Human and Environmental Risk Assessment

on ingredients of household cleaning products

Cocamidopropyl betaine (CAPB)

(CAS No: 61789-40-0, 70851-07-9, 4292-10-8)

Edition 1.0

June 2005

1 EXECUTIVE SUMMARY

Cocamidopropyl betaine (CAPB) is an amphoteric surfactant. The particular behaviour of amphoterics is related to their zwitterionic character; that means: both anionic and cationic structures are found in one molecule. Cocamidopropyl betaine is a high production volume chemical represented by the CAS Nos. 61789-40-0 and 70851-07-9. All relevant physicochemical, toxicological and ecotoxicological data, so far available (April 2005), are included in this document.

The usage of cocamidopropyl betaine in personal-care products has grown in recent years due to its relative mildness compared with other surface active compounds. In Western Europe 59000 metric tons cocamidopropyl betaines were produced in the year 2002 and they are predominately used as a cosmetic ingredient (50 % of the produced volume), such as shampoos, and as a detergent (50 % of the produced volume), such as hand washing agents. The concentration of cocamidopropyl betaine in cleaning and personal care products ranges up to 30% active matter.

Environmental assessment

The environmental risk assessment will be published in a single comprehensive document on a later date at www.heraproject.com.

Human health assessment

With dermal and oral LD_{50} values of > 2000 and ≥ 4900 mg/kg bw, respectively, the acute toxicity of cocamidopropyl betaine is very low. About 30% active formulations are irritating to the skin and the eyes, while ≤ 10 % active solutions caused only mild skin and eye reactions. From subacute and subchronic studies with rats a NOAEL of 1000 mg/kg bw/day for systemic toxicity of the 30% active CAPB was derived. Cocamidopropyl betaine gave no indication for genotoxic or teratogenic effects. Contact allergy to CAPB has been reported although extensive data now suggests that impurities in the final product are responsible for causing this skin sensitization.

Relevant consumer scenarios were described for the usage of household detergent products containing cocamidopropyl betaine and the resulting Margin of Exposures (MOE) were calculated comparing the systemic NOAEL to the estimated exposure values. For each scenario the MOE was above 10^4 (with the exception of one, which had a MOE of 7700 – pre-treatment of clothes), which represents a very high safety margin. Also the estimation of the total consumer exposure resulted in a MOE of about 2800 which is also a high value. No risk is calculated for potential uptake via drinking water or food.

Acute toxic effects after unintentional oral exposure of a few millilitres of the formulations (1 – 30% concentration) are not to be expected.

Neat CAPB is an irritant to skin and eyes. The irritation potential of aqueous solutions of CAPB depends on concentration. Local effects of hand wash solutions containing CAPB do not cause concern given that the concentrations of CAPB in such solutions are well below 1% and therefore not expected to be irritating to eye or skin. Laundry pre-treatment tasks, which may translate into brief hand skin contact with higher concentrations of CAPB, may occasionally result in mild irritation easily avoided by prompt rinsing of the hands in water. Potential irritation of the respiratory tract is not a concern given the very low levels of airborne CAPB generated as a consequence of cleaning sprays aerosols. Immediate eye rinsing with water for several minutes is recommended after accidental splashing of CAPB solutions, as eye irritation reactions may occur.

In view of the available database on toxic effects, the low exposure values calculated and the resulting large Margin of Exposure described above, it can be concluded that use of CAPB in household laundry and cleaning products raises no safety concerns for the consumers.

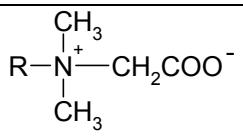
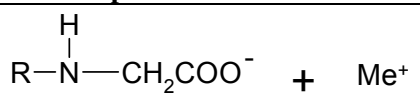
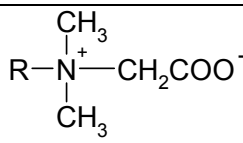
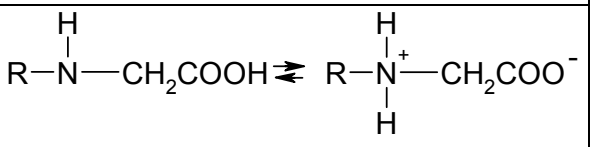
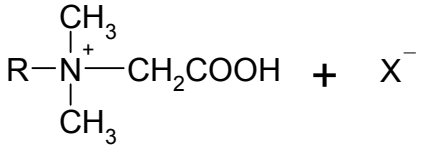
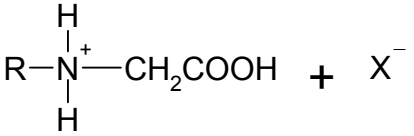
2 CONTENTS

3 SUBSTANCE CHARACTERISATION

Cocamidopropyl betaine is widely used as a surfactant. The usage of cocamidopropyl betaine in personal-care products has grown in recent years due to its relative mildness compared with other surface active compounds. Cocamidopropyl betaine is widely used in various cosmetics like shampoos, bath products, and cleansing agents, shower gels, bath foam, liquid soaps, skin care products, hand wash detergents. Uses in household cleaning products, the scope of HERA, include laundry detergents, hand dishwashing liquids, and hard surface cleaners.

Surface–active compounds with both acidic and alkaline properties are known as amphoteric surfactants. The particular behaviour of amphoterics is related to their zwitterionic character; that means: both anionic and cationic structures are found in one molecule. The betaines described herein belong to this class of surfactants. Irrespective of the pH value, betaines always contain a four bonded nitrogen atom. The betaines may be regarded as inner salts due to their two functional groups with opposite electric charge in one molecule. At very low pH, a cationic character dominates (see Table 1; Madsen et al. 2001; Domsch 1995, Uphues, 1998, BUA, 1997). Contrary to true amphoterics, which form salts in alkaline media, betaines do not take on an anionic behaviour under alkaline conditions.

Table 1: Influence of pH on the structure of the betaines

pH range	Betaines	True amphoterics
Alkaline		
isoelectric	 Domsch 1995, BUA 1997	
Acidic		

In the frame of this HERA risk assessment cocamidopropyl betaines (RCOOH=mainly a mixture of C_{12}-C_{18} fatty acids) are described. The fatty acids of cocamidopropyl betaine are obtained from hydrolysis of coconut oil. Coconut oil has a mixed fatty acid composition, which varies slightly, as it is a natural product. Lauric acid - resulting in lauramidopropyl betaine - is the major ingredient of coconut oil. As the physical chemical properties of cocamidopropyl betaine are not fully available as measured values, calculated values of lauramidopropyl betaine (RCOOH=lauric acid, C_{12} fatty acid) - as the main component in the cocamidopropyl betaine - are indicated instead. If possible the calculated ranges for the cocamidopropyl betaine (C_{12} – C_{18}) are given. In terms of the environmental exposure assessment, the relevant calculated values of the respective betaine derived from the C_{18} fatty acid – Stearamidopropylbetaine are indicated. The characteristics of the stearamidopropylbetaine are regarded as to represent the most hydrophobic properties of the cocamidopropyl betaine.

3.1 CAS No and Grouping Information

Alkylamidopropyl betaines as used on the European market and covered in this targeted risk assessment are represented by the substances listed in Table 2, including the cocamidopropyl betaine and the lauramidopropyl betaine (CAS No. 4292-10-8) which is the main ingredient of cocamidopropyl betaine.

Table 2: CAS Nos. of the substances covered in this risk assessment

CAS No.	EINECS No.	Name
4292-10-8	224-292-6	1-Propanaminium, N-(carboxymethyl)-N,N-dimethyl-3-[(1-oxododecyl)amino]-, inner salt
61789-40-0	263-058-8	1-Propanaminium, 3-amino-N-(carboxymethyl)-N,N-dimethyl-, N-cocoacylderivatives, inner salts
70851-07-9	274-923-4	Amides, coco, N-[3-(dimethylamino)propyl], alkylation products with chloroacetic acid, sodium salts

Cocamidopropyl betaine is a high production volume chemical represented by the CAS Nos. 61789-40-0 and 70851-07-9. All relevant physicochemical, toxicological and ecotoxicological data, so far available (April 2005), are included in this document.

Cocamidopropyl betaine and lauramidopropyl betaine are mainly marketed as 30% aqueous solutions. Sporadically, technical products with 38% active component are manufactured. Several reaction ingredients and other by-products are present as trace components

According to Liebert (1991) the composition of two batches of cosmetic grade cocamidopropyl betaine (CAS-No. 61789-40-0 and 70851-07-9) was as follows:

Active matter	29.5 - 32.5%
Water	62 - 66%
NaCl	4.6 - 5.6%
Carbon number of alkyl chain	
C_8	5.6 - 6.0%
C_{10}	5.4 - 5.7%
C_{12}	53.1 - 53.2%
C_{14}	16.1 - 17.4%
C_{16}	8.1 - 8.3%
C_{18}	10.0 - 10.2%

According to the information provided by the manufacturers (Henkel KGaA, 2001a, b, d), the composition of the technical products is as follows:

Active matter	20 - 38%
Water	<70%
NaCl	<10%
Carbon number of alkyl chain	
C_8	≤ 10%
C_{10}	≤ 10%
C_{12}	47 - 60%
C_{14}	17 - 25%
C_{16}	7 - 14%
C_{18}	7 - 14%

Impurities below 1 % are: sodium monochloroacetate (III – below 5 ppm), sodium dichloroacetate, sodium glycolate, amidoamine (II) and dimethylaminopropylamine (I). According to manufacturer´s information dimethylaminopropylamine and sodium

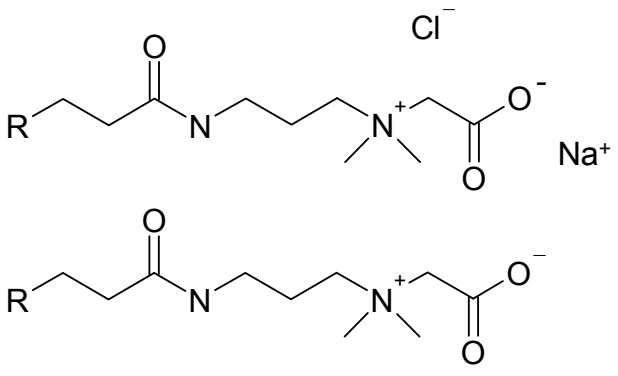
dichloroacetate are not present in lauramidopropyl betaine. (KAO Corporation 1992a, Uphues, 1998, Henkel KGaA, 1996, Sasol, 2004). I, II and III can be included in amidopropyl betaines as impurities resulting from the manufacturing reaction (see above), sodium glycolate is a by-product (see page 5). A small content of glycolic acid seems unavoidable, which results from a partial hydrolysis of monochloroacetate; glycerol may also be present if a triglyceride served as raw material (Uphues, 1998) Cosmetic grade cocamidopropyl betaine may contain a maximum of 3.0 % glycerol (CIR, 1991). Dichloroacetic acid contents - generally present in commercial monochloroacetate - are mainly below 20 ppm (Uphues, 1998).

Unreacted free amines (I, II) seem to be the most critical impurities in cocamidopropyl betaine formulations, as they are likely to be mainly responsible for occasionally seen skin sensitization reactions (see below). These byproducts can be avoided by a moderate excess of chloroacetate and the exact adjustment of pH value during the betainization reaction accompanied by regular control analyses (Uphues, 1998). The amount of amidoamine (II) and dimethylaminopropylamine (I) present in cocamidopropyl betaine formulation decreased during the last 10 years (Armstrong et al, 1999). Typical levels of impurities are now 0 to 15 mg/kg (I) and 0 to 0.3 % (II), (nevertheless there are qualities on the market with up to 3 % of (II).

3.2 Chemical Structure and Composition

Due to the production process of the betaines, the technical grade product is obtained as aqueous solution (active matter: ca. 20-40%). In general, the pure substances are not isolated from the aqueous solution and therefore the physicochemical properties of the pure substances are not determined experimentally. In Table 3 the physicochemical properties available for the technical grade product and the physicochemical properties which can be calculated via EPISUITE (Estimation Program interface suite, may be downloaded from http://www.epa.gov/opptintr/exposure/docs/episuite.htm) are listed.

As sodium chloride is one of the components in the aqueous reaction mixture handled, cocamidopropyl betaine may be described as each the inner salt or as the respective sodium salt. The chemical structures are therefore:



R= with varying Alkylchain lengths representing C_8 to C_{18} fatty acids.

Table 3: Summary of the physicochemical properties of betaines

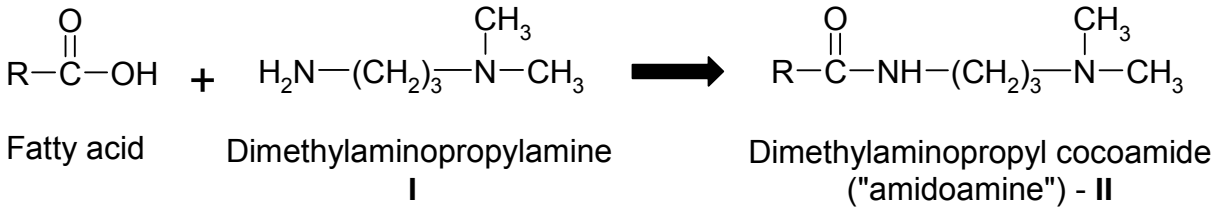
Property	**CAS-No.** **4292-10-8**	**CAS-Nos.** **61789-40-0 and 70851-07-9**
Physical state	Solid liquid*	Solid liquid*
Melting point	283°C (calculated via MPBPWIN v1.41) < 0°C*	260 – 320 °C (calculated via MPBPWIN v1.41)** < 0°C*
Boiling point	650°C (calculated via MPBPWIN v1.41) 100 - 110°C* (at 1000 hPa)	600 – 730 °C (calculated via MPBPWIN v1.41)** ca. 100°C*
Density	1.045 g/cm³ (at 25°C)*	1.05 – 1.07 g/cm³*
Vapor pressure	6.4 x 10^{-15} hPa (calculated via MPBPWIN v1.41 at 25°C)	< 2 x 10^{-13} hPa (calculated via MPBPWIN v1.41 at 25°C)**
Water solubility	> 100 g/l at 20°C* 1755 mg/l at 25°C (calculated via WSKOW v1.41 at 25°C)	≥ 10 g/l at 20°C* 1.62 – 8769 mg/l (calculated via WSKOW v1.41 at 25°C)**
pH	4-6 (1% solution, 20°C)*	4-8 (at 10 g/l, 20°C)*
Flash point	not flammable*	> 230°C*
Partition coefficient n-octanol/water (log value)	0.69 (calculated via KOWWIN v1.67 at 25°C)	-1.28 to 3.63 (calculated via KOWWIN v1.67 at 25°C)**
Henry's law constant	6.27 x 10^{-16} Pa m³/mol (calculated via HENRYWIN v3.10 at 25°C)	< 4 x 10^{-15} Pa m³/mol (calculated via HENRYWIN v3.10)**
Soil sorption coefficient Koc	3063 (log Koc = 3.5; calculated via PCKOCWIN v1.66)	264.7 – 120600 (calculated via PCKOCWIN v1.66)**
Viscosity	ca. 15 mPa s (at 25°C)*	90 mPa s (at 25°C)*

* values related to the product which is a 20-40% aqueous solution of the betaines

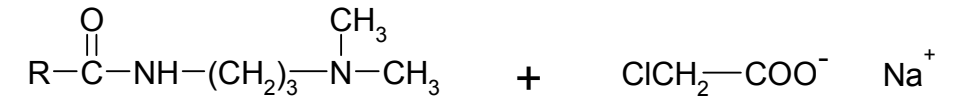
** range of values calculated for specific betaines with $C_{8, 10, 12, 14, 16 \& 18}$- fatty acids

3.3 Manufacturing route and production/Volume statistics

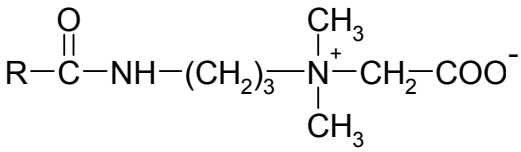
Alkyl amido betaines are synthesized according to the following reaction scheme:



Fatty acid — Dimethylaminopropylamine **I** — Dimethylaminopropyl cocoamide ("amidoamine") - **II**



Dimethylaminopropyl cocoamide ("amidoamine") — Sodium monochloroacetate **III**



Cocamidopropyl betaine

The reaction is carried out in aqueous solution under weak alkaline conditions (Uphues 1998).

Cocamidopropyl betaine (30 % active) is produced in a two-step batch process. Coconut oil or fatty acids hydrolyzed from coconut oil (C_{12}-C_{18}) are reacted with dimethylaminopropylamine (**I**) in aqueous solution at about 160 °C. Coconut oil has a mixed fatty acid composition, which varies slightly, as it is a natural product. The predominant fatty acid is lauric acid (C_{12}). In the second step, the resultant dimethylaminopropyl cocoamide (amidoamine - **II**) is then reacted with sodium monochloroacetate (**III**) under alkaline conditions. The product (cocamidopropyl betaine) is obtained as an aqueous solution in concentrations about 30 % (Hunter et al., 1998, Consortium "Categories Betaine" Information, 05/2004).

In Western Europe 59000 metric tons betaines were produced in the year 2002 (CESIO-statistics, 2004). The relevant producers are located in Germany (5 production sites), France (1 production site), Spain (3 production sites), UK (2 production sites) and Italy (2 production sites).

About 18000 tons/year are produced in the U.S.A. and about 10000 tons/year in Asia (Goldschmidt AG, 2004).

3.4 Use Application Summary

Cocamidopropyl betaine is predominately used as a **cosmetic ingredient** (50 % of the produced volume in Europe – **29500 tons/year**) and as a **detergent** (50 % of the produced volume in Europe – **29500 tons/year**) (Consortium "Categories Betaine" Information, 11/2003).

Its use as cosmetic ingredient includes various shampoos, bath products, and cleaning agents, shower gels, bath foam, liquid soaps, contact lens fluids, skin care products; its use as a detergent includes hand washing agents, and hand dish washing agents. The reported concentrations of cocamidopropyl betaine in cleaning and personal care products range from 0.1 to 50% (0.03 to 15% active) (Hunter et al., 1998, Swiss Product Register, 2004). In addition, it is used for industrial cleaning.

In July 2004, about 200 consumer and commercial products containing 10 to 50% cocamidopropyl betaine with CAS No.: 61789-40-0 (3 to 15% active) and seven industrial products ((car) cleaning agents, washing powder or soap) containing 10 to 50% (3 to 15% active) lauramidopropyl betaine were registered in the Swiss product register (Swiss Product Register, 2004). According to manufacturer information, 4% lauramidopropyl betaine is used in hand dish washing and personal care products (Sasol, 2004).

In the USA, cocamidopropyl betaine was present in 521 out of 19000 cosmetic products in the year 1992 (de Groot, 1997). The percentage of personal care products in the USA using cocamidopropyl betaine increased from 3.3% in 1989 to 6.2% in 1994 (Hunter et al., 1998).

4 ENVIRONMENTAL ASSESSMENT

The environmental risk assessment will be published in a single comprehensive document on a later date at www.heraproject.com.

5 HUMAN HEALTH ASSESSMENT

5.1 Consumer Exposure

5.1.1 Product Types: concentration (%) of the substance in product per product type

Cocamidopropyl betaine is used as a detergent. Its uses are covered by the use category "Cleaning/washing agents and additives" and by use category "Cosmetics", especially in shampoos and shower gels (Use categories according to EC, 2003) . Within the scope of HERA, the exposure assessment in this report is performed for the use category "Cleaning/washing agent and additives". The relevant product types in this use category are: laundry compact, hand dishwashing, surface cleaners and toilet cleaners.

Typical liquid laundry products contain about 4 % cocamidopropyl betaine, regular hand dishwashing liquids contain between 2 and 5 % of the betaine (with maximum values of up to 10 %), the concentrates contain 0.6 – 8 % (up to 11 % as a maximum value). Within the surface cleaners, liquid, spray and wipe formulations are available, containing between 0.1 and 1 % cocamidopropyl betaine with a maximum content of 2 %. The percentages of cocamidopropylamine in the toilet cleaner products are between 0.2 to 0.9 % in the gels and between 0.2 and 30 % in liquid formulations. Details of the ranges as 100 % active ingredient are given in the table 4.

Table 4: Specifications of cocamidopropyl betaine – containing products of the use category: Cleaning/washing agents and additives (HERA, 2003b)

Product categories	**Type of formulation**	**Range of cocamidopropyl betaine (as 100 % of active ingredient) % weight**		
		Minimum	**Maximum**	**Typical**
Laundry regular	Powder	0	0	0
	Liquid	0	4	4
Hand dishwashing	Liquid (regular)	0	10	2-5
	Liquid (concentrate)	0	11	0.6-8
	Gel	0	0	0
Surface cleaners	Liquid	0	2.01	0.2-0.9
	Concentrate	0	0	0
	Powder	0	0	0
	Gel	0	0	0
	Spray	0	2	0.099-0.9
	Wipe	0	2	0.9
Toilet cleaners	Powder	0	0	0
	Liquid	0	30	0.2-30
	Gel	0	0.9	0.2-0.9
	Tablet	0	0	0

5.1.2 Consumer contact scenarios

Based on the product types, the consumer contact scenarios that were identified and considered in this assessment include:

- direct skin contact with hand washed laundry, from pre-treatment of clothes, from hand dishwashing and from hard surface cleaning
- indirect skin contact from wearing clothes
- inhalation of aerosols from cleaning sprays
- oral ingestion derived either from residues deposited on dishes, from accidental product ingestion, or indirectly from drinking water

5.1.3 Consumer exposure estimates

There is a consolidated overview concerning relevant scenarios and habits and practices of use of detergents and surface cleaners in Western Europe which was tabulated and issued by HERA and AISE in the Table of Habits and Practices for Consumer Products in Western Europe (AISE, 2002). The scenarios comprise all relevant consumer use situation, where exposure to cocamidopropyl betaine may occur. This Table of Habits and Practices for Consumer Products in Western Europe reflects the consumer's use of detergents in terms of amount detergent used/task (g/task), frequency and duration of task (Tasks/week) and further intended uses of the respective product. The following exposure estimates were calculated using relevant data from that table and further assumptions specifically indicated in the respective scenarios. The maximum values – as shown in table 4 – have been used for the following calculations.

Direct skin contact from hand washed laundry

The assumptions to determine the consumer exposure during hand washing of laundry are given in the following bases for calculations.

Basis for calculations		**Reference**
Concentration of detergent solution	1 % - 10 mg/ml	AISE, 2002
Concentration of cocamidopropyl betaine in detergent	4 %	HERA, 2003b
Concentration of cocamidopropyl betaine in hand washing solution	0.4 mg/ml = 0.4 mg/cm^3 (10 mg/ml x 0.04)	Calculation
Exposed skin surface (hands and forearms)	1980 cm^2	EU-TGD, 2003
Thickness of liquid layer on skin after immersion	0.01 cm	EU-TGD, 2003
Percutaneous absorption (in 24 h)	10 *	Assumption (Chapter 5.2.1.1)
Duration of task	10 min	AISE, 2002
Maximum task frequency	10/week – max. 2/day	AISE, 2002
Body weight	60 kg	AISE, 2002

* As shown in the ADME study the dermal absorption of the betaine in the range of 2 – 6%. A worst case value of 10% is used for percutaneous absorption in each of the calculations.

Calculation of absorbed cocamidopropyl betaine:

1980 cm^2 x 0.01 cm x 0.1 (assumed skin absorption rate) x 0.4 mg/cm^3 = 0.792 mg
0. 8 mg cocamidopropyl betaine absorbed in 24 hours = 0. 8 mg/day

As the maximum task frequency is twice/day and the duration of one task is assumed to be 10 minutes, the total exposure time to hand washing solution may be 20 minutes. The total daily duration of exposure to cocamidopropyl betaine contained in hand washing solution is calculated according to:

0. 8 mg/day x 20/60 hr x 1/24 day/hr = 11 µg cocamidopropyl betaine absorbed daily within 20 minutes of use.

Assuming a body weight of 60 kg, the resulting estimated systemic dose is:

$Exp_{sys(direct\ skin\ contact)}$ = 11 µg/60 kg = 0. 18 µg/kg bw/day

Direct skin contact from pre-treatment of clothes

Direct skin contact with cocamidopropyl betaine is possible when clothing stains are being removed by spot-treatment with neat liquid. The following assumptions are made for this scenario:

Basis for calculations		**Reference**
Concentration of detergent solution	100 % - 1000 mg/ml (neat liquid)	AISE, 2002
Concentration of cocamidopropyl betaine in detergent	4 %	HERA, 2003b
Concentration of cocamidopropyl betaine in hand washing solution	40 mg/ml = 40 mg/cm^3 (1000 mg/ml x 0.04)	Calculation
Exposed skin surface (hand)	840 cm^2	EU-TGD, 2003
Thickness of liquid layer on skin after immersion	0.01 cm	EU-TGD, 2003
Percutaneous absorption (in 24 h)	10 %*	Assumption (Chapter 5.2.1.1)
Duration of task	10 min	AISE, 2002
Maximum task frequency	1/day	LAS RA, 2004
Body weight	60 kg	AISE, 2002

* As shown in the ADME study the dermal absorption of the betaine in the range of 2 – 6%. A worst case value of 10% is used for percutaneous absorption in each of the calculations.

Calculation of absorbed cocamidopropyl betaine:

840 cm^2 x 0.01 cm x 0.1 (assumed skin absorption rate) x 40 mg/cm^3 = 33.6 mg
33.6 mg cocamidopropyl betaine absorbed in 24 hours = 33.6 mg/day

The task duration is 10 minutes and the maximum frequency is once/day. The maximum daily exposure time is therefore 10 minutes. The amount of cocamidopropyl betaine within one day is calculated to:

33.6 mg/day x 10/60 hr x 1/24 day/hr = 233 µg cocamidopropyl betaine absorbed daily within 10 minutes of use.

Assuming a body weight of 60 kg, the resulting estimated systemic dose is:

$Exp_{sys(direct\ skin\ contact)}$ = 233 µg/60 kg = 3.9 µg/kg bw/day

Direct skin contact from hand dishwashing

The assumptions to determine the consumer exposure during hand dishwashing are given in the following bases for calculations. Within this scenario, the use of a regular hand dish washing and a concentrate liquid is presumed. The assumptions and results of both scenarios are indicated below.

Basis for calculations		**Reference**
Concentration of detergent solution	10 g/5 l (*regular*) = 2 mg/ml 5 g/5 l (*concentrate*) = 1 mg/ml	AISE, 2002
Concentration of cocamidopropyl betaine in detergent	10 % (regular) 11 % (concentrate)	HERA, 2003b
Concentration of cocamidopropyl betaine in hand washing solution	*Regular*: 0.2 mg/ml = 0.2 mg/cm^3 (2 mg/ml x 0.1) *Concentrate*: 0.11 mg/ml = 0.11 mg/cm^3 (1 mg/ml x 0.11)	Calculation
Exposed skin surface (hands and forearms)	1980 cm^2	EU-TGD, 2003
Thickness of liquid layer on skin after immersion	0.01 cm	EU-TGD, 2003
Percutaneous absorption (in 24 h)	10 %*	Assumption (Chapter 5.2.1.1)
Duration of task	45 min (regular and concentrate)	AISE, 2002
Maximum task frequency	21/week – max. 3/day	AISE, 2002
Body weight	60 kg	AISE, 2002

* As shown in the ADME study the dermal absorption of the betaine in the range of 2 – 6%. A worst case value of 10% is used for percutaneous absorption in each of the calculations.

Calculation of absorbed cocamidopropyl betaine:

Liquid regular:
1980 cm^2 x 0.01 cm x 0. 1 (assumed skin absorption rate) x 0.2 mg/cm^3 = 0.396 mg
0. 4 mg cocamidopropyl betaine absorbed in 24 hours = 0. 4 mg/day

Liquid concentrate:
1980 cm^2 x 0.01 cm x 0. 1 (assumed skin absorption rate) x 0.11 mg/cm^3 = 0.218 mg/day
0. 2 mg cocamidopropyl betaine absorbed in 24 hours = 0. 2 mg/day

As the maximum task frequency is three times/day and the duration of one task is assumed to be 45 minutes, the total exposure time to hand washing solution may be 135 minutes. The total daily duration of exposure to cocamidopropyl betaine contained in hand washing solution is calculated according to:

Regular: 0. 4 mg/day x 135/60 hr x 1/24 day/hr = 37.5 µg cocamidopropyl betaine absorbed daily within 135 minutes of use.
Concentrate: 0. 2 mg/day x 135/60 hr x 1/24 day/hr = 18.8 µg cocamidopropyl betaine absorbed daily within 135 minutes of use.

Assuming a body weight of 60 kg, the resulting estimated systemic dose is:

Regular
Exp$_{sys(direct\ skin\ contact)}$ = 37.5 µg/60 kg = **0. 63 µg/kg bw/day**

Concentrate
Exp$_{sys(direct\ skin\ contact)}$ = 18.8 µg/60 kg = **0. 31 µg/kg bw/day**

The potential exposure during hand dishwashing with regular hand dishwashing liquid represents the worst case compared to exposure after hand dishwashing with concentrate. For MOE calculation (see chapter 5.3.1) the value of 0.63 µg/kg bw/day is taken.

Direct skin contact from hard surface cleaning (surface cleaners)

During surface cleaning direct skin contact with cocamidopropyl betaine may occur. The following assumptions are made for the scenario of hard surface cleaning with surface cleaners, which are diluted in water prior to use:

Basis for calculations		**Reference**
Concentration of detergent solution	110 g/5 l = 22 mg/ml	AISE, 2002
Concentration of cocamidopropyl betaine in detergent	2 %	HERA, 2003b
Concentration of cocamidopropyl betaine in hand washing solution	0.44 mg/ml = 0.44 mg/cm^3 (22 mg/ml x 0.02)	Calculation
Exposed skin surface (hand and forearms)	1980 cm^2	EU-TGD, 2003
Thickness of liquid layer on skin after immersion	0.01 cm	EU-TGD, 2003
Percutaneous absorption (in 24 h)	10 %*	Assumption (Chapter 5.2.1.1)
Duration of task	20 min	AISE, 2002
Maximum task frequency	1/day	HERA, 2003a
Body weight	60 kg	AISE, 2002

* As shown in the ADME study the dermal absorption of the betaine in the range of 2 – 6%. A worst case value of 10% is used for percutaneous absorption in each of the calculations.

Calculation of absorbed cocamidopropyl betaine:

1980 cm^2 x 0.01 cm x 0.1 (assumed skin absorption rate) x 0.44 mg/cm^3 = 0.87 mg
0. 87 mg cocamidopropyl betaine absorbed in 24 hours = 0. 87 mg/day

The task duration is 20 minutes and the maximum frequency is once/day. Therefore the maximum daily exposure time is 20 minutes. The calculated amount of cocamidopropyl-betaine within one day is:

0. 87 mg/day x 20/60 hr x 1/24 day/hr = 12.1 µg cocamidopropyl betaine absorbed daily within 20 minutes of use.

Assuming a body weight of 60 kg, the resulting estimated systemic dose is:

$Exp_{sys(direct\ skin\ contact)}$ = 12.1 µg/60 kg = **0. 2 µg/kg bw/day**

Direct skin contact from hard surface cleaning (toilet cleaners)

During surface cleaning of toilets with the neat liquid direct skin contact with cocamidopropyl betaine may occur. The following assumptions are made for this scenario:

Basis for calculations		**Reference**
Concentration of detergent solution	100 % - 1000 mg/ml (neat liquid)	AISE, 2002
Concentration of cocamidopropyl betaine in detergent	30 %	HERA, 2003b
Concentration of cocamidopropyl betaine in hand washing solution	300 mg/ml = 300 mg/cm^3 (1000 mg/ml x 0.3)	Calculation
Exposed skin surface (hand and forearms)	840 cm^2	EU-TGD, 2003
Thickness of liquid layer on skin after immersion	0.01 cm	EU-TGD, 2003
Percutaneous absorption (in 24 h)	10 %*	Assumption (Chapter 5.2.1.1)
Duration of task	< 1min	AISE, 2002
Maximum task frequency	2/week ≈ 0.3/day ≈ 1/day	HERA, 2003a
Body weight	60 kg	AISE, 2002

* As shown in the ADME study the dermal absorption of the betaine in the range of 2 – 6%. A worst case value of 10% is used for percutaneous absorption in each of the calculations.

Calculation of absorbed cocamidopropyl betaine:

840 cm^2 x 0.01 cm x 0.1 (assumed skin absorption rate) x 300 mg/cm^3 = 252 mg
252 mg cocamidopropyl betaine absorbed in 24 hours = 252 mg/day

The task duration is < 1 minute and the maximum calculated frequency is about once/day. Therefore the maximum daily exposure time is 1 minute. The calculated amount of cocamidopropyl betaine within one day is:

252 mg/day x 1/60 hr x 1/24 day/hr = 175 µg cocamidopropyl betaine absorbed daily within 1 minute of use.

Assuming a body weight of 60 kg, the resulting estimated systemic dose is:

Exp$_{sys(direct\ skin\ contact)}$ = 175 µg/60 kg = **2.9 µg/kg bw/day**

Indirect skin contact from wearing clothes

Residues of components of laundry detergents may remain on textiles after washing and could come in contact with the skin via transfer from textile to skin. There are no experimental data available on cocamidopropyl betaine residues remaining on washed fabric. Assuming a worst case scenario, the exposure to cocamidopropyl betaine can be estimated according to the following algorithm recommended by the HERA Guidance document.

$\mathbf{Exp_{sys}} = [F_1 \times C' \times S_{der} \times n \times F_2 \times F_3 \times F_4] / BW$ (mg/kg bw/day)

With $C' = (M \times F' \times FD) / w'$

The following bases for calculations were used

Basis for calculations		**Reference**
F_1 – weight fraction of substance in product	Not used $F_1 = 1$	
Amount of detergent used/task	230 g	AISE, 2002
Concentration of cocamidopropyl betaine in laundry	4 %	HERA, 2003b
M – Amount of undiluted product used	9200 mg (230 g x 0.04)	Calculation
F´ - %age weight fraction of substance deposited on fabric	5 %	HERA, 2003a
W´ - Total weight of fabric	1 kg = 1000000 mg	HERA, 2003a
FD - Fabric density	10 mg/cm^2	P & G, 1996
C´ - product load in mg/cm^2 ((M x F´ x FD)/W´)	0.0046 mg/cm^2 ((9200 mg x 0.05 x 10 mg/cm^2) / 1000000 mg)	Calculation
S_{der} - Exposed skin surface (excluding hand and head)	17600 cm^2	EU-TGD, 2003
F_2 - %age weight fraction transferred from medium to skin	$F_2 = 1$ %	Vermeire et al., 1993
F_3 - %age weight fraction remaining on skin	$F_3 = 100$ %	Worst – case
F_4 – percutaneous absorption (in 24 h)	$F_4 = 10$ %*	Assumption (Chapter 5.2.1.1)
n - Maximum product frequency	Not used – n = 1	
BW - Body weight	60 kg	AISE, 2002

* As shown in the ADME study the dermal absorption of the betaine in the range of 2 – 6%. A worst case value of 10% is used for percutaneous absorption in each of the calculations.

Using the given equation the following calculation for the estimated daily exposure is given:

[0.0046 mg/cm^2 x 17600 cm^2 x 0.01 x 0. 1] / 60 kg =

1.349 x 10^{-3} mg/kg bw/day

$\mathbf{Exp_{sys\ (indirect\ skin\ contact)}}$ = 1.3 µg/kg bw/day

Inhalation of aerosols from cleaning sprays

Cocamidopropyl betaine is present in surface cleaning sprays in maximum concentrations of 2 %. Inhalation exposure may occur during application of the sprays. Assuming a worst case scenario, the exposure to cocamidopropyl betaine from aerosols can be estimated according to the following algorithm recommended by the HERA Guidance Document.

$$\mathbf{Exp_{sys}} = [F_1 \times C' \times Q_{inh} \times T \times n \times F_7 \times F_8] / BW \text{ (mg/kg bw)}$$

The following bases for calculations were used:

Basis for calculations		**Reference**
F_1 – weight fraction of substance in product	F_1 = 2 %	HERA, 2003b
C´ - product concentration in air mg/m^3	0.35 mg/m^3	P & G, 2001
Q_{inh} – ventilation rate of user m^3/hr	0.8 m^3/h	EU-TGD, 2003
T - Duration of exposure	10 min = 0.17 h	AISE, 2002
n - Frequency of use	Once/day	AISE, 2002
F_7 - %age weight fraction respirable	100 %	AISE, 2002; worst case
F_8 - %age weight fraction biooavailable	75 %	EU-TGD, 2003
BW - Body weight	60 kg	HERA, 2003a

Using the given equation, the value for daily systemic exposure after inhalation of aerosols is:

$$[0.02 \times 0.35 \text{ mg/m}^3 \times 0.8 \text{ m}^3\text{/h} \times 0.17 \text{ h} \times 1 \times 0.75] / 60 \text{ kg} = 0.12 \times 10^{-4} \text{ mg/kg bw/day}$$

$$\mathbf{Exp_{sys\ (inhalation\ of\ aerosols)} = 0.01\ \mu g/kg\ bw/day}$$

Oral exposures to cocamidopropyl betaine

Oral exposure to cocamidopropyl betaine may occur during consumption of cocamidopropyl betaine containing drinking water or food and from residues from cutlery and dishware washed in hand dishwashing detergents.

Direct oral exposure via drinking water

For the oral intake from drinking water, a EUSES (FH-ITEM, 2004) calculation for cocamidopropyl betaine, presented, derives an estimated maximum concentration of cocamidopropyl betaine in surface water as to be 17.5 µg/l (regional PEC_{water} according to EUSES calculation, no measured data available).

Basis for calculations		**Reference**
Regional PEC_{water}	17.5 µg/l	EUSES calculation
Water consumption	2 l/day	EC, 2003
Body weight	60 kg	HERA, 2003a
Bioavailability	100 %	Worst case

With these assumptions the daily human exposure to cocamidopropyl betaine can be estimated as:

$$\mathbf{Exp_{(drinking\ water)}} = [17.5\ \mu g/l) \times 2\ l] / 60\ kg = \mathbf{0.58\ \mu g/kg\ bw/day}$$

Regarding potential indirect intake of cocamidopropyl betaine from agricultural food products grown in soils containing cocamidopropyl betaine residues or along the food chain (fish), the Environmental Risk Assessment for cocamidopropyl betaine, which will be presented on the HERA-homepage (www.heraproject.com) demonstrates that cocamidopropyl betaine has a calculated BCF value of 71.

Substances with BCF values below 1000 or molecular masses higher than 700 are unlikely to contribute to indirect dietary exposure, and will not be considered in terms of indirect exposure via fish (ECETOC, 1996).

Indirect oral exposure via dishwashing residues

With the following equation, given in the HERA Guidance Document, the indirect oral exposure via dishwashing residues may be estimated. Within this scenario, both the use of a regular hand dish washing and a concentrate liquid is presumed.

$$\mathbf{Exp_{sys}} = [F_1 \times C' \times Ta' \times Sa] / BW \text{ (mg/kg bw)}$$

The following bases for calculations were used:

Basis for calculations		**Reference**
F_1 – weight fraction of substance in product	F_1 = 10 % (*regular*) F_1 = 11 % (*concentrate*)	HERA, 2003b
C´ - product concentration in air mg/cm^3	*Regular*: 10000 mg/5000 cm^3 = 2 mg/cm^3 *Concentrate*: 5000 mg/5000 cm^3 = 1 mg/cm^3	AISE, 2002
Amount of water left on non-rinsed dinnerware	5.5 x 10^{-4} ml/cm^2 (cm^3/cm^2)	Schmitz, 1973, J.Off.Rep.Fr., 1990
Percent of liquor left after rinsing	10 %	Schmitz, 1973
Ta´ - amount of water on dishes after rinsing ml/cm^2	5.5 x 10^{-5} ml/cm^2 (cm^3/cm^2) (5.5 x 10^{-4} ml/cm^2 x 0.1)	Calculation
Sa – area of dishes in daily contact with food cm^2	5400 cm^2	J.Off.Rep.Fr., 1990
BW - Body weight	60 kg	HERA, 2003a

Using the given equation, the value for daily systemic exposure oral intake of dish residues:

Regular

0.10 x 2 mg/cm^3 x 5.5 x 10^{-5} cm^3/cm^2 x 5400 cm^2/ 60 kg = 9.9 x 10^{-4} mg/kg bw/day

$Exp_{sys\ (oral\ dish\ deposition)}$ = 0.99 µg/kg bw/day

Concentrate

0.11 x 1 mg/cm^3 x 5.5 x 10^{-5} cm^3/cm^2 x 5400 cm^2/ 60 kg = 5.4 x 10^{-4} mg/kg bw/day

$Exp_{sys\ (oral\ dish\ deposition)}$ = 0.54 µg/kg bw/day

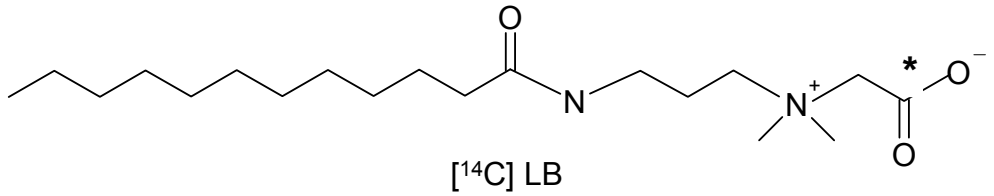
The potential exposure via dishwashing residues with regular hand dishwashing liquid represents the worst case compared to exposure via dishwashing residues with concentrate. For MOE calculation (see chapter 5.3.1) the value of 0.99 µg/kg bw/day is taken.

5.2 Hazard assessment

5.2.1 Summary of available toxicological data

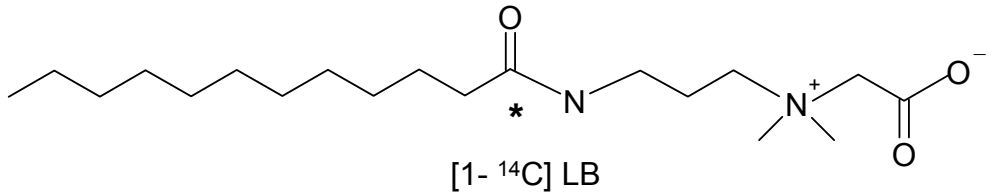
5.2.1.1 Toxicokinetics

One study on the fate of Cocamidopropyl betaine (ADME – Absorption, Distribution, Metabolism, Excretion) in the rat is available (Unilever Research, 1992). Lauramidopropyl betaine (C_{12}-fatty acid of coconut fatty acids LB) - as a model compound for cocamidopropyl betaine – is either ^{14}C-labelled at the carboxymethyl ammonium ([^{14}C]LB – see figure 1) or in the lauryl moiety ([1-^{14}C]LB – see figure 2). The aqueous solutions of the test materials were administered to male and female Wistar rats by gavage or topically and the fate of the ^{14}C labelled test substance was followed for up to 48 hours after dosing. Whole body autoradiography was used to study the tissue distribution of the ^{14}C. Metabolites in the excreta were analyzed by thin layer chromatography (TLC). The levels of ^{14}C excreted were used to estimate intestinal and skin absorption. The relevant results of the ADME – study are summarised in table 5.



[^{14}C] LB

Figure 1: [^{14}C]LB



[1- ^{14}C] LB

Figure 2: [1-^{14}C]LB

Table 5: Results of the ADME (Absorption, Distribution, Metabolism, Excretion) study

Test Substance Dosage	**Protocol**	**Excretion**	**Absorption**
[^{14}C]LB 30 mg/kg bw gavage	5 m, 5 f for excretion TLC* examination of the faecal ^{14}C Sacrifice of animals: after 2, 4, 8, 24, 48 (2 rats at each time point for whole body autoradiography)	24 hours: Faeces: 75% (f), 96% (m) Urine: 4.1% (f), 6.5 % (m) Expired air: 0.75 – 0.77% (m and f) After 48 hours: Faeces: 118% (f) no data (m) Urine: 5.5% (m and f) Expired air: 0.8% (m and f) Metabolites in faeces: only unchanged [^{14}C]LB	< 10% from intestinal tract
[^{14}C]LB 30 mg/kg bw gavage	3 m,3 f for excretion, TLC* examination of the urinary ^{14}C Sacrifice of animals: after 48 h	After 48 h: Faeces: 86-92 % Urine: 2-4 % Expired air: 1-1.4% Carcass: 0.8 – 1.4% No sex differences Metabolites in urine: one more polar metabolite than [^{14}C]LB	< 10% from intestinal tract
[^{14}C]LB 20 mg/kg bw topical, occluded	6 m, 6 f Sacrifice of animals after 48 h	After 48 h Faeces: 0.2 – 0.8% (f > m) Urine: 1.3 – 2.7% (f > m) Expired air: 0.2 – 0.3% Carcass: 0.3 – 2.3% (f > m)	Appr. 6% (f), 2% (m)
[^{14}C]LB 20 mg/kg bw topical, unoccluded	3 m, 3 f Rinsed after 10 minutes	After 48 h Faeces: 0.005 – 0.02% Urine: 0.02 – 0.06% Expired air: 0.0 – 0.02% Carcass: 0.04 – 0.07%	< 0.2% (f and m)
[1-^{14}C]LB 10 mg/kg bw gavage	3 m, 3 f Sacrifice of animals after 48 h TLC* examination of the urinary and faecal ^{14}C	After 24 h: Faeces: 80% Urine: < 5% After 48 h: Faeces: 79-90% Urine: 3.7- 4.9 % Expired air: 1-1.9% Carcass: 1.0-1.8% No sex differences Metabolites in faeces: unchanged [1-^{14}C]LB Metabolites in urine: mainly one polar metabolite, traces of unchanged [1-^{14}C]LB	< 10% from intestinal tract
[1-^{14}C]LB 10 mg/kg bw topical, occluded	3 m, 3 f Sacrifice of animals after 48 h	After 48 h: Faeces: 0.4 - 0.5% Urine: 1.0 - 1.5% Expired air: 0.3 - 0.6% Carcass: 0.4 - 1.7%	3.5%

* TLC - thin layer chromatography

Lauramidopropyl betaine (LB) is poorly absorbed from the intestinal tract following administration in water at 30 mg/kg or 10 mg/kg bw, respectively. Within 48 hours, approximately 5% of the ^{14}C dose was excreted in urine and < 2 % in expired air. 1% remained in the carcass. The remainder was excreted in the faeces as unchanged parent material (as was confirmed by TLC analysis in the case of labelling at the carboxymethylammonium moiety). Whole body autoradiography confirmed that absorption from the gut was low and that the tissues showing detectable levels of ^{14}C were those

predominantly associated with urinary excretion (liver, kidney cortex, urinary bladder). The urine contained traces of parent and an unidentified polar metabolite. Although metabolism of absorbed is extensive, the lauryl moiety is not extensively removed from the rest of the molecule judging by the relatively low amounts of $^{14}CO_2$ produced. There was no sex difference in the overall fate of LB following oral gavage.

Dermal application (approximately 0.3mg/cm^2 of [^{14}C]LB or 0.15mg/cm^2 of [1-^{14}C]LB) in water followed by occlusion gave similar results. After 48 hours, approximately 3.5-6% (females) and 2-3.5% (males) was absorbed. Urine was the major route of excretion for absorbed material with expired air and faeces being relatively minor routes. A further experiment with 10 minutes exposure of [^{14}C]LB followed by rinsing and then a 48 hour occlusion resulted in less than 0.2% absorption. TLC separations were not carried out for on urine from topically treated rats.
As a default value 10% absorption after dermal exposure is used as a worst case default value in the exposure estimation parts of this document (see chapter 5.1.3).

Conclusion

Lauramidopropyl betaine (50% component in cocamidopropyl betaine - as a model for cocamidopropyl betaine) is poorly absorbed from the intestinal tract and through the skin. Rinsing the skin after 10 minutes of contact reduces the absorption even further. Following oral or dermal exposure, there is metabolism of the absorbed material, as indicated by the appearance of a more polar compound in the urine and by the liberation of $^{14}CO_2$.

5.2.1.2 Acute toxicity

The acute toxicity of cocamidopropyl betaine after oral and dermal administration was investigated in rats.

Studies in Animals

Dermal

One acute dermal toxicity study with CD rats (OECD guideline 402) with cocamidopropyl betaine (31 % active content) is available (Kao Corporation, 1987a). 10 male and female rats were administered 1.92 ml cocamidopropyl betaine/kg bw (corresponding to 2000 mg/kg bw 31 % active substance) for 24 h under occlusive conditions. 10 % of the total body surface was covered. No deaths occurred during 14 days post-dose observation period. The only findings were slightly lower body weights in 3/5 females. The acute dermal toxicity (LD_{50}) is > 2000 mg/kg bw for the 31 % active substance.

Oral

Several acute oral toxicity studies in rats (Wistar, Sprague-Dawley, CD) are available (Th. Goldschmidt AG, 1977, Kao Corporation, 1987b, Stepan Chemicals Co. 1982a, b, Wallace, 1977). The results of the studies are summarized in table 6.

In each of the studies cocamidopropyl betaine was administered undiluted (circa 30 % active solution) via gavage. The post-dose observation period was 2 weeks in each of the investigations. Slightly decreased body weights were seen in one study in 4/10 males and 3/10 females after application of 5000 mg cocamidopropyl betaine/kg bw, which returned to

normal at day 15. No deaths occurred (Kao Corporation, 1987b). Observed clinical signs were: diarrhea, nasal hemorrhage, salivation, decreased motor activity, coordination disturbance and abnormal body posture (Th. Goldschmidt AG, 1977, Kao Corporation, 1987b, Stepan Chemicals Co. 1982a, b, Wallace, 1977). The only necropsy findings recorded were: redness of intestinal mucous membranes and blood-like viscous liquid in the intestines, stomach and gastrointestinal tract (Th. Goldschmidt AG, 1977, Stepan Chemicals Co. 1982a, b).

The LD_{50} in rats is ≥ 4900 mg/kg bw.

Table 6: Acute oral toxicity studies with cocamidopropyl betaine

Test substance	**Animals No./Sex Doses**	**LD_{50} (mg/kg bw)**	**Time of deaths Clinical Signs Necropsy findings of descedents**	**Reference**
30 %, pH: 5.5	Wistar rat 5 m, 5 f 5, 6.30, 7.94, 10 ml/kg bw	7900	Day 1 ≥ 5 ml/kg bw: Decreased motor activity, coordination disturbance, abnormal body posture, piloerection, diarrhea, decreased body temperature, (effects were observed 20 min after application, reversible after 24 h), Redness of stomach and intestinal mucus	Th. Goldschmidt, 1977
35.5 %	Sprague-Dawley rats 5 m, 5 f 5000 mg/kg bw	> 5000	Day 3 Decreased motor activity, diarrhea, soft stools Blood-like mucus in the intestines	Stepan Chemicals Co., 1982a
30.6 %	Sprague-Dawley rats 5 m, 5 f 5000 mg/kg bw	Ca. 5000	Days 1 – 3 Decreased motor activity, diarrhoea, salivation, ataxia, soft stools Blood-like mucus in the intestines, stomach, gastrointestinal tract	Stepan Chemicals Co., 1982b
31 %	CD rats 5 m, 5 f 5000 mg/kg bw	> 5000	No deaths Decreased body weights, abnormal body carriage, salivation, diarrhea (complete recovery by day 4)	Kao Corporation, 1987b
30 %	Wistar rats 5 m, 5 f 4000, 5000, 6300, 8000, 16000 mg/kg bw	4900	Days 1-14 ≥ 2000 mg/kg bw: Sluggishness, diarrhea, nasal hemorrhage, wetness around posterior (increased in severity with dose)	Wallace, 1977

Studies in Humans

No human studies are available.

Conclusion

The acute oral and dermal toxicity of cocamidopropyl betaine 30 – 35.5 % active solution in rats is low. The LD_{50} (dermal) is > 2000 mg/kg bw (which was the highest dose applied),

LD_{50} (oral) is ≥ 4900 mg/kg bw. There were no clinical signs reported after acute dermal exposure; after oral exposure to high doses, decreased motor activity, diarrhea, and ataxia as well as signs of gastrointestinal irritation were found.

5.2.1.3 Corrosiveness/Irritation

Several guideline and guideline-comparable studies are available relating to skin and eye irritation in rabbits. There are also studies available investigating the skin irritating properties in humans. No data were found regarding respiratory tract irritation.

Skin Irritation

Studies in Animals

The results of the different studies are shown in table 7. Cocamidopropyl betaine (about 80%) active, obtained as a whitish powder, after spray-drying) showed no signs of erythema or edema in any rabbit at any observation time in an OECD-guideline 404 study, when applied semiocclusively for 4 hours as a moistened paste (Th. Goldschmidt AG, 1991a). In a further study following the OECD 404 guideline, 30 % active cocamidopropyl betaine showed minimal irritation after 4 hours semiocclusive exposure (Th. Goldschmidt AG, 1990a). Two skin irritation tests with 30 and 25 % active cocamidopropyl betaine showed irritating properties after 4 hours (Henkel KGaA, 1986a, Henkel KGaA, 1987a). However, they deviated from the current guideline by using the more stringent occlusive exposure condition.

For almost all other studies a different test protocol was applied, where the irritant properties were tested on intact and abraded skin of rabbits for 24 h under occlusive conditions according to Draize (details see table 7). 14 and 15 % active cocamidopropyl solutions in water showed highly irritating or – according to varying classification schemes - corrosive properties (Goldschmidt Chemical Corporation, 1993a, US-EPA, 1991) after 24 hours occlusive application. About 10 % active cocamidopropyl betaine was mildly irritating after 24 hours occlusive exposure (Stepan Chemicals Corporation, 1982c, d).

Table 7: Skin irritation studies with cocamidopropyl betaine

Test substance	Applied concentration of active substance	Test protocol	Occlusion	Primary dermal irritation index	Result of the study authors	Reference
Spray dried, nearly 80 % active, moistened with water	80 %	OECD 404 , **4 h**, rinsed	Semiocclusive	0.0	Not irritating	Th. Goldschmidt AG, 1991a
30 % active	30 %	OECD 404, **4 h**, not wiped	Semiocclusive	1.28	Not irritating	Th. Goldschmidt AG, 1990a
30 % active	30 %	**4 h**	Occlusive	3.0	Moderately irritating	Henkel KGaA 1986a
25 % active	25 %	OECD 404 **4 h**	Occlusive	4.47	Moderately irritating	Henkel KGaA, 1987a
29.6 % active	50.7 % dilution = **15 %**	**24** h, wiped	Occlusive	4.54	Corrosive (not based on scoring, but on eschar formation in 3/6 animals)*	US-EPA, 1991
38 % active	36 % dilution = **14 %**	**24 h**, wiped	Occlusive	5.4	Highly irritating	Goldschmidt Chemical Corporation, 1993a
10 %	10 %	**24 h**, wiped	Occlusive	1.88	Mildly irritating	Stepan Chemicals Corporation, 1982c
10 %	10 %	**24 h**, wiped	Occlusive	1.75	Mildly irritating	Stepan Chemicals Corporation, 1982d

*according to Federal Hazardous substances Act. CFR 16 Section 1500.3 (eschar formation in 3 rabbits at 72 hours reading)

Studies in Humans

Human patch tests show, that impurities – most likely amidoamine - are responsible for the irritating properties of cocamidopropyl betaine. Tests have been carried out with different batches and concentrations (0.15 to 3 % w/v) of cocamidopropyl betaine for 2 days under occlusive conditions in 39 – 67 patients. Additionally, several non-invasive investigations - transepidermal water loss, cutaneous blood flow and critical micelle concentration - were performed. For all batches slight irritating reactions were recorded after patch testing (score 0.21 -0.79 of maximum 4 scores, score 1 indicates erythema). Cocamidopropyl betaine with the highest amidoamine concentrations showed the highest mean irritation score. The results of the non-invasive investigations confirmed this result (Vilaplana et al., 1992). In this investigation the irritant potency did not increase at higher concentration of the cocamidopropyl betaine. Further human investigations on the potency of the impurities present in cocamidopropyl betaine are summarised in chapter 5.2.1.4 (sensitisation).

Weak irritating effects (slight erythema) have been observed also in patch tests for investigation of sensitizing properties. Occlusive exposure for two days to 1 % dilutions of cocamidopropyl betaine caused erythema in 15 of 1200 patients analyzed (Angelini et al., 1995).

Results of studies with cocamidopropyl betaine containing formulations

In an in vitro predicting irritation assay with red blood cells, the influence of the addition of cocamidopropyl betaine to a sodium lauryl sulphate formulation was studied. A formulation of 8.4 % sodium lauryl sulphate, 1.6 % ethoxylated sulfosuccinate, and 3 % nonionics in water was only moderately irritating in the presence of 3.5 % cocamidopropyl betaine, but was irritating without addition of betaine (Domsch et al, 1996). In a further in vitro assay, the addition of certain amounts of cocamidopropyl betaine to sodium lauryl sulphate inhibited the adsorption of sodium lauryl sulphate to horny human skin (Garcia Dominguez et al., 1981). The induction of swelling of isolated human stratum corneum was studied with sodium lauryl sulphate and with combinations of cocamidopropyl betaine and sodium lauryl sulphate (SLS). Addition of 1 % and 0.5 % cocamidopropyl betaine to a 1 % SLS solution caused a significant reduction in swelling compared to 1 % SLS treatment alone (Rhein et al., 1986).

In a comparative study with 12 human volunteers the irritating potential of sodium lauryl sulphate (SLS) was compared with the irritation reactions of combinations of SLS with amphoteric substances – among them cocamidopropyl betaine using occlusive patch tests. The exposure time was 4 hours. A combination of 20 % SLS and 10 % cocamidopropyl betaine showed decreased erythema formation 1 and 24 hours after patch removal compared to the results with SLS alone. Pure cocamidopropyl betaine was not tested. The irritation was completely reversible after 48 hours (Dillarstone et al., 1993).

Eye Irritation

Studies in Animals

One OECD guideline 405 study and several Draize tests with and without reversibility testing are available. The details of the investigations are summarized in tables 8.

In the guideline study (OECD 405) the 80 % active spray dried substance was tested (Th. Goldschmidt AG, 1991b). The substance was irreversibly irritating. All other studies were performed according to the same protocol with slight variations: concentration of cocamidopropyl betaine used, reversibility testing and classification system (for details see tables 7 and 8). 30 % and 25 % cocamidopropyl betaine is an irreversibly irritating, or highly irritating substance (Th. Goldschmidt AG, 1990b, Th. Goldschmidt AG, 1991b, US-EPA, 1993, Henkel KGaA, 1987b). 14 – 15 % solutions of cocamidopropyl betaine were highly irritating (Goldschmidt Chemical Corporation, 1993b, 1993c) and the results for the ≤ 10 % active compound varies between mildly and moderately eye irritating, reversible after 14 days (Stepan Chemicals Corporation 1982e, 1982f, Goldschmidt Chemical Corporation, 1994, Henkel KGaA, 1986b, 1986c).

Rinsing of the eyes after 30 seconds had no influence on the irritation effect but on the reversibility of the effects observed (US-EPA, 1991).

Table 8: Eye irritation studies with cocamidopropyl betaine (14 – 30 % active)

Test substance	Applied concentration of active substance	Test protocol	Scoring result Scoring system (Draize overall irritation score, if not otherwise indicated)	Result of the study authors	Reference
Spray dried, nearly 80 % active	**80 %**	OECD 405 Reversibility assessed (21 days)	24h/48h/72h Cornea: 0/0/0 Iris: 1/1/1 Conjunctivae (Redness): 2.7/2.0/2.7 Conjunctivae (Chemosis): 3.0/2.7/3.0	Irritating Not reversible	Th. Goldschmidt AG, 1991b
30 % active	**30 %**	OECD 405 Not rinsed Reversibility assessed (7 days)	24h/48h/72h 52.0/48.0/42.8	Highly irritating Not reversible	Th. Goldschmidt AG, 1990b
29.02 % active pH: 7.1	**29 %**	Not rinsed Reversibility assessed (21 days)	24h/48h/72h 37.0/34.3/33.7	Irritating Not reversible	US-EPA, 1993
25 % active	**25 %**	Not rinsed Reversibility assessed (21 days)	24h/48h/72h 28.25/26.75/26.25	Highly irritating Not reversible	Henkel KGaA, 1987b
30 % active	50 % dilution = **15 %**	Not rinsed Reversibility not assessed	24h/48h/72h 38.2/27.7/24.3	Highly irritating*	Goldschmidt Chemical Corporation, 1993b
38 % active	36 % dilution = **14 %**	Not rinsed Reversibility not assessed	24h/48h/72h 32.0/26.7/14.8	Highly irritating*	Goldschmidt Chemical Corporation, 1993c
29.6 % active	**15 %**	Rinsed (after 30 s) and not rinsed Reversibility assessed (21 days)	Rinsed 24h/48h/72h 16.7/31.3/27.3 Not rinsed 24h/48h/72h 18.8/18.3/14.5	Irritating (no effect of rinsing) Not reversible in unrinsed eyes only	US-EPA, 1991
10 %	**10 %**	Not rinsed Reversibility assessed (7 days)	24h/48h/72h 14.8/3.5/0	Mildly irritating Reversible	Stepan Chemicals Corporation, 1982e
10 %	**10 %**	Not rinsed Reversibility assessed (7 days)	24h/48h/72h 27.5/20.3/12	Moderately irritating Reversible	Stepan Chemicals Corporation, 1982f
5 % active	**5 %**	Not rinsed Reversibility assessed (10 days)	24h/48h/72h 39.5/14.7/5	Moderately irritating Reversible	Henkel KGaA, 1986b
30 % active	**3 %**	Not rinsed Reversibility not assessed	24h/48h/72h 12.7/8.3/5.5	Mildly irritating*	Goldschmidt Chemical Corporation, 1994
2 % active	**2 %**	Not rinsed Reversibility assessed (22 days)	24h/48h/72h 26.55/19.3/11.25	Moderately irritating Not reversible in one animal	Henkel KGaA, 1986c

* According to Kay and Calandra, 1962, the results of the studies have to be assigned to the next higher level (moderately irritating to highly irritating), if the following boundary conditions are fulfilled: more than 40 % of the rabbits have scores > 10 or one rabbit has a score > 30.

Conclusion

Skin irritation: According to current OECD guideline, cocamidopropyl betaine (about 30% aqueous solution and nearly 80% spray-dried substance) is not a skin irritant. In human studies up to 3 % solutions were weakly irritating. Impurities like amidoamine may contribute to the irritation reaction. The irritating properties of sodium lauryl sulphate formulations could be significantly reduced by the addition of cocamidopropyl betaine.

Eye irritation: The concentrated and the 25 - 30 % active cocamidopropyl betaine is an irreversible eye irritant. The 15 % concentrations were irritating to highly irritating. At and below 10% active dilution studies show a mild to moderate and reversible eye irritating potential of cocamidopropyl betaine.

5.2.1.4 Sensitization

Studies in Animals

Skin

Two Guinea pig maximization tests (GPMT) performed according to Magnusson and Kligman, one Draize and one modified Draize test are available. A mouse LLNA has also been performed on the impurity DMAPA. Table 9 gives an overview of the results in animal sensitization tests.

Table 9: Results of animal studies on skin sensitization with cocamidopropyl betaine (CAPB) and 3-dimethylaminopropylamine (DMAPA)

Test substance	**Species No. of animals**	**Protocol**	**Result**	**Reference**
CAPB Not further specified	guinea pig at least 10	GPMT (Magnusson and Kligman) Induction: 0.5 % injection, 10 % patch Challenge: 3 % patch	**not sensitizing** (0 % positive reactions)	Arimura et al., 1998
CAPB 30 % active substance	guinea pig 20	GPMT (Magnusson and Kligman) Induction: 0.1 % injection, 10 % patch Challenge: 10 % patch **No Rechallenge performed**	**sensitizing** (2/20 positive, 4/20 ambiguous, 14/20 negative)	Rantuccio et al., 1983
CAPB 30 % active substance	Guinea pig 20	Draize Induction: 5 % injection Challenge: 5 % patch	**not sensitizing** (0/20 positive reactions)	Henkel KgaA, 1976
CAPB 30 % active substance	guinea pig 20	modified Draize Induction: 0.5 % injection Challenge: 0.05 % injection	**not sensitizing** (0/20 positive reactions)	Rantuccio et al., 1983
DMAPA	Mouse	LLNA	**moderately sensitizing**	Wright et al., 2001 Basketter et al., 1999

One GPMT test, the Draize and the modified Draize test with cocamidopropyl betaine showed no sensitizing effects (Arimura et al., 1998, Rantuccio et al., 1983). One GPMT test was weakly positive. However, only 2/20 guinea pigs were scored positive and no rechallenge was performed in this test to prove the result (Rantuccio et al., 1983). A mouse LLNA confirmed

that DMAPA, an impurity in cocamidopropyl betaine, is a moderate sensitiser (Wright et al., 2001, Basketter et al., 1999).

Studies in Humans

Skin

Results of human volunteer studies with commercially available cocamidopropyl betaine

In 3 studies with human volunteers, the sensitizing potential of commercially available cocamidopropyl betaine in various concentrations was tested. No evidence of sensitization was seen. Slight reactions seen in one study were – according to the authors – attributed to irritative properties. However, in view of the fact that no effects have been seen in two other studies, where higher cocamidopropyl betaine -concentrations have been applied, this can rather be attributed to possible impurities in the product. Details of the studies are summarized in table 10.

Table 10: Results of studies with human volunteers with cocamidopropyl betaine

Concentration	Number of volunteers	Test procedure	Result	Reference
0.9 %	93	Induction: 10 min, 3 times/week, 3 weeks Challenge: after 18 days, Application time: 6 h treatment Scoring after Induction (48 h) and Challenge (24, 48, 72 h) Scoring after Induction and Challenge (48, 96 h)	Slight reactions, attributed to irritative properties	CTFA, Feb 1 1984 in CIR
10 %	100	See above	Negative	CTFA, Jan 31, 1984 in CIR
1.5 or 3.0 %	141	Induction: Application time: 24 h, 3 times/week, 3 weeks Challenge: after 10 - 15 days, Application time: 24 h Scoring after Induction and Challenge (24, 72 h)	Negative	CTFA, 1988 in CIR

Results of case reports and surveys with commercially available cocamidopropyl betaine

Several surveys and epidemiologic human sensitization studies are available. Overall, patch tests with cocamidopropyl betaine have been performed on a large number of individuals with occupational exposure, suspected cosmetic contact dermatitis or unspecified eczema. Table 11 summarizes the results. Among the hairdressers the percentage of positive results to cocamidopropyl betaine ranged from 0.5 to 5 %. The range of positive results to cocamidopropyl betaine among people with suspected cosmetic contact dermatitis or unspecified eczema was 0.3 to 3.8 % in the years 1986 – 1998. In view of the wide use of cocamidopropyl betaine in shampoos, conditioners, soaps etc. the observed cases of allergic reactions are very rare (Jackson, 2001).

Table 11: Results of patch tests with commercially available cocamidopropyl betaine (the majority contain impurities like amidoamine or dimethylaminopropylamine) in humans with dermatitis or allergy

Concen-tration	Time frame	Number of patients	History of allergy	% positive	Reference
1 %	1991 - 1998	184	**Hairdressers** (108 with hand dermatitis)	0.5	Armstrong et al., 1999
1 %	1988 – 1989	178	**Hairdressers** (occupational dermatitis)	5	Frosch, 1990
1 %	1989 – 1992	103	**Hairdressers** (hand dermatitis)	3.9	Van der Walle et al., 1994
1 %	1991 – 1994	781	suspected occupational dermatitis (217 were **hairdressers**)	2.2	De Groot et al., 1995
0.1 and 1 %	1986 – 1987	119	**Cosmetic** contact dermatitis	2.5	De Groot et al., 1988
1 %	1992 - 1993	210	**Cosmetic** allergy and dermatitis	3.3	Fowler et al., 1993
1 %	1994	102	**Cosmetic** dermatitis	2.9	De Groot et al., 1995
1 %	1985 - 1990	462	**Cosmetic** contact allergy	1.3	Goossens et al., 1997
1 %	1991 - 1996	486	**Cosmetic** contact allergy	3.1	Goossens et al., 1997
1 %	1992– 1993	285	Dermatitis	2.8	Foti et al., 1995
1 %	1993 - 1994	1190	Unselected eczema	1.4	Pigatto et al., 1995
1 %	1994	1200	Dermatitis of various types	3.8	Angelini et al., 1995
1 %	1991 – 1998	10798	Suspected contact dermatitis	0.3	Armstrong et al., 1999
1 %	1991 - 1998	2504	Eczema at neck, face or scalp	0.4	Armstrong et al., 1999
1%	2001	975	Contact dermatitis	3.3	Fowler, 2004 Fowler et al., 2004
1 %	2001 - 2002	4887	Suspected allergic contact dermatitic	2.8*	Pratt et al., 2004

* 0.3% were classified as definitely relevant (subjects with positive use test or positive after patch-testing with cocamidopropyl betaine -containing product)

Furthermore, several case reports have been published, demonstrating the potential sensitizing effect of cocamidopropyl betaine present as a surfactant in various cosmetic products (shampoos, contact lens solution, shower gels, body lotions) (Andersen et al., 1984, Cameli et al., 1991, Su et al., 1998, Korting et al., 1992, Van Haute et al., 1983, Taniguchi et al., 1992, Mowad, 2001, Ross et al., 1991, Bonneau et al., 1990). These case reports are not described in detail in this document.

Role of impurities – present in cocamidopropyl betaine

The low frequency of contact allergy associated with cocamidopropyl betaine is accompanied by an in depth understanding of its likely basis, and many investigations demonstrate the role

of impurities. The synthesis of cocamidopropyl betaine involves reaction of fatty acids derived from coconut oil with 3-dimethylaminopropylamine (DMAPA). In the second step, the resulting amidoamine (AA) is then reacted with sodium chloroacetate under alkaline conditions to give cocamidopropyl betaine. Both DMAPA and AA have been identified as sensitising impurities in commercially available cocamidopropyl betaine. Both can elicit skin reactions in cocamidopropyl betaine -allergic individuals (Angelini et al., 1995; Fowler et al., 1997; McFadden et al., 2001). The dominance of either impurity in terms of their ability to elicit allergic skin reactions varies geographically (Fowler, 2004). A simultaneous positive reaction to DMAPA and AA could be due to cross-reactivity. At the skin level, AA – an amphiphilic substance with an affinity for keratin – undergoes enzymatic hydrolysis of the amide bond, releasing DMAPA (Foti et al., 2003; Moreau et al., 2004).

The relevant studies – demonstrating, that impurities DMAPA and AA in commercial cocamidopropyl betaine are critically involved in causing skin sensitization - are detailed in table 12 (Pigatto et al., 1995, Angelini et al., 1995, McFadden et al., 2001, Hunter et al., 1998, Fowler et al., 1997, Foti et al., 2003).

Table 12: Studies with persons with confirmed contact allergy to commercial CAPB

Chemical	Time frame	Number of patients	History of allergy	% positive	Reference
1% CAPB (pure) 1% DMAPA 0.5% AA 0.25% AA 0.1% AA	No data	10	Confirmed contact allergy to commercial CAPB	0/10 10/10 10/10 10/10 4/10	Foti et al., 2003
1% CAPB (impure) 1% CAPB (pure) 1%, 0.1% DMAPA 0.05 % DMAPA	1993 – 1994	15	Confirmed contact allergy to commercial CAPB	15/15 1/15 10/12 9/13	Pigatto et al., 1995
1% CAPB (impure) 1% CAPB (purer grade) 0.5% CAPB (purer grade) 1% DMAPA 0.05%AA 0.1% monochloracetic acid	1994	30	Confirmed contact allergy to commercial CAPB	30/30 16/30 3/30 30/30 0/30 0/30	Angelini et al., 1995
1% CAPB (purified)* DMAPA, 1%	2001	6	Confirmed contact allergy to commercial CAPB (contained AA < 3%)	0/6 1/6	McFadden et al., 2001
1% CAPB (impure) 0.1% AA 0.1% DMAPA	No data	9	Confirmed contact allergy to commercial CAPB	1/9-3/9** 6/9 0/9	Fowler et al., 1997
1% CAPB (impure) 1% CAPB (AA-free)	No data	7	Confirmed contact allergy to commercial CAPB	3/7 0/7	Fowler et al., 1997

* contained <0.3% AA and <0.001% DMAPA
** depending on the purity grade of CAPB (0.3 – 3% AA, 0.0003% DMAPA)

The results of the studies shown in tables 11 and 12 likely reflect variation in the levels of each impurity present in cocamidopropyl betaine sourced from different manufacturers, and highlights the importance of controlling the specification of the material. The importance of cocamidopropyl betaine specification is further underscored by the observation that cocamidopropyl betaine purified to apparent homogeneity by thin layer chromatography no

longer possesses the ability to elicit skin reactions in individuals with positive reactions to commercial cocamidopropyl betaine (Angelini et al., 1996, Foti et al., 2003).

Photosensitization

There is no structural element in cocamidopropyl betaine present, which could lead to UV absorption.

Conclusion

Based upon the low frequency of positive diagnostic patch test reactions to cocamidopropyl betaine and the outcome of predictive animal tests, the sensitizing potential of cocamidopropyl betaine is considered low, especially given its widespread distribution in cosmetic and detergent products. Furthermore, the extensive body of data documenting the ability of impurities in cocamidopropyl betaine to cause skin sensitisation demonstrates that the risk of contact allergy can be minimised by strictly controlling the levels of AA and DMAPA in cocamidopropyl betaine. This can be achieved practically by using a higher grade of the material.

There is no evidence for a photosensitizing potential of cocamidopropyl betaine.

5.2.1.5 Repeated Dose Toxicity

One subacute and one subchronic toxicity study – performed according to OECD guideline 407 and 408 respectively – with oral application of cocamidopropyl betaine in rats are available.

Studies in Animals

Oral

In a 28 days study according to OECD guideline 407, 0, 250, 500 and 1000 mg 30 % active cocamidopropyl betaine/kg bw was administered via gavage to each 10 male and female Sprague-Dawley rats at 5 days/week (Henkel KGaA, 1991). The post-exposure period was 28 days in two recovery groups (0, 1000 mg/kg bw). In gross pathology the females of the 1000 mg/kg bw group showed edema in the forestomach. In histopathologic investigations the 1000 mg/kg bw male and female rats showed acanthosis and edema of the forestomach mucosa and multiple ulcerations and hyperplasia in the forestomach. The findings were more severe in females. The forestomach effects were completely reversible in the recovery group. No substance related toxicity was seen in macroscopic and microscopic investigation of the other organs or after clinical chemistry and haematology. The forestomach findings were regarded as an irritant effect and not as symptoms of a cumulative-systemic toxicity of cocamidopropyl betaine 30 % active.

The NOAEL is 500 mg/kg bw based on the forestomach findings and 1000 mg/kg bw with respect to systemic toxic effects.

In a 90 day study according to OECD guideline 408 0, 250, 500, 1000 mg 30 % active cocamidopropyl betaine/kg bw was administered via gavage to each 10 male and female Sprague-Dawley rats at 5 days/week (Th. Goldschmidt AG, 1991c). In gross pathology, each

one male and one female rat of the 1000 mg/kg bw group showed ulcera at the fundus and the cardia region of the stomach. It was concluded by the authors of the study that the only signs of intolerance in the mid and high dose group were dose-related incidence of forestomach gastritis. No substance related toxicity was seen in macroscopic and microscopic investigation of the other organs or in clinical chemistry and haematology. In histopathology forestomach gastritis with squamous hyperplasia, submucosal edema and inflammatory cell infiltration was seen in male and female rats at doses ≥ 500 mg/kg bw.

The NOAEL – based on the forestomach findings – is 250 mg/kg bw and 1000 mg/kg bw with respect to systemic toxic effects.

Conclusion

The oral subchronic toxicity of 30 % active cocamidopropyl betaine is very low. The only findings seen in rats after 28 and 90 days oral administration were reversible forestomach lesions, probably as a result of the irritating potential of the substance. The NOAEL based on the forestomach lesions is 250 mg/kg bw after 90 days application and 500 mg/kg bw after 28 days. The NOAEL for cumulative-systemic toxic effects is 1000 mg/kg bw.

5.2.1.6 Genetic Toxicity

Several Ames assays, one mouse lymphoma test and one micronucleus assay are available investigating the potential genotoxic potential of cocamidopropyl betaine *in vitro* and *in vivo*.

Studies in Animals

In vivo Studies

No mutagenic effect of 27% active cocamidopropyl betaine solution was found in a mouse micronucleus test with OF1 (I.O.P.S. Caw) mice (Goldschmidt France, 1987). In a preliminary study the test animals were orally administered twice (in a 24 hours interval) each 100, 200, 500, 1000 and 2000 mg/kg bw. Clinical signs and mortality were observed up to 30 hours after the first administration. Clinical signs like piloerection and ptosis were seen at doses of ≥ 500 mg/kg bw. At doses ≥ 1000 mg/kg bw the mice died within 30 hours and 4 hours after the first administration. The tolerated doses were in the range of 100 to 500 mg/kg bw. Therefore the dose of 200 mg/kg bw (representing the fifth part of the lethal dose) was selected as the high dose and 20 mg/kg bw (10% of the high dose) as the low dose. As the test substance was applied twice with a 24 h interval (although only one timepoint was chosen for sacrifice), the result of the sacrifice 6h later may be regarded as a result of a 30h and a 6h treatment. The dose level chosen is sufficient based on the effects found in the preliminary study and due to the highly irritating properties of the compound.

The mean number of micronucleated erythrocytes/1000 polychromatic erythrocytes in males and female mice at 20 and 200 mg/kg bw were unaffected compared to the negative controls. The administration of 100 mg cyclophosphamide /kg bw serving as the positive control led to clearly elevated numbers of micronucleated erythrocytes. Therefore cocamidopropyl betaine can be regarded as having no clastogenic effect.

In vitro Studies

In Ames tests with 29 – 31 % active cocamidopropyl betaine with *Salmonella typhimurium* TA 98, 100, 1535, 1537 and 1538 with and without metabolic activation no evidence of mutagenicity was seen (Henkel KGaA, 1988, Jagannath, 1988, Kao Corporation, 1996). Applied test concentrations were 0.001 µl/plate (corresponding to about 1 µg/plate) up to 5000 µg/plate in two investigations – performed according to OECD guideline 471 (Henkel KGaA, 1988, Kao Corporation, 1996) (Details see table 13). As cocamidopropyl betaine has bactericidal properties, cytotoxicity was observed in a concentration of ≥ 580 µg/plate.

The mouse lymphoma test with L5178Y TK+/- mouse lymphoma cells was negative with and without metabolic activation (CTFA, 1982 cited in CIR 1991). Concentrations tested were 0.001, 0.01, 0.1, 1.0, 10, 100 µl/ml; cytotoxicity was determined by comparing cell population growth at each dose with that of the solvent controls. No detailed data on cytotoxicity are given. None of the treated cultures had a significant increase in mutation frequency over the average mutant frequency of the solvent controls.

Table 13: *In vitro* genotoxicity tests with cocamidopropyl betaine

Type of test Concentration of test substance	System/ Strain	Conc. tested	Result	Cytotoxicity	Reference
Ames, OECD 471 30%	TA 98, 100, 1535, 1537, 1538 (+ and – MA)	1st test: 8, 40, 200, 1000, 5000 µg/plate, 2nd test: 1, 4, 16, 64, 256 µg/plate (- S9); 4, 16, 64, 256, 1024 µg/plate (+ S9)	Negative (+ and – S9)	≥ 256 µg/plate	Henkel KGaA, 1988
Ames not further specified	TA 98, 100, 1535, 1537, 1538	Preliminary test: 18 – 150000 µg/plate 1st and 2nd test: 1, 5, 10, 50, 100, 125, 150, 300 µg/plate (+ and – S9)	Negative (+ and – S9)	586 µg/plate (100 % cytotoxicity)	Jagannath, 1988
Ames, OECD 471 29%	TA 98, 100, 1535, 1537, 1538 (+ and – MA)	preliminary test: 0, 50, 150, 500, 1500, 5000 µg/plate, 1st test: 0, 1.5, 5, 15, 50, 150, 500 µg/plate (-S9), 0, 5, 15, 50, 150, 500, 1500 µg/plate (+S9) 2nd test: 0, 0.5, 1.5, 5, 15, 50, 150, 500 µg/plate (-S9), 0, 1.5, 5, 15, 50, 150, 500, 1500, 5000 µg/plate (+S9)	Negative (+ and – S9)	First evidence at 150 µg/plate	Kao Corporation, 1987
Mammalian tests					
Mouse lymphoma test 30.9%	L5178Y	0.001, 0.01, 0.1, 1.0, 10, 100 µl/ml	Negative (+ and – MA)	No data	CTFA, 1982 cited in CIR 1991

Conclusion:

In vitro genotoxicity tests in bacteria and mammalian cells showed no *in vitro* genotoxicity with a circa 30% active cocamidopropyl betaine. A mouse microunucleus test with 31% active cocamidopropyl betaine showed no evidence of clastogenicity *in vivo*.

5.2.1.7 Carcinogenicity

No data available.

5.2.1.8 Developmental Toxicity / Teratogenicity

The developmental toxicity of cocamidopropyl betaine was studied in a teratogenicity study performed according to OECD 414. No multi-generation study is available. Potential effects on fertility are deduced from repeated dose toxicity studies.

Studies in Animals

Effects on Fertility

After one subchronic toxicity study no effects related to reproductive organs were reported after administration of up to 1000 mg cocamidopropyl betaine/kg bw for 13 weeks respectively. Testes and ovaries weights were not affected and no changes were seen after histopathology of testes, prostate, uterus and ovaries (Th. Goldschmidt AG, 1991c).

Developmental Toxicity

In a prenatal developmental toxicity study following OECD guideline 414 with cocamidopropyl betaine 25 female pregnant CD rats/dose were administered 0, 330, 990 and 3300 mg cocamidopropyl betaine (28.9 % active)/kg bw from day 5 to 19 of pregnancy once daily via gavage (CESIO, 2004). Regarding maternal toxicity, the dams of the 990 mg/kg bw group showed decreased body weights, reduced food consumption, and 3/20 presented stomach ulcers and thickened mucosa in the stomach. In the 3300 mg/kg bw group the dams showed reduced body weights, reduced carcass weight, reduced gravid uterus weights, and 20/21 animals had thickened stomach mucosa with ulcers.

The number of early, late and total resorptions was increased in the 3300 mg/kg bw group. Moreover the ratio of viable fetuses to implantation sites was decreased compared to the controls. This was due to a total post-implantation loss of two dams in this dose group. In addition, a statistically significant reduction in fetal weights and number of viable fetuses as compared to the control was observed.

No external, skeletal or soft tissue malformations and no external variations were seen in controls or in dosed groups. The fetal incidence of the skeletal variations was 5 in the controls and 8 (330 mg/kg bw), 13 (990 mg/kg bw) and 6 (3300 mg/kg bw). The finding in the 990 mg/kg bw group was judged as incidental as no dose-relationship was noted. The skeletal retardations (fetal incidence) were 129 in the controls and 137 (330 mg/kg bw), 130 (990 mg/kg bw) and 125 (3300 mg/kg bw) in the dosed groups. No dose-related soft tissue variations were observed, as seen in the following fetal incidences: 8 (control), 12 (330 mg/kg bw), 10 (990 mg/kg bw) and 9 (3300 mg/kg bw)

The NO(A)EL (maternal toxicity) was 330 mg/kg bw (95 mg active substance/kg bw) based on the necropsy findings and the NO(A)EL (embryotoxicity) was 990 mg/kg bw (286 mg active substance/kg bw) based on increased post-implantation loss and decreased mean fetal body weights.

One further developmental toxicity study is available with cocamidopropyl betaine (30 % active substance). Female pregnant rats were administered 0, 30, 90 or 300 mg/kg bw on days 6 through 17 of gestation. No treatment-related effects on the incidence of fetal external, visceral, or skeletal malformations or developmental variations were observed among litters from dams in any of the treated groups.

The maternal and developmental no-observed-effect level (NOEL) of this study was 300 mg/kg bw/d, the highest level (Colgate-Palmolive, 2000).

Conclusion

There is no evidence indicating that cocamidopropyl betaine interferes adversely with reproduction. As organ weights and histopathological examinations of the reproduction organs showed no changes in one 90-days study, it can be assumed, that reproduction organs and fertility are not adversely affected by cocamidopropyl betaine. In one OECD 414 study cocamidopropyl betaine showed no teratogenic potential, even at maternal-toxic doses. Embryotoxicity was noted at the highest maternal-toxic dose in one study. The NOAEL for dams was 333 mg/kg bw (95 mg active substance/kg bw) and 990 mg/kg bw (286 mg active substance/kg bw) for the fetuses.

5.2.1.9 Experience with Human Exposure

Human data are available on potential skin irritating and sensitising properties of cocamidopropyl betaine. These data are summarised under the respective chapters in this documents. No further data on epidemiology and further experiences with human exposure are available.

5.2.2 Identification of relevant endpoints

Lauramidopropyl betaine is poorly absorbed from the intestinal tract and through the skin. Rinsing the skin after 10 minutes of contact reduces the absorption even further. As default values an each 10% absorption is assumed after oral and dermal administration of the test substance. Following oral or dermal exposure, there is metabolism of the absorbed material, as indicated by the appearance of a more polar compound in the urine and by the liberation of $^{14}CO_2$.

The acute oral toxicity of cocamidopropyl betaine 30 – 35.5 % is low, as shown in several acute toxicity tests in rats. The LD_{50} (dermal) is > 2000 mg/kg bw, LD_{50} (oral) is ≥ 4900 mg/kg bw. There were no clinical signs reported after acute dermal exposure; after oral exposure to high doses, decreased motor activity, diarrhea, and ataxia as well as signs of gastrointestinal irritation were found.

According to current OECD guideline, cocamidopropyl betaine (about 30 % active aqueous solution and nearly 80 % spray-dried substance) is not irritating to the skin. In human studies, up to 3 % active solutions were weakly irritating. Impurities like amidoamine may contribute to the irritating reaction. *In vitro* tests indicate, that cocamidopropyl betaine reduces the skin irritating properties in sodium lauryl sulphate containing formulations. The concentrated and the 25 to 30 % active solution of cocamidopropyl betaine were irreversibly irritating to rabbit´s eyes. Up to 10 % active solutions showed mild to moderate and reversible eye-irritating properties.

The sensitizing potential of cocamidopropyl betaine is low. Standard animal tests were predominantly negative. Clinical cases and epidemiological studies show also very low sensitizing potential of cocamidopropyl betaine. Cocamidoamine (I) and/or 3-dimethylaminopropylamine (II), impurities in commercially available cocamidopropyl betaine formulations are more likely to be the actual sensitizers in cocamidopropyl betaine. The content of potentially sensitizing substances in cocamidopropyl betaine was reduced in the

last years and is now in the range of 0 to 15 mg/kg (I) and 0 to 0.3 % (II), (nevertheless there are qualities on the market with up to 3 % of (II)).

The oral subchronic toxicity of cocamidopropyl betaine is very low. The only findings seen in rats after 28 and 90 days were reversible forestomach lesions, probably as a result of the irritating potential of the substance.

The NOAEL (forestomach lesions) is 250 mg/kg bw (75 mg active substance/kg bw) and 500 mg/kg bw (150 mg active substance/kg bw) in the 90 day and 28 days study respectively.

There was no evidence of systemic toxicity seen with a NOAEL (systemic toxic effects) of 1000 mg/kg bw (300 mg active substance/kg bw), which is the highest administered dose.

In vitro genotoxicity tests in bacteria and mammalian cells showed no *in vitro* genotoxicity with cocamidopropyl betaine (about 30% active). A mouse micronucleus test with 27% cocamidopropyl betaine showed no evidence of clastogenicity *in vivo*.

There is no evidence, that cocamidopropyl betaine interferes adversely with reproduction, as indicated by the lack of changes in the reproductive organs (organ weights and histopathology) of animals treated with up to 1000 mg/kg bw (300 mg active substance/kg bw) in one repeated dose study. In one OECD 414 study cocamidopropyl betaine showed no teratogenic potential, even at maternal-toxic doses. Embryotoxicity was noted at the highest maternal-toxic doses.

The NOAEL for dams was 330 mg/kg bw (95 mg active substance/kg bw) and 990 mg/kg bw (286 mg active substance/kg bw) for the fetuses.

Adverse effects related to accidental exposure

The acute toxicity of cocamidopropyl betaine 30 - 35 %, which is the maximum concentration present in toilet cleaners only, is very low after oral and dermal application; serious effects would not be expected after unintentional ingestion.

The 30 % solution of cocamidopropyl betaine is highly irritating to the eyes and the skin of rabbits. No or mild reversible skin irritating properties were observed in concentrations up to 10 % after 24 hours occlusive application. 3 % active concentrations of cocamidopropyl betaine caused weak irritation in humans. Mainly mild to moderate reversible eye irritations were shown in tests with 10 % active cocamidopropyl betaine. The severity of skin irritation reaction increases with increasing application time, as shown in rabbit´s test - see table 6.

The typical concentration of cocamidopropyl betaine in products of the use category is < 10%, only in toilet cleaners a solution up to 30% is used (see table 4). Due to the relatively high viscosity of these toilet cleaners, an unintentional splashing and therefore a risk to eyes is not be expected.

5.2.3 Determination of NOAEL or quantitative evaluation of data

Repeated dose toxicity

One 28-days and one 90-days study each performed in rats via oral gavage – application are available. Both studies confirm the irritating properties of cocamidopropyl betaine, as manifested through reversible forestomach (reversibility was checked in the 28-days study) findings. As the administration of the test substance via gavage represents an unnatural type of exposure and no systemic toxicity - besides the forestomach findings - was seen in each of the studies up to the highest administered dose, a NOAEL for systemic toxicity is 1000 mg/kg

bw (for the aqueous 30% active cocamidopropyl betaine solution) is set up. Related to **100% active ingredient** – to which all exposure assessments were calculated - a **NOAEL of 300 mg/kg bw** is used in the following margin of exposure calculations.

Toxicity on reproduction

Fertility

No changes in the reproductive organs of rats and mice were seen after macroscopic and histopathological examinations in subchronic and chronic studies. The systemic NOAEL of 1000 mg/kg bw (30% aqueous cocamidopropyl betaine solution) – derived from the 90-days-oral rats study is used also for the reproduction endpoints.

Teratogenicity

According to one developmental toxicity study (OECD 414) the NOAEL for the dams is 330 mg/kg bw (95 mg/kg bw for 100% active cocamidopropyl betaine) – again based on stomach ulcers and thickened mucosa in the stomach – and 990 mg/kg bw (286 mg/kg bw for 100% active cocamidopropyl betaine) for the fetuses.

5.3 Risk Assessment

5.3.1 Margin of exposure calculation

The Margin of Exposure (MOE) is the ratio of the No Observed Adverse Effect Level (NOAEL) or an appropriate substitute to the estimated or actual level of human exposure to a substance. A systemic NOAEL for CAPB was determined using the 3 months oral NOAEL of 300 mg/kg bw for 100% active ingredient (see 5.2.3) and an absorption of about 10% from the gastrointestinal tract seen in the ADME study of lauramidopropyl betaine (see 5.2.1.1). The resulting value of **30 mg/kg bw/day** was used as the systemic **NOAEL** to calculate the MOE values in the different exposure scenarios detailed below.

Exposure scenario: direct skin contact from hand washed laundry

For calculation of the MOE, the systemic NOAEL of 30 mg/kg bw/day was divided by the daily systemic dose of 0. 18 µg/kg bw/day for the dermal exposure to cocamidopropyl betaine from hand washed laundry.

$MOE_{direct\ skin}$ = systemic oral NOAEL / estimated systemic dose = 30000 / 0. 18 = **166666.7**

Exposure scenario: direct skin contact from pre-treatment of clothes

For calculation of the MOE, the systemic NOAEL of 30 mg/kg bw/day was divided by the daily systemic dose of 3.9 µg/kg bw/day for the dermal exposure to cocamidopropyl betaine from pre-treatment of clothes.

$MOE_{direct\ skin}$ = systemic oral NOAEL / estimated systemic dose = 30000 / 3.9 = **7692.3**

Exposure scenario: direct skin contact from hand dish washing

For calculation of the MOE, the systemic NOAEL of 30 mg/kg bw/day was divided by the daily systemic dose of 0.63 µg/kg bw/day from regular detergent liquids for the dermal exposure to cocamidopropyl betaine from hand dish washing.

Regular
$MOE_{direct\ skin}$ = systemic oral NOAEL / estimated systemic dose = 30000 / 0. 63 = **47619**

Exposure scenario: direct skin contact from hard surface cleaning (surface cleaners)

For calculation of the MOE, the systemic NOAEL of 30 mg/kg bw/day was divided by the daily systemic dose of 0.2 µg/kg bw/day for the dermal exposure to cocamidopropyl betaine from hard surface cleaning with surface cleaners.

$MOE_{direct\ skin}$ = systemic oral NOAEL / estimated systemic dose = 30000 / 0. 2 = **150000**

Exposure scenario: direct skin contact from hard surface cleaning (toilet cleaners)

For calculation of the MOE, the systemic NOAEL of 30 mg/kg bw/day was divided by the daily systemic dose of 2.9 µg/kg bw/day for the dermal exposure to cocamidopropyl betaine from hard surface cleaning with toilet cleaners.

$MOE_{direct\ skin}$ = systemic oral NOAEL / estimated systemic dose = 30000 / 2.9 = **10344.8**

Exposure scenario: indirect skin contact from wearing clothes

For calculation of the MOE, the systemic NOAEL of 30 mg/kg bw/day was divided by the daily systemic dose of 1.3 µg/kg bw/day for the dermal exposure to cocamidopropyl betaine from wearing clothes washed with cocamidopropyl-containing laundry detergents.

$MOE_{indirect\ skin}$ = systemic oral NOAEL / estimated systemic dose = 30000 / 1.3 = **23076.9**

Exposure scenario: inhalation of aerosols from cleaning sprays

For calculation of the MOE, the systemic NOAEL of 30 mg/kg bw/day was divided by the daily systemic dose of 0.01 µg/kg bw/day for the exposure to cocamidopropyl betaine from inhalation of aerosols generated with surface cleaning sprays.

$MOE_{inhalation\ aerosols}$ = systemic oral NOAEL / estimated systemic dose = 30000 / 0.01 = **3000000**

Exposure scenario: oral route from drinking water containing cocamidopropyl betaine

For calculation of the MOE, the systemic NOAEL of 30 mg/kg bw/day was divided by the daily systemic dose of 0.44 µg/kg bw/day for the oral route via drinking water containing cocamidopropyl betaine.

$MOE_{oral\ route\ drinking\ water}$ = systemic oral NOAEL / estimated systemic dose = 30000 / 0.58 = **51724**

Exposure scenario: oral route from residues left on dishware

For calculation of the MOE, the systemic NOAEL of 30 mg/kg bw/day was divided by the daily systemic dose of 0.99 µg/kg bw/day from regular detergent liquids for the oral route from residues left on dishware.

Regular
$MOE_{oral\ route}$ = systemic oral NOAEL / estimated systemic dose = 30000 / 0.99 = **30303**

The calculated MOE values are summarized in table 13.

Table 13: Calculated MOE values for specific scenarios

Route of exposure	Exposure scenario	Estimated systemic doses µg/kg bw/day	MOE
Dermal	Hand washed laundry	0. 18	166666.7
	Pre-treatment of clothes	3.9	7692
	Hand dish washing - regular	0. 63	47619
	Hard surface cleaning (surface cleaners)	0. 2	150000
	Hard surface cleaning (toilet cleaners)	2.9	10344.8
	Wearing clothes	1.3	23076.9
Inhalation	Aerosolinhalation from cleaning sprays	0.01	3000000
Oral	Drinking water	0.58	51724
	Residues left on dishware -regular	0.99	30303

Total consumer exposure

The consumer exposure from direct and indirect skin contact, as well as from inhalation and from oral route in drinking water and dishware, results in an estimated total body burden of 0. 18 + 3.9 + 0. 63 + 0. 2 + 2.9 + 1.3 + 0.01 + 0.58 + 0.99 = 10.7 µg/kg bw/day. In the case on the hand dish washing scenario each the highest values (derived from the regular detergent liquid scenarios) were used to calculate the total body burden. Division of the systemic NOAEL of 30000 µg/kg bw/day and the estimated total body burden reveals a MOE value of 2800, which is quite a high and safe value.

$MOE_{direct\ skin}$ = systemic oral NOAEL / estimated systemic dose = 30000 / 10.7 = **2803.7**

5.3.2 Risk characterisation

Systemic toxicity

Scenarios relevant to the consumer exposure to cocamidopropyl betaine have been identified and assessed using the margin of exposure assessment. The Margin of Exposure for the combined estimated systemic dose is about 3000.

This is a large Margin of Exposure, large enough to account for the variability of the hazard database and inter species and intra species extrapolations, which is conventionally estimated at a factor of 100. In addition, the Margin of Exposure is based on very conservative estimations of both the exposure (e.g using a value of 10% absorption after dermal exposure seen in an ADME study) and NOAEL (which is a systemic NOAEL given the existence of oral toxicokinetic data). Regarding hazard assessment - no systemic toxicity was observed in any of the animal toxicity tests. Based on the above mentioned arguments, the presence of cocamidopropyl betaine in consumer products does not raise any safety concerns associated to systemic toxicity.

Local effects

Aqueous solutions of cocamidopropyl betaine are irritating to the skin and eyes; the severity of the irritation reactions depends on the concentration.

Skin

Contact of ready-to-use solutions of hand dish washing or surface cleaning products with the skin are not a cause of concern, given that the concentrations of cocamidopropyl betaine in such solutions are well below 1 %. As reported in the irritation part of the hazard assessment of this document, below 10 % aqueous solutions showed no or mild irritation in rabbit skin after 24 hours occlusive application.

In the course of laundry pre-treatment, skin contact with the neat liquid detergent (containing maximal 4 % cocamidopropyl betaine) may occur. The contact is confined to a fraction of the skin or the hands (palms or fingers), it is usually diluted out rapidly in the course of the pre-treatment task, and it is of very short duration (typically a few minutes at most).

Eyes

Accidental contact of such solutions containing cocamidopropyl betaine with the eyes is not expected to cause more than a mild irritation on the basis of the experimental data as reported in the eye irritation section. At and below 10% active dilutions were mild to moderate and reversible irritating to the rabbit´s eyes.

Accidental spillage of cocamidopropyl betaine containing household liquid detergent products (range from 1 – 30%) to the eyes is to be avoided as it can be expected to result in eye irritation. Immediate rinsing of the eyes with water for several minutes should follow the accidental spillage of the neat liquid.

Respiratory tract

Regarding the very low levels of airborne cocamidopropyl betaine generated as a consequence of cleaning sprays aerosols, a potential respiratory tract irritation is not a concern.

Acute effects

As the acute toxicity of cocamidopropyl betaine is very low, occasional ingestion of a few millilitres of the substance as a consequence of accidental ingestion of laundry, hand dishwashing and surface and toilet cleaning products is not expected to result in any significant adverse health effects to humans.

5.4 Discussion and conclusion

With dermal and oral LD_{50} values of > 2000 and ≥ 4900 mg/kg bw, respectively, the acute toxicity of cocamidopropyl betaine is very low. About 30% active formulations are irritating to the skin and the eyes, while ≤ 10 % active solutions caused only mild skin and eye reactions. From subacute and subchronic studies with rats a NOAEL of 1000 mg/kg bw/day for systemic toxicity of the 30% active CAPB was derived. Cocamidopropyl betaine gave no indication for genotoxic or teratogenic effects. Contact allergy to CAPB has been reported although extensive data now suggests that impurities in the final product are responsible for causing this skin sensitization.

Relevant consumer scenarios were described for the usage of household detergent products containing cocamidopropyl betaine and the resulting Margin of Exposures (MOE) were calculated comparing the systemic NOAEL to the estimated exposure values. For each scenario the MOE was above 10^4 (with the exception of one, which had a MOE of 7700 – pre-treatment of clothes), which represents a very high safety margin. Also the estimation of the total consumer exposure resulted in a MOE of about 2800, which is also a high value. No risk is calculated for potential uptake via drinking water or food.

Acute toxic effects after unintentional oral exposure of a few millilitres of the formulations (1 – 30% concentration) are not to be expected.

Neat CAPB is an irritant to skin and eyes. The irritation potential of aqueous solutions of CAPB depends on concentration. Local effects of hand wash solutions containing CAPB do not cause concern given that the concentrations of CAPB in such solutions are well below 1% and therefore not expected to be irritating to eye or skin. Laundry pre-treatment tasks, which may translate into brief hand skin contact with higher concentrations of CAPB, may occasionally result in mild irritation easily avoided by prompt rinsing of the hands in water. Potential irritation of the respiratory tract is not a concern given the very low levels of airborne CAPB generated as a consequence of cleaning sprays aerosols. Immediate eye rinsing with water for several minutes is recommended after accidental splashing of CAPB solutions, as eye irritation reactions may occur.

In view of the available database on toxic effects, the low exposure values calculated and the resulting large Margin of Exposure described above, it can be concluded that use of CAPB in household laundry and cleaning products raises no safety concerns for the consumers.

6 REFERENCES

AISE, 2002 Table of Habits and Practices for Consumer Products in Western Europe, 2002

Andersen KE, Roed - Petersen J & Kamp P (1984) Contact allergy related to TEA - PEG - 3 cocamide sulfate and cocamidopropyl betaine in a shampoo. Contact Dermatitis 11 (3):192-193

Angelini G, Foti C, Rigano L & Vena GA (1995) 3-Dimethylaminopropyl: a key substance in contact allergy to cocamidopropyl betaine. Contact Dermatitis 32 (2):96-99

Angelini G, Rigano L, Foti C, Rossi P, Vena GA (1996) Pure cocamidopropylbetaine is not the allergen in patients with positive reactions to commercial cocamidopropylbetaine. Contact Dermatitis 35, 252-253

Arimura M, Yokozeki H, Katayama I, Nakamura T, Masuda M & Nishioka K (1998) Experimental study for the development of an in vitro test for contact allergens. Int Arch Allergy Immunol 115 (3):228-234

Armstrong DKB, Smith HR, Ross JS & White IR (1999) Sensitization to cocamidopropyl betaine: an 8-year review. Contact Dermatitis 40 (6):335-336

Basketter D, Lea L, Cooper K, Stocks J, Dickens A, Pate I, Dearman R, Kimber I (1999) Threshold for classification as a skin sensitizer in the local lymph node assay: a statistical evaluation. Food Chem Toxicol 37(12), 1167-1174

Bonneau JC (1990) Allergie a la Tegobetaine: a propos d´un cas. Allergie et Immunologie, 22(5), 195

Brey NL, Fowler JF (2004) Relevance of positive patch-test reactions to cocamidopropyl betaine and amidoamine. Dermatitis, 15(1), 7-9

BUA report 206 (1997) BUA report on ecotoxicology of selected surfactants fort he detergent and cleanser sector (original title: Ökotoxikologie ausgewählter Tenside für den Wasch- und Reinigungsmittelbereich) (in German), editor: Beratergremium für umweltrelevante Altstoffe (BUA) der Gesellschaft Deutscher Chemiker

Cameli N, Tosti G, Venturo, N. & Tosti A (1991) Eyelid dermatitis due to cocamidopropyl betaine in a hard contact lens solution . Contact Dermatitis 25 (4):261-262

CESIO (2004) Prenatal development toxicity study in rats with cocamidopropyl betaine by oral administration - according to OECD guideline 414 - DRAFT. Essen, LPT Study No. 17155/03 , 1-50

CESIO-statistics (2004) www.cefic.be/files/Publications/cesio02-010903.xls

CIR - Anonymous(1991) Final report on the safety assessment of cocamidopropyl betaine . J Am Coll Toxicol 10 (1):33-52

Colgate-Palmolive Company (2000) Study for effects on embryo-fetal development in rats, CP 97-010. Non-confidential summary of a confidential study, 2004

Consortium “Categories Betaine” Information 11/2003

Consortium “Categories Betaine” Information 05/2004

Cosmetic,Toiletry and Fragance Association (Feb 1 1984) Repeat insult patch test (human skin sensitization). Unpublished data, cited in CIR (1991) Final report on the safety assessment of cocamidoproyl betaine. J Am Coll Tox 10 (1), 33-52

Cosmetic,Toiletry and Fragance Association (Jan 31, 1984) Repeat insult patch test (human skin sensitization). Unpublished data, cited in CIR (1991) Final report on the safety assessment of cocamidoproyl betaine. J Am Coll Tox 10 (1), 33-52

Cosmetic,Toiletry and Fragance Association (1988) Repeat insult patch test and evaluation of photoallergy for CTFA. Unpublished data, cited in CIR (1991) Final report on the safety assessment of cocamidoproyl betaine. J Am Coll Tox 10 (1), 33-52

de Groot AC, Bryunzeel DP, Bos JD, van der Meeren HLM, van Joost T, Jagtman BA & Weyland W (1988) The allergens in cosmetics. Arch Dermatol 124:1525-1529

de Groot AC, van der Walle HB & Weyland JW (1995) Contact allergy to cocamidopropyl betaine . Contact Dermatitis 33/6:419-422

Dillarstone A & Paye M (1993) Antagonism in concentrated surfactant systems. Contact Dermatitis 28:198

Domsch A (1995) In: Biodegradability of surfactants. Karsa DR, Porter MR (ed.) Blackie Academic & Professional, London – Glasgow – Weinheim – New York – Tokyo – Melbourne – Madras, pp 231-254

Domsch A, Irrgang B, Möller C (1996) Mild Surfactants - Facts and Illusions Vortrag, gehalten anlässlich des IFSCC-Congress 1996 in Montreux. SÖFW-Journal, 6/96, 353-367

ECETOC, (1996) Technical Report No. 67 The Role of Bioaccumulation in Environmental Risk Assessment: The Aquatic Environment and Related Food Webs, Brussels, March 1996

Effendy I & Maibach HI (1995) Surfactants and experimental irritant contact dermatitis . Contact Dermatitis 33 (4):217-225

EC (2003) Technical Guidance Document on Risk Assessment in support of Directive 93/67/EEC on risk assessment for new notified substances, Commission Regulation (EC) No. 1488/94 on risk assessment for existing substances (Parts I, II, III and IV) and Directive 98/8/EC of the European Parliament and the Council concerning the placing of biocidal products on the market. European Chemicals Bureau, Ispra (It.), 2003

FH-ITEM (2004) Calculation of the regional PECwater concentration using EUSES 2.0 (program used for chemical´s and biocide´s risk assessment, http://ecb.jrc.it)

Foti C, Rigano L, Vena GA, Grandolfo M, Liguori G & Angelini G (1995) Contact allergy to oleamidopropyl dimethylamine and related substances . Contact Dermatitis 33 (2):132-133

Foti C, Bonamonte D, Mascolo G, Corcelli A, Lobasso S, Rigano L, Angelini G (2003) The role of 3-dimethylaminopropylamine and amidoamine in contact allergy to cocamidopropylbetaine. Contact Dermatitis, 48, 194-198

Fowler JF (1993) Cocamidopropyl betaine: The significance of positive patch test results in twelve patients. Cutis 52 (5):281-284

Fowler JF, Fowler LM & Hunter JE (1997) Allergy to cocamidopropyl betaine may be due to amidoamine: a patch test and product use test study. Contact Dermatitis 37 (6):276-281

Fowler JF (2004) Cocamidopropyl betaine. Dermatitis 15(1), 3-4

Fowler JF, Zug KM, Tylor JS, Storrs FJ, Sherertz EA, Sasseville DA, Rietschel RL, Pratt MD, Mathia CGT, Marks JG, Maibach HI, Fransway AF, Deleo VA, Belsito DV (2004) Allergy to cocamidopropyl betaine and amidoamine in North America. Dermatitis 15(1), 5-6

Frosch PJ (1990) Aktuelle Kontaktallergene. Der Hautarzt 41 Suppl.10:129-133

Garcia-Dominguez J, Balaguer F, Parra JL, Pelejero CM (1981) The inhibiting effect of some amphoteric, surface active compounds on the skin irritant capacity of alkyl sulphates. Goldschmidt informiert 55, 10-17

Goldschmidt AG (2004) Personal communication

Goldschmidt Chemical Corp. (1993a) FHSA dermal irritation test, Hopewell, Virginia, Goldschmidt Chemical Corp., T - 2183 30.04.1993, 1-8

Goldschmidt Chemical Corp. (1993b) FHSA primary eye irritation test Hopewell, Virginia, Goldschmidt Chemical Corp., T - 2179 06.05.1993, 1-9

Goldschmidt Chemical Corp. (1993c) FHSA primary eye irritation test Hopewell, Virginia, Goldschmidt Chemical Corp., T - 2182 06.05.1993, 1-9

Goldschmidt Chemical Corp. (1994) Primary eye irritation Hopewell, Virginia, Goldschmidt Chemical Corp., 3297 16.09.1993, 1-6

Goldschmidt France S.A. (1987) TEGO Betain L7, batch 9775. Micronucleus test (Schmid method). Report No. 703201 3 March 1987, 1-18

Goossens A & Merckx L (1997) Contact allergy to cosmetics (L´allergie de contact aux cosmétiques). Allerg Immunol 29(10):300-303

Henkel KGaA (1976) Potokar, Dehyton K und Tegobetain L 7-Untersuchungen über sensibilisierende Eigenschaften, report no.: 22, 28.6.1976

Henkel KGaA (1986a) Dehyton K, Dehyquart A, Texapon N 25 und Eumulgin 286 - vergleichende Prüfung der primären Hautirritation . Düsseldorf, Henkel KGaA, Prüfbericht 860073, 1-8

Henkel KGaA (1986b) Amphotenside Sulfobetain, Dehyton K, Mischung aus Sulfobetain und Texapon NSO, Mischung aus Dehyton K und Texapon NSO und Texapon NSO - Vergleichende Prüfung der Schleimhautverträglichkeit am Kaninchenauge. Düsseldorf, Henkel KGaA, Berichts-Nr. 860383, 1-9

Henkel KGaA (1986c) Vergleichende Prüfung der Schleimhautverträglichkeit der Tenside Dehyton K, Dehyquart A, Texapon N 25 und Eumulgin 286. Düsseldorf, Henkel KGaA, Prüfbericht 860104, 1-8

Henkel KGaA (1987a) Aniontenside, Kationtenside, Amphotenside, Niotenside - Prüfung auf primäre Hautirritation. Düsseldorf, Henkel KGaA, Bericht-Nr. 870150, 1-21

Henkel KGaA (1987b) Amphotenside Dehyton AB 30, Dehyton K, Dehyton G und Aminoxid WS 35 - Prüfung auf primäre Schleimhautirritation am Kaninchenauge. Düsseldorf, Henkel KGaA, Berichts-Nr. 870555, 1-12

Henkel KGaA (1988), Banduhn N. Dehyton K - Prüfung auf Mutagenität im Ames-Test (Abschlußbericht). 880078; Feb. 1988, 1-33

Henkel KGaA (1991) Dehyton K; 28-Tage-Test mit wiederholter oraler Verabreichung an Ratten. TED 910119; Juli 1991, 1-139

Henkel KGaA (1996) Dehyton K – Geschlossener Flaschentest/EG-RILI. Henkel KGaA Forschung Biologie/Produktsicherheit, unpublished report, final report No. R-9501454

Henkel KGaA (2001a) Dehyton K 1-Propanaminium, 3-amino-N-(carboxymethyl)-N,N-dimethyl-, N-coco acyl derivs., hydroxides - Ultimate biodegradability in the Modified OECD Screening Test. Henkel KGaA Department of Ecology, unpublished report, final report R-0100970

Henkel KGaA (2001b), Dehyton K 1-Propanaminium, 3-amino-N-(carboxymethyl)-N,N-dimethyl-, N-coco acyl derivs., inner salts - Fish, acute toxicity. Henkel KGaA Department of Ecology, unpublished report, final report R-0100935

Henkel KGaA (2001d) Dehyton K 1-Propanaminium, 3-amino-N-(carboxymethyl)-N,N-dimethyl-, N-coco acyl derivs., inner salts - Ultimate biodegradability in the Coupled Units Test. Henkel KGaA Department of Ecology, final report R-0100951, unpublished report

HERA, 2003a Human Exposure Data

HERA, 2003b, Global aggregated data form exposure, %ages of active ingredient contained in specific product types

Hunter JE & Fowler JF (1998) Safety to human skin of cocamidopropyl betaine: A mild surfactant for personal-care products. J Surf Det 1(2):235-239

Jagannath (1988) Mutagenicity test on cocamidopropyl betaine (Lonzaine C) in the Ames samonella/microsome reverse mutation assay, Hazleton Laboratories Study no.: 10245-0-401, May 3, 1988

J Off Rep Fr (1990) Official publication of the French Legislation ("Journel Officiel de la Republique Francaise") concerning substances used in dish care products which may come into contact with food, 1990

Jackson EM (2001) The case for/against CAPB in shampoos. Cosmet Derm 14(4):60-62

KAO Corporation (1987a) Acute dermal toxicity to rats of Betadet HR. Barcelona, Kao Corporation, 871210D/MLS 6/AC, 1-10

KAO Corporation (1987b) Acute oral toxicity to rats of Betadet HR. Barcelona, Kao Corporation, 871209D/MLS 5/AC, 1-8

KAO Corporation (1996) Betadet HR: reverse mutation assay "Ames Test" using Salmonella Typhimurium. Haga, Tochigi, 140/473, 1-20

KAO Corporation (1992a) Assessment of the ready biodegradability (closed bottle test) of Betadet HR. Unpublished report, project number 309/35

Korting HC, Parsch E-M, Enders F & Przybilla B (1992) Allergic contact dermatitis to cocamidopropyl betaine in shampoo . J Am Acad Dermatol 27 (6 Part 1):1013-1015

LAS, 2004 HERA Risk Assessment of linear alkylbenzyl sulphonates, Consumer scenario: "Direct skin contact from pre-treatment of clothes". www.heraproject.com/files/04%20-HERA%20LAS%20Full%20web%20wd%20version%202%20may1.pdf

Liebert MA (1991) Final report on the safety assessment of cocoamidopropyl betaine. J Am College of Toxicol 10: 33-35

Madsen T, Boyd HB, Nylén D, Rathmann Pedersen A, Petersen GI, Simonsen F (2001) Environmental and health assessment of substances in household detergens and cosmetic detergent products. Environmental Project No. 615, Miljøprojekt, pp 87-89

McFadden JP, Ross JS, White IR & Basketter DA (2001) Clinical allergy to cocamidopropyl betaine: reactivity to cocamidopropylamine and lack of reactivity to 3-dimethylaminopropylamine. Cont Derm Newsletter 5:72-74

Mowad CM (2001) American Journal of Contact Dermatitis, 12 (4), 223-224

Moreau L, Sasseville D (2004) Allergic contact dermatitis from cocamidopropyl betaine, cocamidoamine, 3-(dimethylamino)propylamine, and oleamidopropyl dimethylamine: Co-reactions or cross-reactions? Dermatitis, 15(3), 146-149

P & G (1996) Procter & Gamble, unpublished data, 1996

P & G (2001) Procter & Gamble, unpublished data, 2001

Pigatto PD, Bigardi AS & Cusano F (1995) Contact dermatitis to cocamidopropyl betaine is caused by residual amines: relevance, clinical characteristics, and review of the literature. Am J Contact Dermat 6:13-16

Pratt MD, Belsito DV, DeLeo VA, Fowler JF, Fransway , Maibach HI, marks JG, Mathias CG, Rietschel RL, Sasseville D, Sherertz EF, Storrs FJ, Taylor JS, Zug K (2004) North American Contact Dermatitis Group patch-test results, 2001-2002 study period. Dermatitis 15(4), 176-183

Rantuccio F, Coviello C, Sinisi D, Scardigno A & Conte A (1983) Experimental sensitization of guinea pigs by drugs. Comparison of the maximization test with the wholly intradermal test. Contact Dermatitis 9:479-483

Rhein LD, Robbins CR, Fernee K, Cantore R (1986) Surfactant structure effects on swelling of isolated human stratum corneum. J Soc Cosmet Chem, 37, 125-139

Ross JS, White IR (1991) Eyelid dermatitis due to cocamidopropyl betaine in an eye make-up remover. Contact Dermatitis, 25, 64

SASOL (2004) Personal information

Schmitz, J (1973) Tenside Surf Det, 10, 11-13

Stepan Chemicals Co. (1982a) Acute Oral Toxicity Test in rats – Amphosol CG 35.5 % active FDRL Study number 7330A, 5/12/82

Stepan Chemicals Co. (1982b) Acute Oral Toxicity Test in rats – Amphosol CG 30.6 % active FDRL Study number 7330D, 3 June 1982

Stepan Chemicals Co. (1982c) Primary skin irritation study in albino rabbits . Northfield, Stepan Chemical Co., No. 7330 C, 1-12

Stepan Chemicals Co. (1982d) Primary skin irritation in albino rabbits. Northfield, Stepan Chemical Co., No. 7330 F, 1-12

Stepan Chemicals Co. (1982e) Primary eye irritation study in albino rabbits. Northfield, Stepan Chemical Co., No. 7330 B, 1-13

Stepan Chemicals Co. (1982f) Primary eye irritation study in albino rabbits. Northfield, Stepan Chemical Co., No. 7330 E, 1-13

Su L-H & Sun C-C (1998) Positive patch test to cocamidopropyl betaine in a hairdresser. Contact Dermatitis 38(3):168-169

Swiss Product Register, July 2004

Taniguchi S, Katoh J, Hisa T, Tabata M, Hamada T (1992) Shampoo dermatitis due to cocamidopropyl betaine. Contact Dermatitis 26, 139

Th. Goldschmidt AG (1977) International Bio Research (IBR) Hannover (1977) Rep. No. 1-4-338/1-77

Th. Goldschmidt AG (1990a) Test to evaluate the acute primary cutaneous irritation and corrosivity in the rabbits. report no. 001336, 17th January 1990

Th. Goldschmidt AG (1990b) Test to evaluate the acute ocular irritation and reversibility in the rabbit. Report No. 001337, 17th January 1990

Th. Goldschmidt AG (1991a) Final report. Acute dermal irritation / Corrosion test of "Tego Betain F" (sprühgetrocknet) in Rabbits . Essen, Th. Goldschmidt AG, 10-03-0975/00-91 Oktober 1991, 1-15

Th. Goldschmidt AG (1991b) Final report. Acute eye irritation / Corrosion test of "Tego Betain F" (sprühgetrocknet) in rabbits. Essen, Th. Goldschmidt AG, 10-03-0976/00-91 November 1991, 1-17

Th. Goldschmidt AG (1991c) Tego-Betain. 90 day oral (gavage) subchronic toxicity study in the rat. Essen, Th. Goldschmidt AG, 954-348-155, 26.04.1991, 1-375

Th. Goldschmidt AG (2004), Safety data sheet TEGO Betain F50

Unilever Research (1992) The fate of tegobetaine (TB) in the rat Study AM890809. Authors: Howes D, Moule RC, Fordham SJ, Curnock C, 1-53

Uphues G (1998) Chemistry of amphoteric surfactants. Fett/Lipid100: 490-497

US EPA (1991) Initial submission: summary of results of acute toxicity studies (final report) with attachments and cover. Washington, D.C., US Environmental Protection Agency, EPA / OTS 88920000317/OTS0534768, 1-23

US EPA (1993) Final report: Primary eye irritation study of Mirataine BD-J in rabbits (EPA Guidelines). Washington, D.C., US Environmental Protection Agency, EPA / OTS 88930000401 / OTS0555664, 1-36

Van der Walle HB & Brunsveld VM (1994) Dermatitis in hairdressers. (I) The experience of the past 4 years. Contact Dermatitis 30(4):217-221

Van Haute N, Dooms-Goossens A (1983) Shampoo dermatitis due to cocobetaine and sodium lauryl ether sulphate. Contact Dermatitis 9, 169

Vermeire et al., (1993) Estimation of Consumer Exposure to Chemicals. Application of Simple Models Science of the Total Environment, 136, 155-176

Vilaplana J, Grimalt F & Romaguera C (1990) Contact dermatitis to cocoamidopropylbetaine. Contact Dermatitis 23:274

Vilaplana J, Mascaró JM, Trullás C, Coll J, Romaguera C, Zemba C & Pelejero C (1992) Human irritant response to different qualities and concentrations of cocoamidopropylbetaines: a possible model of paradoxical irritant response. Contact Dermatitis 26(5):289-294

Wallace JM, (1977) Acute oral LD50 toxicity study - Cocamidopropyl betaine 30% solution, Bio-Toxicology Laboratories Inc September 16, 1977

Wright ZM, Basketter DA, Blaikie L, Cooper KJ, Warbrick EV, Dearman RJ, Kimber I (2001) Vehicle effects on skin sensitizing potency of four chemicals: assessment using the local lymph node assay. Int J Cosmet Sci, 23, 75-83

7 CONTRIBUTORS TO THIS REPORT

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