Note D

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

Isobutyl methacrylate (i-BMA) was primarily classified and labelled with R 10; Xi, R 36/37/38; R 43, S24, S37, S61 and adopted into Annex I of Directive 67/548/EEC by the authorities.

Later, in 1995, the Methacrylate Producers Association (MPA), Washington, submitted preliminary results from an algal toxicity study in accordance with TSCA 8e to the Coordinator of the Office of Pollution Prevention and Toxics at the Environmental Protection Agency (EPA), Washington, DC. and submitted in January 1996 the concerning study to EPA.

On this base, ECB amended the classification of i-BMA with N, R50, which was adopted in 1998 in the 25th ATP to the DSD (Annex I of Directive 67/548/EEC; R10; Xi, R 36/37/38; R 43, N, R50, S24, S37, S61) after the introduction of the environmental endpoints into the classification criteria.

In April 2004 OECD SIDS Initial Assessment Report of i-BMA was accepted and published (SIAM 18).

With implementation of the CLP Regulation the substance was classified and labelled with Flam. Liq. 3 (H226), Skin Irrit. 2 (H315), Skin Sens. 1 (H317), Eye Irrit. 2 (H319), STOT SE 3 (H335) and Aquatic Acute 1 (H400).

2.2 Short summary of the scientific justification for the CLH proposal

Data from the REACH registration dossiers were taken as a basis for this CLH proposal.

2.2.1 Revoke of classification

Based on the available/presented data the classification/labelling with Eye Irrit. 2 (H319) and Aquatic Acute 1 (H400) is deemed to be not justified.

<u>Eye Irritation</u>

Two eye irritation studies are available for i-BMA.

In a study following an FDA (Draize) protocol, 6 animals were treated with i-BMA (Poole, 1980a). Eyes were examined at 24, 48 and 72 h from beginning of test with no further observation. There were no signs of damage to iris or cornea. Initially, all rabbits showed signs of slight to moderate erythema and chemosis of the conjunctiva. While the chemosis had almost completely resolved after 72 h, the erythema had decreased but was not completely reversible at that time. In this study i-BMA is considered as slightly irritating to eyes.

In an OECD 405 guideline study, three New Zealand White rabbits were treated with i-BMA (Schreiber, 1988). The eyes were examined at 1, 24, 48 and 72 h as well as 8 d from beginning of test. One hour after dosing, one animal exhibited slight conjunctival redness, chemosis and discharge. Only redness persisted for 24 h. At 48 h following dosing all signs of irritation had been resolved. The remaining animal showed no signs of irritation at any time during the test. In this study i-BMA is considered as not irritating to eyes.

In studies with similar test design, the isomer n-butyl methacrylate (n-BMA) induced slight initial irritation and complete reversibility was shown within 8 d (Schreiber and Wodtke, 1988; Poole, 1980).

The structural similarity of n-BMA is justified by the closely related molecular structure, identical metabolic pathways with common or similar metabolites and half-lives (Jones, 2002) as well as by similar physicochemical properties (i-BMA/n-BMA - molecular weight: 142.2 g/mol/142.2 g/mol; boiling point: 155 °C/163 °C; vapour pressure: 2.11 hPa/2.1 hPa; water solubility: 0.47 g/L @ 20 °C/0.36 g/L @ 25 °C; log P_{ow}: 2.95/3.0).

Overall, i-BMA is considered as not irritating to eyes taking into account the CLP criteria for classification. Current classification/labelling as Eye Irrit. 2, H319 is proposed to be deleted.

Acute Aquatic Effects

The acute toxicity to fresh water organisms is based on measured concentrations each with one reliable study with fish and daphnia: LC50 (96 h) fish: 20 mg/L, EC50 (48 h) daphnia: > 29 mg/L. Algae toxicity is based on the most sensitive value of two reliable studies: ErC50 (72 h) algae: 16 mg/L. The chronic toxicity to fresh water organisms is based on a QSAR using data of five lower alkyl methacrylates with log P_{ow} in the range of 1.32 and 5.59: NOEC (21 d) daphnia magna = 2.1 mg/L. NOEC algae is based on the most sensitive value of two reliable studies: NOECr = 5.8 mg/L.

Isobutyl methacrylate is readily biodegradable in a test according to OECD 301 D and passed the 10-d window. Based on a measured log P_{ow} of 2.95 and an estimated BCF of 64, the substance has a low bioaccumulation potential.

Current classification as Aquatic Acute 1 (H400) is based on a study on algae toxicity according to OECD 201 which has been performed in 1995 and which resulted in an ErC50 (96 h) of > 0.74 mg/L and a NOEC growth rate of 0.047 mg/L (Hoberg, 1995). This result is not consistent with algae toxicity of several other lower methacrylates and could not be reproduced in three further tests according to OECD 201 with i-BMA in a different test laboratory as well as in the same laboratory by the same study director.

2.2.2 Specification of classification of the toxicological endpoint skin sensitisation

In a guideline-compliant mouse local lymph node assay (OECD guideline 429; Harlan CCR, 2013), i-BMA was assessed for its possible skin sensitising potential using test item concentrations of 25, 50 and 100%. On day 4, the animals treated with a test item concentration of 100% showed an 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 was observed.

i-BMA was found to be a skin sensitizer with weak potency due to the derived EC3 value of 41.4% (w/v). Current classification as Skin Sens. 1, H317 is proposed to be concretised as Skin Sens. 1B, H317.

2.3 Current harmonised classification and labelling

2.3.1 Current classification and labelling in Annex VI, Table 3.1 in the CLP Regulation

Table 5: Current classification and labelling in Annex VI, Table 3.1 in the CLP Regulation

Classification		Labelling			Specific Conc. Limits, M-factors	Notes
Hazard Class and Category Code(s)	**Hazard Statement Code(s)**	**Pictogram, Signal Word Code(s)**	**Hazard statement Code(s)**	**Suppl. Hazard statement Code(s)**		
Flam. Liq. 3 Eye Irrit. 2 STOT SE 3 Skin Irrit. 2 Skin Sens. 1 Aquatic Acute 1	H226 H319 H335 H315 H317 H400	GHS02 GHS07 GHS09 Wng	H226 H319 H335 H315 H317 H400	-	-	D

2.4 Current self-classification and labelling based on the CLP Regulation criteria

The following industry self-classification(s) and labelling are publically available in the ECHA C&L Inventory (query from April 2013).

Table 6: Current industry self-classifications and labelling in the ECHA C&L Inventory (08/2015)

Classification		Labelling		Specific Conc. limits, M-Factors	Notes	Number of Notifiers
Hazard Class and Category Code(s)	**Hazard Statement Code(s)**	**Hazard Statement Code(s)**	**Pictograms, Signal Word Code(s)**			
Flam. Liq. 3 Skin Irrit. 2 Skin Sens. 1B STOT SE 3	H226 H315 H317 H335 (respiratory tra...) (Inhalation)	H226 H315 H317 H335	GHS07 GHS02 Wng		Note D	11
Flam. Liq. 3 Skin Irrit. 2 Skin Sens. 1B Eye Irrit. 2 STOT SE 3 Aquatic Acute 1	H226 H315 H317 H319 H335 (respiratory tra...) (Inhalation) H400	H226 H315 H317 H319 H335 H400	GHS07 GHS02 GHS09 Wng		Note D	11
Flam. Liq. 3 Skin Irrit. 2 Skin Sens. 1 Eye Irrit. 2 STOT SE 3 Aquatic Acute 1	H226 H315 H317 H319 H335 (respiratory tra...) (Inhalation) H400	H226 H315 H317 H319 H335 H400	GHS07 GHS02 GHS09 Wng		Note D	11
Flam. Liq. 3 Skin Irrit. 2 Skin Sens. 1 Eye Irrit. 2 STOT SE 3	H226 H315 H317 H319 H335 (Lungs)	H226 H315 H317 H319 H335	GHS07 GHS02 GHS09 Wng			355

Classification		Labelling		Specific Conc. limits, M-Factors	Notes	Number of Notifiers
Hazard Class and Category Code(s)	**Hazard Statement Code(s)**	**Hazard Statement Code(s)**	**Pictograms, Signal Word Code(s)**			
Aquatic Acute 1	H400	H400				
Flam. Liq. 3 Skin Irrit. 2 Skin Sens. 1 Eye Irrit. 2 STOT SE 3 Aquatic Acute 1	H226 H315 H317 H319 H335 H400	H226 H315 H317 H319 H335 H400	GHS07 GHS02 GHS09 Wng		Note D	135
Flam. Liq. 3 Skin Irrit. 2 Skin Sens. 1 Eye Irrit. 2 STOT SE 3 Aquatic Acute 1	H226 H315 H317 H319 H335 (not available) H400	H226 H315 H317 H319 H335 H400	GHS07 GHS02 GHS09 Wng	STOT SE 3: C ≥ 10%		69
Flam. Liq. 3 Skin Irrit. 2 Skin Sens. 1 Eye Irrit. 2 STOT SE 3 Aquatic Acute 1	H226 H315 H317 H319 H335 (Not provided) H400	H226 H315 H317 H319 H335 H400	GHS01 Wng	STOT SE 3: C ≥ 10%		48
Flam. Liq. 3 Skin Irrit. 2 Skin Sens. 1 Eye Irrit. 2 STOT SE 3 Aquatic Acute 1	H226 H315 H317 H319 H335 H400	H226 H315 H317 H319 H335 H400	GHS07 GHS02 GHS09 Wng		Note D	44
Flam. Liq. 3 Skin Irrit. 2 Skin Sens. 1 Eye Irrit. 2 STOT SE 3 Aquatic Acute 1	H226 H315 H317 H319 H335 (not specified) H400	H226 H315 H317 H319 H335 H400	GHS07 GHS02 GHS09 Wng			39
Flam. Liq. 3 Skin Irrit. 2 Skin Sens. 1 Eye Irrit. 2 STOT SE 3 Aquatic Acute 1	H226 H315 H317 H319 H335 (respiratory sys...) H400	H226 H315 H317 H319 H335 H400	GHS07 GHS02 GHS09 Wng		Note D	39
Flam. Liq. 3 Skin Irrit. 2 Skin Sens. 1B STOT SE 3	H226 H315 H317 H335	H226 H315 H317 H335	GHS07 GHS02 Wng		Note D	35
Flam. Liq. 3 Skin Irrit. 2 Skin Sens. 1 Eye Irrit. 2 STOT SE 3 Aquatic Acute 1	H226 H315 H317 H319 H335 (respiratory tra...) H400	H226 H315 H317 H319 H335 H400	GHS07 GHS02 GHS09 Wng			33

Classification		Labelling		Specific Conc. limits, M-Factors	Notes	Number of Notifiers
Hazard Class and Category Code(s)	**Hazard Statement Code(s)**	**Hazard Statement Code(s)**	**Pictograms, Signal Word Code(s)**			
Flam. Liq. 3 Skin Irrit. 2 Skin Sens. 1 Eye Irrit. 2 STOT SE 3 Aquatic Acute 1	H226 H315 H317 H319 H335 (Not applicable) H400	H226 H315 H317 H319 H335 H400	GHS07 GHS02 GHS09 Wng			29
Flam. Liq. 3 Skin Irrit. 2 Skin Sens. 1 Eye Irrit. 2 STOT SE 3 Aquatic Acute 1	H226 H315 H317 H319 H335 (Not provided) H400	H226 H315 H317 H319 H335 H400	GHS07 GHS02 GHS09 Wng			23
Flam. Liq. 3 Skin Irrit. 2 Skin Sens. 1B Eye Irrit. 2 STOT SE 3 Aquatic Acute 1	H226 H315 H317 H319 H335 (respiratory sys...) H400	H226 H315 H317 H319 H335 H400	GHS07 GHS02 GHS09 Wng		Note C	13
Flam. Liq. 3 Skin Irrit. 2 Skin Sens. 1 Eye Irrit. 2 STOT SE 3 Aquatic Acute 1	H226 H315 H317 H319 H335 (Unknown) H400	H226 H315 H317 H319 H335 H400	GHS07 GHS09 Wng			8
Flam. Liq. 3 Skin Irrit. 2 Skin Sens. 1 Eye Irrit. 2 STOT SE 3 Aquatic Acute 1	H226 H315 H317 H319 H335 (not reported) H400	H226 H315 H317 H319 H335 H400	GHS07 GHS02 GHS09 Wng			6
Flam. Liq. 3 Skin Irrit. 2 Skin Sens. 1 Eye Irrit. 2 STOT SE 3 Aquatic Acute 1	H226 H315 H317 H319 H335 (not identified) H400	H226 H315 H317 H319 H335 H400	GHS07 GHS02 GHS09 Wng		Note D	6
Flam. Liq. 3 Skin Irrit. 2 Skin Sens. 1 Eye Irrit. 2 STOT SE 3 Aquatic Acute 1	H226 H315 H317 H319 H335 (Respiratory sys...) H400	H226 H315 H317 H319 H335 H400	GHS07 GHS02 GHS09 Wng	M=1		5
Flam. Liq. 3 Skin Irrit. 2 Skin Sens. 1 Eye Irrit. 2	H226 H315 H317 H319	H226 (H226) H315 (H315) H317 (H317) H319 (H319)	GHS07 GHS02 GHS09 Wng		Note D	4

Classification		Labelling		Specific Conc. limits, M-Factors	Notes	Number of Notifiers
Hazard Class and Category Code(s)	**Hazard Statement Code(s)**	**Hazard Statement Code(s)**	**Pictograms, Signal Word Code(s)**			
STOT SE 3 Aquatic Acute 1	H335 (respiratory sys...) H400	H335 (H335) H400 (H400)				
Skin Irrit. 2 Skin Sens. 1 STOT SE 3 Aquatic Acute 1	H315 H317 H335 (no data) H400	H315 H317 H335 H400 H319 H226	GHS07 GHS09 GHS02 Wng			3
Flam. Liq. 3 Skin Irrit. 2 Skin Sens. 1 Eye Irrit. 2 Aquatic Acute 1	H226 H315 H317 H319 H400	H226 H315 H317 H319 H400 H335	GHS07 GHS02 GHS09 Wng		Note D	2
Flam. Liq. 3 Skin Irrit. 2 Skin Sens. 1 Eye Irrit. 2 STOT SE 3 Aquatic Acute 1	H226 H315 H317 H319 H335 (Not applicable) H400	H226 H315 H317 H319 H335 H400	GHS07 GHS02 GHS09 Wng		Note D	2
Flam. Liq. 3 Skin Irrit. 2 Skin Sens. 1 Eye Irrit. 2 STOT SE 3 Aquatic Acute 1	H226 H315 H317 H319 H335 (Respiratory Sys...) H400	H226 H315 H317 H319 H335 H400	GHS07 GHS02 GHS09 Wng			2
Flam. Liq. 3 Skin Irrit. 2 Skin Sens. 1 Eye Irrit. 2 STOT SE 3 Aquatic Acute 1	H226 H315 H317 H319 H335 H400	H226 H315 H317 H319 H335 H400	GHS07 GHS02 GHS09 Wng		Note D	1
Flam. Liq. 3 Skin Irrit. 2 Skin Sens. 1 Eye Irrit. 2 STOT SE 3 Aquatic Acute 1	H226 H315 H317 H319 H335 (respiratory tra...) (Inhalation) H400	H226 H315 H317 H319 H335 H400	GHS07 GHS02 GHS09 Wng			1
Flam. Liq. 3 Skin Irrit. 2 Eye Irrit. 2 STOT SE 3 Aquatic Acute 1	H226 H315 H319 H335 (respiratory tra...) H400	H226 H315 H319 H335 H400 H317	GHS07 GHS02 GHS09 Wng			1
Flam. Liq. 3 Skin Irrit. 2	H226 H315	H226 H315	GHS07 GHS02		Note D	1

Classification		Labelling		Specific Conc. limits, M-Factors	Notes	Number of Notifiers
Hazard Class and Category Code(s)	**Hazard Statement Code(s)**	**Hazard Statement Code(s)**	**Pictograms, Signal Word Code(s)**			
Skin Sens. 1 Eye Irrit. 2 STOT SE 3 Aquatic Acute 1	H317 H319 H335 (mouth, pharynx,...) H400	H317 H319 H335 H400	GHS09 Wng			
Flam. Liq. 3 Skin Irrit. 2 Skin Sens. 1 Eye Irrit. 2 STOT SE 3 Aquatic Acute 1	H226 H315 H317 H319 H335 (organs) H400	H226 H315 H317 H319 H335 H400	GHS07 GHS02 GHS09 Dgr			1
Flam. Liq. 3 Skin Irrit. 2 Skin Sens. 1 Eye Irrit. 2 STOT SE 3 Aquatic Acute 1	H226 H315 H317 H319 H335 H400	H226 H315 H317 H319 H335 H400	GHS07 GHS09 GHS02 Wng	M=1	Note D	1
Flam. Liq. 3 Skin Irrit. 2 Skin Sens. 1 Eye Irrit. 2 STOT SE 3 Aquatic Acute 1	H226 H315 H317 H319 H335 (Lungs and respi...) H400	H226 H315 H317 H319 H335 H400	GHS07 GHS02 GHS09 Wng		Note D	1
Not Classified						1
Flam. Liq. 3 Skin Irrit. 2 Skin Sens. 1 Eye Irrit. 2 STOT SE 3 Aquatic Acute 1	H226 H315 H317 H319 H335 (RESPIRATORY TRA...) H400	H226 H315 H317 H319 H400 H336	GHS07 GHS02 GHS09 Wng			1
Flam. Liq. 3 Skin Irrit. 2 Skin Sens. 1 STOT SE 3	H226 H315 H317 H335	H226 H315 H317 H335	GHS07 GHS02 Wng		Note D	1

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.

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

A harmonised classification for i-BMA had been developed under 67/548/EC. Assessments performed under the OECD chemicals program and in order to achieve a registration under REACH indicated that according to re-evaluation of existing data and to evaluation of new data the existing classification for the toxicological hazard classes ‘eye irritation’ and ‘hazardous to the aquatic environment’ no longer reflects the criteria for classification and labelling in Annex I of the CLP regulation (1972/2008/EC). Furthermore, the existing classification of the toxicological hazard class ‘skin sensitisation’ needs to be updated.

This document represents an update of the harmonised classification according to the currently available and most reliable information following a comprehensive assessment of the key data on behalf of the 2010 registrants under REACH.

Part B.

SCIENTIFIC EVALUATION OF THE DATA

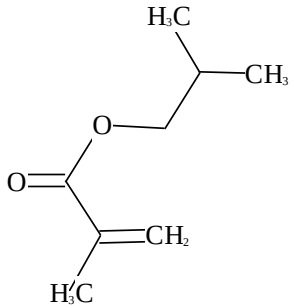
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 7: Substance identity

EC number:	202-613-0
EC name:	Isobutyl methacrylate
CAS number (EC inventory):	97-86-9
CAS number:	97-86-9
CAS name:	2-Propenoic acid, 2-methyl, 2-methylpropyl ester
IUPAC name:	2-methylpropyl 2-methyl-2-propenoate
CLP Annex VI Index number:	607-113-00-X
Molecular formula:	$C_8H_{14}O_2$
Molecular weight range:	142.20

Structural formula:



1.2 Composition of the substance

Table 8: Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
2-propenoic acid, 2-methyl, 2-methylpropylester EC-No.: 202-613-0		98 - 100 % w/w	

Table 9: Impurities (non-confidential information)

Impurity	Typical concentration	Concentration range	Remarks
2-Methyl-2-propenoic acid		0 - 0.1	
Methyl- 2-methyl-2-propenoate		0 - 0.8	
Further Details are given in the 'Confidential annex' or in IUCLID			

Table 10: Additives (non-confidential information)

Additive	Function	Typical concentration	Concentration range	Remarks
Details are given in the 'Confidential annex'				

1.2.1 Composition of test material

Composition of test material used in studies is as described in chapter 1.2 and in the confidential annex.

1.3 Physico-chemical properties

Table 11: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
State of the substance at 20 °C and 101,3 kPa	Liquid Colour: clear, colourless liquid Odour: ester like		
Melting/freezing point	–35 °C.	Evonik Röhm GmbH, 2007	Measured, according to EU Method A.1 (Melting / Freezing Temperature)
Boiling point	155 °C at 1025 hPa	Evonik Röhm GmbH, 2007	Measured , according to EU Method A.2 (Boiling Temperature)
Relative density	0.88 g/cm³ at 25 °C	Luskin, 1971	reliable handbook
Vapour pressure	2.11 hPa at 20 °C	Evonik Röhm GmbH, 1966	Measured according to OECD 104
Surface tension	waiving		In accordance with column 2 of REACH Annex VII, the surface tension of the substance does not need to be tested because due to its chemical structure, no surface activity is predicted.
Water solubility	0.47 g/L at 20 °C.		Value determined by linear regression based on a series of six measured values for alkyl methacrylate esters including the two isomers n-BMA (solubility: 0.41 g/l) and t-BMA (solubility: 0.48 g/l). In this valid scientific study the water solubility was predicted to be 0.47 g/L at 20 °C
Partition coefficient n-octanol/water	2.95 at 20 °C	Jones, 2002	Measured according to OECD 107 (Flask-shake method).
Flash point	42.5 °C at 1013 hPa	Evonik Röhm GmbH, 2007	EU Method A.9 (Flash-Point) similar to DIN 51755/ Abel Pensky (closed cup).
Flammability	waiving	BAM, 2013	Flammability upon ignition (solids, gases): Testing can be waived, substance is a liquid. Flammability in contact with water: The classification procedure needs not to be applied because the substance does not contain metals or metalloids. Pyrophoric properties: The classification procedure needs not to be applied because the substance is known to be stable into contact with air at room temperature for prolonged periods of time (days).

Explosive properties	waiving	BAM, 2013	The classification procedure needs not to be applied because there are no chemical groups associated with explosive properties present in the molecule.
Self-ignition temperature	385 °C at 1013 hPa.	Brandes, 2003	Handbook data
Oxidising properties	waiving	BAM, 2013	The study does not need to be conducted for flammable liquids.
Granulometry	waiving		The substance is a liquid at 20 °C. In accordance with column 2 of REACH Annex VII, the particle size distribution (Granulometry) study does not need to be performed as the substance is marketed or used in a non-solid or granular form.
Stability in organic solvents and identity of relevant degradation products	waiving		In accordance with RAECH annex XI, the study was not conducted because it is not critical
Dissociation constant	waiving		In accordance with REACH annex XI, the study was not conducted as the test substance does not dissociate based on structural alerts
Viscosity	Kinematic viscosity at 20 °C : 1.01 mm²/s Kinematic viscosity at 40 °C : 0.78 mm²/s	Evonik Röhm GmbH, 2008	Measured according to OECD Test Guideline 114 (Viscosity of Liquids), DIN 51562

2 MANUFACTURE AND USES

2.1 Manufacture

i-BMA can be synthesised by catalytic oxidation of isobutylene and subsequent esterification with the appropriate alcohol, or by reacting acetone with hydrocyanic acid and subsequent esterification in sulphuric acid with the appropriate alcohol, or by trans-esterification (Sandmeyer and Kirwin, 1981).

2.2 Identified uses

Most common technical function of substance (what it does):

Use as monomer for polymerisation or intermediate in synthesis of other chemicals.

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Not evaluated in this dossier.

4 HUMAN HEALTH HAZARD ASSESSMENT

In this chapter only irritation and sensitization is discussed

4.1 Irritation

4.1.1 Skin irritation

Table 12: Summary table of relevant skin irritation studies

Method	Results	Remarks	Reference
rabbit (New Zealand White) Coverage: occlusive (shaved or shaved/scarified) Appraisal of the safety of chemicals in foods, drugs and cosmetics, FDA (Draize)(1959) Duration of exposure: 2 h	slightly irritating Erythema score: 0.5 of max. 4 (animal: #2, #4, #6) (Time point: mean 24+72 h) (not fully reversible within: 72 h) (occlusive, exposure time 2h, observation time 72 h, intact skin, reevaluated acc. CLP criteria) 1.5 of max. 4 (animal: #3, #5) (Time point: mean 24+72 h) (not fully reversible within: 72 h) (occlusive, exposure time 2 h, observation time 72 h, intact skin, reevaluated acc. CLP criteria) 2 of max. 4 (animal #1) (Time point: mean 24+72 h) (not fully reversible within: 72 h) (occlusive, exposure time 2h, observation time 72 h, intact skin, reevaluated acc. CLP criteria) 1.08 of max. 4 (animal: #1, #2, #3, #4, #5, #6) (Time point: mean 24+72 h) (not fully reversible within: 72 h) (occlusive, exposure time 2h, observation time 72 h, intact skin, reevaluated acc. DSD (overall mean)) Oedema score: 0 of max. 4 (animal: #2, #6) (Time point: mean 24+72 h) (occlusive, exposure time 2h, observation time 72 h, intact skin, reevaluated acc. CLP criteria) 0.5 of max. 4 (animal: #3, #4) (Time point: mean 24+72 h) (fully reversible within: 72 h) (occlusive, exposure time 2h, observation time 72 h, intact skin, reevaluated acc. CLP criteria) 1 of max. 4 (animal: #1, #5) (Time point: mean 24+72 h) (not fully reversible within: 72 h) (occlusive, exposure time 2h, observation time 72 h, intact skin, reevaluated acc. CLP criteria) 0.5 of max. 4 (animal: #1, #2, #3, #4, #5, #6) (Time point: mean 24+72 h) (not fully reversible within: 72 h) (occlusive, exposure time 2 h, observation time 72 h, intact skin, reevaluated acc. DSD (overall mean))	2 (reliable with restrictions) weight of evidence experimental result **Test material (EC name): isobutyl methacrylate**	Sterner and Stiglic (1977)

rabbit (New Zealand White) Coverage: occlusive (shaved or shaved/scarified) Appraisal of the safety of chemicals in foods, drugs and cosmetics, FDA (Draize)(1959) Duration of exposure: 24 h	slightly irritating Erythema score: 0.5 of max. 4 (animal: #2, #3) (Time point: mean 24+72 h) (not fully reversible within: 72 h) (occlusive, exposure time 24h, observation time 72 h, intact skin, reevaluated acc. CLP criteria) 1 of max. 4 (animal: #4, #6) (Time point: mean 24+72 h) (not fully reversible within: 72 h) (occlusive, exposure time 24h, observation time 72 h, intact skin, reevaluated acc. CLP criteria) 1.5 of max. 4 (animal: #1, #5) (Time point: mean 24+72 h) (not fully reversible within: 72 h) (occlusive, exposure time 2 h, observation time 72 h, intact skin, reevaluated acc. CLP criteria) 0.917 of max. 4 (animal: #1, #2, #3, #4, #5, #6) (Time point: mean 24+72 h) (not fully reversible within: 72 h) (occlusive, exposure time 24 h, observation time 72 h, intact skin, reevaluated acc. DSD (overall mean)) Oedema score: 0 of max. 4 (animal: #2, #3) (Time point: mean 24+72 h) (occlusive, exposure time 24 h, observation time 72 h, intact skin, reevaluated acc. CLP criteria) 0.5 of max. 4 (animal #5) (Time point: mean 24+72 h) (not fully reversible within: 72 h) (occlusive, exposure time 24h, observation time 72 h, intact skin, reevaluated acc. CLP criteria) 1 of max. 4 (animal: #1, #4, #6) (Time point: mean 24+72 h) (not fully reversible within: 72 h) (occlusive, exposure time 24h, observation time 72 h, intact skin, reevaluated acc. CLP criteria) 0.667 of max. 4 (animal: #1, #2, #3, #4, #5, #6) (Time point: mean 24+72 h) (not fully reversible within: 72 h) (occlusive, exposure time 24 h, observation time 72 h, intact skin, reevaluated acc. DSD (overall mean))	2 (reliable with restrictions) weight of evidence experimental result **Test material (EC name): isobutyl methacrylate**	Sterner and Stiglic (1977a)

rabbit (New Zealand White) Coverage: occlusive (abraded and intact skin) Federal Hazardous Substances Labelling Act Regulations, Section 191.11, published in the Federal Register (USA)-29 F.R. 13009, (1964) Duration of exposure: 24 h	irritant Erythema score: 1 of max. 4 (animal: #1, #2) (Time point: mean 24+72 h) (not fully reversible within: 72 h) (exposure time 24 h, observation time 72 h, intact skin, reevaluated acc. CLP criteria) 2 of max. 4 (animal: #3, #4, #5, #6) (Time point: mean 24+72 h) (not reversible within 72 h) (exposure time 24 h, observation time 72 h, intact skin, reevaluated acc. CLP criteria) 1.83 of max. 4 (animal: #1, #2, #3, #4, #5, #6) (Time point: mean 24+72 h) (not fully reversible within: 72 h) (occlusive, exposure time 24 h, observation time 72 h, intact skin, reevaluated acc. DSD (overall mean)) Oedema score: 1 of max. 4 (animal: #1, #2) (Time point: 24+72 h) (note reversible within 72 h) (exposure time 24 h, observation time 72 h, intact skin, reevaluated acc. CLP criteria) 2.5 of max. 4 (animal #3) (Time point: 24+72 h) (not reversible within 72 h) (exposure time 24 h, observation time 72 h, intact skin, reevaluated acc. CLP criteria) 3 of max. 4 (animal: #4, #5, #6) (Time point: 24+72 h) (not reversible within 72 h) (exposure time 24h, observation time 72 h, intact skin, reevaluated acc. CLP criteria) 2.25 of max. 4 (animal: #1, #2, #3, #4, #5, #6) (Time point: mean 24+72 h) (not fully reversible within: 72 h) (occlusive, exposure time 24h, observation time 72 h, intact skin, reevaluated acc. DSD (overall mean))	2 (reliable with restrictions) weight of evidence experimental result **Test material (EC name): isobutyl methacrylate**	Poole (1980a)

rabbit (New Zealand White) Coverage: occlusive and semi-occlusive (shaved) similar to OECD Guideline 404 (Acute Dermal Irritation / Corrosion)	slightly irritating Erythema score: 0.66 of max. 4 (animal #5) (Time point: mean 24+48+72 h) (fully reversible (7 days)) (4-h semi-occlusive exposure, reevaluated acc. CLP criteria) 1 of max. 4 (animal: #1, #2, #6) (Time point: mean 24+48+72 h) (fully reversible within: 7 days) (4-h semi-occlusive exposure, reevaluated acc. CLP criteria) 1.33 of max. 4 (animal #3) (Time point: mean 24+48+72 h) (fully reversible within: 7 days) (4-h semi-occlusive exposure, reevaluated acc. CLP criteria) 1.66 of max. 4 (animal #4) (Time point: mean 24+48+72 h) (fully reversible within: 7 days) (4-h semi-occlusive exposure, reevaluated acc. CLP criteria) 1.11 of max. 4 (animal: #1, #2# #3, #4, #5, #6) (Time point: mean 24+48+72 h) (fully reversible within: 7 days) (4-h semi-occlusive, reevaluated acc. DSD (overall mean)) Oedema score: 0 of max. 4 (animal: #1, #2, #3, #4, #5, #6) (Time point: mean 24+48+72 h) (4-h semi-occlusive exposure, reevaluated acc. CLP criteria) 0.167 of max. 4 (animal: #1, #2# #3, #4, #5, #6) (Time point: mean 24+48+72 h) (fully reversible within: 7 d) (4-h semi-occlusive, reevaluated acc. DSD (overall mean))	1 (reliable without restriction) key study experimental result **Test material (EC name): butyl methacrylate**	Zechel (1982)

rabbit (New Zealand White) Coverage: occlusive (The fur was removed by clipping. Half of the exposed area was abraded and the other half remained intact.) Federal Hazardous Substances Labelling Act Regulations, Section 191.12, Federal Register: 29, 13009 (1964)	irritant Erythema score: 1.5 of max. 4 (animal #5) (Time point: mean 24+72 h) (not fully reversible within: 72 h) (24 h exposure, intact skin; No data in respect to reversibility after > 72 h exposure. Reevaluation acc. CLP criteria) 2 of max. 4 (animal: #1, #4, #6) (Time point: mean 24+72 h) (not fully reversible within: 72 h) (24 h exposure, intact skin; No data in respect to reversibility after > 72 h exposure. Reevaluation acc. CLP criteria) 2.5 of max. 4 (animal: #2, #3) (Time point: mean 24+72 h) (not fully reversible within: 72 h) (24 h exposure, intact skin; No data in respect to reversibility after > 72 h exposure. Reevaluation acc. CLP criteria) 2.08 of max. 4 (animal: #1, #2# #3, #4, #5, #6) (Time point: mean 24+72 h) (not fully reversible within: 72 h) (24 h exposure, intact skin; No data in respect to reversibility after > 72 h exposure. Reevaluation acc. DSD (overall mean)) Oedema score: 1 of max. 4 (animal #5) (Time point: mean 24+72 h) (not fully reversible within: 72 h) (24 h exposure, intact skin; No data in respect to reversibility after > 72 h exposure. Reevaluation acc. CLP criteria) 1.5 of max. 4 (animal: #1, #3) (Time point: mean 24+72 h) (not fully reversible within: 72 h) (24 h exposure, intact skin; No data in respect to reversibility after > 72 h exposure. Reevaluation acc. CLP criteria) 2 of max. 4 (animal #6) (Time point: mean 24+72 h) (not fully reversible within: 72 h) (24 h exposure, intact skin; No data in respect to reversibility after > 72 h exposure. Reevaluation acc. CLP criteria) 2.5 of max. 4 (animal #4 (2.5)) (Time point: mean 24+72 h) (not fully reversible within: 72 h) (24 h exposure, intact skin; No data in respect to reversibility after > 72 h exposure. Reevaluation acc. CLP criteria) 3 of max. 4 (animal #2) (Time point: mean 24+72 h) (not fully reversible within: 72 h) (24 h exposure, intact skin; No data in respect to reversibility after > 72 h exposure. Reevaluation acc. CLP criteria) 1.83 of max. 4 (animal: #1, #2# #3, #4, #5, #6) (Time point: mean 24+72 h) (not fully reversible within: 72 h) (24 h exposure, intact skin; No data	2 (reliable with restrictions) weight of evidence experimental result **Test material (EC name): butyl methacrylate**	Poole (1980)

	in respect to reversibility after > 72 h exposure. Reevaluation acc. DSD (overall mean))		

4.1.1.1 Non-human information

The assessment of skin irritation is based on three studies with i-BMA and two studies with the structurally similar n-BMA.

Only the data for the shaved, intact skin were used for evaluation. In studies carried out with more than three animals both approaches, the overall mean score and the average score determined per animal, were used for evaluation.

Studies with i-BMA

1. Sterner and Stiglic (1977): Application: 2 h; occlusive (shaved and shaved/scarified); six New Zealand White rabbits were assigned to study.

In order to investigate the reproducibility of the effects, each rabbit had two separate dose sites (shaved and shaved/scarified), which were treated with 0.5 ml of undiluted test material. In addition, two untreated areas (shaved and shaved/scarified) were used as the control. Only reactions which were different from those of the control were evaluated as positive reactions. For each treated dose site, 0.5 ml of undiluted test material was soaked onto a gauze patch (approx. 6 cm^2) which was held in place with adhesive tape on the shaved and shaved/scarified skin of the test animals. The animals were fixed in a holding device and their bodies were wrapped in a rubberised cloth for 2 h. After this time, the dressing and adhesive tape were removed and the local reactions were examined. 24 and 72 h after application, the examinations were repeated. The test result is the average of the scores of the 24 and 72 h examination.

Results: Shaved, intact skin: Mean erythema scores (24 + 72 h) per animal were 0.5 (three animals), 1.5 (two animals) and 2.0 (one animal). Evaluated with the second approach the overall mean erythema score was 1.8. Mean oedema scores (24 + 72 h) per animal were 0 (two animals), 0.5 (two animals), 1.0 (two animals). Overall mean oedema score (24 + 72 h) was 0.5. Some erythema and oedema scores persisted at point 72 h.

2. Sterner and Stiglic (1977a): Exposure time: 24 h; occlusive (shaved and shaved/scarified); six New Zealand White rabbits were assigned to study.

The testing animals were restrained in stocks and the fur removed by clipping. Half of the exposed area was abraded and the other half remained intact. 0.5 ml of i-BMA was applied to shaved intact and abraded skin sites and covered with a patch. Two areas remained untreated as control. The animals were fixed and covered with a rubber cloth for 24 h. Then the patches were removed and the local reactions were evaluated after 24 and 72 h in contrast to the control. The test result is the average of the scores of the 24 and 72 h examination.

Results: Shaved, intact skin: Mean erythema scores (24 + 72 h) per animal were 0.5 (two animals), 1.0 (two animals) and 1.5 (two animals). Evaluated with the second approach the overall mean erythema score was 0.917. Mean oedema scores (24 + 72 h) per animal were 0 (two animals), 0.5 (one animal), 1.0 (three animals). Overall mean oedema score (24 + 72 h) was 0.667. Some erythema and oedema scores persisted at point 72 h.

3. Poole (1980): Exposure time: 24 h; six New Zealand White rabbits.

The testing animals were restrained in stocks and the fur removed by clipping. Half of the exposed area was abraded and the other half remained intact. 0.5 ml of i-BMA was applied to the shaved intact and abraded skin sites and covered with surgical gauze. The area was then wrapped with impervious tape and a stockinette sleeve. Test material remained in contact for 24 h and then removed. Irritation scores were determined at 24 and 72 h after patch removal. The test result is the average of the scores of the 24 and 72h examination.

Result: Shaved, intact skin: Mean erythema scores (24 + 72 h) per animal were 1.0 (two animals) and 2.0 (four animals). Evaluated with the second approach the overall mean erythema score was 1.83. Mean oedema scores (24 + 72 h) per animal were 1.0 (two animals), 2.5 (one animal) and 3.0 (three animals). Overall mean oedema score (24 + 72 h) was 2.25. Erythema and oedema scores persisted at point 72 h.

Studies with n-BMA

1. Zechel (1982): In a study comparable to OECD guideline 404, 0.5 ml n-BMA was applied to the intact skin of New Zealand White rabbits under occlusive and semi occlusive conditions for 1 and 4 h. Animals were observed 24 h, 48 h, 72 h and 7 d after patch removal.

Result: Semi occlusive, 4 hours exposure: Mean erythema scores (24 + 48 + 72 h) per animal were 0.66 (one animals), 1.0 (three animals), 1.33 (one animal) and 1.66 (one animal). Evaluated with the second approach the overall mean erythema score was 1.11. Mean oedema scores (24 + 48 + 72 h) were 0 for all animals. All erythema scores were fully reversible within 7 d.

2. Poole (1980): Six New Zealand White rabbits were restrained in stocks and the fur removed by clipping. Half of the exposed area was abraded and the other half remained intact. 0.5 ml of n-BMA was applied to the shaved intact and abraded skin sites and covered with surgical gauze. The area was then wrapped with impervious tape and a stockinette sleeve. Test material remained in contact for 24 h and then removed. Irritation scores were determined at 24 and 72 h after patch removal.

Result: Shaved, intact skin: Mean erythema scores (24 + 72 h) per animal were 1.5 (one animal), 2.0 (three animals) and 2.5 (two animals). Evaluated with the second approach the overall mean erythema score was 2.08. Mean oedema scores (24 + 72 h) per animal were 1 (one animal), 1.5 (two animals), 2.0 (one animal), 2.5 (one animal) and 3.0 (one animal). Overall mean oedema score (24 + 72 h) was 1.83. Erythema and oedema scores persisted at point 72 h.

4.1.1.2 Human information

Human information is not available.

4.1.1.3 Summary and discussion of skin irritation

Three studies for i-BMA are available each of which have an observation time of 72 h. Each study was carried out with 6 animals. Both approaches, the overall mean score and the average score determined per animal, were used for evaluation. In two studies (Sterner and Stiglic, 1977 and 1977a)

all irritation scores were < 2.3 after an exposure time of 2 h in one study and 24 h in the other study; reversibility could not be demonstrated. In the third study (Poole, 1980a) mean oedema scores in 4/6 animals were > 2.3. Overall oedema score in six animals was 2.25. In this study the exposure time was 24 h and the observation time 72 h.

Two studies with the structurally similar n-BMA are available. In a study with n-BMA (Poole, 1980) after 24 h exposure mean irritation scores > 2.3 were found but the observation time was too short to demonstrate reversibility. In a further study with n-BMA (Zechel, 1982) all scores were < 2.3 and were fully reversible within 7 d.

By design, the exposure time of the studies with i-BMA is either shorter (2 h) or longer (24 h) than the current guideline standard (4 h). Furthermore, the observation period of these studies was too short to observe a possibly full recovery of the animals. But on the other hand it cannot be exclude that i-BMA has higher irritating potential at a longer observation time.

Consequently, on balance and in the purpose of precautionary principle, i-BMA is considered as irritating to skin.

4.1.1.4 Comparison with criteria

In one of three studies i-BMA reached the criteria for classification as skin irritant in accordance with CLP criteria. Mean oedema scores were > 2.3 in 4/6 animals.

4.1.1.5 Conclusions on classification and labelling

CLP classification: Skin Irrit. 2, H315; Causes skin irritation.

Present classification is confirmed. This endpoint is given for information.

4.1.2 Eye irritation

Table 13: Summary table of relevant eye irritation studies

Method	Results	Remarks	Reference
rabbit (New Zealand White) Federal Hazardous Substances Labelling Act Regulations, Section 191.12, Federal Register: 29, 13009 (1964)	slightly irritating Cornea score: 0 of max. 4 (animal: #1, #2, #3, #4, #5, #6,) (Time point: mean 24 + 48 + 72 h) Total observation time: 72h Iris score: 0 of max. 2 (animal: #1, #2, #3, #4, #5, #6) (Time point: mean 24 + 48 + 72 h) Total observation time: 72h Conjunctivae score: **Erythema:** 2 of max. 3 (animal #1) (Time point: mean 24 + 48 + 72 h) (not reversible (within 72 h)) 1.33 of max. 3 (animal: #2, #5) (Time point: mean 24 + 48 + 72 h) (not reversible (within 72 h)) 1 of max. 3 (animal #3) (Time point: mean 24 + 48 + 72 h) (not reversible (within 72 h)) 0.66 of max. 3 (animal #4) (Time point: mean 24 + 48 + 72 h) (fully reversible within: 72 h) 0.33 of max. 3 (animal #6) (Time point: mean 24 + 48 + 72 h) (fully reversible (within 72 h)) Total observation time: 72h Swelling: 1.33 of max. 4 (animal #1) (Time point: mean 24 + 48 + 72 h) (not reversible (within 72 h)) 0.66 of max. 4 (animal: #2, #3#, #4) (Time point: mean 24 + 48 + 72 h) (fully reversible within: 72 h) 0 of max. 4 (animal: #5, #6) (Time point: mean 24 + 48 + 72 h) Total observation time: 72h	2 (reliable with restrictions) key study experimental result **Test material (EC name): isobutyl methacrylate**	Poole (1980a)

rabbit (New Zealand White) OECD Guideline 405 (Acute Eye Irritation / Corrosion)	not irritating Cornea score: 0 of max. 4 (animal: #1, #2, #3) (Time point: mean 24 + 48 + 72 h) Total observation time: 8 d Iris score: 0 of max. 2 (animal: #1, #2, #3) (Time point: mean 24 + 48 + 72 h) Total observation time: 8 d Conjunctivae score: Erythema: 0 of max. 3 (animal: #1, #2) (Time point: mean 24 + 48 + 72 h) 0.33 of max. 3 (animal #3) (Time point: mean 24+48+72 h) (fully reversible within: 48 h) 0 of max. 4 (mean (animal #1, #2, #3)) (Time point: mean 24 + 48 + 72 h) Total observation time: 8 d Swelling: 0 of max. 3 (mean (animal #1, #2, #3)) (Time point: mean 24 + 48 + 72 h) Total observation time: 8 d	1 (reliable without restriction) key study experimental result **Test material (EC name): isobutyl methacrylate**	Schreiber (1988)

rabbit (New Zealand White) OECD Guideline 405 (Acute Eye Irritation / Corrosion)	slightly irritating Cornea score: 0 of max. 4 (animal: #1, #2, #3) (Time point: mean 24 + 48 + 72 h) Total observation time: 8 d Iris score: 0 of max. 2 (animal: #1, #2, #3) (Time point: mean 24 + 48 + 72 h) Total observation time: 8 d Conjunctivae score: 0.33 of max. 4 (animal: #1, #3) (Time point: mean 24 + 48 + 72 h) (fully reversible within: 48 h) 0 of max. 4 (animal #2) (Time point: mean 24 + 48 + 72 h) Total observation time: 8 d Chemosis score: 0 of max. 4 (animal: #1, #2) (Time point: mean 24 + 48 + 72 h) 0.33 of max. 4 (animal #3) (Time point: mean 24 + 48 + 72 h) (fully reversible within: 48 h) Total observation time: 8 d	1 (reliable without restriction) key study experimental result **Test material (EC name): butyl methacrylate**	Schreiber and Wodtke (1988)

rabbit (New Zealand White) Federal Hazardous Substances Labelling Act Regulations, Section 191.12, Federal Register: 29, 13009 (1964)	slightly irritating Cornea score: 0 of max. 4 (animal: #1, #2, #3, #4, #5, #6) (Time point: mean 24 + 48 + 72 h) Total observation time: 72 h Iris score: 0 of max. 2 (animal: #1, #2, #3, #4, #5, #6) (Time point: mean 24 + 48 + 72 h) Total observation time: 72 h Conjunctivae score: Erythema 0 of max. 3 (animal: #2, #6) (Time point: mean 24 + 48 + 72 h) 0.66 of max. 3 (animal #4) (Time point: mean 24+48+72 h) (not fully reversible within: 72 h) 1 of max. 3 (animal #3) (Time point: mean 24 + 48 + 72 h) (not fully reversible within: 72 h) 1.33 of max. 3 (animal #1) (Time point: mean 24 + 48 + 72 h) (not fully reversible within: 72 h) 1.67 of max. 3 (animal #5) (Time point: mean 24+48+72 h) (not fully reversible within: 72 h) Total observation time: 72 h Chemosis score: 0 of max. 4 (animal: #1, #2, #3, #6) (Time point: mean 24 + 48 + 72 h) 0.33 of max. 4 (animal #5) (Time point: mean 24 + 48 + 72 h) (fully reversible within: 48 h) 1.33 of max. 4 (animal #4) (Time point: mean 24 + 48 + 72 h) (not fully reversible within: 72 h) Total observation time: 72 h	2 (reliable with restrictions) supporting study experimental result **Test material (EC name): butyl methacrylate**	Poole (1980)

4.1.2.1 Non-human information

Studies with i-BMA

1. In a study following an FDA guideline (Draize protocol) undiluted i-BMA (0.1 mL) was instilled into the right eye (no further specification is mentioned in the study) of six New Zealand White rabbits (Poole, 1980a). The lids were then gently held together for one second. The test eyes were not washed out following the instillation. The left eye remained untreated for control. Total observation time was

72 h. The eyes were examined at 24, 48 and 72 h from beginning of test. Eye irritation was scored for signs of corneal damage (density, area), iris reaction and lesions of the conjunctivae (erythema, chemosis and discharge). Additionally, the cornea was examined with the aid of fluorescein after recording the observations at 24 h. There were no signs of damage to iris or cornea. Initially, all rabbits showed signs of slight to moderate erythema and chemosis of the conjunctiva. While the chemosis had almost completely resolved by 72 h 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 72 h: 0.33-2.0, mean chemosis scores: 0-1.33).

2. In an OECD 405 guideline study (Schreiber, 1988) undiluted i-BMA (0.1 mL) was placed into the conjunctival sac of the right eye of three New Zealand White rabbits. The lids were then gently held together for one second. The test eyes were not washed out following the instillation. The left eye remained untreated for control. The eyes were examined at 1, 24, 48 and 72 h as well as 8 d from beginning of test. Eye irritation was scored for signs of corneal damage (density, area), iris reaction and lesions of the conjunctivae (erythema, chemosis, discharge). Additionally, the cornea was examined with the aid of fluorescein after recording the observations at 24 h. One hour after dosing, one animal exhibited slight conjunctival redness, chemosis and discharge. Only erythema persisted for 24 h. At 48 h following dosing all signs of irritation had resolved. The remaining animal showed no signs of irritation at any time during the test (mean conjunctiva score (redness) over a period of 24, 48 and 72 h: 0-0.33).

i-BMA is considered as not irritating to eyes.

Studies with n-BMA

In studies with the structurally related n-BMA irritation scores and reversibility were similar to i-BMA.

1. In an OECD 405 guideline study, 0.1 ml undiluted n-BMA was placed into the conjunctival sac of the right eye of three New Zealand White rabbits (Schreiber and Wodtke, 1988). The lids were then gently held together for one second. The test eyes were not washed out following the instillation. The left eye remained untreated for control. The eyes were examined at 1, 24, 48 and 72 h as well as 8 d from beginning of test. Eye irritation was scored for signs of corneal damage (density, area), iris reaction and lesions of the conjunctivae (erythema, chemosis and discharge). Additionally, the cornea was examined with the aid of fluorescein after recording the observations at 24 h. One hour after dosing, two animals exhibited slight conjunctival redness, chemosis and discharge, which persisted for 24 h in one animal. The second animal also exhibited conjunctiva erythema at 24 h after dosing. At 48 h following dosing all signs of irritation had resolved. The remaining animal showed no signs of irritation at any time during the test (mean conjunctiva scores and oedema scores over a period of 24, 48 and 72 h: 0-0.33).

2. In addition, in an FDA Draize test (Poole, 1980) 0.1 mL undiluted n-BMA was applied into the conjunctival sac of one eye of six New-Zealand white rabbits, respectively. The ocular reactions were observed at 24, 48 and 72 h after instillation. Observation time was not prolonged. Slight to well defined redness of the conjunctivae was observed in four of six animals. There were no signs of damage to iris or cornea (scores: 0). Mean scores over 24, 48 and 72 h were 0-1.67 for erythema and 0-1.33 for chemosis.

4.1.2.2 Human information

Human information is not available.

4.1.2.3 Summary and discussion of eye irritation

In an OECD 405 guideline study with i-BMA (Schreiber, 1988) 1/3 animals exhibited slight conjunctival redness which persisted for 24 h. At 48 h all signs of irritation had resolved. Additionally in an FDA guideline study with i-BMA (Poole, 1980) there were no signs of damage to iris or cornea in 6 animals but initially all animals showed signs of slight to moderate erythema and chemosis of the conjunctiva which were not reversible during the observation time of 72 h (mean conjunctiva scores 0.33-2.0, mean chemosis scores: 0-1.33).

In studies with the structurally related n-BMA in an OECD 404 guideline study (Schreiber and Wodtke, 1988) 2/3 animals showed slight signs of irritation which had resolved after 48 h. In an FDA Draize test (Poole, 1980) 4/6 animals showed slight to well defined redness of the conjunctivae. Mean scores over a period of 24, 48 and 72 h were 0-1.67 for erythema and 0-1.33 for chemosis.

In summary, i-BMA is considered as not irritating to eyes.

4.1.2.4 Comparison with criteria

The application of i-BMA to rabbit eyes does not induce effects which are relevant for a classification as eye irritant in accordance with the CLP criteria (Corneal opacity: score 0, iritis: score 0, redness: highest score 2 in 1/6 animals and chemosis: highest score 1.33 in 1/6 animals. Full reversibility was shown in a prolonged study after 8 d).

These results are supported by studies with the structurally related n-BMA (Corneal opacity: score 0, iritis: score 0, redness: highest score 1.67 in 1/6 animals and chemosis: highest score 1.33 in 1/6 animals. Full reversibility was shown in a prolonged study after 8 d).

4.1.2.5 Conclusions on classification and labelling

According to CLP criteria, i-BMA has not to be classified as eye irritating. It is proposed to delete the current classification/labelling as Eye Irrit. 2, H319.

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.

4.1.3 Respiratory tract irritation

4.1.3.1 Non-human information

i-BMA

In a no guideline-related inhalation study (Jones, 2002) in five male F344 rats using specialist histopathology techniques to study the nasal tissues, i-BMA did not induce lesions in the olfactory region of the nasal cavity following a single whole body exposure of 200 ppm (one dose group) for 6 h.

n-BMA

In studies with the structurally related isomer n-BMA respiratory irritation was seen after single as well as repeated exposure to very high concentrations (952 ppm and higher).

In an acute inhalation toxicity study with n-BMA according to OECD guideline 403 (Dupont, 1993) male and female rats showed clinical signs of respiratory irritation if their noses/heads were exposed to concentrations of 2370 ppm (14 mg/L) and higher.

In a guideline-compliant repeated dose 28-day inhalation study (OECD guideline 412; Hagan et al. 1993) 10 male and 10 female rats were exposed by whole body to 0, 310, 952 and 1891 ppm (0, 1832, 5626, 11175 mg/m^3) n-BMA for 6 h/day, 5 days/week for 4 weeks. Treatment-related clinical signs included lacrimation, eye squinting and laboured breathing in the 952 and 1891 ppm (5626 and 11175 mg/m^3) concentration groups throughout the study. The only treatment-related histopathological finding was localised as bilateral degeneration of olfactory epithelium lining the dorsal meatus of the nasal cavity at 952 and 1891 ppm (5626 and 11175 mg/m^3) in both sexes.

Methyl methacrylate (MMA), Ethyl methacrylate (EMA), Methacrylic acid (MAA)

Although no olfactory lesions were seen in the acute inhalation study with i-BMA (Jones, 2002) in the same study and under comparable exposure condition the exposure to MMA and EMA resulted

in histological findings consistent with nasal irritation. In the case of MMA the mode of action by which olfactory lesions are formed has been shown to be due to hydrolysis of the parent ester to MAA, an irritant and corrosive substance, by carboxylesterases in the olfactory epithelium (EU Chemicals Bureau, 2002). As this mode of action has been shown to occur with many other common esters, ethers and acetates, it is anticipated that i-BMA acts in a similar manner.

4.1.3.2 Human information

Human information is not available.

4.1.3.3 Summary and discussion of respiratory tract irritation

No respiratory irritation was found in the olfactory region in an acute inhalation study after 6 h whole body exposure with 200 ppm i-BMA in rats (Jones, 2002), but signs of respiratory irritation were observed at 2370 ppm and higher concentrations in an acute inhalation toxicity study (Dupont, 1993) and in a 28-day repeated dose inhalation study at 952 ppm and higher concentrations (Hagen et al., 1993), both performed with the structural analogue n-BMA.

By analogy to n-BMA it is reasonable to expect that the acute LOAEL for i-BMA for respiratory irritation would be between 200 ppm and 952 ppm. The available studies indicate that the threshold concentration for respiratory irritation for the butyl esters is comparable, but higher than that for the smaller alkyl esters MMA and EMA. The common mode of action seems to be the release of an irritating metabolite (MAA) (EU Chemicals Bureau, 2002).

By analogy to the structurally related isomer n-BMA, i-BMA is considered to be irritating to the respiratory tract.

4.1.3.4 Comparison with criteria

On balance and for the purpose of the precautionary principle, i-BMA has to be classified as irritant to the respiratory tract based on the induced respiratory tract irritation by the structural related isomer n-BMA.

4.1.3.5 Conclusions on classification and labelling

CLP classification: STOT SE3, H335; May cause respiratory irritation.

Present classification is confirmed. This endpoint is given for information.

4.2 Corrosivity

See irritation.

4.3 Sensitisation

4.3.1 Skin sensitisation

The results of experimental studies on skin sensitisation are summarised in the following table:

Table 14: Overview of experimental studies on skin sensitisation

Method	Results	Remarks	Reference
mouse (Mice, CBA/CaOlaHsd) female Local lymph node assay OECD Guideline 429 (Skin Sensitisation: Local Lymph Node Assay)	sensitising Stimulation index: Test substance: 25% S.I.=1.78 50% S.I.=3.64 100% S.I.=5.13 EC3 value: 41.4%	1 (reliable without restriction) key study experimental result **Test material (EC name): isobutyl methacrylate**	Harlan CCR (2013)
guinea pig (Hartley) male Guinea pig maximisation test Induction: intradermal Challenge: epicutaneous, occlusive Modified Magnusson and Kligman method (1969). The identification of Contact Allergens by Animal Assay - The Maximisation Test. J. Invest. dermatol. Vol. 52 3, p 268-276, in order to screen for delayed contact hypersensitivity potential.	not sensitising Induction phase A; Induction phase B; Challenge phase: 0 out of 12 (test group); dose: 0.1 mL	4 (not assignable) weight of evidence **(no positive control and no challenge control reported)** **Test material (EC name): isobutyl methacrylate**	Poole (1980b)
guinea pig (Hartley Crl: (HA) BR) male/female Guinea pig maximisation test Induction: intradermal and epicutaneous Challenge: epicutaneous, occlusive Similar to OECD Guideline 406 (Skin Sensitisation) (reduced group size, only 5 animals in the test group)	sensitising No. with positive reactions: 1st reading: 4 out of 5 (test group); 24 h after chall.; dose: 10% 1st reading: 2 out of 5 (test group); 48 h after chall.; dose: 10% 1st reading: 10 out of 10 (positive control); 24 h after chall.; dose: 20% 1st reading: 10 out of 10 (positive control); 48 h after chall.; dose: 20%	2 (reliable with restrictions key study experimental result **Test material (IUPAC name): butyl methacrylate**	CIT (2008)

4.3.1.1 Non-human information

In a guideline-compliant mouse local lymph node assay (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 a test item concentration of 100% showed an 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 was observed. The test item i-BMA was found to be a skin sensitiser with weak potency due to the derived EC3 value of 41.4% (w/v).

A maximisation test with Guinea pigs (Poole, 1980b) is not assignable due to the fact that no positive control and no challenge control were reported.

The isomer n-BMA was investigated in a delayed contact hypersensitivity test in Guinea pigs similar to OECD guideline 406 (Guinea pig maximisation test) with a reduced number of animals (CIT, 2008). The induction phase has been realized both by intradermal route on day 1 (5% in corn oil) and by cutaneous route on day 8 (50% (w/w) in ethanol/purified water (80/20, w/w)) in one group of guinea pigs (2 males and 3 females). The challenge phase was realized on day 22 by cutaneous application of n-BMA (10% (w/w) in acetone) on the right flank (vehicle on the left flank); the cutaneous reactions were scored 24 and 48 h after the challenge phase. After the challenge application, no cutaneous reactions were noted on the left flank (application of the vehicle) of the animals. On the right flank (application of n-BMA) of the animals, a discrete or moderate erythema was noted in 4/5 and 2/5 animals at the 24- and 48-h readings, respectively. An oedema and dryness of the skin were also noted in 1/5 and 2/5 animals, respectively, at the 48-h reading. In conclusion, n-BMA induced delayed contact hypersensitivity in 4/5 (80%) guinea pigs.

4.3.1.2 Human information

No relevant data are available for i-BMA while the isomer n-BMA showed some evidence of skin sensitisation in humans.

Maibach et al. (1978) reported that in 542 dermatitis patients given covered patch tests with 1% n-BMA in petrolatum, one individual responded to n-BMA. Six out of 243 contact dermatitis patients responded to n-BMA if they were given 24 h covered patch tests with n-BMA at a concentration of 2% in petrolatum (Kanerva et al. 1997). Schnuch (1979) reported the prevalence of positive clinical challenge responses in dental clinicians that had been referred with dermatitis and suspected of having allergy to (meth)acrylates as 0.3% (1/347) for n-BMA).

Schnuch (1979) also reported the prevalence in a similar, pre-selected clinical cohort as 0.8% (9/1161) for MMA and 0.3% (2/625) for EMA. The prevalence of positive clinical challenge tests in patients referred with dermatitis with previous contact with (meth)acrylates was reported as 0.6% (2/331) for n-BMA (Tucker and Beck, 1999). n-BMA has frequently been included in the test substance lists of patients with known contact to (meth)acrylates, but response rates were generally lower than with MMA or EMA. It is not entirely clear whether that is due to lower potency or lower exposure.

4.3.1.3 Summary and discussion of skin sensitisation

In a guideline-compliant mouse local lymph node assay i-BMA was found to be a skin sensitiser with weak potency due to the derived EC3-value of 41.4% (w/v) ((Harlan CCR, 2013).

This result is supported by a Guinea pig maximisation test with the structurally related isomer n-BMA (CIT, 2008). n-BMA induced delayed contact hypersensitivity in 4/5 (80%) guinea pigs.

4.3.1.4 Comparison with criteria

A substance should be classified as skin sensitiser Category 1 if the available data are not sufficient for sub-categorisation into Category 1A or 1B. That is not the case for i-BMA.

A substance should be classified as skin sensitiser Category 1A or Category 1B on the basis of detailed data of an appropriate animal test (e.g. adjuvant-type test or local lymph node assay). In the case of a positive local lymph node assay the potency of a positive effect is measured as a function of derived EC3-value (amount of test chemical required to elicit a stimulation index of 3 in a standard local lymph node assay).The determination of the EC3-value allows the allocation of skin sensitisers into sub-category 1A (EC3-value ≤ 2%) or into sub-category 1B (EC3-value > 2%). In accordance with these CLP criteria the results of the guideline-compliant local lymph node assay with i-BMA (stimulation indices of 1.78, 3.64 and 5.13 at concentrations of 25, 50 and 100% and an EC3-value of 41.4%) lead to the conclusion that the substance is considered as sensitsing to skin and should be classified as skin sensitiser Category 1B.

4.3.1.5 Conclusions on classification and labelling

CLP classification: Skin Sens. 1B, H317; May cause allergic skin reaction.

(Based on the available data there is no evidence that i-BMA causes respiratory sensitisation. Therefore, a classification for respiratory sensitisation is considered as not justified).

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**.

5 ENVIRONMENTAL HAZARD ASSESSMENT

5.1 Degradation

Table 15: Summary of relevant information on degradation

Method	Results	Remarks	Reference
Hydrolysis calculated Estimated by linear regression (QSAR) from data of other methacrylates (MMA and EMA) and the physical chemical properties of IBMA. The method has been validated against the test data of MMA	Half-life (DT50): $t_{1/2}$ (pH 7): ca. 32 - ca. 48 months at 20 °C	2 (reliable with restrictions) supporting study estimated by calculation Test material (EC name): isobutyl methacrylate	Staples CA (1996)
Biological degradation Test type: ready biodegradability Seine river water concentrated by factor 100. Final bacteria concentration: 2.102 cfu/mL. OECD Guideline 301 D (Ready Biodegradability: Closed Bottle Test)	readily biodegradable Degradation of test substance: 74.3% after 28 d (O_2 consumption) (passes 10 d window)	2 (reliable with restrictions) key study experimental result Test material (EC name): isobutyl methacrylate	Thiébaud H, Moncel N (1995)

5.1.1 Stability

Hydrolysis

There are no measured data for i-BMA. By analogy to n-BMA (Staples 1996) the substance is expected to be stable under normal environmental conditions and hydrolysis appears not to be an important aqueous degradation process for this chemical.

5.1.2 Biodegradation

5.1.2.1 Biodegradation estimation

As measured data are available estimation is not relevant for this dossier.

5.1.2.2 Screening tests

The readily biodegradability test of i-BMA was performed according OECD guideline 301 D (Closed bottle test). The test was performed over a period of 28 d. Oxygen concentration of the medium was measured at regular intervals (0, 7, 17, 21 and 28 d) by destructive sampling of the flasks. The oxygen consumption of the two replicate test solutions containing 2.81 mg/L of i-BMA was evaluated against that of the control flasks containing medium and inoculum only. A reference test with 4 mg/l sodium benzoate was also performed. Additionally, a substance toxicity control was run alongside the test where reference substance (sodium benzoate at 2 mg/L) and i-BMA (1.41 mg/L) were placed in the same flask and oxygen consumption measured over the test period.

i-BMA degraded with no lag time and no inhibition. In less than 2 d 10% biodegradation was achieved. 61.4% were biodegraded after 7 d (10-day window achieved), ca. 74.1% after 14 d, 74.3% after 28 d. Degradation products were not measured. i-BMA achieved the criteria for ready biodegradability.

5.1.2.3 Simulation tests

As i-BMA is readily biodegradable in an OECD guideline 301 screening test further testing is not required.

5.1.3 Summary and discussion of degradation

I-BMA achieved the criteria for readily biodegradability in an OECD 301 D screening test and passed the 10-day window (> 60% after 10 days). Therefore, i-BMA is rapidly degradable according to CLP criteria.

5.2 Environmental distribution

5.2.1 Adsorption/Desorption

The adsorption rate of i-BMA to soil was measured in a study acc. OECD 106 using a Batch Equilibrium Method. The calculated value of 2767 L/kg indicates a high adsorption potential of i-BMA to the soil solid phase (Christensen KP 1995).

5.2.2 Volatilisation

Henry's Law constant was calculated by EPIWIN calculation (v.4.00). Using the standard river and lake models volatilisation half-lives of i-BMA are 2.552 h for the model-river and 5.326 d for the model lake.

Based on the data base Henry´s Law constant (53.9 $Pa \cdot m^3/mol$ @ 25°C) i-BMA will evaporate moderately from the water surface.

5.2.3 Distribution modelling

The distribution of i-BMA into the media air - biota - sediment(s) – soil – water was calculated acc. Mackay, Level III model which takes into account transport and degradation models. The calculation was performed with EPIWIN 4.0. Vapour pressure (1.57 mm Hg) and Log Kow (2.95) were entered by the user. In this model i-BMA - if released into air- will mainly remain in the air (95.8 %), 3.3 % will remain in water and 0.8 % in soil. If it is released into water, it also mainly remains in the water (98.6 %).

5.3 Aquatic Bioaccumulation

Table 16: Summary of relevant information on aquatic bioaccumulation

Method	Results	Remarks	Reference
different fish Details of method: Formula used in the EEC Guidance Document for Existing Chemicals (for log P values between 2 and 6 (according to Veith et al. (1979)) log BCF = 0.85 x Log K_{ow} – 0.7 calculated according to Veith et al. (1979)	BCF: 64	2 (reliable with restrictions) supporting study estimated by calculation Test material (EC name): isobutyl methacrylate	Evonik Röhm GmbH (2003) Veith G, Defoe DL, Bergstedt BV (1979)

5.3.1 Aquatic bioaccumulation

5.3.1.1 Bioaccumulation estimation

Formula used in the EEC Guidance Document for Existing Chemicals (for log P_{ow} values between 2 and 6 (according to Veith et al. (1979)) log BCF = 0.85 x log K_{ow} – 0.7. The bioaccumulation factor was estimated with BFC = 64.

5.3.1.2 Measured bioaccumulation data

No data available.

5.3.2 Summary and discussion of aquatic bioaccumulation

Based on an experimental determined log K_{ow} of 2.95 and an estimated BCF of 64, i-BMA has a low bioaccumulation potential according to CLP criteria.

5.4 Aquatic toxicity

Table 17: Summary of relevant information on aquatic toxicity

Method	Results	Remarks	Reference
Fish			
Oncorhynchus mykiss freshwater flow-through OECD Guideline 203 (Fish, Acute Toxicity Test)	LC50 (96 h): 20 mg/L act. ingr. (meas. (not specified))	1 (reliable without restriction) key study experimental result Test material (EC name): isobutyl methacrylate	Sousa JV (1995)
Scophthalmus maximus saltwater semi-static OSPAR Protocols on Methods for the Testing of Chemicals Used in the Offshore Oil Industry, 1995	LC50 (96 h): 833 mg/L test mat. (nominal)	2 (reliable with restrictions) supporting study experimental result Test material (EC name): methacrylic acid	Sverdrup LE, Kaellqvist T, Kelley AE, Fuerst CS, Hagen SB (2001)
Daphnia			
Daphnia magna freshwater flow-through OECD Guideline 202 (Daphnia sp. Acute Immobilisation Test)	EC50 (48 h): > 29 mg/L test mat. (meas. (not specified)) based on: mobility	1 (reliable without restriction) key study experimental result Test material (EC name): isobutyl methacrylate	Putt AE (1995)
other aquatic crustacea: *Acartia tonsa* (*Copepoda*) saltwater ISO/CD 14669 Water quality - Determination of acute lethal toxicity to marine copepods (Copepoda, Crustacea)	EC50 (48 h): 210 mg/L test mat. (nominal)	2 (reliable with restrictions) supporting study experimental result Test material (EC name): methacrylic acid	Sverdrup LE, Kaellqvist T, Kelley AE, Fuerst CS, Hagen SB (2001)
Daphnia magna freshwater flow-through OECD Guideline 211 (Daphnia magna Reproduction Test) (Cited as OECD Guide-line 202, part 2 (Daphnia sp., Reproduction Test)) EPA OTS 797.1330 (Daphnid Chronic Toxicity Test)	NOEC (21 d): 2.6 mg/L test mat. (meas. (not specified)) based on: reproduction LOEC (21 d): 4.9 mg/L test mat. (meas. (not specified)) based on: reproduction	1 (reliable without restriction) weight of evidence experimental result Test material (EC name): butyl methacrylate	Putt AE (1995)
Daphnia magna freshwater renewal every 24 hrs OECD Guideline 211 (Daphnia magna Reproduction Test) (Cited as OECD Guide-line 202, part 2 (Daphnia sp., Reproduction Test))	NOEC (21 d): 1.1 mg/L test mat. (meas. (not specified)) based on: reproduction LOEC (21 d): 3.35 mg/L test mat. (meas. (not specified))	1 (reliable without restriction) weight of evidence experimental result Test material (EC name): butyl methacrylate	MoE (1998)
A QSAR was developed based on reliable guideline studies (chronic invertebrate toxicity)	NOEC (21 d): 2.1 mg/L based on: reproduction	2 (reliable with restrictions) key study (Q)SAR Test material (EC name): isobutyl methacrylate	Staples CA, Farr C, Hunt EK, McLaughlin JE, Müllerschön H, Pemberton MA (2009)
Algae			

other algae: *Selenastrum capricornutum* [now called *Pseudokirchneriella subcapitata*] (algae) freshwater static OECD Guideline 201 (Alga, Growth Inhibition Test)	EC50 (72 h): 44 mg/L test mat. (meas. (not specified)) based on: growth rate (median effective concentration) NOEC (72 h): 9.5 mg/L test mat. (meas. (not specified)) based on: growth rate LOEC (72 h): 20 mg/L test mat. (meas. (not specified)) based on: growth rate	1 (reliable without restriction) key study experimental result Test material (EC name): isobutyl methacrylate	Smyth DV, Long KWJ (1999)
Selenastrum capricornutum (new name: *Pseudokirchneriella subcapitata*) (algae) freshwater pseudo closed conditions OECD Guideline 201 (Alga, Growth Inhibition Test) EPA OPPTS 850.5400 (Algal Toxicity, Tiers I and II)	EC50 (96 h): 14 mg/L (meas. (initial)) based on: cell density EC50 (72 h): 8.3 mg/L (meas. (initial)) based on: biomass EC50 (72 h): 16 mg/L (meas. (initial)) based on: growth rate NOEC (96 h): 5.8 mg/L (meas. (initial)) based on: cell density NOEC (72 h): 2.1 mg/L (meas. (initial)) based on: biomass NOEC (72 h): 5.8 mg/L (meas. (initial)) based on: growth rate	1 (reliable without restriction) key study experimental result Test material (EC name): isobutyl methacrylate	Hoberg JR (2002b)
Selenastrum capricornutum (new name: *Pseudokirchneriella subcapitata*) (algae) freshwater Closed test system to minimize volatilization of the test compound. equivalent or similar to OECD Guideline 201 (Alga, Growth Inhibition Test)	EC50 (96 h): 0.29 mg/L test mat. (meas. (not specified)) based on: cell density EC50 (96 h): > 0.74 mg/L test mat. (meas. (not specified)) based on: growth rate NOEC (96 h): 0.047 mg/L test mat. (meas. (not specified)) based on: cell density NOEC (96 h): 0.047 mg/L test mat. (meas. (not specified)) based on: growth rate	3 (not reliable) weight of evidence experimental result Test material (EC name): isobutyl methacrylate	Hoberg JR (1995)
Selenastrum capricornutum (new name: *Pseudokirchneriella subcapitata*) (algae) Freshwater (test medium prepared with deionized water respectively with distilled water) static OECD Guideline 201 (Alga, Growth Inhibition Test) (screening test)	EC50 (96 h) deionized water: 10-100 mg/L test mat. (nominal) based on: cell density EC50 (96 h) distilled water: 10-100 mg/L act. ingr. (nominal) based on: cell density	2 (reliable with restrictions) supporting study experimental result Test material (EC name): isobutyl methacrylate	Hoberg JR (2001)
various species of marine algae, see list below (algae) saltwater, static ISO 10253 (Water quality - Marine Algal Growth Inhibition Test with *Skeletonema costatum* and *Phaeodactylum tricornutum*) (ISO, 1995a)	EC50 (72 h): > 1260 mg/L (meas. (not specified)) based on: growth rate NOEC (72 h): 530 mg/L (meas. (not specified)) based on: growth rate	2 (reliable with restrictions) supporting study experimental result Test material (EC name): methacrylic acid	Sverdrup LE, Kaellqvist T, Kelley AE, Fuerst CS, Hagen SB (2001)

5.4.1 Fish

5.4.1.1 Short-term toxicity to fish

In a valid guideline study according OECD 203 (Sousa, 1995) with *Oncorhynchus mykiss* the LC50 (96 h) value was calculated by nonlinear interpolation to be 20 mg/L (95% confidence limits by binominal probability of 17-28 mg/L). The No Observed Effect Concentration (NOEC) based on mobility was determined to be 4.6 mg/L as at 6.9 mg i-BMA/L several fishes were lethargic, observed at the surface of the test solution and exhibited erratic swimming behaviour. The test substance was i-BMA in mean measured concentrations of 4.6, 6.9, 10, 17 and 28 mg/L (nominal: 6.5, 11, 18, 30 and 50 mg/L). All treatment levels and the controls were maintained in duplicate. It was a flow-through test system with a photoperiod of 16 hours light, a total hardness and total alkalinity range as calcium carbonate of 32 to 36 mg/L and 22 to 25 mg/L and a pH range of 7.1 to 7.2. The dissolved oxygen concentration was 84 to 93% of saturation. The temperature ranged from 12 to 13 degrees C.

Table 18: Mean measured concentrations tested, corresponding cumulative percent mortalities and observation made during the 96-hour flow through exposure of rainbow trout (Oncorhynchus mykiss) to i-butyl methacrylate (Sousa, 1995)

Cumulative Mortality (%)				
Mean measured concentration (mg a.i./L)	**24-hour Mean**	**48-hour Mean**	**72-hour Mean**	**96-hour Mean**
Control	0	0	0	0
Solvent Control	0	0	0	0
4.6	0	0	0	0
6.9	0 [ck]	0 [in]	0 [ino]	0 [adq]
10	0 [cdkm]	0 [abno]	0 [abcdp]	0 [abq]
17	0 [deg]	0 [dgkm]	5 [dgm]	15 [dgk]
28	62 [l]	100	100	100

a Several of the surviving fish were observed at the surface of the test solution.
b One of the surviving fish exhibit partial loss of equilibrium.
c One of the surviving fish exhibited erratic swimming behavior.
d Several of the surviving fish were observed to be lethargic.
e Several of the surviving fish exhibited partial loss of equilibrium.
f Two of the surviving fish exhibited complete loss of equilibrium.
g Several of the surviving fish exhibited complete loss of equilibrium.
h Several of the surviving fish exhibited darkened pigmentation and were observed to be lethargic.
i Two of the surviving fish exhibited darkened pigmentation and were observed at the surface of the test solution.
j Two of the surviving fish was observed at the surface of the test solution.
k One of the surviving fish was observed at the surface of the test solution.
l All of the surviving fish exhibited complete loss of equilibrium.
m Two of the surviving fish exhibited partial loss of equilibrium.
n Two of the surviving fish exhibited erratic swimming behavior.
o Two of the surviving fish were observed to be lethargic.
p One of the surviving fish exhibited darkened pigmentation.
q Several of the surviving fish exhibited erratic swimming behavior.

Table 19: LC50-values (95% confidence limits) and No-Observed-Effect Concentration (NOEC) (Sousa, 1995)

LC50 (mg a.i./L) ab				**NOEC through**
24-hour c	**48-hour c**	**72-hour c**	**96-hour c**	**96-hours c**
27	22	21	20	4.6

a Based on mean measured concentrations.
b Corresponding 95 % Confidence limits are presented in parentheses.
c LC50 value was calculated by nonlinear interpolation with corresponding 95 % confidence limits calculated by binominal probability.

There is no data on marine fish, but studies with the common metabolite of the category lower methacrylates (methyl-, ethyl- n-butyl, isobutyl and ethylhexyl methacrylate) methacrylic acid

(MAA), indicate 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. Quite to the contrary the marine organisms tended to be of equal or lower sensitivity than the corresponding freshwater test organisms. The 96-hour LC50 in the marine fish Scophthalmus maximus (Turbot) was 833 mg/L. The corresponding freshwater 96-hour LC50 in the key study with MAA was 85 mg/L in *Oncorhynchus mykiss* (rainbow trout).

5.4.1.2 Long-term toxicity to fish

No data available

5.4.2 Aquatic invertebrates

5.4.2.1 Short-term toxicity to aquatic invertebrates

In a valid study (Putt, 1995) according OECD 202 i-BMA was tested at the highest, in a flow-through study achievable concentration of 29 mg/L. The test was conducted according to GLP and the analytical verification realized using HPLC. A stock solution was prepared dissolving i-BMA in Acetone wisth a solvent concent in the stock solution of 0.302 mL/mL. The test temperature was 20 +/- 1 degree C and the total hardness amounted 170 mg $CaCO_3$/L. The pH-value was 8.0. At 29 mg/L, all mobile daphnids exhibited lethargic behaviour and were pale in colour. No such effects were observed among daphnids exposed to lower treatment levels (0-22 mg/L).

Table 20: Mean measured concentrations tested, corresponding cumulative percent of immobilized daphnids (Daphnia magna) and observations made during the 48-hour flow-through exposure to i-butyl methacrylate. (Putt, 1995)

Mean measured concentration [mg a.i./L]	**Cumulative percent immobilized organisms [a]**	
	24 hours	**48 hours**
	Mean	**Mean**
Control	0	0
Solvent control	0	0
4.6	0	0
7.0	0	0
13	0	0
22	0	0
29	0	20 [bc]

[a] Number of immobilized daphnids is presented in paranthese.
[b] all mobile daphnids were observed to be pare and lethargic.
[c] Several mobile daphnids exhibited a flared carapace.

The 48-hour EC50 value was empirically estimated to be >29 mg/L, the highest achievable mean measured concentration of isobutyl methacrylate. 20% of the test organisms were immobilised at the highest concentration tested (29 mg/L). The No Observed Effect Concentration (NOEC) for i-BMA and *Daphnia magna* was determined to be 22 mg/L.

There is no data on marine invertebrates, but studies with the common metabolite of the category lower methacrylates, methacrylic acid (MAA), indicate that marine species are not expected to be more sensitive to methacrylates than freshwater species (Sverdrup, 2001). The 48-hour EC50 in the marine invertebrate *Acartia tonsa* (*Copepoda*) was 210 mg/L. The corresponding freshwater 48-hour EC50 in the key study with MAA was > 130 mg/L in *Daphnia magna*.

5.4.2.2 Long-term toxicity to aquatic invertebrates

A QSAR for chronic invertebrate toxicity was developed based on test data of four members of the category lower methacrylates. A regression against logKow showed a good fit with a second order error R^2 of 0.99. The predicted value for i-BMA was 2.1 mg/L:

For methacrylates a QSARs for predicting aquatic toxicity was developed based on chronic invertebrate data and logK_{ow}. A regression of log Kow and number of carbons in the alkyl side-chains showed a strong correlation exists with an R^2 of 0.9973. This indicates that log K_{ow} may be used to predict aquatic toxicity values for the methacrylate esters in the category. The calculations were performed using the statistical and power functions in Microsoft EXCEL. For chronic invertebrate toxicity, the R^2 value was about 99%.

Chronic NOECs (LOECs) used in the calculation (in mg/L)
MAA (Methacrylic acid) 53 (110)
MMA (Methyl methacrylate) 37 (68)
EMA (Ethyl methacrylate) 18 (31)
nBMA (n-Butyl methacrylate) 1.1 (3.35) and 2.6 (4.9); geometric mean 1.69
2-EHMA (2 -Ethylhexyl methacrylate) 0.105 (0.219) and 0.29 (0.64); geometric mean 0.174

Log Kow based on measured data
MAA (Methacrylic acid): 0.93
MMA: Methyl methacrylate): 1.32
EMA (Ethyl methacrylate): 1.87
n-BMA (n-Butyl methacrylate): 3.03
2-EHMA (2 -Ethylhexyl methacrylate): 5.59
i-BMA (isobutyl methacrylate): 2.95

The key structural difference between the methacrylate esters is the number of carbons in the alkyl side chain. The esters dealt with in this context have side chains one to eight carbons. For these methacrylates, log K_{ow} correlate well (R^2 = 99.73%) with the side chain length, thus allowing this property to serve as a surrogate for structure.

The log Kow of i-BMA falls within the lowest and the highest log Kow of the methacrylate esters used for estimating a QSAR for i-BMA.

The data for MAA was not used in the QSAR development because it is an acid and may have different mode of action than narcosis compared to the esters. Only the lowest NOEC for a given study was used if multiple endpoints are reported. For a compound with two or more valid studies conducted with the same species. The geometric mean (GM) of the lowest NOEC was calculated and used in the QSAR.

5.4.3 Algae and aquatic plants

In an OECD guideline 201 study on algae toxicity in 1995 the ErC50 (96 h) for growth rate was estimated to be > 0.74 mg/L and NOEC growth rate 0.047 mg/l at nominal concentration. EC50 for cell density was 0.29 mg/L (nominal), the NOEC for cell density was determined to be 0.047 mg/L (Hoberg 1995).

In the following years numerous studies with similar lower alkyl methacrylates and the primary metabolite methacrylic acid showed 2-3 orders of magnitude higher EC50 values than i-BMA in the

Hoberg study in 1995. (see Chapter 6 Other Information). All studies were conducted with *Pseudokirchneriella subcapitata*.

Methacrylic acid was tested with marine aquatic plants and showed ECr_{50} values in the range of 10-100 mg/L. (see chapter 6: Other Information).

To clarify the extreme difference between the ErC50 value of the Hoberg study (1995) and the other lower methacrylates, respectively to clarify if the result of the Hoberg study is reproducible itself the study was repeated first in a different laboratory (Smyth and Long 1999) and after this two times in the same laboratory by the same study director (Hoberg 2001 and Hoberg 2002b). These studies were also conducted with *Pseudokirchneriella subcapitata*.

The first study which was repeated (Smyth and Long 1999) was conducted in a GLP certified laboratory but was not undertaken under GLP conditions however according OECD guideline 201. The test concentrations were measured by HPLC. The ErC50 was 44 mg/L, the NOErC: 9.5 mg/L.

In 2001 a screening test was conducted in the same laboratory by the same study director (Hoberg 2001) like the test which had to be rechecked (Hoberg 1995). The test was conducted without GLP and without analytical measurement so that the results refer to nominal concentrations. The objective of this study was to conduct screening tests to compare the acute toxicity of i-BMA in algal medium prepared from deionized water (standard medium) and distilled water on the growth of the green algae, *Pseudokirchneriella subcapitata*. Due to the volatility of the substance, the test solutions were maintained in tightly sealed vessels. The methods described were the same as used in the i-BMA study conducted by Hoberg in 1995 with exception of the additional medium. The idea of this study was to find out, if the test medium had an influence on the growth of the green algae. At nominal concentrations of 0.010, 0.10, 1.0 10 and 100 mg a.i./L inhibition of –0.67, 2.0, 9.4, 23 and 100 % was observed in AAP medium formulated with deionized water. Inhibition of –5.8, –0.65, 7.1, 26 and 100 % was observed at the same test concentrations with distilled water. The test concentration-responses were very similar, indicating that the source of water, deionized or distilled water, used to formulate the medium had no impact on the sensitivity of the algae to the test substance. The response for each test indicate the 96 hour EC50 for cell densities between 10 and 100 mg a.i./l.

Afterwards a standard OECD 201 was conducted under GLP incl. HPLC analysis under pseudo closed conditions (Hoberg 2002b) with a result of ECr_{50} (72 h): 16 mg/L, NOErC /72 h): 5.8 mg/L (measured concentrations). The test substance was i-BMA which was placed in a container and diluted with sterile AAP medium containing an additional sodium bicarbonate. To reduce volatilization the stock solution was directly added to the AAP medium for each replicate test solution (13 replicates per treatment level and control). The pH value in the study ranged from 7.5 to 8.9.

Table 21: Mean measured concentrations tested and resulting effect concentrations made during a 96-h exposure with i-butyl methacrylate under pseudo closed conditions (Hoberg, 2002b)

Duration [h]	Endpoint	Effect concentration (mean measured) [mg/L]	Basis for effect
96	NOEC	5.8	Cell density
96	EC50	14	Cell density
72	NOE_bC	2.1	Biomass
72	NOE_rC	5.8	Growth rate
72	E_bC50	8.3	Biomass
72	E_rC50	16	Growth rate

All in all either 3 repeated algae growth inhibition tests acc. OECD 201 with i-BMA as well as the key studies of other lower methacrylates like methyl-, ethyl-, n-butyl and 2-ethylhexyl methacrylate

with the same test organism *Pseudokirchneriella subcapitata* yield ErC50 values in the range of 10-100 mg/L or > 100 mg/L. The primary metabolite methacrylic acid yield EC50 values between 10 and 100 mg/L for *Pseudokirchneriella subcapitata* and marine algae species.

By read across with lower basic methacrylates methyl-, ethyl-, n-butyl and 2-ethylhexyl methacrylates as well as repeated studies with i-BMA there is no correlation with the result of the Hoberg study (1995): ErC50 > 0.74 mg/L.

No clarification of the differing test result was gained, possibly a wrong test substance was tested in 1995. As the result in Hoberg (1995) differs totally from results of algae tests with similar methacrylates and results in several studies acc. OECD 201 with i-BMA, the Hoberg (1995) study was indicated as invalid and therefore the basic for classification with Aquatic Acute 1 is not justified.

In summary, two reliable studies on *Pseudokirchneriella subcapitata* have been carried out with i-BMA according to OECD Guideline 201. The studies were performed in closed vessels and included test substance analysis. The most sensitive relevant toxicity values are ErC50 (72 h) = 16 mg/L, NOErC = 5.8 mg/L (Hoberg, 2002b).

5.4.4 Other aquatic organisms (including sediment)

No data available

5.5 Comparison with criteria for environmental hazards (sections 5.1 – 5.4)

Table 22: Comparison with criteria for environmental hazards

	Criteria for environmental hazards	Isobutyl methacrylate	Conclusion
Rapid Degradation	Readily biodegradable in a 28-day test for ready biodegradability	74.3 % after 28 days (O_2 consumption) 10 day window passed	**Rapidly degradable**
Bioaccumulation	BCF ≥ 500 Log K_{ow} ≥ 4	Log K_{ow} = 2.95 Estimated BCF = 64	**Not bioaccumulative**
Aquatic Toxicity	Acute toxicity data: LC50/EC50/ErC50 ≤ 1 mg/L Chronic toxicity data: NOEC ≤ 1mg/L	Fish: LC50 (96 h) = 20 mg/L NOEC not available Invertebrates: EC50 (48 h) > 29 mg/L NOEC (21d) = 2.1 mg/L Algae: ErC50 (72 h) = 16 mg/L NOEC (72 h) = 5.8 mg/L	**Not acute and chronic toxic**

5.6 Conclusions on classification and labelling for environmental hazards (sections 5.1 – 5.4)

As i-BMA is rapidly degradable, of low potential for bioaccumulation and the values for acute aquatic toxicity are > 1 mg/L and the NOECs for chronic toxicity > 1 mg/L classification and labelling for environmental hazards is not required. The current classification with Aquatic Acute 1 (H400) is not justified.

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 $\log K_{OW}$ 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**.

6 OTHER INFORMATION

Table 23: Read across with Basic Lower Alkyl Methacrylates /Summary of effects on algae and aquatic plants

Ester	CAS No.	EINECS No.	Results			Remarks	Reference
			ErC50 (mg/L)	NOEC (mg/L)	LOEC (mg/L)		
MAA	79-41-4	201-204-4	45	8.2[a]	19[a]	Rel. 1	Comber & Long, 1999
MMA	80-62-6	201-297-1	>110[a]	110[a]	>110[a]	Rel. 1	Smyth DV and Long KWJ, 1999
EMA	97-63-2	202-597-5	>110[a]	110[a]	>110[a]	Rel. 1	Smyth DV and Long KWJ, 1999
			>72[b]	10[c]	27[c]	Rel. 1	Hoberg, 2002a
n-BMA	97-88-1	202-615-1	130[a]	26[a]	54[a]	Rel. 1	Smyth et al., 1993
			31.2[a, d]	24.8[a, d]	47.0[a, d]	Rel. 1	MoE, 1998a
i-BMA	97-86-9	202-613-0	44[a]	9.5[a]	20[a]	Rel. 1	Smyth DV and Long KWJ, 1999
			16[a,]	5.8[a]	14[a]	Rel. 1	Hoberg, 2002b
2-EHMA	688-84-6	211-708-6	3.97 [e]	0.28[a, f]	0.54[a,f]	Rel. 1	MoE, 1998b
MAA (marine) *S. costatum*	79-41-4	201-204-4	> 1260	530	n.d.	Rel 2	Sverdrup et al. 2001
MAA (marine) 9 other alga species	79-41-4	201-204-4	110 - >320	n.d.	n.d.	Rel. 2	Sverdrup et al. 2001

MAA= Methacrylic acid, MMA= Methyl methacrylate, EMA= Ethyl methacrylate, n-BMA= n-Butyl methacrylate, i-BMA = isobutyl methacrylate, 2-EHMA = 2-Ethylhexyl methacrylate

[a] based on measured concentrations; [b] based on initial measured concentrations; [c] based on analytically confirmed nominal concentrations;[d] dispersant used, [e] dispersant used, most test concentrations, including the EC50 were above the limit of solubility; [f] dispersant used, but NOEC and LOEC within the range of solubility

All tests were performed with the test species *Pseudokirchneriella subcapitata* (previously *Selenastrum capricornutum*) and complied with the OECD 201 test protocol. All data presented are 72 h exposure data. Studies by Hoberg followed a 96 h US-EPA protocol (OPPTS 850.5400). However, 72 h values were calculated and are presented.

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7 ANNEXES

Confidential Annex