European Union Risk Assessment Report

AMINES, TALLOW ALKYL

CAS No: 61790-33-8

EINECS No: 263-125-1

(Z)-OCTADEC-9-ENYLAMINE

CAS No: 112-90-3

EINECS No: 204-015-5

OCTADECYLAMINE

CAS No: 124-30-1

EINECS No: 204-695-3

AMINES, HYDROGENATED TALLOW ALKYL

CAS No: 61788-45-2

EINECS No: 262-976-6

AMINES, COCO ALKYL

CAS No: 61788-46-3

EINECS No: 262-977-1

RISK ASSESSMENT

LEGAL NOTICE

Luxembourg: Office for Official Publications of the European Communities, [ECB: year]
ISBN [ECB: insert number here]

Printed in Italy

AMINES, TALLOW ALKYL

CAS No: 61790-33-8

EINECS No: 263-125-1

(Z)-OCTADEC-9-ENYLAMINE

CAS No: 112-90-3

EINECS No: 204-015-5

OCTADECYLAMINE

CAS No: 124-30-1

EINECS No: 204-695-3

AMINES, HYDROGENATED TALLOW ALKYL

CAS No: 61788-45-2

EINECS No: 262-976-6

AMINES, COCO ALKYL

CAS No: 61788-46-3

EINECS No: 262-977-1

RISK ASSESSMENT

October 2008

Germany

Rapporteur for the risk assessment of the primary alkyl amines is Germany

Contact point:

Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (BAuA)
Anmeldestelle Chemikalien / Zulassungsstelle Biozide
(Federal Institute for Occupational Safety and Health
Division for Chemicals and Biocides Regulation)
Friedrich-Henkel-Weg 1-25

44149 Dortmund (Germany)

fax: +49(231)9071-2679
e-mail: chemg@baua.bund.de

Date of Last Literature Search : **[insert year]**
Review of report by MS Technical Experts finalised: **[insert month and year]**
Final report: **[year]**

Foreword

This Draft Risk assessment Report is carried out in accordance with Council Regulation (EEC) 793/93[1] on the evaluation and control of the risks of "existing" substances. "Existing" substances are chemical substances in use within the European Community before September 1981 and listed in the European Inventory of Existing Commercial Chemical Substances. Regulation 793/93 provides a systematic framework for the evaluation of the risks to human health and the environment of these substances if they are produced or imported into the Community in volumes above 10 tonnes per year.

There are four overall stages in the Regulation for reducing the risks: data collection, priority setting, risk assessment and risk reduction. Data provided by Industry are used by Member States and the Commission services to determine the priority of the substances which need to be assessed. For each substance on a priority list, a Member State volunteers to act as "Rapporteur", undertaking the in-depth Risk Assessment and recommending a strategy to limit the risks of exposure to the substance, if necessary.

The methods for carrying out an in-depth Risk Assessment at Community level are laid down in Commission Regulation (EC) 1488/94[2], which is supported by a technical guidance document[3]. Normally, the "Rapporteur" and individual companies producing, importing and/or using the chemicals work closely together to develop a draft Risk Assessment Report, which is then presented at a Meeting of Member State technical experts for endorsement. The Risk Assessment Report is then peer-reviewed by the Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) which gives its opinion to the European Commission on the quality of the risk assessment.

This Draft Risk Assessment Report is currently under discussion in the Competent Group of Member State experts with the aim of reaching consensus. During the course of these discussions, the scientific interpretation of the underlying scientific information may change, more information may be included and even the conclusions reached in this draft may change. The Competent Group of Member State experts seek as wide a distribution of these drafts as possible, in order to assure as complete and accurate an information basis as possible. The information contained in this Draft Risk Assessment Report does not, therefore, necessarily provide a sufficient basis for decision making regarding the hazards, exposures or the risks associated with the priority substance.

This Draft Risk Assessment Report is the responsibility of the Member State rapporteur. In order to avoid possible misinterpretations or misuse of the findings in this draft, anyone wishing to cite or quote this report is advised to contact the Member State rapporteur beforehand.

Contact Details of the Rapporteur(s)

[1] O.J. No L 084, 05/04/199 p.0001 – 0075

[2] O.J. No L 161, 29/06/1994 p. 0003 – 0011

[3] Technical Guidance Document, Part I – V, ISBN 92-827-801 [1234]

0 OVERALL RESULTS OF THE RISK ASSESSMENT

Environment

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to

- Releases into surface waters during production of primary alkyl amines.
- Releases into surface waters during formulation of fertilizers, processing to aminoethoxylates, amides, sulphosuccinamates and other downstream products.
- Releases into surface water using primary alkyl amines as floatation agent.
- Releases into agricultural soils during application of sewage sludge onto agricultural soil due to production, formulation of fertilizers, and use as floatation agent.
- Releases into agricultural soils during the use as anticaking agent in fertilizers.
- Releases into the atmosphere during all life-cycle steps.
- Possible PBT/vPvB properties of the substance.

Human health

Human health (toxicity)

Workers

Conclusion (i) There is a need for further information and/or testing.

Available data on the skin sensitisation potential of the primary alkyl amines are not sufficiently conclusive. Due to the limited hazard information, the occupational risk of skin sensitisation following dermal exposure to the primary alkyl amines cannot be sufficiently assessed.

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

The primary alkyl amines are classified and labelled as skin irritants or corrosives. Skin irritation and corrosive lesions need to be avoided by adequate skin-related risk management measures. In addition, further risk management measures have to be implemented because of concern for repeated dose toxicity (systemic effects) following dust exposure and dermal contact to the solid and skin irritating primary alkyl amines (octadecyl amine and hydrogenated tallow alkyl amine). Based on the actual dermal exposure assessment, there is concern for fertility impairment as well.

To prevent chronic systemic health effects while handling primary alkyl amines, occupational exposure by inhalation is proposed to be controlled down to a level of 0.15 mg/m³ (8-hour time-weighted average). The corresponding health-based reference level for controlling repeated dermal exposure is calculated to be 0.04 mg/kg/day.

Consumers

Conclusion (i) There is a need for further information and/or testing.

Conclusion (i) applies to potential skin sensitisation reactions of primary alkyl amines from the use of metal care products. For the assessment of the possible skin sensitisation potential of the primary alkyl amines the performance of a Local Lymph Node Assay (LLNA) is proposed with an appropriate substance of the category. Test results are needed to perform a firm calculation for consumers.

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion (iii) applies to the dermal route for local and systemic repeated exposure and fertility through uptake of primary alkyl amines from the use of metal care products.

Humans exposed via the environment

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to all other toxicological endpoints and scenarios.

Human health (physico-chemical properties)

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

CONTENTS

EUSES Calculations can be viewed as part of the report at the website of the European Chemicals Bureau: http://ecb.jrc.it

1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

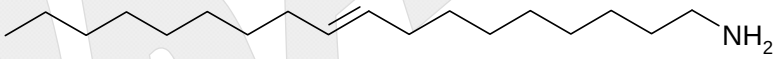
Amines, tallow alkyl

CAS Number: 61790-33-8
EINECS Number: 263-125-1
IUPAC Name: Tallow alkyl amine
Molecular formula: unspecified
Molecular weight: 267 as average (undistilled)
Synonyms: Tallow fatty amines
C14-C18 Alkylamines

CA Index Name: Amines, tallow alkyl

(Z)-Octadec-9-enylamine

CAS Number: 112-90-3
EINECS Number: 204-015-5
IUPAC Name: (Z)-Octadec-9-enylamine
Molecular formula: $C_{18}H_{37}N$
Structural formula:



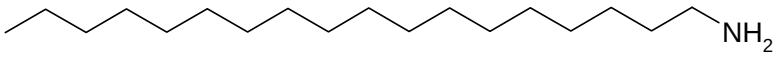
Molecular weight: 267.5 g/mol
Synonyms: Oleylamine
cis-9-Octadecenylamine

CA Index Name: 9-Octadecen-1-amine, (Z)-

Octadecylamine

CAS Number: 124-30-1
EINECS Number: 204-695-3
IUPAC Name: 1-Octadecanamine
Molecular formula: $C_{18}H_{39}N$

Structural formula:



Molecular weight: 269.5 g/mol
Synonyms: Octadecylamine
Stearylamine
1-Aminooctadecane

CA-Index name: 1-Octadecanamine

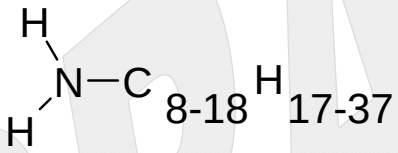
Amines, hydrogenated tallow alkyl-

CAS Number: 61788-45-2
EINECS Number: 262-976-6
IUPAC Name: hydrogenated tallow alkyl amine
Molecular formula: unspecified
Molecular weight: 263 g/mol as average
Synonyms: N-hydrogenated tallow alkyl amine

CAS Index name: Amines, hydrogenated tallow alkyl-

Amines, coco alkyl-

CAS Number: 61788-46-3
EINECS Number: 262-977-1
IUPAC Name: cocos alkyl amine
Molecular formula: unspecified
Structural formula:



Molecular weight: 194 - 204 g/mol (undestilled)
Synonyms: Cocoamine
Coconut oil alkyl amine

CAS index name: Amines, coco alkyl-

1.2 PURITY/IMPURITIES, ADDITIVES

Amines, tallow alkyl

The tallow alkyl amines are to 99 % primary straight chain alkyl amines with the following distribution (a single prime indicates one double bond, a double prime indicates two double bonds):

C_{12}	1 %
C_{14}	3 %
$C_{14'}$	1 %
C_{15}	0.5 %
C_{16}	29 %
$C_{16'}$	3 %
C_{17}	1 %
C_{18}	23 %
$C_{18'}$	37 %
$C_{18''}$	1.5 %

Possible impurities in the technical product are: fatty acid nitriles, secondary fatty acid amides and hydrocarbons.

Additives: none

Commercial tallow alkyl amines have the following distribution:

C_{12}	about 2 %
C_{14}	about 4 %
C_{16}	about 31 %
C_{18}	about 65 %,

where 40 –50 % are unsaturated.

(Z)-Octadec-9-enylamine

The chain length distribution of commercial Oleylamine is:

C_{12}	1 %
C_{14}	2 - 4 %
C_{16} and $C_{16'}$	12 - 14 %
C_{18}, $C_{18'}$ and $C_{18''}$	> 80 % (C_{18}: 8 %, $C_{18'cis}$: 46 %, $C_{18'trans}$: 21 %, $C_{18''}$: 5 %)
C_{20}	1 %

The content of primary amines is > 98 %.

Possible impurities are:

fatty acid amides, fatty acid nitriles, secondary fatty amines and paraffines.

Additives: none

Octadecylamine

Purity: > 90 % w/w

The content of primary amines is > 99 %.

Impurities: 5 % tetradecylamine
0.4 % hexadecylamine

Additives: none

Amines, hydrogenated tallow alkyl-

The typical chain length distribution is (a single prime indicates one double bond):

C_{12}	1 %	
C_{14}	4 %	
$C_{14'}$	0.5 %	
C_{15}	0.5 %	
C_{16}	30 %	
$C_{16'}$	0.5 %	
C_{17}	1.5 %	
C_{18}	60 %	
$C_{18'}$	2 %	(Ullmann, 1985)

The content of primary amines is > 99 %.

Possible impurities:

small amounts of non reacted tallow nitriles, secondary and tertiary fatty amines, bis(hydrogenated tallow alkyl amines), water.

Additives: none

Amines, coco alkyl-

The typical chain length distribution is:

C_6	0.5 %	
C_8	8 %	
C_{10}	7 %	
C_{12}	50 %	
C_{14}	18 %	
C_{16}	8 %	
C_{18}	1.5 %	
$C_{18'}$	6 %	
$C_{18''}$	1 %	(Ullmann, 1985)

The content of primary amines is > 99 %.

Possible impuritites:

small amounts of non reacted tallow nitriles, secondary and tertiary fatty amines, water.

1.3 PHYSICO-CHEMICAL PROPERTIES

Tallow alkyl amine is a white waxy solid with a pungent amine-like smell at 20 °C.

(Z)-Octadec-9-enylamine is a light yellow paste-like liquid with amine-like odour at 20 °C.

1-Octadecanamine is a colourless solid with amine-like odour at 20 °C.

Hydrogenated tallow alkyl amine is a white wax with amine-like odour at 20 °C.

Cocos alkyl amine is a slightly yellow liquid with amine-like odour at 20 °C.

Data on the physical and chemical properties of the five substances are given in table 1.1.

Table 1.1 Summary of physico-chemical properties

Substance	Property	Value	Reference
	Physical State		
Amines, tallow alkyl		white waxy solid at 20 °C	
(Z)-Octadec-9-enylamine		liquid at 20 °C	
Octadecylamine		colourless solid	
Amines, hydrogenated tallow alkyl		white solid	
Amines, coco alkyl		Slightly yellow liquid	
	Melting point		
Amines, tallow alkyl		32 – 40 °C [1)]	Ullmann, 1985
(Z)-Octadec-9-enylamine		15 – 30 °C [2)]	Clariant, 2000
Octadecylamine		49 – 52 °C	Richardson et al., 1994
Amines, hydrogenated tallow alkyl		48-56 °C [1)]	Ullmann, 1985
Amines, coco alkyl		12 – 17 °C	Ullmann, 1985
	Boiling point		
Amines, tallow alkyl		200 – 230 °C at 36 hPa [1)]	Ullmann, 1985
(Z)-Octadec-9-enylamine		128 – 174 °C at 4 hPa 345.55 °C (calculated) 353 – 355 °C at 1013 Pa [3)]	Kao, 2001 Hoechst, 1996c Siemens Axiva, 2002b
Octadecylamine		348.8 °C at 1013 hPa [4)]	Ralston et al., 1959
Amines, hydrogenated tallow alkyl		348 - 351 °C at 1013 hPa [5)]	Siemens Axiva, 2003
Amines, coco alkyl		130 - 227 °C at 133 hPa	Ullmann, 1985

	Relative density		
Amines, tallow alkyl		0.79 g/cm^3 at 60 °C [6)]	Hoechst, 1980a
(Z)-Octadec-9-enylamine		0.8 g/cm^3 at 60 °C [6)]	Clariant, 2000
Octadecylamine		0.8618 at 20 °C [1)]	Richardson et al., 1994
Amines, hydrogenated tallow alkyl		0.94 at 23.2 °C [7)]	Siemens Axiva, 2003
Amines, coco alkyl		0.8 g/cm^3 at 25 °C	Akzo, 2000
	Vapour pressure		
Amines, tallow alkyl		not conducted [8)]	
(Z)-Octadec-9-enylamine		0.005 hPa at 20 °C (calculated)	Hoechst, 1996c
Octadecylamine		4.38 · 10^{-5} mm Hg at 25 °C (≡ 0.006 Pa at 25 °C) (calc.) [9)]	Clariant, 2001a
Amines, hydrogenated tallow alkyl		not conducted [8)]	
Amines, coco alkyl		not conducted [8)]	
	Water solubility		
Amines, tallow alkyl		0.12 mg/l at 25 °C (calc.) [10)]	Clariant, 1998
(Z)-Octadec-9-enylamine		insoluble at 25 °C [11)] 0.07639 at 25 °C (calculated)	CECA, 2000 Hoechst, 1996c
Octadecylamine		insoluble at 25 °C [11)] 0.04875 mg/l at 25 °C (calc.) [9)]	Kao, 2000 Clariant, 2001a
Amines, hydrogenated tallow alkyl		insoluble at 25 °C [11)]	Clariant, 2001b
Amines, coco alkyl		insoluble at 25 °C [11)]	Clariant, 2001c
	Partition coefficient n-octanol/water (log value)		
Amines, tallow alkyl		log Pow 7.1 at 20 °C (calculated) [10)]	APAG, 2003a
(Z)-Octadec-9-enylamine		log Pow 7.5 at 20 °C (calculated)	Hoechst, 1996c
Octadecylamine		log Pow 7.71 (calc.) [9)]	Clariant, 2001a
Amines, hydrogenated tallow alkyl		7.3 (calc.) [12)]	Clariant, 2001a
Amines, coco alkyl		not conducted [13)]	
	Flash point		
Amines, tallow alkyl		159 °C [14)]	Hoechst, 1997
(Z)-Octadec-9-enylamine		156 °C [15)]	Siemens Axiva, 2002b
Octadecylamine		not conducted (solid)	
Amines, hydrogenated tallow alkyl		not conducted (solid)	
Amines, coco alkyl		> 100 °C [16)]	Akzo, 2000

	Autoflammability		
Amines, tallow alkyl		no selfignition up to the melting range	Chemsafe, 2001
(Z)-Octadec-9-enylamine		265 °C [17)]	Siemens Axiva, 2002a
Octadecylamine		no selfignition up to the melting range	Chemsafe, 2001
Amines, hydrogenated tallow alkyl		no selfignition up to the melting range	Chemsafe, 2001
Amines, coco alkyl		255 °C [17)]	Siemens Axiva, 2002a
	Flammability		
Amines, tallow alkyl		non flammable according to A.10 [18)]	Clariant, 1999
(Z)-Octadec-9-enylamine		non flammable according to A.9 [19)]	BAM, 2001
Octadecylamine		non flammable according to A.10 [19)]	Siemens Axiva, 2003
Amines, hydrogenated tallow alkyl		non flammable according to A.10 non flammable according to A.12 and A.13 for structural reasons	Siemens Axiva, 2003
Amines, coco alkyl		non flammable according to A.9 [19)]	BAM, 2001
	Explosive properties		
Amines, tallow alkyl		not explosive (structural reasons)	BAM, 2001
(Z)-Octadec-9-enylamine		not explosive (structural reasons)	BAM, 2001
Octadecylamine		not explosive (structural reasons)	BAM, 2001
Amines, hydrogenated tallow alkyl		not explosive (structural reasons)	BAM, 2001
Amines, coco alkyl		not explosive (structural reasons)	BAM, 2001
	Oxidizing properties		
Amines, tallow alkyl		no oxidising properties (structural reasons)	BAM, 2001
(Z)-Octadec-9-enylamine		no oxidising properties (structural reasons)	BAM, 2001
Octadecylamine		no oxidising properties (structural reasons)	BAM, 2001
Amines, hydrogenated tallow alkyl		no oxidising properties (structural reasons)	BAM, 2001
Amines, coco alkyl		non oxidizing properties (structural reasons)	BAM, 2001

	Surface tension		
Amines, tallow alkyl		not conducted (water solubility < 1 mg/l)	
(Z)-Octadec-9-enylamine		not conducted (water solubility < 1 mg/l)	
Octadecylamine		not conducted (water solubility < 1 mg/l)	
Amines, hydrogenated tallow alkyl		not conducted (water solubility < 1 mg/l)	
Amines, coco alkyl		not conducted (water solubility < 1 mg/l)	
	Dissociation constant (pKa) at 25 °C		
Amines, tallow alkyl		not conducted [20)]	
(Z)-Octadec-9-enylamine		not conducted [20)]	
Octadecylamine	10.60		Hoerr et al, 1943
Amines, hydrogenated tallow alkyl		not conducted [20)]	
Amines, coco alkyl		not conducted [20)]	

[1)] literature value; no information available about the method

[2)] pourpoint

[3)] DSC; the boiling range of 353 – 355 °C was used for the risk assessment because a valid test report was available

[4)] distillation method

[5)] DSC

[6)] DIN 51757

[7)] air comparison pycnometer

[8)] the vapour pressure of primary amines is very low and therefore not relevant with respect to the environmental risk assessment

[9)] calculated values using the program EPIWIN

[10)] weighted average from single compounds calculated with SRC 1995

[11)] due to the characteristic sorption and the potential of forming aggregates the water solubility is expected to be very low

[12)] weighted average of the single compounds of hydrogenated tallow alkyl amine

[13)] the sorption characteristics and the potential to form aggregates prevent the measurement of the Kow for primary amines

[14)] the flash point refers on the molten substance

[15)] determination of the flash point according to Pensky-Martens apparatus EN 22719

[16)] Pensky-Martens, closed cup (ISO 2719)

[17)] the auto-flammability behaviour was determined using the apparatus described in IEC 79-4 (see also DIN 51794)

[18)] the tests according to A.12 and A.13 were not conducted. Due to the properties and the handling of the substance it has not to be assumed that the substance does not form flammable gases on contact with water and does not have pyrophoric properties.

[19)] tests according to A.12 and A.13 not conducted (for structural reasons)

[20)] pKa-values are known for C_8(10.65), C_{10} (10.64), C_{12} (10.63), C_{14} (C10.62) and C_{16} (10.61). They are nearly independent from the chain length.

1.4 CLASSIFICATION

1.4.1 Current classification

none

1.4.2 Proposed classification

Environment

According to the data presented below and the criteria of directive 67/548/EEC the substances in the category "primary alkyl amines" need to be classified for possible effects on the environment as:

N, R 50/R53	Very toxic to aquatic organisms. May cause long-term adverse effects in the aquatic environment.

The classification "R 50" is justified by the results of the short-term toxicity tests using fish, daphniae and algae. The LC/EC_{50} values relevant for classification and labelling were mainly lower than 0.1 mg/l (see section 3.2.1.1 and table 3.2.8). Using river water as test medium, the effective concentrations increase due to reduced bioavailability probably by adsorption of the test substances. However, most of the LC/EC_{50} values determined in river water were also < 0.1 mg/l demonstrating the high toxicity of the primary alky amines for aquatic organisms and supporting clearly the "R50" classification.

In most of the tests on ready biodegradability the pass level criteria were reached failing the 10-day window criterion. Due to the high adsorption of the primary alkyl amines it is assumed that the test substances were only partially accessible for degradation in the tests. Additional tests indicate a comparability of the rates during the exponential part of the degradation curve with readily biodegradable substances. Taking the experimental results together, primary alkyl amines are classified as readily degradable, fulfilling the 10-days window.

However, the available information indicate for a high bioaccumulation potential. The calculated $LogP_{OW}$ is approximately 7, and using a QSAR approach the BCF is estimated to be 158 l/kg. (Meylan et al. 1999). In addition, a preliminary study on bioconcentration using fish and hexadecylamine as test substance was performed. Although the test was performed as research project without GLP and the conditions were not standard, according to this study the BCF for hexadecylamine might range between 200 and 2,400 depending on the parameters assumed to calculate the ratio. Since hexadecylamine is one of the main components of the primary alkyl amines considered in this report, a classification for the group basing on this test is justified: Long term adverse effects in the aquatic environment cannot be excluded (R50/R53).

Human Health

According to the data presented below and the criteria of directive 67/548/EEC the substances in the category "primary alkyl amines" have to be classified with respect to human health as:

Amines, tallow alkyl

Xn; R22	Harmful if swallowed
C	Corrosive
R35	Causes severe burns
Xn; R48/22	Harmful: danger of serious damage to health by prolonged exposure if swallowed

(Z)-Octadec-9-enylamine

Xn; R22	Harmful if swallowed
C	Corrosive
R34	Causes burns
Xn; R48/22	Harmful: danger of serious damage to health by prolonged exposure if swallowed

Octadecylamine

Xi; R38	irritating to skin
Xi; R 41	risk of serious damage to the eyes
Xn; R48/22	Harmful: danger of serious damage to health by prolonged exposure if swallowed

Amines, hydrogenated tallow alkyl

Xi, R38	irritating to skin
Xi; R41	risk of serious damage to the eyes
Xn; R48/22	Harmful: danger of serious damage to health by prolonged exposure if swallowed

Amines, coco alkyl

Xn; R22	Harmful if swallowed
C; R35	Corrosive:Causes severe burns
Xi, R37	Irritating to respiratory system
Xn; R48/22	Harmful: danger of serious damage to health by prolonged exposure if swallowed

2 GENERAL INFORMATION ON EXPOSURE

2.1 PRODUCTION

2.1.1 Production processes

Starting materials in the manufacture of long-chain, primary alkyl amines are natural fats and oils, or synthetic products of the petrochemical industry. Intermediates are alkyl nitriles, which are formed from carboxylic acids and ammonia over dehydrating catalysts (Al_2O_3, ZnO, or salts of Mn or Co) in liquid-phase reactors or liquid- and vapor-phase reactors at 280-360°C. The nitriles are hydrogenated at a temperature of 80-180°C and a pressure of 1 - >10 MPa in the presence of nickel or cobalt catalysts.

$$R - CN + 2\ H_2 \rightarrow R - CH_2 - NH_2$$

The formation of secondary and tertiary amines as by-products is generally inhibited by addition of ammonia. Conversion is usually carried out in autoclaves operated in batch process, although there are also plants which operate in continuous process. Depending on the use, alkyl amines are used as such or purified by distillation under reduced pressure (BUA, 1994; Heilen et al., 1985).

2.1.2 Production, Import and Export

According to the information supplied by industry, primary alkyl amines are produced and/or imported by the following companies in the European Union (State 1999/2000, EU 15). One of the production sites listed in table 2.1 has been closed in the meanwhile. A further site was an importer without own production, the import has been stopped in the meanwhile:

Tab. 2.1: Production and import of primary alkyl amines (1999)

Company	Coco	Tallow	Hydr. Tall.	Octadecyl	Octadecenyl
Akzo Nobel Chemicals S.A., Ghlin (Belgium)	+	+	+	+	+
Akzo Nobel Chemicals Ltd., Littleborough (UK)	+	+	+		+
Akzo Nobel Surface Chemistry AB, Stockviksverken (Sweden)	+	+	+		+
CECA S.A., Feuchy les Arras (France)	+	+	+		+
Clariant GmbH, Gendorf (Germany)	+	+	+	+	+
Ecogreen Oleochemicals, Rodleben (Germany)	+	+	+		+
Infineum UK Ltd., Oxfordshire (UK)					+
Kao Corporation S.A., Barbera del Valles (Spain)	+	+	+	+	+

In the following table the market data received from producers and importes are summarized. The European consumption volumes (EU 15) are calculated from the figures on production, import and export:

Tab. 2.2: Production volume, imports and exports for the period 1999/2000 [t/a] (APAG, 2003b)

	Coco	Tallow	Hydr. Tall.	Octadecyl	Octadecenyl
Production	5760	13339	10620	474	4415
Import	0	394	164	0	12
Export	588	1614	3229	12	405
European Consumption	5172	12119	7555	462	4022

2.2 USES

2.2.1 Introduction

Table 2.3 details the uses of primary alkyl amines within the EU. The use pattern was generated based on manufacturer's data reflecting the European market.

Tab. 2.3: Uses of primary alkyl amines [t/a] (APAG, 2003b)

	Coco	Tallow	Hydr. Tall.	Octadecyl	Octadecenyl
Intermediate (IC 3 / UC 33)	5020 (97%)	11901 (98%)	2577 (34%)	319 (69%)	3385 (84%)
Fertilizers, anticaking (IC 1 / UC 7)		13 (0.1%)	4178 (55%)		
Metal ind., floatation agent (IC 8 / UC 23) *	87 (1.7%)	193 (1.6%)	664 (8.8%)		65 (1.6%)
Metal proc. ind., lubricants		13 (0.1%)	72 (1%)		306 (8%)
Fuel additive				78 (17%)	111 (3%)
Formulations (metal, corrosion inhibitors)	43 (0.8%)				8 (0.2%)
Formulations (textiles)			64 (0.8%)		
Paints, antistatic agent	22 (0.4%)				147 (3.6%)
Rubber additive				65 (14%)	
Total EU consumption	**5172**	**12119**	**7555**	**462**	**4022**

* According to APAG (2005b), about 300 t/a used in floatation agents are exported outside the EU. Considering this amount, the total European consumption of all 5 amines amounts to 29,030 t/a.

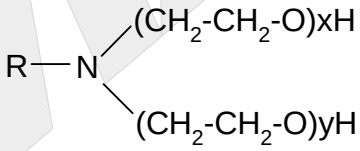
From the table it can be observed that major amounts of the amines are used as intermediate in chemical industry. A further breakdown of this use was generated focusing on major customers, while smaller outlets were omitted. Therefore, the amounts are not quite identical with those referred in table 2.3, but the relative importance of the most important daughter products is shown.

Tab. 2.4: Daughter products from processing of primary alkyl amines [t/a] (APAG, 2001)

	Coco	Tallow	Hydr. Tall.	Octadecyl	Octadecenyl
Ethoxylates	2995 t	5396 t	957 t		1864 t
Amine derivatives	459 t	4491 t	470 t		955 t
Sulphosuccinamate		1216 t			
Amides	32 t		27 t	110 t	85 t
Other intermediates	314 t		104 t	208 t	330 t
Total	**3800 t**	**11103 t**	**1558 t**	**318 t**	**3234 t**

Amino ethoxylates:

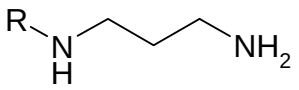
The most important products manufactured from primary alkyl amines are amino ethoxylates. Ethoxylation is carried out through the addition of ethylene oxide to the alkyl amine. At a ratio of 1 mol alkyl amine to 2 mol ethylene oxide, N,N-bis(2-hydroxyethyl)-alkyl amines (2,2'-(alkyl imino)-diethanoles) are formed, while with a ratio of more than 2 mol ethylene oxide per mol alkyl amine, N,N-bis(polyoxyethyl)-alkyl amines are yielded with the following general formula (x,y = number of attached molecules of ethylene oxide):

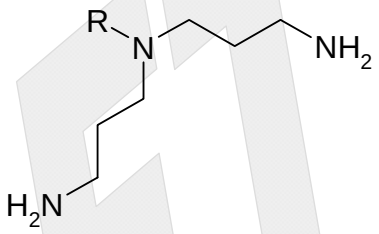


Alkyl amino ethoxylates are surface-active substances, which can be combined with other surfactants, are used as they are or in the form of their salts, as key components or as additional ingredients in a wide range of chemotechnical products. For example, they can be used as an additive in viscose, plastics and mineral oils, as auxiliary agents in the dyeing and textile industries, as wetting agents in pesticide and plant protection products, and as emulsifiers and binding agents (BUA, 1994; Hoechst AG, 1980b, 1989a).

Amine derivatives:

At a molar ratio of 1:1, alkyl amines react with acrylonitrile to form N-(2-cyanoethyl)-alkyl amines, from which N-alkyl-1,3-propyl diamines are formed through catalytic hydrogenation. At a ratio of 1 mol alkyl amine to 2 mol acrylonitrile, N,N-bis(2-cyanoethyl)-alkyl amines are formed, the hydrogenation of which yields N-alkyl-N-(3-aminopropyl)-1,3-propyl diamines (BUA, 1994).





Amine derivatives serve as intermediates for further chemical conversion to disinfectants and other products, for example, to anticarious agents, or are used as they are, mainly in the preparation of diaryl yellow pigments, which are used particularly for intaglio printing of illustrations in short-lived printed matter such as catalogues and illustrated magazines, but also, although to a lesser extent, in colouring plastics. Another area of amine derivatives use is as a lubricant in water-based, sprayable preparations for the hinge-plate chains of conveying plant, for example, in a bottle-filling plant, and as a cationic emulsifier and auxiliary agent in the production of universal, rapidly breaking, acidic bitumen emulsions with good binding properties towards all kinds of filling materials, even in the presence of moisture, for use in road building (Hoechst AG, 1980b; BUA, 1994).

Sulphosuccinamates and other amides:

Primary alkyl amines react with carboxylic acids or their derivatives to amides substituted with long-chained alkyl groups. The following groups with amide structure are of importance:

Sulphosuccinamates (sulphosuccinamic acids) on the basis of tallow alkyl amine are used mainly as emulsifiers in latex emulsions for carpet backings, and to a lesser extent as a component in washing agents for wool. Condensation products with urea and formaldehyde are applied as water-repelling softener for leather and textiles. Alkyl isocyanate is, for example, used as a catalyst in the manufacture of polyamides. Ethylene diamino tetraacetic monoalkyl amide is a complex-forming detergent (BUA, 1994).

Uses without chemical conversion:

To a minor extent, alkyl amines or their salts are applied directly without chemical conversion. Because of the low water solubility, alkyl amines are only exceptionally used as free bases. More frequently they are used as salts which belong to the group of cationic surfactants. The majority of the uses is based on the strong adsorption onto the surface of many different materials like proteins, cellulose, synthetic fabrics, polymers, silicates,

pigments, metals or potassium salts (Hoechst AG, 1980b). The most important applications are:

Floatation:

Floatation involves the separation of a certain mineral from a mineral mix, whereby suspended mineral particles adhering to air bubbles are carried to the surface of the slurry, where they are skimmed off in the laden froth. Selective adhesion to the air bubbles is achieved by hydrophobing agents like alkyl amines and their salts (chloride and acetate), which are suitable in the floatation of halogenides (KCl and NaCl), silicates and zinc ores. In Germany, production of potassium salts for the use in fertilizers is of high importance in this area (BUA, 1994; Hoechst AG, 1978a).

Fertilizers:

Alkyl amines, mainly the potassium salts are used as soil fertilizers in agriculture. In addition to that, acetate and stearyl salts of hydrogenated tallow amine are used by the potash and fertilizer industry as an anticaking agent. On account to their water-repelling properties, they prevent caking during storage and transport, maintaining flowability of the potash or fertilizer in crystal or granular form (BUA, 1994; Hoechst AG, 1978b).

Other direct uses:

In table 2.3 other direct uses of alkyl amines are described (e.g. fuel additive, paints, formulations for textiles…). These uses are regarded to be of minor importance based on the consumption volumes. No relevant environmental releases are expected from these areas and no emission scenarios are calculated for these uses.

2.3 LEGISLATIVE CONTROLS

[click here to insert text]

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

3.1.1 General discussion

3.1.2 Environmental releases

3.1.2.1 Release from production

Primary alkyl amines are manufactured through catalytic hydrogenation of the corresponding fatty nitriles in a batch process carried out in closed systems. Although the catalytic hydrogenation of fatty nitriles to their corresponding fatty amines does not involve water, water is used to recover and reprocess the ammonia used to prevent the formation of secondary and tertiary fatty amines. Following removal of the ammonia by distillation, this water is reused for the same purpose. The aqueous residue is replaced with fresh water and fed as wastewater into a central fat separator. The aqueous phase of the fat separator is fed, after mixing with waste water from other activities, into a biological wastewater treatment plant.

The exposure scenarios for the 6 European production sites are presented in section 3.1.4.1.1. Effluents of all production sites are discharged into rivers, therefore there is no exposure of the marine environment. The total releases after waste water treatment into the hydrosphere are calculated to 1.44 kg/a. As large parts of the primary alkyl amines are processed at the manufacturing sites, releases from processing activities are partially covered.

Releases into the atmosphere are not relevant.

3.1.2.2 Release from formulation

Primary alkyl amines (4178 t/a hydrogenated tallow amine, 13 t/a tallow amine) are used as anticaking agent for inorganic fertilizers. During this formulation step releases into waste water are expected. An exposure scenario is included in section 3.1.4.1.2.

3.1.2.3 Release from industrial/professional use

Processing to ethoxylates:

In the ethoxylation process the primary fatty amines are reacted with ethylene oxide (EO) in closed systems under pressure at temperatures generally above 100°C. In the reaction the fatty amines are almost completely converted into fatty amine ethoxylates leaving only small amounts of primary amine in the final product. The higher the EO number the lower the degree of free fatty amine in the final product.

The reaction gives no wastewater. A minor part of the small amount of primary fatty amines present in the final products may enter wastewater as a result of cleaning of the reactors. Reactors are commonly cleaned only once a year for maintenance purposes. The reactors are thus not cleaned between different batches of amine independent from the type of amine processed. The wastewater is incinerated or treated in a biological wastewater treatment plant.

Exposure scenarios for ethoxylation are included in section 3.1.4.1.3.

Processing to amine derivatives:

Amine derivatives are produced only by the alkyl amine manufacturers. Thus the exposure from these activities is covered by the scenarios for production.

Processing to amides:

Coco alkyl amine, hydrogenated tallow amine, octadecylamine and oleylamine are processed to amides each at 5 sites, the production figures are referred in table 2.4. According to the producers data, there are no releases into the environment (APAG, 2005d).

Processing to sulfosuccinamates:

Tallow amine (totally 1216 t/a) is processed to the sulphosuccinamate at 4 sites. The exposure calculation is included in section 3.1.4.1.3.

Processing to other products:

In Europe, totally 7 sites processed primary alkyl amines to further products. From these 7 sites, 1 did not use the amines since 1999, 1 site is identical with a processor (i.e. releases are covered by the production scenario), 3 further sites have no releases as wastes are incinerated. Exposure scenarios for the remaining 2 sites are included in section 3.1.4.1.3.

Floatation:

During the use as floatation agents, alkyl amines are largely adsorbed onto the surface of mineral crystals or ore particles, due to the strong adsorption. Amines adsorbed onto silicate or zinc or are expected to be destroyed during further processing of the minerals. Potassium salts are mainly used as fertilizers, and the adsorbed amines are expected to be released into agricultural soils.

Tab. 3.1.1: Total European amount of alkyl amines used as floatation agents (EU 15, APAG, 2003b)

Compartment	Coco	Tallow	Hydr. Tall.	Octadecenyl	Total
Agric. soil	87 t/a	193 t/a	664 t/a	65 t/a	1009 t/a

According to APAG (2005b) 28% of the amines used in this area are applied in fertilizers. Therefore, releases of 283 t/a onto agricultural soils are considered for the regional exposure scenario.

For the local exposure assessment, data are available for 8 European sites with a total primary alkyl amines use of 634 t/a. At some sites, no releases into the environment occur, as waste water is incinerated or pumped back into the mine. For the other sites, release scenarios are included in section 3.1.4.1.3. From floatation, the total European releases into surface waters were estimated to about 123 kg/a.

Fertilizers:

In Europe, yearly 13 t tallow amine and 4178 t hydrogenated tallow amine are used as anticaking agents in fertilizers, during their application the total amounts reach agricultural soils.

The application rate of fertilizers varies depending on crop and soil etc. and is normally driven by the nitrogen demand. Depending on the nitrogen content of the granules, the total amount of fertilizer varies from 300 – 700 kg/ha, which is normally divided over two or three times of application. The amount of coating agent varies per type of fertilizer, generally 0.8 g/kg coating agent with an amine content between 3 and 20% are applied. An inquiry among fertilizer customers resulted in the following worst case scenario (APAG, 2005a) which is used for the local exposure calculation:

Fertilizer used per year: 700 kg/ha = 0.07 kg/m^2

Coating agent on fertilizer: 1.1 g/kg

Amine in coating: 16.4%

Amine on farm land: 12.6 mg/m^2

According to the TGD (Appendix I, table A3.1) 5% of the fertilizers might be released into surface waters when applied on agricultural soils. Because of the free corridor between surface water and application area and the sorption behaviour of the amines, 100% release into agricultural soil is assumed to be realistic.

Tab. 3.1.2: Total European releases of alkyl amines from the use in fertilizers

Compartment	Tallow	Hydr. Tall.	Total
Agric. Soil	13 t/a	4178 t/a	4191 t/a

Releases due to residue contents in downstream derivatives

Downstream derivatives contain unreacted primary alkyl amines which may be released into the environment during their use. Residue contents of about 0.2 and 2.2% unreacted amine in >2EO and 2EO ethoxylates and about 7.5% in the diamines are reported, while amides and other intermediates contain much lower percentages (APAG, 2005b). In the report on hand, these releases are considered for the regional exposure scenario.

The European Oleochemicals & Allied Products Group (APAG) estimated the total European releases of the residue contents based on tonnages of downstream derivatives, content of unreacted amines and taking into account the type of use of the products. Based on this information the daily emission rates were calculated using release fractions for the different uses as given in the TGDs (APAG, 2005b).

Table 3.1.3: Releases via use of downstream derivatives [kg/d] (APAG, 2005b)

Substance	Rroduct	Release into surface water	Release into soil
Coco	Ethoxylates	7.25	2.81
	Diamines	2.60	0
	Intermediates	0	0
	Amides	0.12	0
Tallow	Ethoxylates	2.52	36.68
	Diamines	13.55	9.68
	Sulphosuccinamate	0.67	0
Hydr. Tallow	Ethoxylates	4.79	0
	Diamines	0	0
	Intermediates	1.15	0
	Amides	0.30	0
Octadecyl	Ethoxylates	0.69	0
	Intermediates	1.61	0
	Amides	0.06	0
Octadecenyl	Ethoxylates	7.13	3.79
	Diamines	8.37	2.21
	Diamines salts	0.36	0
	Intermediates	0	0
	Amides	0.05	0
Total		51.22	55.17

3.1.2.4 Release from private use

Primary alkyl amines or their preparations are not used in households, therefore releases from this life-cycle step are not expected.

3.1.2.5 Release from disposal

Releases during disposal are not known. Because of their strong adsorption and ready biodegradability, releases via landfills are not expected.

3.1.2.6 Summary of releases

Primary alkyl amines are released into the hydrosphere during production, processing, use as floatation agents and via the use of downstream derivatives containing unreacted primary alkyl amines. Scenarios for the local exposure are included in section 3.1.4.1. The total European releases into surface waters are estimated to 21.0 t/a (cf. 3.1.8).

The main releases into agricultural soils occur during the use of primary alkyl amines as anticaking agents in fertilizers. Further amounts due to the use as floatation agent and the use of downstream derivatives are also considered. In section 3.1.8, the total releases into soils in Europe are estimated to 4490 t/a.

3.1.2.7 Marine risk assessment

In the risk assessment on hand, the PECs for the aquatic compartment are calculated on the basis of either site-specific data or default values. From the first group, only one site was identified which is located at the sea (scenario Float2), and for this site both PEC and PNEC are calculated according to the TGD guidance on marine risk assessment.

The generic scenarios for the other sites are calculated for a freshwater environment, transport via rivers into the sea are not considered. It cannot be excluded that some sites are located at the sea. For a marine risk assessment, both PECs and PNEC have increased by a factor of 10 compared to the freshwater values, leading to the same PEC/PNEC ratio. Therefore, an extra marine risk assessment is not necessary.

3.1.3 Environmental fate

3.1.3.1 Degradation in the environment

3.1.3.1.1 Atmospheric degradation

In the atmosphere primary alkyl amines are likely to be degraded by reaction with hydroxyl radicals. Degradation rates for some components were calculated with the Atmospheric Oxidation Programme according to Atkinson (1987). With a concentration of 500,000 OH-radicals/cm^3, degradation half-lives of 7.9 h for 1-tetradecanamine, 7.1 h for 1-octadecan-amine, and 3.6 resp. 3.4 h for the cis- and trans-isomer of oleylamine are calculated. For the exposure calculations, a mean value for the saturated amines of 7.5 h is used. Because there are no important releases into the atmosphere and volatilisation is expected to be negligible, this removal mechanism is thought to be of low relevance.

3.1.3.1.2 Aquatic degradation (incl. sediment)

Releases of primary alkyl amines into the aquatic environment cannot be estimated by measurements in treatment plant effluents because the sensitivity of the available analytical methods is not sufficient. The substances can be measured in raw sewage where the concentrations are higher. Therefore, biodegradation resp. removal in treatment plants becomes to a crucial parameter for the exposure assessment. Many efforts were made to investigate the biodegradability.

Abiotic degradation

Primary alkyl amines are unlikely to undergo photolytical degradation in the hydrosphere because of the lack of a chromophor. Furthermore, hydrolytic degradation is not to be expected because of the absence of hydrolysable groups.

Screening tests on ready biodegradability

The biodegradbility of primary alkyl amines was tested in a number of screening tests on ready biodegradability following the OECD 301 guidelines. An overwiew of the results is presented in table 3.1.4.

Tab. 3.1.4: Screening tests on ready biodegradability

Amine	Test	Endpoint	TS Conc. [mg/l]	lag Phase	Degradation %		Result	Reference
					28 d	10-d wind.		
Coco	OECD 301 B	CO_2	13	4 d	60%	45%	readily degradable failing 10-d window	Hoechst AG (1996a)
	OECD 301 D	O_2	2	?	56%	?	not readily degradable	Akzo (1992a)
Dodecyl	OECD 301 C	O_2	100 30	7 d	0% (12d) ca. 65% (12d)	ca. 50%	readily degradable failing 10-d window	Yoshimura (1980)
Tallow alkyl	OECD 301 B	CO_2	13	2 d	61%	46%	readily degradable failing 10-d window	Hoechst AG (1996b)
	OECD 301 D	O_2	2	?	55%	?	not readily degradable	Akzo (1992b)
Hydrogenated tallow alkyl	OECD 301 D	O_2	2	?	75%	?	readily degradable, no information on 10-d window	Akzo (1992c)
Octadecyl	OECD 301 C	O_2	100	1	ca. 75% (12d)	ca. 60%	readily degradable	Yoshimura (1980)
	OECD 301 F	O_2	126.5	< 7	70%	< 50%	readily degradable failing 10-d window	Hoechst AG (1994)
Octadecenyl	OECD 301 B	CO_2	24.6	ca. 10 d	66%	52%	readily degradable failing 10-d window	CECA (1994)
	OECD 301 D	O_2	2	?	44%	?	readily degradable failing 10-d window	Akzo (1992d)

In the majority of the tests the pass level for ready biodegradability (60% CO_2 evolution or O_2 consumption) was reached within the test period (generally 28 days), but not within the 10-days window. There are only few exceptions: In one Closed Bottle Test with coco alkyl amine (Akzo 1992a) only 56% O_2 consumption after 20 days was observed, while in one MITI I Test with octadecyl amine (Yoshimura, 1980) the pass level was just reached within the 10-days window. Based on the results of all tests the primary alkyl amines could be classified as "readily degradable, but failing the 10-days window".

In many tests a similar degradation curve was obtained: after a lag phase of a few days, a rapid increase of degradation up to 50 or 60% of total mineralisation was observed, followed by a third phase when further degradation increased only slowly. The flattened slope of the degradation curve could be explained either by formation of a stable metabolite or by reduced bioavailability of the test substances. On respect to the metabolisation pathway (see below), formation of stable metabolites can be excluded, as full mineralization of the alkyl chains is expected. The flattened slope in the 3rd phase can only be explained by a reduced bioavailability of the test substances. Primary alkyl amines have a high tendency to adsorb onto glass surfaces, which was demonstrated by analytical measurements in the media of ecotoxicity tests (cf. 3.2.1) as well as during the test on distribution between water and sediment solids (cf. 3.1.3.2.4).

Considering the problem of bioavailability, degradation was further studied with tallow alkyl amine (Akzo Nobel, 1998). Slightly modified Closed Bottle Tests were conducted using different inocula: secondary activated sludge from a plant treating predominantly domestic wastewater, preadapted activated sludge from a CAS reactor, ditch, river and sea water sampled in the Netherlands. To increase bioavailability the medium was mixed by a stirring rod, and the oxygen consumption was continuously measured by an oxygen electrode. The concentration of tallow amine varied from 1.9 to 3.7 mg/l. For the exponential part of the degradation curve, the average specific growth rate was determined. The results are presented in table 3.1.5, together with similar experiments conducted with 2.5 or 10 mg coco alkyl amine/l (Akzo Nobel, 2002c).

Tab. 3.1.5: Growth rates for tallow alkyl amine (Akzo Nobel, 1998) and coco alkyl amine (Akzo Nobel, 2002c)

	Tallow alkyl amine		**Coco alkyl amine**	
	growth rate μ [d^{-1}]	lag period [h]	growth rate μ [d^{-1}]	lag period [h]
adapted sludge	5.57	21.5		
unadapted sludge	5.49	43.8		
river water	8.97	33	8.4	30
sea water	4.63	46	6.0	35
ditch water	3.67	25	6.5	70

Additional experiments were carried out with benzoate and LAS, which are often used as reference compounds in biodegradation tests. The specific growth rates were 11.41 d^{-1} for

benzoate and 2.33 d^{-1} for LAS (Akzo Nobel, 1998). The results of the modified Closed Bottle Tests indicate that the degradation rates for the primary alkyl amines are within the range found for readily degradable compounds. Furthermore it is obvious that the degradation rates obtained in tests with different inoculi are comparable. This is a strong indication that primary alkyl amines are degraded by microorganisms ubiquitously distributed in the environment, rather than by "specialists".

The relative biodegradability of alkylamines dependent on the chain length was examined by Yoshimura (1980). In an O_2 consumption test similar to MITI I, dispersions (100 mg/l) of a number of primary alkyl amines (C4, C8, C12, C14, C16 and C18) were examined. All amines except of dodecylamine (C12, the main component of coco alkyl amine) were degraded by more than 60% after 12 days. Dodecylamine showed no oxygen consumption at 100 mg/l, but at 30 mg/l about 65% were degraded. However, the results of this study should be taken with care. Primary alkyl amines are toxic to microorganisms, in respiration tests (cf. section 3.2.1.1.4) effects were observed at about 10 mg/l, so the high concentrations tested could possibly lead to non-reproducible results. Considering the similar molecular structures, large differences in degradability are not expected. This is supported by the screening tests (table 3.1.3) where no large differences in the degradation rates of the compounds is observed. The degradation pathway (see below) suggests that comparable rates are expected. Therefore, in this assessment similar degradation characteristics for all members of the category are assumed.

Metabolisation pathway

Yoshimura (1980) isolated a bacterium from a sludge degrading dodecylamine (the major component of coco amine), which was identified as *Pseudomonas putida*. This isolated strain could use dodecylamine as the sole carbon and nitrogen source for its growth. The author suggests that primary alkyl amines are biodegraded through either of 2 pathways: a) oxidative deamination to give the corresponding fatty acid and ammonia, or b) ω-oxidation on the terminal methyl group to give ω-amino fatty acid, followed by β-oxidation in either case.

Further studies about metabolisation were carried out with derivatives of primary alkyl amines. A common pathway was found for alkylbis(2-hydroxyethyl)amine, alkyltrimethyl-ammonium salts, alkyldimethylamine, and dialkylamines. In the initial step, the C_{alkyl}-N bond is attacked through a dehydrogenation reaction, forming alkanal as the breakdown product (van Ginkel, 1996). Ammonia was detected as a degradation product of dodecylamine (van Ginkel et al., 1995). The initial reaction step leads to the loss of the surfactant properties and thus to the loss of toxicity (van Ginkel, 1996). The decanals are further degraded through β-oxidation leading to total mineralisation. Unsatured alkyl chains are degraded through similar reactions (Ratledge, 1994).

Conclusions

Studies about the metabolic pathway reveal that the toxicity of primary alkyl amines is strongly reduced by the initial degradation step. Further degradation of the alkyl chains through β-oxidation leads to total mineralisation. As the molecular structure is similar for all members of the category, large differences in degradability are not expected. Tests in different

environmental media resulted in comparable rates, indicating that degrading microorganisms are ubiquitously distributed in the environment.

Generally, biodegradation of chemical substances is classified on the basis of mineralisation rates. It is known that primary alkyl amines are detoxified by the initial degradation step. The alkyl aldehydes being formed are part of the natural fat metabolism occurring in most organisms, therefore it can be assumed that they are much less toxic than the amines. In this case the rate of primary degradation is decisive for the classification, rather than mineralisation.

In the screening tests on ready biodegradability, the pass level criteria were shortly failed within the 10-days window, probably because of reduced bioavailability under the specific test conditions. Because of adsorption onto the glass surface, the test substances are only partially accessible to degradation. Further tests (Akzo Nobel, 1998) demonstrated that the rates during the exponential part of the degradation curve are comparable with readily degradable substances. In screening tests mineralisation is detected, the rates for primary degradation are always higher. Furthermore, in CAS-tests (cf. section 3.1.3.2.4) removal percentages were found which are characteristic for readily degradable substances. Considering all experimental results, primary alkyl amines can be classified as readily degradable, fulfilling the 10-days window.

In the following exposure calculations, degradation half-lives of 15 days for freshwater and 50 days for seawater according to the TGD are used. The rates determined in the Closed-Bottle Test with river-, ditch- or seawater are not accepted as simulation tests because the test substance concentrations (1.9 – 10 mg/l) are far above the levels expected in the environment.

Sediments

No studies about degradation of primary alkyl amines in sediments are available. Therefore, for the degradation rate the default value according to the TGD is estimated, assuming that no degradation takes place in the bound phase. As no tests under anaerobic conditions are available, it is assumed that the substances are not degraded in the anoxic sediment layer. The Kpsed was determined as 697 l/kg (section 3.1.3.2.1). The suggested half-life for a readily degradable substance with a Kpsed in the range >100 - ≤ 1000 l/kg is 300 days for the aerobic layer and 3000 days for bulk sediment.

3.1.3.1.3 Degradation in soil

There is only one test on biodegradation of tallow alkyl amine by soil microorganisms available (Akzo Nobel, 1996). The bacteria were pre-adapted to the amine and isolated from soil. In two parallel tests, elimination percentages of 27 and 34% were determined after 2 days, while after 4 weeks 58 and 84% were eliminated. The test demonstrates that soil microorganisms are capable to degrade the amines. Because of the unsufficient documentation and the probably unsuitable test system, the rates cannot be used for the exposure assessment.

Therefore, for the degradation rate the default value according to the TGD is estimated, assuming that no degradation takes place in the bound phase. The Kpsoil was determined as

697 l/kg (section 3.1.3.2.1). The suggested half-life for a readily degradable substance with a Kpsoil in the range >100 - ≤ 1000 l/kg is 300 days.

3.1.3.1.4 Summary of environmental degradation

Primary alkyl amines released into the atmosphere are likely to be degraded by reaction with hydroxyl radicals, with a half-life around 7.5 h. Because there are no important releases into the atmosphere and volatilisation is expected to be negligible, this removal mechanism is considered not to be relevant.

Primary alkyl amines are unlikely to undergo photolytical or hydrolytic degradation. Thus abiotic degradation in the environment is not expected.

Based on the available studies on biodegradation, the substances are estimated to be readily biodegradable, fulfilling the 10-days-window criterion. No simulation tests for degradation rates under environmental conditions are available, therefore for the aquatic environment the default values suggested by the TGD are used. For soil and sediments, the TGD approach was applied as well, taking into account that degradation in these compartments is inhibited by adsorption. In table 3.1.6, the degradation rates used for the preliminary exposure assessment are summarized.

Tab. 3.1.6: Degradation rates used in the exposure assessment:

	k	**DT50**
$kdeg_{freshwater}$	$4.62 \cdot 10^{-2}$ d^{-1}	15 d
$kdeg_{seawater}$	$1.39 \cdot 10^{-2}$ d^{-1}	50 d
$kbio_{sed}$ (aerobic)	$2.31 \cdot 10^{-3}$ d^{-1}	300 d
$kbio_{sed}$ (bulk)	$2.31 \cdot 10^{-4}$ d^{-1}	3000 d
$kbio_{soil}$	$2.31 \cdot 10^{-3}$ d^{-1}	300 d
$kdeg_{air}$	2.22 d^{-1}	7.5 h

3.1.3.2 Distribution

Primary alkyl amines are surface-active substances. They consist of a hydrocarbon part which on its own would be poorly soluble in water, and a hydrophilic amino group. The substances are strong organic bases with pKa values for C8 – C18 amines around 10.6. Under environmental conditions the main fraction will exist as alkyl ammonium ions. Salts with anorganic acids like sulfate, phosphate or silicate are poorly or not soluble and are not surface-active in water. Salts with organic acids like acetic acid, benzoic acid, benzoesulfinic acid and others are more soluble (Hoechst AG, 1980b).

3.1.3.2.1 Adsorption

Due to the surface-active properties, long-chained alkyl amines adsorb strongly onto the solid phase of soil and sediments. The substances can adsorb both onto the organic fraction and, dependent on the chemical composition, onto the surface of the mineral phase, where sodium and potassium ions can be exchanged against the alkyl ammonium ion (Hoechst AG, 1980b).

The determination of a Koc from log Kow is not opportune, because the common equations for Koc derivation are not valid for both ionic and surface active substances.

Slangen (2000) studied the adsorption behaviour of 1-^{14}C-labelled n-octadecylamine in a batch equilibrium experiment according OECD 106. Two soils collected in UK (Cranfield 164 soil, 21.8% clay, 6.6% organic matter, silt loam; Cranfield 266 soil, 50.2% clay, 2.6% organic matter, clay), one sediment collected in The Netherlands (18.7% clay, 4.1% organic matter, silt loam) and a sewage sludge (45.9% clay, 51.9% organic matter, silty clay) were used, encompassing a range of % clay and organic material. The test substance adsorbed partially onto the container walls which was considered for the determination of the adsorption coefficients. Adsorption kinetics was determined by measurements at different sampling times (up to 24 h), an equilibrium was reached after 3 hours. Desorption occurred to a lesser extent than adsorption: for Cranfield 164 soil 24.4% desorption after 47 hours and 24.2% after 166 hours were determined, while desorption for Cranfield 266 soil was 13.7% after 47 hours and 19.1% after 166 hours. The Freundlich adsorption isotherms were determined to:

Tab. 3.1.7: Freundlich adsorption isotherms determined by Slangen (2000):

Compartment	K_F^{Ads} ($\mu g^{1-1/n}(cm^3)^{1/n}g^{-1}$)	1/n
Soil: Cranfield 164 silt loam	3065	1.5384
Soil: Cranfield 266 clay	30053	1.8897
Sediment: Oostvaardersplassen silt loam	6433	1.4478
Sewage sludge: DB1 silty clay	821	1.0322

Apparently, the sorption onto Cranfield 266 soil is much higher than to Cranfield 164 despite of the higher organic matter content in Cranfield 164 soil. This can be explained that ionic interactions play a more important role than hydrophobic partitioning with organic matter. Alkyl ammonium ions can interact with the surface of mineral particles or with negative charges of humic substances. The influence of the chain length on the sorption behaviour is therefore expected to be low, and the experimental results obtained in the test with octadecyl amine can be taken as representative for the other products. As well, an influence of the double bond (in octadecenylamine) onto sorption is not expected.

The adsorption isotherms determined by Slangen (2000) are non-linear. The distribution constants for soils and sediment decrease dramatically as the concentrations decrease. The lowest aquatic equilibrium concentration in the experiment (5 µg/l) is more than one order of

magnitude higher than the calculated PEC values. For example, with the isotherm determined for the sediment and an aquatic concentration of 10 ng/l, a Kp value of 37 l/kg is calculated, which is far below the constants determined in the experiment (707 – 3140 l/kg). Apparently, extrapolation to low concentrations would lead to unrealistic results.

According to the Danish EPA (2004) a more reliable method of extrapolation is to use the data originating from the lowest measured concentrations and to assume that the coefficient remains constant at lower concentrations. At the 2 lowest concentrations, values of 707 and 687 l/kg were experimentally determined, the mean value (697 l/kg) is used for the exposure assessment.

The mean values for the two soils are 252 and 342 l/kg, respectively. Because there is no principal difference between soil and sediments on respect to the sorption properties, as a worst case approach the value for sediment is also used for soils and suspended particles.

For the adsorption onto sludge, values of 687 and 674 l/kg were determined for the 2 lowest concentrations. The mean value (680 l/kg) is used for the exposure calculation.

In table 3.1.8, the distribution constants used in this assessment are summarized:

Tab. 3.1.8: Distribution constants for primary alkyl amines

Kp_{soil}	697 $l \cdot kg^{-1}$	$K_{soil\text{-}water}$	1050 $m^3 \cdot m^{-3}$
Kp_{susp}	697 $l \cdot kg^{-1}$	$K_{susp\text{-}water}$	175 $m^3 \cdot m^{-3}$
Kp_{sed}	697 $l \cdot kg^{-1}$	$K_{sed\text{-}water}$	349 $m^3 \cdot m^{-3}$
Kp_{sludge}	680 $l \cdot kg^{-1}$		

With a Kp_{susp} of 697 l/kg and a concentration of 15 mg/l suspended matter in surface waters, the adsorbed fraction is calculated as 1.0%.

3.1.3.2.2 Precipitation

As primary alkyl amines are not released into air in relevant amounts, volatilisation from surface waters is not expected, and degradation half-lives in the atmosphere are relatively short (about 7.5 h), the compounds are not expected to occur in precipitation.

3.1.3.2.3 Volatilisation

Volatilisation of organic compounds from surface waters is generally estimated by the Henry's law constant. Calculated QSAR values based on the molecular structure of the amines at pH 7 are available, considering the degree of protonation. For the technical

mixtures, the weighted mean value and, in brackets, the range for the components is presented:

Tab. 3.1.9: Henry's law constants for protonated primary alkyl amines [Pa.m³/mol]

Coco	0.0030 (0.001-0.019)
Tallow	0.0091 (0.001-0.016)
Hydr. Tallow	0.0110 (0.001-0.016)
Octadecyl	0.016
Octadecenyl	0.0038

Considering the low values, volatilisation at environmental conditions is expected to be negligible. For the model calculations, a mean value of 0.01 Pa.m^3/mol is used.

3.1.3.2.4 Distribution in wastewater treatment plants

The removal of tallow amine in biological treatment plants was simulated in a continuous activated sludge (CAS) unit (Akzo Nobel, 1998). One unit was fed with domestic wastewater and 50 mg/l tallow amine, the control unit was fed with domestic wastewater only. The aeration vessel had a capacity of 0.36 l, the flow rate was 1.1 l/day (i.e. the hydraulic retention time was 8 hours). The sludge concentration varied between 1 and 4 g dw/l, the sludge retention time decreased from 18 days at the start to 7 days. The unit was maintained at room temperature. Removal of tallow amine was monitored by non purgeable organic carbon (NPOC) analyses. Tallow amine was readily adsorbed by the sludge particles which immediately led to 100% disappearance from wastewater. After one week removal of sludge was started, and after one further week removal was 99.8% (mean of 5 measurements), as shown by NPOC analyses. From day 19-21, effluent was collected and used for a growth inhibition test with the green alga *Selenastrum capricornutum*. Even in the undiluted effluent, no growth inhibition was observed.

Further CAS tests were conducted with coco alkyl amine (Akzo Nobel, 2002a,b). A CAS unit was fed with primary settled sewage collected from a municipal treatment plant and spiked with coco alkyl amine (57 mg/l), secondary activated sludge from the same plant was used as inoculum. Parallel to this experiment a further test was conducted using activated sludge and wastewater from an industrial treatment plant spiked with the same test substance concentration. The test conditions were largely identical: hydraulic retention time 6 hours, sludge concentration 1-3 g dw/l, sludge retention time 10 days, incubation temperature 20-22°C. The test units were pre-conditioned for one week after which sludge wasting was started. After introduction of the test substance at day 0, removal was measured as non purgeable organic carbon (NPOC). 14 measurements from day 3-23 resulted in mean removal percentages of 97±1% for the test with domestic wastewater and 98±2% for the test with industrial wastewater. During the last week, 5 GC/MS measurements of the components were conducted, the detection limit was 1 µg/l for the saturated C12, C14, C16, and C18 amine resp. 3 µg/l for the unsaturated oleylamine. Based on the measurements, removal percentages for coco amine of >99.98% (municipal) resp. 99.83% (industrial) were calculated.

Removal determined in CAS tests is equal to the sum of degradation and adsorption onto sludge. The results reveal that removal of the test substances is more effective than removal of their organic carbon. The algal toxicity determined in the effluent from tallow amine treatment (Akzo Nobel, 1998) reveals that the water soluble metabolites being formed during the process are much less toxic than the parent compounds. Considering the degradation mechanism (cf. 3.1.3.1.2) this result is expected, as primary degradation leads to a fission of the amino group which means the loss of the surfactant properties and thus to the loss of toxicity. Therefore, the environmental exposure assessment can be based on primary degradation, i.e. removal of the test substances.

A control calculation with the SIMPLETREAT model results in the following distribution: 72.9% degradation, 15.6% adsorption onto primary sludge, 0.7% adsorption onto surplus sludge, 10.8% are directed to water and 0% to air. For the calculation the following parameters were used: for primary settlement $Kp_{raw\ sewage}$ and sludge $Kp_{sludge\text{-}water}$ = 680 l/kg (cf. 3.1.3.2.1), and the TGD default value for ready biodegradability ($k = 1\ h^{-1}$). Comparison with the results of the CAS tests shows that removal of the test substance is strongly underestimated by the model calculation, indicating that the rate of primary degradation is far above the TDG default value.

According to the TGD results of simulation tests should only be used when the concentrations used in the tests are in the same order of magnitude as expected in reality. At sites with the highest release, the influent concentration is lower compared to the CAS tests, so the demand is only approximately fulfilled. Therefore, for the exposure assessment the lowest value, i.e. the removal percentage from the test with industrial sewage (99.83%) is used. The test was run with a hydraulic retention time of 6 hours which is lower than in most industrial treatment plants, so this approach appears to be a realistic worst case.

3.1.3.3 Accumulation and metabolism

Reliable experimental data about bioaccumulation of primary alkyl amines are not available at the moment. Because of the ionic and surface-active properties, the commonly used regression equations estimating BCF from log Kow are not suitable. Therefore, data from other compounds with structural similarity are considered alternatively for a preliminary estimation of the bioaccumulation potential of the primary alkyl amines.

Meylan et al. (1999) studied the relation between log Kow and experimentally determined fish BCF data for 84 ionic compounds, including carboxylic acids, sulfonic acids and salts, and 7 quarternary ammonium compounds. No linear correlation was found, instead of this the relation is predicted as follows: log BCF = 0.50 for log Kow <5, log BCF = 0.75 for log Kow 5.0-6.0, log BCF = 1.75 for log Kow 6.0-7.0, log BCF = 1.00 for log Kow 7.0-9.0, and log BCF = 0.50 for log Kow >9.0. Among the 84 compounds 5 ionics with long alkyl chains (≥ 11 carbons) were examined, with log Kow values between 1.2 and 4.78. Their log BCF values were generally close to 2, with a maximum value of 2.2.

As a provisional approach, the maximum log BCF value of 2.2 (i.e. BCF = 158 l/kg) found for ionic surfactants (Meylan et al., 1999) was used to estimate the bioaccumulation potential till the indicative BCF-study was submitted.

For tallow alkyl Amines and hydrogenated tallow alkyl-Amine the chain-length distribution is as follows:

	Amines, tallow alkyl	(Z)-Octadec-9-enylamine	Octadecylamine	Amines, hydrogenated tallow alkyl	Amines, coco alkyl
C_8 [%]					8
C_{10} [%]					7
C_{12} [%]	1 – 2	1		1	50
C_{14} [%]	4	2 – 4	5	4 – 5	18
C_{16} [%]	31 – 32	12 – 14	1	31	8
C_{18} [%]	62 – 65	> 80	> 90	62	8
C_{20} [%]		1			

Concerning the bioaccumulation potential of the primary amines under consideration, the C16 Primary amine was chosen by the APAG group as representative for the other components of the group to test possible bioaccumulation in fish. C16 and C18 are the dominating constituent of the primary amines. Taking into account the relevant properties (molecular weight, chain lenght, lipophilicity, adsorption, ...) the C 16 constituent might be useful as a representative for testing bioconcentration for practical reasons. In addition to that, C16 was chosen for solubility reasons and the availability of an analytical method in concentrations low enough to exclude toxic effects during exposure. Taking this arguments into account, a preliminary test for bioconcentration in fish was performed using hexadecylamine. However, the main intention of the test (Akzo, 2006) was the PBT assessment of (bis)hydrogenated tallow alkyl amine.

Considering the lower water-solubility of the C18-component, and the expected decrease of bioconcentration compared to the C16-component, this approach might be useful to represent a worst-case situation for the chain lenghts <C16. However, the bioconcentration of the components with chain lenghts >C 16 might be higher than the BCF determined with C16. This need to be considered for the risk assessment of the primary alkyl amines.

In the preliminary test on bioconcentration of primary alky amines, uptake and bioconcentration of 1-hexadecylamine in the common carp (*Cyprinus carpio*) were determined following an exposure for 11 months according OECD 305 with several modifications. As the test was performed within an internal research project of the company with several modifications, and without GLP, the results can only be used as indicative values. However, to calculate the BCF, the Rapporteur followed a wort-case approach. Hence, teh calculated data should be considered as upper limit of the bioaccumulation potential of the substance.

During the study using 1-Hexadecylamine as test substance, analytics were performed using GC/MS. The solution for the analytics was taken from the stock solution and the dilution water. Although the aquaria (80 l, glass) were sealed with silicon, due to adsorption problems during sampling and the extraction procedure only 50 – 80 % of the nominal concentration in the aquaria was found back.

The stock solution was prepared with 300 µg/l. During the uptake-phase of the study, the nominal concentration in the aquaria was 3 µg/l.

After 11 months of exposure, the concentration in fish was ranging from 1,500 to 3,600 µg/kg (whole fish) and from 8,000 to 15,000 µg/kg for mucous/scales. After removing mucous and scales and washing with chloroform the concentration was 650 to 850 µg/kg. Following the removing procedure with acid/methanol, the concentration was 280 to 600 µg/kg. Hence, it can be concluded that adsorption and binding to surfaces of the organisms was included in the measurements of the whole fish which might represent a worst case situation for the bioconcentration of the substance.

Considering these effects for worst case estimation, and using the nominal concentration in the aquaria as input, the BCF for the whole fish might reach 1,200. Using only the level found back in the dilution water in the aquaria, the BCF might increase to 2,400. Using the concentrations measured in the fish following the procedures to remove adsorbed substance, and 50 % of the nominal concentration in the dilution water of the aquaria as input values, the calculated BCF is between 400 and 567.

Taking these findings into account, the possible BCFs for hexadecylamine might range between 200 (nominal water concentration, concentration in fish after the removal procedure) and 2,400 (lower found back level in the aquaria, concentration in whole fish without treatment), depending on the assumptions used as input values for this calculation, and whether include the fraction possibly only adsorbed to the surface of the fish.

At least it can be concluded that the Meylan et al. (1999) QSAR-approach estimating a maximum BCF of 158 was not conservative enough to estimate the bioconcentration of hexadecylamine. In contradiction to earlier suggestions, it can be assumed that the approach is not reliable for primary amines.

Taking this findings together, accumulation of the primary amines with BCF-values > 100 can be assumed. According to several worst case estimations a BCF of 2,400 might be the upper level at least for the C16-components of the Primary alky amines.

Data on metabolism of primary alkyl amines in higher organisms are not available.

3.1.4 Aquatic compartment (incl. sediment)

As elaborated in section 3.3, the ecological effects of primary alkyl amines are strongly dependent on the test medium, differences are caused by adsorption onto suspended matter and complexation with organics. Therefore the relevant ecotoxicity values are derived from tests in river water. Consequently, for the aquatic risk assessment the PECbulk (which includes the fraction adsorbed onto suspended matter) is calculated as the PEC being adequate to the tests conducted in river water.

3.1.4.1 Calculation of predicted environmental concentrations (PEC_{local})

3.1.4.1.1 Calculation of PEC_{local} for production

Releases of primary alkyl amines via waste water cannot be estimated by measurements in treatment plant effluents because the sensitivity of the available analytical methods is not sufficient. Alternatively, the releases can be measured in raw sewage where the concentrations are higher. Consequently, the substances were monitored in the effluent of the fat separator. At the 6 European production sites, monitoring based on GC/MS measurements was conducted taking the most significant or sensitive peak in the homologue range as the indicator for the quantitative determination (APAG, 2002).

Octadecylamine is produced at 3 sites, but measured only at 1 site. The substance is produced in low amounts and infrequently, therefore the release data are limited. The PECs are expected to be of the same order as for the other substances.

Large parts of the primary alkyl amines are further processed at the producing sites. Therefore releases from production and processing activities can overlap in waste water. As the monitoring campaigns were conducted over prolonged periods, the data are representative for both production and processing activities.

Effluents of all production sites are discharged into rivers, therefore a marine exposure assessment for this life-cycle step is not necessary.

The calculated PECs and release amounts are summarized in table 3.1.8. The parameters are calcuated according to:

$Ceffluent = C_{FS} * flow_{FS} / flow_{stp} * Fstp_{water}$

$Clocal_{aqua\ bulk} = Ceffluent * flow_{stp} / (flow_{river} + flow_{stp})$

$PEClocal_{aqua\ bulk} = Clocal_{aqua\ bulk} + PECregional_{bulk}$

$PEClocal_{sed} = (K_{susp\text{-}water} / RHO_{susp}) * PEClocal_{aqua\ bulk} * 1000 / (1 + Kp_{susp} * SUSP_{water} * 10^{-6})$

with:

Ceffluent	concentration in treatment plant effluent
C_{FS}	measured concentration in fat separator (>/= 90 %ile)
$flow_{FS}$	waste water flow through fat separator
$flow_{stp}$	waste water flow through biological treatment plant
$Clocal_{aqua\ bulk}$	local concentration in surface water inclusive fraction adsorbed onto suspended matter
$Fstp_{water}$	fraction directed to effluent by stp (0.0017)
$flow_{river}$	flow of the receiving surface water upstreams from the inlet
$PECregional_{bulk}$	1.07 E-2 µg/l (cf. section 3.1.8)

$K_{susp\text{-}water}$	175 m^3/m^3 (cf. section 3.1.3.2.1)
RHO_{susp}	1,150 kg/m^3
Kp_{susp}	697 l/kg (cf. section 3.1.3.2.1)
$SUSP_{water}$	15 mg/l

The yearly releases cannot be calculated for the individual substances, because the average effluent concentrations and the duration of production are not available. Therefore, for all sites the average of the mass flow in effluents is taken as the basis, assuming a production period for all substances of 360 d/a.

Tab. 3.1.10: Exposure from production of primary alkyl amines

Site	Substance	Ceff [µg/l]	$Clocal_{aqua\ bulk}$ [µg/l]	$PEClocal_{aqua\ bulk}$ [µg/l]	Release [kg/a]	$PEClocal_{sed}$ [µg/kg ww]
A	Coco	6.8 E-02	3.1 E-06	1.1 E-02	0.004	1.62
	Tallow	4.5 E-03	2.0 E-07	1.1 E-02		1.62
	Hydr.Tallow	2.2 E-02	1.4 E-06	1.1 E-02		1.62
	C18=	1.0 E-02	5.6 E-07	1.1 E-02		1.62
B	Coco	5.8 E-03	3.2 E-03	1.4 E-02	0.028	2.11
	Tallow	1.6 E-03	8.9 E-04	1.2 E-02		1.75
	Hydr.Tallow	4.0 E-03	2.2 E-03	1.3 E-02		1.95
	C18	1.0 E-04	5.7 E-05	1.1 E-02		1.62
	C18=	1.0 E-03	5.8 E-04	1.1 E-02		1.70
C	Coco	3.2 E-01	8.8 E-03	2.0 E-02	0.310	2.95
	Tallow	6.8 E-02	1.9 E-03	1.3 E-02		1.90
	Hydr.Tallow	4.0 E-02	1.1 E-03	1.2 E-02		1.78
	C18=	4.3 E-02	1.2 E-03	1.2 E-02		1.79
D	Coco	3.4 E-03	1.5 E-03	1.2 E-02	0.027	1.84
	Tallow	1.3 E-03	5.5 E-04	1.1 E-02		1.70
	Hydr.Tallow	1.3 E-03	5.4 E-04	1.1 E-02		1.70
	C18=	6.3 E-04	2.7 E-04	1.1 E-02		1.66
E	Coco	7.7 E-01	4.4 E-03	1.5 E-02	1.03	2.28

Site	Substance	Ceff [µg/l]	$Clocal_{aqua\ bulk}$ [µg/l]	$PEClocal_{aqua\ bulk}$ [µg/l]	Release [kg/a]	$PEClocal_{sed}$ [µg/kg ww]
	Tallow	3.2 E-01	1.8 E-03	1.3 E-02		1.89
	Hydr.Tallow	1.3 E+01	7.5 E-02	8.5 E-02		12.89
	C18=	1.9 E-01	1.1 E-03	1.2 E-02		1.78
F	Coco	3.2 E-01	2.6 E-05	1.1 E-02	0.036	1.62
	Tallow	2.0 E-03	1.7 E-07	1.1 E-02		1.62
	Hydr.Tallow	4.1 E-03	3.3 E-07	1.1 E-02		1.62
	C18=	4.1 E-04	3.3 E-08	1.1 E-02		1.62

ww: wet weight

The total release of primary alkyl amines at the production sites, where releases from processing activities are partially included, amounts to 1.44 kg/a.

Although emission of the different primary alkyl amines take place at the same sites, the PECs for the single alkyl amines have not to be added, because production and processing occur in batch processes and not continuously.

3.1.4.1.2 Calculation of PEC_{local} for formulation of fertilizers

Production of inorganic fertilizers coated with primary alkyl amines is carried out at a number of sites. The European Oleochemicals & Allied Products Group (APAG) collected data about yearly processing amounts and site-specific river flows.

Table 3.1.11: Site-specific data for formulators of fertilizers (APAG, 2005c)

Substance	Tallow	Hydr.Tallow
No. of sites	1	22
Amount per site [t/a]	13	15 – 450
Total amount [t/a]	13	2442
River MNQ [m^3/s]	0.23	0.23 – 581

As a worst case scenario, data are used from those site which emissions are leading to the highest PECs. For the model the following parameters are chosen:

Processing amount: the selected site uses 116 t/a. There are few sites with higher amounts, but all of them are located at rivers with large flows.

Number of days: 300 (TGD, Appendix I, table B2.1 for > 1000 t fertilizer per year, as the amine content ranges only from 0.004 to 0.01%), i.e. processing amount 387 kg/d.

Release factor: The default value of 0.003 (TGD, Appendix I, table A2.1) is used. The release into waste water is calculated to 1.16 kg/d.

With a removal in treatment plants of 99.83%, the mass flow in effluent is calculated to 1.97 g/d. Assuming an effluent flow of 2000 m^3/d (TGD default value), an effluent concentration of 0.986 µg/l and a local concentration (dilution 1:10) of 0.0986 µg/l is calculated. Considering a PECregional of 1.07 E-2 µg/l, the local exposure is calculated to

$PEClocal_{aqua\ bulk}$ = 0.11 µg/l

PECsed = 16.5 µg/kg ww

Total releases:

For coating of inorganic fertilizers, totally 4191 t/a primary alkyl amines are used. 1445 t/a are used by the producers themselves, and these releases are covered by the scenarios about production. The remaining 2746 t/a are applied by customers. With a release factor of 0.003, releases of 8.24 t/a into the waste water are considered for the calculation of the regional background concentration.

3.1.4.1.3 Calculation of PEC_{local} for industrial/professional use

Releases during ethoxylation:

Ethoxylation is carried out in dedicated equipment which is not cleaned between batches. Releases into waste water are related to cleaning of the equipment which is done once a year, i.e. only intermittent releases occur.

Large parts of the primary alkyl amines are ethoxylated at the manufacturers site, releases due to processing of these parts are included in the scenarios for production. Further parts of the products are processed at one large site and a number of customers consuming relatively small amounts. Two scenarios are calculated, based on site-specific data of the large processing site, and a generic scenario representing the small consumers.

Scenario Eth 1

4 substances of the primary alkyl amine category are processed at one site in large amounts. Site-specific data are reported about yearly processing amounts, the number of processing days per year, release factors into waste water, and the low flow of the receiving river. This site has no sewage treatment plant. The PECs and the yearly releases are:

Tab. 3.1.12: Intermittent exposure from ethoxylation of primary alkyl amines at one large site

Substance	Amount [t/a]	Release [kg/a]	$Clocal_{aqua\ bulk}$ [µg/l]	$PEClocal_{aqua\ bulk}$ [µg/l]	$PEClocal_{sed}$ [µg/kg ww]
Coco	531	0.031	2.5 E-3	1.3 E-2	2.0
Tallow	1600	0.38	3.0 E-2	4.1 E-2	6.2
Hydr.Tallow	460	0.015	1.8 E-3	1.3 E-2	1.9
Oleyl	1058	0.25	2.0 E-2	3.1 E-2	4.6

ww: wet weight

The total release of primary alkyl amines into the hydrosphere at this site is 0.68 kg/a.

Scenario Eth 2

4 substances of the primary alkyl amine category are processed in relatively small amounts at a number of customers sites. The European Oleochemicals & Allied Products Group (APAG) collected site-specific data about yearly processing amounts, number of processing days per year, and the river flows (APAG, 2005c).

Table 3.1.13: Site-specific data of small ethoxylating sites (APAG, 2005c)

Substance	Coco	Tallow	Hydr.Tallow	Oleyl
No. of sites	11	23	4	12
Amount per site [t/a]	6 – 261	4 - 730	2 – 29	6 - 107
Total amount [t/a]	897	1627	83	549
River MNQ [m^3/s]	0.4 – 957 (7 sites)	0.24 – 957 (13 sites)	0.28 – 957 (4 sites)	1.24 – 581 (5 sites)

For a worst case scenario, data are used from those site which emissions are leading to the highest PECs. For the model the following parameters are chosen:

Processing amount: a value of 203 t/a is chosen. There are few sites with higher amounts, but all of them are located at rivers with large flows.

Release factor: There are no measured values from customers sites available. Measurements were performed at the producers sites were ethoxylation is carried out. The highest value out of three is used, i.e. a release factor of 3 ppm. As releases occur only from equipment cleaning, the intermittent release into waste water is calculated to 609 g/d.

With a removal in treatment plants of 99.83%, the mass flow in effluent is calculated to 1.03 g/d. Assuming an effluent flow of 2000 m^3/d (TGD default value), an effluent concentration of 0.52 µg/l and a local concentration (dilution 1:10) of 0.052 µg/l is calculated. Considering a PECregional of 1.07 E-2 µg/l, the local exposure is calculated to

$PEClocal_{aqua\ bulk}$ = 0.063 µg/l

PECsed = 9.5 µg/kg ww

Total releases:

Totally 3156 t/a primary alkyl amines are ethoxylated by customers. With a release factor of 3 ppm, emissions of 9.5 kg/a into waste waters are considered for the calculation of the regional background concentration.

Releases during processing to sulphosuccinamates:

The sulphosuccinamates are produced at 4 sites in a water free batch process in a closed and dedicated system from tallow alkylamine (APAG, 2005d). The exposure is calculated on the basis of site-specific data (processing volume, waste water flow for site 3, river flow) resp. TGD default values (duration of processing period, waste water flow for sites 1, 2, and 4). At sites 1, 2, and 4, the processing is done in series of batches without cleaning between the consecutive batches, i.e. only intermittent releases are expected. For these sites, an emission factor of 0.001 is assumed to be realistic. For site 3, a default emission factor of 0.02 is used.

Tab. 3.1.14: Exposure from processing to sulphosuccinamates

Site	Amount [t/a]	Ceffluent [µg/l]	Release [kg/a]	$Clocal_{aqua\ bulk}$ [µg/l]	$PEClocal_{aqua\ bulk}$ [µg/l]	$PEClocal_{sed}$ [µg/kg ww]	Type of release
Sulph1	150	4.25	0.26	0.13	0.15	22	intermittent
Sulph2	121	4.25	0.20	9.8 E-03	2.1 E-02	3.1	intermittent
Sulph3	603	2.89	20.4	4.1 E-03	1.5 E-02	2.2	continous
Sulph4	342	4.25	0.58	1.6 E-02	2.7 E-02	4.1	intermittent

ww: wet weight

The total release of tallow amine into the hydrosphere amounts to 21.4 kg/a.

Releases during processing to other products:

Releases into waste water from processing of octadecylamine to other products occur at 2 sites (APAG, 2005d). The exposure is calculated on the basis of site-specific data (processing volume, river flow, release factors) resp. TGD default values (duration of processing period, waste water flow). The resulting PECs are

Tab. 3.1.15: Exposure from processing to other products

Site	Amount [t/a]	Ceffluent [µg/l]	Release [kg/a]	$Clocal_{aqua\ bulk}$ [µg/l]	$PEClocal_{aqua\ bulk}$ [µg/l]	$PEClocal_{sed}$ [µg/kg ww]
Other1	21	0.26	0.0073	5.2 E-05	1.1 E-02	1.6
Other2	29	8.8	0.246	7.3 E-04	1.1 E-02	1.7

ww: wet weight

The total release of octadecyl amine into the hydrosphere is 0.25 kg/a.

Releases during floatation:

Primary alkyl amines are used as floatation agents for production of halogenides, silicates and ores. Site-specific data for 8 sites are available (APAG, 2005d), covering about 2/3 of the total volume of primary alkyl amines used in the EU as floatation agent. The processing amount ranges from 20t/a to 181 t/a. From these, 2 sites have no emissions to surface waters. From the remaining 6 sites, exposure scenarios are calculated for 3 sites that have no wastewater treatment plant and thus represent worst-case conditions. To verify this calculations and to refine the resulting PEC/PNEC-ratios, at two of these sites an additional measuring campaign was performed.

Scenario Float1:

One site uses 20 t/a oleylamine. As floatation is a semi-continuous process, 150 processing days per year are regarded as a realistic worst case. The user estimated the release factor to 9.07 E-04, i.e. 121 g/d are released into the surface water (there is no treatment plant). With a river low flow of 3.50 m^3/s, the PECs are calculated to

$Clocal_{aqua\ bulk}$ = 0.40 µg/l

$PEClocal_{aqua\ bulk}$ = 0.41 µg/l

PECsed = 62 µg/kg ww

According to the scenarios proposed by the TGD, the release into surface water is 18.2 kg/a.

Refinement scenario Float1 by measured data:

According to APAG (2006a), a monitoring campaign was performed for this site in April and May 2006. The sampling included the amounts extracted from the sample vessel walls. The detection limit of the method used was 0.08 µg/l.

The undiluted effluents were monitored before entering the river for oleyl amine on 5 consecutive days with two samples each. The minimum concentration in the samples was 0.34 µg/l, and the maximum level 0.77 µg/l. To calculate the dilution in the river, the mean (low) flow of the river (3,500 l/s), and an effluent flow of 8 l/s are proposed leading to a dilution factor of 437. This assumption is in line with standard assumptions for small rivers and could be regarded as a conservative approach.

Together with this dilution factor the concentrations in the river downstream the point of discharge are estimated between 0.001 and 0.002 µg/l.

$Clocal_{aqua\ bulk}$ = 0.002 µg/l

$PEClocal_{aqua\ bulk}$ = 0.013 µg/l

PECsed = 2.1 µg/kg ww

Scenario Float2:

A second site - situated near the seaside - uses 70 t/a oleylamine for kaolin production. At 150 processing days per year 470 kg are used daily. The amine is for >99% sorbed to kaolin. 85% of the water used during floatation is recycled, thus <700 g/d are emitted into a central water ring system. The surplus water from the ring (about 160000 m^3/d) is emitted (there is no treatment plant) mainly into the sea. The concentration in the ring is calculated to 4.3 µg/l as a worst case. In the pipe, the ring water is diluted with 10% additional waste water, i.e. the effluent concentration is 3.9 µg/l. With a dilution factor of 100 entering the sea, the PECs are calculated to

$Clocal_{seawater\ bulk}$ = 0.039 µg/l

$PECregional_{seawater\ bulk}$ = 8.16 E-04 µg/l

$PEClocal_{seawater\ bulk}$ = 0.040 µg/l

PECsed = 6.0 µg/kg ww

According to the generic scenarios proposed by the TGD, the release into seawater is 105 kg/a.

Refinement scenario Float2 by measured data:

According to APAG (2006a), a monitoring campaign was performed for this site in April and May 2006. The effluents and the river water were monitored at three sampling sites for oleyl amine with 18-20 samples each. The sampling included the amounts extracted from the sample vessel walls. The detection limit of the method used was 0.08 µg/l.

Although the site is situated nearby the seaside, it was noticed during the campaign that earlier information on direct emission to the Sea was not correct. The monitoring was performed on freshwater rivers which are close to the Sea but still some kilometers from the coast.

Following the floatation, the mixture of clay and water is dried in a drying plant. The effluents from the plant are discharged into the river. The undiluted effluent stream was sampled 18 times with a maximum concentration measured of 0.2 µg/l one day. However, most of the samples were below the limit of detection (0.08 µg/l). Downstream of the discharge point the concentrations remained below the limit of detection for all samples, including the sample corresponding to the maximum level in the effluent. The limit of detection was also never exceeded at a second route with discontinous emissions, but also occurring during the sampling period.

The effluent concentration is not representative for the concentration in the river. However, to calculated the dilution by the river water, specific characteristics of the river are not available.

As a very conservative approach, the effluent concentraton together with a dilution factor of 10 might be used to estimate the concentration in the river, resulting in a maximum local concentration of 0.02 µg/l. As a more worst-case approach, it is proposed to alternatively use the limit of detection as maximum local concentration in the river (0.08 µg/l). This concentration was not exceeded at the downstream sampling point.

$Clocal_{aqua\ bulk}$ = < 0.08 µg/l

$PEClocal_{aqua\ bulk}$ < 0.08 µg/l

PECsed < 12 µg/kg ww

Scenario Float 3:

One site uses 101 t/a hydrogenated tallow amine as floatation agent. 150 processing days per year are assumed. With a release factor of 2.7 E-06 estimated by the user an amount of 1.82 g/d is emitted into the surface water (there is no treatment plant). With a river low flow of 0.62 m^3/s, the PECs are calculated to

$Clocal_{aqua\ bulk}$ = 0.034 µg/l

$PEClocal_{aqua\ bulk}$ = 0.045 µg/l

PECsed = 6.7 µg/kg ww

The yearly release into surface water is 0.27 kg/a.

The other 3 sites have wastewater treatment plants, the releases to surface water are expected to be much lower. Thus, the release in Europe due to floatation is caused by the 3 sites without treatment plant, i.e. totally 123 kg/a.

3.1.4.2 Measured levels

With exception of the measured data at the floatation sites described in the section before, monitoring data for primary alkyl amines in environmental compartments are not available.

3.1.5 Terrestrial compartment

3.1.5.1 Calculation of PEC_{local}

3.1.5.1.1 Calculation of PEC_{local} for production / processing

Primary alkyl amines reaching waste water treatment plants are partially removed via adsorption onto sewage sludge. When sewage sludge is used as fertilizer, agricultural soils

may be contaminated. Several scenarios are calculated for the sites with the highest releases into the waste water.

Prod E, site-specific:

The highest effluent concentration is calculated for the production site E (cf. 3.1.4.1.1, production of hydrogenated tallow amine). At this site, a monitoring campaign was performed. Octadecylamine was measured in surplus sludge at 6 days, with 3 replications per sample (APAG, 2005d). The maximum mean value of the replicates was 887 mg octadecylamine/kg sludge. As hydrogenated tallow amine contains about 65% C18-amine, the total amine content in sludge is calculated to 1360 mg/kg. The monitoring data from this site reflect site-specific conditions and cannot be considered as representative for the sludge concentration at other sites.

The PECs in soil are calculated according to the TDG model, with two exceptions: The sludge from this site is mixed with soil with a mixing depth of 50 cm, and sludge is applied only once every three years on the same plot (APAG, 2005d). Therefore, the TGD eq (62) is adapted as follows:

Csludge soil 10 (0) = Csludge1.agric*(1+Facc.agric+Facc.agric^4+Facc.agric^7+Facc.agric^10)

The resulting PECs after 10 years application are

Tab. 3.1.16: PECsoil for the use of sewage sludge from production site E as fertilizer

Parameter	Value	Remarks
Kp_{soil}	697 l/kg dw	cf. 3.1.3.2.1
Henry's law const.	0.01 $Pa \cdot m^3/mol$	cf. 3.1.3.2.3
$k_{bio\ soil}$	$2.31 \cdot 10^{-3}\ d^{-1}$	DT50 = 300 d; cf. 3.1.3.1.3
$PEClocal_{soil}$	1.1 mg/kg dw 1.0 mg/kg ww	endpoint: terrestrial ecosystem
$PEClocal_{agr.soil}$	0.96 mg/kg dw 0.85 mg/kg ww	endpoint: crops for human consumption
$PEClocal_{grassland}$	0.96 mg/kg dw 0.85 mg/kg ww	endpoint: grass for cattle
$PEClocal_{soil,porew}$	1.8 µg/l	endpoint: terrestrial ecosystem
PECagri,porew	1.6 µg/l	endpoint: drinking water
PECgrass,porew	1.6 µg/l	endpoint: grass for cattle

dw = dry weight ww = wet weight

Generic scenarios:

Further scenarios are calculated for the following life-cycle steps:

Production: sludge from the production site A is amended to agricultural soils (APAG, 2005d).

Formulation of fertilizers: Sludge from the site with the highest releases into wastewater is not applied to soils, instead of this the site with the second-highest releases is considered. This site is not identical with those in section 3.1.4.1.2, as it is located at a large river and causes low aquatic PECs.

Ethoxylation: Releases from this use are intermittent, i.e. only 1 day per year. Because it is unlikely to assume that sludge from this day is applied on one plot over 10 years, no scenario is calculated.

Sulphosuccinamates and other products: Sludge from all sites with release factors >0 are not applied on soils (APAG, 2005d), therefore no scenario is calculated.

Flotation: A scenario is calculated for the site with the highest releases into a treatment plant (not identical with those in section 3.1.4.1.3).

For all senarios, the concentration in sludge is calculated based on results of a SIMPLETREAT calculation (cf. 3.1.3.2.4), although it was concluded that degradation in sewage treatment plants is underestimated by the model. As no better data are available, the SIMPLETREAT results are taken as a worst case approach. The concentration in sewage sludge is calculated according to the TGD models (Eq. 36 and 37):

$$C_{sludge} = Fstp_{sludge} * Elocal_{water} * 10^6 / SLUDGERATE$$

$$SLUDGERATE = 2/3 * SUSPCONF_{inf} * EFFLUENT_{stp} + SURPLUSsludge * CAPACITY_{stp}$$

with:

$Fstp_{sludge}$	fraction of emission directed to primary and secondary sludge (16.3%, cf. 3.1.3.2.4)
$Elocal_{water}$	local emission rate to water [kg/d]
$SUSPCONF_{inf}$	Concentration of susp. matter in influent (0.45 kg/m^3)
$EFFLUENT_{stp}$	effluent discharge rate [m³/d]
SURPLUSsludge	surplus sludge per inhabitant (0.011 kg/d/eq)
$CAPACITY_{stp}$	capacity of local stp [eq]

The concentration in agricultural soil is calculated according to the TGD model, assuming that sludge application takes place for 10 consecutive years:

Tab. 3.1.17: PECsoil for the use of sewage sludge

Parameter	Producer A	Formul. Fert.	Floatation	Remarks
$Elocal_{water}$	0.015 kg/d	2.77 kg/d	0.78 kg/d	
EFFLUENTstp	379 m³/d	2000 m³/d	2000 m³/d	
C_{sludge}	18.2 mg/kg	636 mg/kg	179 mg/kg	
$PEClocal_{soil}$	0.045 mg/kg dw 0.040 mg/kg ww	1.6 mg/kg dw 1.4 mg/kg ww	0.45 mg/kg dw 0.40 mg/kg ww	endpoint: terrestrial ecosystem
$PEClocal_{agr.soil}$	0.038 mg/kg dw 0.034 mg/kg ww	1.3 mg/kg dw 1.2 mg/kg ww	0.38 mg/kg dw 0.34 mg/kg ww	endpoint: crops for human consumption
$PEClocal_{grassland}$	0.015 mg/kg dw 0.013 mg/kg ww	0.54 mg/kg dw 0.48 mg/kg ww	0.15 mg/kg dw 0.13 mg/kg ww	endpoint: grass for cattle
$PEClocal_{soil,porew}$	0.074 µg/l	2.6 µg/l	0.73 µg/l	endpoint: terrestrial ecosystem
PECagri,porew	0.062 µg/l	2.2 µg/l	0.61 µg/l	endpoint: drinking water
PECgrass,porew	0.025 µg/l	0.87 µg/l	0.25 µg/l	endpoint: grass for cattle

dw = dry weightww = wet weight

3.1.5.1.2 Calculation of PEC_{local} for private use

Fertilizer:

The local scenario is based on an application rate of 12.6 mg/m² into agricultural soil as determined in section 3.1.2.3. For the PEC calculation, the TGD model for sewage sludge is used provisionally as no model for fertilizers is available.

The initial concentration in soil is calculated according to

$$C_{agr.soil}(0) = APPL / (DEPTH \cdot RHO)$$

with

APPL Application rate of amines (12.6 mg/m²)

DEPTH mixing depth of soil (0.2 m)

RHO bulk density of soil (1700 kg wet soil/m³)

$$C_{agr.soil}(0) = 0.037 \text{ mg/kg ww} = 0.042 \text{ mg/kg dw}$$

Tab. 3.1.18: PECsoil for the use as anti-caking agent in fertilizer

Parameter	Value	Remarks
Kp_{soil}	697 l/kg dw	cf. 3.1.3.2.1
Henry's law const.	0.01 Pa·m^3/mol	cf. 3.1.3.2.3
$k_{bio\ soil}$	$2.31 \cdot 10^{-3}$ d^{-1}	DT50 = 300 d; cf. 3.1.3.1.3
$PEClocal_{soil}$	0.071 mg/kg dw 0.063 mg/kg ww	endpoint: terrestrial ecosystem
$PEClocal_{agr.soil}$	0.060 mg/kg dw 0.053 mg/kg ww	endpoint: crops for human consumption
$PEClocal_{grassland}$	0 mg/kg	endpoint: grass for cattle
$PEClocal_{soil,porew}$	0.11 µg/l	endpoint: terrestrial ecosystem
PECagri,porew	0.10 µg/l	endpoint: drinking water
PECgrass,porew	0	endpoint: grass for cattle

dw = dry weight

3.1.5.2 Measured levels

With excemption of the floatation site data, monitoring data for primary alkyl amines in environmental compartments are not available.

3.1.6 Atmosphere

There are no releases into the atmosphere during production, processing or use of primary alkyl amines. Volatilization from aqueous solution is expected to be negligible. Therefore, an exposure assessment for the atmosphere is not necessary.

3.1.7 Secondary poisoning

Primary alkyl amines are highly adsorptive substances, according the criteria of the *Technical Guidance Documents* an accumulation via the food chain cannot be excluded. The concentration in fish-eating predators is calculated to

$$PEC_{oral,predator} = PEC_{water} * BCF_{fish} * BMF$$

with:

$PEC_{oral,predator}$ Predicted environmental concentration in food

PEC_{water} 0.06 µg/l (arithmetic mean between highest PEC [fertiliser use] and PECregional)

BCF_{fish} 200 – 2,400 l/kg (cf. 3.1.3.3)

BMF Biomagnification factor in fish = 1 (TGD default)

$PEC_{oral,predator}$ = 12 - 144 µg/kg

3.1.8 Calculation of PECregional and PECcontinental

For the regional exposure scenario, relevant releases of primary alkyl amines from all life-cycle steps are summarized. Releases into surface waters occur during production and downstream uses. The amounts for some scenarios (formulation of fertilizers and Eth 2) are calculated from the emission into waste water assuming 20% direct emission and 80% treatment in a wwtp, where only 0.07% are directed to surface waters. Releases into agricultural soils are dominated by the use of amines in fertilizers and the use of floatation agent. Therefore, releases via sewage sludge from treatment plants are neglected.

Tab. 3.1.19: Summary of releases for the regional and continental scenarios [kg/a]

Life-cycle step	Waste water	Hydrosphere		Agric. soil	
		Regional	Contin.	Regional	Contin.
Production		0.144	1.30		
Formulation of fertilizers	8240	211	1898		
Eth 1		0.068	0.61		
Eth 2	9.5	0.24	2.19		
Sulphosucc.		2.14	19.3		
Other prod.		0.025	2.25		
Float 1		1.82	16.4		
Float 2		10.5	94.5		
Float 3		0.027	0.243		
Floatation				28 300	254 700

Fertilizers				419 100	3771 900
Downstream derivatives		1 870	16 830	2 014	18 123
Total		**2 096**	**18 865**	**449 400**	**4 044 700**

In the following table, the resulting PECs of the EUSES calculation are presented (cf. Appendix 1).

Table 3.1.10: Calculation of PECregional

Parameter	**regional**	**continental**
PECwater,bulk [µg/l]	1.07 E-2	1.22 E-03
PECseawater,bulk [µg/l]	8.16 E-04	4.07 E-10
PECair [µg/m^3]	9.17 E-04	7.53 E-05
PECagric.soil [µg/kg dw] [µg/kg ww]	66.2 58.4	6.81 6.01
PECagric.soil, porewater [µg/l]	0.095	9.77E-03
PECind.soil [µg/kg dw] [µg/kg ww]	0.0418 0.0369	3.43 E-03 3.03 E-03
PECnat.soil [µg/kg dw] [µg/kg ww]	0.0418 0.0369	3.43 E-03 3.03 E-03
PECsediment [µg/kg dw] [µg/kg ww]	13.7 2.97	1.55 0.336

3.2 EFFECTS ASSESSMENT: HAZARD IDENTIFICATION AND DOSE (CONCENTRATION) - RESPONSE (EFFECT ASSESSMENT)

3.2.1 Aquatic compartment (incl. sediment)

3.2.1.1 Toxicity test results

Criteria for validation

The five primary fatty amines under consideration rank among the group of difficult substances in aquatic toxicity testing. They are practically insoluble in water and have a strong tendency to adsorb on surfaces such as test vessels or organic material. In order to class a study as valid, it is of particular importance that - besides information on test substance, test method / conditions and test organism used - suitable precautions are taken to prevent the loss of test substance by adsorption.

Concerning the ecotoxic effects of primary fatty amines only a small dataset is available revealing several data gaps. The most relevant test results for aquatic vertebrates, invertebrates and algae are summarized in tab. 3.2.1-3.2.3 and tab. 3.2.8.

3.2.1.1.1 Fish

Tab. 3.2.1 and 3.2.8 show the most relevant test results for fish exposed to primary fatty amines.

Acute toxicity

Most of the tests were conducted in the end of the 1980s. Since the concentrations were not analytically verified, the reliability of the results is limited. Hence, most of the tests were considered to be valid with restrictions.

The available data reveal an increasing toxicity with raising chain length. The only exception is stearylamine (C18) where only a summary test report is available which indicates a slight drop of toxicity.

The lowest, well documented 96h-LC50 reported for fish is 0.11 mg/l (nominal) for oleylamine (C18). In this study the short-term toxicity to *Pimephales promelas* was examined by Akzo Nobel (1995b) in the presence and absence of humic acid using a static water test system according to the OECD Guideline 203 (1984). Fish were exposed at about 21°C for 96 h in reconstituted freshwater (pH 7.7-8.3, oxygen content 9.0-8.3 mg/l). Since the test material was insoluble in water, stock dispersions (approx. 0.1 g/l) were freshly prepared by ultrasonic treatment before each test was started. During each dosing step, the stock solutions were stirred to prevent any inhomogeneity of the stock solutions. At the start of the tests, all test solutions were clear and homogeneous. Five test concentrations in the nominal concentration

range between 0.05 and 0.49 mg/l were employed. As test substance Armeen OD with a purity of 94% was used. During all tests the test substance content decreased strongly showing a rather wide spread of the recovery rates. The test protocol explained this by the following factors:

- Adsorption onto the walls of test vessels or – especially - on other surfaces (such like the surfaces of the test animals).
- Reaction with organic materials (humic acid).
- Humic acid might act as an emulsifier and hence is likely to influence the extraction process during the chemical analysis (HPLC).
- An incomplete water removal during the analytical procedure causes disturbances of the chemical analysis.

However, based on nominal concentrations a 96 h-LC50 of 0.11 mg/l was derived from this study. When taking the results of the chemical analysis into account by using the mean recovery rate (about 51%) as the actual test concentration throughout the test, the 96 h-LC50 can be calculated as 0.06 mg/l.

From this study it can also be concluded that humic acid clearly has an effect on bioavailability of oleylamine for fish. . As compared to the test results without humic acid, the addition of 10 mg/l humic acid resulted in an approximate 14-fold decrease the calculated LC50 based on nominal concentrations and about 20-fold based on analytically determined concentrations.

Long-term toxicity

Long-term test results for fish are not available.

Testing of vertebrates should be avoided due to animal welfare reasons. Comparing the available data on acute toxicity for fish and invertebrates indicates that additional chronic tests using fish might not contribute additional information relevant for risk assessment for aquatic ecosystems.

Tab. 3.2.1: most relevant results of toxicity tests using fish

Species	Chemical tested		Temp. [°C]	pH	Experimental conditions, type of test	Tested concentrations*) [mg/l]	Endpoint	Concentration*) (95%-CI) [mg/l]	Reference	Validity
Pimephales promelas	C8	Octylamine	24.5	7.9+/-0.02	Flow through, water hardness 44.5 mg/l CaCO3, oxygen content 7.1 mg/l	3.7 – 20 mg/l	96h-LC50	5.2 (measured)	Geiger et al. (1988)	validation not possible
Brachydanio rerio	C8	Octylamine "Genamin 8R 100D" purity 99%	22 +/-1	8-8.2	OECD 203, static, complete test report, GLP, O2-saturation > 80 %, dispersion treatment: Ultra-Turrax, no analytics	1.0, 10, 100, 500	96h-LC0 96h-LC50 96h-LC100	1 10-100 100 (nominal)	Hoechst AG (1988a)	Valid with restrictions
Pimephales promelas	C10	Decylamine	25.1	7.45	Flow through, water hardness 44.5 mg/l CaCO3, oxygen content 6.2 mg/, concentrations analytically verified	1.0 – 250	96h -LC50	1.04 (measured) (0.99-1.09)	Brooke et al. (1984)	validation not possible
Brachydanio rerio	C10	Decylamine			OECD 203, static, no further information (summary test report)	1, 10	48,96h-LC0 48,96h-LC50 48,96h-LC100	1 > 1 and < 10 10	Hoechst AG (1988b)	validation not possible
Pimephales promelas	C12	Dodecylamine					96h-LC50	0.1	Newsome et al. (1993)	validation not possible
Brachydanio rerio	C12	Dodecylamine "Genamin 12 R 100 D" purity 99.9%	22 +/- 1	7.5-8.3	OECD 203, static, complete test report, GLP, O2-saturation > 80 %, solubilizer: 0.1 ml/l ethanol, dispersion treatment: Ultra-Turrax/ Ultrasound, no pre-treatment of test vessels, no analytical verification	0.25-3.5	48h-LC0 48h-LC50 48h-LC100 96h-LC0 96h-LC50 96h-LC100	0.35 0.42 0.71 0.35 0.42 0.5	Hoechst AG (1988c)	Valid with restrictions
Brachydanio rerio	C12/ C14	Coco alkyl amines "Genamin CC100D" purity 99-100%	21.6-22.9	7.1-8.3	OECD 203, static, complete test report, GLP O2: 5.7-9.7 mg/l, solubilizer: 0.1 ml/l ethanol, dispersion treatment: Ultra-Turrax/ Ultrasound, no pre-treatment of test vessels, no analytical data	0.01-10	48h-LC0 48h-LC50 48h-LC100 96h-LC0 96h-LC50 96h-LC100	0.12 0.30 0.50 0.12 0.24 (0.20-0.30) 0.35	Hoechst AG (1988e)	Valid with restrictions

Tab. 3.2.1 continued overleaf *) nominal

Tab. 3.2.1 continued: most relevant results of toxicity tests with **aquatic vertebrates**

Species	Chemical tested		Temp. [°C]	pH	Experimental conditions, type of test	Tested concentrations*) [mg/l]	Endpoint	Concentration*) (95%-CI) [mg/l]	Reference	Validity
Oncorhynchus mykiss	C12/ C14	Coco alkyl amines "Amine KK" purity at least 94%	14	7.3-7.6	OECD 203, semi-static (daily renewal), complete test report, GLP, dissolved oxygen 9.9-10.1 mg/l, solubilizer: Tween 80-acetone, **test vessels were soaked with test substance overnight**, no analytical data	0.1-1	96h-NOEC 96h-LC50 96h-LC100	0.1 0.16 (0.13-0.19) 0.32	Berol Nobel (1991a)	Valid with restrictions
Brachydanio rerio	C16/ C18	Amines, hydrogenated tallow alkyl "Armeen HT" purity 99%	22.7-23.8	8.0-8.3	OECD 203, semi-static (renewal after 48 hours), complete test report, GLP, lowest measured oxygen concentration 79%, solubilizer: 1 mg/l Tween 80, dispersion treatment: ultrasonic treatment, heating up to 50°C, no pre-treatment of test vessels, no analytical data	0.1-1.05	96h-$NOEC_{mort}$ 96h-$NOEC_{beh}$ 96h-LC50	0.58 0.1 0.88 (0.72-1.1)	Akzo (1991)	Valid with restrictions
Brachydanio rerio	C16/ C18	Tallow alkyl amine "Genamin TA 100D" purity 100%	21.0-22.9	7.2-8.2	OECD 203, static, complete test report, GLP Oxygen content 5.4-9.3 mg/l, solubilizer: 0.1 ml Tween 80/l, dispersion treatment: Ultra-Turrax/ Ultrasound, no pre-treatment of test vessels, no analytical data	0.01-10	48h-LC0 48h-LC50 48h-LC100 96h-LC0 96h-LC50 96h-LC100	0.18 0.32 0.50 0.18 0.18-0.25 0.35	Hoechst AG (1988g)	Valid with restrictions
Brachydanio rerio	C18	Stearylamine "Genamin 18 R 100D" purity: 100% Octadecylamine distilled			OECD 203, static, no further information (summary test report)	1, 10	48,96h-LC0 48,96h-LC50 48,96h-LC100	1 > 1 and < 10 10	Hoechst AG (1988d)	validation not possible
Brachydanio rerio	C18	Stearylamine D "Genamin SH 100D" purity: 100% Stearylamine distilled			OECD 203, static, no further information (summary test report)	1, 10	48,96h-LC048,96h-LC50 48,96h-LC100	1 > 1 and < 10 10	Hoechst AG (1988f)	validation not possible

Tab. 3.2.1 continued overleaf *) nominal

Tab. 3..2.1 continued: most relevant results of toxicity tests with **aquatic vertebrates**

Species	Chemical tested		Temp. [°C]	pH	Experimental conditions, type of test	Tested concentrations*) [mg/l]	Endpoint	Concentration*) (95%-CI) [mg/l]	Reference	Validity
Brachydanio rerio	C18'	(Z)-octadec-9-enylamine "Genamin OL 100D" purity: 100% Oleylamine distilled			OECD 203, static, no further information (summary test report)	0.1, 1	48,96h-LC0 48,96h-LC50 48,96h-LC100	0.1 > 0.1 and < 1 1	Hoechst AG (1988h)	validation not possible
Pimephales promelas	C18'	(Z)-octadec-9-enylamine (Oleylamine) "Armeen OD" purity 94%	20.4-21.4	7.7-8.3	OECD 203, static, GLP, complete test report, toxicity was determined in the presence or absence of humic acid, dispersion treatment: ultrasound at RT, no pre-treatment of test vessels, measured concentrations (HPLC) decreased during the test period, results based on nominal concentrations → addition of humic acid reduces toxicity significantly	Without humic acid: 0.05-0.49 recovery 13-82% → mean 51% 10 mg/l humic acid: 0.61-9.8 recovery 70-116% → mean 92% 20 mg/l humic acid: 0.61-9.8 recovery 17-88% → mean 59%	96h-LC50 96h-LC0 96h-LC50 96h-LC0 96h-LC50 96h-LC0	Without humic acid: 0.11 (0.09-0.15) 0.085 10 mg/l humic acid 1.50 (1.24-1.83) 0.61 20 mg/l humic acid: 2.13 (1.81-2.50) 0.61	Akzo Nobel (1995b)	Valid with restrictions

*) nominal

Tab. 3.2.2: most relevant results of toxicity tests with **aquatic invertebrates**

Species	Chemical tested		Temp. [°C]	pH	Experimental conditions, type of test	Tested concentrations*) [mg/l]	Endpoint	Concentration*) (95%-CI) [mg/l]	Reference	Validity
Daphnia magna	C12/ C14	Coco alkyl amines "Genamin CC100D" purity 99.1%	21.0-21.8	7.46-7.62	OECD 202, static, GLP, complete test report, dispersion treatment: 30 min ultrasound at 40°C, no pre-treatment of test vessels, no analytical data	0.018-0.58	48h-EC0 48h-EC50 48h-EC100	0.058 0.09 (0.11-0.15) 0.18	Noack (1994a)	Vailid with restrictions
Daphnia magna	C12/ C14	Coco alkyl amines "Amine KK" purity 94%	21	7.5-7.7	OECD 202, static, GLP, complete test report, solubilizer: Tween 80-acetone, **test vessels were soaked with test substance overnight**, no analytical data	0.010-1	24h-EC0 24h-EC50 48h-EC0 48h-EC50	0.032 0.057 0.032 0.045 (0.042-0.049)	Berol Nobel (1991b)	Valid with restrictions
Daphnia magna, Reproduction test (21d)	C12/ C14	Coco alkyl amines "Armeen CD" purity 100.8%	19.6-21.4	7.72-8.58	OECD 211, semi-static (renewal 3 times per week), GLP, complete test report, test medium**: unfiltered river water**, dispersion treatment: 30 min ultrasound at 40°C, no pre-treatment of test vessels, due to strongly varying recovery rates (GC / MS) test results were based on nominal concentrations (only highest test concentration analytically verified)	0.013-0.5 recovery rates: 80-0% mean: 20%	21d-$NOEC_{repro}$ 21d-$LOEC_{repro}$ 21d-$EC50_{repro}$	0.013 0.032 0.34	Noack (2002a)	Valid with restrictions
Daphnia magna	C16/ C18	Amines, hydrogenated tallow alkyl "FARMIN TH"	21.8-22.4	7.3-8.1	OECD 202, static, GLP, complete test report, solubilizer: Tween 80 (100 mg/l), no pre-treatment of test vessels, no analytical data	0.05-0.78	48h-EC0 48h-EC50 48h-EC100	0.05 0.16 (0,116-0.21) 0.78	Kao (1995)	Valid with restrictions

Tab. 3.2.2: continued overleaf *) nominal

Tab. 3.2.2 : continued most relevant results of toxicity tests with **aquatic invertebrates**

Species	Chemical tested		Temp. [°C]	pH	Experimental conditions, type of test	Tested concentrations*) [mg/l]	Endpoint	Concentration*) (95%-CI) [mg/l]	Reference	Validity
Daphnia magna	C16/ C18	Amines, hydrogenated tallow alkyl "NORAM SH"	19.5-20	7.47-8.39	OECD 202, static, complete test report, test substance was dissolved in reconstituted water and heated to 60-70°C. Before dilution, the stock solution was **centrifugated** for one hour and the subnatant collected (undissolved particles had a density <1 g/m³), all glassware was silanised to prevent the test substance adhering to the surface, 100% immobilization at concentrations below the limit of quantification (1 mg/l, GLC / FID)	1-50	48h-EC50 48h-EC100	< 1 (limit of quantification) < 1 (limit of quantification)	CECA (1995)	Valid with restrictions
Daphnia magna	C16/ C18	Tallow alkyl amine "Adogen 170"	20	7.7	Acute toxicity test, static, dilution water: Town River water (CaCO3 = 50 mg/l, suspended solids 7.5 mg/l), solubilzer: acetone, no pre-treatment of test vessels, no analytical data	0.04-0.5	24h-LC50 48h-LC50	0.23 0.093 (0.076-0.11	Witco (1986)	Valid with restrictions
Daphnia magna, Reproduction test (21d)	C16/ C18	Tallow alkyl amine "Armeen TD" purity 101.0%	19.6-21.6	7.37-8.58	OECD 211, semi-static (renewal 3 times per week), GLP, complete test report, test medium: **unfiltered river water**, dispersion treatment: 30 min ultrasound at 40°C, no pre-treatment of test vessels, due to strongly varying recovery rates (GC / MS) test results were based on nominal concentrations (only highest test concentration analytically verified)	0.013-0.5 recovery rates: 80-0% mean: 37.5%	21d-$NOEC_{repro}$ 21d-$LOEC_{repro}$ 21d-$EC50_{repro}$ 21d-$EC10_{immo}$ 21d-$EC50_{immo}$ 21d-$NOEC_{imm}$ 21d-$LOEC_{imm}$	0.013 0.032 0.24 (0.1-0.54) 0.21 0.36 (0.29-0.45) 0.08 0.2	Noack (2002b)	Valid with restrictions
Daphnia magna	C18	Stearylamine "Genamin SH 100D"	20.9-21.8	7.4-7.6	OECD 202, static, GLP, complete test report, dispersion treatment: 30 min ultrasound at 40°C, no pre-treatment of test vessels, no analytical data	0.018-0.58	48h-EC0 48h-EC50 48h-EC100	0.032 0.13 (0.10-0.18) 0.58	Noack (1994c)	Valid with restrictions

Tab. 3.2.2 : continued overleaf *) nominal

Tab. 3.2.2: continued most relevant results of toxicity tests with **aquatic invertebrates**

Species	Chemical tested		Temp. [°C]	pH	Experimental conditions, type of test	Tested concentrations*) [mg/l]	Endpoint	Concentration*) (95%-CI) [mg/l]	Reference	Validity
Daphnia magna, Reproduction test (21d)	C18'	(Z)-octadec-9-enylamine "Armeen OD" purity 99.1%	20.1-21.4	7.6-9.31	OECD 211, semi-static (renewal 3 times per week), GLP, complete test report, test medium: **unfiltered river water**, dispersion treatment: 30 min ultrasound at 40°C, no pre-treatment of test vessels, due to strongly varying recovery rates (GC / MS) test results were based on nominal concentrations (only highest test concentration analytically verified)	0.013-0.5 recovery rates: 56-0% mean: 36.5%	21d-$NOEC_{repro}$ 21d-$LOEC_{repro}$ 21d-$EC50_{repro}$ 21d-$EC20_{immo}$ 21d-$EC50_{immo}$	0.013 0.032 0.27 (0.18-0.40) 0.2 0.36 (0.29-0.45)	Noack (2002c)	Valid with restrictions
Daphnia magna	C18'	(Z)-octadec-9-enylamine (Oleylamine) "Armeen OD" purity 94%	19.1-19.7	8.0-8.2	OECD 202, static, GLP, complete test report, toxicity was determined in the presence or absence of humic acid, dispersion treatment: ultrasound at RT, no pre-treatment of test vessels, measured concentrations (HPLC) decreased strongly during the test period, results therefore based on nominal concentrations	<u>Without humic acid</u>: 0.006-0.09 recovery 48-118% → mean 81% <u>10 mg/l humic acid:</u> 0.08-1.20 recovery 23-98% → mean 56% <u>20 mg/l humic acid:</u> 0.08-1.20 recovery 0-23% → mean 7.4%	48h-EC50 48h-EC0 48h-EC100 48h-EC50 48h-EC0 48h-EC100 48h-EC50 48h-EC0 48h-EC100	<u>Without humic acid</u>: 0.011(0.01-0.013) 0.0056 0.045 <u>10 mg/l humic acid</u> 0.43 (0.39-0.45) 0.15-0.30 1.20 <u>20 mg/l humic acid:</u> 0.56 (0.48-0.65) 0.30 1.20	Akzo Nobel (1995a)	Valid with restrictions

*) nominal

Tab. 3.2.3 : most relevant results of toxicity tests with **algae**

Species	Chemical tested		Temp. [°C]	pH	Experimental conditions, type of test	Tested concentrations*) [mg/l]	Endpoint	Concentration*) (95%-CI) [mg/l]	Reference	Validity
Selenastrum capricornutum	C8	Octylamine	Not given	Not given	Cell multiplication inhibition test (based on a standard test from the US Federal Register: Vol. 50, No. 188, Part 797, Sec. 797.1050, Algal Acute Toxicity Test)		96h-EC50	0.22 (0.03-0.42)	Bollmann et al. (1989)	Not assignable
Scenedesmus subspicatus	C12/ C14	Coco alkyl amines "Amine KK" purity 94%	24	7.8-8.7	OECD 201, static, GLP, complete test report, solubilizer: 1%-Tween 80-acetone, **test vessels were soaked with test substance overnight**, no analytical data	0.0001-0.0016	48h-ERC50 96h-EBC50 96h-NOEC	0.0014 0.0008 0.0002	Berol Nobel (1991c)	Not valid **)
Scenedesmus subspicatus	C12/ C14	Coco alkyl amines "Genamin CC100D" purity 99.1%	23+/-2	7.90-8.14	OECD 201, static, GLP, complete test report, dispersion treatment: 30 min ultrasound at 40°C, no pre-treatment of test vessels, no analytical data	0.0032-1	72h-ERC0 72h-ERC10 72h-ERC50 72h-EBC0 72h-EBC10 72h-EBC50	0.032 0.071 0.17 0.032 0.041 0.14	Noack (1994b)	Valid with restrictions
Desmodesmus subspicatus *(Scenedesmus subspicatus)*	C12/ C14	Coco alkyl amines "Armeen CD" purity 100.8%	22.5-24.0	8.06-8.16	OECD 201, static, GLP, complete test report, test medium: **unfiltered river water**, dispersion treatment: 30 min ultrasound at 40°C, no pre-treatment of test vessels, due to strongly varying recovery rates (GC / MS) test results were based on nominal concentrations (only highest test concentration analytically verified)	0.03-1 recovery rates: 0-120% mean: 60%	72h-ERC50 72h-LOEC 72h-NOEC 72h-EBC50 72h-LOEC 72h-NOEC	0.16 (0.15-0.18) 0.13 0.06 0.08 (0.07-0.09) 0.06 0.03	Noack (2002d)	Valid with restrictions

Tab. 3.2.3: continued overleaf *) nominal **) increase of cell concentration in the control to low, no analytical data at very low effect level

Tab. 3.2.3: continued most relevant results of toxicity tests with **algae**

Species	Chemical tested		Temp. [°C]	pH	Experimental conditions, type of test	Tested concentrations*) [mg/l]	Endpoint	Concentration*) (95%-CI) [mg/l]	Reference	Validity
Scenedesmus subspicatus	C16/ C18	Amines, hydrogenated tallow alkyl "Amine HBG" purity 95%	24	8.0-9.0	OECD 201, static,GLP, complete test report, solubilizer: iso-propyl alcohol, **test vessels were soaked with test substance overnight**, no analytical data	0.001-0.016	48h-ERC50 96h-EBC50 96h-NOEC	0.010 0.012 0.008	Berol Nobel (1991e)	Not valid **)
Scenedesmus subspicatus	C16/ C18	Tallow alkyl amine "Amine BG" purity 95%	24	7.8-9.9	OECD 201, static, GLP, complete test report, solubilizer: iso-propyl alcohol, **test vessels were soaked with test substance overnight**, no analytical data	0.001-0.016	24h-ERC50 96h-EBC50 96h-NOEC	0.008 0.007 0.002	Berol Nobel (1991d)	Not valid ***)
Scenedesmus subspicatus	C16/ C18	Tallow alkyl amine" Genamin TA 100D"	23+/-2	7.6-8.3	OECD 201, static, GLP, complete test report, dispersion treatment: 30 min ultrasound at 40°C, no pre-treatment of test vessels, no analytical data	0.001-0.32	72h-ERC0 72h-ERC10 72h-ERC50 72h-EBC0 72h-EBC10 72h-EBC50	0.032 0.045 0.083 0.032 0.036 0.068	Noack (1996)	Valid with restrictions
Desmodesmus subspicatus *(Scenedesmus subspicatus)*	C16/ C18	Tallow alkyl amine "Armeen TD" purity 101.0%	21.8-23.2	8.06-8.23	OECD 201, static, GLP, complete test report, test medium: **unfiltered river water**, dispersion treatment: 30 min ultrasound at 40°C, no pre-treatment of test vessels, due to strongly varying recovery rates (GC / MS) test results were based on nominal concentrations (only highest test concentration analytically verified)	0.125-4 recovery rates: 72.5-22.5% mean: 47.5%	72h-ERC50 72h-LOEC 72h-NOEC 72h-EBC50 72h-LOEC 72h-NOEC	0.39 (0.38-0.41) 0.25 0.125 0.31 (0.30-0.32) 0.25 0.125	Noack (2002e)	Valid with restrictions

Tab. 3.2.3: continued overleaf *) nominal **) increase of cell concentration in the control to low, no analytical data at very low effect level
***) no analytical data at very low effect level

Tab. 3.2.3: continued most relevant results of toxicity tests with **algae**

Species	Chemical tested		Temp. [°C]	pH	Experimental conditions, type of test	Tested concentrations*) [mg/l]	Endpoint	Concentration*) (95%-CI) [mg/l]	Reference	Validity
Scenedesmus subspicatus	C18	Octadecylamine (Stearylamine) "Genamin SH 100D"	23+/-2	7.93-8.15	OECD 201, static, GLP, complete test report, dispersion treatment: 30 min ultrasound at 40°C, no pre-treatment of test vessels, no analytical data	0.001-0.32	72h-ERC0 72h-ERC10 72h-ERC50 72h-EBC0 72h-EBC10 72h-EBC50	0.01 0.029 0.12 0.01 0.018 0.062	Noack (1994d)	Valid with restrictions
Desmodesmus subspicatus *(Scenedesmus subspicatus)*	C18'	(Z)-octadec-9-enylamine "Armeen OD" purity 99.1%	21.8-23.2	8.04-8.23	OECD 201, static, GLP, complete test report, test medium: **unfiltered river water**, dispersion treatment: 30 min ultrasound at 40°C, no pre-treatment of test vessels, due to strongly varying recovery rates (GC / MS) test results were based on nominal concentrations (only highest test concentration analytically verified)	0.15-2.5 recovery rates: 72-0% mean: 36%	72h-ERC50 72h-LOEC 72h-NOEC 72h-EBC50 72h-LOEC 72h-NOEC	0.46 (0.44-0.49) 0.3 0.15 0.38 (0.36-0.39) 0.3 0.15	Noack (2002f)	Valid with restrictions
Selenastrum capricornutum	C18'	(Z)-octadec-9-enylamine (Oleylamine) "Armeen OD" purity 94%		7.6-9.4	OECD 201, static, GLP, complete test report, toxicity was determined in the presence or absence of humic acid, dispersion treatment: 5 min ultrasound at RT, no pre-treatment of test vessels, measured concentrations (HPLC) decreased strongly during the test period, results therefore based on nominal concentrations → addition of humic acid reduces toxicity significantly	<u>Without humic acid</u>: 0.01-0.15 recovery 28-100% → mean 64% <u>5 mg/l humic acid:</u> 0.09-1.50 recovery 8-100% → mean 54% <u>10 mg/l humic acid:</u> 0.19-3.01 recovery 8-79% → mean 44%	96h-ERC50 96h-EBC50 96h-NOEC 96h-ERC50 96h-EBC50 96h-NOEC 96h-ERC50 96h-EBC50 96h-NOEC	<u>Without humic acid</u>: 0.04 (0.04-0.04) 0.03 (0.03-0.03) 0.01 <u>5 mg/l humic acid:</u> 0.37 (0.34-0.39) 0.23 (0.22-0.25) < 0.09 <u>10 mg/l humic acid:</u> 0.76 (0.72-0.82) 0.49 (0.45-0.53) 0.19	Akzo Nobel (1995c)	Valid with restrictions

*) nominal

3.2.1.1.2 Aquatic invertebrates

Tab. 3.2.2, 3.2.4 and 3.2.8 summarize the most relevant test results of primary fatty amines for aquatic invertebrates.

Acute toxicity

Regarding the acute toxicity data towards *Daphnia magna* (table 3.2.2 and 3.2.8) a dependence on the chain length of primary fatty amines cannot be stated.

Tab. 3.2.4: toxicity tests with aquatic stages of mosquitoes **(aquatic invertebrates)**

Species	Chemical tested		Experimental conditions	Endpoint	Concentration*) (95%-CI) [mg/l]	Reference
Culex pipiens quinquefasciatus	C12	Dodecylamine	T = 26°C pH = 8-8.5 pH = 7.5-8 Effects on different aquatic stages of the mosquitoes groups of larvae (n=25) groups of pupae (n=25) static incubation with the test substance for 24 hours in tap water test substance dissolved in acetone	24h-LC50 24h-LC90 24h-LC50 24h-LC90 24h-LC50 24h-LC90	2 (2nd and 3rd larval stage) 4 (2nd and 3rd larval stage) 3 (4th larval stage) 5 (4th larval stage) 15 (Pupal stage) 25 (Pupal stage)	Mulla (1967a) Mulla (1967b)
	C12/ C14	Coco alkyl amines		24h-LC50 24h-LC90 24h-LC50 24h-LC90 24h-LC50 24h-LC90	0.8 (2nd and 3rd larval stage) 1.6 (2nd and 3rd larval stage) 2.2 (4th larval stage) 4.4 (4th larval stage) 13.0 (Pupal stage) 30.0 (Pupal stage)	
	C16	Hexadecylamine		24h-LC50 24h-LC90 4h-LC50 24h-LC90 24h-LC50 24h-LC90	2 (2nd and 3rd larval stage) 7 (2nd and 3rd larval stage) 1.5 (4th larval stage) 4 (4th larval stage) 50 (Pupal stage) > 50 (Pupal stage)	
	C16/ C18	Tallow alkyl amine		24h-LC50 24h-LC90 24h-LC50 24h-LC90 24h-LC50 24h-LC90	1.5 (2nd and 3rd larval stage) 3 (2nd and 3rd larval stage) 3.3 (4th larval stage) 4.8 (4th larval stage) 21.5 (Pupal stage) 38.0 (Pupal stage)	
	C18	Octadecylamine		24h-LC50 24h-LC90 24h-LC50 24h-LC90 24h-LC50 24h-LC90	6.2 (2nd and 3rd larval stage) 12 (2nd and 3rd larval stage) 8 (4th larval stage) 15 (4th larval stage) > 50 (Pupal stage) - (Pupal stage)	
	C18'	Oleylamine		24h-LC50 24h-LC90 24h-LC50 24h-LC90 24h-LC50 24h-LC90	1.2 (2nd and 3rd larval stage) 2.3 (2nd and 3rd larval stage) 1.5 (4th larval stage) 2.5 (4th larval stage) 5.8 (Pupal stage) 15.0 (Pupal stage)	

Tab. 3.2.4: continued overleaf *) nominal

Tab. 3.2.4: continued toxicity tests with aquatic stages of mosquitoes **(aquatic invertebrates)**

Species	Chemical tested		Experimental conditions	Endpoint	Concentration*) [mg/l]	Reference
Aedes aegypti	C8	Octylamine	24 h exposure of the 4th larval stage (n=25) to various fatty amine concentrations in 100 ml of tap water	24h-LC50	80 (4th larval stage)	Cline (1972) Wilton & Fay (1969)
	C10	Decylamine		24h-LC50	45 (4th larval stage)	
I) *Anopheles albimanus*	C12/ C14	Coco alkyl amines	Effects on different aquatic stages of the mosquitoes groups of larvae (n=25) groups of pupae (n=25) static incubation with the test substance for 24 h in tap water test substance dissolved in acetone	24h-LC50 24h-LC90 24h-LC50 24h-LC90	I) 3.0 (4th larval stage) 6.0 (4th larval stage) 3.5 (Pupal stage) 7.0 (Pupal stage)	Mulla et al. (1970)
II) *Aedes aegypti*				24h-LC50 24h-LC90 24h-LC50 24h-LC90	II) 2.0 (4th larval stage) 5.2 (4th larval stage) 10.0 (Pupal stage) 18.0 (Pupal stage)	
III) *Aedes nigro-manculis*				24h-LC50 24h-LC90 24h-LC50 24h-LC90	III) 3.0 (4th larval stage) 6.0 (4th larval stage) 3.5 (Pupal stage) 7.0 (Pupal stage)	
I) *Anopheles albimanus*	C18'	Oleylamine		24h-LC50 24h-LC90 24h-LC50 24h-LC90	I) 0.6 (4th larval stage) 1.9 (4th larval stage) 0.7 (Pupal stage) 1.7 (Pupal stage)	
II) *Aedes aegypti*				24h-LC50 24h-LC90 24h-LC50 24h-LC90	II) 1.7 (4th larval stage) 3.1 (4th larval stage) 2.3 (Pupal stage) 4.5 (Pupal stage)	
III) *Aedes nigro-manculis*				24h-LC50 24h-LC90 24h-LC50 24h-LC90	III) 1.7 (4th larval stage) 4.5 (4th larval stage) 1.0 (Pupal stage) - (Pupal stage)	

*) nominal

The lowest short-term result for *Daphnia magna* was found for oleylamine (Akzo Nobel, 1995a). This study was conducted according to the OECD Guideline 202 (1984) in the presence or absence of humic acid with Armeen OD (purity 94%) as test substance. Daphnia were exposed to five test concentrations in the nominal concentration range between 0.006 and 0.09 mg/l in a static system for 48 h at a temperature of 19.1-19.7°C and a pH of 8.0-8.2. For the preparation of the stock dispersions (0.1 g/l) ultrasonic treatment was used and during each dosing step the stock solutions were stirred. At the start of the tests, all test solutions were clear and homogeneous. Again, during all tests the test substance content (measured at 0 h and 48 h via HPLC) decreased strongly showing a wide spread of the recovery rates (test without humic acid: recovery 48-118%, mean value 81%; test with 10 mg/l humic acid: recovery 23-98%, mean value 56%; test with 20 mg/l humic acid: recovery 0-23%, mean value 7.4%). Due to this, no calculations based on measured concentrations were performed.

Based on nominal concentrations the 48h-EC50 values were calculated as 0.011 mg/l (without humic acid), 0.43 mg/l (10 mg/l humic acid) and 0.56 mg/l (20 mg/l humic acid). Compared to the test results without humic acid, the addition of 10 mg/l humic acid resulted in an approximate 40-fold higher EC50.

Tab. 3.2.5: relevant results of toxicity tests with **aquatic invertebrates**

Species	Chemical tested		Temp. [°C]	pH	Experimental conditions	Endpoint	Concentration*) [mg/l]	Reference
Elminius modestus Darwin, larvae	C8	Octylamine		7	Time of exposure: 6 minutes	6 min-LC50	310	Christie & Crisp (1966)
	C8	Octylamine		9		6 min-LC50	3.9	
	C10	Decylamine		7		6 min-LC50	378	
	C10	Decylamine		9		6 min-LC50	4.7	
	C10	Decylamine	28			6 min-LC50	3.6	
	C10	Decylamine	6			6 min-LC50	7.4	

*) nominal

Additionally, studies using different species of invertebrates describing effects of pH, temperature and stage of insect development are reported for different primary fatty amines (table 3.2.4 and 3.2.5). An enhancement of toxicity of octylamine and decylamine on larval mortality of *Elminius modestus* at higher pH and lower temperature is described by Christie & Crisp (1966). Larvae of *Culex pipiens* quinquefasciatus are more sensitive to primary fatty amines than pupae (Mulla 1967 a, b) and *Aedes aegypti* (Cline 1972). Larvae and pupae of *Anopheles* sp. and *Aedes* sp. are of similar sensivity to oleylamine and coco alkyl amines (Mulla 1970).

Long-term toxicity

The chronic toxicity of coco alkyl amine (Armeen CD), tallow alkyl amine (Armeen TD) and oleylamine (Armeen OD) to *Daphnia magna* was studied under comparable conditions by Noack (2002 a-c) using a semi-static test system according to the OECD Guideline 211 (Sept. 1998). Five test concentrations in the nominal concentration range between 0.013 and 0.5 mg/l were applied by diluting a stock dispersion (10 mg/l). Test solutions were renewed three times per week. As dilution water natural river water of agricultural background (middle reach of the river "Böhme", lower Saxony) was used. This river has been chosen due to its properties representing typical conditions of a German medium sized river. The concentration of suspended matter measured in the river water was in a range of 11.2 to 32.8 mg/l (mean value 18.4 mg/l) for coco alkyl amine and tallow alkyl amine and in a range of 10.0 to 26.2 mg/l (mean value 17.4 mg/l) for oleylamine. The content of humic acid amounted to 11.8 mg/l in all tests. A pre-treatment of the test vessels was not performed.

The concentrations of the active ingredient were determined in the old and new test media once per week in the stock solution, the highest test concentration of 0.5 mg/l and the control via GC-analysis. All samples were taken and analyzed without filtration to include test item adsorbed on suspended matter. In all tests the test item concentration decreased at the end of the test and recovery rates varied strongly (see table 3.2.6). According to the test protocol the most probable reason for the decrease or incomplete recovery during the test was seen in adsorption on particulate matter and humic acids. The variation in the recovery rates were explained by small differences in the concentration of suspended matter. The results were therefore based on nominal concentrations representing the total exposure concentration (dissolved and adsorbed on humic acid / suspended matter).

Tab. 3.2.6: Daphnia magna repro test with natural river water- analytically verified concentrations of the highest test item concentration (0.5 mg/l) [mg/l]

	Coco alkyl amine			**Tallow alkyl amine**			**Oleylamine**		
Sample No.	new media (0 hours)	old media (3 days)	recovery	new media (0 hours)	old media (3 days)	recovery	new media (0 hours)	old media (3 days)	recovery
1	0.4	< LOQ	40%	0.2	< LOQ	20%	0.14	0.11	25%
2	0.2	< LOQ	20%	0.2	< LOQ	20%	0.22	< LOQ	22%
3	< LOQ	0.2	20%	0.3	0.2	50%	0.28	0.24	52%
4	< LOQ	< LOQ	0%	0.4	0.2	60%	0.24	0.23	47%
			mean 20%			mean 37.5%			mean 36.5%

< LOQ below limit of quantification

Referring to nominal concentrations a 21d-NOECrepro of 0.013 mg/l was derived for coco alkyl amine, tallow alkyl amine and oleylamine. When considering the validity of these studies, the following factors should be taken into account:

- No measures were taken to prevent the loss of test substance by adsorption onto surface of the test vessels. Therefore, a quantification of the fraction lost by adsorption onto the glass ware is not possible.
- Only the highest test concentration was analytically verified showing highly variable recovery rates. At concentrations around the NOEC even lower recovery rates have to be expected. Due to this, the exposure concentrations maintained during the studies are highly uncertain.

3.2.1.1.3 Algae

Tab. 3.2.3 and 3.2.8 summarize the most relevant toxicity test results for aquatic algae.

The lowest effect values (nominal) for aquatic algae have been found for coco alkyl amine (96h-EBC50 = 0.0008 mg/l, 96-NOEC = 0.0002 mg/l), hydrogenated tallow alkyl amine (96h-EBC50 = 0.012 mg/l, 96-NOEC = 0.008 mg/l) and tallow alkyl amine (96h-EBC50 = 0.007 mg/l, 96-NOEC = 0.002 mg/l). These studies were conducted according to the OECD Guideline 201 (1984) with *Scenedesmus subspicatus* as test organism by Berol Nobel (1991c-e):

For the preparation of the stock solutions solubilizer were used. The test vessels were exposed to the test substance overnight to allow pre-adsorption onto the surface of the glassware. At the start of the tests the glassware was rinsed with the test solution to be tested and then refilled with the fresh test solution. Samples for measurement of growth were taken every 24 hours and the absorbance was determined with a photometer at 665 nm. The cell densities of the control cultures at initiation and at termination were measured by direct counting. As no analytical measurements were performed, test results were based on nominal concentrations.

The actual cell concentration in the control after 72 hours is not given in the test reports but an estimation can be made by plotting the absorbance against cell number of the 0 and 96 h

control values and assuming that the calibration was linear up to the maximum absorbance used. This estimation leads to conclusion that in the studies with coco alkyl amine and hydrogenated tallow alkyl amine the increase of cell concentration in the control was to low (well below factor 16). For this reason and due to the missing analytical data at very low effect concentration levels, the test results of Berol Nobel (1991c-e) are regarded as not suitable for effects assessment purposes.

Other EC50-values reported for primary fatty amines are in the nominal concentration range between 0.04 mg/l (oleylamine, tested in synthetic medium) and 0.46 mg/l (oleylamine, tested in natural river water).

For coco alkyl amine (Armeen CD), tallow alkyl amine (Armeen TD) and oleylamine (Armeen OD) test results are available, which were determined in natural, unfiltered river water (Noack 2002 d-f). Studies were conducted according to the OECD Guideline 201 (1984) in a static test system (temperature approx. 23°C, pH approx. 8) with *Desmodesmus subspicatus* (*Scenedesmus subspicatus*) as test organism. A pre-treatment of test vessels was not performed. Again, water of the river "Böhme" was used as dilution water (see section 3.2.1.1.3, long term toxicity). Exposure concentrations were analytically verified at 0 and 72 h in the highest tested concentration using GC/MS-analysis. Again, due to variations in the content of suspended matter and the adsorbing properties of the test substances, decreasing test concentrations associated with strongly varying recovery rates were observed (coco alkyl amine: 0-120%, mean 60%; tallow alkyl amine: 73-23%, mean 48%; oleylamine: 72-0%, mean 36%). Test results were therefore based on nominal concentrations. Referring to nominal concentrations for coco alkyl amine a 72h-ERC50 of 0.16 mg/l (72h-NOEC of 0.06 mg/l), for tallow alkyl amine a 72h-ERC50 of 0.39 mg/l (72h-NOEC of 0.125 mg/l) and for oleylamine a 72h-ERC50 of 0.46 mg/l (72h-NOEC of 0.15 mg/l) was determined indicating a slight decrease of toxicity with raising chain length.

3.2.1.1.4 Microorganisms

A number of tests on inhibition of respiration according to OECD Guideline 209 was conducted. An overview of the results is presented in table 3.2.7.

Tab. 3.2.7: Respiration tests according to OECD 209 [mg/l]

Substance	EC10	EC20	EC50	EC80	Remarks	Reference
Coco	5.5	7.5	14	25	Suspended with ultra-turrax	Hoechst AG (1989b)
		2.7	14.2	75.3	direct addition of TS	Hoechst AG (1992a)
Tallow	7	12	32	90		Hoechst AG (1989c)
Hydrog. tallow		214	490	>1000	direct addition of TS	Hoechst AG (1993b)
Octadecenyl		62.7	222.5	790	direct addition of TS	Hoechst AG (1992b)

The results of the respiration tests suggest that the toxicity of hydrogenated tallow amine and octadecenylamine to sewage sludge is much lower than that of coco and tallow amine. Regarding the test results with other organisms, similar toxicity of the compounds is expected. It can be assumed that the different results may be caused by different bioavailability of the test substances. As discussed earlier, bioavailability of the test substances is largely dependent on the method of preparation of the test medium, although there is no real explanation for the differences of individual tests. For the PNEC derivation, the lowest effect value found with coco amine as test substance are used.

3.2.1.2 Calculation of Predicted No Effect Concentration (PNEC)

Surface water

For the five primary fatty amines under consideration short-term studies are available for fish, aquatic invertebrates and algae. Long-term data are available for aquatic invertebrates and algae.

The standard tests submitted were conducted using synthetic growth media. These tests do not take into account particulate matter and dissolved organic carbon (DOC). Since primary fatty amines are poorly soluble in water, and as they are positively charged under environmental conditions, they might adsorb to test organisms such as algae. The results ofecotoxicity testing might be influenced by these secondary effects. In order to reduce the influence of secondary effects modifications such as river water tests or tests in the presence of humic acids) can be introduced as more realistic conditions. Then the additional studies might be used as higher tier studies.

For the aquatic risk assessment of strongly sorbing substances the current *Technical Guidance Documents* do~~es~~ not provide sufficient guidance concerning both effects and exposure assessment. An alternative for strongly sorbing substances can be the $PEC/PNEC_{aquatic\ bulk}$ approach (ECETOC 2003). This approach is based on a $PNEC_{aquatic\ bulk}$ which is derived from a modified ecotoxicity test using humic acid, natural water or effluent and a $PEC_{local,\ aquatic\ bulk}$ which represents the total aquatic concentration (dissolved and sorbed = bulk). The risk quotient for the aquatic compartment is calculated by using nominal concentrations.

Testing primary fatty amines under more realistic conditions in the presence of humic acids or in river water indicate that bioavailability is lower compared to studies using standard media. Following the reasoning above, tests conducted under environmentally realistic conditions (i.e. in river water) will be used for effects assessment of primary fatty amines.

Based on the available lowest short-term toxicity values (table 3.2.8) it can be concluded that aquatic invertebrates and algae are in general more sensitive towards primary fatty amines than fish. However, the difference in toxicity is not significant (in most cases not an order of magnitude).

The most sensitive species in long term studies using river water appears to be the freshwater invertebrate *Daphnia magna* with a NOEC from a 21d-reproduction study of 0.013 mg/l (nominal) for coco alkyl amine, tallow alkyl amine and oleylamine.

The $PNEC_{aquatic\ bulk}$ is calculated using the assessment factor proposed by the TGD. As long-term NOECs from species representing two trophic levels are available (algae and daphnia) an assessment factor of 50 may be used. Applying this factor to the long-term NOEC for aquatic invertebrates derived from a river water tests leads to

$$\mathbf{PNEC_{aquatic\ bulk} = 0.013\ mg/l / 50 = 0.26\ \mu g/l}$$

This $PNEC_{aquatic\ bulk}$ covers all 5 primary alkyl amines that are subject of this risk assessment.

Tab. 3.2.8: Summary of the lowest toxicity values (nominal) of primary fatty amines for aquatic species [mg/l]

	Chain	Fish, LC50	Crustacea, LC50	Algae, EC50 / NOEC
Octylamine	C8	*Brachydanio rerio* 96h-LC50 = 10-100		*Selenastrum capricornutum* 96h-EC50 = 0.22
		Pimephales promelas 96h-LC50 = 5.19 **m?**		
Decylamine	C10	*Brachydanio rerio* 96h-LC50 = 1-10		
		Pimephales promelas 96h-LC50 = 1.04 **m?**		
Dodecylamine	C12	*Pimephales promelas* 96h-LC50 = 0.103 **m?**		
		Brachydanio rerio 96h-LC50 = 0.42 **S**		
Coco alkyl amines	C12/ C14	*Oncorhynchus mykiss* 96h-LC50 = 0.16 **S, P(s)**	*Daphnia magna* 48h-EC50 = 0.045 **S, P(s)**	*Scenedesmus subspicatus* 96h-EBC50 = 0.0008 ***) S, P(s)** 96h-NOEC = 0.0002 ***)**
		Brachydanio rerio 96h-LC50 = 0.24 **S**	*Daphnia magna* 48h-EC50 = 0.09	*Scenedesmus subspicatus* 72h-ERC50 = 0.17 72h-ERC10 = 0.071
			Daphnia magna 21d-NOECrepro = 0.013 **R, A**	*Desmodesmus subspicatus* 72h-ERC50 = 0.16 **R, A** 72h-NOEC = 0.06
Tetradecylamine	C14			
Hydrogenated tallow alkyl amines	C16/ C18	*Brachydanio rerio* 96h-LC50 = 0.88 **S**	*Daphnia magna* 48h-EC50 = 0.16 **S**	*Scenedesmus subspicatus* 96h-EBC50 = 0.012 ***) S, P(s)** 96h-NOEC = 0.008 ***)**
			Daphnia magna 48h-EC50 < 1 **C, P(si), A**	
Tallow alkyl amines	C16/ C18	*Brachydanio rerio* 96h-LC50 = 0.18-0.25 **S**	*Daphnia magna* 48h-EC50 = 0.093 **R, S**	*Scenedesmus subspicatus* 96h-EBC50 = 0.007 ***) S, P(s)** 96h-NOEC = 0.002 ***)**
			Daphnia magna 21d-NOECrepro = 0.013 **R, A**	*Scenedesmus subspicatus* 72h-ERC50 = 0.083 72h-ERC10 = 0.045
				Desmodesmus subspicatus 72h-ERC50 = 0.39 **R, A** 72h-NOEC = 0.125
Octadecylamine	C18	*Brachydanio rerio* 96h-LC50 = 1-10	*Daphnia magna* 48h-EC50 = 0.13	*Scenedesmus subspicatus* 72h-ERC50 = 0.12 72h-ERC10 = 0.029
(Z)-octadec-9-enylamine	C18'	*Pimephales promelas* 96h-LC50 = 0.11 **A** 96h-LC50 = 1.50 **(10 mg/l ha)** 96h-LC50 = 2.13 **(20 mg/l ha)**	*Daphnia magna* 48h-EC50 = 0.011 **A** 48h-EC50 = 0.43 **(10 mg/l ha)** 48h-EC50 = 0.56 **(20 mg/l ha)**	*Selenastrum capricornutum* 96h-ERC50 = 0.04 **A** 96h-NOEC = 0.01 96h-ERC50 = 0.37 **(5 mg/l ha)** 96h-NOEC = 0.09 96h-ERC50 = 0.76 **(10 mg/l ha)** 96h-NOEC = 0.19
		Brachydanio rerio 96h-LC50 = 0.1-1	*Daphnia magna* 21d-NOECrepro = 0.013 **R, A**	*Desmodesmus subspicatus* 72h-ERC50 = 0.46 **R, A** 72h-NOEC = 0.15

m measured **R** River water **C** undissolved particles removed via centrifugation **S** solubilizer / solvent
P(s) Pre-treatment of test vessels (soaked with test substance overnight) **P(si)** Pre-treatment of test vessels (silanized)
***)** not valid **A** Analytical data available **ha** humic acid

Sewage treatment plants (PNECmicro-organisms)

There are 5 respiration tests on sewage sludge available. The lowest effect value was found with coco amine as test substance, the EC10 was determined to 5.5 mg/l (Hoechst AG (1989b). According to the *Technical Guidance Documents*, an assessment factor of 10 has to be applied. The PNEC for the assessment of microbial activity in biological treatment plants is calculated to

$PNEC_{micro\text{-}organisms}$ = 550 µg/l.

This $PNEC_{micro\text{-}organisms}$ is used for the risk characterization for sewage treatment plant for all 5 primary alkyl amine that are subject of this risk assessment.

3.2.1.3 Toxicity test results for sediment organisms

For primary fatty amines only one test result is available regarding the sediment toxicity of tallow alkyl amine:

Höß examined the toxicity of tallow alkyl amine (test substance Genamin TA 100 D) on the nematode *Caenorhabditis elegans* using artificial sediment according to the method of Traunspurger et al. 1997. *C. elegans* is a widespread, free living nematode which is primarily found in terrestrial soils but also occurs in aquatic sediments. The nematode feeds primarily on bacteria but also on small particles such as sediment.

During the study artificial sediment (particle size distribution: 44% sand, 48% silt, 8% clay, organic content: 2%) was spiked with the test substance in various concentrations (nominal concentration range between 811 and 2030 mg/kg sed dw). Two test series were carried out, a range finding test and the main test. For spiking of sediments tallow alkyl amine was dissolved in pure ethanol and 10 µl of the ethanol stock solution was added to 0.5 g sediment that was already mixed with 0.5 ml of M9-medium (phospate buffer). Thus, the maximum ethanol concentration did not exceed 1% which is tolerated by the nematodes. In order to allow the chemicals to equally distribute between aqueous and solid phase, the spiked sediment was incubated for 24 h before the start of the test.

Test parameters were growth (body length in µm), egg production (number of eggs inside the body) and fertility (percentage of gravid worms). Before the start of the assay, 0.25 ml of bacterial suspension (*E. coli* in M9 medium) were added to each vessel as food for the nematodes. After that 10 juvenile worms of the first stage (J1) were added to each vessel, containing now 0.5 g sediment (ww), 0.5 ml test solution and 0.25 ml bacterial suspension. The vessels were then incubated for 72 h on the shaker at 20°C. Five (three) replicates were set up for the main test (range finding test). In order to stop the assay, the nematodes were heat killed and stained with Rose Bengal. After extracting the nematodes from the sediment, body length and number of eggs inside the body were determined under a microscope. For tallow alkyl amine no effect up to the highest tested concentration of 2030 mg/kg sed (dw) was found. Therefore a nominal NOEC of 2030 mg/kg sed (dw) was derived from this study.

Due to their physico-chemical properties primary fatty amines are expected to sorb on sediments to a significant extent resulting in a very low concentration in the porewater. Thus, in the environment, sediment organisms will mainly be exposed to the bound substance in the solid phase by sediment ingestion and direct contact. In the available study these exposure pathways are not adequately covered as the nematodes are not representative organisms for

the exposure via sediment ingestion. In addition, the nematodes were supplementary fed with a bacteria suspension, thus further reducing possible uptake of contaminated sediment by the test organisms. Summarising, it can be assumed that the available study with nematodes is not appropriate to study the effect of primary alkyl amines to the benthic community. It might be used as additional information if tests using standard sediment dwelling organisms (e.g.*Lumbriculus variegatus* and *Chironomus* spec.) are already available.

3.2.1.4 Calculation of Predicted No Effect Concentration (PNEC) for sediment organisms

In the absence of measured data the $PNEC_{sed}$ can be provisionally calculated using the equilibrium partitioning method (EPM). According to the TGD this method uses the $PNEC_{aquatic}$ and the sediment/water partitioning coefficient as inputs. However, since the available $PNEC_{aquatic}$ is based on the bulk concentration present in surface water a re-calculation is necessary first:

$$PNEC_{aquatic,\ dissolved} = PNEC_{aquatic\ bulk} / (1 + Kp_{susp} * SUSP_{water} * 10^{-6})$$

Where:
- $PNEC_{aquatic\ bulk}$ = 0.26 µg/l
- Kp_{susp} = 697 $l.kg^{-1}$
- $SUSP_{water}$ = 15 $mg.l^{-1}$ (TGD)

The $PNEC_{sed}$ is then calculated using the equations detailed in the TGD:

$$PNEC_{sed} = K_{susp\text{-}water} * PNEC_{aquatic\ dissolved} * 1000 * 1 / RHO_{susp}$$

Where:
- $PNEC_{aquatic\ dissolved}$ = 0.257 µg/l
- $K_{susp\text{-}water}$ = 175 $m^3.m^{-3}$
- RHO_{susp} = 1150 $kg.m^{-3}$ (TGD, equ. 18)

$PNEC_{sed}$ = 39 µg/kg ww

3.2.2 Terrestrial compartment

3.2.2.1 Toxicity test results

3.2.2.1.1 Plants

Two acute studies have been performed on terrestrial organisms (plants and earthworms) using both tallow alkyl amine (Genamin TA 100 D) as test substance:

The growth test with terrestrial plants was conducted according to the OECD Guideline 208 by Noack (2000). Test systems were a monocotyledon (oat) and two dicotyledons (red clover and radish). Seeds of each plant were exposed to different concentrations of tallow alkyl amine (1, 10, 100 mg test item per kg soil dry weight) and a control. No vehicles were used to dissolve the test substance. The toxic effects of the soil incorporated test item on the emergence of seedlings and the early stages of growth were determined by visual observations and dry weight determination. No phytotoxic effects were observed throughout the test in all replicates resulting in a LC50 (emergence) and a EC50 (growth) of > 100 mg/kg dw.

3.2.2.1.2 Earthworms

Acute toxicity

Noack (1999) determined the acute effects of tallow alkyl amine on earthworm *Eisenia fetida* according to OECD Guideline 207. Different concentrations of tallow alkyl amine (100, 180, 320, 580, 1000 mg/kg dry weight) were applied once at the beginning of the test. No significant mortality was observed in any of the tested concentrations after 14 days of exposure. As test result a LC50 > 1000 mg/kg dry weight was obtained from this study.

Long-term toxicity

The effects of amines, hydrogenated tallow (Armeen HT) on mortality, biomass and reproduction of Eisenia fetida were tested according to OECD 222 under a static exposure for 28 days. Natural soil (Lufa 2.2) was used as substrate, and the different concentration of the substance mixed with the substrate. The concentrations applied were 50, 100, 200, 500, and 1,000 mg/kg soil dry weight. In addition tests using control and vehicle control were performed.

The test is valid without restrictions and the results are reliable. After 28 days of exposure, no effects on survival of the adult worms were observed in all concentrations. After the following four weeks, the reproduction rate (average number of juveniles) was significantly reduced in the concentrations of 500 and 1,000 mg/kg soil compared to the control. Hence, the LOEC is 500 mg/kg soil and the NOEC 200 mg/kg soil.

3.2.2.1.3 Other terrestrial organisms

The results of three studies of the nematodical effect of primary fatty amines on three different species of nematode are summarized in table 3.2.9. The tests were carried out under comparable conditions at 37°C in NaCl solution. The EC100 values determined with *Ancylostoma cannium* reveal an increasingly toxic effect with increasing chain length of the fatty amines (Ishizuka et al. 1971).

Tab. 3.2.9: Nematodical effect of primary fatty amines (test conditions 37°C, NaCl-solution)

Species	effect [mg/l]	C8	C10	C12	C16	C18	Reference
Toxocara canis (larvae) (dog ascarid)	3h-EC100	-	79	-	-	-	Kiuchi et al. 1987
Ancylostoma cannium (larvae) (dog hookworm)	24h-EC100	200	200	6.25	3.13	1.6	Ishizuka et al. (1971)
Ascaris lumbricoides (human ascarid)	1h-EC0 0.5h-EC100	- -	1000 -	- 1000	- -	- -	Anderson and Hurwitz (1953)

Nagase et al. (1982) exposed the nematode *Bursaphelenchus lignicolus* to different fatty amines in an aqueous test solution for 24 hours at 25°C (100 worms/ml; amine concentration 10 E-3 – 10 mmol/l; at chain lengths of and above 14 C atoms using solubilizer). The toxic effect on the nematodes increased from octylamine (24h-LC50 = 15.5 mg/l) to decylamine (24h-LC50 = 11.8 mg/l) and then remained constant for the longer chain homologous at 24h-LC50 = 2.1-2.3 mg/l.

However, as unsuitable test systems were used, the test results obtained for *Ancylostoma cannium* and *Bursaphelenchus lignicolus* can only give a rough indication of the nematodical effect of primary fatty amines and are therefore not used for the further assessment.

3.2.2.2 Calculation of Predicted No Effect Concentration (PNEC)

For primary fatty amines terrestrial effects data on earthworms (acute and long-term) and a growth test with terrestrial plants were submitted.

In the acute tests no effects were observed up to the highest concentration tested (earthworms: 1000 mg/kg soil, plants: 100 mg/kg soil). In the reproduction tests using earthworms a NOEC of 200 mg/kg soil was determined.

According to the TGD, an assessment factor of 100 is applied to the lowest effect value, leading to a **$PNEC_{soil}$ of 2.0 mg/kg dw**.

3.2.3 Atmosphere

There are no fumigation tests with primary alkyl amines as test substance available. Because an exposure of the atmosphere is not expected, an assessment for this compartment is not necessary.

3.2.4 Secondary poisoning

3.2.4.1 Effect data

So far there is no PNECoral available, thus this endpoint cannot be assessed.

3.2.4.2 Calculation of $PNEC_{oral}$

[click here to insert text]

3.3 RISK CHARACTERISATION [4]

3.3.1 Aquatic compartment (incl. sediment)

The risk assessment for aquatic organisms resulted in a $PNEC_{aqua,bulk}$ of 0.26 µg/l derived from a chronic study using daphniae and river water as test medium. For the assessment of microorganisms in biological treatment plants the $PNEC_{micro-organism}$ was calculated to 550 µg/l, and for benthic organisms the PNECsediment to 39 µg/kg ww. For releases into the sea, a PNEC of 0.026 µg/l for seawater and 3.9 µg/kg ww for sediments were determined.

Production:

Exposure scenarios were calculated based on site-specific data for 6 European production sites. As parts of the products are processed at the same sites, releases due to processing activities are partially included.

Tab. 3.3.1: RCRs for production of primary alkyl amines

Site	Substance	Ceff [µg/l]	Ceffluent / $PNEC_{microorg.}$	$PEClocal_{aqua\ bulk}$ [µg/l]	$PEClocal_{aqua\ bulk}$ / $PNEC_{aqua}$	$PEClocal_{sed}$ [µg/kg ww]	$PEClocal_{sed}$ / $PNEC_{sediment}$
A	Coco	6.8 E-02	1.2 E-04	1.1 E-02	4.1 E-02	1.62	4.1E-02
	Tallow	4.5 E-03	8.2 E-06	1.1 E-02	4.1 E-02	1.62	4.1E-02
	Hydr.Tallow	2.2 E-02	4.1 E-05	1.1 E-02	4.1 E-02	1.62	4.1E-02
	C18=	1.0 E-02	1.9 E-05	1.1 E-02	4.1 E-02	1.62	4.1E-02
B	Coco	5.8 E-03	1.1 E-05	1.4 E-02	5.4 E-02	2.11	5.4E-02
	Tallow	1.6 E-03	2.9 E-06	1.2 E-02	4.5 E-02	1.75	4.5E-02
	Hydr.Tallow	4.0 E-03	7.2 E-06	1.3 E-02	5.0 E-02	1.95	5.0E-02
	C18	1.0 E-04	1.9 E-07	1.1 E-02	4.1 E-02	1.62	4.2E-02
	C18=	1.0 E-03	1.9 E-06	1.1 E-02	4.3 E-02	1.70	4.4E-02
C	Coco	3.2 E-01	5.9 E-04	2.0 E-02	7.5 E-02	2.95	7.6E-02
	Tallow	6.8 E-02	1.2 E-04	1.3 E-02	4.8 E-02	1.90	4.9E-02
	Hydr.Tallow	4.0 E-02	7.2 E-05	1.2 E-02	4.5 E-02	1.78	4.6E-02

[4] Conclusion (i) There is a need for further information and/or testing.
Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.
Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Site	Substance	Ceff [µg/l]	Ceffluent / $PNEC_{microorg.}$	$PEClocal_{aqua\ bulk}$ [µg/l]	$PEClocal_{aqua\ bulk}$ / $PNEC_{aqua}$	$PEClocal_{sed}$ [µg/kg ww]	$PEClocal_{sed}$ / $PNEC_{sediment}$
	C18=	4.3 E-02	7.8 E-05	1.2 E-02	4.6 E-02	1.79	4.6 E-02
D	Coco	3.4 E-03	6.2 E-06	1.2 E-02	4.7 E-02	1.84	4.7 E-02
	Tallow	1.3 E-03	2.3 E-06	1.1 E-02	4.3 E-02	1.70	4.4 E-02
	Hydr.Tallow	1.3 E-03	2.3 E-06	1.1 E-02	4.3 E-02	1.70	4.4 E-02
	C18=	6.3 E-04	1.2 E-06	1.1 E-02	4.2 E-02	1.66	4.2 E-02
E	Coco	7.7 E-01	1.4 E-03	1.5 E-02	5.8 E-02	2.28	5.8 E-02
	Tallow	3.2 E-01	5.8 E-04	1.3 E-02	4.8 E-02	1.89	4.9 E-02
	Hydr.Tallow	1.3 E+01	2.4 E-02	8.5 E-02	3.3 E-01	12.9	3.3 E-01
	C18=	1.9 E-01	3.4 E-04	1.2 E-02	4.5 E-02	1.78	4.6 E-02
F	Coco	3.2 E-01	5.9 E-04	1.1 E-02	4.1 E-02	1.62	4.2 E-02
	Tallow	2.0 E-03	3.7 E-06	1.1 E-02	4.1 E-02	1.62	4.1 E-02
	Hydr.Tallow	4.1 E-03	7.4 E-06	1.1 E-02	4.1 E-02	1.62	4.1 E-02
	C18=	4.1 E-04	7.4 E-07	1.1 E-02	4.1 E-02	1.62	4.1 E-02

ww: wet weight

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Formulation of fertilizers:

A generic scenario was calculated covering releases into freshwater.

Tab. 3.3.2: RCRs for releases during formulation of fertilizers

Ceff [µg/l]	Ceffluent / $PNEC_{microorg.}$	$PEClocal_{aqua\ bulk}$ [µg/l]	$PEClocal_{aqua\ bulk}$ / $PNEC_{aqua}$	$PEClocal_{sed}$ [µg/kg ww]	$PEClocal_{sed}$ / $PNEC_{sediment}$
0.986	1.8 E-03	0.11	0.42	16.5	0.42

ww: wet weight

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Processing to aminoethoxylates:

For this endpoint, 2 scenarios were calculated.

Scenario Eth 1

This scenario was calculated on the basis of specific data for one site processing primary alkyl amines in large amounts. This site has no sewage treatment plant, thus an assessment for microorganisms is not performed.

Releases from this site are expected to occur at 1 day per year, therefore the risk characterisation for the aquatic compartment is performed using the PNECintermittent of 2.6 µg/l (derived from the PNECaqua using a factor of 10). For the sediment compartment the PNECsed of 39 µg/kg ww is used as exposure of the sediment is not regarded as intermittent.

Tab. 3.3.3: RCRs for intermittent exposure from ethoxylation of primary alkyl amines at one large site

Substance	$PECIocal_{aqua\ bulk}$ [µg/l]	$PECIocal_{aqua\ bulk}$ / $PNEC_{aqua}$	$PECIocal_{sed}$ [µg/kg ww]	$PECIocal_{sed}$ / $PNEC_{sediment}$
Coco	1.3 E-2	5.0 E-3	2.0	5.1 E-2
Tallow	4.1 E-2	1.6 E-2	6.2	0.16
Hydr.Tallow	1.3 E-2	5.0 E-3	1.9	4.9 E-2
Oleyl	3.1 E-2	1.2 E-2	4.6	0.12

ww: wet weight

Scenario Eth 2

A generic scenario was calculated covering intermittent releases of a number of processing sites consuming relatively small amounts.

Tab. 3.3.4: RCRs for intermittent exposure from ethoxylation of primary alkyl amines at a number of small sites

Ceff [µg/l]	$Ceffluent$ / $PNEC_{microorg.}$	$PECIocal_{aqua\ bulk}$ [µg/l]	$PECIocal_{aqua\ bulk}$ / $PNEC_{aqua}$	$PECIocal_{sed}$ [µg/kg ww]	$PECIocal_{sed}$ / $PNEC_{sediment}$
0.52	9.5 E-04	6.3 E-2	2.4 E-2	9.5	0.24

ww: wet weight

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Processing to sulphosuccinamates:

There are scenarios calculated for 4 sites, based partially on site-specific and default parameters. For the sites 1, 2, and 4, the $PNEC_{intermittent}$ of 2.6 µg/l is used for the risk characterisation for surface waters. For the sediment compartment the PNECsed of 39 µg/kg ww is used as as exposure of the sediment is not regarded as intermittent.

Tab. 3.3.5: RCRs for releases during processing to sulphosuccinamates

Scenario	Ceff [µg/l]	Ceffluent / $PNEC_{microorg.}$	$PEClocal_{aqua\ bulk}$ [µg/l]	$PEClocal_{aqua\ bulk}$ / $PNEC_{aqua}$	$PEClocal_{sed}$ [µg/kg ww]	$PEClocal_{sed}$ / $PNEC_{sediment}$	Type of release
Sulph1	4.25	7.7 E-03	0.15	5.8 E-2	22	0.56	intermittent
Sulph2	4.25	7.7 E-03	2.1 E-02	8.1 E-3	3.1	7.9 E-2	intermittent
Sulph3	2.89	5.3 E-03	1.5 E-02	5.8 E-2	2.2	5.6 E-2	continous
Sulph4	4.25	7.7 E-03	2.7 E-02	1.0 E-2	4.1	0.11	intermittent

ww: wet weight

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Processing to other products:

There are scenarios calculated for 2 sites, based partially on site-specific and default parameters.

Tab. 3.3.6: RCRs for releases during processing to other products

Scenario	Ceff [µg/l]	Ceffluent / $PNEC_{microorg.}$	$PEClocal_{aqua\ bulk}$ [µg/l]	$PEClocal_{aqua\ bulk}$ / $PNEC_{aqua}$	$PEClocal_{sed}$ [µg/kg ww]	$PEClocal_{sed}$ / $PNEC_{sediment}$
Other1	0.26	4.7 E-04	1.1 E-02	4.2 E-2	1.6	4.1 E-2
Other2	8.8	1.6 E-02	1.1 E-02	4.2 E-2	1.7	4.4 E-2

ww: wet weight

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Releases during floatation:

For the use of primary alkyl amines as floatation agents, 3 exposure scenarios were calculated. For two of the sites, the concentration in the effluent stream and the receiving river bodies were measured to refine the assumptions. The results are also included in table 3.3.7.

Tab. 3.3.7: RCRs for releases during floatation

Scenario	$PECloca l_{aqua\ bulk}$ [µg/l]	$PECloca l_{aqua\ bulk}$ / $PNEC_{aqua}$	$PECloca l_{sed}$ [µg/kg ww]	$PECloca l_{sed}$ / $PNEC_{sediment}$	Compartment
Float1[5]	0.023	0.09	2.1	0.05	Freshwater
Float2[6]	< 0.09	< 0.4	<12	<0.3	Freshwater
Float3	0.055	0.21	6.7	0.17	Freshwater

ww: wet weight

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

3.3.2 Terrestrial compartment

The risk assessment for terrestrial organisms resulted in a $PNEC_{soil}$ > 1.77 mg/kg ww (> 2.0 mg/kg dw).

Production / Processing:

Several scenarios were calculated for the sites with the highest releases into waste water.

Tab. 3.3.8: RCRs for terrestrial exposure due to application of sewage sludge

Scenario	$PECloca l_{soil}$ [mg/kg ww]	$PECloca l_{soil}$/ $PNEC_{soil}$
Prod E	1.0	0.57
Prod A	0.040	0.02
Formulation Fertilizer	1.4	0.79
Floatation	0.40	0.23

ww: wet weight

[5] PEC refined using measured data
[6] PEC refined using measured data

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Use as anticaking agent in fertilizers:

The exposure scenario, based on worst case assumptions for application rate and applied concentrations in fertilizer resulted in a PECsoil of 0.063 mg/kg ww, leading to a PEC/PNEC ratio of 0.04.

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

3.3.3 Atmosphere

Since no relevant release into the atmosphere is expected, a risk characterisation for this compartment is not necessary.

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

3.3.4 Secondary poisoning

The exposure assessment resulted in a concentration in fish-eating predators $PEC_{oral,predator}$ of 42 - 504 µg/kg. So far there is no PNECoral available, thus this endpoint cannot be assessed.

3.3.5 PBT Assessment

The available data are sufficient for a PBT assessment of primary alkyl amines.

As discussed in chapter 3.1.3.1.2, primary alkyl amines can be classified as readily degradable, fulfilling the 10-days window. Hence, the screening criteria for persistence is not met. Considering the sorption behaviour as an additional indication for possible persistence in the environment, a half life for soil and sediment can be derived using the adsorption koefficient (K_d) of 697 L/kg. According to the TGD a half life of 300 days for soil and sediment can be estimated. Taking this into further account the persistence criterion for soil and sediment ($T_{1/2}$: 120 d) might be met.

The $logP_{OW}$ calculated for the primary alkyl amines of approximately 7 indicate for a potential for bioaccumulation. The BCF is estimated using a QSAR approach for different ionic coumpounds (Meylan et al. 1999) is 158 l/kg.

In addition to that, a preliminary study on bioconcentration using fish using hexadecylamine was submitted (Akzo 2006). Since C16 and C18 are the dominating constituent of the primary amines considered in this report, this component might be useful to represent the bioaccumulation potential of the group to a certain degree. In addition to that, this approach was taken for practical reasons (solubility, availability of an analytical method). The test and the main results are described in the section on accumulation and metabolism (3.1.3.3) of this report.

However, it need to be stressed that the bioconcentration of the components with chain lenghts >C 16 might be higher than the BCF determined with C16. This need to be considered for the risk assessment of the primary alkyl amines.

The preliminary findings are only of indicative value, and the influence of the high adsorption of the primary alkyl amines in the test could only be determined to a certain degree. Using several worst case assumptions, the possible BCFs for hexadecylamine might range between 200 (nominal water concentration, concentration in fish after the removal procedure) and 2,400 (lower found back level in the aquaria, concentration in whole fish without treatment).

Although a BCF of 2,400 might be the upper level at least for the C16-components of the primary alky amines, a reliable BCF cannot be determined from the available studies. According to this (worst-case) assumptions for the BCF, the TGD criterion for bioaccumulative “vB” (BCF > 5,000) is not fulfilled. However, from the available study it cannot be excluded for some components being “B” with a BCF > 2,000 (but < 5,000).

To conclude about the “T”-criterion, the long-term effects were also considered. the lowest long-term effect value as determined for *Daphnia magna* (0.013 mg/l) does not meet the T criterion (< 0.01 mg/l) indicating that this criterion is not met.

Taking these findings together, additional hazards to the environment arising from possible PBT- or vPvB properties are not expected. Considering the degradation behaviour and bioaccumulation potential, the primary alkyl amines under consideration are neither PBT- nor vPvB-candidates.

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

4.1.1.1 General discussion

The starting materials for manufacturing long-chain, primary alkyl amines are natural fats and oils or synthetic products of the petrochemical industry (Kirk Othmer, 1994).

The discussed five primary alkyl amines are mixtures of primary straight chain alkyl amines partially with one or more double bonds.

	Tallow alkyl amine	(Z)-Octadec-9-enylamine	Octadecyl amine	Hydrogenated tallow alkyl amine	Coco alkyl amine
CAS-No.	61790-33-8	112-90-3	124-30-1	61788-45-2	61788-46-3
m.p.	32 – 40 °C	15 - 30 °C	49 – 52 °C	48 – 56 °C	12 – 17 °C
vp.	< 1 Pa	< 1 Pa	< 1 Pa	< 1 Pa	< 1 Pa
form	paste	liquid	solid (flake, prill)	solid (flake, prill)	liquid
C & L	R 35	R 35	R 38	R 38	R 35

The five primary alkyl amines are produced by several manufactures in the EU and the total European consumption amounts 29.330 t/year.

In 2001, about 80 % of the primary fatty amine consumption was accounted for their use as intermediates in the production of ethoxylates fatty amines, diamine derivates, sulphosuccinic amides, other intermediates and particularly products with amide structure. The remaining approx. 20 % of primary fatty amine consumption was accounted for their direct use or in the form of their salts (chlorides, acetates, stearates, oleates), mainly as anticacking agents for fertilizers (14 %), as flotation agents (3 %), as lubricant and fuel additives (2 %) and, to a lesser content, as corrosion inhibitors, as dispersing agents for pigments, rubber additive and in textile formulations (1 %).

In the literature there is often no distinction between the use of primary alkyl amines in general, primary alkyl amine salts or products on basis of primary alkyl amines (ethoxylates, fatty amine, diamine derivate, amide).

The detailed production process is described in chapter 2.1.

For workers the inhalation and dermal exposure routes are the most likely.

A new request at the Swedish (KEMI, personal communication, 2008) and the Swiss product registers (Swiss Federal Office of Public Health, personal communication, 2008) demonstrated that primary alkyl amines are used as ingredients of consumer products (detailed information see chapter 4.1.1.3). The information from the Swiss product register had included exposure information until the end of year 2005 latest.

4.1.1.2 Occupational exposure

Industrial activities using primary alkyl amines present opportunities for exposure. Exposure ranges depend on the particular operation and the risk reduction measures in use.

OELs (Occupational exposure limit) are not established in the EU (ARIEL, 2006).

The exposure assessment generally aims at assessing exposure levels representing the reasonable worst case situation. The reasonable worst case is regarded as the level of exposure which is exceeded in a small percentage of cases over the whole spectrum of likely circumstances of use for a specific scenario.

The assessment of inhalation exposure is mainly based on measured exposure levels from which – if possible – 90^{th} percentiles are derived as representing reasonable worst case situations. Scenarios are clustered as far as possible to make the description transparent. If quantitative exposure data are not available, model estimates are used.

Beside inhalation exposure, dermal exposure is assessed for each scenario. Two terms can be used to describe dermal exposure:

Potential dermal exposure is an estimate of the amount of a substance landing on the outside of work wear and on the exposed skin.

Actual dermal exposure is an estimate of the amount of a substance actually reaching the skin.

Within the framework of existing substances there is an agreement between the EU member states, to assess – as a rule – dermal exposure as exposure to hands and parts of the forearms. In this, the main difference between both terms – potential and actual - is the protection of hands and forearms by work wear and – more important – the protection by gloves. Within this exposure assessment, the exposure-reducing effect achievable by gloves is only considered if information is provided indicating that, for a certain scenario, gloves are a widely accepted protective measure and that the gloves are fundamentally suitable for protection against the substance under consideration. As a measure for the latter, tests according to DIN EN 374 are taken as a criterion. For most downstream uses it is commonly known that gloves are not generally worn. In these cases, dermal exposure is assessed as actual dermal exposure for the unprotected worker. Since quantitative information on dermal exposure is often not available, the EASE model is mostly used for assessing dermal exposure.

Relevant occupational exposure scenarios are to be expected in the following areas:

Scenario 1: Occupational exposure from production and further processing (4.1.1.2.1)

Scenario 2: Further processing of primary alkyl amines (4.1.1.2.2)

Scenario 3: Use of primary alkyl amines in floatation process (4.1.1.2.3)

Scenario 4: Formulation of products containing primary alkyl amines (4.1.1.2.4)

In the literature further uses as corrosion inhibitors, as photochemical, as fertilisers, as fungicides, as limestone removers, as carpet cleaners, as human medicines or as preservatives in paints, leather and cosmetics are mentioned. The possible exposure during the use of this kind of preparations is not described in this exposure assessment, because it is not known, whether the uses of primary alkyl amines in the mentioned formulations really exist, and, if they do, the concentration of primary alkyl amines is considered to be low.

On account of the low concentration of primary alkyl amines in fertilisers (< 0.2 %), exposure scenarios in the context of handling of fertilisers are regarded to be of minor relevance. Therefore they are not discussed within the framework of this exposure assessment.

4.1.1.2.1 Occupational exposure from production (scenario 1)

Starting materials in the manufacture of long-chain, primary alkyl amines are natural fats and oils, or synthetic products of the petrochemical industry. The primary alkyl amines are manufactured by catalytic hydrogenation of nitriles obtained from fatty acids at high temperatures (80 – 180 °C) and pressures (1 – > 10 MPa). After separation from the catalyst, the reaction products are purified by distillation under reduced pressure. The production takes place continuously or partially batchwise in closed systems.

All of these products are predominanly handled as molten liquids at temperatures typically up to 80°C. The end products are conveyed in a system of closed pipes and filled into tank trucks or drums via closed pipelines (BUA, 1996). The products are stored in tanks as liquids with nitrogen as protective gas (Hoechst, 1996; Akzo Nobel, 1997). Exposure is therefore effectively limited to sampling or loading activities.

An exception exists for hydrogenated tallow alkyl amine and octadecylamine which are processed in a solid form either as prills or flakes (APAG, 2003).

Inhalation exposure

On account of the melting points the primary alkyl amines are transferred in a molten state via heated pipelines and tanks to the next processing stage. Octadecylamine and hydrogenated tallow amine are produced as solids (flakes, prills). During the handling of the liquid octadecenylamine and coco alkyl amine as well as during handling of the pasty tallow alkyl amine, on account low vapour pressure (< 1 Pa), inhalation exposure to vapour is expected to be low. Inhalation exposure to dust is possible if solid octadecylamine and hydrogenated tallow amine are handled.

Measured data

Tab. 4.1.: Exposure at workplaces during production of hydrogenated tallow alkyl amine (provided by four producers) (APAG, 2003).

Job category Activities	Year of measurment	Number of samples	Inhalable dust [mg/m³]	Respirable dust [mg/m³]	Total primary amines [mg/m³]
TWA					
Bagging operator	2003	1 (pers) 4 (stat)	< 0.38 < 0.21 – 0.85	- -	0.1 0.16 – 0.57
Filling section Flaking section	2003	1 1	0.46 0.71	0.07 0.125	- -
Bag filling Pellet machine	2003	2 (stat) 2 (stat)	< 0.09 < 0.08	-	< 0.009 0.04
Hydrogenated tallow amine production	2003	1 (stat)	-	0.51	-

pers = personal sampling , stat = stationary sampling

Exposure concentration of dust were determined by a gravimetric method (inhalable: BIA 7552, NIOSH 500; respirable: BIA 7284). The quantity of amines on the dust filter was determined by gas chromatography coupled to mass spectrometry. Due to the measurement method and the sampling strategy applied, the results are regard as valid.

During manufacturing of liquid primary alkyl amine products (distilled C12- amine and coco amine) the concentration of total amine in air have been determined (Akzo, 2008). Sampling was performed with stationary pumps inside the reactor hall and pumps carried by operators during drumm filling in the packing hall. The air was drawn through a gas bubble flask filled with a solution that captures the amines and analysed with a liquid chromatography method. The portable samples (sampling time one hour) show a total amine concentration of 0.04 mg/m^3.

On account of the low number of measurement values (primary alkyl amine specifically) for handling of solids the highest value of 0.57 mg/m^3 (see Tab. 4.1) is taken.

Summary of the exposure level

Inhalation exposure has to be assessed for the production of solid primary alkyl amines (C18-amine) in large-scale chemical industry. Normally the primary alkyl amines are handled in melted form. Due to the low vapour pressure inhalation exposure is expected to be low. Octadecylamine and hydrogenated tallow alkyl amine are solids (prills or flakes).

For the assessment of the risks of daily inhalation exposure to octadecylamine and hydrogenated tallow alkyl amines an 8-h time weighed average concentration (8-h TWA) of 0.6 mg/m^3 (highest measurement value, round off) should be taken. The level represents the reasonable worst case situation. It is to be assumed that the substances are processed daily. Consequently, the duration and the frequency of exposure are assumed to be daily and for the entire length of the shift.

Dermal exposure

For assessing actual dermal exposure levels, it has to be considered that the substances are produced and further processed primarily in closed systems. Due to the melting temperature of maximal 56°C, the molten primary alkyl amines are transferred and filled at elevated temperatures (T >80°C). As a consequence worker would avoid any direct dermal contact to the hot primary alkyl amines.

Another point of avoiding of dermal contact is the corrosive effect of tallow alkyl amine, coco alkyl amine and octadecenylamine (labelled with R 35). For the handling of corrosive substances, immediate dermal contacts occur only occasionally. It can be assumed that, as a rule, daily repeated immediate skin contact is avoided to a large extent by using suitable personal protective equipment (PPE, here: gloves and eye protection).

Dermal exposure is not assessed for corrosive substances.

Octadecylamine and hydrogenated tallow alkyl amine are labelled with R 38 and sold as flakes or prills. For the handling of the solid substances, as a rule, the suitability of the gloves can be assumed and low levels of daily dermal exposure are to be expected. However, in spite of this, dermal exposure may occur due to e.g.

- unintended contamination during the handling of used gloves
- limited protection of suitable gloves at real working conditions (e.g. mechanical stress)

Since no measurement results are available, an attempt is made to quantify dermal exposure for the above mentioned situations (solid primary alkyl amines, R 38) in application of the EASE model.

During activities like bagging, filling, cleaning and maintenance dermal exposure could occur.

Modelled data

According to the EASE model, potential dermal exposure is assessed as follows:

Input parameters: Non dispersive use, direct handling, intermittent

Level of exposure: 0 - 1 mg/cm^2/day.

The consideration of an exposed area of 420 cm² (equivalent of one hand) leads to exposure levels of 42 - 420 mg/person/day.

It is assumed that the use of PPE (here gloves) is highly accepted in the large scale chemical industry. The protection of gloves is considered in a default value of 90 %.

Summary of the exposure level

For assessing the health risks from daily dermal exposure in the area of production of solid octadecylamine and hydrogenated tallow alkyl amine (prills, flakes) is considered.

For handling the solid primary alkyl amine, dermal exposure is assessed to 42 – 420 mg/person/day. The use of suitable gloves reduces dermal exposure to 10% leading to exposure of 4.2 – 42 mg/person/day. The upper value is regarded to represent the reasonable worst case.

Dermal exposure is not assessed for corrosive substances tallow alkyl amine, coco alkyl amine and octadecenylamine.

Exposure to the eyes is largely avoided by using eye protection.

4.1.1.2.2 Further processing of primary alkyl amines (scenario 2)

The following uses are clusterd within scenario 2. This scenario is not only further processing as an chemical intermediate, but, because it is large-scale industry, the scenario for formulation of ferilizers, fuel additives and lubricants is integrated.

	Coco alkyl amine	Tallow alkyl amine	Hydrogenated tallow amine	Octadecyl amine	Octadecenyl amine
Intermediate (IC 3/UC 33)	5020 t/a (97 %)	11901 t/a (98 %)	2577 t/a (34 %)	319 t/a (69 %)	3385 t/a (84 %)
Fertilizers (IC 1/UC 7)	-	13 t/a (0.1 %)	4178 t/a (55 %)	-	-
Fuel additive	-	-	-	78 t/a (17 %)	111 t/a (3 %)
Lubricants	-	13 t/a (0.1 %)	72 t/a (1 %)	-	306 t/a (8 %)

Source: APAG, 2003b

Intermediates

The major amounts (80 %) of the produced primary alkyl amines are used as intermediates in the chemical industry.

Tallow alkyl amine, octadecenylamine, hydrogenated tallow alkyl amine and coco alkyl amine are partially converted into diamines within a closed system or used as intermediates to produce mainly ethoxylated amines, amine acetates and amides. By reaction of primary fatty alkyl amine with acrylonitrile *N*-fatty alkyl-1,3-propandiamine is produced.

According to information provided by a manufacturer of tallow alkyl amine the reaction takes place at 40 C – 80°C in closed systems. The same reaction conditions are valid for octadecenylamine, hydrogenated tallow alkyl amine and coco alkyl amine.

The produced diamines are the starting material for numerous syntheses, e.g. to disinfectants and anticarious agents, are added to pigments or used as slipping agents in conveying plants e.g. bottle-filling plant.

Fertilisers

Primary alkyl amines, mainly the potassium salts are used as soil fertilisers in agriculture. In addition to that, acetate and stearyl salts of hydrogenated tallow amine are used by the potash and fertiliser industry as an anticacking agent. On account to their water-repelling properties, they prevent caking during storage and transport. (BUA, 1994; Hoechst AG, 1978b).

About 4.191 t/year primary alkly amines are used in the production of fertilisers, mainly the solid hydrogenated tallow alkyl amine (4.178 t/year) and also tallow alkyl amine (13 t/year).

According to information provided by manufacturer fertilisers contain the primary alkyl amine as anticaking agent in a concentration of up to 0.2 %. The pure alkyl amines or

10 - 20 % solutions in mineral oil are heated to 70 °C and sprayed on the powdery fertiliser. The conditioning takes place in a closed system.

On account of the low concentration of primary alkyl amine in fertilisers (up to 0.2 %), an exposure scenario in the context of handling of fertilisers is regarded to be of minor relevance. Therefore it is not discussed within the framework of this exposure assessment.

Petrochemical industry

Primary alkyl amines are used in the petrochemical industry as additive in lubricating oils, greases and fuels. Octadecenylamine (306 t/year), hydrogenated tallow alkyl amine (72 t/year) and tallow alkyl amine (13 t/year) are used predominantly in lubricants, octadecenylamine (111 t/year) and octadecylamine (78 t/year) in fuels. The term "lubricant" applies to products based predominantly on mineral oils or on synthetic oils, which are intended as lubricants, power and heat transmission media, engine oils and process oils.

Preparations are produced at room temperature or at elevated temperature, when the substances are manufactured in the liquid state. At the formulation of lubricating oil, gear oil and grease e.g. tallow alkyl amine is used in liquid form. In general the concentration of primary alkyl amine in lubricating oil, transmission oil and gear oil amounts to 0.1 - 1.5 % (MSDS of several producers). But also oils with a concentration of 10 % are known. About the concentration of octadecenylamine in fuels no information is available.

Industry has not provided any specific information on the uses of lubricating oils. According to the Nordic Product Register and The Finnish Product Register, the substance is used in the classes ‘Sale, maintenance and repair of motor vehicles and motorcycles, Retail sale of automotive fuel’ and ‘Manufacture of machinery and equipment’.

Inhalation exposure

On account of the melting points the primary alkyl amines are transferred in a molten state via heated pipelines and tanks to the next processing stage. Octadecylamine and hydrogenated tallow amine are produced as solids (flakes, prills). During the handling of the liquid octadecenylamine and coco alkyl amine as well as during handling of the pasty tallow alkyl amine, on account low vapour pressure (< 1 Pa), inhalation exposure to vapour is expected to be low. Inhalation exposure to dust is possible if solid octadecylamine and hydrogenated tallow amine are handled.

Measured data

Workplace measurements are not available.

Modelled data

The Version EASE for Windows 2.0, Aug. 1997 was used.

EASE estimation for exposure of solid primary alkyl amines (hydrogenated tallow alkyl amine, octadecylamine), during bagging or drumming

Input parameters:	T = 20 °C, exposure type is dust, low dust technique (prills, flakes), LEV present
Level of exposure:	0 - 1 mg/m^3

Summary of the exposure level

Inhalation exposure has to be assessed for the further processing of solid primary alkyl amines in fields with high levels of protection, e.g. in the large-scale chemical-, petrochemical industry.

Normally the primary alkyl amines are handled in melted form. Due to the low vapour pressure inhalation exposure is expected to be low. Octadecylamine and hydrogenated tallow alkyl amine are solids and sold as prills or flakes.

For the assessment of the risks of daily inhalation exposure to octadecylamine and hydrogenated tallow alkyl amines an 8-h time weighed average concentration (8-h TWA) of 1 mg/m^3 (EASE model estimation) should be taken. The level represents the reasonable worst case situation. It is to be assumed that the substances are processed daily. Consequently, the duration and the frequency of exposure are assumed to be daily and for the entire length of the shift.

Dermal exposure

For assessing actual dermal exposure levels, it has to be considered that the substances are produced and further processed primarily in closed systems. Due to the melting temperature of maximal 56°C, the molten primary alkyl amines are transferred and filled at elevated temperatures (T >80°C). As a consequence worker would avoid any direct dermal contact to the hot primary alkyl amines.

Another point of avoiding of dermal contact is the corrosive effect of tallow alkyl amine, coco alkyl amine and octadecenylamine (labelled with R 35). For the handling of corrosive substances, immediate dermal contacts occur only occasionally. It can be assumed that, as a rule, daily repeated immediate skin contact is avoided to a large extent by using suitable personal protective equipment (PPE, here: gloves and eye protection).

Dermal exposure is not assessed for corrosive substances.

Octadecylamine and hydrogenated tallow alkyl amine are labelled with R 38 and sold as flakes or prills. For the handling of the solid substances, as a rule, the suitability of the gloves can be assumed and low levels of daily dermal exposure are to be expected. However, in spite of this, dermal exposure may occur due to e.g.

- unintended contamination during the handling of used gloves
- limited protection of suitable gloves at real working conditions (e.g. mechanical stress)

Since no measurement results are available, an attempt is made to quantify dermal exposure for the above mentioned situations (solid primary alkyl amines, R 38) in application of the EASE model.

During activities like drumming, bagging, cleaning and maintenance dermal exposure could occur.

Modelled data

According to the EASE model, potential dermal exposure is assessed as follows:

Input parameters: Non dispersive use, direct handling, intermittent

Level of exposure: 0 - 1 mg/cm^2/day.

The consideration of an exposed area of 420 cm² (equivalent of one hand) leads to exposure levels of 42 - 420 mg/person/day.

It is assumed that the use of PPE (here gloves) is highly accepted in the large scale chemical industry. The protection of gloves is considered in a default value of 90 %.

Summary of the exposure level

For assessing the health risks from daily dermal exposure in the area of production of solid octadecylamine and hydrogenated tallow alkyl amine (prills, flakes) is considered.

For handling the solid primary alkyl amine, dermal exposure is assessed to 42 – 420 mg/person/day. The use of suitable gloves reduces dermal exposure to 10% leading to exposure of 4.2 – 42 mg/person/day. The upper value is regarded to represent the reasonable worst case.

Dermal exposure is not assessed for corrosive substances tallow alkyl amine, coco alkyl amine and octadecenylamine.

Exposure to the eyes is largely avoided by using eye protection.

4.1.1.2.3 Use of primary alkyl amines in floatation process (scenario 3)

Floatation involves the separation of a certain mineral from a mineral mix, whereby suspended mineral particles adhering to air bubbles are carried to the surface of the slurry, where they are skimmed off in the laded froth. Selective adhesion to the air bubbles is achieved by hydrophobing agents like alkyl amines and their salts (chloride and acetate), which are suitable in the floatation of halogenides (KCl and NaCl), silicates and zinc ores (BUA 199, Hoechst AG, 1978a).

The used primary alkyl amines in floatation processes are mainly hydrogenated tallow alkyl amine (solid, 664 t/year), tallow alkyl amine (paste, 193 t/year), coco alkyl amine (liquid, 87 t/year) and octadecenylamine (liquid, 65 t/year).

The flotation step is accomplished by the preparation of a pulp, consisting of a solid-liquid slurry that may contain up to 40 % solids, to which chemical reagents are added in a conditioning tank (automated, semi-automated). The products from the flotation cell are a concentrate which proceeds to the next step for further cleaning or treatment. Flotation cells usually arranged in batteries and in industrial plants and individual cells can be any size from few to 30 m^3 in volume.

Inhalation exposure

For the floatation process inhalation exposure to dust in the area of charging, dosing of hydrogenated tallow amine is considered.

During the handling of the liquid octadecenylamine and coco alkyl amine as well as during handling of the pasty tallow alkyl amine, on account low vapour pressure (< 1 Pa), inhalation exposure to vapour is expected to be low.

Measured data

Workplace measurements are not available.

Modelled data

The Version EASE for Windows 2.0, Aug. 1997 was used.

EASE estimation for exposure of solid hydrogenated tallow amine during charging, dosing.

Input parameters: T = 20 °C, exposure type is dust, low dust technique (prills, flakes), LEV absent

Level of exposure: 0 - 5 mg/m^3

The duration of exposure is not known for the particular case but it is estimated to be at maximum 1 hour per day. Considering the reduced exposure duration of 1 hour the resulting exposure level is 0.625 mg/ m^3.

Summary of the exposure level

Inhalation exposure has to be assessed for the charging, dosing of solid hydrogenated tallow amine during floatation.

For the assessment of health risks of daily inhalation exposure to an 8 h time weighted average concentration (8 h TWA) of 0.625 mg/m^3 (EASE estimation) should be taken to represent a reasonable worst case situation.

It is to be assumed that hydrogenated tallow amine is used daily. Consequently, the duration and the frequency of exposure to hydrogenated tallow amine are assumed to be daily and for 1 hour.

During the handling of the liquid octadecenylamine and coco alkyl amine as well as during handling of the pasty tallow alkyl amine, on account low vapour pressure (< 1 Pa), inhalation exposure to vapour is expected to be low.

Dermal exposure

In floatation processes mainly the R 38 labelled hydrogenated tallow alkyl amine (solid) are used. The R 35 labelled tallow alkyl amine (paste), coco alkyl amine (liquid) and octadecenylamine (liquid) are used in a minor extent.

For the handling of corrosive substances (tallow alkyl amine, coco alkyl amine and octadecenylamine), immediate dermal contacts occur only occasionally and it is to be assumed that skin contact is largely avoided by using PPE.

Dermal exposure is not assessed for corrosive substances.

For the use of hydrogenated tallow alkyl amine (R 38) in floatation it cannot be excluded that gloves are not regularly worn and that immediate dermal contacts occur during activities like charging and dosing.

Since no measurement results are available, an attempt is made to quantify dermal exposure for the above mentioned situations (solid hydrogenated tallow amines, R 38) in application of the EASE model.

Modelled data

Therefore dermal exposure is assessed according to the EASE model:

Input parameters: non dispersive use, direct handling, intermittent

Level of exposure: 0 - 1 mg/cm^2/day

Considering an exposed area of 420 cm^2 (equivalent of one hand) an exposure level of 42 - 420 mg/person/day is obtained.

Summary/statement of the exposure level

By using hydrogenated tallow alkyl amine which is not labelled as corrosive repeated intermediate skin contact can not be excluded. For assessing the health risks of daily dermal exposure in the area of use of preparations, an exposure level of 420 mg/person/day should be taken. This exposure assessment is based on the assumption that suitable gloves are not worn.

Dermal exposure is not assessed for corrosive substances tallow alkyl amine, coco alkyl amine and octadecenylamine.

4.1.1.2.4 Formulation of products containing primary alkyl amines (scenario 4)

To a minor extent, primary alkyl amines are applied directly (without chemical conversion).

	Coco alkyl amine	Tallow alkyl amine	Hydrog. tallow amine	Octadecyl amine	Octadecenyl amine
Formulations (metal corrosion inhibitors)	43 t/a (0.8 %)	-	-	-	8 t/a (0.2 %)
Formulations (textiles)	-	-	64 t/a (0.8 %)	-	-
Paints, antistatic agent	22 t/a (0.4 %)	-	-	-	147 t/a (3.6 %)
Rubber additive	-	-	-	65 t/a (14 %)	

Source: APAG, 2003b

The majority of the uses are based on the strong adsorption onto the surface of many different materials like cellulose, synthetic fabrics, polymers, pigments, metals or potassium salts (Hoechst AG, 1980b).

For this assessment, a generic scenario is derived based on the assumption that the formulation process for all above mentioned products and formulations is similar. The exposure to primary alkyl amines mainly takes place when the compounds are added (weighing, dosing, charging or mixing).

For the above mentioned work places it must be assumed, that LEV is not generally present and protective gloves are not regularly worn. The duration and the frequency of exposure are not known for the particular case but it is estimated to be at maximum 1 hour per day.

It can be expected that the products and formulations are object of wide dispersive use. There is no detailed information available about the concentration of the primary alkyl amines in the products and formulations. However, in order to develop sufficient exposure estimation, more specific information would be needed.

Inhalation exposure

Octadecyl amine and hydrogenated tallow amine are solids (flakes, prills) and used in rubber additives (65 t/year) or in finishing agents for textiles (64 t/year). At the handling of solids exposure to dust is possible.

During the handling of the liquid octadecenylamine and coco alkyl amine, on account low vapour pressure (< 1 Pa), inhalation exposure to vapour is expected to be low.

Measured data

Workplace measurements are not available.

Modelled data

The Version EASE for Windows 2.0, Aug. 1997 was used.

EASE estimation for exposure of solid octadecylamine and hydrogenated tallow amine during charging, dosing.

Input parameters:	T = 20 °C, exposure type is dust, low dust technique (prills, flakes), LEV absent
Level of exposure:	0 - 5 mg/m^3

The duration of exposure is not known for the particular case but it is estimated to be at maximum 1 hour per day. Considering the reduced exposure duration of 1 hour the resulting exposure level is 0.625 mg/m^3.

Summary of the exposure level

Inhalation exposure has to be assessed for the formulation of products and formulations containing primary fatty amines in different industrial companies.

For the assessment of the risks of daily inhalation exposure to an 8 h time weighted average concentration (8 h TWA) of 0.625 mg/m^3 (EASE) should be taken. It is to be assumed that the products and formulations are processed daily. Consequently, the duration and the frequency of exposure to octadecylamine and hydrogenated tallow are assumed to be daily and for one hour per shift.

During the handling of the liquid octadecenylamine and coco alkyl amine, on account low vapour pressure (< 1 Pa), inhalation exposure to vapour is expected to be low.

Dermal exposure

Dermal exposure has to be assessed for the formulation of products and formulations containing primary alkyl amines in the industrial area. Dermal exposure is possible when primary alkyl amines are added into mixers or reactors (weighing, dosing, mixing and charging) and by contact to contaminated surfaces.

For the handling of corrosive substances (coco alkyl amine and octadecenylamine), immediate dermal contacts occur only occasionally and it is to be assumed that skin contact is largely avoided by using PPE.

Dermal exposure is not assessed for corrosive substances.

For the use of hydrogenated tallow alkyl amine and it cannot be excluded that gloves are not regularly worn and that immediate dermal contacts occur during activities like charging and dosing.

Since no measurement results are available, an attempt is made to quantify dermal exposure for the above mentioned situations (solid hydrogenated tallow amines and octadecylamine, R 38) in application of the EASE model.

Modelled data

The corresponding exposure is assessed in application of the EASE model:

Input parameters: Direct handling, non dispersive use, intermittent

Level of exposure: 0.1 - 1 mg/cm^2/day

Considering an exposed area of 420 cm^2 (equivalent of one hand) the model yields an exposure level of 42 - 420 mg/person/day.

Summary of the exposure level

By using hydrogenated tallow alkyl amine and octadecylamine which are not labelled as corrosive repeated intermediate skin contact can not be excluded. For assessing the health risks of daily dermal exposure in the area of use of preparations, an exposure level of 420 mg/person/day should be taken. This exposure assessment is based on the assumption that suitable gloves are not worn.

Dermal exposure is not assessed for corrosive substances coco alkyl amine and octadecenylamine.

It cannot be presupposed that eye protection is regularly used. For assessing the risks, hand eye contacts as well as possible splashes to the eye should be considered.

4.1.1.2.5 Summary of occupational exposure

The five primary alkyl amines are produced by several manufactures in the EU and the total European consumption amounts to 29.330 t/year. About 80 % of the primary fatty amine consumption was accounted for their use as intermediates. The remaining approx. 20 % of primary fatty amine consumption was used as pure substances or in the form of their salts (chlorides, acetates, stearates, oleates).

In the literature there is often no distinction between the use of primary alkyl amines in general, primary alkyl amine salts or products on basis of primary alkyl amines (ethoxylates, fatty amine, diamine derivate, amide).

For occupational exposure there are four scenarios relevant:

Scenario 1: Occupational exposure from production
Scenario 2: Further processing of primary alkyl amines
Scenario 3: Use of primary alkyl amines in floatation process
Scenario 4: Formulation of products containing primary alkyl amines

The first both scenarios describe the production of primary alkyl amines (scenario 1) and the further processing as a chemical intermediate, the production of fertilisers and the formulation of lubricants/fuels in the petrochemical industry (scenario 2). On account of the melting points the primary alkyl amines are transferred in a molten state via heated pipelines and tanks to the next processing stage. Octadecylamine and hydrogenated tallow amine are produced as solids (flakes, prills). Inhalation exposure to dust is possible if solid primary alkyl amines are handled. For assessing dermal exposure levels, it has to be considered that the substances are produced and further processed primarily in closed systems. The molten primary alkyl amines are transferred and filled at elevated temperatures (T >80°C). As a consequence worker would avoid any direct dermal contact to the hot primary alkyl amines. Another point of avoiding of dermal contact is the corrosive effect. For the handling of the solid substances, as a rule, the suitability of the gloves can be assumed.

In Scenario 3 the use of primary alkyl amines (mainly hydrogenated tallow alkyl amine) in floatation processes is described. Floatation involves the separation of a certain mineral from a mineral mix. For the floatation process inhalation exposure to dust in the area of charging, dosing of hydrogenated tallow amine is considered. It is to be assumed that hydrogenated tallow amine is used daily. For this use it cannot be excluded that gloves are not regularly worn and that immediate dermal contacts occur during activities like charging and dosing.

To a minor extent, primary alkyl amines are applied for the formulation of products and formulations (scenario 4). In detail they are used in different products and preparations like dispersing and emulsifying agents in paints or rubber, in water repellent finishing agents for textiles and in corrosion inhibitors. The exposure to primary alkyl amines mainly takes place when the compounds are added (weighing, dosing, charging or mixing). For the above mentioned work places it must be assumed, that LEV is not generally present and protective gloves are not regularly worn. The duration and the frequency of exposure are not known for the particular case but it is estimated to be at maximum 1 hour per day.

It can be expected that the products and preparations are object of wide dispersive use. There is no detailed information available about the concentration of the primary alkyl amines in the formulated products. However, in order to develop a detailed exposure assessment, more specific information would be needed.

There are five primary alkyl amines to assess, two liquids (coco alkyl amine and octadecenyl amine), a paste (tallow alkyl amine) and two solids (octadecyl amine and hydrogented tallow alkyl amine). The liquid and paste primary alkyl amines are corrosive (labelled with R 35). The solid amines are skin-irritating substances (R 38). For the liquids and the paste primary alkyl amines inhalation exposure is only assumed via vapour, and because the vapour pressure is less than 1 Pa the inhalation exposure is considered to be low (no quantitative assessment). These three substances are also corrosive substances. For corrosive substances, it is the convention not to perform quantitative dermal exposure assessment. In summary, for three of the five primary alkyl amines occupational exposure could not be assessed quantitatively.

Table 4.2 Overview of the physical state and R-phrases of primary alkyl amines

	Coco alkyl amine	(Z)-Octadec-9-enylamine	Tallow alkyl amine	Octadecyl amine	Hydrogenated tallow alkyl amine
	R 35	R 35	R 35	R 38	R 38
	liquid	liquid	paste	solid	solid
Inhalation	low	low	low	Tab. 4.3	Tab. 4.3
Dermal	corrosive	corrosive	corrosive, hot	Tab. 4.3	Tab. 4.3

The remaining two, octadecyl amine and the hydrogenated tallow alkyl amine, are solids leading to dust exposure, and they are not corrosive, but skin-irritating substances. Only for these two substances, according to TGD, quantitative inhalation and dermal exposure assessments were performed (see Tab. 4.3). Since no measurement data are available EASE estimates are taken for exposure assessment.

Table 4.3 Conclusions of the occupational exposure assessment for octadecyl amine and hydrogenated tallow alkyl amine.

Scenario	Activity	Frequence days/year	Duration hours/day	Inhalation		Dermal	
				Reasonable worst case		Reasonable worst case	
				Unit mg/m³	Method	Unit mg/p/day	Method
Production							
1) Production	Drumming	daily	8 h/day	0.6	Workplace measurements	42	EASE
2) Further processing	charging, dosing	daily	8 h/day	1	EASE	42	EASE
3) Floatation	charging, dosing	daily	1 h/day	0.625	EASE	420	EASE
Formulation							
4) Formulation of products	charging, dosing	daily	1 h/day	0.625	EASE	420	EASE

4.1.1.3 Consumer exposure

A recent request at the Swedish and the Swiss product registers revealed that primary alkyl amines are used as ingredients of consumer products. Out of this group (Z)-octadec-9-enylamine (CAS 112-90-3) has been identified as a major substance in transmission and hydraulic fluids, lubricating agents and additives for lubricants.

Octadecylamine (CAS 124-30-1), hydrogenated tallow alkyl amines (CAS 61788-45-2), Coco alkyl amines (CAS 61788-46-2) and tallow alkyl amines (CAS 61790-33-8) have been identified in non further specified consumer products.

The Swiss product register confirms the information from Sweden regarding (Z)-octadec-9-enylamine as ingredient in lubricants. This substance has also been identified as an ingredient of paints.

Octadecylamine (CAS 124-30-1) and tallow alkyl amines (CAS 61790-33-8) are identified also as ingredients of lubricants and in metal care products due to the information from the Swiss product register.

Coco-alkyl amines are used in products used as hardeners/activators

In addition, the German association of textile industry (TEGEWA) has submitted information about occurrences of residues of tallow alkyl amines from textile finishing, particularly CAS Nos 61790-33-8 and 61788-45-2.

Based on this information, the following major product types can be identified having primary alkyl amines as ingredients.

- *Lubricants.:* *with maximum concentration of 5%*
- *Metal care products,* *with maximum concentration of 5 %*
- *Hardeners/activators:* *with maximum concentration 25 %*
- *Paints:* *with maximum concentration of 5 %*
- *Textiles:* *an estimate provided by TEGEWA revealed an residual amount of0.015mg per 100g of textile.*

Exposure scenarios have been developed for these five uses as follows.

Scenario: Use of lubricants

In a worst case scenario it is assumed, that the palms of both hands ($AREA_{der}$ = 420 cm^2) have contact with the lubricant.

For the estimation of dermal exposure the following equation is chosen:

$U_{der,pot} = C_{der} \times TH_{der} \times AREA_{der} / BW$ (mg/kg BW/d)

TH_{der} = the thickness of product layer on skin account 0.01 cm and C_{der} = dermal concentration of substance on skin < 5 %.
The amount of Octadecylamine or (Z)-Octadec-9-enylamine on skin per day due to use of lubricants can reach a value up to ~ 210 mg, thus resulting in an external dermal exposure of 3.5 mg/kg bw/d assuming a body weight of 60 kg

Scenario: Use of paints

No information about the type of paint has been provided regarding to the substances under evaluation. The use of the paint is estimates as infrequent and seldom.
Exposure may occur from paint splashes during painting. The RIVM fact sheet "paint products" is mentioning a maximum amount of 800 mg of paint from splashing during painting. Taking the maximum concentration of 5%, maximum dermal exposure from paint would account for 40 mg which is 0.7 mg/kg of b.w., assuming 60 kg.

Scenario: Metal care

This scenario is based on the use of car cleaning using a product containing 5% of a primary alkylamine. As a worst case scenario, the undiluted product may be applied to the car surface by hand wiping the product. This procedure leads to exposure of one side of the hand being in contact with a rag being soaked with the product.

In this scenario the amount of substance on skin (one hand) is 210 cm^2* 0.01 cm * 5% reveals an amount in contact with skin of 105 mg (which is 1.8 mg/kg) per event, due a body weight of 60 kg. Taking into account that car care may be performed once a week, the total amount per year accounts for about 95 mg (1.8 * 52) which is equivalent to 0.26 mg/kg of b.w. per day.

Scenario: Hardeners/activators

For this scenario, a two component adhesive has been characterized. These compounds must be applied by using specific applicators such as scrapers. Dermal exposure will normally be an exception because to products are in pasty form that will be mixed with the hardener not occur. Is is assumed that unintentional splashing (if possible) will not exceed the exposure from paints.

Scenario: Wearing softened fabrics

The assessment is based on the model of the BfR working group "Textiles" (Krätke/Platzek, 2004).
The mean dermal chronic exposure is calculated by the equation

E_{mean} = G/100 x 83 µg/kg bw/wearing event
and the acute dermal exposure by the equation
E_{acute} = G/100 x 833 µg/kg bw/ wearing event.

G corresponds to the residual content in the fabric (%). A value of 0.000015 % is used for the estimation basing on the information of TEGEWA.
The E_{mean} amount 0.01 ng/ kg bw/ wearing event and the E_{acute} about 0.1 ng/ kg bw/ wearing event .

These amounts are considered to be negligible.

Conclusion

Under worst case conditions dermal exposure by application of lubricants can reach a value up to 3.5 mg/kg bw/d of primary tallow alkyl amines, by one event of use of lubricants This exposure value may be taken for acute risk assessments, because this use is not a regular frequently repeated use.

Chronic exposure may be represented by metal (car) care products which is 0.26 mg/kg per day. This estimate does not include paints due to infrequent use.

4.1.1.4 Humans exposed via the environment

4.1.1.4.1 Exposure via air

There are no releases into the atmosphere during production, processing or use of primary alkyl amines. Volatilization from aqueous solution is expected to be negligible. Therefore an exposure of humans via the atmosphere is not expected.

4.1.1.4.2 Exposure via food and water

Primary alkyl amines were detected in Mango fruits (*Mangifera indica*). Fruits purchased in india were submitted to steam distillation. Based on the weight of fresh fruits, 0.29% of volatile essential oils were obtained. In this oil, 1-octadecanamine (0.29%) and 1-dodecanamine (0.37%) were detected and identified by GC-MS (Ansari et al., 2000). Based on fresh fruit weight, contents of 8.4 mg/kg (1-octadecanamine) and 10.7 mg/kg (1-dodecanamine) are calculated. There is no information about the origin (natural or anthropogenic) of the compounds.

4.1.1.4.3 Exposure Scenarios

For the human intake of primary alkyl amines via the environment, a number of scenarios representing the most relevant releases is considered. An overview about the resulting total doses and the underlying PECs is presented in table 4.1.1.4.3.

Production

This scenario is based on the highest exposure of the aquatic environment caused by a production site, i.e. releases of hydrogenated tallow amine at site E (cf. 3.1.4.1.1). The most important uptake routes are fish with about 90% and drinking water with about 10% of the total intake.

Formulation of fertilizers

A generic scenario was calculated covering releases into freshwater (cf. 3.1.4.1.2). The most important uptake routes are fish with about 90% and drinking water with about 10% of the total intake.

Processing (Ethoxylation)

This scenario is based on the highest exposure of the aquatic environment caused by a site where primary alkyl amines are ethoxylated, i.e. releases from processing at customers sites

calculated in scenario Eth2 (cf. 3.1.4.1.3). The most important uptake routes are fish with about 90% and drinking water with about 10% of the total intake.

Processing (Sulphosuccinamates)

This scenario is based on the highest exposure of the aquatic environment caused by a site where primary alkyl amines are processed, i.e. releases from processing of tallow amine calculated in scenario Sulph1 (cf. 3.1.4.1.3). The most important uptake routes are fish with about 90% and drinking water with about 10% of the total intake.

Processing to other products

This scenario is based on the highest exposure of the aquatic environment caused by a site where primary alkyl amines are processed, i.e. releases from processing of octadecylamine calculated in scenario Other1 and Other2 (cf. 3.1.4.1.3). The most important uptake routes are fish with about 90% and drinking water with about 10% of the total intake.

Floatation

This scenario is based on the highest exposure of the aquatic environment caused by a site where primary alkyl amines are used as floatation agent, i.e. releases from the use of oleylamine calculated in scenario Float1 (cf. 3.1.4.1.3). The most important uptake routes are fish with about 90% and drinking water with about 10% of the total intake.

Exposure of agricultural soils / sewage sludge

Based on the assumption, that sewage sludge from the treatment plant is used as fertilizer, 4 exposure models for agricultural soils were calculated (cf. 3.1.5.1.1). As a worst case, the indirect exposure of human is calculated for the scenario resulting in the highest PECs in soil, i.e. the formulation of fertilizers. The most important uptake routes are belowground plants with 96.3% and aboveground plants with 3.5% of the total intake.

Exposure of agricultural soils / use in fertilizers

Primary alkyl amines are released into agricultural soil during the use as anticaking agents in fertilizers, the exposure scenario is presented in section 3.1.5.1.2. The most important uptake routes are belowground plants with 96.3% and aboveground plants with 3.5% of the total intake.

Regional Exposure

The scenario of human intake on the regional scale is based on the regional PECs calculated in section 3.1.8. The most important uptake routes are belowground plants with 35.1%, aboveground plants with 62.5% and fish with 1.7% of the total intake.

Tab. 4.1.1.4.3: Indirect exposure of humans via the environment

Scenario	**PEClocal$_{aqua}$ [µg/l]**	**PECsoil [mg/kg ww]**	**PECsoil,porewater [µg/l]**	**DOSE$_{tot}$ [mg.kg bw^{-1}.d^{-1}]**
Production	0.085	0	0	2.45 E-05
Formulation of fertilizers	0.11	0	0	3.17 E-05
Processing (Ethoxylation)	0.063	0	0	1.82 E-05
Processing (Sulphosuccinamates)	0.15	0	0	4.32 E-05
Processing (Other products)	0.011	0	0	3.17 E-06
Floatation	0.0941	0	0	4.00 E-05
Agric. soils, sludge	0	1.4	2.2 (agric) 0.87 (grass)	1.42 E-03
Agric. soils, ferlilizers	0	0.053	0.10 (agric) 0 (grass)	6.44 E-05
Regional	cf. 3.1.8			1.68 E-04

The highest indirect exposure of humans to primary alkyl amines results from the consumption of plants grown in agricultural soils on which sewage sludge from treatment plants was used as fertilizer. The total intake from this scenario is calculated as 1.4 µg/kg bw/d. This value will be taken forward for risk characterisation. All other scenarios lead to exposure values that are at least one order of magnitude lower and hence appear neglectable.

4.1.2 Effects assessment: Hazard identification and dose (concentration)-response (effect) assessment

Introduction

The substances assessed in this report (five (groups of) alkylamines) share structural similarities, i.e.: the amine group and the linear chain, so that they are described in one RAR. Each of the primary alkylamines compounds, which are assessed in this RAR, represents a mixture of alkylamines derived from fatty acids of varying carbon chain length. Details on the mixtures compositions are presented in chapter 1.2 of this report. There are two import features in this group of alkylamines: increasing chain length and increasing unsaturation. It is important to note, that coco alkylamines [CAS 617-88-46] - compared to the other alkylamines mixtures discussed in this RAR - consist of **shorter** carbon chainlengths (mainly C-12) whereas all other mixtures mainly consist of primary alkylamines of **longer** carbon chain lengths (mainly C-16 and C-18). Therefore, chain lengths run from coco alkylamines (mainly C12) via tallow alkylamines and hydrogenated tallow alkylamines (mainly C16 and C18) to octadecylamine and octadecenylamine (mainly C18).
Concerning unsaturation, the degree of unsaturation runs from octadecylamine and hydrogenated tallow alkylamines (0-<5%) via coco alkylamines (5-<10%) and tallow alkylamines (40-45%) to octadecenylamine (>70%).
As to reactivity, all posses the amine group, which is responsible for the basicity of the compounds.

The most prominent toxic property of the primary alkylamines mixtures assessed in this report is their corrosive property, which can be put down to the fact of strong basicity of the compounds. Thus, as far as basicity is of relevance for any endpoint under consideration, a similar toxic profile might be expected across the various alkylamines mixtures under investigation. However, basicity of the various alkylamines mixtures under investigation does not seem to be influenced by the carbon chain lengths of their mixture constituents.

Further, the presence of a double bond is more reactive than a single bond because it is more electrophylic. The longer the alkyl chain attached to a double bond, the more positive charge is pushed towards the double bond, which will increase its electrophilicity. Based on these considerations the reactivity in this group(s) of alkylamines is expected to increase in the following order: octadecylamine, hydrogenated tallow alkylamines, coco alkylamines, tallow alkylamines, octadecenylamine.

An overview of data availability for all compounds and all endpoints is given in table 4.1.2. As far as data had been available these were assessed and individual effect assessments were prepared for each of the alkylamines mixtures under investigation (c.f. 4.1.3.1).

As far as no data had been available for the various endpoints different approaches were pursued, which are summarised in the following:

- Acute toxicity: for the oral route of exposure data are available for all compounds to be assessed. Data waiving was applied, however, for the inhalatory route of exposure due the physical properties of the data poor compounds and likewise for the dermal route of exposure due to their corrosive properties and/or low bioavailability.

- Irritation/Corrosivity: data are available for all compounds to be assessed.

- Sensitisation: data are available only for coco alkylamines and hydrogenated tallow alkylamines. Read across could not applied to all members of the group since the degree of unsaturated alkyl chains and the chain length may be significantly different with respect to the sensitizing potential. For octadecenylamine testing was proposed and when data are available read across considerations of the results for octadecenylamine for tallow alkylamines could be applied.

- Repeated dose toxicity: valid data are available for the oral route of exposure for tallow alkylamines and for octadecenylamine indicating a toxic potential after repeated exposure. No further testing is required, since it is assumed that due to their structural similarities the other compounds assessed in this report would display a similar toxic profile for this endpoint. Thus, it is proposed that all compounds assessed in this report are labelled uniformly and the lowest NOAEL will be taken for quantitative risk assessment for this endpoint.

- Mutagenicity: data availability does not meet data requirements according to Annex VII for each of the compounds assessed in this report. However, due to (i) structural similarities, (ii) availability of at least tests on bacterial mutagenicity for all compounds except hydrogenated tallow alkylamines as well as (iii) the fact that none of the available mutagenicity tests indicate concern for a mutagenic potential, the data base is considered sufficient to exclude a mutagenic potential for any of the compounds assessed in this report.

- There are no valid carcinogenicity data for the alkyl amines assessed in this report. Negative data from mutagenicity testing, scarce data from chronic toxicity testing and negative predictions from the Danish QSAR database indicate no concern.

- Reproductive toxicity: valid data for the oral route of exposure with regard to fertility/reproduction are available only for tallow alkylamines and with regard to developmental toxicity only for octadecenylamine. Additional information on the toxic performance to reproductive organs is recruited from 28-day studies available for tallow alkylamines and for octadecylamine as well as from limited chronic studies available for octadecylamine. Besides indications of systemic toxicity, none of these tests indicated a specific toxic potential for impairment of reproduction/organs of the reproductive system and/or of prenatal development. Read across for either of the two endpoints of reproductive toxicity is considered possible to all of the compounds assessed in this report, and the lowest NOAEL will be taken for quantitative risk assessment.

Table 4.1.2. Data availability for human health effects (brackets indicate limited reliability).

Amines	Coco alkyl	Tallow alkyl	Hydrogenated tallow alkyl	Octadecyl	(Z)-Octa-dec-9-enyl
CAS No.	61788-46-3	61790-33-8	61788-45-2	124-30-1	112-90-3
Composition [%]					
<C12	15.5	-	-	-	-
C12	50	1	1	-	1
C14	18	3	4	5	2-4
C16	8	32	30.5	0.5	12-14
C18	8.5	61.5	62	90	80
unsaturated fraction	<10%	>40%	<5%	<5%	>70%
Molecular weight	194 – 204	267	263	269.5	267.5
Physical state (20 °C)	liquid	waxy solid	solid	solid	liquid
Vapour pressure [Pa]	no data	no data	no data	0.006 (25°C)	0.005 (20°C)
Water solubility [mg/l]	no data	0.12	no data	0.05	0.08
log K_{OW}	no data	7.1	7.3	7.7	7.5
pKa	C8 - C16: 10.6 (nearly independent from chain length)				
Acute toxicity					
- inhalation	+	-	-	-	-
- dermal	+	-	-	-	-
- oral	+	+	+	+	+
Irritation/corrosivity					
- skin	+	+	+	+	+
- eye	n.a.*	n.a.*	+	+	n.a.*
- respiratory tract	-	-	-	-	-
Sensitisation					
- skin	-	-	+	-	-
- respiratory tract	-	-	-	-	-
Repeated dose toxicity					
- inhalation	-	-	-	-	-
- dermal	-	-	-	(+)	(+)
- oral	-	+	(+)	(+)	+
Mutagenicity					
- *in vitro* bacterial	+	+	-	+	+
- *in vitro* mammalian	-	-	-	-	+
- *in vivo* mammalian	-	+	-	-	+
Carcinogenicity	-	-	-	((+))	-
Reproductive toxicity					
- fertility	-	+	-	((+))	((+))
- development	-	((+))	-	-	+

* Not applicable; compound classified as corrosive.

4.1.2.1 Toxicokinetics, metabolism and distribution

Each of the primary alkylamines which are assessed in this RAR represents a mixture of alkylamines derived from fatty acids (Tab. 4.1.2.1) of varying carbon chain length.

Table 4.1.2.1: Nomenclature of fatty acids related to alkylamines

Chain length	Systematic name	Common name
C6	Hexanoic acid	Caproic acid
C8	Octanoic acid	Caprylic acid
C10	Decanoic acid	Capric acid
C12	Dodecanoic acid	Lauric acid
C14	Tetradecanoic acid	Myristic acid
C16	Hexadecanoic acid	Palmitic acid
C18	Octadecanoic acid	Stearic acid
	9-Octadecenoic acid	Oleic acid
	9,12-Octadecadienoic acid	Linoleic acid

It is important to note, that coco alkylamines [CAS 617-88-46] - compared to all other alkylamines discussed in this RAR - consists of shorter chainlengths (mainly C-12) whereas all other mixtures mainly consist of primary alkylamines of longer chain lengths (mainly C-16 and C-18).

Tallow alkylamines [CAS 61790-33-8] differ from hydrogenated tallow alkylamines [CAS 61788-45-2] by a higher content of unsaturated bonds in the hydrocarbon chain.

Data on toxicokinetics, metabolism and distribution of either substance assessed in this RAR i.e. coco alkylamines [CAS 61788-46-3], tallow alkylamines [CAS 61790-33-8], hydrogenated tallow alkylamines [CAS 61788-45-2], octadecylamine [CAS 124-30-1] and octadecenylamine [CAS 112-90-3]) are not available. However, there are studies on toxicokinetics, metabolism and distribution of single definite constituents of the mixtures.

Experimental data concerning toxicokinetic aspects are available for:

1-Octanamine (present at about 8 % in coco alkylamines)

1-Decanamine (present at about 7 % in coco alkylamines)

1-Dodecanamine (present at about 1 % in tallow alkylamines [2% in the commercial product], at about 1 % in octadecenylamine, at about 1 % in hydrogenated tallow alkylamines and at about 50 % in coco alkylamines)

That means, experimental data are available for some of the major constituents of coco alkylamines, whereas no experimental toxicokinetic information is available for octadecylamine and hexadecylamine, the main components of tallow alkylamines and hydrogenated tallow alkylamines. Toxicokinetic data on dodecanamine, which is a minor constituent of tallow alkylamines, hydrogenated tallow alkylamines and octadecenylamine is also available.

4.1.2.1.1 Studies in animals

In vivo studies

Inhalation

Data from inhalative exposure of animals to alkylamines relevant for this report (i.e. C-8 - C-20) are not available.

Dermal

The dermal absorption of [^{14}C]-1-dodecanamine (purity > 98 %) has been investigated in three hairless HR/DE mice (no information on sex was given) (Iwata et al., 1987). 100 µl of the compound was applied to a skin area of 2 cm^2 after dilution in different solvents (squalane, castor oil, triethylcitrate) at different concentrations (50 %, 5 % and 0.5 %). After 24 h of occlusive exposure, percutaneous absorption was determined by analysis of whole body radioactivity, exhaled [^{14}C]-carbon dioxide and excreted radioactivity. At the highest concentration, up to 5 % of 1-dodecanamine was dermally absorbed - independent from the solvent used. By using 5 and 0.5 % dilutions, 28 % and 57 % of the substance were dermally absorbed with squalan as solvent yielding the highest absorption rates. On the average, from the amount of absorbed radioactivity, 80.1 ± 8.1 % was exhaled as [^{14}C]-carbon dioxide within 24 h.

Oral

Data from oral exposure of animals to alkylamines relevant for this report (i.e. C-8 - C-20) are not available.

Other routes of application

After injection of [^{11}C]-octanamine hydrochloride (as a solution in 0.9 % saline) into the marginal ear vein of male and female Albino New Zealand rabbits (data were given as means of three rabbits), distribution of radioactivity (from time of injection to 20 - 40 min thereafter) and exhalation of [^{11}C]-carbon dioxide was determined. Initial uptakes of [^{11}C]-octanamine hydrochloride 1 min after injection were 70 ± 6 % of the administered dose. Lung activity peaked at 40 - 60 s and declined thereafter, so that after 15 min approximately 40 % of the injected dose remained in the lungs. It could be demonstrated, that the initial radioactivity in the lung is mainly dependent upon blood perfusion. Within the first 30 min after injection, approximately 12 % of the applied radioactivity was exhaled as [^{11}C]-carbon dioxide (Fowler et al., 1976a). This confirms the previously established metabolic pathway of aliphatic amines (Blaschko, 1952): in vivo, amines are oxidised by monoamine oxidase to aldehydes, that undergo subsequent oxidation to the corresponding carboxylic acids. Ultimatively, carbon dioxide is formed by ß-oxidation.

Tissue distribution and metabolism of [^{11}C]-Octanamine and [^{11}C]-Decanamine (and also other [^{11}C]-labelled amines with chain lengths C-4, C-5, C-6, C-7, C-9, and C-13) have been investigated after i.v. injection of 0.5 - 5 x 10^{-10} moles of the respective substance into the tail veins of male Swiss albino mice (Fowler et al., 1976b). In the case of tissue distribution, results were given as means obtained from three animals with the exception of data obtained after 1 min, where a mean of 11 or 9 animals was given. [^{11}C]-Labelled amines were determined in organs 1, 5 and 15 min after injection. 1 minute after injection, 12 % of the

applied radioactivity from [^{11}C]-octanamine was detected in the kidneys, 8 % in the liver, 7 % in the lungs, 5 % in blood, 2 % in brain and 0.5 % in spleen. After 5 and 15 minutes, lower values were observed in all tissues investigated (with the exception of spleen, where highest tissue concentrations were achieved after 5 minutes). 1 min after injection of [^{11}C]-decanamine, percentages of the applied radioactivity in tissues were 10 % in lungs, 9 % in liver, 6 % in kidneys, 5 % in blood, 3 % in brain, 1.4 % in heart and 0.5 % in spleen. With the exception of spleen and liver, lower values were obtained after 5 and 15 minutes. In lungs, brain and heart, the uptake of aliphatic amines into different tissues was dependent from chain length: in these tissues, increasing tissue concentrations of alkylamines could be observed in the order C4 < C5 < C6 < C7 < C8 < C9 < C10 < C13. No regular trends in tissue distribution with increasing carbon chain length could be observed in spleen, kidneys, liver and blood. Metabolism of [^{11}C]-octanamine was investigated by determination of non-amine metabolites and by exhalation of [^{11}C]-carbon dioxide. Within 0.5 minutes, 58 % of the total radioactivity in the blood was present as nonamine metabolites and this value increased up to 95 % within 5 minutes. The appearance of metabolites in the lungs was slower with 50 % and 70 % values being attained after 5 and 15 minutes, respectively. Among the nonamine metabolites in the blood, approximately 25 % were present as [^{11}C] -carbon dioxide after 5 minutes.

20 min after injection of [^{11}C]-octanamine, 48 % of the applied radioactivity was exhaled as [^{11}C]-carbon dioxide. Exhaled amounts of [^{11}C]-carbon dioxide from [^{11}C]-decanamine was lower. When comparing alkylamines of different chain lengths, metabolism - as determined by carbon dioxide expiration - was maximal at carbon chain lengths consisting of six carbon atoms.

The role of monoamine oxidase (MAO) in the deamination of [^{11}C]-octanamine has been investigated by using the MAO inhibitor iproniazid. After pre-treatment of three male swiss albino mice with iproniazid, lower levels of nonamine metabolites (compared to animals without iproniazid pre-treatment) in tissues (e.g. 5 min postinjection in blood: 12.4 ± 2.2 % in pre-treated animal vs 94.4 ± 0.8 % in non pre-treated animals) and lungs (3.2 ± 0.6 % in pre-treated animals vs 48.9 % in non pre-treated animals) could be observed. Furthermore, an increased accumulation of tissue radioactivity in various organs (brain, heart, lungs, spleen, kidneys, liver and muscle) which reached statistical significance in the brain (1 min after injection) and in the lungs (5 min after injection), lower amounts of [^{11}C]-carbon dioxide in blood and dramatically reduced exhalation of [^{11}C]-carbon dioxide compared to non-iproniazid pre-treated animals was observed (48.1 % in pre-treated animals compared to 7 % in non pre-treated animals). Another MAO inhibitor, pargyline, also decreased the cumulative [^{11}C]-carbon dioxide excretion after injection of [^{11}C]-octanamine (Fowler et al., 1976b).

By using pargyline as an inhibitor of MAO, it could be demonstrated, that formation of [^{11}C]-carbon dioxide from intravenously applied [^{11}C]-octanamine was reduced in three pargyline-treated male swiss albino mice compared to non-pargyline treated animals. Direct measurement of MAO activity using [^{14}C]-octanamine demonstrated that activities declined in the order intestine > liver > lung > brain >> kidney (Gallagher et al., 1977a).

Aqueous solutions (200 µl, approximately 30 µCi per animal) of [^{13}N]-octanamine hydrochloride (> 90 % radiochemical purity) were injected into the tail veins of male C3H mice. After 1, 5, 15 and 30 minutes, animals (3 animals per time point) were killed and radioactivity in brain, blood, heart and lungs was determined. 1 min after application, highest amounts of radioactivity could be determined in the lungs (30 % of the applied radioactivity), followed by heart (20 % of the applied radioactivity), brain (8 % of the applied radioactivity), liver (7 % of the applied radioactivity) and blood (approximately 2.5 % of the applied radioactivity). Whereas in lung, brain, heart and blood maximum levels of radioactivity have

been observed 1 min after injection, radioactivity in the liver reached its maximum 15 min after injection (Tominaga et al., 1987).

In vitro studies

Oxidation of NADPH by octanamine, decanamine and dodecanamine has been investigated by using pulmonary and hepatic flavin monooxygenases from female Dub:ICR mice and from male White New Zealand rabbits and by using the pig hepatic enzyme. Species differences and differences between the hepatic and the pulmonary enzyme could be observed as well as differences between the different alkylamines investigated. Investigation of the metabolism of octanamine in rabbit and mouse pulmonary enzymes demonstrated that alkylamines bind at or near the active site of the enzyme. N-octylhydroxylamine has been identified as a metabolite after incubation of octanamine with the rabbit pulmonary enzyme (Tynes et al., 1986).

The contribution of the two forms of MAO (MAO-A and B) to the deamination of octanamine and decanamine has been investigated by using homogenates from rat brain, rat liver, rat heart, beef brain cortex and human placenta. In rat liver and brain, both amines were preferentially metabolised by MAO-B. In rat heart and human placenta, deamination was preferentially mediated by MAO-A. In bovine brain, octanamine revealed preference for MAO-B whereas decanamine showed preference for MAO-A (Tenne et al., 1985).

In rat liver monoamine oxidase preparations, the kinetics of deamination of aliphatic amines by MAO-A and MAO-B has been investigated. It could be demonstrated, that primary aliphatic amines were preferentially metabolised by MAO-B. By comparing alkyl chain lengths from C-5 to C-10, C-12 and C-18, an increase in chain length reduced the affinity of aliphatic amines towards MAO-B. Nevertheless, true kinetic parameters could not be obtained due to differences of the amines in solubility: solubilities decreased with increasing chain length, which means that the number of carbon atoms is not the only factor influencing substrate properties towards MAO. However, it could be stated that optimal chain lengths for aliphatic amines being substrates for MAO range between 5 and 10 carbon atoms (Yu, 1989).

Apart from deamination by monooxygenase, the possibility of sulphoconjugation as a further metabolic pathway for alkylamines has been investigated by Iwasaki et al. (1986). In experiments using 5 mmol octanamine, conjugation with 35SO3 was more efficient at pH 10 compared to pH 7.4, where 0.02 nmol 35SO3 per mg protein per minute were metabolically incorporated. The results suggest, that sulphoconjugation plays a minor role at physiological pH.

In rabbit liver submicrosomal particles, octanamine, decanamine and dodecanamine were able to bind to oxidized Cytochrome P450 (CYP) enzymes. Octanamine was also able to bind to CYP enzymes in rabbit liver microsomes after pre-treatment with phenobarbital and methylcholanthrene. Decamine bound to CYP from methylcholanthrene induced rabbit liver microsomes (Jefcoate, 1969).

The formation of toxic nitrosamines from octadecylamine or the thermolysis products of octadecylamine have been regarded as minor pathways because of the chemical inertness of octadecylamine and the fact, that nitrosation of octadecylamine only occurs under certain circumstances as acidic conditions and long reaction times (Lüderitz and Großer, 1986).

4.1.2.1.2 Studies in humans

In vivo studies

Inhalation

Data from inhalation exposure of humans to alkylamines relevant for this report (i.e. C-8 - C-20) are not available.

Dermal

Data from dermal exposure of humans to alkylamines relevant for this report (i.e. C-8 - C-20) are not available.

Oral

Data from oral exposure of humans to alkylamines relevant for this report (i.e. C-8 - C-20) are not available.

Other routes

After intravenous application of 3 - 4 mCi [^{11}C]-octanamine to human volunteers (the number of individuals was not given), 65 - 70 % of the applied radioactivity was taken up by the lungs and decreased to 16 - 19 % after 30 min. Oxidation by MAO was rapid with 95 % of the blood radioactivity at 2 min present as deaminated metabolites. The build-up of deaminated metabolites in blood was followed by accumulation of radioactivity in the liver (18 - 27 % of the injected dose after 30 min). Cumulative [^{11}C]-carbon dioxide excretion within 35 min was 10 - 13 % of the injected dose and urine accounted for 1-2 % of the applied dose after 1 hour (Gallagher et al., 1977b).

In vitro studies

In vitro human data from alkylamines relevant for this report (i.e. C-8 - C-20) are not available.

4.1.2.1.3 Summary of toxicokinetics, metabolism and distribution

Experimental data concerning dermal, oral or inhalative absorption of the alkylamines mixtures described in this report are not available. Therefore, the amounts of absorption can be deduced from the physico-chemical properties and from the results of toxicological investigations of the compounds. Two compounds, i.e. coco alkylamines and octadecenylamines are liquid under normal ambient conditions, whereas the other three substances are waxy solids. The average molecular weights range between 194 (coco alkylamines) and 269.5 g/mol (octadecylamine). Apart from the calculated water solubility of 0.12 mg/l for tallow alkylamines, all other alkylamines are insoluble in water. Log Pow values have been calculated for all amines with the exception of coco alkylamines and range between 7.1 and 7.71. The vapour pressure of all amines is very low. Taken together, based on physico-chemical properties of the respective alkylamines mixtures, a low inhalative and oral bioavailability could be anticipated. However, based on information concerning single aliphatic alkylamines (cited from toxline (Patty, F. ed., 1963) quantitative data are not available) absorption of primary alkylamines from gut and respiratory tract is possible. Data

from acute and repeated dose studies in animals performed with compounds summarised in this RAR indicate, that the compounds exhibit systemic effects after oral administration. Therefore, as a worst case, a value of 100 % oral absorption is taken for risk characterisation. Based on the physico-chemical parameters and the low volatility, absorption by inhalation is low. However, due to the corrosive effects, inhalative uptake - as far as inhalative exposure is possible - might by facilitated after corrosive action of the compounds at the site of entry. Therefore, 100 % inhalative absorption is taken as a value for risk characterisation.

Based on the basicity and corrosive properties of the primary alkylamines, dermal absorption as a consequence of facilitated penetration through damaged skin can be anticipated. 1-Dodecanamine, as a constituent of the alkylamines mixtures, was absorbed from the skin of mice. Dependent on solvent and concentration, up to 60 % were absorbed, so this value for dermal absorption may be taken as a worst case for risk characterisation.

As exemplified by single alkylamines of varying chain lengths (see section 4.1.2.1.1 studies in animals - other routes), bioavailable amounts of alkylamines are rapidly distributed into the lungs, brain, heart, spleen, kidneys and liver. In lungs, brain and heart, distribution was dependent on chain length: when chain lengths C8, C10 and C13 were compared, tissue concentrations of amines increased with increasing chain length.

Alkylamines are oxidatively deaminated by monoaminooxidases with concomitant formation of ammonia and the corresponding alkylamine aldehyde. Oxidative deamination decreases with increasing carbon chain length. Subsequently, the aldehydes are oxidised by aldehydedehydrogenases to the corresponding carboxylic acids, which, in turn, are further metabolised by ß-oxidation. Carbon dioxide as a product from ß-oxidation is exhaled. Urinary excretion is a minor elimination pathway.

4.1.2.2 Acute toxicity

4.1.2.2.1 Studies in animals

In vivo studies

Inhalation

Coco alkylamines [Cas No. 61788-46-3]

In a range finding study groups of ten male Sprague-Dawley rats were exposed to a vapour of coco alkylamines ("Armeen C") at mean analytical concentrations of 0.063 and 0.099 mg/l for one hour by whole-body exposure. Chamber concentrations were monitored during the entire one-hour exposure period at a rate of 0.52 l/min. Rats were observed for mortality and signs of toxicity and/or abnormal behaviour throughout the exposure and daily for 14 days after the termination of exposure. Body weights were recorded prior to exposure and on day 14. All surviving rats were subjected to a gross necropsy, and the following tissues excised and preserved in 10% neutral buffer formalin: brain, liver, kidney, heart, pancreas, stomach, lungs, spleen and testes. The tissues from the animals in the 0.099 mg/l group were examined under a light microscope. There were no deaths, accordingly, the one hour LC50 was found to exceed 0.099 mg/l. After five minutes of exposure several rats in the 0.063 mg/l dose group were preening and inactive. All animals were hypoactive after ten minutes. After 40 minutes, several animals exhibited a slight irritation around the muzzle. This latter effect, as well as hypoactivity in all rats, continued for the remainder of the exposure period. After ten minutes of exposure all rats in the 0.099 mg/l dose group were hypoactive. After 30 minutes, several animals showed signs of irritation, were preening, and exhibited a nasal discharge. At the end of the one-hour exposure, all rats showed mild to severe irritation around the muzzle and had reddish areas of discoloration on the fur. All rats in both groups exhibited normal appearance and behaviour throughout the 14-day postexposure observation period. A mean body weight gain in both dose groups was noted at the end of the observation period. No necropsy findings were noted in any rats from both dose groups. Microscopic evaluation of selected tissues from the rats in the 0.099 mg/l dose group included minimal to slight peribronchial lymphoid hyperplasia present in the lung, as well as minimal focal interstitial nephritis in seven of the ten rats, but these findings were believed not to reveal compound-related histomorphologic alterations. All other tissues were within normal histological limits (Hazleton Laboratories America Inc., 1975, cited from Toxicology Regulatory Services Inc., 2003).

Tallow alkylamines [Cas No. 61790-33-8]

No data available.

Hydrogenated tallow alkylamines [Cas No. 61788-45-2]

No data available.

Octadecylamine [Cas No. 124-30-1]

No data available.

Octadecenylamine [112-90-3]

No data available.

Dermal

Coco alkylamines [Cas No. 61788-46-3]

In a GLP-compliant study similar to OECD TG 402, coco alkylamines ("Amine KK"), a yellow liquid (purity 100%), was dermally applied under occlusion to Sprague-Dawley rats. At a dose level of 500 mg/kg body weight, coco alkylamines was applied undiluted (application volume 0.63 ml/kg bw), at a dose level of 2000 mg/kg bw the substance was diluted to a 40% solution (w/v) in distilled water (application volume 5 ml/kg). Compared to a regular OECD TG 402 study a reduced number of animals was used (2 instead of 5 animals/sex/dose). There were no mortalities, hence, the LD50 is > 2000 mg/kg bw. No clinical signs were observed at 500 mg/kg bw. At 2000 mg/kg, hunched posture, abnormal gait, lethargy and decreased respiratory rate were noted. Signs of dermal reactions at the application site of both treatments were well defined to moderate oedema until days 4-5. Hard scabs, persisting to the end of the observation period, frequently prevented the assessment of oedema (Huntingdon Research Centre, 1985).

In a GLP-compliant study similar to OECD TG 402, coco alkylamines (“Armeen CD“), purity 99%, was dermally applied to New Zealand White rabbits under semi-occlusive conditions for 24 hours. Three rabbits of each sex were administered a single dermal dose of the undiluted test substance at a volume of 2.0 ml (1600 mg)/kg bw. The hair on the backs of the rabbits was clipped 24 hours prior to test substance administration. Abraded areas of one male and two female rabbits in each treatment group were prepared by penetrating the horny layer of the epidermis without causing bleeding. The treatment was applied to the intact or abraded exposure site of each rabbit. Animals were observed daily for mortality and signs of toxicity for a period of 14 days. Individual body weights of surviving animals were measured at study initiation and termination (day 14). Necropsy was performed on all rabbits and all abnormalities were recorded. One male animal with intact exposure site died on day 3. Upon necropsy, cause of death was concluded to be non-treatment related. This animal was replaced and no further animals died during the study. All animals showed small to moderate body weight gains by the end of the observation period. Skin irritation reactions were produced in all animals following treatment. Necrosis and eschar formations were reported for all animals. Moderate to severe oedema during day 1 to 4 was replaced by hard dry skin with marked atonia. Some exfoliation was noted at the end of the observation period revealing the presence of beet red lesions. Necropsy revealed the presence of hard necrotic treated skin with thickened new skin or normal to beet red colour underneath. No marked abnormalities were noted in any other organs. The estimated dermal LD50 was > than 2 ml (1600 mg)/kg bw for both sexes (Hazleton Laboratories Europe Ltd., 1979, cited from Toxicology Regulatory Services Inc., 2003).

Tallow alkylamines [Cas No. 61790-33-8]

No data available. Studies on skin irritation do not indicate significant systemic toxicity after dermal application.

Hydrogenated tallow alkylamines [Cas No. 61788-45-2]

No data available. Studies on skin irritation do not indicate significant systemic toxicity after dermal application.

Octadecylamine [Cas No. 124-30-1]

No data available. Studies on skin irritation do not indicate significant systemic toxicity after dermal application.

Octadecenylamine [112-90-3]

No data available. Studies on skin irritation do not indicate significant systemic toxicity after dermal application.

Oral

Coco alkylamines [Cas No. 61788-46-3]

In an OECD TG 401 study, coco alkylamines ("Armeen C"), a clear light-yellow, oily liquid (purity not given), was orally applied to Wistar rats at doses of 500, 1000, 1500 and 2000 mg/kg bw. The substance was applied as a 20% solution in peanut oil (pH 8.1). At 500 mg/kg bw, two males died 5 and 7 days after treatment, respectively. At 1000 mg/kg bw, two males and two females died between days 5-14 (40%). At 1500 mg/kg bw, four males and four females and at 2000 mg/kg bw (80%), ten males and nine females died between days 5-14 (95%). An LD50 of 1300 mg/kg bw (1240 mg for male and 1390 mg for female rats) was calculated (probit analysis after Finney). Clinical signs, observed in all treatment groups, included apathia, slight to pronounced irregular postures, uncoordinated movements, reduced reflexes, cyanosis, salivation, piloerection, slightly reduced breathing rate and some cases of slight hypothermia. Symptoms started from 20 minutes after dosing on and were present until death or up to 7 days in survivors. After dissection of dead animals, slight reddening and liquid congregations were detected in the gastrointestinal tract. There were no pathological findings in the surviving animals (IBR Forschungs GmbH, 1983a).

In a GLP-compliant study according to OECD TG 401 (regular use of animals only at 2000 mg/kg bw, only five females used at 2500 and 3000 mg/kg bw), coco alkylamines ("Genamin CC 100 D"), a nearly colourless to light-yellow liquid (purity 99-100%), was orally applied to Wistar rats using sesame oil as a vehicle. After treatment with 2000 mg/kg bw, one male and one female died (20%). Two and three females died after treatment at 2500 and 3000 mg/kg bw (20 and 30%). The LD50 was established at > 2000 mg/kg for males and 2820 mg/kg bw for females. Clinical signs, observed in all treatment groups, included reduced flanks, hunched posture, stilted gait, irregular breathing, diarrhoea, irregular breathing and reduced spontaneous activity. Some animals showed bloody encrusted edges of the palpebral fissures. Symptoms started between 10-60 minutes after onset of treatment and were present until death or up to 5-10 days in survivors. Partly darkened liver, brightened spleen and yellow-dark red filling of the gastrointestinal tract was observed in dissected bodies, whilst there were no findings in survivors (Hoechst AG, 1988k).

In a study according to OECD TG 401 (GLP-compliance not stated), five Sprague-Dawley rats of each sex were administered a 40% w/v aqueous solution of coco alkylamines (“Armeen CD”, purity 99%) as a single oral dose (dose levels 1800, 2560, 3620 or 5120 mg/kg bw). Additionally, five rats of each sex were treated with the test vehicle (distilled water) at a level equal in volume (12.8 ml/kg bw) to the highest dose level of the test substance solution administered. Animals were observed for overt signs of toxicity at ¼, ½, 1, 2 and 4 hours after dosing and daily thereafter for a total of 14 days. Individual body weights were measured at study initiation and termination (day 14). Necropsy was performed on all animals to assess any treatment-related gross pathological changes. Mortalities were at 1800 mg/kg bw, 0/5 males and 0/5 females; at 2560 mg/kg bw 1/5 males and 1/5 females; at 3620

mg/kg bw 1/5 males and 4/5 females; at 5120 mg/kg 5/5 males and 4/5 females. Mortality in all treatment groups occurred within the first 6 days of the observation period, with one additional death of a male animal from the 1800 mg/kg bw treatment group on day 8. Animals in the 3620 and 5120 mg/kg bw treatment groups appeared lethargic within 15 minutes of treatment and throughout Day 1. The acute oral LD50 of the test substance for male and female animals combined (calculated by Finney 's Probit Methods (1964)), was 2 040 mg/kg bw with 95% confidence limits of 1510 to 2760 mg/kg bw. Clinical observations through the fist week of observation included lethargy, chromodacryorrhea, epistaxis with closed eyes and emaciation. All animals in the 2560 mg/kg bw treatment group appeared subdued and lethargic on day 1 beginning 1 hour after treatment. Additional clinical signs reported on day 2 were chromodacryorrhea, and epistaxis with half closed eyes by day 5 for all animals in this group. One animal in the 1800 mg/kg bw treatment group appeared lethargic 1 hour after treatment. Lethargy was observed in all animals in the group at day 2, with epistaxis in two animals at day 3 and recovery of all animals in the group by Day 4. All control animals appeared normal through the observation period. The one surviving animal in the 5120 mg/kg bw treatment group and 2 males and 1 female in the 2560 mg/kg bw treatment group lost weight by the end of the observation period. The majority of animals necropsied revealed no abnormalities. Abnormalities detected included gaseous distended stomach with fluid filled gastrointestinal tract, congestion of the lungs, intestinal and renal adhesions, and hard and discoloured spleen (Hazleton Laboratories Europe Ltd., 1979a, cited from Toxicology Regulatory Services Inc., 2003).

From a corresponding study, which used coco alkylamines ("Armeen CD") in an aqueous dilution of 20% w/v, an LD50 of > 6000 mg/kg was concluded (Hazleton Laboratories Europe Ltd., 1979b, cited from Toxicology Regulatory Services Inc., 2003).

Tallow alkylamines [Cas No. 61790-33-8]

In an OECD TG 401 study, tallow alkylamines ("Genamin TA 100 D"), a whitish wax (purity 99-100%), was orally applied to Wistar rats at a doses of 2000 (5 males + 5 females) and 2500 mg/kg bw (5 males only). The test substance was suspended in sesame oil. In the 2000 mg/kg dose group, 1/5 males was found dead on day 6; all females survived. After administration of 2500 mg/kg bw, 1/5 male died within 24 hours. Hence, the oral LD50 of tallow alkylamines exceeded 2000 mg/kg bw (2500 mg for males). The following clinical signs were observed following dosing: hunched posture, flanks drawn in, pilo-erection, irregular breathing, abnormal gait, diarrhea, crusted eyelids and snout (both males and females); decreased spontaneous activity, uncontrolled movements, crawling-like movements, emaciation, drowsiness, gasping (males). All symptoms disappeared by day 11 or 12. Decreased body weight gain was observed the first week postdosing. Necropsy of animals that had died revealed stained liver, pale-coloured lungs and gastrointestinal tract swollen with gases. Animals sacrificed at the termination of the experiment did not show gross pathological changes. (Hoechst AG, 1988i).

In a non-GLP and not guideline-compliant oral toxicity study according to OECD TG 401, tallow alkylamines ("Armeen T ", a dirty-white, waxy substance, purity not given), was applied to groups of 5 male and 5 female Wistar rats . The test substance was heated to 37° C (pH 8.7) and the liqified substance was applied via gavage at the following doses: 1.5, 2.5, 3.5, and 5.0 ml/kg bw (corresponding to approx. 1188, 1979, 2771, and 3958 mg/kg bw). Animals were observed for signs of toxicity at approximately 30 minutes, at 1, 2, 3, 6, 24 and 48 hours and on days 4, 6, 7 and 14 following dosing. Body weights were determined on day 0 and 14 for all surviving animals. The LD50 value was determined by probit analysis. Following mortalities were reported: 1/5 male and 1/5 females at 1.5 ml/kg; 3/5 males and 2/5

females at 2.5 ml;, 4/5 males and 3/5 females at 3.5 ml and 5/5 males and 5/5 females at 5.0 ml, resulting in an LD50 of 2.23 ml/kg (approx. 1765 mg/kg) for males, 2.61 ml/kg (approx. 2066 mg/kg) for females and 2.40 ml/kg (approx. 1900 mg/kg) bw for both sexes. Clinical observations revealed incoordination, cyanosis, excessive salivation, piloerection, reduced respiration, and hypothermia. The surviving animals appeared normal at the end of the 14-day post dosing observation period (IBR Forschungs GmbH, 1983b).

Hydrogenated tallow alkylamines [Cas No. 61788-45-2]

In an OECD TG 401 study, hydrogenated tallow alkylamines ("Lilamin AC-HBG-P"), a white granular solid (purity not given), was orally applied to Wistar rats at a dose of 5000 mg/kg bw. The substance was applied as a 50% suspension in 1% methylcellulose (limit-test). There were no deaths, hence, the LD50 exceeded 5000 mg/kg. Clinical signs were diarrhea, piloerection, hunched posture, abnormal gait and pallor of extremities. Complete recovery from these clinical signs was observed by day 5. Body weights were initially reduced but body weight gain was not different from controls by the end of the study (day 15). No treatment-related effects were observed at necropsy (Huntingdon Research Centre, 1995).

In an OECD TG 420 study, hydrogenated tallow alkylamines ("Farmin TH"), a white solid (purity not given), was orally applied to female Sprague-Dawley rats at doses of 500 and 2000 mg/kg bw. The test substance was suspended in 5% aqueous Tween 80. One female treated at 2000 mg/kg died in the course of the last day of the observation period. There were no mortalities in the 500 mg/kg bw treatment group. Hence, the LD50 exceeded 2000 mg/kg bw. Clinical signs included hunched posture, rattling breath, piloerection, ataxia, decreased motor activity and muscle tone, pallor and traces of blood in the snout. Necropsy revealed no pathological findings (Centro de Investigacion Y Desarollo Aplicado, S.A.L., 1995a).

In a well-conducted non-GLP compliant study according to OECD TG 401 (6 animals/ dose group), hydrogenated tallow alkylamines ("Amin HBG"), a semi-solid beige-coloured paste (purity not given) was orally applied in water to Sprague-Dawley rats at doses of 3000, 3900, 5070, 6590 and 8560 mg/kg bw at 20 ml/kg bw. Deaths were observed from 3900 mg/kg bw on (one animal died on day 2) and an LD50 of 4800 mg/kg bw was established (method: Thompson Moving Average Interpolation). All deaths occurred within one to three days following dosing. According to the main study, no deaths were reported in a pre-study in the dose groups ≤ 3000 mg/kg bw. Clinical signs, present in all treatments, were piloerection and hyperkinesia. Necropsy findings were normal at 3000 mg/kg. At 3900 mg/kg bw gut contents fluid and red stain in gut and at doses higher than 5070 mg/kg bw test substance in stomach, gut contents fluid, red stain in gut, lungs patchy, kidneys pale coloured were found. (Inveresk Research International, 1979).

Octadecylamine [Cas No. 124-30-1]

In an OECD TG 401 study, octadecylamine ("Genamin 18 R 100 D"), a whitish waxy solid (purity approximately 100%), was orally applied to Wistar rats at a dose of 2000 mg/kg bw (limit-test). The substance was solubilised in sesame oil under heating. One male died on day 4, hence, the LD50 exceeded 2000 mg/kg bw. Clinical signs: all animals showed reduced spontaneous activity, piloerection, hunched posture, abnormal gait, reduced activity, and irregular breathing. One male had a swollen abdomen. All animals recovered by day 9. The animal that died had a decrease in body weight on day 4. No other effects on body weight were noted. The following observations were noted at necropsy for the animal that died: stomach filled with test substance and gas, flanks drawn in, dark-coloured liver, red staining

of lungs, intestine and pancreas, intestines filled with gas, and shrunken spleen. All surviving animals had no remarkable findings at necropsy (Hoechst AG, 1989d).

In an OECD TG 401-like study (GLP-compliance not stated), approximately 100% octadecylamine ("Genamin SH 100 D") in sesame oil was orally applied to Wistar rats at a dose of 2000 mg/kg bw (limit-test). The dose was non-lethal; however, for up to 7 hours following treatment, reduced spontaneity, crouching and retracted flanks were observed in the animals (Hoechst AG, 1988l).

Accordingly, Griffin et al. (1991) stated that "octadecylamine treatment caused no acute toxicity in mice" (no details given).

Octadecenylamine [112-90-3]

In an OECD TG 401 study, octadecenylamine ("Noram O", oleylamine), an opaque, non-homogenous liquid (purity 97.9%), was orally applied to Sprague Dawley rats at a doses of 2000, 1000, 500 and 200 mg/kg bw. In a pre-test (limit test) with 2000 mg/kg bw, no vehicle was used. The substance was heated to approximately 30°C and mixed with corn oil for the lower dose groups in the main test. Mortalities were 70, 20, 0, and 10% in the respective dose groups. Males (LD50 approximately 1200 mg/kg bw) were more sensitive compared to females (LD50 approximately 2000 mg/kg bw); the LD50 for both sexes was established at 1689 mg/kg (probit analysis). Clinical signs included: hypokinesia and/or sedation, piloerection and dyspnea, abdominal swelling. Decreases in body weight gain were noted between day 1 to 5 at 200 and 500 mg/kg bw, persisting in one male and one female at 200 mg/kg bw; and at 1000 mg/kg and returning to normal by day 8. Body weight gain was also decreased at 2000 mg/kg bw from day 1 to 8, returning to normal by day 15. No abnormalities were noted at necropsy (Centre International Toxicologie, 1993).

In vitro studies

No data available.

4.1.2.2.2 Studies in humans

In vivo studies

No data available.

Inhalation

No data available.

Dermal

No data available.

Oral

No data available.

In vitro studies

No data available.

4.1.2.2.3 Summary of acute toxicity

There are no human data available on acute toxicity of the alkylamines assessed in this report.

Coco alkylamines [Cas No. 61788-46-3]

One acute inhalation rat study (1 hour whole body exposure) does not point to high systemic inhalation toxicity of coco alkylamines. Due to its highly irritative potential, causing local effects at a test concentrations as low as 0.099 mg/l, testing of higher concentrations is not warranted. In one acute dermal study with rats, an LD50 > 2000 mg/kg bw was demonstrated for coco alkylamines ("Amine KK"). Hence, no classification and labelling is needed for acute toxicity via inhalation and the dermal route. In acute oral toxicity studies LD50 values of 1300 mg/kg bw, 2040 mg/kg bw and > 2000 mg/kg bw were established with three coco alkylamines products. For the oral route, classification as “Xn” (harmful) and labelling with R22 (harmful if swallowed) is proposed.

Tallow alkylamines [Cas No. 61790-33-8]

Data from animal studies are available neither for the inhalation nor for the dermal route. In a well conducted oral study with rats, an LD50 of > 2000 mg/kg bw was detected for the tallow alkylamine “Genamin TA 100 D”. For the tallow alkylamine “Armin T”, an oral LD50 of approximately 1900 mg/kg was derived in a not GLP-compliant, but well conducted study. In consequence, classification as “Xn” (harmful) and labelling with R22 (harmful if swallowed) is warranted for the oral route . Taking into account the moderate systemic toxicity of the substance via the oral route and its corrosive properties, there is no need to perform acute toxicity testing via the inhalation and dermal routes.

Hydrogenated tallow alkylamines [Cas No. 61788-45-2]

Data from animal studies are available neither for the inhalation nor for the dermal route. In well conducted rat oral toxicity studies, hydrogenated tallow alkylamines clearly showed an LD50 exceeding 2000 mg/kg bw. Therefore, classification and labelling for acute oral toxicity of tallow alkylamines is not required. Taking into account the low systemic toxicity of the substance via the oral route and its pronounced irritative potential, there is no need to perform acute toxicity testing via the inhalation and dermal routes.

Octadecylamine [Cas No. 124-30-1]

Data from animal studies are available neither for the inhalation nor for the dermal route. In three well conducted rat oral toxicity studies, octadecylamine showed an LD50 exceeding 2000 mg/kg. Therefore, classification and labelling for acute oral toxicity of tallow alkylamines is not required. Taking into account the low systemic toxicity of the substance via the oral route and its corrosive potential, there is also no need to perform acute toxicity testing via the inhalation and dermal routes.

Octadecenylamine [112-90-3]

Data from animal studies are available neither for the inhalation nor for the dermal route. There exists one acute oral toxicity study, which was well performed and compliant to OECD

guideline 401. The LD50 was clearly below 2000 mg/kg, hence, octadecenylamine have to be classified as "Xn" (harmful) and labelled with R22 (harmful if swallowed). Taking into account the moderate systemic toxicity of the substance via the oral route and its corrosive properties, there is no need to perform acute toxicity testing via the inhalation and dermal routes.

Data gaps (see Table 4.1.2.2.3)

Table 4.1.2.2.3. Data gaps and data availability with resulting classification for acute toxicity

Alkylamines	**Coco alkylamines**	**Tallow alkylamines**	**Hydrogenated tallow alkylamines**	**Octadecylamines**	**Octadecenylamines**
CAS no.	61788-46-3	61790-33-8	61788-45-2	124-30-1	112-90-3
Acute toxicity					
inhalation	1x OECD 403; R(-)	na R(-)	na R(-)	na R(-)	na / R(-)
dermal	Based on 2x OECD 402 R(-)	na / R(-)	na / R(-)	na / R(-)	na / R(-)
oral	1x OECD 401, 2x similar to OECD 401; R22	1x OECD 401; 1x similar to OECD 401; R22	1x OECD 401, 1x OECD 420, 1x non-GLP OECD 401; R(-)	2x OECD 401, 1x non-GLP OECD 401; R(-)	1x similar to OECD 401 R22

R = risk phrase (-) not classified; na = not analysed (no data)

4.1.2.3 Irritation

4.1.2.3.1 Skin

Studies in animals

Coco alkylamines [Cas No. 61788-46-3]

In an OECD TG 404 study, 0.5 ml coco alkylamines ("Farmin C"), a light brown clear liquid (purity 100%), were semi-occlusively applied to the shaved skin of two female and one male New Zealand White rabbits for 4 hours. Coco alkylamines produced grade 3.00 erythema and grade 3.00 oedema (mean values from 24 - 72 hours). These symptoms were reversible within 7 - 14 days. In the area of application, brown staining was observed up to 7 days. Eschar and scabbing were observed up to 14 days and subsequent scarring was noted up to the end of the observation period of 21 days (Research and Consulting Co. Ltd., Pfister, 1994a).

In an OECD TG 404 study, 0.5 ml coco alkylamines ("Noram C"), a light brown clear liquid (purity 98.9%), were semi-occlusively applied to the shaved skin of two New Zealand White rabbits for 3 minutes and 4 hours). Since clear effects were observed in both treatments, no additional animals were used. After a 3-minute contact, a well defined and moderate erythema (grade 2 and 3) was recorded 24 and 48 hours post exposure. No cutaneous necrosis was observed. After a 4-hours contact, a well defined erythema and severe erythema and a severe oedema was noted 24 and 48 hours post exposure. At the 48 hours reading, necrosis of the skin was observed (Centre International de Toxicologie, 1999a).

In an OECD TG 404 study, 0.5 ml coco alkylamines ("Genamin CC 100 D"), a clear, pale yellow liquid (purity approx. 99%), were semi-occlusively applied to the shaved skin of six New Zealand White rabbits for 3 and 60 minutes (three animals/ exposure). Both treatments caused moderate-severe erythema (24-72 hours average scores for the three animals at 3 min contact were 1.7/ 2.0/ 2.0) and oedema (24-72 hours average scores for the three animals at 3 min contact were 2.7/ 1.7/ 1.0). Eschar, scabbing and necroses were observed up to 14 days and subsequent scarring was noted up to the end of the observation period of 21 days (Hoechst AG, 1984).

In an OECD TG 404 study with minor modifications[7], 0.5 ml coco alkylamines ("Cesio 5"), a clear, straw-coloured liquid (purity not given), were semi-occlusively applied to the shaved skin of six New Zealand White rabbits for 3 minutes. The rabbits were treated at their left and right flanks. After 3 minutes of contact, the left hand treatment site was washed by gentle swabbing with cotton wool soaked in sterile distilled water; the right hand treatment site was decontaminated using 3% (w/v) aqueous acetic acid followed by distilled water. Slight haemorrhages prevented scoring of erythema between 24-72 hours (degree: moderate- well-defined). 24-72 hours average scores for oedema were 3.8/ 3.3/ 2.5. Scar tissue, indicative of dermal corrosion, was noted at three treated skin sites. Severe dermal responses were noted at all remaining skin sites (Safepharm Laboratories Ltd., 1989).

[7] In addition to regular treatment, effect of decontamination procedure was studied using distilled water alone and 3% (v/v) aqueous acetic acid followed by distilled water

In an OECD TG 404 study with minor modifications[8], 0.5 ml coco alkylamine ("Amine KK"), a clear, straw-coloured liquid (purity not given), was semi-occlusively applied to the shaved skin of three New Zealand White rabbits for 3 minutes and 1 hour. The rabbits were treated at their left and right flanks. After 3 minutes of contact, the first treatment site was washed by gentle swabbing with cotton wool soaked 3% aqueous acetic acid, followed by another decontamination performed with sterile distilled water. After 1 hour of treatment, the same procedure was repeated at the second treatment site. 24, 48 and 72 hours later, evaluations were performed. After 1 hour of contact, blanching of the skin and areas of brown discolouration of the epidermis were noted at all treated skin sites. Eschar, sometimes surrounde by blanching and/or well-defined erythema, was noted at all treated skin sites at subsequent 24, 48 and 72-hour observations. On day 7 eschar persisted at all treated sites but at one site appeared sunken and was becoming detached to underlying tissues. On day 14 two small areas of blood-stained tissue, persisted at the treated skin site of the two remaining rabbits. Desquamation, glossy skin and lack of fur growth were also noted at this time. Average scores for erythema were 4.0 between 1 hour and 7 days and for oedema, values for 1/ 24/ 48/ 72 hours/ 7 days were 3.0/ 4.0/ 3.7/ 2.0/ 0.7. Severe irritation but no corrosivity was noted after a 3-minutes contact (Safepharm Laboratories Ltd., 1987).

In a non-guideline compliant study, concentrations from 0.1%-50% lauramine (the major C12 component of coco alkylamines; no further information on the substances identity given) were applied to the back of three hairless mice under occlusive patches. Strong irritation and necrosis occurred at concentrations of 0.5% or greater (Iwata et al, 1987).

In a non-GLP study according to OECD TG 404 (FDA, Fed. Reg. 37 (244), 27635, 1972), 0.5 g coco alkylamine (“Armeen C”), a partly solid and partly liquid slightly brown-coloured substance (purity not given) was applied occlusively for 4 hours to the shaved skin of six New Zealand White Rabbits under a 1 inch x 1 inch surgical patch. Examination of the treated skin sites were performed 4 and 48 hours after patch removal. After 4 hours, severe ischemia, moderate oedema and brown discolouration of the treated skin were observed. After 48 hours, severe necrosis (incrustation) was noted. Scores for erythema/ oedema were 4.0/ 3.0 after 4 hours and 48 hours. Comparable results were obtained for a different batch of the test substance (TNO, 1979).

Tallow alkylamines [Cas No. 61790-33-8]

In an OECD TG 404 study with minor modification[9], 0.5 g tallow alkylamines ("Farmin T"), a white to yellow hard paste (purity 96%), was applied semi-occlusively for 3 minutes and 1 hour to the shaved skin of one male and two female New Zealand White rabbits, respectively. Prior to application, the pH-value of the undiluted test article was determined with a test strip and was found to be 6. The substance was applied to the right flank as delivered by the sponsor. Since no effects were observed after 3 minutes, exposure was repeated. After approximately 1 hour, the dressing was removed and the skin was flushed with lukewarm tap water to clean the application site. The skin was examined 1 hour, 24, 48 and 72 hours as well as 7, 14 and 21 days after removal of the dressing. Average skin irritation scores for erythema/ oedema after 1, 4, 24, 48, 72 hours: 0/0, 1.0/1.3, 1.3/ 2.0/ 3.0, 1.3/ 1.3, 1.0/ 1.3; no erythema/ oedema remaining after 7 days. Corrosive effects, i.e. formation of eschar, scabbing and subsequent scarring, were noted at the application sites of all animals (RCC, 1994c).

[8] contact was 1 hour compared to 4 hours in a regular study

[9] regular exposure time shortened from 4 hours to 1 hour

In an OECD TG 404 study, 0.5 g tallow alkylamines ("Genamin TA 100 D"), a whitish wax (purity 99-100%), was applied semi-occlusively for 3 minutes or 4 hours to the shaved skin of three or one New Zealand White rabbits, respectively. The substance was applied to the right flank as delivered by the sponsor. The skin was examined 30 minutes, 1 hour, 24, 48 and 72 hours after removal of the dressing. Since effects were still present after 72 hours, additional examinations were performed after 7 and 14 days. Results for a 3 minutes contact (3 animals): From 30 minutes to 14 days after patch removal, treated skin areas showed mild to moderate erythema and mild to strong oedema. Between 24 hours and 14 days, the treated skin areas were sclerotic, vaulted, brownish discoloured, cracked, dry-brittle, scaly, translucent and pink-coloured. Additionally scaling was observed. After 7 days, all animals showed scars. Due to severity of effects, scoring of erythema and oedema was restricted. Results for a 4 hours contact (1 animal): From 30 minutes to 7 days after application of the test substance, the skin was temporarily sclerotic, vaulted, encrusted, scabby, white and brown-white discoloured. Additionally, exudations were observed. Full thickness destruction of the epidermis had occurred after 7 days and the animal was killed for humane reasons on day 7. Due to severity of effects, scoring of erythema and oedema was restricted (Hoechst AG, 1988j).

In an OECD TG 404 study with minor modifications[10], 0.5 ml/mg tallow alkylamines ("Cesio 10"), a colourless liquid (purity not given), was applied semi-occlusively for 3 minutes to the shaved skin of six New Zealand White rabbits, as provided by the sponsor. The rabbits were treated at their left and right flanks. After 3 minutes of contact, the left hand treatment site was washed by gentle swabbing with cotton wool soaked in sterile distilled water; the right hand treatment site was decontaminated using 3% (w/v) aqueous acetic acid followed by distilled water. The skin was examined 1 hour, 24, 48 and 72 hours after removal of the dressing. Additional examinations were performed after 7 and 14 days. Corrosivity was noted in 3/6 animals after water decontamination. Due to severity of effects, erythema and oedema could not be evaluated quantitatively. Between 24 and 72 hours, blanching of skin was noted. Moderate to well-defined erythema surrounded the treatment site. On day 7, light brown coloured scabs and dark-brown hard scabs appeared. On day 14, desquamation, keratinolysis, scattered scabs, reduced growth of fur and thickening of dermal tissues were noted. Effects were comparable for both decontamination procedures (Safepharm Laboratories Ltd., 1989).

In an OECD TG 404 study with minor modifications[10] 0.5 ml/mg tallow alkylamines ("Cesio 11"), an off-white coloured liquid (purity not given), was applied semi-occlusively for 3 minutes to the shaved skin of six New Zealand White rabbits. Prior to application, the test substance was moistened with water to enhance skin contact. The rabbits were treated at their left and right flanks. After 3 minutes of contact, the left hand treatment site was washed by gentle swabbing with cotton wool soaked in sterile distilled water; the right hand treatment site was decontaminated using 3% (w/v) aqueous acetic acid followed by distilled water. The skin was examined 1 hour, 24, 48 and 72 hours after removal of the dressing. Additional examinations were performed after 7 and 14 days. Corrosivity was noted in 4/6 animals. Due to severity of effects, erythema could not be evaluated. Between 24 and 72 hours, blanching of skin was noted. Moderate to well-defined erythema surrounded the treatment site. On day 7, dark brown, hard scabs appeared. On day 14, scattered scabs, reduced growth of fur and thickening of dermal tissues were noted. Corrosivity was noted in 4/6 animals. Average scores for oedema (decontamination with water) were 4.0 (24 hours), 3.5 (48 hours) and 3.2 (72

[10]ect of decontamination procedure was studied using distilled water alone and 3% (v/v) aqueous acetic acid followed by distilled water

hours). Results of both decontamination procedures were comparable (Safepharm Laboratories Ltd., 1989).

In a non-GLP study according to OECD TG 404 (FDA, Fed. Reg. 37 (244), 27635, 1972), 0.5 g tallow alkylamine ("Armeen TD"), a white waxy substance (purity not given) was applied occlusively for 4 hours to the shaved skin of six New Zealand White Rabbits under a 1 inch x 1 inch surgical patch. Examination of the treated skin sites were performed 4 and 48 hours after patch removal. After 4 hours, distinct ischemia and moderate oedema were observed. After 48 hours, severe necrosis (incrustation) was noted. Scores for erythema/ oedema were 4.0/ 3.0 after 4 hours and 48 hours (TNO, 1979).

In a non-GLP skin irritation study (US-Guideline, Fed. Reg. No. 38 , p 27019, 1973), 27635, 1972), 0.1 g tallow alkylamine ("Genamin TA 100 D"), a white waxy substance (purity not given) was applied for 20 seconds and unlimited to the shaved skin (3 x 3 cm, two different application sites, type of patch not reported) of six Himalayan White Rabbits. Examination of the treated skin sites were performed after 24 and 72 hours after start of treatment. After 72 hours corrosivity was observed (no detailed signs reported). Average scores for erythema/ oedema were 4.0/ 2.2 after 24 hours and 4.0/ 2.0 after 72 hours (Hoechst AG, 1977).

Hydrogenated tallow alkylamines [Cas No. 61788-45-2]

In an OECD TG 404 study, 0.5 g hydrogenated tallow alkylamines ("Lilamin AC-HBG-P"), a white granular solid (purity not given), was applied semi-occlusively for 4 hours to the shaved skin of three New Zealand White Rabbits. The test substance was moistened with 0.5 ml water applied to a 2.5 cm^2 gauze patch. Examination of the treated skin was started approx. 30 minutes after patch removal and on days 2, 3 and 4. Additional observations were performed on days 5 through 11. Well-defined erythema and oedema were observed in all three animals. A slight increase in the level of reaction was noted in two animals during days 4 and 5. The reactions abated by the beginning of the second week and by day 11 all skins were normal. Hyperkeratinisation was seen in one animal on day 5. Average scores for erythema were 2.0 (24 hours), 2.0 (48 hours) and 2.0 (72 hours). Scores for oedema were 2.0, 2.3 and 2.3 for the same time points (Huntingdon Research Centre, 1984).

In a non-GLP study similar to OECD TG 404, 0.5 g hydrogenated tallow alkylamine ("Armeen HT"), a white granular solid (purity not given), was applied for 4 hours to the shaved skin of three New Zealand White Rabbits. The test substance was moistened with 0.5 ml water applied to a 2.5 cm^2 gauze patch. After transfer to the shaved skin, the patch was covered with sleek plaster. After removal of the patch, the treated skin area was washed with water to remove excess sample. Average scores for erythema/ oedema evaluated after 24, 48, and 72 hours were 1.0/ 1.0, 1.0/ 0.5 and 1.0/ 0.5. No signs of corrosivity were present 72 hours after patch removal (Huntingdon Research Centre, 1982).

In a non-GLP study similar to OECD TG 404, 0.5 g hydrogenated tallow alkylamine ("Fatty Amine 73/312", "Armeen HT"), a beige solid (purity not given, pH-value of the liquified substance = 8.5), was applied for 4 hours to the shaved skin of three New Zealand White Rabbits. The test substance, liquified after warming, was applied to a 2.5 cm^2 gauze patch. Immediately after removing the patches a well-defined erythema and a slight oedema were observed in all animals. Until 5 days after patch removal, these symptoms had increased but eased off until day 14. Average scores for erythema/ oedema were 2.0/ 2.0 (1 h), 2.0/ 2.7 (24 h) 2.3/ 3.3 (48 h), 3.7/ 3.7 (72 h). Beginning 3 days after patch removal, a slight exfoliation and partly a decreased growth of hair were recorded. By the end of the observation period of

14 days, partly exfoliation still was present, but the growth of hair became normal again. No necrosis was noted throughout this study (IBR Forschungs GmbH, 1982).

In an OECD TG 404 study hydrogenated tallow alkylamines ("Farmin TH"), a white solid (pH = 9.93, purity not given), was applied semi-occlusively for 4 hours to the shaved skin of three New Zealand White Rabbits. 0.5 g of the test substance, wetted with water, were applied on 2.5 cm^2 surgical gauze and applied to the shaved backs of the rabbits. Average scores for erythema were 2.0 (24 hours), 2.0 (48 hours) and 2.0 (72 hours). Scores for oedema were 2.3, 0.7 and 0.0 for the same time points. Erythema were still present after 7 days and reversed within 14 days (Centro de Investigacion Y Desarollo Aplicado, S.A.L., 1995b).

In a GLP-compliant skin irritation study based on OECD TG 404, 0.5 ml of hydrogenated tallow alkylamines ("Amin HBG"), a white granular solid, (purity not given), was applied semi-occlusively for 4 hours to the shaved skin of three New Zealand White Rabbits. In a pre-test, no corrosivity was observed after a 3 minutes and 1 hour exposures. Well-defined erythema was observed at all treated skin sites one hour after patch removal. A slight haemorrhage of the dermal capillaries was also noted at one treated skin site at this time. Well-defined erythema and a brown discoloration of the skin was noted at all treated skin sites at the 24 and 48 hours observations and at two sites after 72 hours. A slight haemorrhage of the dermal capillaries and loss of skin suppleness was noted at one of the treatment sites after 24 and 48 hours. Loss of skin suppleness was noted in one animal after 72 hours. On day 7 dry, thickened, straw-coloured skin (possible hyperkeratinisation) and loss of skin suppleness were observed in two animals. Glossy skin, reduced fur growth, and small scattered scabs were noted in the remaining animal. Average scores for erythema were 2.0 (24 hours), 2.0 (48 hours) and 2.0 (72 hours). Scores for oedema were 2.3, 1.7 and 1.7 for the same time points. Due to severity of skin reactions, reversibility of erythema could not be assessed. Oedema reversed within 7 days (Safepharm Laboratories Ltd., 1987).

In an OECD TG 404 study with minor modifications[11], 0.5 ml hydrogenated tallow alkylamines ("Cesio 12"), a white flaky solid (purity not given), was applied semi-occlusively for 3 minutes or 1 hour to the shaved skin of six New Zealand White rabbits. Prior to application, the test substance was moistened with water to enhance skin contact. The rabbits were treated at their left and right flanks. After 3 minutes or 1 hour of contact, the left hand treatment site was washed by gentle swabbing with cotton wool soaked in sterile distilled water; the right hand treatment site was decontaminated using 3% (w/v) aqueous acetic acid followed by distilled water. The skin was examined 1 hour, 24, 48 and 72 hours after removal of the dressing. Additional examinations were performed after 7 and 14 days. No evidence of skin irritation was noted for the 3 minutes contact (Draize Scores 0 for all time points, water decontamination). Very slight erythema responses were noted for the 1 hour contact. In addition, desquamation was observed in 5/6 animals after 7 days. Average scores for erythema (decontamination with water) were 1.0 (24 hours), 1.0 (48 hours) and 1.0 (72 hours). Scores for oedema were 0.0 for the same time points. Results of both decontamination procedures were comparable (Safepharm Laboratories Ltd., 1989).

In a non-GLP-compliant skin irritation study according to OECD TG 404, 0.5 ml of hydrogenated tallow alkylamines (Amin HBG), a semi-solid beige-coloured paste (purity not given), was applied as supplied to the shaved skin of six New Zealand White rabbits (males and females). Results of readings were given for the 24 hours and 72 hours readings only: mean Draize scores at 24 hours for erythema and oedema were 1.4 and 1.2, respectively. After

[11] In addition to regular treatment, effect of decontamination procedure was studied using distilled water alone and 3% (v/v) aqueous acetic acid followed by distilled water

72 hours, scores for erythema and oedema were 0.9 and 0.9, respectively (Inveresk Research International, 1979).

In a non-GLP study according to OECD TG 404 (FDA, Fed. Reg. 37 (244), 27635, 1972), 0.5 g hydrogenated tallow alkylamine ("Armeen HT"), a brownish waxy substance (purity not given) was applied occlusively for 4 hours to the shaved skin of six New Zealand White Rabbits under a 1 inch x 1 inch surgical patch. Examination of the treated skin sites were performed 4 and 48 hours after patch removal. After 4 hours, well-defined erythema, very slight to slight oedema were observed. After 48 hours, distinct ischemia and slight to distinct necrosis were noted. Scores for erythema/ oedema were 3.5/ 1.2 after 4 hours and 48 hours (TNO, 1979).

Octadecylamine [Cas No. 124-30-1]

In an OECD TG 404 study, 0.5 g octadecylamine ("Genamin 18 R 100 D"), a whitish waxy solid (purity approximately 100%), was applied semi-occlusively for 4 hours to the shaved skin of three New Zealand White Rabbits. The substance was moistened with 0.4 ml polyethylene 400. Examination of the treated skin was started approx. 30 minutes after patch removal and continued on days 2, 3 and 4. Additional observations were performed on days 7, 14, 21 and 28. 30-60 minutes up to 7 days after patch-removal, treated skin areas showed pronounced erythema and slight-moderate oedema. Average scores for erythema were 3.0 (24 hours), 3.0 (48 hours) and 3.0 (72 hours). Scores for oedema were 2.7, 1.3 and 1.3 for the same time points. Over time, skin was frequently dried and brittle, crusty and cracked. Additionally, enduration and desquamation was observed. Effects were reversible after 14 days in one rabbit and 28 days in two rabbits (Hoechst AG, 1989e).

In an OECD TG 404 study, octadecylamine ("Noram SH"), a yellow-beige solid (purity not given), was semi-occlusively applied for 4 hours to the shaved skin of three New Zealand White rabbits. The test substance was moistened with water to ensure good skin contact and test substance remaining after patch removal was removed with water. Average scores for erythema were 2.0 (24 hours), 1.7 (48 hours) and 1.7 (72 hours). Scores for oedema were 2.3, 1.7 and 1.3 for the same time points. Erythema cleared by day 10 and oedema by day 9 (Centre International Toxicologie, 1986).

In an OECD TG 404 study (short report without details, GLP-compliance not stated), 0.5 g octadecylamine ("Genamin SH 100 D", purity approximately 100%) was applied for 4 hours to the shaved skin of New Zealand White Rabbits. No further details are presented. As a result labelling with "R38" was concluded from the authors (Hoechst AG, 1988p).

In a non- guideline compliant study, 10% octadecylamine ("stearylamine in olive oil") was repeatedly applied to shaved guinea pig skin. After the third treatment, the skin showed a brown colour and was thickened. Histology revealed full thickness destruction of the epidermis (Gewerbehygienisches I.G. Laboratorium, 1934).

In a non-guideline study, Rockland male albino mice received 0.2 ml octadecylamine ("stearamine") (30 mg) in ether applied to their shaved backs on days 1, 3 and 5. Histological analysis of the treated epidermis showed absence of sebaceous glands and hair follicles (Brooks et.al., 1957).

In a non-guideline compliant study, octadecylamine ("stearylamine") was applied to the ventral skin of rabbit (no details provided). After reddening and wetting, necrosis was noted. Treated skin areas were rejected after 14-21 days (Hoechst AG, 1932).

In an in vitro study similar to OECD guideline 430 (Transcutaneous electrical resistance assay, TER), octadecanamine ("stearylamine", CAS No. 124-30-1) was classified as skin corrosive (transport packing group III, Oliver et al., 1988).

Octadecenylamine [112-90-3]

In an OECD TG 404 study, 0.5 ml octadecenylamine ("Noram O", oleylamine), a light brown, translucient and pasty liquid (purity 97.7%), was applied semi-occlusively for 4 hours to the shaved skin of one New Zealand White Rabbit. The substance was applied as delivered by the sponsor onto a 6 cm^2 gauze pad, which was then applied to the right flank. The skin was examined 1 hour, 24, 48 and 72 hours after removal of the dressing. Average Draize scores after 24 hours were 4.0 for erythema and 4.0 for oedema. At the same time necrosis was noted and the study was terminated for humane reasons (Centre International Toxicologie, 1999b).

In another well conducted OECD TG 404 study, 0.5 ml octadecenylamine ("Farmin O"), a pale, yellow liquid (purity 100%), was applied semi-occlusively for 4 hours to the shaved skin of three New Zealand White Rabbits (1 male, 2 females). The substance was applied as delivered by the sponsor. Prior to application, the pH-value was determined with a test-strip and was found to be 10. No systemic symptoms were observed. Average Draize scores after 24, 48 and 72 hours for erythema and oedema were 4.0, 3.7 and 3.7. Corrosive effects (eschar, scabbing and scarring) were noted at the application sites of all animals (Research and Consulting Company Ltd., 1994b).

In a non-guideline compliant study, octadecenylamine ("oleylamine") was applied to the ventral skin of rabbit (no details provided). After reddening, wetting, necrosis and suppurating was noted. Treated skin areas were rejected after 14-21 days (Hoechst AG, 1932).

Human skin and muscle fibroblasts were exposed for 24 hours to 5 and 10 % octadecenylamine ("oleylamine"). No significant reduction of cell viability was observed in both concentrations (viability > 90%) (Santa Maria et al., 1996).

Studies in humans

There are no human data available on skin irritation of the alkylamines mixtures assessed in this report.

4.1.2.3.2 Eye

Studies in animals

Coco alkylamines [Cas No. 61788-46-3]

No data available.

Tallow alkylamines [Cas No. 61790-33-8]

In a non-GLP eye irritation study (US-Guideline, Fed. Reg. No. 38 , no. 187, p 27019, 1973), 27635, 1972), 0.1 ml of a 10% solution of tallow alkylamine (“Genamin TA 100 D”), a white waxy substance (purity not given) diluted in sesam oil, was applied for 20 seconds (left eye, rinsing with PEG 400 or borate buffer) and unlimited (right eye) to the eyes of six Himalayan White Rabbits. Examination of the treated eyes were performed after 1, 7, 24, 72 hours and 7 days after start of treatment. After 72 hours corrosivity was observed (no detailed signs

reported). Average scores for erythema/ chemosis were 2.4/ 2.0 between 1 hour and 72 hours and 0.2/ 0.0 after 7 days and for cornea opacity 1.1 between 1 hour and 72 hours and 1.5 after 7 days. Due to limitations in reporting of the study, no conclusions on corrosivity and reversibility of effects can be drawn (Hoechst AG, 1977).

Hydrogenated tallow alkylamines [Cas No. 61788-45-2]

In an OECD TG 405 study, 100 mg hydrogenated tallow alkylamines ("Farmin TH"), a white solid (pH = 9.93, purity not given), was applied to the eyes of three New Zealand White rabbits. Pronounced conjunctiva redness and chemosis was observed throughout the entire observation period. Additionally, severe cornea opacity and moderate iris lesions was noted. Mean Draize scores for conjunctiva redness at 24, 48 and 72 hours were 3.0, 3.0 and 3.0. Mean scores for conjunctiva chemosis were 3.0, 3.0 and 3.3 for the same time points. These effects were not reversible within the observation period of 21 days. Related scores for iris were 1.0, 1.0 and 1.0, reversible between 14 and 21 days. Scores for cornea density were 3.0, 3.3 and 3.7, respectively and showed a value of 2.0 at the end of the observation period (Centro de Investigacion Y Desarollo Aplicado, S.A.L., 1995c).

Octadecylamine [Cas No. 124-30-1]

In an OECD TG 405 study, 0.1 ml octadecylamine ("Genamin 18 R 100 D"), a whitish waxy solid (purity approximately 100%), was applied to the eye of one New Zealand White rabbit. 24 hours after treatment, the eye was washed with 0.9% tepid NaCl solution. From 1 hour on, the conjunctiva showed red beefy discoloration and pronounced chemosis. Iris and cornea showed lesions. Additionally, a clear colourless to whitish-slimy discharge was noted. Due to progressed vascularisation of the eye, the study was terminated after 7 days. Mean Draize scores for conjunctiva redness and chemosis at 24, 48 and 72 hours were 3.0, 3.0 and 3.0. Mean scores for iris were 1.0, 1.0 and 1.0 and for cornea opacity were 2.0, 2.0 and 2.0 (same time points) (Hoechst AG, 1989f).

In an OECD TG 405 study (short report, GLP-compliance not stated), 100 mg octadecylamine ("Genamin SH 100 D") was applied to the eye of one New Zealand White rabbit. No details were given, as a result with "R 41" was concluded from the authors (Hoechst AG, 1988q).

Octadecenylamine [112-90-3]

No data available

Studies in humans

There are no human data available on eye irritation of the alkylamines assessed in this report.

4.1.2.3.3 Respiratory tract

Studies in animals

Coco alkylamines [Cas No. 61788-46-3]

In a range finding study groups of ten male Sprague-Dawley rats were exposed to a vapour of coco alkylamines (“Armeen C”) at mean analytical concentrations of 0.063 and 0.099 mg/l for one hour by whole-body exposure. For full details, refer to section 4.1.2.2.1 (inhalation).

After 30 minutes, several animals of the 0.099 mg/l dose group showed signs of irritation, were preening, and exhibited a nasal discharge. At the end of the one-hour exposure, all rats showed mild to severe irritation around the muzzle and had reddish areas of discoloration on the fur (Hazleton Laboratories America Inc., 1975, cited from Toxicology Regulatory Services Inc., 2003).

There are no animal data available on respiratory tract irritation of the remaining alkylamines assessed in this report.

Studies in humans

There are no human data available on respiratory tract irritation of the alkylamines assessed in this report.

4.1.2.3.4 Summary of irritation

There are no human data available on skin, eye and respiratory tract irritation of the alkylamines assessed in this report.

Coco alkylamines [Cas No. 61788-46-3]

A strong skin irritating potential including corrosivity was demonstrated in well conducted skin irritation animal studies using various coco alkylamines. In consequence, classification as "C" (corrosive) and labelling with R35 (causes severe burns) is proposed (see 4.1.2.4). Results from skin irritation studies are in accordance with local symptoms reported from acute dermal toxicity studies (refer to 4.1.2.2.1). Since the substance was evaluated as corrosive, in vivo testing of eye irritation must not be performed.

Rat inhalation studies indicated that coco alkylamines has irritative properties on the respiratory tract. A LOAEC of 0.063 mg/l for local effects on the respiratory tract for these alkyl amine was established. Classification as 'irritant'and labelling with Xi, R37 is proposed.

Tallow alkylamines [Cas No. 61790-33-8]

Tallow alkylamines cause severe skin irritations and damage in various animal studies. In consequence, classification as "C" (corrosive) and labelling with R35 (causes severe burns) is proposed (see 4.1.2.4).

Hydrogenated tallow alkylamines [Cas No. 61788-45-2]

All skin irritation studies with rabbits concordantly showed pronounced moderate effects which require classification as irritant ("Xi") and labelling with R38 ("irritating to skin"). One eye irritation study demonstrated severe ocular lesions. Hence, additional labelling with R41 ("risk of serious damage to the eyes") is proposed.

Octadecylamine [Cas No. 124-30-1]

Some well conducted skin irritation studies with octadecylamine using rabbits showed pronounced moderate effects which require classification as irritant ("Xi") and labelling with R38 ("irritating to skin"). In addition, a few outdated, non-guideline compliant studies and one in vitro study demonstrated a possible corrosive potential of octadecylamine. However, the test substances used in outdated studies may not be representative for currently used

octadecylamines. The in vitro study result of the in vitro study is borderline. The current guideline states that the method cannot be used for discrimination between corrosivity and pronounced irritation Accordingly, the results from the more recent in vivo studies are regarded as valid.. One eye irritation study demonstrated severe ocular lesions. Hence, classification with R41 (“risk of serious damage to the eyes”) is proposed.

Octadecenylamine [112-90-3]

A strong skin irritating potential including corrosivity was demonstrated in well conducted skin irritation animal studies using various octadecenylamine (oleylamines) in various products. In consequence, classification as “C” (corrosive) and labelling with R34 (causes burns) is proposed (see 4.1.2.4). Since the substance was evaluated as corrosive, in vivo testing of eye irritation must not be performed.

4.1.2.4 Corrosivity

Studies in animals

Coco alkylamines [Cas No. 61788-46-3]

In skin irritation studies, coco alkylamines were shown to be corrosive (refer to 4.1.2.3.1).

In an in vitro study according to OECD guideline 430 (Transcutaneous electrical resistance assay, TER), lauramine (the major C12 component of coco alkylamines), was evaluated as skin corrosive (Oliver et al., 1988).

Tallow alkylamines [Cas No. 61790-33-8]

In skin irritation studies, tallow alkylamines were shown to be corrosive (refer to 4.1.2.3.1).

Hydrogenated tallow alkylamines [Cas No. 61788-45-2]

Available skin and eye irritation studies did not show any corrosive potential of hydrogenated tallow alkylamines (refer to 4.1.2.3).

Octadecylamine [Cas No. 124-30-1]

Former studies point to a corrosive potential of octadecylamine, which could not be confirmed by more recent and guideline-compliant studies (refer to 4.1.2.3).

Octadecenylamine [112-90-3]

In skin irritation studies, octadecenylamines were shown to be corrosive (refer to 4.1.2.3.1).

Studies in humans

Coco alkylamines [Cas No. 61788-46-3]

In an in vitro phototoxicity test using the skin cutaneous model ZK 1300/ ZK 1350, cell viability was seriously affected (19.1% ± 18.8) after application of tallow alkylamines ("Armeen TD") and evaluated as "corrosive" by the authors (Liebsch et al., 1995).

No further human data on corrosivity of alkylamines are available.

Summary of corrosivity

With the exception of one in vitro study with coco alkylamines ("Armeen TD"), there are no human data available on corrosivity to the skin, eyes and respiratory tract of the alkylamines assessed in this report. There are no human or animal data available to assess the potential to cause corrosion of the respiratory tract.

Coco alkylamines [Cas No. 61788-46-3]

A clear corrosive potential was demonstrated for skin in studies using various coco alkylamines (for details, refer to 4.1.2.3.1). In consequence, classification as corrosive "C" and labelling with R35 (causes severe burns) is proposed.

Tallow alkylamines [Cas No. 61790-33-8]

The substance is proposed to be classified as "C" (corrosive) and labelled with R35 (causes severe burns) because skin corrosion was caused by a 3-minutes skin contact in three skin irritation studies with rabbits (Hoechst AG, 1988j; Safepharm Laboratories Ltd., 1989).

Hydrogenated tallow alkylamines [Cas No. 61788-45-2]

Skin and eye irritation data from animal studies (refer to 4.1.2.3) clearly indicate that hydrogenated tallow alkylamines are not corrosive.

Octadecylamine [Cas No. 124-30-1]

A few outdated non-guideline studies indicate a corrosive potential of octadecylamine. In contrast, some well conducted skin irritation studies (4.1.2.3) did not reveal a corrosive potential. However, the test substances used in outdated studies may not be representative for currently used octadecylamine and the result of the in vitro study cannot be used for discrimination between corrosivity and pronounced irritation. Hence, no classification of octadecylamine as corrosive is proposed.

Octadecenylamine [112-90-3]

Corrosivity was demonstrated in well conducted skin irritation animal studies using 4-hour dermal exposure to various octadecenylamine (oleylamines) in different products (for details, refer to 4.1.2.3). In consequence, classification as "C" (corrosive) and labelling with R34 (causes burns) is proposed.

Data gaps (see Table 4.1.2.3.4)

Table 4.1.2.3.4 Data gaps and data availability with resulting classification for irritation/corrosivity

Alkylamine	**Coco alkylamine**	**Tallow alkylamines**	**Hydrogenated tallow alkylamines**	**Octadecylamine**	**Octadecenylamine**
CAS No.	61788-46-3	61790-33-8	61788-45-2	124-30-1	112-90-3
Irritation/Corrosivity					
skin	4x OECD 404 R35	1x OECD 404, 2x similar to OECD 404; R35	5x OECD 404; R38	2x OECD 404, 2x non-GLP OECD 404; R38	2x OECD 404, 2x rabbit skin (non-guideline compliant); R34
eye	na R35	na R35	1x OECD 405; R41	1x OECD 405, 1x non-GLP OECD 405; R41	na R34
respiratory	Acute inhalation studies R37	na R(-)	na / R(-)	na / R(-)	na R(-)

R = risk phrase (-) not classified; na = not analysed (no data)

4.1.2.5 Sensitisation

4.1.2.5.1 Studies in animals

Skin

In vivo studies

Coco alkylamines [Cas No. 61788-46-3]

In a GLP-compliant OECD TG 406 skin sensitisation study according to Magnusson-Kligmann (guinea pig - maximisation test, GPMT), 10 female guinea pigs + 5 control animals (strain Dunkin-Hartley) were treated with coco alkylamine ("Genamin CC 100 D", technical grade, purity 99.9%, liquid) using cotton seed oils as a vehicle. Based on the results of a pretest, a test substance concentration of 0.1% was used for intradermal induction (0.1 mL), followed by a 1% concentration at epidermal induction. Challenge was performed using a 0.5% substance concentration. For epidermal treatments, patches were loaded with 0.5 mL. In contrast to results of the pretest, no dermal irritation was observed after epidermal induction. After challenge treatment, 2/10 animals showed grade 1 erythema at the 24h reading (positive rate = 20%). One out of these positive animals showed scaling after 48 and 72h. No second challenge treatment was performed (BSL, 2008). These results do not allow to derive a clear conclusion, since the number of positive animals is borderline. According to the testing guideline, additional animals should be used if the result of a test using only 5 control animals and 10 animals in the treatment group is unequivocal. Since epidermal induction treatment using a 1% substance concentration did not cause any signs of irritation, the performance of this study is not fully compliant with TG 406.

Tallow alkylamines [Cas No. 61790-33-8]

No data available.

Hydrogenated tallow alkylamines [Cas No. 61788-45-2]

In a non-GLP-compliant skin sensitisation study according to OECD TG 406 (Magnusson-Kligmann guinea pig - maximisation test), 10 female guinea pigs (strain Dunkin-Hartley + 5 control animals) were treated with hydrogenated tallow alkylamines ("Amin HBG"), a semi-solid beige-coloured paste (purity not given). At the intradermal induction stage, 0.5 ml test substance emulsified with 0.05 ml Freund's adjuvant was injected s.c. (additional injections: 0.1 ml Freund's adjuvant alone + 0.1 ml test agent). Prior to injection, the test substance was diluted with water to 1% w/w. 6 days after injections, the skin at the treatment site was shaved once again and treated with 10% sodium lauryl sulfate to provoke an inflammatory reaction. 24 hours later, the treatment sites were occlusively covered with a 2 x 2 cm filter patch, saturated with 5% aqueous hydrogenated tallow alkylamines for 48 hours (topical induction, volume not given). A 2% concentration of hydrogenated tallow alkylamines was selected for the final challenge. 14 days after the first challenge, the second challenge was performed (24h closed patch exposure). No positive responses were observed in the 10 induced and rechallenged animals (readings not given) (Inveresk Research International, 1979). Since the test substance is nearly insoluble in water, reported nominal test concentrations of up to 10%

could not be achieved. In consequence, this study results are not valid and cannot be used for risk assessment.

Octadecylamine [Cas No. 124-30-1]

No data available.

Octadecenylamine [112-90-3]

No data available.

In vitro studies

There are no in vitro data available on skin sensitisation of the alkylamines assessed in this report.

Respiratory tract

In vivo studies

There are no in vivo data available on respiratory tract sensitisation of the alkylamines assessed in this report.

In vitro studies

There are no in vitro data available on respiratory tract sensitisation of the alkylamines assessed in this report.

4.1.2.5.2 Studies in humans

Skin

In Ullmann´s Encyclopedia of Industrial Chemistry (2005) in its section on Fatty Amines it is reported that "A small number of workers became sensitized to selected fatty amines. Symptoms included skin rash, dermatitis, eye swelling, and a sensation of the skin, described as "crawling". On the request of the rapporteur to validate this information no relevant data had been provided sofar from the authors of this section and no other sources of information were found to substantiate this reporting. Therefore, this data is not further considered for hazard characterisation of the alkylamines mixtures assessed in this report.

Octadecylamine [Cas No. 124-30-1]

In a general study on the effects of anti-corrosives is stated, that sensitisation is less frequent after contact to octadecylamine compared to triethanolamine, monoethanolamine and cyclohexylamine chromate (Selisskij et al., 1978). Since no details on method and results were provided, this statement cannot be used for hazard identification.

In vivo studies

There are no in vivo data available on skin sensitisation of the alkylamines assessed in this report.

In vitro studies

There are no in vitro data available on skin sensitisation of the alkylamines assessed in this report.

Respiratory tract

In vivo studies

There are no in vivo data available on respiratory tract sensitisation of the alkylamines assessed in this report.

In vitro studies

There are no in vitro data available on respiratory tract sensitisation of the alkylamines assessed in this report.

4.1.2.5.3 Summary of sensitisation

Coco alkylamines [Cas No. 61788-46-3]

Human data are not available. Since coco alkylamines have a high degree of components with shorter chain length (C_8 to C_{14}) as compared to hydrogenated tallow alkylamines (more than 95% C_{16} and C_{18}), there may be some limitation to conclude on the potential of coco alkylamines to cause sensitisation on the basis of read-across to hydrogenated tallow alkylamines. Accordingly, performance of a Local Lymph Node Assay (LLNA) was proposed. Finally, a guinea pig maximisation test was conducted, which gave an inconclusive result. Based on these data, a potential of coco alkylamines to cause skin sensitisation in humans cannot be excluded.

Hydrogenated tallow alkylamines [Cas No. 61788-45-2]

There are no human data available. In a not GLP-compliant guinea pig - maximisation test according to Magnusson and Kligman, there was no evidence for a potential of the tested hydrogenated tallow amines ("Amin HBG") to induce skin sensitisation. However, since an unsuitable vehicle was selected and reported nominal concentrations could technically not be achieved, the negative results of this study cannot be accepted.

Tallow alkylamines [Cas No. 61790-33-8]

Neither human data, nor data on sensitisation in animal studies are available. Tallow alkylamines show a certain content of unsaturated octadecenylamine (37%), which is nearly absent in hydrogenated tallow alkylamines. The presence of a double bond in 37% of the alkyl chains (unsaturation) may contribute to a sensitising potential (Fedorowicz et al., 2004). Thus, the negative data available from hydrogenated alkylamines cannot be used to exclude a sensitising potential of tallow alkylamines. Since testing for a skin sensitising potential is proposed for octadecenylamine, which shows a higher degree of unsaturated alkyl chains, read-across from octadecenylamine is proposed, when data are available.

Octadecylamine [Cas No. 124-30-1]

Neither human data, nor data on sensitisation in animal studies are available. Octadecylamine is a major component of hydrogenated tallow alkylamines, read across could be applied.

Although the Danish QSAR database prediction was positive, the negative data from the guinea pig - maximisation test with the hydrogenated tallow alkylamines was given higher priority to conclude no significant potential of octadecylamine to induce skin sensitisation. Hence, further testing is not required.

Octadecenylamine [112-90-3]

Neither human data, nor data on sensitisation in animal studies are available. Octadecenylamines show a high content (about 80%) of double bonds in the alkyl chain, which are nearly absent in octadecylamine. Since the presence of a single double bond in the alkyl chains (unsaturation) may contribute to a sensitising potential, the negative data available from hydrogenated alkylamines cannot be used to exclude a sensitising potential of octadecenylamine. Accordingly, the Danish QSAR database predicts a positive potential of octadecenylamine to cause skin sensitisation. Hence, the performance of an appropriate animal study for assessment of a possible skin sensitising potential of octadecenylamines is proposed. The use of a Local Lymph Node Assay (LLNA) is highly recommended.

Table 4.1.2.5.3 Data gaps and data availability with resulting classification for sensitisation

Alkylamines	**Coco alkylamines**	**Tallow alkylamines**	**Hydrogenated tallow alkylamines**	**Octadecylamines**	**Octadecenylamines**
CAS no.	61788-46-3	61790-33-8	61788-45-2	124-30-1	112-90-3
4.1.2.5 sensitisation					
skin	1x OECD 406 (GPMT) inconclusive result R(-)/	na, Read-across (-), if test on octadecenylamines will be available, read-across (+), R(-)/	1x OECD 406 (GPMT) negative result, but study not valid R(-)	low quality human data negative, Read-across (+) to hydrogenated tallow alkylamines, Danish QSAR Database Report positive, R(-)	na, Read-across (-), Danish QSAR Database Report positive, testing proposed, R(-)
respiratory	na R(-)	na R(-)	na R(-)	na, Danish QSAR Database Report equivocal R(-)	na, Danish QSAR Database Report equivocal R(-)

Legend to table. R = risk phrase (-) not classified; na = not analysed (no data)

4.1.2.6 Repeated dose toxicity

4.1.2.6.1 Studies in animals

In vivo studies

Inhalation

No data available.

Dermal

Coco alkylamines [Cas No. 61788-46-3]

No data available.

Tallow alkylamines [Cas No. 61790-33-8]

No data available.

Hydrogenated tallow alkylamines [Cas No. 61788-45-2]

No data available.

Octadecylamine [Cas No. 124-30-1]

To male albino (Rockland) mice 0, 3, or 30 mg of octadecylamine ("n-octadecylamine") in ether as vehicle (≈0, 1.5 or 15 g/kg bw/d for a 20 g mouse) was applied to the shaved back on days 1, 3, and 5 of the experiment (Brooks et al., 1957). On day 6, skin was analysed for cholesterol content, sterol and epidermal weight per cm². 3 mg of the test substance produced substantial hyperplasia of the epidermis with increase in cholesterol. Severe hyperplasia with 5fold increase of weight/cm² epidermis and absence of sebaceous glands and hair follicles was observed. [No data on systemic toxic effects were generated. No other information available.]

Octadecenylamine [112-90-3]

Octadecenylamine (oleylamine) was dermally applied on two 5-days periods with intermediate 2-day non dosing-period to male and female Sprague-Dawley rats (Intox Laboratories, 1985). Animals of the control groups received the vehicle only (mineral oil).

Based on the results of a pilot study, groups of young adult rats (4 males and 4 females) were treated dermally with the test substance at concentrations of 0, 0.3, 1.5 and 3.0% in mineral oil (corresponding to doses of 0, 12.5, 62.5 and 125 mg/kg bw/d). Rats were treated for two five-day dosing periods with an intermediate two-day non-dosing period in order to more closely reproduce conditions of human exposure to the test substance. The first day of dosing was designated as Day 1. Due to excessive tissue destruction indicated by sloughing, scores of moderate to severe erythema, scabbing, hardening of the skin, and sensitivity to touch, the dosing at the intermediate and high dose levels (1.5 and 3.0%) was discontinued on Day 9. These animals were subsequently sacrificed on Day 10. At initiation of dosing the rats' body weights ranged from 205.7 to 321.3 g. Rats were acclimated to the laboratory for seven days prior to test substance application. Water and food were provided ad libitum. Approximately

24 hours prior to test substance application, the fur was clipped from the dorsal area of each animal. Shaving was repeated one week later. The test substance was applied at a volume dosage of 5 ml/kg. The application site was covered by a porous gauze dressing that was held in place with tape, and covered with a taped elastic bandage. Each day, wrappings were removed approximately six hours after test substance application and the test sites were washed with warm water to remove excess test substance. Observations of signs of toxicity were made once each day. Body weights were recorded during acclimation, weekly during the study and at sacrifice. Food consumption was recorded weekly during the study. Morbidity/mortality checks were examined prior to test substance administration on days 2, 4, 6, 8, 10, 12 and 14 for signs of erythema and necropsies were performed. Animals were killed and discarded three days following the completion of dosing.

All rats survived until scheduled sacrifice. Concentrations of 1.5 and 3.0% produced moderate to severe irritation (erythema scores 2-4), which in some instances progressed to hardening and sloughing of the skin. A number of rats were sensitive to touch. In the 0.3 % group, erythema scores of 1 to 2 were observed, indicating mild to moderate irritation, and flaking of the outer layers of the epidermis was observed. An increased sensitivity in females to the irritant effects of the test substance as compared to males was observed. In the control group, one male showed an erythema score of 1 at one observation. All rats in the 1.5 and 3% groups were sacrificed on day 9 of the study due to the irritant/corrosive effects of the test substance. No other treatment-related irritant effects or clinical signs were observed. A significant treatment-related effect on body weight was observed for males at day 7. Individual group comparisons revealed that body weights in both the 1.5 and 3% groups were significantly lower than controls. Females in the 3.0% group showed a mean weight loss during the first week of the study, although this finding was not significant. Food consumption during the first week of study was reduced significantly in the 1.5% group males when expressed as total food consumed. No significant difference was noted when expressed on a per weight basis. The study provides additional data on the toxicity of repeated dermal dosing, including severe irritation, of this test substance at concentrations of 0.3, 1.5 and 3.0%. A NOAEL for local dermal effects could not be derived, the LOAEL was 0.3% (≈ 12.5 mg/kg bw/d). No NOAEL for systemic toxicity was derivable because of lack of histomorphology data from other organs and tissues.

Oral

Coco alkylamines [Cas No. 61788-46-3]

No data available.

Tallow alkylamines [Cas No. 61790-33-8]

In an oral 28-day study (gavage, SD rats) tallow alkylamines (GENAMIN TA 100) was administered in sesame oil (vehicle) to Sprague Dawley Crl:CD rats at dosages of 0, 12.5, 50 and 150 mg/kg bw/day once a day for 4 consecutive weeks (Instituto di Ricerche Biomediche, 2000a). The subacute test procedure was in accordance with OECD TG 407 except that all specific investigations on the neurofunction were lacking.

At 150 mg/kg bw/day two males and three females of the high dose group died between day 8 and 27. Animals at this dose level showed salivation after treatment, piloerection, hunched posture, fur loss and soft stools.

At 50 mg/kg bw/day salivation and piloerection were observed. One female died at day 11 showing lung changes as described for the high dose animals (see below).

At 12.5 mg/kg bw/day no toxicological relevant clinical signs occurred.

There was a dose-related body weight decrease. For males this reduction involved the intermediate and high dose group, i.e. -5% and -25% vs. controls, while in females all treated groups were effected, i.e. -5%, -12%, -21% vs. controls. Food consumption during administration period of animals treated at 50 and 150 mg/kg bw/d was generally lower than in controls. At 12.5 mg/kg bw/d food consumption was comparable to the controls.

Hematology revealed a slight increase in erythrocyte count at 150 mg/kg bw/d, which was accompanied by reduced values for MCV. A dose related moderate to marked increase in leukocyte counts and a slight to moderate increase in platelets were recorded at 50 and 150 mg/kg bw/d. The leukocyte enhancement was generally accompanied by variations in the white blood cell differential count, consisting of increases in neutrophiles percentage (i.e. at 50 mg/kg bw/d in males and at 150 mg/kg bw/day in both sexes).

Clinical-chemistry tests showed a number of alterations. Toxicologically relevant changes were markedly increased activities of ALAT and ASAT at 150 mg/kg bw/d. GGT activity was slightly increased in females of this dose group. The serum concentrations of protein and albumin and the A/G ratios were dose-dependently reduced in the 50 and 150 mg/kg bw/d groups.

Compared to control levels, a decrease in total cholesterol in high dose females and increases in the urea level were observed in both sexes of this group.

Organ weight of almost all organs of the surviving high dose group animals showed statistically significant absolute and/or relative changes (most often decreases). This was considered to be indirectly related to the growth depression in this group. There was, however, a decrease in the thymus weight and an increase in the adrenal weight indicating a direct effect of the treatment.

At the intermediate dose there were significant decreases in liver and kidney weights in males indicating again relation to general body weight loss.

Gross pathology findings were mainly slight to moderate dilations of the intestinal tract in intermediate and high dose animals.

Histopathologically, the premature descendents of the high dose group showed erosions in the gastric and small intestinal mucosa with marked accumulation of vacuolated histiocytes in mesenteric lymph nodes and lamina propria of the small intestine as well as epithelial hyperplasia in the mucosa. Histiocytic effects were more pronounced in the jejunum and ileum than in the duodenum. In the lungs abnormalities were mainly localised to the bronchi/bronchioli and consisted of inflammation associated with fibrosis and bronchial oedema.

Similar histopathological findings were observed in surviving animals of that dose group together with single cell necrosis and focal inflammation in the liver and areas of hyperplasia in the small intestinal mucosa as well as atrophy of the thymus and splenic follicle. In one male and one female there was a slight cortical hypertrophy of the adrenal glands.

At the dose of 50 mg/kg bw/d signs of atrophy of thymus were seen in one male and one female. Histiocytic involvement in small intestine and mesenteric lymph nodes was still present in moderate degree and also mucosal hyperplasia occurred in the intestine, and the lungs had similar changes compared to the high dose.

At the low dose histopathological changes were limited to slight histiocytic vacuolation in mesenteric lymph nodes and small intestine, without abnormal accumulation of histiocytes.

In conclusion, the primary adverse effects following repeated gavage administration into the stomach were gastrointestinal dilatation and erosions of the gastric and small intestine mucosa. Repeated exposures over time appears to exacerbate the gastrointestinal damage and the bad general health status and is suggested to be the cause of unscheduled deaths. Reduced food consumption, emaciation, mucosal hyperplasia and leukocytosis were related effects. Histiocytosis and histiocytic vacuolation indicated that the test substance was absorbed and accumulated intracellularly in the lymphoid tissues of the intestine. Liver cell necrosis associated with inflammatory response and increased activities of liver enzymes demonstrated that the test substance also has a hepatotoxic potential. The elevated urea concentrations might point to a minor renal toxicity. The follicle atrophy in the spleen and thymus atrophy indicated an immunosuppressive effect (most likely T-cells targeted). Since thymus atrophy was observed not only at 150 mg/kg bw/d, but also 50 mg/kg bw/d, at which no mucosa erosion was seen, it is concluded that immunosuppression was an independent adverse effect. Increases in adrenal weights fit to the hyperplasia of the gland which may be a non-specific effect. Increased erythrocyte counts (hemoconcentration) might be assumed as secondary to reduced water consumption (no data) which could accompany reduced appetite due to painful lesions in the gastrointestinal tract.

Bronchiolar and peribronchiolar inflammatory and fibrotic changes were interpreted to be related to the gavage application and thereby to the unintended aspiration of some material of the irritative test substance. Whether the lung effects contributed to the premature deaths could not clearly be identified (except for the one death at 50 mg/kg bw/d where the lung lesion was the only effect observed).

Histiocytic vacuolation of the mesenteric lymph nodes and small intestine, observed at slight degree at 12.5 mg/kg bw/d, occurred at all dose levels and increased dose-dependently to higher severity and progressed in accumulation. Therefore, a NOAEL could not be derived, the LOAEL was 12.5 mg/kg bw/d.

Hydrogenated tallow alkylamines [Cas No. 61788-45-2]

No standard test on repeated dose toxicity was available for hydrogenated tallow amines. Few data from studies with limited study design were reported for a metabolite or components of the tallow amine:

One group of 10 Sprague-Dawley rats (5/sex) received a diet containing 3000 ppm of *stearic acid* (a metabolite of hydrogenated tallow amine, ≈ 200 mg/kg bw/d based on a food consumption of 7% per kg bw) for 206 days (Deichmann et al., 1958). Another group was fed with diet containing octadecylamine that was dissolved in corn oil (CAS 124-30-1), while a control group was not carried along. Food consumption and the weekly change of body weights were recorded. Gross and microscopic examinations were made on major tissues (20 organs/tissues).

Two out of five female rats died spontaneously (no further details). Average weight gain was 12 g in males and 58 g in females, the animals were reported to be anorexic. Tissues from rats fed with stearic acid showed severe pulmonary infection consisting of tracheobronchitis, lobular pneumonia, lipoid histiocytic response, and abscess formation. No histomorphologic abnormalities were observed in the other organs. The authors concluded anorexia and increased mortalities as beeing substance-related toxic effects of stearic acid.

Comparative investigations on the hypolipidemic activity were conducted in rats receiving *isolated components* of hydrogenated tallow alkylamines, which were octadecylamine (C18-alkylamine, see next page) (content in hydrogenated tallow alkylamine: 60%, CAS 124-30-1), hexadecylamine (C16-alkylamine, content in hydrogenated tallow alkylamine: 30%) or tetradecylamine (C14-alkylamine, content in hydrogenated tallow alkylamine: 4%) (Griffin et al., 1991):

Six male Sprague-Dawley rats had been administered by gavage to 0, 8 or 20 mg/kg bw/d of tetradecylamine (C14-alkylamine) or of hexadecylamine (C16-alkylamine) (purities not further characterised, no data on vehicle) for 14 days. The liver, small intestine, aorta and faecal materials (24 h collection) were removed, extracted and analysed for cholesterol levels, triglyceride levels, neutral lipid content and phospholipid content. Blood was collected from the abdominal vein and lipoprotein fractions were obtained and analysed for cholesterol, triglyceride, neutral lipids and protein levels. The daily food consumption was significantly reduced in rats fed with these substances without any clear effect on growth; significantly reduced concentrations of cholesterol and triglyceride were observed in serum. In faeces triglyceride concentrations were significantly lower in tetradecylamine-treated rats, while rats receiving hexadecylamine had significantly lower concentrations of triglyceride and cholesterol than control rats. In both alkylamine groups the faeces concentrations of phospholipids were also reduced. No data on organ weights or (histo)morphology were available.

A consistent finding of all three alkylamine constituents of hydrogenated tallow amine was the hypolipidemic effect on serum triglycerides and cholesterol in rats.

Octadecylamine [Cas No. 124-30-1]

No repeated-dose toxicity study with compliance to the present standards on test protocols is available.

Rat

Two male Sprague-Dawley rats were fed with a diet containing 1% *octadecylamine sulfate* (about 700 mg/kg bw/d) (Carroll, 1960). Within six days body weight of the rats reduced up to 30% and animals died. [No other information available.]

In preliminary studies, the effect of *1-octadecylamine sulfate* on the growth of male and female rats was estimated at diet concentrations of 0, 0.01, 0.025, 0.05, 0.1, 0.25, 0.5, and 1.0% of 1-ocatadecylamine sulfate (Parenteau et al., 1991). All test concentrations of 0.01% (≈ 7 mg/kg bw/d) and above produced concentration-related lower body weight gain compared to the controls by day 16. At concentrations of 0.5% and 1.0% the body weight was progressively reduced reaching maximal losses of about 40-60% on day 8-11.

Six male Sprague-Dawley rats had been administered by gavage to 0 or 8 mg/kg bw/d of octadecylamine (C18-alkylamine) (not further characterised, no data on vihicle) for 14 days (Griffin et al., 1991). The liver, small intestine, aorta and fecal materials were removed, extracted and analysed for cholesterol levels, triglyceride levels, neutral lipid content and phospholipid content. Blood was collected from the abdominal vein and lipoprotein fractions were obtained and analysed for cholesterol, triglyceride, neutral lipids and protein levels. Significant reduction of body weight gain and daily food consumption; significant reduction of cholesterol- and triglyceride concentration in serum and liver as well as significant increased concentrations of triglycerides and phospholipids in faeces were observed. Phospholipid content was reduced in chylomicron, VLDL, LDL and HDL lipoprotein

fractions; no difference was found between treated and untreated animals on organ weights, histopathology of the liver, kidney and spleen and clinical chemistry.

Five male and five female Sprague-Dawley rats were fed 3000 ppm octadecylamine ("stearamine") in their diet for 209 days (reviewed by Pang, 1995, original data University of Miami, 1957; Deichmann et al., 1958). Calculated on the average daily diet consumption, 3000 ppm corresponded to 88 mg/kg bw/d for males and 138 mg/kg bw/d for females. No untreated control animals were used in the experiment, but the results were compared with those for animals fed 3000 ppm stearic acid. Tissues examined by histopathology examination included brain, viscera, gonads, skeletal muscle, bone marrow, heart, lungs, liver, spleen, kidneys, gastroenteric tract (3 levels), pancreas and lymph nodes. The two chemicals were equally toxic, causing anorexia, weight loss in male rats, reduced weight gain in female rats and increased mortality. The animals fed the stearamine diet had a lower daily feed intake (9.8 gr (males), 11.5 gr (females) than those fed the stearic acid diet (15 gr and 13.5 gr, resp.). The average weight change was –31g for males compared to +30 g for females, both sexes were fed the stearamine diet. One of five male rats and four of five female rats from the stearamine group survived to the end of the study. The average survival time was 87 days for the males and 199 days for the females. When microscopic examinations were performed on the tissues from five rats in the stearamine group, accumulated histiocytes with pale or foamy cytoplasm were observed in the mucosa of the small intestine and mesenteric lymph nodes. The lymph nodes were enlarged and matted, and revealed a marked granulomatous inflammation with abundant histiocytes, nodule or tubercle formation, necrosis, and fibrosis. Sections of the livers of three of five animals showed nodular aggregates of histiocytes, with slight necrosis. The lungs from rats fed stearamine showed varying degrees of pulmonary infection. Hepatic focal granulomas were also found in three rats. [No other information available.] - Reductions in food consumption of male rats treated with stearamine was interpreted to be as not as marked compared to the females to explain the significant weight loss and high mortality rates in male rates. Whether (respiratory tract) infections or other effects had contributed to unscheduled deaths, remains open.

A 2-year toxicity study of octadecylamine ("stearamine") was conducted using Sprague-Dawley rats. Four groups of 24 rats (12/sex) were fed diets containing 20, 100, 200, and 500 ppm stearamine (reviewed by Pang, 1995, original data University of Miami, 1957, Deichmann et al., 1958). A control group of animals was fed the base diet alone. The organs examined microscopically included the heart, lungs, liver, spleen, kidneys, gastroenteric tract (3 levels), pancreas, lymph nodes, bone marrow, brain, pituitary, adrenals, and ovary or testis. The feed consumption, growth rate, death rate, and blood cell counts for the experimental animals were comparable to those of the control animals. The survival rate for this study was 17-33% including the control group (meaning that 2, 3 or 4 animals/dose only survived until the end of study). In both control and experimental rats there was a higher than expected rate of mortality due to respiratory infections associated with chronic pneumonia and multiple organ inflammation. One rat receiving 500 ppm showed histiocytic hyperplasia of the mesenteric lymph node. At necropsy, no significant differences were found between the experimental and control groups in the incidence and types of lesions observed. [Calculated from diet consumption/day, the mean dose was about 1.05, 5.79, 10.68, and 27.15 mg/kg/day for 350 g males and 1.20, 5.80, 10.08, and 28.20 mg/kg/day for 250 g females. No other information available.] Having the histiocytic accumulations at 3000 ppm (seen in the 209 day-study in rats) and lesions of the same nature in the dog in mind, the single case of histiocytic hyperplasia in the mesenteric lymph node of the single rat treated with 500 ppm (25 mg/kg bw/d) for 2 years (in this study) could also be interpreted as a treatment-related

adverse effect. Therefore the rapporteur does not follow the authors'conclusion and proposes 200 ppm (10 mg/kg bw/d) as NOAEL for the 2-year rat studies.

Because of the high rates of mortalities primarily due to respiratory infections in the study of Deichmann and coworkers (1958), another 2-year study on groups of 10 male and 10 female Sprague-Dawley rats fed with diet containing 0, 200, or 500 ppm octadecylamine (0, 10 and 25 mg/kg bw/d) (dissolved in corn oil) was conducted (MacDonald et al., 1962). Respiratory tract infections and inflammatory lesions in multiple organs were observed in control and treatment groups. There were no significant differences between experimental and control rats in regard to the mean daily food consumption, mean weight gain, and mean survival time. No treatment-related pathological lesions could be attributed the feeding with the test substance. [No data on group incidences and severity of microscopic findings available].

Dog

In a 1-year toxicity study using dogs, three groups of three dogs (2 females and 1 male or 2 males and 1 female) each were fed 0.6, 3.0, and 15.0 mg/kg bw/d octadecylamine ("stearamine") in corn-oil solution that was administered by capsule once daily (5 d/wk) (reviewed by Pang, 1995, original data University of Miami, 1957, Deichmann et al. 1958). A control group of dogs was given untreated feed. Dogs were housed in individual cages and fed once daily. Hematological examinations consisted of total red blood cell count, hemoglobin concentration, total and differential white cell counts and were performed on all dogs at the start of the experiment and at 1, 2, 3, 6, 8, 11, and 12 months thereafter. The organs examined microscopically included the heart, lungs, liver, spleen, kidneys, gastroenteric tract (3 levels), pancreas, lymph nodes, bone marrow, brain, pituitary, adrenals, and ovary or testis. The high dose group gained less weight than the control and lower-dose animals. The weight gain for the two lower-dose groups was similar to that of the controls. Blood cell counts were comparable in experimental and control animals. Only one dog died before study termination (after week 22); this dog was from the group receiving 15.0 mg/kg bw/d octadecylamine and suffered from anorexia, bloody diarrhea and what appeared to be gastroenteric irritation. At necropsy, two animals from the high-dose group had lesions suggestive of the mesenteric lymph nodes, which were filled with pale histiocytes. Also, pale staining of the tips of the villi of the small intestine mucosa was observed in these dogs. However, no definite lesions were identified in the intestinal tracts of these animals or in any of the other experimental animals. [No other information available.] Considering the mortality associated with anorexia and hemorrhagic diarrhea in one dog, growth depression in two other dogs, and the lymph node histiocytosis observed at 15 mg/kg bw/d as a treatment-related toxic effect, the NOAEL in dogs fed with octadecylamine (CAS 124-30-1) for 1 year was 3 mg/kg bw/d.

Octadecenylamine [112-90-3]

Groups of five male and female SD-rats received octadecenylamine (Genamin OL 100 D, vehicle sesame oil) by oral gavage at dose levels of 0, 3.25, 12.5 or 50 mg/kg bw/day for a period of 28 days (Aventis, 2003). On day 29 animals were necropsied. In the control and high dose groups, additional five male and females were examined and necropsied after a recovery period of 14 days. The study design and examinations conducted were in full accordance to the EU method B.7 (OECD 407) for subacute oral toxicity (including neurobehavioral observation and functional observation battery testing).

In a preliminary study on dose-range finding three males and females received the test substance at doses of 25, 100 and 400 mg/kg bw/d over a period of 14 days and surviving animals were necropsied on day 15. After administration of 400 mg/kg bw/d one male and

one female died at days 4 and 7, respectively. The other animals of this dose group were killed for animal welfare reasons. The animals of the 100 mg/kg bw/d group showed clinical signs of impaired motility and respiration. The male animals were clearly more sensitive than the female animals. After administration of 25 mg/kg bw/d no symptoms were observed except of one female rat, which showed uncoordinated gait at study day 2. The body weight gains of animals exposed to doses of 25 and 100 mg/kd bw/d were impaired. Necropsy of the descendent and prior killed animals showed changes in the stomach and intestinal mucosa. The animals of 100 mg/kg bw/d showed reddening of the stomach mucosa. No macroscopically visible changes were observed in the 25 mg/kg dose groups.

In the main study, treatment resulted in no unscheduled deaths throughout the study. Behaviour and state of health remained unaffected by the administration of the test compound in the low and mid dose groups. Clinical findings in the high dose group (2 males and 5 females out of 10) from the 2nd or 3rd week onwards comprised impairments of motility (stilted and/or uncoordinated gait) and lasted until the end of treatment, with subsequent recovery. In addition, respiratory sounds were noted in one high dose female only on study day 13. No opacity of the refracting media of the eyes, changes of the oral mucosa, or impairment of dental growth was observed. No abnormal neurobehavior was observed in any group.

Mean body weight was significantly lower for high dose males from study day 11 and for high dose females from day 22 until the end of treatment, and remained to be different as compared to the controls at the end of recovery period. Also mean body weights for mid dose males were significantly lower from day 22 onwards to the end of treatment**. At the end of treatment, body weight in males was -5.3% (nonsign.) at low dose (3.25 mg/kg/day), -7.5% (sign.) at mid dose (12.5 mg/kg/day) -10% (sign.) at high dose compared to the body weight of controls. At the end of recovery, body weight in high dose males remained at the same, significantly lower level (-9.8%). Body weights in high dose females were -10.4% lower than the control values at the end of treatment and a clear tendency to recover was seen at the end of 4-week recovery (difference was still -5.9% (non-sign.)).**

Compared to control animals, mean body weight gain was significantly lower at the end of treatment for high dose males (-19%), high dose females (-20%) and for mid dose males (-15%). A dose-dependent, small (-9%, statistically non-significant) reduction of body weight gain was also reported for the low dose males. The weight gain was normalised at the end of the recovery for high dose males or even higher in the high dose female group indicating a tendency to recovery (no recovery conducted for the mid dose group). Food consumption remained unaffected throughout the study in all dose groups.

Hematology findings in high dose groups included significantly increased hematocrit and decreased reticulocyte counts (males only) and slightly increased white blood cell counts with a shift towards increased neutrophils (both genders), all findings being reversible. Clinical chemistry changes comprised significantly increased total bilirubin for the high dose group, slightly increased urea nitrogen for mid and high dose females and very slightly increased ASAT and ALAT activity in the liver of high dose males. Urinalysis remained unaffected in all dose groups. Likewise the urine sediment was unobtrusive for control and high dose group animals.

No anatomic pathology correlates (organ weights, macroscopy, microscopy) of toxicological significance were detected.

In conclusion, repeated administration of octadecenylamine (Genamin OL 100 D) at a dose of 50 mg/kg bw/day induced clinical signs as gait abnormalities, reduction in body weight gain and clinical pathology findings indicating mild toxic effects on the liver and kidneys. The only treatment-related effects observed at the mid-dose level were reduction in growth and increased urinary concentration of urea nitrogen. By standard requirements on screening for neurotoxicology given for this type of study, stilted gait or uncoordinated gait was not associated with any other symptom of altered neurobehavior or neurotoxicity and may be discussed as being of unspecific nature. In the preliminary study, macroscopic findings in the gastrointestinal mucosa were observed in early deaths and in animals receiving 100 mg/kg bw/d, but were absent in animals at a dosage of 25 mg/kg bw/d from the 14-day study and in dose groups receiving 50 mg/kg bw/d where gait abnormalities were also present. Thus, regarding the absence of other severe clinical symptoms that may explain gait abnormalities and considering the screening nature of 28-day study design for neurotoxicity uncertainty on the cause of gait abnormality remains.

Except for growth reduction, full recovery of findings was seen at the end of recovery period.

Based on the significantly reduced body growth at 12.5 mg/kg bw/d observed in the present 28-day study, the NOAEL of 3.25 mg/kg bw/d was derived. As far as no other equivalent studies with longer treatment periods are available this value can be taken for quantitative risk assessment procedures.

In vitro studies

No data available.

4.1.2.6.2 Studies in humans

In vivo studies

No data availbale.

In vitro studies

No data available.

4.1.2.6.3 Summary of repeated dose toxicity

Coco alkylamines [Cas No. 61788-46-3]

No data available

Tallow alkylamines [Cas No. 61790-33-8]

In a 28-day study on tallow alkylamines, which was compliant to the OECD 407 test guideline for the general toxicity, the predominant toxic effects were dilation and mucosal erosion of the gastrointestinal tract associated with emaciation, general poor health status and unscheduled deaths at 150 mg/kg bw/d. Besides, a dose-dependent slight to marked accumulation enteropathy was predominant in the distal parts of the small intestine of rats at all test doses. The accumulation of the test substance in histiocytes was obvious in the draining (mesenteric) lymph nodes, but also in the intestinal submucosa. Other treatment-

related adverse effects were liver toxicity, immunosuppression of lymphoid tissues, adrenal hyperplasia. Additional effects (mucosal hyperplasia in the intestine, leukocytosis) were associated with the primary damage of the gastrointestine. The LOAEL was 12.5 mg/kg bw/d.

Hydrogenated tallow alkylamines [Cas No. 61788-45-2]

No guideline-compliant study on repeated dose toxicity is available for hydrogenated tallow amines.

Anorexia and increased mortality became evident in rats from a chronic study on 3000 ppm *stearic acid* (≈ 200 mg/kg bw/d), a metabolite of hydrogenated tallow amine. However the study was less reliable through that only 5 animals per sex were treated, the study did not include a control group and animals suffered from spontaneous respiratory infectious diseases.

In specific investigations on the lipid fractions in the serum, *isolated components* of hydrogenated tallow alkylamines: octadecyl (60%, CAS 124-30-1), hexadecylamine (30%) or tetradeylamine (4%), reduced cholesterol and phospholipid concentrations.

Octadecylamine [Cas No. 124-30-1]

No repeated-dose toxicity study on animals that fully meets the testing standards is available.

Three dermal administrations of ≥3 mg octadecylamine during 5 days caused epidermal hyperplasia in mice (Brooks et al., 1956).

Oral administration of octadecylamine caused reductions in food consumption and body weight gain in all doses tested in subacute studies (≥8 mg/kg bw/d) (Griffin, et al., 1991). Related to anorexia, dramatic weight loss occurred at 350 mg/kg bw/d (0.5%), mortalities were observed at doses of 700 mg/kg bw/d (1%) octadecylamine sulfate (Parenteau et al., 1991). Besides, lowered serum concentrations of cholesterol and phospholipid in rats receiving 8 mg/kg bw/d indicated hypolipidemic activity of octadecylamine (Griffin et al., 1991).

The authors of early chronic toxicity studies (Deichmann et al., 1958) on octadecylamine concluded that no adverse effect was observed in rats receiving up to 500 ppm with diet during 2 years. This concentration corresponded to 25 mg/kg bw/day. However it should be noted, that the prevalence of infectious diseases of multiple organs limits the reliability of these studies.

In the context of findings of the same nature seen at 3000 ppm in rats of other studies and in dogs, the single case of histiocytic hyperplasia in the mesenteric lymph node of the single rat treated with 500 ppm (25 mg/kg bw/d) for 2 years could also be interpreted as a treatment-related adverse effect . Therefore, 200 ppm (10 mg/kg bw/d) is proposed as NOAEL for the 2-year rat studies from the study of Deichmann et al. (1958).

In rats at a high dietary concentration of 3000 ppm octadecylamine (88 mg/kg bw/d in male rats, 138 mg/kg bw/d in female rats, calculated from food consumption data), granulomatous histiocytosis of lymphoid tissues in the intestine and mesenteric lymph nodes as well as histiocytic granuloma formation in the liver indicated the resorption of the test substance and the intracellular accumulation in liver histiocytes associated with secondary necrotic-inflammatory lesions. Although other diagnostic terms have been used, these findings corresponded well to those reported in the 28-day study on tallow alkylamines (CAS 61790-33-8). Moreover an accumulation of loaded histiocytes was not only observed in the intestine

submucosa and in mesenteric lymph nodes; the evidence of histiocytic granuloma formation in the liver might be interpreted that non-sessile histiocytes migrate from the intestine into the liver parenchyma.

Dogs appeared to be more sensitive towards the chronic irritative properties of octadecylamine on the gastrointestinal tract than rats. Similarly to the effects in rats, an accumulation of histiocytes were seen in the mesenteric lymph nodes and in the villi of the small intestine mucosa.

Considering the mortality associated with anorexia and hemorrhagic diarrhea in one dog, growth depression in two other dogs, and the lymph node histiocytosis observed at 15 mg/kg bw/d as a treatment-related toxic effect, the NOAEL in dogs fed with octadecylamine (CAS 124-30-1) for 1 year was 3 mg/kg bw/d.

Overall, all data from a number of repeated-dose studies with limitations were not fully reliable to derive a firm NOAEL.

Octadecenylamine [112-90-3]

Repeated dermal application of octadecenylamine caused concentration-dependent mild to severe irritative to corrosive skin effects in rats. The lowest concentration tested (0.3%, ≈12.5 mg/kg bw/d) in the dermal studies was the $LOAEL_{local}$ for this route. Systemic toxicity was not adequately addressed in these studies.

A guideline-compliant oral 28-day study in rats did not induce adverse effects at 3.25 mg/kg bw/d (NOAEL). Indications of toxicity at 50 mg/kg bw/d were growth depression at normal food consumption and increased enzyme activities indicative for minor liver or/and kidney dysfunctions. Motoric abnormalities (stilted gait), hemoconcentration and leucocytosis/ neutrophilemia observed at 50 mg/kg bw/d could not be related to other primary organ damage. Doses up to 50 mg/kg bw/d had no irritative properties on the mucosa of the gastrointestinal tract, while such effects associated with mortalities were seen at 400 mg/kg bw/d during week one of a preliminary study.

Overall NOAEL for quantitative risk assessment

Oral route

Information from 28-day studies with full compliance to the actual testing protocol is available only for one fatty alkylamine regarded in this report (octadecenylamine CAS 112-90-3). For a second alkylamines mixture, tallow alkylamines (CAS 61790-33-8), the test design of the oral 28-day test followed the guideline protocol except that specific investigations on neurobehavior and neurofunction were not incorporated.

For two other fatty alkylamines, hydrogenated tallow alkylamines (CAS 61788-45-2) and octadecylamine (CAS 124-30-1), there is some information on repeated dose toxicity. However, none of the studies available complies to the present days' standard. No single study was reported for coco alkylamines (CAS 61788-46-3).

To satisfy the minimal repeated dose information requirements for each of the fatty alkylamines according to the existing chemicals regulation, read-across of data available for octadecenylamine and tallow alkylamines (those with complete or nearly complete 28-day studies) were applied for those with no or poor data on repeated dose toxicity. This approach implies that the most sensitive NOAEL for this endpoint was derived from the two valid 28-day studies and is applied for all members of the category.

The NOAEL proposed for quantitative risk assessment of all alkylamines assessed in this report is derived from the valid oral 28-day study on octadecenylamine (CAS 112-90-3) and is 3.25 mg/kg bw/d.

Proposed classification

The outcome of the oral 28-day study on tallow alkylamines (CAS 61790-33-8) indicated that fatty alkylamines may pose a risk for serious health effects after chronic oral exposure.

Leading health effects were delayed mortalities associated with precedent bad general health status and gait abnormalities, erosions of the mucosa of the gastrointestinal tract, accumulation of (material-) loaded histiocytes in the submucosa of the distal parts of the small intestine and in the mesenterial lymph nodes associated with inflammatory granuloma formation, liver toxicity and indications of immunosuppression occurring at 150 mg/kg bw/d which is within the critical dose range for R48.

The adverse effects in the lungs were not considered for the classification proposal on the oral route, but the potential for damaging the surface epithelia of the respiratory tract should be considered elsewhere if the inhalation route is relevant.

Data from the range-finding study on octadecenylamine (CAS 112-90-3) indicated that bad general health condition (gait abnormalities) and stomach reddening was already seen in rats receiving 100 mg/kg bw/d for 14 days. Treatment-related reductions in food consumption and body growth started at ≥8 mg/kg bw/d in subacute studies on octadecylamine.

Also a dose of 50 mg/kg bw/d in the valid 28-day study on octadecenylamine confirmed similar signs of impaired health condition (reduced body weight gain, impaired motility, stilted and uncoordinated gait) and hepatotoxicity. Although there was no histopathological evidence of mucosa damage in the gastrointestinal tract at this dose of octadecenylamine, 50 mg/kg bw/d of tallow alkylamines induced mucosal hyperplasia and histiocyte accumulation. Since higher doses up to 150 mg/kg bw/d were not tested in this 28-day study, mortalities and other toxic effects that were observed at 150 mg/kg bw/d of tallow alkylamines could not be ruled out for octadecenylamine.

Taking all data on fatty alkylamines into consideration, the lowest dose with a depressive effect on the growth was 0.01% (about 7 mg/kg bw/d, estimated from repeated dose studies on octadecylamine, body weight loss was first seen at 50 mg/kg bw/d (also demonstrated for tallow alkylamines (Institutio di Richerche Biomediche, 2000a and for octadecylamine, see Parenteau et al., 1991). This is also the lowest dose associated with histopathological lesions of the gastrointestinal mucosa.

With respect to the classification of ‘local’ effects, the data available clearly demonstrated that fatty alkylamines caused damage along the exposure route, the mucosa of the gastrointestinal tract. Although gavage administration is not a usual exposure condition for man, the data also demonstrated a cytotoxic potential at any site of contact (as intended in the studies via the oral or dermal route or as non-intended for the bronchial mucosa). Repeated exposure resulting in ‘local cytotoxicity’, i.e. erosions of the gastrointestinal mucosa, that was associated with secondary effects of systemic significance and progressed continuously with the duration of treatment leading to body weight loss, bad general health status and unscheduled deaths. Besides, the accumulation and migration of test substance loaded histiocytes along the intestinal passage into lymphnodes and other tissues (intestine

submucosa and putatively liver), the liver toxicity and the immunosuppression are judged as adverse (systemic) effects.

Critical effects for R48/22:

- Delayed mortalities and erosion of gastrointestinal mucosa at 150 mg/kg bw/d, 28 day study, tallow alkyl amines)
- Gait abnormalities at non-lethal, non-irritating concentrations (50 mg/kg bw/d, 28 day study, octadecenylamine)
- Treatment-related reduction in food consumption (≥7-8 mg/kg bw/d, subacute study, hydrogenated tallow alkylamines) resulting in growth depression, anorexia. Effects could be interpreted as non-specific toxicity. However, intestine dysfunction such as malabsorption could also possible as consequence of morphological damage of the intestine (through intramural substance accumulation and responsive inflammation and hyperplasia of intestinal wall).
- Accumulation of test material in the intestinal wall and in mesenteric lymph nodes (≥12 mg/kg bw/d, 28 day study, rat; 15 mg/kg bw/d, tallow alkylamines; 12 mo, dog, octadecylamine). Effect is already present at non-irritating dosages. There is no excretion pathway for intracellular material, some redistribution among cells or among organs may be possible through re-phagocytosis or migration of loaden histiocytes. The effect is irreversible.
- Accumulation enteropathy is associated to inflammatory and hyperplastic responses of the intestine: Histiocytic granuloma in intestinal wall and mesenteric lymph nodes, histiocytic hyperplasia in mesenteric lymph nodes, mucosal hyperplasia in the intestine. Related to the persistence of accumulated material granuloma formation will also persist during life.
- Disturbance of lipid metabolism (8 mg/kg bw/d, 14 day study, octadecylamine): significance could not clearly be estimated, a lack of phospholipids for example might affect central nervous function or lung function.
- Treatment-related liver toxicity (150 mg/kg bw/d, 28 day study, tallow alkylamines, 50 mg/kg bw/d, 28 day study, octadecenylamine). In addition, histiocytic granuloma formation in the liver is likely to be secondary effect from accumulated (and migrated) material from intestinum.
- Thymus atrophy and atrophy of spleen follicles indicated immunosuppression (T-cell) (≥50 mg/kg bw/d, 28 day study)

In conclusion,

a) delayed mortalities occurred at 'irritating' high concentrations/doses and

b) other serious health effects occurred at **non-irritating** concentrations/doses

Both, a) and b) were seen within the critical dose range for R48.

Category approach on all fatty alkylamines

The assumption has been raised that octadecylamine and hydrogenated tallow alkylamines might have lower potency in chronic toxicity that does not call for R48 classification.

From some studies, e.g. the chronic rat studies (Deichmann et al., 1958) it might appear that octadecylamine exerts its toxicity at concentrations, which are not critical for R48 classification, e.g. cumulative enteropathy observed at ≥500 ppm (25 mg/kg/day). However, read-across among the whole group of alkylamines and classification as "harmful" is suggested for the following reasons:

The data available for octadecylamine are clearly limited. There were high mortality rates of 67-83 % in limited dose groups (12 rats/sex/group) in the 2-year study (Deichmann et alt. 1958) and respiratory infectious diseases associated to mortalities in all three long-term studies (two from the Deichmann publication and one from his colleague McDonald (McDonald et al., 1962). The test methods and results, gained in no GLP or guideline compliant studies, were roughly summarised and poorly documented in the publications.

The subacute study of Griffin et al. (1991) confirmed that already at low doses (8 mg/kg/day) disturbed lipid metabolism occurred.

The available repeated dose data, which were considered for hydrogenated tallow alkylamines, included a limited study on a metabolite, i.e. stearic acid, and studies on hypolipidemic activities of single components of hydrogenated tallow alkylamine.
No reliable repeated dose study on hydrogenated tallow alkylamines itself is available.

Therefore, a lower potency in chronic toxicity of octadecylamine and hydrogenated tallow alkylamines could not be verified. It is concluded that there is no sufficient evidence to exclude these substances from read across and classification as "harmful", R48, is warranted.

Applying the category approach due to the data gaps on this endpoint for three of the fatty alkylamines, (see Table 4.1.2.6), a classification with R48/22 is proposed for all representatives of fatty alkylamines.

No further studies on repeated dose toxicity are required for an adequate risk assessment of the alkylamines of this report.

Dermal route

For none of the fatty alkylamines exists a guideline-compliant repeated dose study on this route. For two of them (octadecylamine (CAS 124-30-1) and octadecenylamine (CAS 112-90-3)) data from non-guideline studies with repeated dermal administration were available. However, due to limitations in the study design or/and reporting, no study appeared suitable to deliver valid information about systemic toxic effects following dermal administration.

No $NOAEL_{sys}$ for systemic toxicity could be estimated for the dermal route.

The only information that can be derived from these data is the overall minimal concentration that induces adverse skin effects. This value can be used also for the risk assessment of those alkylamines lacking any repeated dose data on the dermal route.

The overall $LOAEC_{local}$ for local effects on the dermis was 0.3% (corresponding to 12.5 mg/kg bw/d).

Table 4.1.2.6: Overview on repeated dose toxicity studies with primary alkylamines

Alkylamine (CAS No.)	**Repeated dose toxicity NOAEL**	**Informations on carcinogenicity from repeated dose toxicity studies**
Coco alkylamines (1788-46-3)	No data	No data
Tallow alkylamines (61790-33-8)	EU method B.7-equivalent[12] oral 28 day study-rat LOAEL 12.5 mg/kg bw/d	No data
Hydrogenated tallow alkylamines (61788-45-2)	No guideline-compliant study: Limited data from chronic oral study on a metabolite Additional data on hypolipidemic effects from oral 14 d studies in rats on structurally related components of hydrogenated tallow alkylamines A reliable NOAEL could not be derived from the data available.	No data
Octadecylamine (124-30-1)	No guideline-compliant study: Limited dermal 5-day study - mouse Limited oral 6-14 day-studies –rat Limited oral chronic studies –rat NOAEL 200 ppm (10 mg/kg bw/d) Limited oral chronic studies - dog NOAEL 3 mg/kg bw/d	Limited data from oral chronic studies in rats
Octadecenylamine (112-90-3)	One limited dermal 14-day studiy – rat $LOAEC_{local}$ 0.3% (12.5 mg/kg bw/d) EU method B.7 equivalent oral 28 day study – rat NOAEL 3.25 mg/kg bw/d	No data
Overall NOAEL	Oral route: Overall NOAEL 3.25 mg/kg bw/d Dermal route: $LOAEC_{local}$ 0.3% (12.5 mg/kg bw/d)	No reliable data

[12] Limited by lack of specific studies on neurobehaviour/function

4.1.2.7 Mutagenicity

4.1.2.7.1 Studies in vitro

Generally, strong cytotoxicity of alkylamines was observed in vitro. In most experiments, cytotoxic effects were induced at lower doses/concentrations in experiments without S-9 mix compared to experiments with S-9 mix.

Coco alkylamines [Cas No. 61788-46-3]

An investigation on induction of gene mutations in bacteria (OECD 471) was performed with coco alkylamines ("Genamin CC 100 D") (Hoechst AG, 1988m). The test compound (purity approx. 100%) was solved in acetone and tested in doses of 0.16 µg to 10 mg/plate with and without liver S-9 mix from Arochlor induced male Sprague Dawley rats. Only doses up to 100 µg/plate could be evaluated due to strain specific strong cytotoxic effects at doses of 20 or 100 µg/plate and higher doses. In TA1537 the bacterial background lawn was reduced already at 4 µg/plate in the second experiment. Precipitaions were seen at 500 µg/plate and higher doses. No increases in the number of revertants were induced in any of the tester strains, e.g. Salmonella typhimurium TA100, TA1535, TA1537, TA1538, TA98 and E. coli WP2uvrA.

Tallow alkylamines [Cas No. 61790-33-8]

A bacterial gene mutation test (OECD TG 471) with tallow alkylamines ("Genamin TA 100 D") was negative with and without Aroclor-induced rat liver S-9 mix in five Salmonella typhimurium tester strains (TA98, TA100, TA1535, TA1537, TA1538) and Escherichia coli WP2uvrA (Hoechst AG, 1988n). The test substance (purity 99-100%) was solved in ethanol and tested in doses of 0.16 µg to 10 mg/plate. Due to strong and dose-dependent cytotoxicity in all tester strains only concentrations up to doses of 100 µg/plate without S-9 mix and 500 µg/plate with S-9 mix were evaluable. Visible precipitations of the test compound were found for all doses from 20 µg/plate upwards with and without S-9 mix.

Hydrogenated tallow alkylamines [Cas No. 61788-45-2]

No genotoxicity tests with hydrogenated tallow alkylamines are available.

Octadecylamine [Cas No. 124-30-1]

Data on negative bacterial mutagenicity tests with octadecylamine were compiled by Zeiger et al. (1988). Negative results were reported for Salmonella typhimurium strains TA100, TA1535, TA97 and TA98 with and without metabolic activation with 10% and 30% Arochlor induced rat and hamster liver S-9 mix at doses of 100 to 6666 µg/plate. Water was used as solvent. Precipitations were found at 333 µg/plate and higher doses on plates with metabolic activation. No signs of toxicity were reported apart from a slight clearing of background lawn at the highest dose without metabolic activation in TA97. The absence of cytotoxic effects at lower doses was possibly caused by the use of water as solvent.

Further bacterial mutagenicity tests (OECD 471) with octadecylamine ("Genamin 18 R 100 D") were performed with tester strains Salmonella typhimurium TA 100, TA1535, TA1537, TA1538, TA98 and E. Coli WP2uvrA (Hoechst AG, 1988). The test substance (purity approx. 100%) was dissolved in ethanol and tested in doses of 4, 20, 100, 500, 2500 and 10000

µg/plate with and without Arochlor induced liver S-9 mix from male Wistar rats. Strain specific dose dependent cytotoxic effects (decrease in the number of spontaneous revertants and/or incomplete bacterial lawn) were seen at 100 or 500 µg/plate and higher doses. No increases in the number of revertant colonies were induced in any of the tester strains. Precipitations were found at doses of 500 µg/plate and higher doses.

Octadecylamine ("stearylamine", purity not stated) was tested as component of multilammellar lipid vesicles (MLV) containing L-α-phosphatidyl choline (PC) and octadecylamine (PC/Octadec 7:2) in human heteroploid EUE cell line (embryonic human explants) and lymphocytes from a healthy human donor (Nuzzo et al. 1985). Cells were incubated with 0.14 to 4.44 mg lipids in buffer in the presence of 6 mmol/l $CaCl_2$ for 24 and 48 h. In EUE cells the mitotic index (MI) was markedly reduced at 4.44 mg lipids after 48 h. Increases in percentages of mitoses with structural chromosomal aberrations compared to controls were seen in EUE cells after 24 h at doses of 1.39 and 4.44 mg lipids and after 48 over the whole dose range tested. In lymphocytes the MI was markedly reduced at 1.39 mg lipids after 24 h and no mitoses were found at both incubation times with 4.44 mg lipids. For these cells an increase of mitoses with structural chromosomal aberrations under conditions that did not lead to extreme cytotoxicity was found at 1.39 mg lipids after 24 h. Since the number of mitoses with structural chromosomal aberrations in control cultures was extremely high in EUE cells (14% after 24h and 10 % after 48 h) and was also reported to be higher (up to 5.4%) than under standard culture conditions in lymphocytes the test sytems or test conditions do not seem to be adequate for cytogenetic investigations. Additionally, octadecylamine was not tested alone but only in combination with PC. The study is therefore difficult to interpret and of low relevance for the risk assessment of octadecylamine.

Octadecenylamine [Cas No. 112-90-3]

Octadecenylamine was not mutagenic in bacterial tester strains Salmonella typhimurium TA 98, TA 100, Ta1535, TA1537 and TA1538 in doses up to 20 µg/plate without metabolic activation and up to 200 µg/plate with metabolic activation (Arochlor induced rat liver S-9 mix) (Microbiological Associates Inc. 1985a, cited from IUCLID, original data not yet available).

Negative results for mutagenicity of octadecenylamine (named "Oleylamine" in the test report) were obtained in a L5178Y TK+/- mouse lymphoma assay (OECD TG 476) (Microbiological Associates Inc., 1989a). Mutation frequency was determined after incubation with 0.13 to 1.8 nl/ml octadecylamine (purity not given) in the absence of metabolic activation and with 1.3 to 13 nl/ml in the presence of Arochlor induced rat liver S-9 mix for 4 h (solvent acetone). Concentrations were equivalent to ca. 0.1 to 1.5 ng/ml (0.39 nmol/l to 5.4 nmol/l) without S-9 mix and 1.0 to 10.6 ng/ml (3.9 nmol/l to 39.5 nmol/l) with S-9 mix. No increases in mutation frequency as compared to solvent controls were found. At 1.8 nl/ml without metabolic activation and at 13 nl/ml with metabolic activation remarkable decreases in cell growth compared to solvent controls were found. At higher concentrations the cells were unable to form clones.

Octadecenylamine (ODA-FG-11-27-84) did not induce chromosomal aberrations in CHO cells in the absence and presence of aroclor 1254 induced Sprague dawley rat liver S-9 mix (Microbiological Associates Inc., 1985b). Cells were treated with 0.05 to 5 nl/ml of the test substance for 16 h in the absence of S-9 mix and with 0.2 to 20 nl/ml for 2 h in the presence of S-9 mix and cells were harvested after 18 h . Cell survival was reduced to 24% with and without S9 mix at the highest concentrations tested.

Mutagenicity at the hprt locus was investigated in Chinese hamster ovary cells at concentrations of 0.1 to 2.0 nl/ml without S-9 mix and of 5.0 to 10 nl/ml with S-9 mix (Microbiological Associates Inc., 1985c). No relevant cytotoxicity (decrease in cloning efficiency) was found for the analysed concentrations; without S-9 mix concentrations higher than 2.0 nl/ml led to strong cytotoxicity so that cloning was not successful. In general, there was no increase in mutation frequencies after treatment, with the exception of the highest concentrations of 2.0 nl/ml (without S-9 mix) and 9.0 nl/ml (with S-9 mix) in the first experiment. Since no genetic effects were seen at lower concentrations and the second experiments were clearly negative with and without S-9 mix, these increased mutation frequencies can be interpreted as outliers (due to the low statistical power of this test system). Altogether, the test result is negative.

Other primary alkylamines

Bacterial gene mutation tests with **Hexadecylamine (Cas No. 143-27-1)** in Salmonella typhimurium TA100, TA1535, TA97 and TA98 revealed negative results (Zeiger et al., 1988). Doses of 300 to 33 000 µg/plate solved in DMSO were tested with 10% and 30% Arochlor induced rat and hamster liver S-9 mix. No precipitations or signs of toxicity were found up to the highest dose tested.

4.1.2.7.2 Studies in vivo

Coco alkylamines [Cas No. 61788-46-3]

No in vivo genotoxicity tests with coco alkylamines are available.

Tallow alkylamines [Cas No. 61790-33-8]

A bone marrow micronucleus test (OECD TG 474) with tallow alkylamines (Genamin TA 100) in 50 Sprague Dawley rats (25 male and 25 female) led to a negative result after a single oral dose of 2000 mg/kg bw (Instituto di Ricerche Biomediche (2000c). The test substance was applicated in sesame oil by intragastric gavage. Sampling times were 24 h and 48 h after treatment. The tested dose induced clinical signs of toxicity (piloerectin, hunched posture, hypoactivity and shallow breathing) in all animals and led to a lethal effect in one male rat at the 48 h sampling time group; no local cytotoxicity on bone marrow cells (PCE/NCE) was observed.

Hydrogenated tallow alkylamines [Cas No. 61788-45-2]

No in vivo genotoxicity tests with hydrogenated tallow alkylamines are available.

Octadecylamine [Cas No. 124-30-1]

No in vivo genotoxicity tests with octadecylamine are available.

Octadecenylamine [Cas No. 112-90-3]

Negative results were reported form an chromosomal aberration test in mice bone marrow cells with octadecenylamine ("Oleylamine") (Microbiological Associates Inc., 1989b). Groups of five male and five female mice were administered single doses of 500, 2500 or 5000 mg/kg bw in corn oil by oral gavage at a volume of 10 ml/kg bw (purity 90%). Bone marrow cells were collected 6, 12 and 24 h after treatment. No increases in percentages of aberrant cells were observed in the test substance treated animals regardless of dose or harvest

time. One female in the 2500 mg/kg bw group died prematurely. No significant reduction in the rate of body weight gain was observed. Clinical signs of toxicity were observed in test substance-treated mice indicating that the test substance was systemically available after oral application.

4.1.2.7.3 Summary of mutagenicity

For all alkylamines assessed in this report only negative results were obtained in mutagenicity tests.

There is no evidence for mutagenicity of **coco alkylamines** from the available gene mutation test in bacteria.

Tallow alkylamines were tested negative in bacteria and in bone marrow cells in vivo.

No tests on mutagenicity of **hydrogenated tallow alkylamines** are available.

From the available data on mutagenicity in bacteria there is no evidence for mutagenicity of **octadecylamine**.

Octadecenylamine was tested negative in vitro in bacteria and in mammalian cells. A bone marrow chromosomal aberration test in vivo did not reveal any mutagenic effects of octadecenylamine up to systemically toxic doses.

Only negative results were obtained in mutagenicity tests with the investigated alkylamines mixtures.

For the group of alkylamines mixtures with **longer** chainlengths, mainly consisting of C18 and C16 chains (tallow alkylamines, hydrogenated tallow alkylamines, octadecenylamine, octadecylamine) negative results from tests on bacterial mutagenicity and data on gene mutations in mammalian cells in vitro and on chromosomal aberrations and micronuclei in vivo are available. The whole amount of data is judged as sufficient to exclude mutagenic potential for the group of alkylamines with **longer** chainlengths in vivo.

For coco alkylamines, an alkylamines mixture of **shorter** chainlengths, only data on bacterial mutagenicity exist. No further genotoxicity tests in mammalian cells in vitro or in vivo are available. Altogether, the negative data from the bacterial tests together with negative data on structurally similar long chained alkylamines is considered as sufficient to exclude a mutagenic potential of coco alkylamines in vivo.

No classification in respect to germ cell mutagenicity is proposed for the alkylamines mixtures assessed in this report.

Table 4.1.2.7: Overview on mutagenicity studies with primary alkylamines

Alkylamine	Test system	Concentration range	Result	Toxicity	Solvent	Reference
Coco alkylamines	Bacterial gene mutation test	0.16 to 10000 µg/plate with and without S-9 mix	Negative	Strain specific at 20 µg/plate and higher doses	Acetone	Hoechst AG, 1988 m
Tallow alkylamines	Bacterial gene mutation test	0.16 µg to 10000 µg/plate without S-9 mix and 0.16 to 500 µg/plate with S-9 mix	Negative	Strain specific at 20 µg/plate without S-9 mix and at 100 µg/plate with S-9 mix	Ethanol	Hoechst AG, 1988 n
Tallow alkylamines	Micronucleus test in rat bone marrow cells	2000 mg/kg bw, single oral dose	Negative	Systemic toxicity: yes, local toxicity : no	Sesame oil	Instituto di Ricerche Biomedice, 2000c
Octadecyl-amine	Bacterial gene mutation test	100 to 6666 µg/plate with and without S-9 mix	Negative	No	Water	Zeiger et al., 1988
Octadecyl-amine	Bacterial gene mutation test	4 to 10000 µg/plate with and without S-9 mix	Negative	Strain specific, generally at 100 µg/plate and higher doses	Ethanol	Hoechst AG, 1988 o
Octadecenyl-amine	Bacterial gene mutation test	up to 20 µg/plate without S-9 mix and up to 200 µg/plate with S-9 mix	Negative	No data		Microbiological Associates Inc. ,1985a
Octadecenyl-amine	Chromosomal aberrations in CHO cells	0.05 to 5 nl/ml without S-9 mix and 0.2 to 20 nl/ml with S-9 mix	Negative	At the highest concentrations tested	Acetone	Microbiological Associates Inc., 1985b

Octadecenyl-amine	Mouse lymphoma assay	0.13 to 1.8 nl/ml without S-9 mix and 1.3 to 13 nl/ml with S-9 mix.	Negative	At 1.4 ng/ml without S-9 mix and 10.4 ng/ml with S-9 mix and higher concentrations	Acetone	Microbiological Associates Inc., 1989a
Octadecenyl-amine	HPRT gene mutation test in mammalian cells	0.1 to 2.0 nl/ml without S-9 mix and 5.0 to 10 nl/ml with S-9 mix	Negative	no strong toxicity for the analysed concentr.; without S-9 mix higher concentr. could not be tested due to toxicity	Acetone	Microbiological Associates Inc., 1985c
Octadecenyl-amine	Chromosomal aberrations in mouse bone marrow cells	500 to 5000 mg/kg bw , single oral doses	Negative	Systemic toxicity: yes, no local cytotoxicity (mitotic index)	Corn oil	Microbiological Associates Inc., 1989b

4.1.2.8 Carcinogenicity

4.1.2.8.1 Studies in animals

In vivo studies

Inhalation

No data available.

Dermal

No data available.

Oral

Coco alkylamines [Cas No. 61788-46-3]

There are no animal and human data on carcinogenicity of coco alkylamines.

Tallow alkylamines [Cas No. 61790-33-8]

There are no animal and human data on carcinogenicity of tallow alkylamines.

Hydrogenated tallow alkylamines [Cas No. 61788-45-2]

There are no animal and human data on carcinogenicity on hydrogenated tallow alkylamines itself. From a limited rat study with chronic administration of stearic acid, a metabolite, no reliable information on carcinogenic potential of hydrogenated tallow alkylamines could be derived.

Octadecylamines [Cas No. 124-30-1]

A 2-year toxicity study of octadecylamine ("stearamine") was conducted using Sprague-Dawley rats. Four groups of 24 rats (12/sex) were fed diets containing 20, 100, 200 and 500 ppm stearamine (reviewed by Pang, 1995, original data University of Miami, 1957, Deichmann et al., 1958). A control group of animals was fed the base diet alone. The feed consumption, growth rate, death rate, and blood cell counts for the experimental animals were comparable to those of the control animals. The survival rate for this study was 17-33% including the control group. At necropsy, no significant differences were found between the experimental and control groups in the incidence and types of lesions observed. No significant increase occurred in the incidence of lesions. [No other information available.]

The Danish QSAR database predicts the absence of a positive potential of octadecylamines for carcinogenicity.

Other information:

Tumor promotion studies with Octadecylamine (CAS 124-30-1)

The effects of octadecylamine ("stearamine") on mammary carcinogenesis induced by 7,12-dimethyl-benz(a)anthrazene (DMBA) was investigated using female Sprague-Dawley rats on high-fat diets (Parenteau et al., 1991). Four groups of 21 rats each were given a single 5 mg dose of DMBA intragastrically at 47 to 51 days of age. One week later, the rats were fed diets containing 5% corn oil, 20% corn oil, 20% corn oil and 0.01% stearamine, or 20% corn oil and 0.1% stearamine. Stearamine was converted to the sulfate salt by mixing with a solution of sulfuric acid in ethanol. At 2-week intervals, the rats were weighed, examined, and palpated for neoplasms. All the rats were killed 16 to 17 Weeks following DMBA administration; necropsies were performed.

As expected, a greater number of neoplasms with a shorter latency period was observed among rats fed the 20% corn oil diet than among those fed the 5% corn oil diet. The addition of 0.01% stearamine to the 20% corn oil diet slightly reduced body weight gain and potentiated the effect of the high-fat diet, increasing the number of neoplasms that developed and shortening the latency period beyond that observed with the high-fat diet alone. However. 0.1% stearamine appeared to inhibit tumor growth as well as markedly reduce body weight gain. Significantly fewer neoplasms were found in the rats fed the 0.1% stearamine and 20% corn oil diet compared with the other three groups. All the neoplasms were mammary adenocarcinomas. Authors discussed the reduced tumor response in the high (0.1%) stearamine group as being related to the growth inhibition or to the inhibitory effect on protein kinase C. [No other information available.]

Octadecenylamine [112-90-3]

There are no animal and human data on carcinogenicity of octadecenylamine.

The Danish QSAR database predicts the absence of a positive potential of octadecenylamines for carcinogenicity.

In vitro studies

No data available.

4.1.2.8.2 Studies in humans

In vivo studies

There are no human data on carcinogenicity on any of the alkylamines available to be assessed in this report.

In vitro studies

No data available.

4.1.2.8.3 Summary of carcinogenicity

There are no human data on the carcinogenicity of the alkylamines asessed in this report.

There are no conventional carcinogenicity studies in rodents with compliance to the current standard of test guidelines for this endpoint on the alkylamines asessed in this report.

Earlier studies on the chronic toxicity of octadecylamine, the main C18-component of hydrogenated tallow alkylamines (content of 60%) (Deichmann et al., 1958: oral S-D rats, doses up to 25 mg/kg bw, 2 years; MacDonald et al., 1962: oral, S-D rats, doses up to 25 mg/kg bw, 2 years) provide no indication of a carcinogenic effect.

No positive potential for carcinogenicity was predicted for octadecylamines and octadecenylamines from the Danish QSAR database.

Due to the lack of reliable data no final conclusion can be drawn on the carcinogenic potential of any of the fatty alkylamines under consideration. Negative data from mutagenicity and sparce data from chronic toxicity do not give a concern that alkylamines may have a carcinogenic potential.

4.1.2.9 Toxicity for reproduction

4.1.2.9.1 Effects on fertility

Studies in animals

Coco alkylamines [Cas No. 61788-46-3]

No data available.

Tallow alkylamines [Cas No. 61790-33-8]

For tallow alkylamines a GLP conform Reproduction/Developmental Toxicity Screening Test according to OECD TG 421 with "GENAMIN TA 100" (> 96% active compound) is available (Instituto di Richerche Biomedice, 2000b). Groups of 10 rats (Crl:CD (SD) BR) per sex were treated with dosages of 0, 12.5, 50, and 150 mg/kg bw/day by gavage (administration volume 10 ml/kg bw/day) using sesame oil as a vehicle. Males were treated daily from 14 days prior to mating until the end of the mating period for a maximum of 28 days. Females were treated daily for 14 days before start of the mating period, throughout the same, during pregnancy and until day 3 of lactation. The animals were mated one male with one female.

At daily doses of 150 mg/kg bw 6/10 males and 5/10 females died between day 9 and day 25 of treatment (during the premating and mating period). At daily doses of 50 mg/kg bw 1/10 males and 1/10 females died on day 13 respectively on day 24 of treatment. No animals died at 12.5 mg/kg bw/day, and in the control group 1 female died by accident.

Clinical observations at 150 mg/kg bw/day revealed salivation after treatment, hunched posture and in some cases soft stools and piloerection. The only clinical sign present at 50 mg/kg bw/day was salivation. No changes were seen at 12.5 mg/kg bw/day.

Body weight loss of about 22 g at the 150 mg/kg bw dose group and statistically significant ($p > 0.01$) lower body weight gain at the 50 mg/kg bw dose group during the premating period together with a lower mean food consumption was observed in the males. Also in the females body weight loss of about 17 g at the 150 mg/kg bw dose group and statistically significant lower body weight gain at the 50 mg/kg bw dose group together with a lower mean food consumption during the premating period was observed.

At sacrifice of the parental animals organ weights of ovaries, testes and epididymides were determined from all experimental groups. Histopathology was carried out on testes, epididymides and ovaries of the controls and of the animals of the 150 mg/kg bw dose group. A statistically significant ($p> 0.01$) lower absolute and relative weight of epididymides and a statistically significant ($p> 0.01$) higher value of relative testis weight was observed at 150 mg/kg bw/day. No significant differences were noted in ovary weights among the various experimental groups. Histopathology of testes and epididymides of high dose group animals did not show any compound-related changes. In particular, no changes were seen in the testicular staging performed in the PAS-hematoxylin stained sections of final sacrificed animals of control and of the high dose groups. In the ovaries, moderate increased frequency of atrophic corpora lutea was seen in the animals of the high dose group which died or were sacrificed, compared to the controls, this finding was considered a secondary effect to the decrease in body weight growth induced by treatment in this group.

At the dosages of 150 mg/kg bw/day only 3 females out of 7 mated females had positive vaginal smears and of these only one was pregnant, but with only implantation sites and no live pups. At this dosage level also the mean pre-coital interval was longer (13.4 days) than that of the control group (2.3 days). With regard to the mating index in the control, the 12.5 and the 50 mg/kg bw dose level groups 9/9 (100%), 9/10 (90%) and 9/9 (100%) mated females were sperm positive. With regard to the fertility index 9/9 (100%), 8/10 (80%) and 7/9 (78%) of the mated females became pregnant in the control, the 12.5 and the 50 mg/kg bw

dose level groups. Mean pre-coital time and parturition were unaffected in the low and mid dose treated groups.

With regard to the conception rate in the control, the 12.5 and the 50 mg/kg bw dose level groups 9/9 (100%), 8/9 (89%) and 7/9 (78%) of the sperm positive females became pregnant and delivered live pups. Numbers of corpora lutea had not been determined during this study. Thus, any pre-implantation loss was not evaluated. Staining for the presence of implantation sites was only performed with the uteri of apparently non-pregnant females. The mean number of visible implantation sites per dam in the control, the 12.5 and the 50 mg/kg bw dose level groups were 17.6, 13.9 and 15.0. There were no stillborns or litters with only implantations in the control, low, and mid dose groups. The mean number of total pups born per litter was 16.9, 12.3 and 14.3 in the control, the 12.5 and the 50 mg/kg bw/day dose groups. Thus, the mean litter index for post-implantation loss was calculated to 3.4, 9.9 and 4.5% in the control, the low and the mid dose groups.

No effects were noted on the pup sex ratio. No abnormalities were observed in any pup either at birth or at autopsy on day 4 of lactation neither in the 12.5 nor in the 50 mg/kg bw/day treated groups. Lower mean values of live born per litter and of pups per litter alive at day 4 were found for both the low and the intermediate dose groups in comparison to those of the control group, however, the decreases were not dose dependent and the differences were statistically significant for the 12.5 mg/kg bw dose group only. Thus, these findings were considered unlikely to be related to the compound. A slightly lower pup body weight was observed in the 50 mg/kg bw/day treated group in comparison with the control group at birth and at day 4 of lactation but not for the pups of the 12.5 mg/kg bw/day treated group.

Based on findings of general toxicity (death, clinical signs, reduced body weight gain) at daily dosages of 50 mg/kg bw/d a NOEL/systemic toxicity of 12.5 mg/kg bw/d can be derived from the study. Based on the findings of a lower fertility index and a lower conception rate at daily dosages of 50 mg/kg bw/d a NOEL/fertility of 12.5 mg/kg bw/d can be derived from the results of this screening study.

Further, during an oral 28-day study (OECD TG 407) with tallow alkylamines ("Genamin TA 100") in rats (cf. 4.1.2.6.1) also reproductive organ weights and reproductive organ histopathology of testes and epididymides, as well as organ weights of ovaries and uteri had been investigated. No substance-related findings had been observed during this study on these organs at oral doses up to and including 150 mg/kg bw/day (Instituto di Richerche Biomedice, 2000a).

Hydrogenated tallow alkylamines [Cas No. 61788-45-2]

No data available.

Octadecylamine [Cas No. 124-30-1]

Experimental studies on the effects of octadecylamine on fertility or reproductive functions are not available.

From several chronic studies (c.f. 4.1.2.6) with commercial octadecylamine (containing 20 % hexadecylamine), from which the original study reports are not available to the rapporteur, it is reported that also investigation of the gonads had been performed:

From a 2-year feeding study with rats it is reported, that tissues taken for micropathological examination included ovary or testis (Deichmann et al., 1958). From a further 2-year feeding study with rats (MacDonald et al., 1962) it is indicated that organ weights had been

determined for testes and that micropathological examinations had been conducted on the gonads of seven rats from each group. Since any results from these two studies on the reproductive organs are not explicitly reported, it is assumed that toxicologically relevant effects had not been observed during the studies. It is therefore deduced from these studies, that chronic treatment up to and including the highest tested concentration of 500 ppm (according to oral daily dosages of approximately 25 mg/kg bw) did not adversely affect organs of the reproductive system. Higher dosages, however, had not been tested during these studies.

From a 1-year feeding study with young mongrel dogs (Deichmann et al., 1958) it is reported, that gross pathological organ changes in gonads (ovary and testis) were not observed after administration of daily oral dosages up to and including the highest tested dose of 15 mg/kg bw/day. Higher dosages, however, had not been tested during these studies.

Octadecenylamine [112-90-3]

Experimental studies on the effects of octadecenylamine on fertility or reproductive functions are not available.

During an oral 28 d study with octadecenylamine ("Genamin OL 100 D") in rats (c.f. 4.1.2.6.1) also organ weights of testes and epididymides were determined and histopathological investigations of testes, epididymides, prostate, seminal vesicles, ovaries including oviducts and of uteri were performed. No substance-related findings had been observed on these organs at oral doses up to and including 50 mg/kg bw/day (Aventis, 2003).

Studies in humans

No data available on any of the primary alkylamines assessed in this report.

4.1.2.9.2 Developmental toxicity

Studies in animals

Coco alkylamines [Cas No. 61788-46-3]

No data available.

Tallow alkylamines [Cas No. 61790-33-8]

No data available.

Hydrogenated tallow alkylamines [Cas No. 61788-45-2]

No data available.

Octadecyl amine [Cas No. 124-30-1]

No data available.

Octadecenylamine [112-90-3]

For octadecenylamine ("Oleylamine", no further substance identification provided) a guideline according teratology study in Sprague Dawley rats had been performed (Springborn Laboratories Inc., 1989a). Prior to initiation of the main study, a range-finding study had been

conducted, for which no separate report is available to the rapporteur. During the range finding-study, treatment-related deaths had occurred in the 100, 150 and 250 mg/kg bw/day groups. Outward clinical signs of toxicity and body weight loss or reduced weight gain occurred at the 50, 100, 150 and 250 mg/kg bw/day dose levels. A dose level of 100 mg/kg bw/day was considered to be excessive for a high dose level of the main study due to the induced mortality. Conversely, 50 mg/kg bw/day did not produce sufficient maternal toxicity to be considered suitable as a high dose level. Thus, 80 mg/kg bw/day was selected for the main study in anticipation of producing sufficient maternal toxicity.

In the main study groups of 28 pregnant females were treated orally (gavage) with dosages of 10, 40 or 80 mg/kg bw/day or with the vehicle (Mazola corn oil) during gestation days 6 to 15. During the study animals were examined daily. Any clinical signs of toxicity including physical or behavioural abnormalities were recorded. Individual body weights and food consumption were recorded on gestation days 0, 6, 9, 12, 16, and 20. Two animals in each group were selected to be sacrificed and necropsied after treatment on gestation day 15 to determine the appearance and severity of gastrointestinal tract irritation. On gestation day 20 caesarean section was performed on all surviving animals. The numbers of viable fetuses, early and late resorptions as well as the number of corpora lutea were recorded. Fetuses were examined for external, visceral and skeletal abnormalities.

All animals survived to scheduled sacrifice. Outward clinical signs of toxicity were observed at the 40 and 80 mg/kg bw/d dose levels. The observations most likely indicated a generalised irritative effect of the test substance as characterised by rales, salivation, unkempt appearance and changes in the amount, colour and consistency of the feces. However, no other signs of treatment-related gastrointestinal irritation or other internal changes were observed at the gestation day 15 and 20 necropsies. More pronounced signs of toxicity were apparent only in the 80 mg/kg bw/d dose group and included emaciation, rough coat and dark red material around the eyes, nose and/or mouth. Similar clinical signs were infrequently noted during the post-dose observations. Dose-dependent body weight loss (during gestation days 6-9) or reduced weight gain (during gestation days 12-16), along with a corresponding reduction in food consumption occurred during the treatment period in the 40 and 80 mg/kg bw/d dose groups. Net body weight gain (adjusted for gravid uterine weight) was also lower at these levels. Following cessation of treatment (days 16-20), increase in weight gain and food consumption were noted at both dose levels. No such effects were observed in the dose group treated with 10 mg/kg bw/d. Caesarean section data obtained from the treated groups did not reveal any meaningful differences (concerning number of corpora lutea, implantation sites, viable fetuses, fetal sex and fetal weight) when compared with the controls. Fetal evaluations of type and frequency of malformations and variations did not reveal any indications for a treatment related teratogenic effect. In summary, oral administration of octadecenylamine to pregnant rats produced dose-dependent maternal toxicity in the 40 and 80 mg/kg bw/d dose groups. No indications of an embryotoxic, fetotoxic or teratogenic effect was observed at any tested level. A NOAEL/maternal toxicity of 10 mg/kg bw/d and a NOAEL/developmental toxicity of $\geq$ 80 mg/kg bw/d can be derived from the study.

Further, a guideline according teratology study in New Zealand rabbits with "Oleylamine" (no further substance identification provided) had been performed (Springborn Laboratories Inc., 1989b). Prior to initiation of the main study, a range-finding study at dose levels of 5, 25, 50, 100 and 150 mg/kg bw/d had been conducted, for which no separate report is available to the rapporteur. During the range finding-study, treatment-related deaths had occurred in the 50, 100, and 150 mg/kg bw/d groups. Outward clinical signs of toxicity were observed at the 5 mg/kg bw/d dose level and above. Body weight losses occurred in the 25, 50, 100 and 150

mg/kg bw/d dose groups. A dose level of 50 mg/kg bw/d was considered to be excessive for a high dose level for the main study. Conversely, 25 mg/kg bw/d did not produce sufficient maternal toxicity to be considered suitable as a high dose level. Thus 30 mg/kg bw/d was selected for the main study in anticipation of producing sufficient maternal toxicity.

In the main study groups of 22 inseminated females were treated orally (gavage) with dosages of 3, 10, and 30 mg/kg bw/d or with the vehicle (Mazola corn oil) during gestation days 6 to 18. During the study animals were examined daily. Any clinical signs of toxicity including physical or behavioural abnormalities were recorded. Individual body weights were recorded on gestation days 0, 6, 9, 12, 1, 19, 24 and 29. Individual food consumption was measured daily. Two animals in each group were selected to be sacrificed and necropsied after treatment on gestation day 18 to determine the appearance and severity of gastrointestinal tract irritation. On gestation day 29 caesarean section was performed on all surviving animals. The numbers of viable fetuses, early and late resorptions as well as the number of corpora lutea were recorded. Fetuses were examined for external, visceral and skeletal abnormalities.

As result of the study, treatment-related mortality occurred as two females died in the 30 mg/kg bw/d group, one on gestation day 9 and the other on gestation day 25. In addition, one female each at the 3, 10, and 30 mg/kg bw/d levels aborted prior to scheduled sacrifice. Outward clinical signs of toxicity were observed at the 10 and 30 mg/kg bw/d levels. In the 10 mg/kg bw/d dose group, rales and laboured breathing were noted. Additional findings in the 30 mg/kg bw/d level included few or no feces and emaciation. Irritation of the mouth area also developed in females in this group. The irritation was characterised by swollen raised white areas, scab-like lesions and /or sloughing of the skin of the lips and the chin. No other signs of treatment-related gastrointestinal irritation or internal changes were observed at gross necropsy at gestation days 18 and 29. Dose-dependent body weight loss (gestation days 6-9, respectively 6-19) or reduced weight gain, along with a corresponding reduction in food consumption occurred during the treatment period in the 10 and 30 mg/kg bw/d groups. Net body weight gain (adjusted for gravid uterine weight) was also lower. Following cessation of treatment, weight gain increased in the 30 mg/kg bw/d group. No such effects were observed in the dose group treated with 3 mg/kg bw/d. Caesarean section data obtained from the treated groups did not reveal any meaningful differences (concerning number of corpora lutea, implantation sites, viable fetuses, implantation loss, fetal sex and fetal weight) when compared with the controls. Fetal evaluations of type and frequency of malformations and variations did not reveal any indications for a treatment related teratogenic effect. In summary, oral administration of octadecenylamine to pregnant rabbits produced dose-dependent maternal toxicity in the 10 and 30 mg/kg bw/d dose groups. No indications of an embryotoxic, fetotoxic or teratogenic effect was observed at any tested level. A NOAEL/maternal toxicity of 3 mg/kg bw/d and a NOAEL/developmental toxicity of $\geq$ 30 mg/kg bw/d can be derived from the study.

Studies in humans

No data available on any of the primary alkylamines assessed in this report.

4.1.2.9.3 Summary of toxicity for reproduction

Coco alkylamines [Cas No. 61788-46-3]

Human data on any effects of coco alkylamines on fertility, respectively on reproductive functions or on development are not available.

Any experimental studies on the effects of coco alkylamines on fertility, respectively on reproductive functions or on developmental toxicity are neither available.

However, data relevant for hazard assessment with respect to the endpoints fertility and developmental toxicity are available from a screening test according to OECD TG 421 and from guideline according prenatal developmental toxicity testing of the closely related alkylamines mixtures tallow alkylamines and octadecenylamine.

Although coco alkylamines differ from the other alkylamines mixtures assessed in this report by their higher degree of components with shorter carbon chain length it is considered appropriate to extrapolate from data derived from testing of the the two alkylamines mixtures with a higher degree of components of longer carbon chain length. Therefore read across from the test results of both of tallow alkylamines and of octadecenylamine are considered adequate for hazard assessment of coc alkylamines with respect to fertility and developmental toxicity.

Thus, according to the results from tallow alkylamines testing and from octadecenylamine testing there is no recommendation for classification and labelling of the hydrogenated tallow alkylamines as a reproductive toxicant.

For quantitative risk characterisation a NOAEL/fertility of 12.5 mg/kg bw/d and a NOAEL/developmental toxicity of $\geq$ 30 mg/kg bw/d should be taken forward.

Tallow alkylamines [Cas No. 61790-33-8]

Human data on any effects of tallow alkylamines on fertility or on reproductive functions or on development are not available.

The potential of tallow alkylamines to adversely affect reproduction has been investigated so far at a screening level with a study according to OECD TG 421 using the oral route of administration. During this study signs of severe general toxicity were observed after repeated administration of the high dose of 150 mg/kg bw/d in both sexes, leading to more than 50% deaths of the animals, severe body weight loss in the surviving animals and impairment of reproductive performance in the surviving animals. These findings of severe general toxicity are in close accordance to the findings reported from the 28-day repeated dose toxicity study (c.f. 4.1.2.6) during which the same test compound (GENAMIN TA 100) and identical dose levels had been investigated. Since severe general toxicity appears to be the predominating substance-related toxic effect and since no histological compound-related changes were observed on testes, epididymides and ovaries (neither in the OECD 421 nor in the OECD 407 study), the impairment of reproductive performance at the dose level of 150 mg/kg bw/d is not considered to represent a specific effect in terms of giving evidence for a substance-related toxic potential adverse to reproduction. Further, signs of general toxicity were also observed at the intermediate dose level of 50 mg/kg bw/d in terms of 10% death, clinical signs and of significantly reduced body weight growth. No such toxic effects were observed at the low dose treatment with 12.5 mg/kg bw/d. At this dose level no significant differences in comparison to the controls were revealed for reproductive performance including mating, fertility and gestational indices and pup viability and growth. Based on findings of general toxicity (death, clinical signs, reduced body weight gain) at daily dosages of 50 mg/kg bw/d a NOEL/systemic toxicity of 12.5 mg/kg bw/d can be derived from the study. Based on the findings of a lower fertility index and a lower conception rate at daily dosages of 50 mg/kg bw/d a NOEL/fertility of 12.5 mg/kg bw/d can be derived from the results of this screening

study and should be taken forward for risk characterisation with respect to fertility. Based on the results of this test there is no recommendation for classification and labelling for tallow alkylamines as a reproductive toxicant.

Experimental studies on the effects of tallow alkylamines on developmental toxicity are not available. However, data relevant for hazard assessment with respect to developmental toxicity are available from guideline according prenatal developmental toxicity testing of the closely related primary alkylamines octadecenylamine. Since both, tallow alkylamines as well as octadecenylamine from their chemical components constitute very similar mixtures of primary alkylamines qualitatively as well as quantitatively, read across from the test results of prenatal developmental toxicity testing of octadecenylamine are considered adequate. Therefore, a NOAEL/developmental toxicity of $\geq$ 30 mg/kg bw/d should be taken forward for risk characterisation with respect to developmental toxicity.

Hydrogenated tallow alkylamines [Cas No. 61788-45-2]

Human data on any effects of hydrogenated tallow alkylamines on fertility, respectively on reproductive functions or on development are not available.

Any experimental studies on the effects of hydrogenated tallow alkylamines on fertility, respectively on reproductive functions or on developmental toxicity are neither available.

However, data relevant for hazard assessment with respect to the endpoints fertility and developmental toxicity are available from a screening test according to OECD TG 421 and from guideline according prenatal developmental toxicity testing of the closely related primary alkylamines tallow alkylamines and of octadecenylamine.

Since both, tallow alkylamines as well as octadecenylamine from their chemical components constitute very similar mixtures of primary alkylamines qualitatively as well as quantitatively, it is assumed that testing of each of these two compounds would also be representative for hydrogenated tallow alkylamines. Therefore read across from the test results of both of tallow alkylamines and of octadecenylamine are considered adequate for hazard assessment of hydrogenated tallow alkylamines with respect to fertility and developmental toxicity.

Thus, according to the results from tallow alkylamines testing and from octadecenylamine testing there is no recommendation for classification and labelling of the hydrogenated tallow alkylamines as a reproductive toxicant.

For quantitative risk characterisation a NOAEL/fertility of 12.5 mg/kg bw/d and a NOAEL/developmental toxicity of $\geq$ 30 mg/kg bw/d should be taken forward.

Octadecylamine [Cas No. 124-30-1]

Human data on any effects of octadecylamine on fertility or on reproductive functions or on development are not available. Experimental studies on the effects of octadecylamine on fertility or reproductive functions or on developmental are neither available.

Results from chronic toxicity testing with commercial octadecylamine did not report on any effects on male/female gonads in rats and in dogs during two-year exposures to daily dosages of up to and including about 25 mg/kg bw/d (rats) and of up to and including 15 mg/kg bw/d in dogs.

Data relevant for hazard assessment with respect to fertility and developmental toxicity, however, are available from guideline conform, respectively guideline according testing of the

closely related primary alkylamines tallow alkylamines and octadecenylamine. Octadecylamine represents the C18 moiety of the various constituents of both of the two primary alkylamines mixtures tallow alkylamines and octadecenylamine. It is assumed that testing of each of these two compounds would also be representative for their major constituents. Therefore read across from the test results of both of tallow alkylamines and of octadecenylamine is considered adequate for hazard assessment of octadecylamine with respect to fertility and developmental toxicity. Thus, according to the results from tallow alkylamines and from octadecenylamine testing there is no recommendation for octadecylamine for classification and labelling as a reproductive toxicant. For risk characterisation a NOAEL/fertility of 12.5 mg/kg bw/d and a NOAEL/developmental toxicity of > 30 mg/kg bw/d should be taken forward.

Octadecenylamine [112-90-3]

Human data on any effects of octadecenylamine on fertility or on reproductive functions or on development are not available.

Experimental studies on the effects of octadecenylamine on fertility, respectively reproductive functions are neither available, except information from an oral 28 d study with no substance-related findings on reproductive organs. Data relevant for hazard assessment with respect to fertility, however, are available from guideline conform testing of the closely related primary alkylamines tallow alkylamines. Since both, tallow alkylamines as well as octadecenylamine from their chemical components constitute very similar mixtures of primary alkylamines qualitatively as well as quantitatively, read across from the test results of OECD 421 test with tallow alkylamines are considered adequate. Therefore, according to the results from tallow alkylamines testing there is no recommendation for classification and labelling of octadecenylamine as a reproductive toxicant and for risk characterisation a NOAEL/fertility of 12.5 mg/kg bw/d should be taken forward. In addition to this, also the results from an oral 28 day study with octadecenylamine did not reveal any specific impairment (weight changes or histopathological changes) of the reproductive organs under investigation.

Prenatal developmental toxicity of octadecenylamine had been investigated for two different species (rat, rabbit) with no indications for an embryo-/fetotoxic or teratogenic potential even at clearly maternally toxic dose levels. From the study with rabbits based on findings of general toxicity (clinical signs, reduced body weight gain) at daily dosages of 10 mg/kg bw/d a NOAEL/maternal toxicity of 3 mg/kg bw/d and a NOAEL/developmental toxicity of $\geq$ 30 mg/kg bw/d can be derived and should be taken forward for quantitative risk assessment. Based on the results of the two developmental toxicity studies there is no recommendation for classification and labelling of octadecenylamine as a reproductive toxicant.

Table 4.1.2.9: Overview on studies on toxicity for reproduction with primary alkylamines

Alkylamines mixture	**Data availability**	**NOAEL**	**LOAEL**	**Reference**
Coco alkylamines	Fertility: no data			
	Dev. Tox.: no data			
Tallow alkylamines	Fertility: OECD 421, rat, oral (gavage) GENAMIN TA 100 12.5/50/150 mg/kg/d	$NOAEL_{syst. tox}$: 12.5 mg/kg/d $NOAEL_{reprotox}$: 12.5 mg/kg/d	$LOAEL_{syst. tox}$: 50 mg/kg/d (based on 10% death, clin. signs, ↓ body wt gain) $LOAEL_{reprotox}$: 50 mg/kg/d (based on dose-dependently ↓ fertility index)	Instituto di Richerche Biomedice, 2000b
	OECD 407, rat, oral (gavage) GENAMIN TA 100; 12.5/50/150 mg/kg/d	no effects on reproductive organ weights and on reproductive organ histopathology at doses up to and including 150 mg/kg/d → Results support data/results from OECD 421		Instituto di Richerche Biomedice, 2000a
	Dev. Tox.: no data, limited information from OECD 421			
Hydrogenated tallow alkylamines	Fertility: no data			
	Dev. Tox.: no data			
Octadecylamine	Fertility: chronic study (1year) dog, oral	$NOAEL_{reprod organ tox}$: > 15 mg/kg/d		Deichmann et al., 1958
	2 chronic studies (2 years), rat, oral	$NOAEL_{reprod organ tox}$: > 25 mg/kg/d		Deichmann et al., 1958 MacDonald et al., 1962
	Dev. Tox.: no data			
Octadecenylamine	Fertility: OECD 407, rat, oral (gavage) GENAMIN OL 100;3.25/12.5/50 mg/kg/d	no effects on reproductive organ weights and on reproductive organ histopathology at doses up to and including 50 mg/kg/d		Aventis, 2003
	Dev. Tox.: OECD 414-like, rat, oral (gavage), Oleylamine, 10/40/80 mg/kg/d	$NOAEL_{mat. tox}$: 10 mg/kg/d $NOAEL_{dev. tox}$: ≥ 80 mg/kg/d	$LOAEL_{mat. tox}$: 40 mg/kg/d (based on clin. signs, ↓ body wt gain)	Springborn Laboratories Inc., 1989a

	OECD 414-like, rabbit, oral (gavage), Oleylamine, 3/10/30 mg/kg/d	$NOAEL_{mat.\ tox}$: 3 mg/kg/d $NOAEL_{dev.\ tox}$: $\geq$ 30 mg/kg/d	$LOAEL_{mat.\ tox}$: 10 mg/kg/d (based on clin. signs, ↓ body wt gain)	Springborn Laboratories Inc., 1989b

4.1.3 Risk characterisation

4.1.3.1 General aspects

Toxicokinetics

Experimental or empirical data concerning dermal, oral or inhalative absorption of the alkylamines mixtures described in this report are not available. Therefore, the extents of absorption are deduced from the physico-chemical properties and from the results of toxicological investigations of the compounds.

Coco alkylamines and octadecenylamine are liquid under normal ambient conditions, whereas the other three substances are waxy solids. The average molecular weights range between 194 g/mol (coco alkylamines) and 269.5 g/mol. Apart from the tallow alkylamines with a calculated water solubility of 0.12 mg/l, the other alkylamine mixtures are insoluble in water. With the exception of coco alkylamines, log P_{OW} values have been calculated for all amines and range between 7.1 and 7.71. The vapour pressure of all amines is very low..

Based on information concerning single aliphatic alkylamines, absorption of primary alkylamines from gut and respiratory tract is possible. Data from acute dose and repeated dose toxicity studies in animals performed with the compounds assessed in this RAR indicate, that the compounds exhibit systemic effects after oral administration. Therefore, as a worst case, a value of 100 % oral absorption is recommended to be taken for risk characterisation.

Based on the physico-chemical parameters, inhalative exposure will be low. However, due to the corrosive effects, inhalative uptake - as far as exposure does occur - might by facilitated after corrosive action of the compounds at the site of entry. Therefore, 100 % inhalative absorption is recommended to be taken as a value for risk characterisation.

Based on the basicity and corrosive properties of the primary alkylamines, dermal absorption as a consequence of facilitated penetration through damaged skin can be anticipated. 1-Dodecanamine, as a constituent of the alkylamines mixtures, was absorbed from the skin of mice. Dependent on solvent and concentration, up to 60 % were absorbed, so this value for dermal absorption may be taken as a worst case for risk characterisation.

Bioavailable amounts of alkylamines are rapidly distributed into the lungs, brain, heart, spleen, kidneys and liver. In lungs, brain and heart, tissue concentrations of amines increased with increasing chain length. Alkylamines are oxidatively deaminated by monoaminooxidases with concomitant formation of ammonia and the corresponding alkylamine aldehyde. Subsequently, the aldehydes are oxidised by aldehyde dehydrogenases to the corresponding carboxylic acids, which, in turn, are further metabolised by ß-oxidation. Carbon dioxide as the final product from ß-oxidation is exhaled. Urinary excretion is a minor elimination pathway.

Acute toxicity, Irritation/Corrosivity, Sensitisation

There are no human data available on acute toxicity of the alkylamines mixtures assessed in this report. For the inhalation route, there is one rat study available for coco alkylamines, which did not indicate a strong toxic potential of this mixture, when applied at a non-corrosive concentration. For the dermal route, one rat study performed with coco alkylamines did not reveal evident acute toxicity (LD50 > 2000 mg/kg bw).. Studies for the oral route are available for all alkylamine mixtures discussed in this risk assessment report: Coco alkylamines, tallow alkylamines and octodecenylamines demonstrated moderate oral toxicity

(200 mg/kg bw < LD50 < 2000 mg/kg bw, "Xn", R 22), which may be explained from the corrosive properties of the tested substances, whilst hydrogenated tallow alkylamines and octadecylamine displayed LD50 values exceeding 2000 mg/kg bw and thus do not need classification and labelling for acute oral toxicity. Considering the apparently low systemic toxicity of the alkylamine mixtures, there is no need for further inhalative or dermal testing.

There are no human data available on skin or eye irritation of the alkylamines mixtures assessed in this report. All alkylamines mixtures were shown to cause skin irritation in rabbit Draize tests. Coco alkylamines, tallow alkylamines and octadecenylamine were shown to be corrosive to rabbit skin (R 35) and, in consequence, not tested in rabbit eye. Hydrogenated tallow alkylamines and octadecylamine induced less severe effects in skin (R 38) and caused severe eye irritation/ irreversible damage in rabbit eye (R 41). There is no data available on respiratoory tract irritation of the alkylamine mixtures with the exception of coco alkylamines, for which rat inhalation studies indicated irritative properties on the respiratory tract (R 37).

There are no valid human data available on sensitisation of the long chain alkylamines assessed in this report. Animal data exist for hydrogenated tallow alkylamines from a not GLP-compliant guinea pig - maximisation test according to Magnusson and Kligman, which gave no evidence for a potential to induce skin sensitisation. However, since an unsuitable vehicle was used and reported nominal test concentrations are technically not possible, this study cannot be accepted and the negative outcome is not valid. Since octadecylamine is a major component of hydrogenated tallow alkylamines, any data from hydrogenated tallow alkylamines can also be used to conclude on a potential of octadecylamine to induce skin sensitisation. Recently, another guinea pig - maximisation test according to Magnusson and Kligman was conducted with coco alkylamine, which gave an inconclusive result. Accordingly, additional data are needed to finalise risk assessment of alkyl amines containing fatty acids of shorter chain length compared to hydrogenated tallow alkylamines.

Tallow alkylamines and octadecenylamines show a high degree of unsaturated oleylamine, which is nearly absent in hydrogenated alkylamines. There are no data available to assess the potential of oleylamine to induce skin sensitisation. Accordingly, in order to meet annex VII requirements, a Local Lymph Node Assay (LLNA) should be performed with an octadecenylamine. Results obtained with octadecenylamines can then be used for read-across of tallow alkylamines.

Repeated dose toxicity

There are no human data available on repeated dose toxicity of the alkylamines mixtures to be assessed in this report.

For the inhalatory route of exposure there are no data available on experimental studies for any of the alkylamines mixtures assessed in this report.

For the dermal route of exposure guideline-compliant repeated dose toxicity studies do not exist for any of the alkylamines mixtures. For octadecylamine (CAS 124-30-1) and octadecenylamine (CAS 112-90-3) some data from non-guideline studies with repeated dermal administration are available. However, due to limitations in the study design or/and reporting, none of the studies appears suitable to deliver valid information about systemic toxic effects following dermal administration. Therefore, no $NOAEL_{sys}$ for systemic toxicity could be estimated for any of the alkylamines mixtures under consideration for the dermal route of exposure. The only information that can be derived from the available data is the

overall minimal concentration that induces adverse skin effects ($LOAEC_{local}$ for effects on the dermis is 0.3% corresponding to 12.5 mg/kg bw/d).

For the oral route of exposure information from a guideline-compliant 28-day study is available only for octadecenylamine (CAS 112-90-3). For tallow alkylamines (CAS 61790-33-8) the available oral 28-day test followed the guideline protocol, however, without specific investigations on neurobehavior and neurofunction. Also for hydrogenated tallow alkylamines (CAS 61788-45-2) and for octadecylamine (CAS 124-30-1) there is some information on repeated dose toxicity available, however, respective studies do not comply with the present days' standards. No single study was reported for coco alkylamines (CAS 61788-46-3). Leading health effects of systemic toxicity after oral exposure were delayed mortalities associated with precedent bad general health status and gait abnormalities, erosions of the mucosa of the gastrointestinal tract, accumulation in material-loaden (vacuolated) histiocytes in the submucosa of the distal parts of the small intestine and in the mesenteric lymph nodes, liver toxicity and indications of immunosuppression. Adverse effects in the lungs observed after oral exposure are considered indicative for a potential for damaging the surface epithelia of the respiratory tract and should be considered elsewhere if the inhalation route is relevant.

With respect to the 'local' effects, the available data clearly demonstrate that the alkylamines mixtures assessed in this report cause damage along the exposure route, i.e. the mucosa of the gastrointestinal tract. The data also demonstrate a cytotoxic potential at any site of contact (even at the bronchial mucosa as a side effect of oral exposure). Repeated exposure resulting in 'local cytotoxicity', i.e. erosions of the gastrointestinal mucosa, was associated with secondary effects of systemic significance and progressed continuously with the duration of treatment leading to body weight loss, bad general health status and unscheduled deaths. Besides, the accumulation and migration of test substance loaded histiocytes along the intestinal passage into lymphnodes and other tissues (intestine submucosa and putatively liver), the liver toxicity and the immunosuppression are qualified as adverse (systemic) effects.

To satisfy the minimal repeated dose information requirements according to the existing chemicals regulation for each of the alkylamines mixtures assessed in this report, read-across of data available for octadecenylamine (CAS 61790-33-8) and for tallow alkylamines (CAS 61790-33-8) is applied for those mixtures with no or poor data on repeated dose toxicity. This approach implies that the most sensitive NOAEL for this endpoint was derived from the two valid 28-day studies and is applied for all members of the category. The category approach is also applied for classification, and R48/22 is proposed for all alkylamines mixtures assessed in this report. The NOAEL proposed for quantitative risk assessment of all alkylamines covered by this report is derived from the valid oral 28-day study on octadecenylamine (CAS 112-90-3) and is 3.25 mg/kg bw/d. No $NOAEL_{sys}$ for systemic toxicity could be estimated for the dermal route of exposure The overall $LOAEC_{local}$ for effects on the dermis was 0.3%, corresponding to 12.5 mg/kg bw/d.

Mutagenicity

Only negative results were obtained in mutagenicity tests with the investigated alkylamines mixtures.

For the group of alkylamines mixtures with longer chainlengths, mainly consisting of C18 and C16 chains (tallow alkylamines, hydrogenated tallow alkylamines, octadecenylamine, octadecylamine) negative results from tests on bacterial mutagenicity and data on gene mutations in mammalian cells in vitro and on chromosomal aberrations and micronuclei in

vivo are available. The whole amount of data is judged as sufficient to exclude mutagenic potential for the group of alkylamines with longer chainlengths in vivo.

For coco alkylamines, an alkylamines mixture of shorter chainlengths, only data on bacterial mutagenicity exist. No further genotoxicity tests in mammalian cells in vitro or in vivo are available. Altogether, the negative data from the bacterial tests together with negative data on structurally similar long chained alkylamines is considered as sufficient to exclude a mutagenic potential of coco alkylamines in vivo.

Carcinogenicity

There are no human data available on the carcinogenicity of the alkylamines mixtures to be assessed in this report. There are also no experimental carcinogenicity studies available for the alkylamines mixtures assessed in this report.

Earlier studies on the chronic toxicity of octadecylamine, the main C18-component of hydrogenated tallow alkylamines (content of 60%) did not provide indications for induction of carcinogenic effects.

The Danish QSAR database predicted no carcinogenic potential for octadecylamines or octadecenylamines.

Due to the lack of reliable data no final conclusion can be drawn on the carcinogenic potential of any of the fatty alkylamines under consideration. Negative data from mutagenicity and sparce data from chronic toxicity tests do not give a concern that alkylamines may have a carconogenic potential.

Reproductive toxicity

There are no human data available on toxicity to reproduction (fertility impairment and/or developmental toxicity) on any of the alkylamines mixtures assessed in this report.

Concerning effects on fertility there are no data available on experimental studies for any of the alkylamines mixtures assessed in this report with the inhalatory or the dermal route of exposure. Data from animal studies with the oral route of exposure are available only for tallow alkylamines (according to OECD TG 421, TG 407) and for octadecylamine (limited chronic studies). The results from these studies did not provide evidence for adverse effects on the gonads or any indications for a specific toxic potential adverse to fertility. Based on the findings of a lower fertility index and a lower conception rate at daily dosages of 50 mg/kg bw/d a NOAEL/fertility of 12.5 mg/kg bw/d is derived from the results of the guideline-compliant test according to OECD TG 421 with tallow alkylamines (CAS 61790-33-8) and should be taken forward for risk characterisation with respect to fertility.

Concerning developmental toxicity there are no data available on experimental studies for any of the alkylamines mixtures assessed in this report with the inhalatory or the dermal route of exposure. Data from animal studies with the oral route of exposure are available only for octadecenylamine, however, on two species. The results from these studies did not provide evidence for any embryo-/fetotoxic or teratogenic potential even at clearly maternally toxic dose levels. From the study with rabbits based on findings of general toxicity (clinical signs, reduced body weight gain) at daily dosages of 10 mg/kg bw/d a NOAEL/maternal toxicity of 3 mg/kg bw/d and a NOAEL/developmental toxicity of $\geq$ 30 mg/kg bw/d is be derived and should be taken forward for quantitative risk assessment.

Table 4.1.3.1 Toxicological hazard identification Coco alkylamines [CAS No. 61788-46-3]

Coco alkylaminess [CAS No. 61788-46-3]	**Inhalation**	**Dermal**	**Oral**
Acute toxicity	LC50 (rat) >0.099 mg/l	LD50 (rat) >2000 mg/kg bw	LD50 (rat) = 1.240 mg/kg bw R22 - harmful if swallowed
Irritation / corrositivity	Skin: strong irritating potential including corrosivity, R35 - causes severe burns Eye: no data, testing not necessary due to corrosive properties Respiratory tract: acute inhalation studies, R 37 – irritating to respiratoory system		
Sensitisation	Skin: guinea pig maximization test, inconclusive result Respiratory tract: no data		
Repeated dose toxicity (local)	no data	no data, read across to octadecenylamine, mild to moderate skin irritating effects LOAEL 12.5 mg/kg bw/d (12-day dermal study, rat)	no data, read across to octadecylamine and tallow alkylamines damage along the exposure route, cytotoxicity at site of contact
Repeated dose toxicity (systemic)	no data	no data	no data, read across to octadecenylamine and tallow alkylamines mortality, bad general health conditions, body weight loss, gastrointestinal lesions, liver toxicity, immunosuppression NOAEL 3.25 mg/kg bw/d (28-day study (OECD TG 407), rat) R48/22 - harmful: danger of serious damage to health by prolonged exposure if swallowed
Mutagenicity	no evidence on mutagenicity in vitro and in vivo		
Carcinogenicity	no data	no data	no data
Fertility impairment	no data	no data	no data, read across to tallow alkylamines no specific effects adverse to fertility and/or reproductive organs NOAEL $_{syst.tox.}$ 12.5 mg/kg bw7d NOAEL $_{reprotox}$ 12.5 mg/kg bw/d (OECD 421, rat)
Developmental toxicity	no data	no data	no data read across to octadecenylamine no specific toxic effects adverse to development NOAEL $_{mat.tox.}$ 3 mg/kg bw/d NOAEL $_{dev.tox.}$ $\geq$ 30 mg/kg bw/d (OECD 414-like, rabbit)

Table 4.1.3.2 Toxicological hazard identification Tallow alkylamines [CAS N0. 61790-33-8]

Tallow alkylamines [CAS N0. 61790-33-8]	**Inhalation**	**Dermal**	**Oral**
Acute toxicity	No data	No data	LD50 (rat) 1900 mg/kg bw R22 - harmful if swallowed
Irritation / corrositivity	Skin: strong irritating potential including corrosivity, R35 - causes severe burns Eye: no data, testing not necessary due to corrosive properties Respiratory tract: no data		
Sensitisation	Skin: no data, , limitations to conclude on the sensitising potential on the basis of read across to hydrogenated tallow alkyamines Respiratory tract.: no data		
Repeated dose toxicity (local)	no data	no data, read across to octadecenylamine mild to moderate skin irritating effects LOAEL 12.5 mg/kg bw/d (12-day dermal study, rat)	no data, read across to octadecylamine and tallow alkylamines damage along the exposure route, cytotoxicity at site of contact
Repeated dose toxicity (systemic)	no data	no data	data and read across to octadecenylamine mortality, bad general health conditions, body weight loss, gastrointestinal lesions, liver toxicity, immunosuppression NOAEL 3.25 mg/kg bw/d (28-day study (OECD TG 407), rat) R48/22 - harmful: danger of serious damage to health by prolonged exposure if swallowed
Mutagenicity	no evidence on mutagenicity in vitro and in vivo		
Carcinogenicity	no data	no data	no data
Fertility impairment	no data	no data	no specific effects adverse to fertility and/or reproductive organs NOAEL $_{syst.tox.}$ 12.5 mg/kg bw/d NOAEL $_{reprotox}$ 12.5 mg/kg bw/d (OECD 421, rat)
Developmental toxicity	no data	no data	limited data from OECD 421 read across to octadecenylamine no specific toxic effects adverse to development NOAEL $_{mat.tox.}$ 3 mg/kg bw/d NOAEL $_{dev.tox.}$ $\geq$ 30 mg/kg bw/d (OECD 414-like, rabbit)

Table 4.1.3.3 Toxicological hazard identification Hydrogenated Tallow alkylamines [CAS No. 61788-45-2]

Hydrogenated Tallow alkylamines CAS No. 61788-45-2]	**Inhalation**	**Dermal**	**Oral**
Acute toxicity	No data	No data	LD50 (rat) >2000 mg/kg bw
Irritation / corrositivity	Skin: pronounced moderate effects in rabbit tests, R38 - irritating to skin Eye: severe ocular lesions in rabbit tests, R41 - risk of serious damage to eyes Respiratory tract: no data		
Sensitisation	Skin: no skin sensitising properties in a giunea pig maximisation test Respiratory tract: no data		
Repeated dose toxicity (local)	no data	no data, read across to octadecenylamine mild to moderate skin irritating effects LOAEL 12.5 mg/kg bw/d (12-day dermal study, rat)	no data, read across to octadecylamine and tallow alkylamines damage along the exposure route, cytotoxicity at site of contact
Repeated dose toxicity (systemic)	no data	no data	non-valid data, read across to octadecenylamine and tallow alkylamines mortality, bad general health conditions, body weight loss, gastrointestinal lesions, liver toxicity, immunosuppression NOAEL 3.25 mg/kg bw/d (28-day study (OECD TG 407), rat) R48/22 - harmful: danger of serious damage to health by prolonged exposure if swallowed
Mutagenicity	no evidence on mutagenicity in vitro and in vivo		
Carcinogenicity	no data	no data	no data
Fertility impairment	no data	no data	no data, read across to tallow alkylamines no specific effects adverse to fertility and/or reproductive organs NOAEL $_{syst.tox.}$ 12.5 mg/kg bw7d NOAEL $_{reprotox}$ 12.5 mg/kg bw/d (OECD 421, rat)
Developmental toxicity	no data	no data	no data read across to octadecenylamine no specific toxic effects adverse to development NOAEL $_{mat.tox.}$ 3 mg/kg bw/d NOAEL $_{dev.tox.}$ $\geq$ 30 mg/kg bw/d (OECD 414-like, rabbit)

Table 4.1.3.1.4 Toxicological hazard identification Octadecylamine [CAS No. 124-30-1]

Octadecylamine [CAS No. 124-30-1]	**Inhalation**	**Dermal**	**Oral**
Acute toxicity	No data	No data	LD50 (rat) >2000 mg/kg bw
Irritation / corrositivity	Skin: pronounced moderate effects in rabbit tests, R38 - irritating to skin Eye: severe ocular lesions in rabbit tests, R41 - risk of serious damage to eyes Respiratory tract: no data		
Sensitisation	Skin: no data, read across to hydrogenated tallow alkylamines: no concern for skin sensitising properties Respiratory tract: no data		
Repeated dose toxicity (local)	no data	no data, read across to octadecenylamine, mild to moderate skin irritating effects LOAEL 12.5 mg/kg bw/d (12-day dermal study, rat)	no data, read across to octadecylamine and tallow alkylamines damage along the exposure route, cytotoxicity at site of contact
Repeated dose toxicity (systemic)	no data	data available, NOAEL not established	non-valid data, read across to octadecenylamine and tallow alkylamines mortality, bad general health conditions, body weight loss, gastrointestinal lesions, liver toxicity, immunosuppression NOAEL 3.25 mg/kg bw/d (28-day study (OECD TG 407), rat) R48/22 - harmful: danger of serious damage to health by prolonged exposure if swallowed
Mutagenicity	no evidence on mutagenicity in vitro and in vivo		
Carcinogenicity	no data	no data	no data
Fertility impairment	no data	no data	data and read across to tallow alkylamines no specific effects adverse to fertility and/or reproductive organs NOAEL $_{syst.tox.}$ 12.5 mg/kg bw/d NOAEL $_{reprotox}$ 12.5 mg/kg bw/d (OECD 421, rat)
Developmental toxicity	no data	no data	no data read across to octadecenylamine no specific toxic effects adverse to development NOAEL $_{mat.tox.}$ 3 mg/kg bw/d NOAEL $_{dev.tox.}$ $\geq$ 30 mg/kg bw/d (OECD 414-like, rabbit)

Table 4.1.3.5 Toxicological hazard identification Octadecenylamine [CAS No. 112-90-3]

Octadecenylamine [CAS No. 112-90-3]	**Inhalation**	**Dermal**	**Oral**
Acute toxicity	No data	No data	LD50 (rat) = 1.689 mg/kg bw R22 - harmful if swallowed
Irritation / corrositivity	Skin: strong irritating potential including corrosivity, R35 - causes severe burns Eye: no data, testing not necessary due to corrosive properties Respiratory tract: no data		
Sensitisation	Skin: no data, , limitations to conclude on the sensitising potential on the basis of read across to hydrogenated tallow alkyamines Respiratory tract: no data		
Repeated dose toxicity (local)	no data	mild to moderate skin irritating effects LOAEL 12.5 mg/kg bw/d (12-day dermal study, rat)	data and read across to tallow alkylamines damage along the exposure route, cytotoxicity at site of contact
Repeated dose toxicity (systemic)	no data	data available, NOAEL not established	mortality, bad general health conditions, body weight loss, gastrointestinal lesions, liver toxicity, immunosuppression NOAEL 3.25 mg/kg bw/d (28-day study (OECD TG 407), rat) R48/22 - harmful: danger of serious damage to health by prolonged exposure if swallowed
Mutagenicity	no evidence on mutagenicity in vitro and in vivo		
Carcinogenicity	no data	no data	no data
Fertility impairment	no data	no data	no data, read across to tallow alkylamines no specific effects adverse to fertility and/or reproductive organs NOAEL $_{syst.tox.}$ 12.5 mg/kg bw/d NOAEL $_{reprotox}$ 12.5 mg/kg bw/d (OECD 421, rat)
Developmental toxicity	no data	no data	no specific toxic effects adverse to development NOAEL $_{mat.tox.}$ 3 mg/kg bw/d NOAEL $_{dev.tox.}$ $\geq$ 30 mg/kg bw/d (OECD 414-like, rabbit)

4.1.3.2 Workers

Introductory remarks

The term primary alkyl amines stands for a group of substances which share essential chemical key aspects so that it seems appropriate to perform a joint risk assessment for all the members of the group. Occupational exposure may be different for the individual substances because of differing physico-chemical properties and varying areas application. As basis for the risk assessment in this report the occupational exposure assessment (chapter 4.1.1.2) does not solely follow the group approach but gives differentiated information on the individual substances where necessary.

From toxicological aspects, however, there is indication that the primary alkyl amines may have a closely related effect spectrum. On that background read across of data from one substance to another is broadly accepted. As a consequence the data base for some endpoints becomes rather small because few studies are available which are used as basis for the assessment of the whole group. The toxicological profile of primary alkyl amines (chapter 4.1.2) and the threshold levels identified in the hazard assessment are taken forward to characterise the risks at the workplace and give indication for concern according to the MOS approach as outlined in the TGD (Human Health Risk Characterisation, Final Draft).

Systemic availability for different routes of exposure

Very little is known on the absorption and bioavailability of the primary alkyl amines in question. For this report information on absorption mainly comes from considerations on physico-chemical properties in combination with some data on alkylamines with shorter chain length. On that background a value of 100 % for oral and inhalative absorption is taken forward to worker risk assessment. For dermal absorption a value of 60 % is considered reasonable based on absorption data for 1-dodecanamine.

Occupational exposure and internal body burden

In table 4.1.3.2.A. the exposure levels of table 4.1 which concern primary alkyl amines are summarised and the route-specific internal body burdens are identified. To this end the route-specific percentages for absorption (100 % for inhalation and 60 % for dermal exposure) are taken into account. For combined exposure the internal budy burdens by inhalation and dermal contact are summed up to give a total internal body burden.

There are five primary alkyl amines to assess, two liquids (coco alkyl amine and octadecenyl amine), a paste (tallow alkyl amine) and two solids (octadecyl amine and hydrogenated tallow alkyl amine). The liquid and paste primary alkyl amines are corrosive (labelled with R 35). The solid amines are skin-irritating substances (R 38).

For the liquids and the paste primary alkyl amines inhalation exposure is only assumed via vapour, and because the vapour pressure is less than 1 Pa the inhalation exposure is considered to be low (no quantitative assessment). These three substances are also corrosive substances. For corrosive substances, it is the convention not to perform quantitative dermal exposure assessment.

The remaining two, octadecyl amine and the hydrogenated tallow alkyl amine, are solids leading to dust exposure, and they are not corrosive, but skin-irritating substances. Only for

these two substances, according to TGD, quantitative inhalation and dermal exposure assessments were performed (see Tab. 4.2).

Table 4.1.3.2.A: Occupational exposure levels and internal body burden for octadecyl amine and hydrogenated tallow alkyl amine

Exposure scenario		Inhalation shift average	Dermal contact shift average		Internal body burden of workers after repeated exposure(1)		
					Inhalation(1)	Dermal(2)	Combined
		mg/m³	mg/pers/d	mg/kg/d	mg/kg/d		
1.	Production	0.6	42	0.6	0.09	0.36	0.45
2.	Further processing	1	42	0.6	0.14	0.36	0.5
3.	Use of primary alkyl amines in flotation process	0.625	420	6	0.09	3.6	3.7
4.	Formulation of products containing primary alkyl amines	0.625	420	6	0.09	3.6	3.7

(1) based on the assumption of 100% inhalative absorption; breathing volume of 10 m³ per shift
(2) based on the assumption of 60 % systemic availability after dermal contact

MOS Approach

The MOS approach for human risk characterisation is described in detail in the TGD (Human Health Risk Characterisation, Final Draft). The following paragraphs contain a short introduction to aspects relevant in case of primary alkyl amines. The basic principle of the MOS approach is a comparison of scenario-specific MOS values (the relationship between the experimental NOAEL respectively the adjusted starting point and the exposure level) with a reference MOS (product of various assessment factors).

MOS calculation and the adequate starting point

Basically, MOS values are calculated as quotient of a relevant NOAEL from experimental animal testing or human studies and actual workplace exposure levels. In specific situations, the MOS approach requires converting the original NOAEL into an adequate starting point or corrected NOAEL previously to MOS calculation in order to be directly comparable to the exposure assessment. If the route of application in animal or human studies is different from the actual occupational exposure, the dose units of the experimental data are converted to the dose unit of the exposure data. Additionally, possible differences in bioavailability between routes, as well as possible differences in bioavailability between animals and humans are accounted for in the calculation of the corrected NOAEL. If necessary in occupational risk assessment, the starting point for inhalation risk assessment also includes a correction for the difference between the standard respiratory volume of a person at rest (6.7 m³) and the respiratory volume of workers under light activity (10 m³).

MOS values are calculated for different routes of exposure and for different toxicological endpoints. In occupational risk assessment inhalation and dermal contact generally resemble

the relevant exposure routes. In addition, for assessment of combined risks the simultaneous exposure by inhalation and dermal contact needs to be considered. To this end the internal body burdens obtained by dermal and inhalation exposure are determined and summed up and compared to the internal equivalent of the respective NOAEL for the endpoint in question. Inhalation exposure and dermal exposure to primary alkyl amines may contribute differently to the internal body burden. With respect to the possible outcome of an assessment for combined risks, interest focuses on scenarios with conclusion ii at both exposure routes. Based on theoretical considerations, combined exposure will not increase the most critical route-specific risk component more than twice.

Reference MOS

The MOS values calculated have to be compared with a reference MOS. The reference MOS results as an overall assessment factor from the multiplication of the different specific factors for a certain risk situation. The Technical Guidance Document emphasis the different aspects which are involved in these considerations, especially the extrapolation of experimental data to the human situation. For several aspects default assessment factors are recommended. It is important to point out that any relevant substance-specific data and information may overrule the defined default values.

Interspecies extrapolation as one central element is based on allometric scaling (factor 4 for rats, factor 7 for mice, and factor 2.4 for rabbits). For remaining interspecies differences the TGD proposes an additional factor of 2.5. Another element is adjustment for intraspecies differences. For workers, a default factor of 5 is recommended, based on an evaluation of empirical data by Schneider et al. (2004). It is anticipated that a default factor of 5 will be sufficient to protect the major part of the worker population (about 95%).

It is usually expected that the experimental NOAEL will decrease with increasing duration of application. Furthermore, other and more serious adverse effects may appear with prolonged exposure duration. For duration adjustment, a default factor of 6 is proposed for extrapolation from a subacute to chronic exposure. The duration adjustment factor could be lower for the transition from subchronic studies. However, for the primary alkyl amines the relevant data come from subacute studies.

The TGD describes two further adjustment factors (uncertainty in route-to-route extrapolation and dose-response relationship including severity of effect) which in specific cases may be different from one. For primary alkyl amines route-to-route extrapolation is associated with a high degree of uncertainty because the local effects and their secondary consequences probably depend on the site of contact. However, in this report the few data available on this aspect are specifically evaluated to avoid using an additional default factor.

Comparison of MOS and reference MOS

The different scenario- and endpoint-specific MOS values are compared with the respective reference MOS. MOS values clearly above the reference MOS do not lead to concern, whereas MOS values that are clearly below the reference MOS give reason for concern. There are also risk-related aspects which cannot be covered quantitatively by assessment factors. These additional aspects are considered qualitatively when performing the risk assessment and have adequate influence on the finding of the conclusions. Especially in case of borderline scenarios these aspects might be decisive.

Critical Exposure Levels

In a parallel procedure, which gives identical but more direct results, the adjusted toxicological starting point is directly divided by the reference MOS. As a result, an exposure level (in mg/m³ or mg/kg/d) is identified, which may serve as a direct trigger for decisions when compared with the occupational exposure levels. In the context of this risk assessment report this trigger value is called "critical exposure level". Concern will be expressed for scenarios with occupational exposure levels higher than the relevant "critical exposure level".

4.1.3.2.1 Acute toxicity

Rats were exposed to a coco alkyl vapour in the mean analytical concentrations of 0.063 and 0.099 mg/l for one hour. All animals showed signs of irritation but there were no other relevant clinical symptoms or necropsy findings.

The dermal studies with coco alkyl amines demonstrated no mortality. Dose levels of 500 and 2000 mg/kg/day were tested on rats, a single dose of 1600 mg/kg/day was used on rabbits. At all doses severe skin reactions were observed, clinical signs were noted at 2000 mg/kg/day in the rat study.

Several oral studies are available for the different primary alkyl amines. For each substance at least one acute study has been performed so that these data can be used for comparison: for some of the substances the LD50 is in a range between 1000 and 2000 mg/kg/day, for others it exceeds 2000 mg/kg/day. In some cases there was mortality also below 1000 mg/kg/day.

Based on the data available it is preferred to perform a semi-quantitative risk characterisation for workers using the acute inhalation and dermal toxicity data.

Inhalation exposure

The only inhalation study available did show signs of respiratory tract irritation in rats following a 1-hour exposure to about 100 mg/m³. These experimental conditions did not result in clinical symptoms.

For the three corrosive primary alkyl amines there is no dust exposure; the vapour pressure is less than 1 Pa. Exposure to vapour is considered very small; under these conditions acute systemic effects are not anticipated to occur.

For the two irritating primary alkyl amines dust exposure is estimated to be up to 1 mg/m³. The margin of safety between 100 mg/m³ without clinical effects in experimental animals and the occupational exposure up to 1 mg/m³ is considered high enough to recognize no concern.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Dermal contact

Human data on acute dermal toxicity of primary alkyl amines are not available. For coco alkyl amine, acute dermal exposure to 2,000 mg/kg bw caused clinical effects, but did not result in mortality. The highest dermal occupational exposure is estimated to be 6 mg/kg bw (based on the exposure assessment for the two irritating primary alkyl amines). For systemic effects

following acute dermal exposure the margin of safety is judged to be sufficient.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Combined exposure

Based on the available data on occupational exposure, on route-specific acute systemic toxicity and on the semi-quantitative route-specific acute risk assessments there is no indication of a corresponding risk following combined exposure to the primary alkyl amines in the different exposure scenarios.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

4.1.3.2.2 Irritation and corrosivity

Skin

Based on classification and labelling, the primary alkyl amines to be assessed can formally be differentiated in three corrosive and two skin irritating primary alkyl amines (see introduction of occupational risk assessment).

For the corrosive substance octadecenylamine a 14-day dermal study is available. The lowest tested concentration of 0.3% still caused moderate irritation.

It is not considered necessary to define a LOAEL-to-NOAEL extrapolation factor for local effects, because all occupational dermal exposure scenarios only refer to the undiluted primary alkyl amines. Without personal protective equipment, dermal exposure to the corrosive primary alkyl amines will result in skin erosion, and dermal exposure to the irritating amines in skin irritation.

For all primary alkyl amines for acute dermal irritation and for corrosivity conclusion ii is proposed on the grounds that control measures exist which can minimise exposure thereby reducing the risk of irritation and corrosivity adequately. However, these controls must be implemented and complied with for all primary alkyl amines to make sure that skin damage is prevented and that there is no reason for concern.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Eyes

For some primary alkyl amines corrosive properties have been identified in skin irritation studies, for others, eye irritation tests have been performed. In summary primary alkyl amines homogeniously demonstrated a potential to induce severe ocular lesions. This is expressed in the according proposals for classification and labelling.

Conclusion ii is proposed on the grounds that control measures exist which can minimise exposure thereby reducing the risk of irritation/corrosivity adequately. However, these controls must be implemented and complied with to make sure that eye damage is prevented and that there is no reason for concern.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Respiratory tract

In the only inhalation study available, exposure to coco alkyl amine vapour for 1 hour showed signs of respiratory tract irritation at concentrations of 63 and 99 mg/m^3.

The highest inhalation exposure) estimated for the primary alkyl amines is 1 mg/m³ (8-hour shift average). The margin of safety is considered sufficient to assume that acute inhalation exposure to primary alkyl amines does not result in acute respiratory tract irritation.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

4.1.3.2.3 Sensitisation

Skin

Available data on the skin sensitisation potential of the different primary alkyl amines are not sufficiently conclusive. Due to the limited hazard data, the occupational risk of skin sensitisation following dermal exposure to the different primary alkyl amines cannot be sufficiently assessed. As to the substance-specific skin sensitisation data and the specific considerations on the need for further information and testing reference is made to the corresponding chapter on hazard assessment.

Conclusion (i) There is a need for further information and/or testing.

Respiratory tract

No information on the sensitising potential of the substance at the respiratory tract is available. For the time being a valid study to investigate respiratory sensitisation in experimental animals cannot be recommended. However, primary alkyl amines are not suspected to be potent respiratory sensitisers in humans according to the fact that during all the years of use no notice of specific case reports has been given. There is no concern with respect to respiratory sensitisation at the workplace.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

4.1.3.2.4 Repeated dose toxicity

Local effects

For skin irritation following repeated dermal exposure full reference is made to chapter 4.1.3.2.2. The considerations and conclusions in chapter 4.1.3.2.2 are considered valid for local effects following repeated exposure as well.

For respiratory tract irritation following repeated exposure reference is made to chapter 4.1.3.2.2 as well. In the only inhalation study available, exposure to coco alkyl amine vapour for 1 hour showed signs of respiratory tract irritation at concentrations of 63 and 99 mg/m^3. The highest inhalation exposure estimated for the primary alkyl amines is 1 mg/m³ (8-hour shift average). The margin of safety was considered sufficient to assume that acute inhalation exposure to primary alkyl amines does not result in acute respiratory tract irritation. There is no information of the influence of repeated inhalation exposure to primary alkyl amines on respiratory tract irritation. Additional reference is made to the reference exposure level of 0.15 mg/m³ which should be adhered to because of systemic effects (see below). Lowering the maximum inhalation exposure of 1 mg/m³ significantly will probably be sufficient to exclude local effects as well. Against that complex background there is no reason to indicate additional concern for respiratory tract irritation.

Inhalation exposure

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Dermal exposure

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Systemic effects

There is no inhalation study available with repeated exposure. The only dermal study with repeated application suffered the lack of histomorphology data. Therefore evaluation of systemic toxicity after repeated exposure has to rely on oral data.

The most relevant study which gave the most sensitive results was performed with octadecenylamine in an oral 28-day test on rats. Groups of five male and female SD-rats received octadecenylamine (Genamin OL 100 D) by oral gavage at dose levels of 0, 3.25, 12.5 or 50 mg/kg/day for a period of 28 days (Aventis, 2003). At a dose of 50 mg/kg/day clinical signs as gait abnormalities, reduction in body weight gain and clinical pathology findings indicating mild toxic effects on the liver and kidneys were found. Effects observed at the mid-dose level (12.5 mg/kg/day) were reduction in growth and increased urinary concentration of urea nitrogen. At the low dose group of 3.25 mg/kg/day no effects were observed.

Inhalation exposure

Inhalation risk assessment will be based on the oral NOAEL for rats of 3.25 mg /kg/day. This value is taken forward to the inhalation exposure situation of workers, assuming similar absorption by oral and inhalation route and a bodyweight for workers of 70 kg (please be aware that the sequence of extrapolation steps in this report is not identical to the proposal in the actual Reach guidance documents; however, this different sequence does not lead to different results). As reference serves an 8 hours shift exposure with a respiratory volume of 10 m^3. The resulting air concentration is 23 mg/m^3 (3.25 mg/kg/day x 70 kg x / 10 m^3).

For the identification of the reference MOS the standard factor for duration adjustment is modified: For octadecyl amine a NOAEL of 10 mg/kg/day for a 2-year rat study is reported. It is clearly indicated in the hazard assessment, that this 2-year rat study is less valid than the 28-day study chosen as starting point for risk assessment. However, from the 2-year rat study there is at least no indication for a stringent necessity of applying the unchanged standard adjustment factor of 6. Based on the indicative results from the 2-year rat study with octadecyl amine it is considered proportionate to somewhat lower the standard factor for duration adjustment.

The following adjustment factors are applied for the identification of the reference MOS: (1) for duration adjustment a factor of 3 is used, (2) the allometric scaling factor for the rat is 4; (3) a default factor of 2.5 accounts for additional interspecies differences; (4) for intraspecies differences (workers) the default factor is 5. This gives a reference MOS of 150 (3 x 4 x 2.5 x 5). The respective critical inhalation exposure level at the workplace is identified as 0.15 mg/m^3 (23/150) representing a shift average value for long-term exposure.

This value leads to concern for all scenarios (for MOS values see table 4.1.3.2.C). This conclusion applies only to the two solid primary alkyl amines; for the other three primary alkyl amines there is conclusion ii for this toxicological endpoint (see introduction or summary to worker risk assessment).

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Dermal contact

Dermal risk assessment is based on the oral NOAEL of 3.25 mg/kg/day from the rat study as well. Taking into account the differences in oral (100%) and dermal (60%) absorption a value of 5.4 mg/kg/day (3.25 mg /kg/day /0.6), corresponding to 378 mg/person/day (bodyweight 70 kg), is obtained as corrected NOAEL for the dermal route which is used as starting point for the evaluation of dermal exposures.

The following adjustment factors are applied for the identification of the reference MOS: (1) for duration adjustment a factor of 3 is used, (2) the allometric scaling factor for the rat is 4; (3) a default factor of 2.5 accounts for additional interspecies differences; (4) for intraspecies differences (workers) the default factor is 5. This gives a reference MOS of 150 (3 x 4 x 2.5 x 5). The respective critical dermal exposure level at the workplace is identified as 0.04 mg /kg/day (5.4/150) or 2.8 mg/person/day (bodyweight 70 kg).

There is concern for all scenarios (for MOS values see table 4.1.3.2.C). This conclusion applies only to the two skin irritating primary alkyl amines; for the other three corrosive

primary alkyl amines there is conclusion ii for this toxicological endpoint (see introduction or summary to worker risk assessment).

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Combined exposure

Taking into account 100% oral absorption the internal level of primary alkyl amines directly corresponds to the oral NOAEL of 3.25 mg/kg/day. This value is used as starting point for combined risk assessment concerning repeated dose toxicity, systemic effects.

The reference MOS is 150. The critical internal level of primary alkyl amines with respect to chronic toxicity results as 0.02 mg/kg/day.

For all exposure scenarios there is already concern for both routes of exposure and thus for combined exposure as well. For quantitative data see table 4.1.3.2.C. This conclusion applies only to the two solid primary alkyl amines; for the other three primary alkyl amines there is conclusion ii for this toxicological endpoint (see introduction or summary to worker risk assessment).

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Table 4.1.3.2.C: Repeated dose toxicity, systemic effects (octadecyl amine and hydrogenated tallow alkyl amine)

	Inhalation			Dermal			Combined		
Starting point for MOS calculation	23 mg/m^3			5.4 mg/kg/day (external value)			3.25 mg/kg/day (internal value)		
Reference MOS	150			150			150		
Critical exposure level	0.15 mg/m^3			0.04 mg/kg/day (external value)			0.02 mg/kg/day (internal value)		
	Exposure (mg/m^3)	MOS	Conclusion	Exposure (mg/kg/d)	MOS	Conclusion	Internal body burden (mg/kg/d)	MOS	Conclusion
1. Production	0.6	38	iii	0.6	9.5	iii	0.45	7.2	iii[(1)]
2. Further processing	1	23	iii	0.6	9.5	iii	0.5	6.5	iii[(1)]
3. Use of primary alkyl amines in flotation process	0.625	37	iii	6	0.95	iii	3.7	0.9	iii[(1)]
4. Formulation of products containing primary alkyl amines	0.625	37	iii	6	0.95	iii	3.7	0.9	iii[(1)]

[(1)]conclusion iii already results from dermal and inhalation exposure, therefore no specific concern for the combined exposure scenario is indicated

4.1.3.2.5 Mutagenicity

Several mutagenicity tests have been performed with the different substances of the primary alkyl amines. Only negative results were obtained. Although for some substances the data base is not complete, read across can be performed. Altogether the data are judged sufficient to exclude a mutagenic potential of primary alkyl amines. There is no reason for concern.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

4.1.3.2.6 Carcinogenicity

Conventional carcinogenicity studies with primary alkyl amines are not available. Earlier studies on the chronic toxicity of octadecylamine provided no indication of a carcinogenic effect. There are no human data on the carcinogenicity of the primary alkyl amines. No potential for carcinogenicity was predicted for octadecylamines and octadecenylamines from the Danish QSAR database.

Due to the lack of reliable data no final conclusion can be drawn on the carcinogenic potential of any of the fatty alkylamines under consideration. Taking into account that all available mutagenicity tests gave negative results no indication may be seen for a carcinogenic potential of primary alkyl amines.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

4.1.3.2.7 Toxicity for reproduction

Effects on fertility

From oral tests on tallow alkyl amines, octadecylamine and octadecenylamine information on fertility is available which is judged to be sufficient for the evaluation of the other primary alkyl amins.

Repeated oral studies with octadecylamine and octadecenylamine did not show any adverse effect on reproductive organs. The most relevant result concerning fertility has been observed in a rat screening test with tallow alkyl amines with doses of 12.5, 50, 150 mg/kg/day. At a dose of 50 mg/kg/day a lower fertility index and a lower conception rate compared to the control group was observed. Also maternal toxicity occurred at that dose. The NOAEL for fertility and for maternal toxicity likewise was 12.5 mg/kg/day. This value will be taken forward for quantitative worker risk assessment.

Inhalation exposure

Inhalation risk assessment will be based on the oral NOAEL for rats of 12.5 mg /kg/day. This value is taken forward to the inhalation exposure situation of workers, assuming similar absorption by oral and inhalation route and a bodyweight for workers of 70 kg. For an 8- hour shift exposure a respiratory volume of 10 m^3 is assumed. The resulting air concentration is 88 mg/m^3 (12.5 mg/kg/day x 70 kg x / 10 m^3).

The following adjustment factors are applied for the identification of the reference MOS: (1) the allometric scaling factor for the rat is 4; (2) a default factor of 2.5 accounts for additional interspecies differences; (3) for intraspecies differences (workers) the default factor is 5. A duration adjustment factor is not judged necessary. Overall the reference MOS is 50 (4 x 2.5 x 5). The respective critical inhalation exposure level at the workplace is identified as 1.8 mg/m^3 (88/50) representing a shift average value.

As can be seen from table 4.1.3.2.D there is no concern regarding fertility effects after inhalation.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Dermal contact

Dermal risk assessment is also based on the NOAEL of 12.5 mg/kg/day from the fertility study with tallow alkyl amines. Taking into account the differences in oral (100%) and dermal (60%) absorption a value of 21 mg/kg/day (12.5 mg /kg/day /0.6) is obtained as corrected NOAEL for the dermal route.

The following adjustment factors are applied for the identification of the reference MOS: (1) the allometric scaling factor for the rat is 4; (2) a default factor of 2.5 accounts for additional interspecies differences; (3) for intraspecies differences (workers) the default factor is 5. A duration adjustment factor is not judged necessary. Overall the reference MOS is 50 (4 x 2.5 x 5). The respective critical dermal exposure level at the workplace is identified as 0.4 mg /kg/day (21/50).

As can be seen from table 4.1.3.2.D there is concern for all three scenarios. It is realised, that exposure reduction is in any case necessary because of systemic toxicity. This will similarly and effectively reduce the assessed fertility risks too. This conclusion applies only to the two skin irritating primary alkyl amines; for the other three corrosive primary alkyl amines there is conclusion ii for this toxicological endpoint (see introduction or summary to worker risk assessment).

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Combined exposure

Taking into account 100% oral absorption the internal level of primary alkyl amines directly corresponds to the oral NOAEL of 12.5 mg/kg/day. This value is used as starting point for combined risk assessment concerning fertility.

The reference MOS is 50. The critical internal level of primary alkyl amines with respect to fertility results as 0.25 mg/kg/day (12.5 / 50).

For all exposure scenarios there is already concern for the dermal route of exposure and thus for combined exposure as well. This conclusion applies only to the two solid primary alkyl amines; for the other three primary alkyl amines there is conclusion ii for this toxicological endpoint (see introduction or summary to worker risk assessment).

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Table 4.1.3.2.D: Fertility effects (octadecyl amine and hydrogenated tallow alkyl amine)

	Inhalation			Dermal			Combined		
Starting point for MOS calculation	88 mg/m³			21 mg/kg/day (external value)			12.5 mg/kg/day (internal value)		
Reference MOS	50			50			50		
Critical exposure level	1.8 mg/m³			0.4 mg/kg/day (external value)			0.25 mg/kg/day (internal value)		
	Exposure (mg/m³)	MOS	Conclusion	Exposure (mg/kg/d)	MOS	Conclusion	Internal body burden (mg/kg/d)	MOS	Conclusion
1. Production	0.6	147	ii	0.6	35	iii	0.45	28	iii(1)
2. Further processing	1	88	ii	0.6	35	iii	0.5	25	iii(1)
2. Use of primary alkyl amines in flotation process	0.625	141	ii	6	3.5	iii	3.7	3.4	iii(1)
3. Formulation of products containing primary alkyl amines	0.625	141	ii	6	3.5	iii	3.7	3.4	iii(1)

(1)conclusion iii already results from dermal exposure, therefore no specific concern for the combined exposure scenario is indicated

Developmental toxicity

Two guideline-conform studies on teratology in rats and rabbits are available for octadecenylamine. This is judged to be sufficient for the evaluation of the other primary alkyl amins. Up to oral doses of 80 mg/kg/day in the rat and 30 mg/kg/day in the rabbit, which clearly induced maternal toxicity, no indications for an embryotoxic, fetotoxic or teratogenic effect were observed.

On that background adverse effects on development by occupational exposure towards primary alkyl amines are not to be expected. A quantitative assessment is not deemed necessary. There is no concern for workers from this aspect.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

4.1.3.2.8 Summary of risk characterisation for workers

There are five primary alkyl amines to assess, two liquids (coco alkyl amine and octadecenyl amine), a paste (tallow alkyl amine) and two solids (octadecyl amine and hydrogenated tallow alkyl amine). The liquid and paste primary alkyl amines are corrosive (labelled with R 35). The solid amines are skin-irritating substances (R 38).

For the liquids and the paste inhalation exposure is only assumed via vapour, and because the vapour pressure is less than 1 Pa the inhalation exposure is considered to be low (no quantitative assessment). These three substances are also corrosive substances. For corrosive substances, it is the convention not to perform quantitative dermal exposure assessment.

The remaining two primary alkyl amines (octadecyl amine and the hydrogenated tallow alkyl amine) are solids leading to dust exposure, and they are not corrosive, but skin-irritating substances. Only for these two substances, according to TGD, quantitative inhalation and dermal exposure assessments were performed. It is implicitly assumed that there is a higher probability of repeated dermal exposure towards the skin irritating, but not to the corrosive primary alkyl amines. However, it is recognized that the clear-cut differentiation between corrosive and skin irritating primary alkyl amines is a formal simplification; in reality there seem to be gradual differences of skin irritation potency.

Based on the available data, the skin sensitising potential of the primary alkyl amines is difficult to assess; further testing is considered necessary.

Further risk management measures have to be implemented because of concern for repeated dose toxicity (systemic effects). It is the result and interpretation of the hazard data, that the oral NOAEL taken forward to risk characterisation should not be considered secondary to local effects. RDT risk assessment mainly relies on oral studies in combination with route-to-route extrapolation. 100% absorption is used as estimate for the oral and inhalation route. For dermal absorption a value of 60 % is taken.

Table 4.1.3.2.3.E summarizes the conclusions for the different toxicological endpoints.

Table 4.1.3.2.E: Endpoint-specific overall conclusions for the occupational risk assessment of primary alkyl amines

Toxicological endpoints		concern
Acute toxicity	inhalation	ii
	dermal	ii
	combined	ii
Irritation/ Corrosivity	dermal	ii
	eye	ii
	acute respiratory tract	ii
Sensitisation	skin	i
	respiratory	ii
Repeated dose toxicity	local, inhalation	ii
	local, dermal	ii
	systemic, inhalation	iii
	systemic, dermal	iii
	systemic, combined	iii(1)
Mutagenicity		ii
Carcinogenicity	inhalation	ii
	dermal	ii
	combined	ii
Fertility impairment	inhalation	ii
	dermal	iii
	combined	iii(1)
Developmental toxicity	inhalation	ii
	dermal	ii
	combined	ii

(1) conclusion iii already results from dermal exposure and/or inhalation, therefore no specific concern for the combined exposure scenario is indicated

Tables 4.1.3.2.F (inhalation) and 4.1.3.2.G (dermal contact) intend to visualize the risk profile of the primary alkyl amines. According to the arrangement of the tables relatively high risks occur on the upper left side, relatively low risks on the lower right side of the table-matrix.

With respect to inhalation, exposure levels to primary alkyl amines should be controlled to values in the range of 0.15 mg/m^3 (critical exposure level for repeated dose toxicity). It is assumed, that adherence to this reference value prevents respiratory irritation as well.

Dermal contact to primary alkyl amines needs to be avoided because these substances are either skin irritating or corrosive. However, especially for the skin irritating primary alkyl amines, repeated dermal exposure cannot be ruled out. With respect to systemic effects,

repeated dermal exposure at the workplace should be controlled to a level below 0.04 mg/kg/day.

Table 4.1.3.2.I: Ranking of health risks for workers (inhalation exposure to octadecyl amine and hydrogenated tallow alkyl amine)

Exposure scenario	Exposure level in mg/m³	Repeated dose toxicity, systemic effects	Fertility
		Critical exposure level in mg/m³	
		0.15	1.8
2. Further processing	1	iii	ii
3. Use of primary alkyl amines in flotation process	0.625	iii	ii
4. Formulation of products containing primary alkyl amines	0.625	iii	ii
1. Production	0.6	iii	ii

Table 4.1.3.2.I: Ranking of health risks for workers (dermal contact to octadecyl amine and hydrogenated tallow alkyl amine)

Exposure scenario	Exposure level in mg/kg/day	Repeated dose toxicity, systemic effects	Fertility
		Critical exposure level in mg/kg/day	
		0.04	0.4
3. Use of primary alkyl amines in flotation process	6	iii	iii
4. Formulation of products containing primary alkyl amines	6	iii	iii
1. Production	0.6	iii	iii (borderline)
2. Further processing	0.6	iii	iii (borderline)

4.1.3.3 Consumers

Consumer Exposure

Exposure of consumers to primary alkyl amines occurrs via the dermal route - through the application of lubricants and by metal (car) care products.

For acute toxicity, the dermal route from the use of lubricants was selected which may reach a value up to 3.5 mg/kg bw/day of primary tallow alkyl amines..

For chronic dermal toxicity the use of metal (car) care products is relevant which is 0.26 mg/kg bw/day.

The bioavailability is estimated as 60 % after skin contact.

Acute toxicity

Human data on the acute dermal toxicity of primary alkyl amines are not available. For coco alkyl amines, an available dermal acute toxicity test gives a LD50 value above 2000 mg/kg bw. The highest external dermal consumer exposure of 3.5 mg/kg bw/day corresponds to an internal exposure of 2.1 mg/kg bw/day. The margin of safety is judged to be sufficient. The substances seem of no concern for the consumer with regard to acute toxicity.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Irritation/Corrosivity

All considered alkyl amine mixtures were shown to have skin irritating properties in rabbit Draize tests. Coco alkyl amines, tallow alkyl amines and octadecenyl amine were classified as corrosive. Hydrogenated alkyl amines and octadecyl amine were classified as irritating to skin and as causing severe eye damage. Consumers may have dermal contact to products containing up to 5 % alkyl amines (metal (car) care products). Since adequate classification and labelling measures are in place there is no concern for consumers.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Sensitisation

Valid human data on the sensitising potential of primary alkyl amines are not available. Coco alkyl amines and hydrogenated tallow alkyl amines were studied in an animal test, that showed negative and inclusive results. These results may be further used for read-across to other alkyl amines in the category. However, read-across to the other primary alkyl amines considered in this report is limited by structural differences: Coco alkyl amines are of considerably shorter chain length, and tallow alkyl amines as well as octadecenyl amine have a higher degree of unsaturation, which significantly affects the overall molecular structure. Relevant skin contact of consumers with primary alkyl amines occurrs from the use of metal care products. Due to the lacking hazard data, the resulting risk of sensitisation cannot be assessed. Industrial testing with octadecenyl amine is ongoing. Test results may then also be used for read-across to other alkyl amines in the category.

Conclusion (i) There is a need for further information and/or testing. The ongoing performance of an animal study with octadecenylamine (112-90-3) by industry for assessment of skin sensitizing potential is announced.

Repeated dose toxicity

Data on repeated dose toxicity are available for tallow alkyl amines and octadecenyl amine from valid oral 28 day studies in rats, for octadecyl amine from oral studies of limited reliability in rats and dogs, and for octadecyl amine and octadecenyl amine from dermal studies of limited reliability in rats and mice. From the best-conducted of these studies, NOAEL / LOAEL values are derived for the overall class of compounds.

In an oral 28 day study in rats, octadecenyl amine induced growth depression, increased enzyme activities, motoric and haematologic abnormalities. The NOAEL is 3.25 mg/kg bw/d. For the dermal route, no NOAELsys could be derived. Repeated dermal application of octadecenyl amine caused concentration-dependent irritative skin effects. The lowest tested concentration was 0.3%, which is converted to a dermal LOAELlocal of 12.5 mg/kg bw/d.

For the dermal route, the exposure via the use of metal (car) care products is calculated as 0.26 mg/ kg bw/day.

For the decision on the appropriateness of MOS, the following aspects have been considered and taken into account.

- overall confidence in the database:
The data taken into account for performing the risk characterisation have been evaluated with regard to their reliability, relevance and completeness according to section 3.2 of the TGD. Only two of the five alkyl amine mixtures under consideration were investigated in toxicity tests consistent with internationally recognized guidelines. For one further substance mixture, supportive data are available from studies of limited reliability. As the overall information derived from all studies is not contradictory, an overall risk characterisation for the primary alkyl amines based on this database seems justified. However, data gaps remain and the chosen category approach is associated with a special extent of uncertainty.

- uncertainty arising from the variability in the experimental data:
The data on toxicity after dermal exposure is limited to allow a firm identification of an effect level for risk characterisation. For oral exposure, even though the experimental data is also limited, the available information appears to be in good consistency, in both qualitative and quantitative terms, with regard to observed adverse effects. There are no reasons to assume a special extent of uncertainty which has to be taken into account.

- intra- and interspecies variation:
Available data do not allow a conclusion on the intraspecies or interspecies variability of the toxicokinetic or toxicodynamic characteristics of the substances under consideration.

- the nature and severity of the effect:
The observed adverse effects in animals are regarded as serious. The systemic health effects are the basis for a proposed classification as R48/22.

- dose-response relationship:
There is no reason to assume a special concern.

- differences in exposure (route, duration, frequency and pattern):
The estimated year-average daily dermal exposure is compared with a dermal LOAELlocal derived from a 12 day study in rats. This procedure is consistent with established risk assessment methodology.

- the human population to which the information on exposure applies:
Following the exposure pattern there is no reason to assume a special risk for children, elderly, or pregnant women.

- other factors:
There are no other factors known that might require a particular margin of safety.

MOS for the dermal exposure scenario, local effects:

The external dermal exposure to primary alkyl amines is calculated as 260 µg/kg bw/d. The margin of safety between the

external dermal exposure estimate of 0.260 mg/kg bw/d

and the

dermal LOAELlocal of 12.5 mg/kg bw/d

is judged to be not sufficient additionally taken also into account that a LOAEL value was selected.

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

MOS for the dermal exposure scenario, systemic effects:

Assuming a bioavailability of 60 %, the external dermal exposure of 260 µg/kg bw/d corresponds to an internal exposure of 156 µg//kg bw/d. The margin of safety between the

internal dermal exposure estimate of 0.156 mg/kg bw/d

and the

oral NOAELsys of 3.25 mg/kg bw/d

is judged to be not sufficient.

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Mutagenicity

Mutagenicity tests with the alkyl amine mixtures under consideration gave only negative results. For the longer chain compound mixtures (C16/C18), results are available from tests with bacteria and with mammalian cells *in vitro* and *in vivo*. For the shorter chain coco alkyl amines (C12/C14), only data from bacterial mutagenicity tests are available. However, taken together and in view of the consistency of the results the data base on mutagenicity is judged to be sufficient to exclude a concern for the consumer with regard to this endpoint.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Carcinogenicity

Data on the carcinogenic potential of primary alkyl amines from human experience or from valid animal carcinogenicity studies are not available. Limited data from older chronic toxicity studies, negative data from a variety of mutagenicity tests and negative predictions from the Danish QSAR database indicate no specific concern regarding the carcinogenic potential of these substances.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Toxicity for reproduction

Fertility impairment

Concerning effects on fertility, valid data are only available for tallow alkyl amines from a study according to OECD TG 421 (oral exposure). Additionally, data of limited reliability can be derived from oral chronic studies with octadecylamine. Based on the findings of a lower fertility index and a lower conception rate at daily dosages of 50 mg/kg bw/d a NOEL/fertility of 12.5 mg/kg bw/d is derived from the guideline-compliant test with tallow alkylamines.

For the dermal route, the exposure via the use of metal (car) care products is calculated as 0.26 mg/ kg bw/day.

For the decision on the appropriateness of MOS, the following aspects have been considered and taken into account.

- overall confidence in the database:
The data taken into account for performing the risk characterisation have been evaluated with regard to their reliability, relevance and completeness according to section 3.2 of the TGD. Only one of the five alkyl amine mixtures under consideration was investigated in a screening test for reproductive toxicity, which complied with an internationally recognized guideline. For one further substance mixture, supportive data of limited reliability are available. As the available information does not indicate a specific toxic potential adverse to fertility, an overall risk characterisation for the primary alkyl amines for this endpoint can be based on this database. However, the uncertainty associated with the present data gaps and the chosen category approach needs to be taken into account.

- uncertainty arising from the variability in the experimental data:
There are no reasons to assume a special extent of uncertainty.

- intra- and interspecies variation:
Available data do not allow a conclusion on the intraspecies or interspecies variability of the toxicokinetic or toxicodynamic characteristics of the substances under consideration.

- the nature and severity of the effect:
The observed adverse effects on fertility occur at dose levels which also produced non-specific signs of toxicity. There is no reason to assume a special potential for toxicity on fertility.

- dose-response relationship:
There is no reason to assume a special concern.

- differences in exposure (route, duration, frequency and pattern):
The estimated year-average daily dermal exposures was compared with an oral NOAEL. This procedure is consistent with established risk assessment methodology.

- the human population to which the information on exposure applies:
Following the exposure pattern there is no reason to assume a special risk.

- other factors:
There are no other factors known that might require a particular margin of safety.

MOS for the dermal exposure scenario:

The external dermal exposure to primary alkyl amines is calculated as 260 µg/kg bw/d. Assuming a bioavailability of 60%, this corresponds to an internal exposure of 156 µg//kg bw/d. The margin of safety between the

internal dermal exposure estimate of 0.156 mg/kg bw/d

and the

oral $NOAEL_{fertility}$ of 12.5 mg/kg bw/d

is judged to be not sufficient.

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Developmental toxicity

Concerning developmental toxicity, valid data are only available for octadecenylamine from oral studies in two species (rat and rabbit). These studies did not provide an indication of any embryo-/fetotoxic or teratogenic potential even at maternally toxic dose levels. From the study in rabbits, the $NOAEL_{dev.tox.}$ is derived to be above 30 mg/kg bw/d.

For the dermal route, the exposure via the use of metal (car) care products is calculated as 0.26 mg/ kg bw/day.

For the decision on the appropriateness of MOS, the following aspects have been considered and taken into account.

- overall confidence in the database:
The data taken into account for performing the risk characterisation have been evaluated with regard to their reliability, relevance and completeness according to section 3.2 of the TGD. Only one of the five alkyl amine mixtures under consideration was investigated in animal studies for developmental toxicity. As the available information does not indicate a specific toxic potential adverse to the development, an overall risk characterisation for the primary alkyl amines for this endpoint can be based on this database. However, the uncertainty associated with the present data gaps and the chosen category approach needs to be taken into account.

- uncertainty arising from the variability in the experimental data:
There are no reasons to assume a special extent of uncertainty.

- intra- and interspecies variation:
Available data do not allow a conclusion on the intraspecies or interspecies variability of the toxicokinetic or toxicodynamic characteristics of the substances under consideration.

- the nature and severity of the effect:
No adverse effect on development was observed in the tested dose range.

- dose-response relationship:
There is no reason to assume a special concern.

- differences in exposure (route, duration, frequency and pattern):
The estimated year-average daily dermal and oral exposures are compared with an oral NOAEL. This procedure is consistent with established risk assessment methodology.

- the human population to which the information on exposure applies:

Following the exposure pattern there is no reason to assume a special risk.

- other factors:
There are no other factors known that might require a particular margin of safety.

MOS for the dermal exposure scenario:

The external dermal exposure to primary alkyl amines is calculated as 260 µg/kg bw/d. Assuming a bioavailability of 60%, this corresponds to an internal exposure of 156 µg//kg bw/d. The margin of safety between the

internal dermal exposure estimate of 0.156 mg/kg bw/d

and the

oral $NOAEL_{dev.tox.}$ of >30 mg/kg bw/d

is judged to be sufficient.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

4.1.3.4 Humans exposed via the environment

There are no releases into the atmosphere during production, processing or use of primary alkyl amines. Volatilization from aqueous solution is expected to be negligible. Therefore an exposure of humans via the atmosphere is not expected.

4.1.3.4.1 Exposure via food and water

Data from several local exposure scenarios indicate that the most relevant indirect exposure path to primary alkyl amines is the consumption of plants grown in agricultural soils on which sewage sludge from treatment plants was used as fertilizer. This scenario accounts for an average oral uptake of 1.4 µg/kg bw/d. On a regional scale, indirect exposure may arise from the consumption of contaminated mango fruits and processed products thereof. The sum of 1-octadecanamine and 1-dodecanamine concentrations in fruits is 19.1 mg/kg. Assuming that 1.2 kg fruits are consumed the daily intake of primary alkyl amines can be calculated to 0.32 mg/kg/bw/day. Due to inconsequencies in the data base, eg a possible scenario of mango consumption, fruit consumption did not use for regional exposure scenarios.

When considering possible risks to human health arising from indirect exposure to primary alkyl amines via the environment the key areas of possible concerns are for repeated dose toxicity, mutagenicity, carcinogenicity, and reproductive toxicity.

Repeated dose toxicity

Data on repeated dose toxicity are available for tallow alkyl amines and octadecenyl amine from valid oral 28 day studies in rats, for octadecyl amine from oral studies of limited reliability in rats and dogs, and for octadecyl amine and octadecenyl amine from dermal studies of limited reliability in rats and mice. From the best-conducted of these studies, NOAEL / LOAEL values are derived for the overall class of compounds.

In an oral 28 day study in rats, octadecenyl amine induced growth depression, increased enzyme activities, motoric and haematologic abnormalities. The NOAEL is 3.25 mg/kg bw/d.

For the dermal route, no $NOAEL_{sys}$ could be derived. Repeated dermal application of octadecenyl amine caused concentration-dependent irritative skin effects. The lowest tested concentration was 0.3%, which is converted to a dermal $LOAEL_{local}$ of 12.5 mg/kg bw/d.

Exposure levels via food and water are 1.4 µg/kg bw/d on a local scale

For a conclusion about the appropriateness of the MOS for this endpoint, the following aspects were considered and taken into account:

- overall confidence in the database:
The data taken into account for performing the risk characterisation have been evaluated with regard to their reliability, relevance and completeness according to section 3.2 of the TGD. Only two of the five alkyl amine mixtures under consideration were investigated in toxicity tests consistent with internationally recognized guidelines. For one further substance mixture, supportive data are available from studies of limited reliability. As the overall information derived from all studies is not contradictory, an overall risk characterisation for the primary alkyl amines based on this database seems justified. However, data gaps remain and the chosen category approach is associated with a special extent of uncertainty.

- uncertainty arising from the variability in the experimental data:
Even though the experimental data is limited, the available information appears to be in good consistency, in both qualitative and quantitative terms, with regard to observed adverse effects after oral exposure. There are no reasons to assume a special extent of uncertainty which has to be taken into account.

- intra- and interspecies variation:
Available data do not allow a conclusion on the intraspecies or interspecies variability of the toxicokinetic or toxicodynamic characteristics of the substances under consideration.

- the nature and severity of the effect:
The observed adverse effects in animals are regarded as serious. The systemic health effects are the basis for a proposed classification as R48/22.

- dose-response relationship:
There is no reason to assume a special concern.

- differences in exposure (route, duration, frequency and pattern):
The estimated year-average daily oral exposure is compared with an oral NOAEL derived from 28 day toxicity studies in rats. This procedure is consistent with established risk assessment methodology.

- the human population to which the information on exposure applies:
For the regional scenario (consumption of mangos), separate data are availbale for adults and children of two different age groups.

- other factors:
There are no other factors known that might require a particular margin of safety.

MOS for the local exposure scenario

The daily intake was calculated to be 0.0014 mg/kg bw/d (local scenario). The margin of safety between the

exposure level of 0.0014 mg/kg bw/d

and the

oral NOAEL of 3.25 mg/kg bw/d

is judged to be sufficient.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

There is no concern for mutagenicity, carcinogenicity and developmental toxicity for the substances in the category. The exposure values are very low therefore a MOS calculation for fertility is not necessary.

4.1.3.4.2 Summary of risk characterisation for exposure via the environment

When considering the risks to human health arising from indirect exposure to primary alkyl amines via the environment no concern is derived for mutagenicity, carcinogenicity, and toxicity to reproduction.

Conclusion (ii) There is at present no need for further information and/or testing or for risk reduction measures beyond those which are being applied already.

4.1.3.5 Combined exposure

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

4.2.1 Exposure assessment

Primary alkyl amines are not explosive, not flammable and due to its chemical structure, primary alkyl amines are not expected to possess any oxidising properties.

4.2.2 Effects assessment: Hazard identification

4.2.3 Risk characterisation

4.2.3.1 Workers

not applicable

Conclusion (ii) There is at present no need for further information and/or testing or for risk reduction measures beyond those which are being applied already.

5 RESULTS [13]

5.1 INTRODUCTION

5.2 ENVIRONMENT

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to

- Releases into surface waters during production of primary alkyl amines.
- Releases into surface waters during formulation of fertilizers, processing to aminoethoxylates, amides, sulphosuccinamates and other downstream products.
- Releases into surface water using primary alkyl amines as floatation agent.
- Releases into agricultural soils during application of sewage sludge onto agricultural soil due to production, formulation of fertilizers, and use as floatation agent.
- Releases into agricultural soils during the use as anticaking agent in fertilizers.
- Releases into the atmosphere during all life-cycle steps.
- Possible PBT/vPvB properties of the substance.

5.3 HUMAN HEALTH

5.3.1 Human health (toxicity)

5.3.1.1 Workers

Conclusion (i) There is a need for further information and/or testing.

Available data on the skin sensitisation potential of the primary alkyl amines to be assessed are not sufficiently conclusive. Due to the limited hazard information, the occupational risk of skin sensitisation following dermal exposure to the primary alkyl amines cannot be sufficiently assessed.

[13] Conclusion (i) There is a need for further information and/or testing.
Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.
Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

The primary alkyl amines are classified and labelled as skin irritants or corrosives. Skin irritation and corrosive lesions need to be avoided by adequate skin-related risk management measures. In addition, further risk management measures have to be implemented because of concern for repeated dose toxicity (systemic effects) following dust exposure and dermal contact to the solid and skin irritating primary alkyl amines (octadecyl amine and hydrogenated tallow alkyl amine). Based on the actual dermal exposure assessment, there is concern for fertility impairment as well.

To prevent chronic systemic health effects while handling primary alkyl amines, occupational exposure by inhalation is proposed to be controlled down to a level of 0.15 mg/m³ (8-hour time-weighted average). The corresponding health-based reference level for controlling repeated dermal exposure is calculated to be 0.04 mg/kg/day.

5.3.1.2 Consumers

Conclusion (i) There is a need for further information and/or testing.

Conclusion (i) applies to potential skin sensitisation reactions of primary alkyl amines from the use of metal care products. For the assessment of the possible skin sensitisation potential of the primary alkyl amines the performance of a Local Lymph Node Assay (LLNA) is proposed with an appropriate substance of the category. Test results are needed to perform a firm calculation for consumers

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion (iii) applies to potential local and systemic health effects after repeated exposure via the skin through the aggregated uptake from grease, corrosion inhibitors and fabric softeners.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to all other toxicological endpoints and scenarios.

5.3.1.3 Humans exposed via the environment

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to all other toxicological endpoints and scenarios.

5.3.1.4 Combined exposure

5.3.2 Human health (risks from physico-chemical properties)

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

6 REFERENCES

Akzo (1991): Acute Toxicity of Armeen HT to *Brachydanio rerio*. Report number: CRL F91082. unpublished study of AKZO Research Laboratories Arnhem, The Netherlands

Akzo (1992a): Biodegradability of Armeen CD. Report No. CRL F91125. Akzo Research Laboratories Arnhem, The Netherlands

Akzo (1992b): Biodegradability of Armeen TD. Report No. CRL F91124. Akzo Research Laboratories Arnhem, The Netherlands

Akzo (1992c): Biodegradability of Armeen HTD. Report No. CRL F91050. Akzo Research Laboratories Arnhem, The Netherlands

Akzo (1992d): Biodegradability of Armeen OD. Report No. CRL F91123. Akzo Research Laboratories Arnhem, The Netherlands

Akzo Nobel (1995a): Acute Toxicity of Oleylamine to *Daphnia magna*. Report No.: RGL F95063 T94003 DA 1995.10.24. Unpublished study of AKZO NOBEL Central Research Arnhem, The Netherlands

Akzo Nobel (1995b): Acute Toxicity of Oleylamine to *Pimephales promelas*. Report No.: RGL F95031 T94003 V 1995.09.05. Unpublished study of AKZO NOBEL Central Research Arnhem, The Netherlands

Akzo Nobel (1995c): Acute Toxicity of Oleylamine to the Freshwater Alga *Selenastrum capricornutum*. Report No.: RGL F95037 T94003 AL 1995.10.24. Unpublished study of AKZO NOBEL Central Research Arnhem, The Netherlands

Akzo Nobel (1996): Degradation of amines by soil microorganisms, Report No. 80AC0073. Akzo Research Laboratories Arnhem, The Netherlands

Akzo Nobel (1998): Biodegradation and Environmental Fate of Tallow Amine. Final Research Report March 4, 1998. Akzo Research Laboratories Arnhem, The Netherlands

Akzo Nobel (2000): safety data sheet of Armeen C (28.03.2000). Akzo Nobel Surface Chemistry AB

Akzo Nobel (2002a): Determination of the Removal of Cocoamine in a Simulation Test of an Activated Sludge Plant Treating Domestic Wastewater. Final Research Report, July 29, 2002. Akzo Research Laboratories Arnhem, The Netherlands

Akzo Nobel (2002b): Determination of the Removal of Cocoamine in a Simulation Test of an Activated Sludge Plant Treating Industrial Wastewater. Final Research Report, July 29, 2002. Akzo Research Laboratories Arnhem, The Netherlands

Akzo Nobel (2002c): Assessment of the Biodegradation Kinetics of Cocoamine in Aqueous Ecosystems using the Closed Bottle Test. Akzo Nobel Memorandum, July 16, 2002. Akzo Research Laboratories Arnhem, The Netherlands

Akzo Nobel (2006): Bioconcentration of 1-Hexadecylamine (C16 Primary Amine) in the carp under flow-through conditions. Interim Research Report ICS 103. Akzo Nobel, February 13, 2006. Akzo Research Laboratories Arnhem, The Netherlands

Akzo Nobel (2008): Exposure information to fatty amines during their manufacturing, letter from 14.04.2008

Anderson, H.H. and Hurwitz, G.K. (1953): Dodecylamine and Ohter Agents Active Against *Ascaris lumbricoides* and Their Toxicity in Mammals. Arch. Exp. Pathol. Pharmakol. (219), 119-129

Ansari et al. (2000): Journal of Medicinal and Aromatic Plant Sciences 22(1B), 582-585

APAG (2001): The European Oleochemicals & Allied Products Group (APAG). Information about end-uses of primary amines, 23nd Oct 2001

APAG (2002): The European Oleochemicals & Allied Products Group (APAG). Emission due to production of primary alkyl amines. 30th August 2002

APAG (2003): Information about exposure due to the manufacture of hydrogenated tallow alkyl amine, letter from 16.07.2003

APAG (2003a): The European Oleochemicals & Allied Products Group (APAG). Environmental Fate Effects Assessment – Primary Fatty Amines. September 2003

APAG (2003b): The European Oleochemicals & Allied Products Group (APAG). Information about end-uses of primary amines, 11nd Sept 2003

APAG (2005a): The European Oleochemicals & Allied Products Group (APAG). Emission due to the use of (hydrogenated) tallow amine as coating agent on inorganic fertilisers.

APAG (2005b): The European Oleochemicals & Allied Products Group (APAG). Information about sludge application and regional background concentrations, 20th July 2005

APAG (2005c): The European Oleochemicals & Allied Products Group (APAG). Information about exposure due to downstream uses, 20th May 2005

APAG (2005d): The European Oleochemicals & Allied Products Group (APAG). Information about exposure due to sludge application and downstream uses, 16th September 2005

APAG (2006a): The European Oleochemicals & Allied Products Group (APAG). Predicted local concentration in surface water at two downstream user sites (describing the new monitoring studies at both locations), 9th June 2006

Atkinson (1987): International J. of Chemical Kinetics 19, 799-828

Aventis (2003) Aventis Pharma, Hattersheim, Genamin OL 100 D. Rat repeat dose 28-day oral toxicity and 14-day recovery, Toxicology study report PT01-0326

BAM (2001): validation of the safety data through the Bundesanstalt für Materialforschung und –prüfung on 19.09.2001

Berol Nobel (1991a): The acute toxicity of Amine KK to rainbow trout (*Oncorhynchus mykiss*). Project number: 116/69. Unpublished study Safepharm Laboratories Limited, Derby, U.K.

Berol Nobel (1991b): The acute toxicity of Amine KK to *Daphnia magna*. Project number: 116/68. Unpublished study Safepharm Laboratories Limited, Derby, U.K.

Berol Nobel (1991c): Assessment of the Algistatic effect of Amine KK. Project number: 116/70. Unpublished study Safepharm Laboratories Limited, Derby, U.K.

Berol Nobel (1991d): Assessment of the algistatic effect of Amine BG. Bericht Nr. 116/77. Unveröffentlichte Untersuchung der Safepharm Laboratories Ltd. im Auftrag von Berol Nobel

Berol Nobel (1991e): Assessment of the Algistatic effect of Amine HBG. Project number: 116/78. Unpublished study Safepharm Laboratories Limited, Derby, U.K.

Blaschko H (1952) Amine oxidase and amine metabolism. Pharmacol. Rev. 4, 415 - 458.

Bollmann, M.A. et al. (1989): Report on algal toxicity tests on selected office of toxic substances (OTS) chemicals. Corvallis Environ. Res. Lab., Corvallis/Oregon, USA, EPA Rep. No. EPA/600/3-90/041. pp 1-3, 10

Brooke, L.T. et al. (1984): Acute toxicities of organic chemicals to fathead minnows (*Pimephales promelas*), Vol. I. Center for Lake Superior Environmental Studies University of Wisconsin-Superior, Wisconsin, USA. pp3-13, 370-373

Brooks SC, Lalich JJ, Baumann, CA (1957) Skin sterols. XII. Contrasting effects of certain mercaptans, amines, and related compounds on sterols and sebaceous glands. Cancer Res. 17, 148-153

BUA (1994): Primary Fatty Amines. BUA Report 177. Ed. by German Chemical Society – Advisory Committee on Existing Chemicals of Environmental Relevance. S. Hirzel Wissenschaftliche Verlagsgesellschaft Stuttgart.

Caroll KK (1960) Toxicity of Sphingosine and other long-chain amines. Proc. Soc. Exp. Biol. Med. 103, 734–737

CECA (1994): NORAM O, Determination de la biodegredabilite facile essai de degagement de CO2, Study report Elf Atochem/CAL 4658/93/A

CECA (1995): NORAM SH, Acute toxicity in Daphnia. Study report CIT 12947 EAM

CECA (2000): safety data sheet of NORAM O (23.08.2000). CECA SA, France

Centre International Toxicologie (1986) Noram SH; evaluation de l'irritation cutanee chez le lapin. Unpublished study report, Etude N° 1886 TAL

Centre International Toxicologie (1993) Noram O; determination of acute oral toxicity in rats. Unpublished study report No. 9428 TAR

Centre International Toxicologie (1999a) Noram C; acute dermal irritation study in rabbits. Unpublished study report No. 18253 TAL

Centre International Toxicologie (1999b) Noram O; acute dermal irritation study in rabbits. Unpublished study report No. 18254 TAL

Centro de Investigacion Y Desarollo Aplicado (1995a) S.A.L., Casellas N, Acute oral toxicity test in rats. Fixed Dose Method. Test Substance: Farmin TH, unpublished study report (CD-95/4308T)

Centro de Investigacion Y Desarollo Aplicado (1995b) S.A.L., Casellas N, Primary skin irritation in rabbits. Test substance: Farmin TH, unpublished study report (CD-95/4310T)

Centro de Investigacion Y Desarollo Aplicado (1995c) S.A.L., Casellas N, Primary eye irritation in rabbits. Test substance: Farmin TH, unpublished study report (CD-95/4309T)

Chemsafe (2001): national database for safety data of the Physikalisch-technische Bundesanstalt, Braunschweig, established by expert judgement

Christie, A.O. & Crisp, D.J. (1966): Toxicity of aliphatic amines to barnacle larvae. Comp. Biochem. Physiol. (18), 59-69

Clariant (1998): Draft Environmental Risk Assessment Report from 25.06.1998.Clariant.

Clariant (1999): Determination of the Flammability of Genamin TA 100 D. Report No. B-46644, dated November, 1999. Clariant GmbH – Division Surfactants. Industriepark Hoechst. Frankfurt.

Clariant (2000): safety data sheet of Genamin OS 100 D (23.03.2001). Clariant GmbH, Frankfurt am Main

Clariant (2001a): Calculations using the program EPIWIN Version 3.01, "Estimation Programs Interface" by William Meyland, Philip Howard, Syracuse Research Corporation, Environmental Science Center , Merill Lane, Syracuse, NY 13210,2001

Clariant (2001b): safety data sheet of Genamin SH 100 D (23.03.2001). Clariant GmbH, Frankfurt am Main

Clariant (2001c): safety data sheet of Genamin CC 100 (24.01.2001). Clariant GmbH, Frankfurt am Main

Cline, R.E. (1972): Lethal effects of aqueous formulations containing fatty amines or acids against eggs and larvae of *Aedes aegypti*. J. Econ. Entomol. (65), 177-181

Danish EPA (2004): Pesticides Research 63, Scenarios and Model Describing Fate and Transport of Pesticides in Surface Water for Danish Conditions. *Appendix D* - Uncertainty Analysis of the Registration Model. Version 1.0 May 2004. http://www.mst.dk/udgiv/publications/2004/87-7614-251-5/html/appd_eng.htm

Deichmann WB, Radomski JL, MacDonald WE, Kascht RL and Erdmann RL (1958) The Chronic Toxicity of Octadecylamine. Archives of Industrial Health, 18, 483-487

ECETOC (2003): Environmental Risk Assessment of Difficult Substances. Technical Report No. 88

EU (2002): Risk Assessment Report Dimethyldioctadecylammonium chloride. Final Draft 16.7.02

Fedorowicz A, Zheng LY, Singh H, and Demchuk E.(2004) QSAR study of skin sensitization using local lymph node assay data. Int.J.Mol.Sci. 5 (2):56-66

Fowler JS, Gallagher BM, MacGregor RR, Wolf AP, Ansari AN, Atkins HL and Slatkin DN (1976a) Radiopharmaceuticals. XIX. ^{11}C-Labeled octylamine, a potential diagnostic agent for lung structure and function. J. Nucl. Med. 17, 752-754

Fowler JS, Gallagher BM, MacGregor RR and Wolf AP (1976b) Carbon-11 labeled aliphatic amines in lung uptake and metabolism studies: potential for dynamic measurements in vivo. J. Pharmacol. Exp. Ther. 198, 133-145

Gallagher BM, Fowler JS, MacGregor RR, and Wolf AP (1977a) Evaluation of radiorespirometry for the determination of monoamine oxidase activity in vivo utilizing [^{11}C] octylamine as a substrate. Biochem. Pharmacol. 26, 1917-1922

Gallagher B, Christman D, Fowler J, MacGregor R, Wolf A, Som P, Ansari AN, and Atkins H (1977b) Radioisotope scintigraphy for the study of dynamics of amine regulation by the human lung. Chest 71, 282-284

GDCH-advisory committee on existent chemicals of environmental relevance (BUA) (1994). Primary fatty amines, Report N° 177, S. Hirzel, Wissenschaftliche Verlagsanstalt Stuttgart

Geiger et al. (1988): Acute toxicities of organic chemicals to fathead minnows (*Pimephales promelas*), Vol. IV. Center for Lake Superior Environmental Studies University of Wisconsin-Superior, Wisconsin, USA

Geiger et al. (1990): Acute toxicities of organic chemicals to fathead minnows (*Pimephales promelas*), Vol. V.. Center for Lake Superior Environmental Studies University of Wisconsin-Superior, Wisconsin, USA

Geurts, M. (2003): Environmental Fate & Effects Assessment - Primary Fatty Amines. The European Oleochemicals & Allied Products Group (APAG), September 2003

Gewerbehygienisches I.G. Laboratorium (1934) I.G. Farbenindustrie AG, Werk Wuppertal-Elberfeld Bericht über die gewerbehygienische Prüfung von Stearylamin, Stearylamin-acetat 33%, Amin PK 3. Unpublished study report, Doc. No. 04/34A

Griffin TS, Docks EL, Brotherton RJ, Hall JH (1991) The hypolipidemic activity of alkylamines and their borane derivates: structure-activity relationship in rodents. Eur J Med Chem 26, 517-527

Hazleton Laboratories America Inc. (1975) Coate WB, Range Finding Acute Inhalation Toxicity Study in Albino Rats. Armeen C and Armeen T. Unpublished study report, Project No. M931-100; cited from Toxicology Regulatory Services Inc. (2003)

Hazleton Laboratories Europe Ltd. (1979) Jones JR, Acute Percutaneous Toxicity in the Rabbit; Test Article: E8286; ECM BTS 278. Unpublished report (No. 1665-110/214); cited from Toxicology Regulatory Services Inc. (2003)

Hazleton Laboratories Europe Ltd. (1979a) Jones JR, Acute Oral LD50 in the Rat – ECM BTS 278;Test Article: E8286. Unpublished report (No. 1691-110/213); cited from Toxicology Regulatory Services Inc. (2003)

Hazleton Laboratories Europe Ltd. (1979b) Jones JR, Acute Oral LD50 in the Rat – ECM BTS 278;Test Article: E8296. Unpublished study report (No.1703-110/211); cited from Toxicology Regulatory Services Inc. (2003)

Heilen, C. et al. (1985): Amines, aliphatic. In: Ullmann's Encyclopedia of Industrial Chemistry, 5th ed., Vol. A2. VCH Verlagsgesellschaft mbH, Weinheim, pp. 1-36

Hoechst AG (1932) Lautenschlaeger, Bockmuehl, Wulff, Betr.: Stearyl-Oleylamin, Stearine- und Oelsäurenitril/ Wirkung an der Haut. Prüfung an der rasierten Kaninchenbauchhaut. Unpublished study report no. 07/32

Hoechst AG (1977): Vergleich der Behandlung mit Polyethylenglykol 400 und 1%iger Essigsäure (bzw. Borsäurepuffer) bei Verätzung von Haut und Schleimhaut durch Genamin TA 100 D = primäres Talgfettamin an Kaninchen. Unpublished study report no. 748/77

Hoechst AG (1978a): Flotigam-Marken – Kationische Sammler für die Flotation von Kalisalzmineralien. Hoechst AG, Frankfurt/Main, pp. 1-17

Hoechst AG (1978b): Antibackmittel für die Düngemittelindustrie. Hoechst AG, Frankfurt/Main, pp. 1-16

Hoechst AG (1980a): Fettamine und Folgeprodukte, Kerndatentabelle, Hoechst AG, Frankfurt, p. 4

Hoechst AG (1980b): Fettamine und Folgeprodukte – Eigenschaften und Anwendungsmöglichkeiten. Hoechst AG, Frankfurt/Main, pp. 1-30

Hoechst AG (1984) Markert and Weigand, Genamin CC100 D, Prüfung auf Hautreizung am Kaninchen. Unpublished study report no. 84.0921

Hoechst AG (1988a): Genamin 8 R 100 D – Prüfung der akuten Toxizität am Fisch Zebrabärbling (*Brachydanio rerio*) über 96 h. Bericht Nr.: 86.1365. Unveröffentlichte Untersuchung Hoechst Pharma Forschung Toxikologie und Pathologie, Frankfurt (Main), Germany

Hoechst AG (1988b): Genamin 10 R 100 D – Prüfung der akuten Toxizität am Fisch Zebrabärbling (*Brachydanio rerio*). Bericht Nr.: 88.0816. Unveröffentlichte Untersuchung Hoechst Pharma Forschung Toxikologie und Pathologie, Frankfurt (Main), Germany

Hoechst AG (1988c): Genamin 12 R 100 D – Prüfung der akuten Toxizität am Fisch Zebrabärbling (*Brachydanio rerio*) über 96 h. Bericht Nr.: 88.0256. Unveröffentlichte Untersuchung Hoechst Pharma Forschung Toxikologie und Pathologie, Frankfurt (Main), Germany

Hoechst AG (1988d): Genamin 18 R 100 D – Prüfung der akuten Toxizität am Fisch Zebrabärbling (*Brachydanio rerio*). Bericht Nr.: 88.1404. Unveröffentlichte Untersuchung Hoechst Pharma Forschung Toxikologie und Pathologie, Frankfurt (Main), Germany

Hoechst AG (1988e): Genamin CC 100 D – Prüfung der akuten Toxizität am Fisch Zebrabärbling (*Brachydanio rerio*) über 96 h. Bericht Nr.: 88.0558. Unveröffentlichte Untersuchung Hoechst Pharma Forschung Toxikologie und Pathologie, Frankfurt (Main), Germany

Hoechst AG (1988f): Genamin SH 100 D – Prüfung der akuten Toxizität am Fisch Zebrabärbling (*Brachydanio rerio*). Bericht Nr.: 88.0712. Unveröffentlichte Untersuchung Hoechst Pharma Forschung Toxikologie und Pathologie, Frankfurt (Main), Germany

Hoechst AG (1988g): Genamin TA 100 D – Prüfung der akuten Toxizität am Fisch Zebrabärbling (*Brachydanio rerio*) über 96 h. Bericht Nr.: 88.0614. Unveröffentlichte Untersuchung Hoechst Pharma Forschung Toxikologie und Pathologie, Frankfurt (Main), Germany

Hoechst AG (1988h): Genamin OL 100 D – Prüfung der akuten Toxizität am Fisch Zebrabärbling (*Brachydanio rerio*). Bericht Nr.: 88.1597. Unveröffentlichte Untersuchung Hoechst Pharma Forschung Toxikologie und Pathologie, Frankfurt (Main), Germany

Hoechst AG (1988i) Pharma Forschung Toxikologie und Pathologie, Hofman and Jung, Genamin TA 100 D. Prüfung der akuten oralen Toxizität an der Wistar-Ratte. Unpublished report No. 88.0359

Hoechst AG (1988j) Pharma Forschung Toxikologie und Pathologie, Kreiling and Jung, Genamin TA 100 D. Prüfung auf Hautreizung am Kaninchen. Unpublished report No. 88.0283

Hoechst AG (1988k) Hofman and Jung, Genamin CC 100 D, Prüfung der akuten oralen Toxizität an der Wistar-Ratte. Unpublished study report no. 88.0414

Hoechst AG (1988l) Pharma Forschung Toxikologie, Genamin SH 100 D. Kurzbericht zur Prüfung der akuten oralen Toxizität an der Wistar-Ratte. Unpublished study (Bericht Nr. 88.0969)

Hoechst AG (1988m) Pharma Research Toxicology and Pathology, Müller W, Genamin CC 100 D. Study of the mutagenic potential in strains of Salmonella typhimurium (Ames test) and Escherichia coli. Unpublished study report no. 88.0193 (lab. study no.88. 0092)

Hoechst AG (1988n) Pharma Research Toxicology and Pathology, Müller W, Genamin TA 100 D. Study of the mutagenic potential in strains of Salmonella typhimurium (Ames Test) and Escherichia coli. Unpublished study report no. 88.0411 (lab. study no. 88.0148)

Hoechst AG (1988o) Pharma Research Toxicology and Pathology, Müller W, Genamin 18 R 100 D. Study of the mutagenic potential in strains of Salmonella typhimurium (Ames Test) and Escherichia coli. Unpublished study report no. 88.0407 (lab. study no. 88.0089)

Hoechst AG (1988p) Pharma Forschung Toxikologie, Kreiling, Genamin SH 100 D. Kurzbericht zur dermalen Reizwirkung. Unpublished study report (Bericht Nr. 88.1035)

Hoechst AG (1988q) Pharma Forschung Toxikologie, Kreiling, Genamin SH 100 D. Kurzbericht zur Reizwirkung am Auge. Unpublished study report (Bericht Nr. 88.1024)

Hoechst AG (1989a): Genamin-Marken – Fettamin-Oxethylate. Hoechst AG, Frankfurt/Main, pp. 1-12

Hoechst AG (1989b): Prüfung auf Bakterientoxizität nach OECD 209. Unpublished study, Journal-Nr 8.696, 24.01.1989)

Hoechst AG (1989c): Prüfung auf Bakterientoxizität nach OECD 209. Unpublished study, Journal-Nr 8.685, 24.01.1989)

Hoechst AG (1989d) Pharma Forschung Toxikologie und Pathologie, Hofmann T and Jung R. Genamin 18 R 100 D, Prüfung der akuten oralen Toxizität an der Wistar-Ratte. [Genamin 18 R 100 D; Acute oral toxicity study in the Wistar rat]. Unpublished study report No. 89.0840

Hoechst AG (1989e) Pharma Forschung Toxikologie und Pathologie, Kreiling and Jung, Genamin 18 R 100 D, Prüfung auf Hautreizung am Kaninchen. Unpublished study report No. 89.0260

Hoechst AG (1989f) Pharma Forschung Toxikologie und Pathologie, Kreiling and Jung, Genamin 18 R 100 D. Prüfung auf Augenreizung am Kaninchen. Unpublished study report No. 89.0261

Hoechst AG (1992a): Kurzbericht über die Prüfung der toxischen Wirkung von Genamin CC 100 (D) auf Bakterien, "Bakterientoxizität". Unpublished study, Report-No. 92-0098-01, 15.10.1992

Hoechst AG (1992b): Kurzbericht über die Prüfung der toxischen Wirkung von Genamin OL 100 D auf Bakterien, "Bakterientoxizität". Unpublished study, Report-No. 92-0096-01, 16.10.1992

Hoechst AG (1993a): BUA-Stoffbericht Primäre Fettamine. Communication from 22nd Dec 1993

Hoechst AG (1993b): Kurzbericht über die Prüfung der toxischen Wirkung von Genamin SH 100 D auf Bakterien, "Bakterientoxizität". Unpublished Study, Report-No. 93-0041-11, 30.08.1993

Hoechst AG (1994): Pruefung der leichten biologischen Abbaubarkeit von Genamin 18 R 100 D (2.11.1994)

Hoechst AG (1996a): Genamin CC 100 D, Ready Biodegradability, Modified Sturm Test. Study No. AST49491, 08.03.1996

Hoechst AG (1996b): Genamin TA 100 D, Ready Biodegradability, Modified Sturm Test; Study-No. AST49481

Hoechst AG (1996c): Calculations using the program EPIWIN Version 2.0b, "Estimation Programs Interface" by William Meyland, Philip Howard, Syracuse Research Corporation, Environmental Science Center , Merill Lane, Syracuse, NY 13210,1996

Hoechst AG (1997): EC safety data sheet Genamin RA100 (02.08.1996) and EC safety data sheet Genamin TA 100 D (17.01.1997)

Hoechst AG. Test report No. 88.0411, March 24th 1988a

Hoerr, C.W., McCorkie, M.R., Ralston, A.W. (1943) (cited in BUA 1994): Studies on high molecular weight aliphatic amines and their salts. X. Ionization constants of primary and symmetrical secondary amines in aqueous solution. J. Am. Chem. Soc., 65: 328-329

Höß, S. (?): Toxicity of Sodium tetrapropenyl benzene sulfonate, Cocos dimitylamine, Di hardened tallow dimethyl ammonium chloride, and Tallow alkylamine on the nematode *Caenorhabditis elegans* in artificial sediment. Year unknown. Bsb – Boden & Sediment-Bewertung, München, Germany

Huntingdon Research Centre (1982) Ligget MP, Seaber JA: Irritant effects of Armeen HT LOT. 312 and Crodamine IHT Ref. 682 on rabbit skin. Unpublished study report 8285D/AKZ 131/SE

Huntingdon Research Centre (1984) Leggett MP, Parcell BI, Irritant effects of rabbit skin of Lilamin AC-HBG-P, unpublished study report No. 84562D/KND2/SE

Huntingdon Research Centre (1985) Kynoch, Acute dermal toxicity to rats of Amine KK, unpublished study report no. 851001D/KND 10/AC

Huntingdon Research Centre (1995) Kynoch, SR Acute oral toxicity to rats of Liliamin AC-HBG/P, unpublished study report (0170/8000 291)

IBR Forschungs GmbH (1982) Fatty Amine 73/312 Acute dermal corrosion in rabbits, unpublished study report (project no. 1-3-7-82)

IBR Forschungs GmbH (1983a) Akute orale Toxizität an Ratten mit Armeen C, unpublished study report (project no. 1-4-299-83)

IBR Forschungs GmbH (1983b) Akute orale Toxizität an Ratten mit Armeen T, unpublished study report (project no. 1-4-298-83)

Instituto di Ricerche Biomediche (2000a) Instituto di Richerche Biomediche "Antoine Marxer" RBM S.p.A., Torino (Italy), Genamin TA 100, 4-week toxicity study by oral route, RBM Exp. No. 990716, unpublished report

Instituto di Ricerche Biomediche (2000b) Instituto di Richerche Biomedice "Antoine Marker" RBM S.p.A., Torino (Italy), Genamin TA 100, Reproduction/Developmental Toxicity Screening Test in rats by oral route, RBM Exp. No. 990717, unpublished report

Instituto di Ricerche Biomediche (2000c) Instituto di Ricerche Biomediche“Antoine Marxer” RBM S.p.A., Toriono (Italy), Genamin TA 100, Micronucleus test in rat bone marrow cells treated by oral route, RBM Exp. No. 990718, unpublished report

Intox Laboratories (1985) Report 14–day dermal toxicity range–finding study of Oleylamine in rats Protocol No. CMA-SC-001, EPA/OTS; Doc #40–8584196

Inveresk Research International (1979) Cuthbert JA, Safety Tests on Commercial Stearyl Amine. IRI Project No. 413132, unpublished study report No. 1375

Ishizuka, H. et al. (1971): Fundamental Studies o Anthelmintics (18) on the Antiparasitic Effects of Monoamine Compounds upon Various Parasites in vitro. (Japanese, German short translation). Oyo Yakuri (5), 261-271

Iwasaki K, Shiraga T, Noda K, Tada K and Noguchi H, (1986) N-sulphoconjugation of alicyclic, alkyl- and arylamines in vivo and in vitro. Xenobiotica 16, 651-659

Iwata Y, Moriya Y, and Kobayashi T (1987) Percutaneous absorption of aliphatic compounds. Cosmet. Toiletries 102, 53-68

Jefcoate CRE, Gaylor JL, and Calabrese RL (1969) Ligand interactions with cytochrome P450: Binding of primary amines. Biochemistry 8, 3455-3465

Kao (1995): Acute Immobilization Test in Daphnia Test Substance: Farmin TH. Report No. CD-95/4307T. KAO Corporation, S.A.

Kao (2000): safety data sheet of FARMIN® 80 (08.06.2000). Kao Corporation S.A., Spain

Kao (2001): safety data sheet of FARMIN® O (13.03.2001). Kao Corporation S.A., Spain

Kiuchi, F. et al. (1987): Studies on crude drugs effective on visheral larva migrans. Identification of larvicidal principles in betel nuts. Chem. Pharm. Bull (35), 2880-2886

Liebsch, M, Spielmann . (1995) Balb/c 3T3 cytotoxicity test. Meth. Mol. Biol. 43,177-178

Lüderitz P and Großer J (1986) Octadecylamin - ein nicht toxischer Korrosionsinhibitor für Dampferzeuger in Krankenhäusern. Hyg. & Med. 11, 480 - 481

MacDonald WE, Deichmann WB, Radomski JL, Austin BS (1962) The chronic toxicity of octadecylamine in the rat - A supplemental report. Toxicol Appl Pharmacol 4, 610-612

Meylan, W.M. et al. (1999): Environ. Toxicol. Chem. 18(4), 664-672

Microbiological Associates Inc. (1985a) Salmonella/Mammalian-Microsome plate incorporation mutagenicity assay (Ames Test). EPA doc no. FYI-AX-0485-0391 fiche OTS 0000391-0, cited from IUCLID

Microbiological Associates Inc. (1985b) Chromosome aberration assay in Chinese hamster ovary (CHO) cells. Unpublished report no. T2693.337010

Microbiological Associates Inc. (1985c) CHO/HGPRT mutation assay in presence and absence of exogenous metabolic activation. Unpublished study report EPA/OTS doc no. 40-8584199, fiche no. OTS0525402, cited from IUCLID

Microbiological Associates Inc. (1989a) Harbell JW, L5178Y TK+/- mouse lymphoma mutagenesis assay with confirmation. Unpublished study report no. T8461.701020

Microbiological Associates Inc. (1989b) Donald DL, Acute in vivo cytogenetic assay in mice. Unpublished study report no. T8461.107004

Mulla, M.S. (1967a): Biocidal and Biostatic Activity of Aliphatic Amines Against Southern House Mosquito Larvae and Pupae. J. Econ. Entomol. (60) 515-522

Mulla, M.S. (1967b): Biological activity of surfactants and some chemical intermediates against pre-imaginal mosquitoes. Proc. Pap. Annu. Conf. Calif. Mosquito Contr. Assoc. (35), 111-117

Mulla, M.S. (1970): Evaluation of aliphatic amines against larvae and pupae of mosquitoes. J. Econ. Entomol. (63), 1472-1475

Nagase, A. et al. (1982): Nematidical Activity of Akylamine against the Pine Wood Nematode, *Bursaphelenchus lignicolus*. Agric. Biol. Chem. (46), 167-172

Newsome et al. (1993): Validation and Upgrade of a QSAR Study of the Toxicity of Amines to Freshwater Fish. Environmental Toxicology and Risk Assessment, ASTM STP 1179, 413-426

Noack (1994a): Akuter Immobilisierungstest (48h) an *Daphnia magna* STRAUS von Genamin CC 100 D gem. OECD-Richtlinie Nr. 202 (1984). Projekt-Nr. 940905HM, Prüf-Nr. DAI42591. Dr. Noack-Laboratorium für angewandte Biologie, Hildesheim, Germany

Noack (1994b): Prüfung auf Hemmung der Algenzellvermehrung von Genamin CC 100 D gem. OECD-Richtlinie Nr. 201 (1984). Projekt-Nr. 940905HM, Prüf-Nr. SSO42591. Dr. Noack-Laboratorium für angewandte Biologie, Hildesheim, Germany

Noack (1994c): Akuter Immobilisierungstest (48h) an *Daphnia ma*gna STRAUS von Genamin SH 100 D gem. OECD-Richtlinie Nr. 202 (1984). Projekt-Nr. 940905HM, Prüf-Nr. DAI42621. Dr. Noack-Laboratorium für angewandte Biologie, Hildesheim, Germany

Noack (1994d): Prüfung auf Hemmung der Algenzellvermehrung von Genamin SH 100 D gem. OECD-Richtlinie Nr. 201 (1984). Projekt-Nr. 940905HM, Prüf-Nr. SSO42621. Dr. Noack-Laboratorium für angewandte Biologie, Hildesheim, Germany

Noack (1996): Genamin TA 100 D – Algen, Zellvermehrungs-Hemmtest gem. OECD-Richtlinie 201 (1984). Dr. Noack-Laboratorium für angewandte Biologie, Hildesheim, Germany

Noack (1999): Genamin TA 100 D Earthworm (*Eisenia fetida*), Acute Toxicity Test in Artificial Soil. Project-No. 990614CK, Study-No. RRA65341. Dr. Noack-Laboratorium für angewandte Biologie, Sarstedt, Germany

Noack (2000): Genamin TA 100 D Terrestrial Plants, Growth Test. Project-No. 990614CK, Study-No. TPH65342. Dr. Noack-Laboratorium für angewandte Biologie, Sarstedt, Germany

Noack (2002a): Cocoalkylamine, *Daphnia magna* Reproduction Test (21 d) with Natural River Water. Study No. DRE84311. Dr. Noack Laboratorium für Angewandte Biologie, Sarstedt, Germany

Noack (2002b): Tallowalkylamine, *Daphnia magna* Reproduction Test (21 d) with Natural River Water Study No. DRE84291. Dr. Noack Laboratorium für Angewandte Biologie, Sarstedt, Germany

Noack (2002c): Octadec-9-enylamine, *Daphnia magna* Reproduction Test (21 d) with Natural River Water. Study No. DRE84301. Dr. Noack Laboratorium für Angewandte Biologie, Sarstedt, Germany

Noack (2002d): Cocoalkylamine, Alga, Growth Inhibition Test with Natural River Water with *Desmodesmus subspicatus*, 72h. Dr. Noack Laboratorium für Angewandte Biologie, Sarstedt, Germany

Noack (2002e): Tallowalkylamine, Alga, Growth Inhibition Test with Natural River Water with *Desmodesmus subspicatus*, 72h. Study No. SSO84293. Dr. Noack Laboratorium für Angewandte Biologie, Sarstedt, Germany

Noack (2002f): Octadec-9-enylamine, Alga, Growth Inhibition Test with Natural River Water with *Desmodesmus subspicatus*, 72h. Study No. SSO84302. Dr. Noack Laboratorium für Angewandte Biologie, Sarstedt, Germany

Noack (2006): Amines, hydrogenated tallow, Earthworm (*Eisenia fetida*), Effects on Reproduction in Natural Soil. Project-No. 050727AT, Study-No. RRR102611. Dr. Noack-Laboratorium für angewandte Biologie, Sarstedt, Germany

Nuzzo F, Sala F, Biondi O, Casati A, Cestaro B, De Carli L (1985) Liposomes induce chromosomal aberrations in human cultured cells. Experimental cell research 157, 397-408

Oliver, GJA, Pemberton M A, Rhodes C, (1988) An Invitro Model for Identifying Skin-Corrosive Chemicals .I. Initial Validation. Toxicology in Vitro, 2, 7-17

Pang S (1995) Final report on the safety assessment of lauramine and stearamine. J Americ College Toxicol 14,196-2003

Parenteau H, Ho TFL, Eckel LA, Carroll KK (1991) Effects of a long-chain fatty amine on mammary carcinogenesis induced in female Sprague-Dawley rats by DMBA. Nutr Cancer 17, 235-41

Patty F, ed. Industrial Hygiene and Toxicology: Volume II:Toxicology. 2nd ed. New York: Interscience Publishers, 1963, 2041

Ralston A.W., Selby, W.M., Pool W.O. and Potts R.H. (1959): Boiling Points of n-Alkyl Primary Amines in Industrial and Engineering Chemstry, vol. 32(8); page 1093f

Ratledge, C. (1994): Biodegradation of Oils, fats and fatty acids. In: Biochemistry of Microbial Degradation, ed. by C. Ratledge. Kluwer Academic Publishers, The Netherlands.

Research and Consulting Company Ltd. (1994a) Pfister T, Primary skin irritation study (corrosivity-test) with Farmin C in rabbits (semi-occlusive application). Unpublished study report RCC Project 385290

Research and Consulting Company Ltd. (1994b) Pfister T, Primary skin irritation study (corrosivity-test) with Farmin O in rabbits (semi-occlusive application). Unpublished study report, RCC Project 385301

Research and Consulting Company Ltd. (1994c) Pfister T, Primary skin irritation study (corrosivity-test) with Farmin T in rabbits (semi-occlusive application). Unpublished study report, RCC Project 385288

Richardson M.L., Gangolli S. (1994): The Dictionary of Substances and their Effects. The Royal Society of Chemistry. Thomas Graham House, The Science Park, Cambridge, CB4 4WF. ISBN 0-85186-330-2; page 313f

Safepharm Laboratories Ltd. (1987) Guest RL, Amine KK: Acute dermal irritation/corrosion test in the rabbit. Unpublished study report, Project No. 116/27

Safepharm Laboratories Ltd. (1987) Guest RL, Amine HBG, Acute dermal irritation/corrosion test in the rabbit. Unpublished study report, Project No. 116/32

Safepharm Laboratories Ltd. (1989) Cesio 1 to Cesio 18, Acute dermal irritation/corrosion study in the rabbit. Unpublished study report no. 1594-191/1-18

Santa Maria A, Pozuelo JM, Lopez A, Sanz F (1996) Toxicity of potential irritants in mammalian cells in vitro. Ecotox. Environ. Safety 34, 56-58

Selisskij GD, Obuchova AS, Anton'ev AA, Somov BA, Saparenko MV, Alčangjan LV (1978) Die Prophylaxis von Berufsdermatosen unter der Einwirkung von Schutzmitteln gegen atmosphärische Metallkorrosion. German short summary from original russian paper. Vestnik dermatologii i venerologii H.9, 36-39

Siemens Axiva (2002a): Study for determination of the auto-flammability. Report no. 20020766.01. Siemens Axiva GmbH Co.KG, Industriepark Höchst/Frankfurt

Siemens Axiva (2002b): Study for determination of the boiling point/boiling range, flash point and auto-flammability. Report no. 20020763.01. Siemens Axiva GmbH Co.KG, Industriepark Höchst/Frankfurt

Siemens Axiva (2003): Amines, hydrogenated tallow alkyl: Boiling point/boiling range – relative density – flammability (solids). Unpublished test report from March 19,2003. Report-no. 20030218.1

Siemens Axiva (2003): Study for determination of the auto-flammability. Unpublished report from 19 May 2003. Siemens Axiva GmbH Co.KG, Industriepark Höchst/Frankfurt

Slangen, P.J. (2000): Adsorption/Desorption of Octadecylamine on Soil, Sediment and Sludge. Notox Project 288697

Springborn Laboratories Inc. (1989a) Mammalian Toxicology Division, Spencerville, OH 45887, Study Director M.D.M. Mercier, Teratology Study in rats with Oleylamine, Final Report, SLS Study No. 3205.9

Springborn Laboratories Inc. (1989b) Mammalian Toxicology Division, Spencerville, OH 45887, Study Director M.D.M. Mercier, Teratology Study in rabbits with Oleylamine, Final Report, SLS Study No. 3205.11

Tenne M, Youdim MBH, Ulitzur S and Finberg JPM (1985) Deamination of aliphatic amines by monoamine oxidase A and B studied using a bioluminescence technique. J. Neurochem. 44, 1373-1377

Tominaga T, Inoue O, Susuki K, Yamasaki T, and Hirobe M (1987) Evaluation of ^{13}N-amines as tracers. Nucl. Med. Biol.14, 485-490

Toxicology Regulatory Services Inc. (2003) American Chemistry Council´s Fatty Nitrogen Derivates Panel Amines Task Group; FND Amines Category HPV Chemicals Challenge -

Appendix A, Robust Summaries for Reliable Studies; December 29, 2003; http://www.epa.gov/chemrtk/pubs/summaries/amines/c14171rr1.pdf

Tynes RE, Sabourin PJ, Hodgson E and Philpot RM (1986) Formation of hydrogen peroxide and N-hydroxylated amines catalyzed by pulmonary flavin-containing monooxygenases in the presence of primary alkylamines. Arch. Biochem- Biophys. 251, 654-664

TNO (1979) Primary dermal corrosion test with four chemical products in albino rabbits. Van Beek L, unpublished study report no. R 6249

Ullmann (1985): Ullmann's Encyclopedia of Industrial Chemistry. Wolfgang Gerhartz at al. 5th edition- vol.2: Amines, Aliphatic to Antibiotics-XII. Weinheim Verlag Chemie, 1985

Ullmann's Encyclopedia of Industrial Chemistry (2005) Amines, Aliphatic. Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

University of Miami, School of Medicine, Department of Pharmacology (1957) The chronic toxicity of octadecylamine. (Submitted by FDA in response to FOI request-1991)

Van Ginkel, C.G. (1996): Biodegradation 7, 151-164

Van Ginkel, C.G. et al. (1995): Tenside Surf. Det. 32(4), 355-359

Wilton, D.P. & Fay, R.W. (1969): Action of amine ovicides on *Aedes aegypti* mosquitoes. Mosquito News (29), 361-365

Witco (1986): 48-Hour Static toxicity Test: Freshwater Invertebrate. Report number: BW-86-3-1956. Unpublished study of Springborn Bionomics Inc. Wareham, Massachusetts,USA

Yoshimura, K. et al. (1980): J. Am. Oil. Chem. Soc. 57, 238-241

Yu PH (1989) Deamination of aliphatic amines of different chain lengths by rat liver monoamine oxidase A and B. J. Pharm. Pharmacol. 41, 205-208

Zeiger E, Anderson B, Haworth S, Lawlor T, Mortelmans C (1988) *Salmonella* mutagenicity test: IV. Results from the testing of 300 chemicals. Env and Mol Mutagen 11 Suppl. 12: 1-158

ABBREVIATIONS

[update the list to correspond to the substance RAR]

ADI	Acceptable Daily Intake
AF	Assessment Factor
ASTM	American Society for Testing and Materials
ATP	Adaptation to Technical Progress
AUC	Area Under The Curve
B	Bioaccumulation
BBA	Biologische Bundesanstalt für Land- und Forstwirtschaft
BCF	Bioconcentration Factor
BMC	Benchmark Concentration
BMD	Benchmark Dose
BMF	Biomagnification Factor
bw	body weight / *Bw*, *b.w.*
C	Corrosive (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
CA	Chromosome Aberration
CA	Competent Authority
CAS	Chemical Abstract Services
CEC	Commission of the European Communities
CEN	European Standards Organisation / European Committee for Normalisation
CMR	Carcinogenic, Mutagenic and toxic to Reproduction
CNS	Central Nervous System
COD	Chemical Oxygen Demand
CSTEE	Scientific Committee for Toxicity, Ecotoxicity and the Environment (DG SANCO)
CT_{50}	Clearance Time, elimination or depuration expressed as half-life
d.wt	dry weight / dw
dfi	daily food intake
DG	Directorate General
DIN	Deutsche Industrie Norm (German norm)
DNA	DeoxyriboNucleic Acid
DOC	Dissolved Organic Carbon
DT50	Degradation half-life or period required for 50 percent dissipation / degradation
DT90	Period required for 50 percent dissipation / degradation
E	Explosive (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
EASE	Estimation and Assessment of Substance Exposure Physico-chemical properties [Model]

EbC50	Effect Concentration measured as 50% reduction in biomass growth in algae tests
EC	European Communities
EC10	Effect Concentration measured as 10% effect
EC50	median Effect Concentration
ECB	European Chemicals Bureau
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECVAM	European Centre for the Validation of Alternative Methods
EDC	Endocrine Disrupting Chemical
EEC	European Economic Communities
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EN	European Norm
EPA	Environmental Protection Agency (USA)
ErC50	Effect Concentration measured as 50% reduction in growth rate in algae tests
ESD	Emission Scenario Document
EU	European Union
EUSES	European Union System for the Evaluation of Substances [software tool in support of the Technical Guidance Document on risk assessment]
F(+)	(Highly) flammable (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
FAO	Food and Agriculture Organisation of the United Nations
FELS	Fish Early Life Stage
GLP	Good Laboratory Practice
HEDSET	EC/OECD Harmonised Electronic Data Set (for data collection of existing substances)
HELCOM	Helsinki Commission -Baltic Marine Environment Protection Commission
HPLC	High Pressure Liquid Chromatography
HPVC	High Production Volume Chemical (> 1000 t/a)
IARC	International Agency for Research on Cancer
IC	Industrial Category
IC50	median Immobilisation Concentration or median Inhibitory Concentration
ILO	International Labour Organisation
IPCS	International Programme on Chemical Safety
ISO	International Organisation for Standardisation
IUCLID	International Uniform Chemical Information Database (existing substances)
IUPAC	International Union for Pure and Applied Chemistry
JEFCA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
Koc	organic carbon normalised distribution coefficient

Kow	octanol/water partition coefficient
Kp	solids-water partition coefficient
L(E)C50	median Lethal (Effect) Concentration
LAEL	Lowest Adverse Effect Level
LC50	median Lethal Concentration
LD50	median Lethal Dose
LEV	Local Exhaust Ventilation
LLNA	Local Lymph Node Assay
LOAEL	Lowest Observed Adverse Effect Level
LOEC	Lowest Observed Effect Concentration
LOED	Lowest Observed Effect Dose
LOEL	Lowest Observed Effect Level
MAC	Maximum Allowable Concentration
MATC	Maximum Acceptable Toxic Concentration
MC	Main Category
MITI	Ministry of International Trade and Industry, Japan
MOE	Margin of Exposure
MOS	Margin of Safety
MW	Molecular Weight
N	Dangerous for the environment (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC
NAEL	No Adverse Effect Level
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NOEC	No Observed Effect Concentration
NTP	National Toxicology Program (USA)
O	Oxidizing (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
OECD	Organisation for Economic Cooperation and Development
OEL	Occupational Exposure Limit
OJ	Official Journal
OSPAR	Oslo and Paris Convention for the protection of the marine environment of the Northeast Atlantic
P	Persistent
PBT	Persistent, Bioaccumulative and Toxic
PBPK	Physiologically Based PharmacoKinetic modelling
PBTK	Physiologically Based ToxicoKinetic modelling
PEC	Predicted Environmental Concentration

pH	logarithm (to the base 10) (of the hydrogen ion concentration $\{H^+\}$
pKa	logarithm (to the base 10) of the acid dissociation constant
pKb	logarithm (to the base 10) of the base dissociation constant
PNEC	Predicted No Effect Concentration
POP	Persistent Organic Pollutant
PPE	Personal Protective Equipment
QSAR	(Quantitative) Structure-Activity Relationship
R phrases	Risk phrases according to Annex III of Directive 67/548/EEC
RAR	Risk Assessment Report
RC	Risk Characterisation
RfC	Reference Concentration
RfD	Reference Dose
RNA	RiboNucleic Acid
RPE	Respiratory Protective Equipment
RWC	Reasonable Worst Case
S phrases	Safety phrases according to Annex III of Directive 67/548/EEC
SAR	Structure-Activity Relationships
SBR	Standardised birth ratio
SCE	Sister Chromatic Exchange
SDS	Safety Data Sheet
SETAC	Society of Environmental Toxicology And Chemistry
SNIF	Summary Notification Interchange Format (new substances)
SSD	Species Sensitivity Distribution
STP	Sewage Treatment Plant
T(+)	(Very) Toxic (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
TDI	Tolerable Daily Intake
TG	Test Guideline
TGD	Technical Guidance Document
TNsG	Technical Notes for Guidance (for Biocides)
TNO	The Netherlands Organisation for Applied Scientific Research
UC	Use Category
UDS	Unscheduled DNA Synthesis
UN	United Nations
UNEP	United Nations Environment Programme
US EPA	Environmental Protection Agency, USA
UV	Ultraviolet Region of Spectrum
UVCB	Unknown or Variable composition, Complex reaction products of Biological material

vB	very Bioaccumulative
vP	very Persistent
vPvB	very Persistent and very Bioaccumulative
v/v	volume per volume ratio
w/w	weight per weight ratio
WHO	World Health Organization
WWTP	Waste Water Treatment Plant
Xn	Harmful (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
Xi	Irritant (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)

Appendix A

[click here to insert text]

European Commission

EUR [ECB: click here to insert EUR No.] - European Union Risk Assessment Report
[ECB: click here to insert SUBSTANCE NAME, and volume no.]

Editors: (keep this updated)

Luxembourg: Office for Official Publications of the European Communities

[ECB: insert year] – VIII pp., [ECB: insert number of pages] pp. – 17.0 x 24.0 cm

Environment and quality of life series

ISBN [ECB: insert ISBN No.]

Price (excluding VAT) in Luxembourg: EUR [ECB:insert price]

The report provides the comprehensive risk assessment of the substance [ECB: insert SUBSTANCE NAME] It has been prepared by [ECB: insert country] in the frame of Council Regulation (EEC) No. 793/93 on the evaluation and control of the risks of existing substances, following the principles for assessment of the risks to man and the environment, laid down in Commission Regulation (EC) No. 1488/94.

The evaluation considers the emissions and the resulting exposure to the environment and the human populations in all life cycle steps. Following the exposure assessment, the environmental risk characterisation for each protection goal in the aquatic, terrestrial and atmospheric compartment has been determined. For human health the scenarios for occupational exposure, consumer exposure and humans exposed via the environment have been examined and the possible risks have been identified.

[ECB, insert abstract]