Committee for Risk Assessment

RAC

Annex 1
Background document
to the Opinion proposing harmonised classification and labelling at EU level of

3-aminomethyl-3,5,5-trimethylcyclohexylamine

EC Number: 220-666-8
CAS Number: 2855-13-2

CLH-O-0000001412-86-284/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

13 June 2019

CLH report

Proposal for Harmonised Classification and Labelling

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

International Chemical Identification:

3-aminomethyl-3,5,5-trimethylcyclohexylamine;

isophorone diamine [IPD]

EC Number: 220-666-8

CAS Number: 2855-13-2

Index Number: 612-067-00-9

Contact details for dossier submitter:

BAuA
Federal Institute for Occupational Safety and Health
Federal Office for Chemicals
Friedrich-Henkel-Weg 1-25
44149 Dortmund, Germany

Version number: 2.1 (post ACC)

Date: August 2018

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON 3-AMINOMETHYL-3,5,5-TRIMETHYLCYCLOHEXYLAMINE

CONTENTS

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON 3-AMINOMETHYL-3,5,5-TRIMETHYLCYCLOHEXYLAMINE

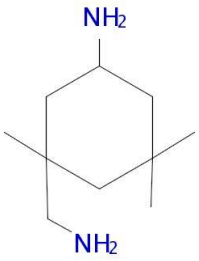
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the substance

EC number:	220-666-8
EC name:	3-Aminomethyl-3,5,5-trimethylcyclohexylamine
CAS number (EC inventory):	2855-13-2
CAS name:	Cyclohexanemethanamine, 5-amino-1,3,3-trimethyl-
IUPAC name:	3-Aminomethyl-3,5,5-trimethylcyclohexanamine
Annex I index number:	612-067-00-9
Molecular formula:	$C_{10}H_{22}N_2$
Molecular weight range:	170.2951 g/mol

Structural formula:



1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	Concentration range (% w/w minimum and maximum in multi-constituent substances)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)
3-Aminomethyl-3,5,5-trimethylcyclohexylamine EC no.: 220-666-8	≥ 99.7 — ≤ 100.0		

Table 3: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The impurity contributes to the classification and labelling
-				

Table 4: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	Function	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The additive contributes to the classification and labelling
-					

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 5:

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors, and ATE	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)		
Current Annex VI entry	612-067-00-9	3-aminomethyl-3,5,5-trimethylcyclohexylamine	220-666-8	2855-13-2	Acute Tox. 4* Acute Tox. 4* Skin Corr. 1B Skin Sens. 1 Aquatic Chronic 3	H302 H312 H314 H317 H412	GHS07 GHS05 Dgr	H302 H312 H314 H317 H412			
Dossier submitters proposal					**<u>Retain</u>** Skin Corr. 1B **Add** Eye Dam. 1 **Modify** Acute Tox. 4 Skin Sens. 1A **Remove** Acute Tox. 4* Aquatic Chronic 3	**Retain** H314 **Add** H318 **Modify** H302 H317 **Remove** H312 H412	GHS07 GHS05 Dgr	**Retain** H314 **Modify** H302 H317 **Remove** H312 H412		Oral; ATE = 1030 mg/kg bw	
Resulting Annex VI entry if agreed by RAC and COM					Acute Tox. 4 Skin Corr. 1B Skin Sens. 1A Eye Dam. 1	H302 H314 H317 H318	GHS07 GHS05 Dgr	H302 H314 H317		Oral; ATE = 1030 mg/kg bw	

Table 6: Reason for not proposing harmonised classification and status under public consultation

Hazard class	Reason for no classification	Within the scope of public consultation
Explosives	Hazard class not assessed in this dossier	No
Flammable gases (including chemically unstable gases)		
Oxidising gases		
Gases under pressure		
Flammable liquids		
Flammable solids		
Self-reactive substances		
Pyrophoric liquids		
Pyrophoric solids		
Self-heating substances		
Substances which in contact with water emit flammable gases		
Oxidising liquids		
Oxidising solids		
Organic peroxides		
Corrosive to metals		
Acute toxicity via oral route	Harmonised classification proposed	**Yes**
Acute toxicity via dermal route	Data conclusive but not sufficient for classification, removal from harmonised classification proposed	**Yes**
Acute toxicity via inhalation route	Hazard class not assessed in this dossier	No
Skin corrosion/irritation		
Serious eye damage/eye irritation	Harmonised classification proposed	**Yes**
Respiratory sensitisation	Data lacking	No
Skin sensitisation	Harmonised classification proposed	**Yes**
Germ cell mutagenicity	Hazard class not assessed in this dossier	No
Carcinogenicity		
Reproductive toxicity		
Specific target organ toxicity-single exposure		
Specific target organ toxicity-repeated exposure		
Aspiration hazard		
Hazardous to the aquatic environment	Data conclusive but not sufficient for classification, removal from harmonised classification proposed	**Yes**
Hazardous to the ozone layer	Hazard class not assessed in this dossier	No

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

The substance 3-aminomethyl-3,5,5-trimethylcyclohexylamine (IPD) has been evaluated by EU authorities and inserted into Annex I of the Dangerous Substance Directive 67/548/EEC via its 19th adaptation to the technical progress (93/72/EEC) with the following classification and labelling:

Classification: Xn ; R 21 /22 C ; R 34 R 43
Labelling: C; R : 21 /22-34-43; S : (l /2-)26-36/37/39-45

This classification and labelling was extended by R-Phrases 52 and 53 with the 22nd adaptation to the technical progress (96/54/EC) of dangerous substances directive 67/548/EEC. The resulting classification and labelling was as follows:

Classification: Xn; R 21 /22 C; R 34 R 43 R 52-53,
Labelling: C, R: 21 /22-34-43-52/53; S: (l /2-)26-36/37/39-45-61

This classification has been inserted into Annex VI, Table 3.1 and 3.2 of the original CLP regulation 1272/2008.

Classification, Table 3.1: Acute Tox. 4*, H312; Acute Tox. 4*, H302; Skin Corr. 1B, H314; Skin Sens. 1, H317; Aquatic Chronic 3, H412
Labelling, Table 3.1: GHS05, GHS07, Dgr; H312, H302, H314, H317, H412

Classification, Table 3.2: Xn; R 21 /22 C; R 34 R 43 R 52-53
Labelling, Table 3.2: C, R: 21 /22-34-43-52/53; S: (l /2-)26-36/37/39-45-61

(In the meantime, Table 3.2 has been removed from the CLP regulation.)

RAC general comment
3-aminomethyl-3,5,5-trimethylcyclohexylamine, or isophorone diamine (IPD), is a substance that is used as a hardener, raw material for production of isocyanates and polyamides, as a components for chain extension in PUR systems and an intermediate product for organic syntheses. IPD is currently listed in Annex VI of the CLP Regulation and the Dossier Submitter (DS) proposed to revise the current classification.

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Reason for a need for action at Community level:

- Change in existing entry due to new data (acute dermal toxicity).
- Change in existing entry due to changes in the criteria (subcategory skin sensitisation).
- Change in existing entry due to new interpretation/evaluation of existing data (aquatic chronic toxicity).

5 IDENTIFIED USES

The following uses were identified for the registered substance:

- Use as hardener

- Use as raw material for production of isocyanates
- Use as components for chain extension in PUR systems
- Use as raw material for production of polyamides
- Use as intermediate product for organic syntheses

6 DATA SOURCES

- REACH registration dossiers

7 PHYSICOCHEMICAL PROPERTIES

Table 7: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3 kPa	Liquid at 20°C and 101.3 kPa	Hüls (1992)	
Melting/freezing point	8 °C at 101.3 kPa	AQura (2010)	Measured
Boiling point	526.05 K at 101.3 kPa	BASF (1990)	
Relative density	Density range: 0.92 – 0.925	VEBA-Chemie (1975) Ullmann (2001) Hommel (1998)	As the substance is a cis/trans isomer mixture, the density may vary with the isomer composition. Therefore a single precise value is not adequate and a range is to be preferred.
Vapour pressure	1.57 Pa at 293.15 K	BASF (1990)	
Surface tension			
Water solubility	492 g/L at 23.8 °C and pH13.3	AQura (2010)	Measured
Partition coefficient n-octanol/water	0.99 at 23 °C	Hüls Infracor (1998)	Measured
Flash point	110 and 112 °C (open cup),	VEBA-Chemie (1975) Ullmann (2001)	Measured
Flammability			The substance is a liquid. The EU method is not applicable for liquids.
Explosive properties	Non-explosive		There are no chemical groups associated with explosive properties present in the molecule. Therefore a test is not required according to REACH Annex VII, 7.11, column 2.
Self-ignition temperature	380 °C at 997 hPa	AQura (2010)	Measured
Oxidising properties	No		Based on the chemical structure, the substance is incapable of reacting exothermically with combustible materials. Therefore, according to REACH Annex VII, 7.13, column 2 testing is not required.
Granulometry			
Stability in organic solvents and identity of relevant degradation products			The stability of the substance is not considered to be critical. Therefore testing is not required according to REACH Annex IX, 7.15, column 1.
Dissociation constant	pKa at 20°C: 10.7	STN (2003) VEBA-Chemie (1975)	

Property	Value	Reference	Comment (e.g. measured or estimated)
Viscosity	Viscosity at 20°C: 19 mm^2/s (static)	AQura (2010)	Measured

8 EVALUATION OF PHYSICAL HAZARDS

Not evaluated in this report

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Not evaluated in this report

10 EVALUATION OF HELTH HAZARDS

10.1 Acute toxicity - oral route

Table 8: Summary table of animal studies on acute oral toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance (vehicle)	Dose levels duration of exposure	Value LD_{50}	Reference
Equivalent or similar to OECD Guideline TG 401 (Acute Oral Toxicity) Reliability 3 (not reliable) Non-GLP Only IUCLID summary available to the DS, relevant information such as purity of the test substance, mortality rates, details on examinations, or details on the statistical method used are missing; only male animals were used	Rat, Sprague-Dawley, male, 5/sex/group	3-Aminomethyl-3,5,5-trimethylcyclohexyl-amine Purity unknown 50 % solution in water	0.5-1.0-1.5-2.0-2.5 mL/kg bw	1030 mg/kg bw/d	Institut für Pharmakologie (1965)

10.1.1 Short summary and overall relevance of the provided information on acute oral toxicity

Only a REACH registration dossier for one LD_{50} study in Sprague-Dawley rats from 1965 was available (Institut für Pharmakologie, 1965). According to this summary *"The LD_{50} value of acute oral toxicity in male rats of the test substance isophorone diamine was determined to be 1030 mg/kg bw.* […] *Doses of 0.5, 1.0, 1.5, 2.0, or 2.5 ml/kg bw of a 50 % v/v solution in water were applied by gavage followed by a post dose observation period of 14 days. Clinical signs observed from 1 hour after dosing were restlessness, thirst, rough fur and tiredness. At necropsy, irritation of the intestinal mucosa was observed. A few animals (no further data) showed a slight increase in kidney weight and protein in the urine, which may indicate that the kidney is a target organ"*.

It is noted that these results are unreliable, since the summary (and possibly the report itself) are deficient in reporting important aspects of the study such as purity, mortality rates/group or in total, details on the examinations performed, or the statistical methodology used. Furthermore, only male animals were used.

However, as noted by the lead registrant of IPD (who acknowledged the above deficiencies) *"evidence from repeated dose studies indicates that there is no significant difference in sensitivity between males and females and that the acute oral toxicity is not higher by an order of magnitude or more (chapter 7.5.1 entry # 1: 13 week LOAEL ca. 150 mg/g bw/day for males and females)"*.

In conclusion, the DS finds that the above result, while not reliable on its own, is sufficiently robust when seen in concert with the rest of the toxicological database to allow for changing the current transitional classification in Annex VI as Acute Tox. 4* into a permanent one.

10.1.2 Comparison with the CLP criteria

Table 9: Comparison of the findings for IPD regarding acute dermal toxicity with the respective CLP classification criteria

CLP criteria (up to and including 9th ATP)	Findings for IPD
Acute oral toxicity categories based on Acute Toxicity Estimates (ATE) according to Table 3.1.1 of the CLP regulation: Category 1: ATE ≤ 5 mg/kg bw Category 2: 5 < ATE ≤ 50 mg/kg bw Category 3: 50 < ATE ≤ 300 mg/kg bw Category 4: 300 < ATE ≤ 2000 mg/kg bw	ATE = 1030 mg/kg bw With this ATE, IPD falls into Acute Toxic Category 4

10.1.3 Conclusion on classification and labelling for acute oral toxicity

With an ATE of 1030 mg/kg bw classification of IPD as Acute Tox. 4 (hazard statement H302) is indicated.

10.2 Acute toxicity - dermal route

Table 10: Summary table of animal studies on acute dermal toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance (vehicle)	Dose levels duration of exposure	Value LD_{50}	Reference
OECD Guideline TG 402 (Acute Dermal Toxicity), fixed dosed procedure Reliability 1 (reliable without restriction) GLP	Rat, Sprague-Dawley, Crl:CD(SD), SPF, male and female, 5/sex/group	3-Aminomethyl-3,5,5-trimethylcyclohexylamine Purity > 99 % unchanged (no vehicle)	2000 mg/kg bw, 24 h of occlusive exposure	> 2000 mg/kg bw	Biotoxtech (2010)

10.2.1 Short summary and overall relevance of the provided information on acute dermal toxicity

The background of the original classification as Acute Tox 4* is unknown to the DS, to which only one study on acute dermal toxicity was available (Biotoxtech, 2010), which was conducted according to OECD TG 402.

All animals at 2000 mg/kg treatment survived the duration of the study.

Discolouration of skin and crust formation from days 1 to 14 after dosing and scar from days 11 to 14 were observed on the treated sites of all animals at 2000 mg/kg treatment. These were considered to be test substance-related effects. No test substance-related effects on body weights were observed. In necropsy findings, crust was observed on the treated sites of all animals at 2000 mg/kg bw. Mild to moderate scar formation was observed on the treated sites of all animals. These were considered to be skin wounds caused by the test substance.

Based on the results of this study the dermal LD_{50} was > 2000 mg/kg in male and female rats.

10.2.2 Comparison with the CLP criteria

Table 11: Comparison of the findings for IPD regarding acute dermal toxicity with the respective CLP classification criteria

CLP criteria (up to and including 9th ATP)	Findings for IPD
Acute dermal toxicity categories based on Acute Toxicity Estimates (ATE) according to Table 3.1.1 of the CLP regulation: Category 1: ATE ≤ 50 mg/kg bw Category 2: 50 < ATE ≤ 200 mg/kg bw Category 3: 200 < ATE ≤ 1 000 mg/kg bw Category 4: 1000 < ATE ≤ 2000 mg/kg bw	ATE > 2000 mg/kg bw As the dermal LD_{50} was determined to be > 2000 mg/kg bw, the CLP classification criteria for acute dermal toxicity are not fulfilled.

10.2.3 Conclusion on classification and labelling for acute dermal toxicity

Based on the available data the CLP classification criteria for acute dermal toxicity are not fulfilled. Hence classification regarding acute dermal toxicity is not indicated and previous classification/labelling for acute dermal toxicity (Acute Tox. 4*, H312) should be removed from entry 612-067-00-9 in Annex VI to the CLP regulation.

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

Regarding acute toxicity, the DS suggested to remove the asterisk "*" denoting the current minimum classification as Acute Tox. 4*; H302 (oral toxicity) and to remove the existing classification as Acute Tox. 4*; H312 (dermal toxicity).

The DS provided one acute oral toxicity study (Institut für Pharmakologie, 1965) with Sprague-Dawley rats that was available in the REACH registration dossier. In this study the test substance (50% (v/v) solution in water) was administered to male rats (5 animals per dose) by oral gavage - 0.5; 1.0; 1.5; 2.0; 2.5 mL/kg bw corresponding to 230; 460; 690; 920; 1150 mg/kg bw, respectively. A post dosing observation period of 14 days was carried out. Clinical signs observed from 1 hour after dosing were restlessness, thirst, rough fur and tiredness. At necropsy, irritation of the intestinal mucosa was observed. A few animals showed a slight increase in kidney weight and protein in the urine, which may indicate that the kidney is a target organ. The DS acknowledged that this study has deficiencies in reporting important aspects, such as purity of the test substance and mortality rates, as well as the fact that male animals only were used.

The DS also noted that the lead registrant referred to repeated dose studies where a LOAEL of 150 mg/kg bw/day (actually, 160 mg/kg bw/day) was determined and proving that there is no significant difference in sensitivity between male and female rats (cited from SIAR for SIAM 18 (Paris, April 2004)). The DS concluded that the acute oral toxicity should not differ by an order of magnitude or more between the sexes, and thus the existing evidence taken together allows the acute oral toxicity classification to be reassessed.

Comments received during public consultation

One MSCA agreed with the proposal to classify the substance as Acute Tox. 4; H302 and to remove the classification for acute dermal toxicity.

One company, a downstream user, expressed some doubts about changing of the minimum classification due to insufficient additional data when compared with real human health experience. However, this comment was deemed unclear by both the DS and RAC as to which additional data was referred to.

Assessment and comparison with the classification criteria

Acute oral toxicity

The DS claimed that the study was carried out according to a protocol equivalent or similar to OECD TG 401. Nevertheless, significant deficiencies are present: missing information on the purity of the test substance, details on the examinations performed, mortality rates per group, information on the statistical methodology used, etc. Despite the study provided is old and lacking in detail, the acute oral LD50 obtained was 1030 mg/kg bw.

According to Table 3.1.1 of the CLP Regulation, the Acute Toxicity Estimate (ATE) of 1030 mg/kg bw confirms the classification for Acute Tox. 4; H302 (300 < ATE ≤ 2000 mg/kg bw).

RAC agrees with the argumentation provided by the DS in relation to **classification as Acute Tox. 4; H302 (Harmful if swallowed) and with setting an ATE value of 1030 mg/kg bw.**

Acute dermal toxicity

With respect to acute dermal toxicity, the DS provided one animal study on Sprague-Dawley and Crl:CD(SD) specific-pathogen-free rats performed according to OECD TG 402 and assessed as "reliable" (Biotoxtech, 2010). Five animals per sex and per group were treated with 2000 mg/kg bw of the test substance (purity > 99%) using occlusive exposure. All animals survived the duration of the study up to 14 days after dosing showing discolouration of skin, crusts formation from days 1 to 14, and scars from days 11 to 14 on the treated sites. No test substance-related effects on body weights were observed. The acute dermal LD50 was determined to be > 2000 mg/kg bw.

According to Table 3.1.1 of the CLP Regulation, the criterion for classification as Acute Tox. 4; H312 is 1000 < ATE ≤ 2000 mg/kg bw, and based on the results of the acute dermal study, it is not fulfilled. RAC agrees with the DS **to remove the existing classification Acute Tox. 4*; H312**.

10.3 Acute toxicity - inhalation route

Not evaluated in this report

10.4 Skin corrosion/irritation

Not evaluated in this report. IPD has a harmonised classification as Skin Corr. 1B and to the knowledge of the Dossier Submitter (DS) no new data are available that would change this classification.

10.5 Serious eye damage/eye irritation

Table 12: Summary table of animal studies on serious eye damage/eye irritation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Results - Observations and time point of onset - Mean scores/animal - Reversibility	Reference
OECD Guideline TG 405 (Acute Eye Irritation/ Corrosion) Reliability 2 (reliable with restrictions): Original study report was not available, only IUCLID summary Non-GLP	Rabbit, Small white Russian, female	Unchanged (no vehicle), undiluted No details on purity of the test material are provided	0.1 mL	Serious injury almost immediately after application (corrosive effects, opalescence). Conjunctiva showed necrosis 24 h after treatment Due to the corrosive effect of the test material, only 1 animal was used and the experiment was terminated after 24 hours.	Hüls 1983b

10.5.1 Short summary and overall relevance of the provided information on serious eye damage/eye irritation

In a valid study according to OECD TG 405 with rabbits (Small white Russian), undiluted 3-aminomethyl-3,5,5-trimethylcyclohexylamine produced serious injury (corrosive effects, opalescence) almost immediately after application. Twenty-four hours after application of the test substance, conjunctivae showed necrosis (Hüls, 1983a). Due to the corrosive effect of the test material, only 1 animal was used and the experiment was terminated after 24 hours.

10.5.2 Comparison with the CLP criteria

Table 13: Comparison of the findings for IPD regarding serious eye damage/eye irritation with the respective CLP classification criteria

CLP criteria (up to and including 9th ATP)	Findings for IPD
Definition of Serious Eye Damage Category 1 according to Table 3.3.1 of the CLP regulation: Category 1: A substance that produces: (a) in at least one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days; and/or (b) in at least 2 of 3 tested animals, a positive response of: (i) corneal opacity ≥ 3; and/or (ii) iritis > 1,5; calculated as the mean scores following grading at 24, 48 and 72 hours after instillation of the test material.	IPD produced serious injury (corrosive effects, opalescence) almost immediately after application. Twenty-four hours after application of the test substance, conjunctivae showed necrosis. The experiment was terminated after 24 h, since these effects were not expected to fully reverse within 21 days. Hence the criterion given in column 2 letter (a) of Table 3.3.1 of the CLP regulation is fulfilled.

10.5.3 Conclusion on classification and labelling for serious eye damage/eye irritation

In line with the CLP criteria and based on the strong corrosive effect on the eye almost immediately after application, 3-aminomethyl-3,5,5-trimethylcyclohexylamine should be classified as "Eye Damage Category 1" corresponding to H318: "Causes serious eye damage".

RAC evaluation of serious eye damage/irritation

Summary of the Dossier Submitter's proposal

The DS proposed to add the classification as Eye Dam. 1; H318 (causes serious eye damage) based on the eye damage/irritation study available (Hüls, 1983b).

Comments received during public consultation

One MSCA and one company - downstream user agreed to classify as Eye Dam. 1; H318.

Assessment and comparison with the classification criteria

No human data are available. The DS evaluated one animal eye damage/irritation study with a small white Russian rabbit (female) performed according to OECD TG 405 and assessed as "reliable with restrictions" (Hüls, 1983b). Details on purity of the test material were not provided. Undiluted test substance (0.1 mL) was instilled in rabbit's eye. Serious injury occurred almost immediately after application, expressed as corrosive effects and opalescence. Conjunctiva showed necrosis 24 hours after treatment. Due to the corrosive effect of the test material, only 1 animal was used and the experiment was terminated after 24 hours since these effects were not expected to fully reverse within 21 days.

According to criteria in the Table 3.3.1 of the CLP Regulation, classification for Eye Dam. 1 is justified: the substance produced effects on the cornea, iris or conjunctiva in at least one animal that are not expected to reverse within an observation period of 21 days.

RAC agrees to the DS' proposal to **classify the substance as Eye Dam. 1; H318**.

10.6 Respiratory sensitisation

Not evaluated in this report.

10.7 Skin sensitisation

Table 14: Summary table of animal studies on skin sensitisation

<table>
<tr><th>Method, guideline, deviations if any</th><th>Species, strain, sex, no/group</th><th>Test sub-stance,</th><th>Dose levels duration of exposure</th><th>Results</th><th>Refe-rence</th></tr>
<tr>
<td>OECD Guideline TG 406 (Skin Sensitisation)
Reliability 2
Guideline study with acceptable restrictions: no positive control group (not required by 1981 version of guideline)
Non-GLP</td>
<td>Guinea pig, Dunkin-Hartley, male, 20/dose group; 10/control group</td>
<td>3-amino-methyl-3,5,5-trimethyl-cyclohexy lamine</td>
<td>1st application: Induction 0.1 % intracutaneous
2nd application: Induction 7.5 % occlusive epicutaneous (48 h)
3rd application: Challenge (2.5 %, 5 %) occlusive, epicutaneous
Vehicle: 10 % Ethanol</td>
<td>
<table>
<tr><th rowspan="2">Group</th><th rowspan="2">Chal-lenge concen-tration</th><th colspan="3">Number of animals with positive reactions</th><th rowspan="2">Classif. acc. to CLP regulation for intradermal induction concentration <= 0,1 %</th></tr>
<tr><th>24 h</th><th>48h</th><th>72h</th></tr>
<tr><td>Control</td><td>2.5 %</td><td>0/9 (0 %)</td><td>0/9 (0 %)</td><td>0/9 (0 %)</td><td>-</td></tr>
<tr><td>Test group</td><td>2.5 %</td><td>7/20 (35 %)</td><td>5/20 (25 %)</td><td>2/20 (10 %)</td><td>Skin Sens. 1 A</td></tr>
<tr><td>Control</td><td>5 %</td><td>0/9 (0 %)</td><td>0/9 (0 %)</td><td>0/9 (0 %)</td><td>-</td></tr>
<tr><td>Test group</td><td>5 %</td><td>18/20 (90 %)</td><td>15/20 (75 %)</td><td>10/20 (50 %)</td><td>Skin Sens. 1 A</td></tr>
</table>
</td>
<td>Hüls (1983b)</td>
</tr>
<tr>
<td>Equivalent or similar to OECD Guideline TG 406 (Skin Sensitisation)
Reliability 2 :
Guideline study with acceptable restrictions: no positive control group (not required by 1981 version of guideline)
Non-GLP</td>
<td>Guinea pig (Dunkin-Hartley) female
20/dose group; 10/control group</td>
<td>3-Amino-methyl-3,5,5-trimethyl-cyclohexy lamine</td>
<td>1st application: Induction 1 % intracutaneous
2nd application: Induction 1 % occlusive epicutaneous
3rd application: Challenge 5 % and 10 % occlusive, epicutaneous
Vehicle: water</td>
<td>
<table>
<tr><th>Group</th><th>Challenge concentra-tion</th><th>Number of animals with positive reactions
24 h</th><th>Classif. acc. to CLP regulation for intradermal induction concentration <= 0,1 %</th></tr>
<tr><td>Control</td><td>5 %</td><td>0/10 (0 %)</td><td>-</td></tr>
<tr><td>Test group</td><td>5 %</td><td>0/20 (0 %)</td><td>-</td></tr>
<tr><td>Control</td><td>10 %</td><td>0/10 (0 %)</td><td>-</td></tr>
<tr><td>Test group</td><td>10 %</td><td>12/20 (60 %)</td><td>Skin Sens. 1 A</td></tr>
</table>
</td>
<td>Inveresk (1981)</td>
</tr>
<tr>
<td>According to Magnusson B, Kligman AM (1969). J. Invest. Dermatol. 52, 268
Reliability 2
Publication (Non-GLP)
Guinea pig maximisation test</td>
<td>guinea pig
strain: no data
No. of animals per dose: no informati on</td>
<td>3-amino-methyl-3,5,5-trimethyl-cyclohexy lamine</td>
<td>1st application: Induction 0.5 % intracutaneous
2nd application: Induction 0.5 % other: epicutaneous, occlusion not reported
3rd application: Challenge 2 % occlusive epicutaneous
Vehicle: acetone, CAS No. 67-64-1</td>
<td>Two weeks after the epidermal application all animals were challenged with 2 % test substance (24 hours occlusive). All test animals showed positive reactions. Therefore isophorone diamine is considered to be a dermal sensitizer for guinea pigs under the conditions of the study.</td>
<td>Thorgeirsson, A. (1978)</td>
</tr>
</table>

The skin sensitising properties of 3-aminomethyl-3,5,5-trimethylcyclohexylamine were determined in a guinea pig maximisation test according to OECD TG 406 (Hüls, 1983b). Twenty female guinea

pigs were intradermally injected with 3-aminomethyl-3,5,5-trimethylcyclohexylamine at 0.1 % in 10 % ethanol and one week later epidermally exposed to a 7.5 % concentration of test substance for 48 hours (occlusive). Ten control animals were similarly treated, but with vehicle alone. Two weeks after the epidermal application all animals were challenged with 2.5 % and 5 % test substance and with vehicle (24 hours occlusive). At challenge concentration of 2.5 % 7/20 animals showed a sensitisation 24 hours after the patch test, 5/20 animals 48 hours after the test and 2/20 72 hours after the test. At the challenge concentration of 5%, 18/20 animals showed a sensitisation 24 hours after the patch test, 15/20 animals 48 hours after the patch test and still 10/20 72 hours after the test. No animal of the control group showed any positive reaction.

The skin sensitising properties of 3-aminomethyl-3,5,5-trimethylcyclohexylamine were also determined in a guinea pig maximisation test according to OECD TG 406 (Inveresk, 1981). Twenty female guinea pigs were intradermally injected with 3-aminomethyl-3,5,5-trimethylcyclohexylamine at 1 % in dist. water and one week later epidermally exposed to a 1 % concentration of test substance for 48 hours (occlusive). Ten control animals were similarly treated, but with vehicle alone. Two weeks after the epidermal application all animals were challenged with 5 % and 10 % test substance and with vehicle (24 hours occlusive). No control group animal showed erythema at either 10 or 5 % challenge concentration, no erythema was noted in test group animals after challenge with 5 % test item, in test group challenged with 10 % 3-aminomethyl-3,5,5-trimethylcyclohexylamine 12/20 animals showed erythema.

In a third test on the skin sensitising properties of isophorone diamine according to Magnusson and Kligman (Thorgeirsson, 1978) guinea pigs were intradermally injected with 3-aminomethyl-3,5,5-trimethylcyclohexylamine 0.5 % in acetone and later epidermally exposed to a 0.5 % concentration of test substance occlusive. Control animals were similarly treated, but with vehicle alone regarding to the induction. Two weeks after the epidermal application all animals were challenged with 2 % test substance (24 hours occlusive). All test animals showed positive reactions.

10.7.1 Short summary and overall relevance of the provided information on skin sensitisation

In a reliable guinea pig maximisation test according to OECD TG 406, sensitisation was observed in 18 of 20 animals 24 h after using a challenge concentration of 5 %. With a challenge concentration of 2.5 %, 7 of 20 animals were positive (Hüls, 1983b). In a second reliable guinea pig maximisation test according to OECD TG 406, sensitising properties of 3-aminomethyl-3,5,5-trimethylcyclohexylamine were observed (Inveresk, 1981). In a previous (supporting) study according to Magnusson and Kligman (1969. J. Invest. Dermatol. 52, 268), sensitisation was observed in all challenged animals (Thorgeirsson, 1978).

Based on the studies summarised above, 3-aminomethyl-3,5,5-trimethylcyclohexylamine is considered to be a strong dermal sensitiser in guinea pigs.

10.7.2 Comparison with the CLP criteria

Table 15: Comparison of the findings for IPD regarding skin sensitisation with the respective CLP classification criteria

CLP criteria (up to and including 9th ATP)	Findings for IPD
Definition of Skin Sens. 1A based on Guinea Pig Maximisation Test (GPMT) data according to Table 3.4.3 of the CLP regulation: ≥ 30 % responding at ≤ 0,1 % intradermal induction dose or ≥ 60 % responding at > 0,1 % to ≤ 1 % intradermal induction dose	Hüls (1983b): 1st induction with 0.1%, 2nd induction with 7.5% IPD. At 24 h after challenge with 2.5 or 5% IPD, 35 or 90% of the animals showed a positive test reaction. Inveresk (1981): 1st and 2nd induction with 1% IPD. At 24 h after challenge with 10% IPD, 60% of the animals showed a positive test reaction. Thorgeirson (1978): 1st and 2nd induction with 0.5% IPD. At 24 h after challenge with 2% IPD, 100% of the animals showed a positive test reaction. In summary, there are three results from GPMT tests all fulfilling the CLP criteria for classification as Skin Sens. 1A

10.7.3 Conclusion on classification and labelling for skin sensitisation

Based on the available data and the criteria of the CLP regulation IPD has to be classified as Skin Sens. 1A.

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

The DS proposed to modify the current Annex VI classification for skin sensitisation from Skin. Sens. 1 to Skin. Sens 1A. The DS assessed three Guinea Pig Maximisation Test (GPMT) studies:

- Dunkin-Hartley male Guinea pigs were treated with IDP in 10% ethanol as a vehicle (20 animals per dose group; 10 animals per negative (vehicle) control group) (Hüls, 1983b):
  - 1st application: intradermal induction with 0.1% of the substance; control animals were treated with the vehicle only;
  - 2nd application after one week: epicutaneous induction (occlusive administration) of 7.5% of the substance for 48 hours; control animals were treated with the vehicle only;
  - 3rd application after two weeks from 2nd application for all animals including control group: challenge (epicutaneous occlusive administration) with 2.5% and 5% of the substance and with vehicle for 24 hours.

Detailed summary of studies performed by Hüls (1983b):

Group	**Challenge concentration**	**Number of animals with positive reactions**			**Classif. acc. to CLP regulation for intradermal induction concentration <=0,1 %**
		24 h	**48 h**	**72 h**	
Control	2.5 %	0/9 (0 %)	0/9 (0 %)	0/9 (0 %)	-
Test group	2.5 %	7/20 (35 %)	5/20 (25 %)	2/20 (10 %)	Skin Sens. 1 A
Control	5 %	0/9 (0 %)	0/9 (0 %)	0/9 (0 %)	
Test group	5 %	18/20 (90 %)	15/20 (75 %)	10/20 (50 %)	Skin Sens. 1 A

The study was performed according to OECD TG 406 and considered as "reliable with restriction". The missing positive control was not required by the 1981 version of the guideline. A sensitisation response was observed in 7/20, 5/20 and 2/20 animals after 24h, 48h and 72h, respectively, from the challenge at concentration of 2.5%. When the challenge was conducted with a concentration of 5%, 18/20, 15/20 and 10/20 animals showed a sensitisation response after 24h, 48h and 72h, respectively. No animals on the control group showed any positive reaction.

- Dunkin-Hartley female Guinea pigs were treated with the test substance in distilled water as a vehicle (20 animals per dose group; 10 animals per negative (vehicle) control group) (Inveresk, 1981):
    - 1st application: intradermal induction of 1% of the substance; control animals were treated with the vehicle only;
    - 2nd application after one week: epicutaneous induction (occlusive administration) of 1% of the substance for 48 hours; control animals were treated with the vehicle only;
    - 3rd application after two weeks from 2nd application for all animals including control group: challenge (epicutaneous occlusive administration) with 5% and 10% of the substance and with vehicle for 24 hours.

Detailed summary of studies performed by Inveresk (1981):

Group	**Challenge concentration**	**Number of animals with positive reactions**	**Classif. acc. to CLP regulation for intradermal induction concentration <=0,1 %**
		24 h	
Control	5 %	0/10 (0 %)	-
Test group	5 %	0/20 (0 %)	-
Control	10 %	0/10 (0 %)	-
Test group	10 %	12/20 (60 %)	Skin Sens. 1 A

The study was performed according to a protocol equivalent to OECD TG 406 and considered "reliable with restriction". The missing positive control was not required by 1981 version of the guideline.

No animals on the control group showed erythema at either 5 or 10% challenge concentration. No erythema was noted in the test group animals after challenge with 5% IPD, however in the test group challenged with 10% IPD, 12/20 animals showed erythema.

- Guinea pigs (no information on strain and number of animals) were intradermally injected with 0.5% of the test substance in acetone and later epidermally exposed in occlusive conditions to a 0.5% IPD. Control animals were similarly treated (intradermal injection and later occlusive epidermal exposure), but with vehicle alone. Two weeks after the epidermal application all animals were challenged with 2% test substance (24 hours occlusive). All test animals showed positive reactions (Thorgeirsson, 1978).

This third study was not performed according to OECD guidelines, however it was considered as "reliable with restriction" and used as supportive study by the DS.

Comments received during public consultation

One MSCA generally supported the DS' proposal while indicating that the results are borderline between sub-categorisation 1A and 1B.

One company – a downstream user supported the proposed classification for Skin Sens. 1A.

One international non-Governmental Organisation (European Environmental and Contact Dermatitis Research Group) supported the classification for Skin Sens. 1A and provided additional clinical human data (these are summarised in the Background Document under Additional Key Elements).

Additional key elements

European Environmental and Contact Dermatitis Research Group provided during public consultation additional clinical human data concerning dermal exposure to IPD. These studies are summarised below.

Ref.	Type of study	No. positive to IPD/no. tested (%)	Conclusion on frequency§	Conclusion on exposure§
(Dahlquist and Fregert, 1979)	Case report of two workers exposed to IPD and other epoxy resin-related substances	2/2 (100)	High, but only two cases	Presumably high
	Patch testing in 23 males with eczema	0/23 (0)	Not applicable	Not possible

(van Putten *et al.*, 1984)	exposed to epoxy resin			
	Patch testing in 112 males without eczema exposed to epoxy resin	3/112 (2.7)	High	
(Guerra *et al.*, 1992)	Case report of three workers exposed to IPD and other epoxy resin-related substances	3/3 (100)	High, but only three cases	Presumably high
(Lodi *et al*., 1993)	Case report of two parquet layers exposed to two-component glues containing, inter alia, IPD	2/2 (100)	High, but only two cases	Presumably high
(Patussi *et al*., 1995)	Case report of a parquet layer	1/1 (100)	High, but only one case	Presumably high
(Kanerva *et al*., 1996)	Case report of a car painter; unclear whether IPD was tested at all; only one case			
(Tarvainen *et al*., 1998)	Case report of one worker exposed to IPD	1/1 (100)	High, but only one case	Presumably high
(Kelterer *et al*., 2000)	Case report of one worker exposed to two-component epoxy resin glue including IPD	1/1 (100)	High, but only one case	Presumably high
(Rademaker, 2000)	Case report of 16 cases of occupational allergy to epoxy resins over a period of 5 years	1/16	Unclear, how many patients had been exposed to IPD (and, if so, at what level).	
(Geier *et al*., 2004)	Multi-centre study in patients with suspected ER allergy and patients with previous positive patch test to ER in standard series (including IPD)	5/87 (5.7)	High	Unknown
(Foti *et al*., 2010)	Case study of a brick layer using two-component	1/1 (100)	High, but only one case	Presumably high

	grout containing IPD			
(Canelas *et al*., 2010)	Review of patch test data base of a dermatological clinic between 1999 and 2008	4/2440 (0.16)	Low/moderate	Unknown
(Aalto-Korte *et al*., 2014)	Review of patch test data base of a dermatological clinic between 1992 and 2014	12/642 (1.9)	High	Unknown
(Aalto-Korte *et al*., 2015)	Patch testing of male sewage repair workers applying ER	2/8 (25)	High, but small number of cases	Presumably high
(Geier *et al*., 2016)	Multi-centre review of allergic reactions to ER hardeners 2002-2011	56/580	High	Unknown, possibly high

§In line with the CLP Guidance, section 3.4.2.2.3.1

Assessment and comparison with the classification criteria

Based on the GPMT studies summarised above, the DS concluded that the substance is a strong dermal sensitiser. The CLP criteria for classification as Skin Sens. 1A and 1B for GPMT studies are provided in Tables 3.4.3 and 3.4.4 of the CLP Regulation. RAC agrees with the DS to modify the existing classification as Skin Sens. 1A; H317.

All three studies fit with the CLP classification criteria for Skin Sens. 1A, however the study performed by Inveresk (1981) showed a positive outcome at the highest challenge concentration of 10% only. Thus, one study indicates extreme potency (Hüls, 1983b) and the other two studies indicate a strong potency for skin sensitisation (Thorgeirsson, 1978; Inveresk, 1981); the Thorgeirsson (1978) study does not contradicting extreme potency since 100% of the tested animals were sensitised with challenge a concentration of 2% after 24h.

In conclusion, RAC proposes a SCL of 0.001% w/v in line with the CLP criteria, taking into account the potential for extreme potency determined in the study by Hüls (1983b) with challenge a concentration of 5% after 24 h, and supported by the Thorgeirsson (1978) study.

The human data provided during the Public Consultation qualitatively support the classification of the substance as a skin sensitiser, but do not allow for any quantitative analysis, i.e. cannot provide evidence for Skin. Sens 1A, because only a low number of cases are reported and/or the level and frequency of exposure in most cases are unknown. Overall, RAC considers that **classification as Skin Sens. 1A; H317 with an SCL of 0.001% w/v is warranted**.

10.8 Germ cell mutagenicity

Not evaluated in this report

10.9 Carcinogenicity

Not evaluated in this report

10.10 Reproductive toxicity

Not evaluated in this report

10.11 Specific target organ toxicity-single exposure

Not evaluated in this report

10.12 Specific target organ toxicity-repeated exposure

Not evaluated in this report

10.13 Aspiration hazard

Not evaluated in this report, but IPD is not a pure hydrocarbon.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

11.1 Rapid degradability of organic substances

Table 16: Summary of relevant information on rapid degradability

Method	Results	Remarks	Reference
EU Method C.4-A (Determination of the "Ready" Biodegradability - Dissolved Organic Carbon (DOC) Die-Away Test)	under test conditions no biodegradation observed % Degradation of test substance: 8 after 28 d (DOC removal)	1 (reliable without restriction) key study experimental result Test material (EC name): 3-aminomethyl-3,5,5-trimethylcyclohexylamine	Hüls (1993a)

11.1.1 Ready biodegradability

The ready biodegradability was evaluated by Hüls (1993a) in a DOC-DIE AWAY Test according to EU-method C.4-A. The DOC removal following inoculation with activated sludge was measured at defined sampling intervals. The mean biodegradability derived from the DOC-DIE AWAY Test was 8 % indicating that the test item is not ready biodegradable.

11.1.2 BOD_5/COD

11.1.3 Hydrolysis

The hydrolysis as a function of pH of the test substance was determined by Infracor (2002) according to OECD TG 111 (1981) and EU method C.7 (1992). In the preliminary test, less than 10 % of the test substance was observed to hydrolyse at 50 °C at pH 4,7 and 9 after 5 days. There was no need to perform a main test.

11.1.4 Other convincing scientific evidence

11.2 Environmental transformation of metals or inorganic metals compounds

11.3 Environmental fate and other relevant information

Using QSAR models of U.S. EPA (PCKowWin Version 1.66), the sorption coefficient of the substance was calculated to be log Koc = 2.532. The calculated Henry's law constant of 0.000446 Pa m3/mol (HenryWin v3.10) indicates very low volatility from surface waters (registration dossier).

11.4 Bioaccumulation

11.4.1 Estimated bioaccumulation

QSAR calculations with EPIWIN v3.10 resulted in a BCF value of 3.16.

11.4.2 Measured partition coefficient and bioaccumulation test data

The partition coefficient 1-octanol/water of isophorone diamine was determined according to OECD TG 107 (1995) and EC Method A.8 (1992) with the shake-flask method. The result was log Kow = 0.99 (Kow = 9.8) at 23 °C (pH 6.34 for water phase without test substance).

11.5 Acute aquatic hazard

Table 17: Summary of relevant information on acute aquatic toxicity

Method	Species	Test material	Results[1]	Remarks	Reference
freshwater semi-static EU Method C.1 (Acute Toxicity for Fish) (Cited as Directive 84/449/EEC, C.1 ("Acute toxicity for fish"))	*Leuciscus idus*	3-aminomethyl-3,5,5-trimethylcyclohexylamine	LC_{50} (96 h): 110 mg/L test mat. (nominal) based on: mortality	1 (reliable without restriction) key study experimental result	Hüls (1993b)
freshwater static OECD Guideline 202 (Daphnia sp. Acute Immobilisation Test) (1984) EU Method C.2 (Acute Toxicity for Daphnia) (1992)	*Daphnia magna*	3-aminomethyl-3,5,5-trimethylcyclohexylamine	EC_{50} (48 h): 23 mg/L test mat. (nominal) based on: mobility (17-31 mg/L) EC_{50} (24 h): 27 mg/L test mat. (nominal) based on: mobility (18-40 mg/L)	1 (reliable without restriction) supporting study experimental result	Infracor (2002)
freshwater static OECD Guideline 202 (Daphnia sp. Acute Immobilisation Test)	*Daphnia magna*	3-aminomethyl-3,5,5-trimethylcyclohexylamine	EC_{50} (24 h): 37.4 mg/L (nominal) based on: mobility EC_{50} (48 h): 17.4 mg/L (nominal) based on: mobility	2 (reliable with restrictions) key study experimental result	Danish Environmental Protection Agency (2000)
freshwater static DIN 38412, part 11	*Daphnia magna*	3-aminomethyl-3,5,5-trimethylcyclohexylamine	EC_{50} (24 h): 44 mg/L test mat. (nominal) based on: mortality (35-50 mg/L)	2 (reliable with restrictions) supporting study experimental result	Hüls (1996a)
saltwater semi-static	*other aquatic crustacea: Chaetogammarus marinus*	3-aminomethyl-3,5,5-trimethylcyclohexylamine	LC_{50} (24 h): 572 mg/L test mat. (nominal) based on:	1 (reliable without restriction)	Adema (1982)

Method: other: see Test Conditions			mortality (505-648 mg/L) LC_{50} (48 h): 388 mg/L test mat. (nominal) based on: mortality (229-444 mg/L) LC_{50} (72 h): 362 mg/L test mat. (nominal) based on: mortality (318-412 mg/L) LC_{50} (96 h): 324 mg/L test mat. (nominal) based on: mortality (286-366 mg/L)	key study experimental result	
freshwater static EU Method C.3 (Algal Inhibition test) (Cited as Directive 87/302/EEC, part C, p. 89 (Algal inhibition test))	*Scenedesmus subspicatus (new name: Desmodesmus subspicatus)* (algae)	3-aminomethyl-3,5,5-trimethylcyclohexylamine	EC_{50} (72 h): 37 mg/L test mat. (nominal) based on: cell number EC_{50} (72 h): > 50 mg/L test mat. (nominal) based on: growth rate	2 (reliable with restrictions) key study experimental result	Hüls (1993d)

[1] Indicate if the results are based on the measured or on the nominal concentration

11.5.1 Acute (short-term) toxicity to fish

In a semi-static test with *Leuciscus idus* according to 84/449/EEC, C.1, 1984, fish were exposed for 96 h to concentrations of 70 - 280 mg/L 3-aminomethyl-3,5,5-trimethylcyclohexylamine. The LC_{50} (96 h) was determined to be 110 mg/L (Hüls, 1993a). A possible contribution of the basic properties of the test substance and of the resulting high pH (up to 9.6 at the LC_{100}) to the observed effects was not discussed by the authors, but cannot be excluded.

11.5.2 Acute (short-term) toxicity to aquatic invertebrates

The acute toxicity of 3-aminomethyl-3,5,5-trimethylcyclohexylamine to Daphnia magna was determined in a static test conducted according to OECD 202 (I) (1984). After 48 h of exposure, the EC_{50} was calculated as 23 mg/L (Infracor, 2002b). In a test according to DIN 38412, part 11 a nominal EC_{50} (24 h) of 44 mg/L was reported (Hüls, 1996a). The aquatic toxicity of 3-aminomethyl-3,5,5-trimethylcyclohexylamine was also tested in the marine invertebrate *Chaetogammarus marinus*. The 96 hour-EC_{50} determined in this semi-static test is 324 mg/L (Adema, 1982). However, despite of good test performance and documentation, the result with this non-standard organism may at present only serve as an indication that the sensitivity of marine invertebrates towards the test substance is probably not higher than that of freshwater organisms.

11.5.3 Acute (short-term) toxicity to algae or other aquatic plants

The growth inhibition of 3-aminomethyl-3,5,5-trimethylcyclohexylamine on the freshwater alga *Scenedesmus subspicatus* was tested by Hüls (1993b) according to a test procedure similar to OECD Guideline 201. The algae were exposed to 7 concentrations between 0.75 and 50 mg/L and one control. Based on growth rate an ErC_{50} of > 50 mg/L and a 72h-ErC_{10} of 11 mg/L (NOEC 1.5 mg/L) were determined (nominal concentrations). Based on biomass development an EbC_{50} of 37 mg/L and a 72h-EbC_{10} of 3 mg/L were determined.

11.5.4 Acute (short-term) toxicity to other aquatic organisms

No data available

11.6 Long-term aquatic hazard

Table 18: Summary of relevant information on chronic aquatic toxicity

Method	Species	Test material	Results[1]	Remarks	Reference
OECD 202, part 2 (1984) freshwater, semi-static	*Daphnia magna*	3-aminomethyl-3,5,5-trimethylcyclohexylamine	NOEC (21 d): 3 mg/L test mat. (nominal) based on: reproduction LOEC (21 d): 10 mg/L test mat. (nominal) based on: reproduction	1 (reliable without restriction) key study experimental result	Hüls (1993c)
Freshwater static EU Method C.3 (Algal Inhibition test) (Cited as Directive 87/302/EEC, part C, p. 89 (Algal inhibition test))	*Scenedesmus subspicatus (new name: Desmodesmus subspicatus)* (algae)	3-aminomethyl-3,5,5-trimethylcyclohexylamine	NOEC (72 h): 1.5 mg/L test mat. (nominal) based on: cell number EC10 (72 h): 3.1 mg/L test mat. (nominal) based on: cell number EC10 (72 h): 11.2 mg/L test mat. (nominal) based on: growth rate	2 (reliable with restrictions) key study experimental result	Hüls (1993d)

[1] Indicate if the results are based on the measured or on the nominal concentration

11.6.1 Chronic toxicity to fish

No data available.

11.6.2 Chronic toxicity to aquatic invertebrates

The effects of 3-aminomethyl-3,5,5-trimethylcyclohexylamine on the reproduction rate of *Daphnia magna* were tested in a chronic test according to OECD 202, part 2, but modified according to EC requirements (Hüls, 1993c). Under semi-static conditions, the daphnids were exposed for 21 days to concentrations ranging from 0.1 – 30.0 mg/L. Concentrations up to 3.0 mg/L (NOEC) had no influence on survival of the daphnids or their reproduction rate. At 10 mg/L (LOEC), survival was reduced to 80 % with no significant reduction of the reproduction rate. The next (highest)

concentration of 30.0 mg/L led to 100 % mortality. Hence the NOEC (21 d) for reproduction was determined as 3.0 mg/L.

11.6.3 Chronic toxicity to algae or other aquatic plants

The growth inhibition of 3-aminomethyl-3,5,5-trimethylcyclohexylamine on the freshwater alga *Scenedesmus subspicatus* was tested by Hüls (1993b) according to a test procedure similar to OECD Guideline 201. The algae were exposed to 7 concentrations between 0.75 and 50 mg/L and one control. Based on growth rate a NOEC of 1.5 mg/L and an ErC_{10} of 11.2 mg/L were determined (nominal concentrations).

11.6.4 Chronic toxicity to other aquatic organisms

No data available

11.7 Comparison with the CLP criteria

11.7.1 Acute aquatic hazard

Table 19: Comparison with criteria for acute aquatic hazards

	Criteria for environmental hazards	**3-aminomethyl-3,5,5-trimethylcyclohexylamine**	**Conclusion**
Acute Aquatic Toxicity	Cat. 1: $LC_{50}/EC_{50}/ErC_{50} \leq 1$ mg/L	Fish: 96h-LC_{50} = 110 mg/L (nominal) Invertebrates: 48h-EC_{50} = 17.4 mg/L (nominal) Algae: 72h-ErC_{50} > 50 mg/L (nominal)	**No classification**

11.7.2 Long-term aquatic hazard (including bioaccumulation potential and degradation)

Table 20: Comparison with criteria for long-term aquatic hazards

	Criteria for environmental hazards	**3-aminomethyl-3,5,5-trimethylcyclohexylamine**	**Conclusion**
Rapid Degradation	Half-life hydrolysis < 16 days Readily biodegradable in a 28-day test for ready biodegradability (> 70 % DOC removal or > 60 % theoretical oxygen demand, theoretical carbon dioxide)	Hydrolytically stable 8 % after 28 days (DOC removal) => not readily biodegradable	**Not rapidly degradable**
Bioaccumulation	Log Kow ≥ 4 BCF ≥ 500	Log Kow = 0.99	**Not bioaccumulative**
Aquatic Toxicity	Non-rapidly degradable substances: Cat. 1: NOEC ≤ 0.1 mg/L Cat. 2: NOEC ≤ 1 mg/L	Fish: no chronic toxicity data Invertebrates: 21d-NOEC = 3 mg/L (nominal) Algae: 72h-ErC10 = 11.2 mg/L (nominal)	**No classification**

	For trophic levels where no chronic toxicity data are available: Cat. 1: $LC_{50}/EC_{50}/ErC_{50} \leq 1$ mg/L Cat. 2: $LC_{50}/EC_{50}/ErC_{50} > 1 \leq 10$ mg/L Cat. 3: $LC_{50}/EC_{50}/ErC_{50} > 10 \leq$ 100 mg/L	Fish: 96h-LC_{50} = 110 mg/L (nominal)	

11.8 CONCLUSION ON CLASSIFICATION AND LABELLING FOR ENVIRONMENTAL HAZARDS

Based on acute ecotoxicity data *Daphnia* is the most sensitive organism. Long-term ecotoxicity data is available for *Daphnia* and algae. According to CLP Guidance Annex I 1.3.2 (c) no long-term fish toxicity test is necessary as fish is not the most sensitive species and the substance does not fulfil the criteria for the classification with Aquatic Chronic 4 due to its low bioaccumulative potential.

According to Figure 4.1.1 of the CLP regulation, substances with adequate chronic toxicity data available for one or two trophic levels should be assed as following:

a) according to the criteria in Table 4.1.0(b)(i) or 4.1.0(b)(ii) depending on information on rapid degradation

b) (if for the other trophic level(s) adequate acute toxicity data are available) according to the criteria given in Table 4.1.0(b)(iii) and classified according to the most stringent outcome.

Assessment for 3-aminomethyl-3,5,5-trimethylcyclohexylamine:

a) NOEC (invertebrates and algae) > 1 mg/L → no classification

b) LC_{50} (fish) > 100 mg/L → no classification

Based on the available data the CLP classification, criteria for acute and chronic hazard classification are not fulfilled. Hence environmental classification for this substance is not indicated.

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

IPD is currently listed in Annex VI of the CLP Regulation with a classification for environmental hazards as Aquatic Chronic 3; H412. The DS proposed to remove the classification as hazardous to the aquatic environment due to new interpretation/evaluation of existing data for aquatic chronic toxicity.

Degradation

In the preliminary test performed following OECD TG 111 and EU method C.7, less than 10% of the IPD was observed to hydrolyse at 50°C at pH 4, 7 and 9 after 5 days.

A ready biodegradation test according to EU Method C.4-A (Dissolved Organic Carbon (DOC) Die-Away Test) using activated sludge (adaptation not specified) resulted in 8% degradation after 28 days. The substance is therefore not readily biodegradable.

Based on this, the DS concluded that IPD is not considered rapidly degradable.

Bioaccumulation

The experimentally derived log K_{OW} is 0.99 at 23°C (OECD TG 107 and EU method A.8).

QSAR calculations with EPIWIN v3.10 resulted in a BCF value of 3.16.

Based on available data, the DS concluded that IPD has a low potential for bioaccumulation.

Aquatic toxicity

A summary of the relevant information on aquatic toxicity is provided in the following table. The results of the studies are expressed in terms of nominal concentrations.

Table: *Summary of relevant information on aquatic toxicity*

Method/Exposure	Test organism	Endpoint	Toxicity values in mg/L	Reliability/Reference
Short-term toxicity				
EU Method C.1 (Cited as Directive 84/449/EEC, C.1, 1984) semi-static	*Leuciscus idus*	96h LC_{50}	110*	Rel. 1 Hüls, 1993b
OECD TG 202, EU Method C.2 static	*Daphnia magna*	48h EC_{50}	23*	Rel. 1 Infracor, 2002
OECD TG 202 static	*Daphnia magna*	48h EC_{50}	17.4	Rel. 2 Danish Environmental Protection Agency, 2000
DIN 38412, part 11 static	*Daphnia magna*	24h EC_{50}	44	Rel. 2 Hüls, 1996a
Test procedure in accordance with generally accepted scientific standards and described in sufficient detail semi-static	*Chaetogammarus marinus*	96h LC_{50}	324	Rel. 1 Adema, 1982
EU Method C.3 (Cited as Directive 87/302/EEC, part C, p. 89) static	*Desmodesmus subspicatus*	72h EC_{50} 72h E_rC_{50}	37 > 50	Rel. 2 Hüls, 1993d
Long-term toxicity				
OECD TG 202, part 2 semi-static	*Daphnia magna*	21d NOEC	3*	Rel. 1 Hüls, 1993c

EU method C.3 (Cited as Directive 87/302/EEC, part C, p. 89) static	*Desmodesmus subspicatus*	72h NOEC 72h EC_{10} 72h E_rC_{10}	1.5 3.1 11.2	Rel. 2 Hüls, 1993d

Note: * - Studies in which the analytical verification of the test concentrations was carried out. In these studies, all analytical measurements were within the 20% range accepted for the use of nominal concentrations.

Additional information related to maintenance of the test concentrations is provided for the acute fish study (Hüls 1993b) in the Background Document.

Acute toxicity

Acute aquatic toxicity data on IPD are available for fish, invertebrates and algae, with invertebrates being the most sensitive trophic level (48h LC_{50} = 17.4 mg/L for *D. magna*). The DS proposed not to classify the substance IPD as acutely hazardous to the aquatic environment. The basis for this proposal is that the short-term (acute) aquatic ecotoxicity test results showed no toxicity effects to aquatic organisms (algae, daphnia and fish) at concentrations ≤ 1 mg/L.

Chronic toxicity

Long-term aquatic toxicity data on IPD are available for aquatic invertebrates and algae, whilst data for fish are lacking. Based on the available aquatic chronic toxicity data for invertebrate (21d NOEC of 3 mg/L for *D. magna*) and algae (72h E_rC_{10} of 11.2 mg/L for *D. subspicatus*), the DS concluded that IPD does not meet the classification criteria for aquatic chronic hazard. Due to the lack of chronic toxicity data for the fish, the DS used the surrogate approach. Considering that IPD is not rapidly degradable this resulted in a no classification for aquatic chronic hazard.

Comments received during public consultation

Two Member States (MS) and one company submitted comments on the environmental part of the DS's proposal during the Public Consultation (PC). One MS and the company agreed with the proposal to remove the existing classification (Aquatic Chronic 3, H412) for IPD. The second commenting MS asked for clarifications regarding analytical verification of the test item concentrations.

Assessment and comparison with the classification criteria

Degradation

RAC agrees with the DS that IPD does not meet the criteria for rapid degradability. This outcome is based on available hydrolysis data (stable to hydrolysis at acidic, neutral and alkaline conditions at 50°C) and the results obtained in a biodegradation study (8% degradation after 28 days).

Bioaccumulation

RAC agrees with the DS that IPD has a low potential for bioaccumulation in aquatic organisms. The basis for this is that log K_{OW} value of 0.99 is below the CLP Regulation threshold of 4.

Aquatic toxicity

Aquatic acute toxicity data on IPD are available for fish, invertebrates and algae. Since no effects on aquatic organisms were observed at or below the threshold value of 1 mg/L, IPD does not meet the criteria for classification for acute aquatic hazard. Therefore, RAC supports the DS´s proposal that no classification for acute aquatic hazards is warranted.

Chronic toxicity

Aquatic chronic toxicity data on IPD are available for two trophic levels, invertebrate and algae. In the absence of adequate chronic toxicity data for fish, the surrogate method is applied (CLP Regulation, Annex I Table 4.1.0(b)(iii)). The substance is considered non-rapidly degradable and does not fulfil the criteria for bioaccumulation potential.

- Classification based on adequate chronic toxicity data: Invertebrate *D. magna* long-term testing provided a 21d NOEC of 3 mg/L, while algae long-term testing provide a 72h E_rC_{10} of 11.2 mg/L. Both values are above threshold value of 1 mg/L and the substance is not rapidly degradable. IPD does not fulfil the criteria for chronic hazard classification, based on Table 4.1.0 (b)(i).
- Classification based on surrogate data for fish. The acute toxicity value is a 96h LC_{50} of 110 mg/L for fish *Leuciscus idus*. The 96h LC_{50} value is above 100 mg/L and the substance is not rapidly degradable. IPD does not fulfil the criteria for chronic hazard classification, based on Table 4.1.0(b)(iii).

RAC additional analysis

It should be noted that, due to some uncertainties regarding the maintenance of test concentrations in the acute fish toxicity study (Hüls, 1993b), in which the result was based on nominal concentrations, RAC requested the full study report. Late on in the process of the preparation of the draft opinion, RAC received the full study report by the DS. From the full study report it was evident that the test concentrations were maintained throughout the test, with the test concentrations being verified by analytical measurements and being within 80 % of nominal at the end of the test. In addition to this, the substance has very low volatility, is hydrolytically stable and is unlikely to degrade over the test period, therefore, no major losses are expected. The same data were also agreed in an OECD SIAR document. For that reason, results based on nominal concentrations were used in this specific case for classification by the RAC. The measured values were also above 100 mg/L.

In summary, on the basis of the available data, RAC supports the DS proposal that **no classification for environmental hazards is warranted**.

12 REFERENCES

Adema, D.M.M. (1982). Tests and desk studies carried out by MT-TNO during 1980-1981 for annex II of marpol 1973. TNO, Delft, Netherlands. Report. Testing laboratory: MT-TNO. Report no.: CL 82/14. Report date: 1982-02-23. Unpublished

Biotoxtech (2010): Acute dermal dose toxicity study of VESTAMIN IPD in Sprague-Dawley rats. Testing laboratory: Biotoxtech Co., Ltd. Owner company: Evonik Degussa Japan Co., Ltd. Study number: J10232. Unpublished

Danish Environmental Protection Agency (2000). Immobilization Test of Selected Organic amines with the Crustacean Daphnia magna. Report no.: VKI study: 11531.

Degussa (2002). Unpublished calculation using standard methods / equations (Isophorone diamine). Degussa AG, Coatings & Colorants, 4 pp. Unpublished

Evonik Degussa (2009). Safety data sheet "Vestamin IPD" - Isophorondiamin, Version 9.3 / DE. Evonik Degussa GmbH, Business Unit Coatings & Additives, Marl (Germany). Owner company: Evonik Degussa GmbH. Report date: 2009-08-03.

Hommel, G. (1998). Handbuch der gefährlichen Güter, 5th Ed. 1998, Merkblatt 783. Springer-Verlag, Berlin.

Hüls (1983a). Prüfung der akuten Augen- und Schleimhautreizwirkung von Isophorondiamin. Hüls AG, Marl. Report. Testing laboratory: Department of Toxicology, Hüls AG, Marl. Report no.: 0175. Owner company: Evonik Degussa GmbH. Report date: 1983-11-29. Unpublished.

Hüls (1983b). Prüfung auf hautsensibilisierende Wirkung am Meerschweinchen von Isophorondiamin (IPD). Hüls AG, Marl. Report. Testing laboratory: Department of Toxicology, Hüls AG, Marl. Report no.: 0124. Owner company: Evonik Degussa GmbH. Report date: 1983-10-19. Unpublished

Hüls (1992). Eigenschaften und Handling VESTAMIN IPD/TMD. Hüls AG Information sheet 43.01.065/05.92/gu. Owner company: Evonik Degussa GmbH. Report date: 1992-05-01.

Hüls (1993a). Bestimmung der biologischen Abbaubarkeit von Vestamin IPD im DOC-DIE Away test. Hüls AG, Marl. Report. Testing laboratory: Department of Biology, Hüls AG, Marl. Report no.: DDA-02. Owner company: Evonik Degussa GmbH. Report date: 1993-11-12.

Hüls (1993b). Bestimmung der akuten Wirkungen von Vestamin IPD gegenüber Fischen (nach EG 84/449 C 1). Hüls AG, Marl. Report. Testing laboratory: Department of Biology, Hüls AG, Marl. Report no.: F-1230. Owner company: Evonik Degussa GmbH. Report date: 1993-08-02.

Hüls (1993c). Bestimmung der Auswirkungen von Vestamin IPD auf die Reproduktionsrate von Daphnia magna (nach OECD-Guideline 202 Teil II). Hüls AG, Marl. Report. Testing laboratory: Department of Biology, Hüls AG, Report no.: DL-149. Owner company: Evonik Degussa GmbH. Report date: 1993-04-23.

Hüls (1993d). Bestimmung der Auswirkungen von Vestamin IPD auf das Wachstum von Scenedesmus subspicatus 86.81. SAG (Algenwachstumshemmtest nach Richtlinie 88/302/EWG). Hüls AG, Marl. Report. Testing laboratory: Department of Biology, Hüls AG, Marl. Report no.: AW-266. Owner company: Evonik Degussa GmbH. Report date: 1993-02-22.

Hüls (1996a). Bestimmung der Auswirkungen von Isophorondiamin auf das Schwimmverhalten von Daphnia magna. Hüls AG, Marl. Report. Testing laboratory: Department of Biology, Hüls AG, Marl. Report no.: DK-159. Owner company: Evonik Degussa GmbH. Report date: 1996-07-09. Unpublished

Hüls (1996b). Bestimmung der Bakterientoxizität von Isphorondiamin nach Bringmann und Kühn. Hüls AG, Marl. Report. Testing laboratory: Department of Biology, Hüls AG, Marl. Report no.: ABBK-IPDA. Owner company: Evonik Degussa GmbH. Report date: 1996-02-08. Unpublished

Hüls Infracor (1998). Vestamin IPD - Determination of the partition coefficient (log pow), shake flask method. Hüls Infracor GmbH, Marl. Report. Testing laboratory: Department of Analytics, Hüls Infracor GmbH, Marl. Report no.: AN-ASB 0093. Owner company: Evonik Degussa GmbH. Report date: 1998-06-08. Unpublished

IBR (1977). Prüfung von "IPD" auf primäre Hautreizwirkung beim Kaninchen. IBR, Hannover. Report. Testing laboratory: IBR International Bio-Research, Hannover. Report no.: 1-3-170/1-77. Owner company: Evonik Degussa GmbH. Report date: 1977-07-01. Unpublished

Infracor (2002). Isophorone diamine, determination of the immobilisation of Daphnia magna Straus (acute immobilisation test). Infracor GmbH, Marl. Report. Testing laboratory: Department of Biology, Infracor GmbH, Marl. Report no.: DK-781. Owner company: Evonik Degussa GmbH. Report date: 2002-08-28.

Institut für Pharmakologie.(1965): Toxikologische Prüfung von IPD und TMD. Institut für Pharmakologie der Universität, Bonn. Report. Testing laboratory: Institut für Pharmakologie der Universität, Bonn. Report no.: -. Owner company: Evonik Degussa GmbH. Report date: 1965-06-10. Unpublished

Inveresk (1981). Isophorondiamin: Sensitisation potential in guinea pigs. Inveresk Research Int., Musselburgh, Scotland. Report. Testing laboratory: Inveresk Research Int., Musselburgh, Scotland. Report no.: 417048. Owner company: Evonik Degussa GmbH. Report date: 1981-06-26. Unpublished

Kirk-Othmer (1992). Kirk-Othmer encyclopedia of chemical technology. John Wiley & Sons (New York). 4th Ed., Vol. 2, p. 388.

STN, (2003). Database Beilstein (as searched by BUA on 22 October 2003).

Thorgeirsson, A. (1978): Sensitization capacity of epoxy resin hardeners in the guinea pig. Acta Derm. Venereol. 58, 332-336. Report date: 1977-05-09.

Ullmann (2001): 8.1.3 Higher diamines. Ullmann's Encyclopedia of Industrial Chemistry on CD-ROM, WILEY-VCH GmbH, Weinheim.

VEBA-Chemie (1975): Isophorondiamin - IPD - 3-Aminomethyl-3.5.5-trimethylcyclohexylamin. VEBA-Chemie AG, Geksenkirchen (Germany). Information sheet. Report no.: 22-MD-175-1. Owner company: Evonik Degussa GmbH.

13 ANNEXES

Annex I