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

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Version number: 2.1 (post ACC)

Date: August 2018

CONTENTS

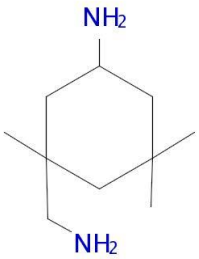
1 IDENTITY OF THE SUBSTANCE

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.)

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	

Property	Value	Reference	Comment (e.g. measured or estimated)
		(1975)	
Viscosity	Viscosity at 20°C: 19 mm²/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.

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".

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 rowspan="2">Group</th><th rowspan="2">Challenge concentra-tion</th><th>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></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 informatio n</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>Thorgeir sson, 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.

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 Method: other:	*other aquatic crustacea: Chaetogammarus marinus*	3-aminomethyl-3,5,5-trimethylcyclohexylamine	LC_{50} (24 h): 572 mg/L test mat. (nominal) based on: mortality (505-648	1 (reliable without restriction)	Adema (1982)

see Test Conditions			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 For trophic levels where no chronic toxicity data are available:	Fish: no chronic toxicity data Invertebrates: 21d-NOEC = 3 mg/L (nominal) Algae: 72h-ErC10 = 11.2 mg/L (nominal) Fish:	**No classification**

	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	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.

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13 ANNEXES

Annex I