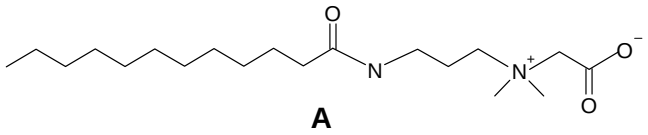
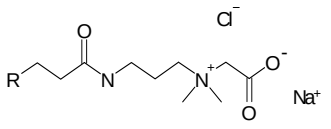
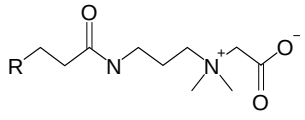
SIDS INITIAL ASSESSMENT PROFILE

Chemical Category Name	**Alkylamidopropyl betaines**		
CATEGORY MEMBERS: **Chemical Names**	1-Propanaminium, N-(carboxy-methyl)-N,N-dimethyl-3-[(1-oxododecyl) amino]-, inner salts (A) **Lauramidopropyl betaine**	1-Propanaminium, 3-amino-N-(carboxymethyl)-N,N-dimethyl-, N-coco acyl derivatives, inner salts (B) **Cocamidopropyl betaine inner salts**	Amides, coco, N-[3-(dimethyl-amino)propyl], alkylation products with chloroacetic acid, sodium salt (C) **Cocamidopropyl betaine sodium salts**
CAS Registry Numbers	**4292-10-8**	**61789-40-0**	**70851-07-9**
STRUCTURAL FORMULAS	 **A**  **C**  **B**		

SUMMARY CONCLUSION OF THE SIAR

Category Justification

The members of the alkylamidopropyl betaines category are amphoteric surfactants containing a quarternary ammonium ion, a carboxylic structure, and an amide bond. The alkylamidopropyl betaines are referred to as inner salts due to their zwitterionic character. They are all manufactured from oils, usually coconut oil, containing mixtures of C_8 to C_{18} fatty acids and marketed as aqueous solutions (20 - 40 %).

Because of the structural and functional similarities and comparable physico-chemical properties of cocamidopropyl betaine inner salts and sodium salts, a similar ecotoxicological and toxicological profile can be expected. Values for physico-chemical endpoints for lauramidopropyl betaine are similar or within the range of values for cocamidopropyl betaines, supported by accepted (Q)SARs even though there may be limitations for surface active substances. Therefore similar ecotoxicological properties were assumed. All available physico-chemical and environmental fate data are similar for lauramidopropyl betaine and cocamidopropyl betaine and hence support this category approach.

Only the alkyl chain length differs for the chemicals in the mixture, therefore they should have the same mode of action for aquatic toxicity.

The main component of the category, **lauramidopropyl betaine** (C_{12}; ca. 50-60%) is in the middle of the alkyl-chain distribution of the mixture. The distribution ranges from C_8 (ca. 5%) to C_{18} (ca. 10%) in steps of two.

Based on (Q)SAR the aquatic toxicity is expected to increase with increasing chain length. The aquatic toxicity of C_{12} should be in the order of the toxicity of the mixture. So data from the mixture can also be used to address the toxicity of lauramidopropyl betaine.

However, the lack of (eco-) toxicity data for lauramidopropyl betaine must be noted.

Human Health

No reliable toxicokinetic or metabolism studies were available for the category members. As amphoteric surfactants are easily absorbed by the oral route and are excreted partly unchanged via the feces or are metabolized to short-chained fatty acids and carbon dioxide, this can also be expected for the alkylamidopropyl betaines.

The acute toxicity of cocamidopropyl betaine (30 – 35.5 % aqueous solutions) in rats is low, with a dermal LD_{50} value greater than 2000 mg/kg bw (i.e., greater than 600 mg active substance/kg bw), and oral LD_{50} values generally greater than 5000 mg/kg bw (i.e., greater than 1500 mg active substance/kg bw). Other than irritation, there were no clinical signs reported after acute dermal exposure; after oral exposure to high doses, decreased motor activity, diarrhea, and ataxia were found. The acute toxicity of lauramidopropyl betaine is expected to be in the same range. No studies were available for the respiratory route of exposure.

In studies according to OECD TG 404, cocamidopropyl betaine (as ca. 30 % aqueous solution) was only very slightly irritating to the skin of rabbits. When tested as moistened, spray-dried powder, it was not irritating. Clear signs of irritation were seen in rabbits after occlusive treatment with concentrations of about 30 %. Aqueous 30 % solutions and the spray-dried cocamidopropyl betaine powder induced corneal and/or iris damage in rabbits which was still present in some animals at the end of the observation period of 21 d. 5 to 10 % solutions caused mild to moderate effects, which were all reversible within the observation period. The skin and eye irritation potential of lauramidopropyl betaine is expected to be similar.

Three out of four animal studies gave no indication of a sensitizing potential of cocamidopropyl betaine; the lack of concurrent positive control data weakens, however, their reliability. Ambiguous results in the fourth study, a Guinea pig maximization test, may have been caused by impurities. In humans, the sensitizing potential of cocamidopropyl betaine is low. Commercial cocamidopropyl betaine may, however, contain impurities identified as sensitizers (amidoamine and/or 3-dimethylaminopropylamine) which may explain positive results in human patch tests. There is no evidence for a photosensitizing potential. Overall, the sensitizing potential of the alkylamidopropyl betaines category is considered to be low.

The repeated dose toxicity with 250, 500, and 1000 mg/kg bw/day of a 30 % aqueous solution of cocamidopropyl betaine (corresponding to about 75, 150, and 300 mg active substance/kg bw/day, resp.) was tested in 28-and 90-day oral studies with rats in accordance with OECD TG 407 and 408, respectively. The only substance related findings were forestomach lesions, probably as a result of the irritant effect at dose levels of 500 mg/kg bw/day (after 90 days) and 1000 mg/kg bw/day (after 28 days). The NOAELs were 250 mg/kg bw/day after 90 days and 500 mg/kg bw/day after 28 days (corresponding to about 75 and 150 mg active substance/kg bw/day). A similar repeated dose toxicity pattern is expected for lauramidopropyl betaine. No repeat dose dermal or inhalation studies were available for this category.

In vitro tests in bacteria (Ames) and mammalian cells (Mouse lymphoma test; no information on cytotoxicity) showed no genotoxicity of the 30 % aqueous solution of cocamidopropyl betaine. A limited i.p. mouse micronucleus test with 27 % active cocamidopropyl betaine showed no evidence of clastogenicity *in vivo* at non-toxic dose-levels of 200 mg/kg bw/day (highest tested dose, corresponding to 54 mg active substance/kg bw). There is no evidence for a genotoxic potential of the alkylamidopropyl betaines category.

There are no valid carcinogenicity studies available.

There were no fertility studies with alkylamidopropyl betaines available. From a 90-day oral study there is no evidence, that 30 % aqueous cocamidopropyl betaine has an adverse effect on reproductive organs up to the highest dose tested (1000 mg/kg bw/day, corresponding to 300 mg active substance/kg bw/day).

In a developmental toxicity study according to OECD TG 414, 330, 990, and 3300 mg/kg bw/day of a 28.9 % aqueous solution of cocamidopropyl betaine (corresponding to 95, 286, and 950 mg/kg bw/day, resp.) showed dose-related maternal toxic effects (reduced body weights and stomach ulcers) at 990 mg/kg bw/day and above. Embryotoxic effects (increased numbers of resorptions, decreased number of viable fetuses, decreased fetal body weight) were found only at the maternal toxic dose level of 3300 mg/kg bw/day. The NOAEL for maternal toxicity was 330 mg/kg bw/day (corresponding to 95 mg active substance/kg bw/day) and the NOAEL for developmental toxicity was 990 mg/kg bw (corresponding to 286 mg active substance/kg bw). Similar results would be expected for lauramidopropyl betaine.

Environment

Alkylamidopropyl betaines are usually not available as a 100 % pure substance; they are mainly marketed in about 30% aqueous solutions. Therefore experimentally determined physico-chemical properties of the pure substances are only available for selected endpoints. Often measured physico-chemical properties exist only for the aqueous solutions. The following physico-chemical properties have been calculated for the alkylamidopropyl betaines with C_8 – C_{18} fatty acids, i.e. for the shortest and longest chain length in the mixtures. The alkylamidopropyl betaines are solid substances with melting point ranges from 260 to 320°C while measured values for purified fractions range between 55 to 208°C. For purified fractions calculated values for boiling points range from 600 to 730°C, for vapor pressure they are less than 2 x 10^{-13} hPa, for the log K_{OW} they range from -1.28 to 3.63 and for water solubility they range from 1.62 to 8769 mg/l. For these kinds of chemicals there is uncertainty associated with the calculated water solubility. For example the calculated water solubility for lauramidopropyl betaine is 1755 mg/l the measured value is > 100 g/l at 20°C. Whereas melting and boiling points as well as log K_{OW} increase with an increase in alkyl chain length, the water solubility decreases. The particular behavior of these amphoterics is related to their zwitterionic character, so they are completely dissociated in aqueous systems. At very low pH values they are present in a protonated form.

According to the Mackay Level I model calculation, the main target compartment for lauramidopropyl betaine is the hydrosphere (> 99 %). Based on the calculation for caprylamidopropyl betaine (C_8 fatty acid derivate) and stearamidopropyl betaine (C_{18} fatty acid derivate), cocamidopropyl betaine will be mainly distributed to the hydrosphere (59 - 100 %), and to a lesser extent to soil and sediment (0 - 20 % each). The Henry's law constants for alkylamidopropyl betaines calculated for every single fatty acid chain length indicate a very low potential for volatilization from surface waters under environmentally relevant conditions. The soil sorption coefficients (K_{OC}) calculated for the alkylamidopropyl betaines indicate a low to very high potential for sorption to organic matter of soils and sediments. The low sorption potential is confirmed by experimentally obtained values for laurylamidopropyl betaine (C_{12} derivative) and tetradecylamidopropyl betaine (C_{14} derivative) from the screening HPLC-method according to OECD TG 121. A high potential for sorption applies only for the alkylamidopropyl betaines with the C_{16} and C_{18} fatty acid chain length.

Based on the calculated half lives ranging from 6 - 9 h, photodegradation in air by the reaction with OH radicals is expected to be very rapid. However, due to the very low vapor pressure of the alkylamidopropyl betaines this degradation pathway is assumed to be of low environmental significance. No information on direct photolysis is available. With regard to their chemical structure, alkylamidopropyl betaines are not expected to hydrolyze under environmental conditions; a hydrolysis half life of $t_{1/2}$ >1 year has been calculated.

According to the results obtained in guideline studies, the alkylamidopropyl betaines can be considered as being readily biodegradable under aerobic conditions. In guideline tests biodegradation rates of 86 – 100 % after 28 days (OECD TG 301A/B/D/E), 90 – 93 % after 35 days (OECD TG 301B) and 100 % after 20 days (Directive 84/449/EEC, C.5) were determined with cocamidopropyl betaine. Lauramidopropyl betaine was degraded by 95 % based on COD after 28 days in the Modified MITI Test (Directive 92/69/EEC). In a "Coupled Unit Test" (OECD TG 303A) a DOC removal of 97 % (+/-4 %, 95 % probability level) after 35 days and in a "Porous Pot activated sludge simulation test" a removal of 96.8 – 105.2 % (95 % confidence limits) after 161 days were observed indicating that cocamidopropyl betaine is easily removable in sewage treatment plants. Under anaerobic conditions, 80 – 90 % mineralization after 60 days or 56 % after 56 days were observed for cocamidopropyl betaine.

Based on the calculated BCFs between 3 (with C_8 fatty acid) and 71 (with C_{10} – C_{18} fatty acids), a low potential for bioaccumulation is to be expected for alkylamidopropyl betaines. However, it should be noted that results of BCF calculations for surfactants should be used with care.

For the acute toxicity of cocamidopropyl betaine to aquatic species reliable results from tests with fish, daphnia, algae, and microorganisms are available. The lowest acute LC/EC_{50} values for the three trophic levels fish, *Daphnia*, and algae are in each case in the range of 1.3 – 2 mg active substance/l. Furthermore, one long-term test with fish (according to OECD TG 215), and several chronic tests with *Daphnia* and algae were conducted. The lowest NOECs are 0.16 mg active substance/l for fish (*Oncorhynchus mykiss*), 0.03 mg active substance/l for *Daphnia magna*, and 0.09 mg active substance/l for green algae (*Desmodesmus subspicatus*). These values were derived with analytical monitoring (photometric) except for the algae test. However, the effect values within the same species (e.g., *Desmodesmus subspicatus*, *Daphnia magna*) have shown a high variability. Recent guideline studies performed in accordance with OECD TG 211 and 201 using state-of-the-art analytical monitoring and a quality of cocamidopropyl betaine currently commercialized, resulted in a lower aquatic toxicity. In these studies the lowest NOEC for daphnids was determined to be 0.932 mg active substance/l. the lowest NOEC (72 h, based

on growth rate) for algae was determined to be 3.55 mg active substance/l (72 h-E_rC_{50}= 9.86 mg active substance/l). This latter NOEC for algae is further supported by the similar NOEC of 3.53 mg active substance/l calculated using the geometric mean of all valid tests with this algae species. Furthermore, for algae a potential for recovery from the effect up to a concentration of 96 mg active substance/l has been observed.

Because of a proportion of approx. 50 % lauramidopropyl betaine in a mixture of cocamidopropyl betaines it could be assumed, as a worst case, that if lauramidopropyl betaine was the only component responsible for toxic effects of this mixture, the respective toxicity value would decrease by 50 % for lauramidopropyl betaine as single substance.

Two studies (without analytical monitoring) of effects on terrestrial organisms (earthworm and higher plants) showed low toxicity. Taking additionally into account that the adsorption potential of the main components of cocamidopropyl betaine (the C_8 to C_{14} derivatives) is low, a risk for the terrestrial compartment is not expected.

Exposure

In Western Europe 59 000 tons alkylamidopropyl betaines (as 100 % active matter) were produced in the year 2002. Among the 59 000 tons alkylamidopropyl betaines produced in 2002, < 5 % account for lauramidopropyl betaine. The values for sales and captive use in the year 2002 for the alkylamidopropyl betaines are 57 000 tons. About 18 000 tons were produced in USA and 10 000 tons in Asia in the year 2003. European producers are located in Germany, Spain, France, Italy, and UK. Cocamidopropyl betaine and lauramidopropyl betaine are predominately used as cosmetic ingredients, mainly in shampoos and shower gels (50% of the produced volume), and as detergents, mainly in cleaning agents (50 % of the produced volume).

Occupational exposure may occur during manufacture, processing, transport, and use of alkylamidopropyl betaine containing products, mainly through the dermal route. In the Sponsor country appropriate safety measures are in place and controlled regularly by safety inspections. Workers wear protective clothing, gloves, and safety glasses or face shields. They are trained regularly with regard to the safety instructions.

Consumers are mainly exposed through the dermal route by using personal cleansing products and detergents. The betaine concentrations in these products which are between 0.03 and 15% (for cocamidopropyl betaine), and up to 4 % (for lauramidopropyl betaine), do not cause skin irritation. Accidental eye contact is another possible route of exposure. Exposure of the general public via the environment or via the food chain is not expected.

During production, manufacturing, storage, transport, and transfer processes no intended release of the alkylamidopropyl betaines into the environment will occur. Only in case of accidents the product may be released into the environment. Incidental environmental releases may occur during formulation processes such as decanting or transfer processes (e.g., transfer between tanks), and during cleaning processes, mainly into waste water treatment.

As cocamidopropyl betaine and lauramidopropyl betaine are used in personal care products (e.g., shampoos, shower gels), or hand washing agents, it is to be expected that the product will almost entirely be discharged mainly into the waste water treatment.

Data on emissions of the alkylamidopropyl betaines into the environment from production and processing processes are lacking. Also, there is no data available from wastewater treatment plants and surface waters.

RECOMMENDATION, RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health:
The chemicals in this category are currently of low priority for further work. Alkylamidopropyl betaines possess properties indicating a hazard for human health (aqueous solutions with ≥ 30 % active ingredient caused corneal and/or iris damage in rabbits which was still present in some animals at study end, fetotoxicity at maternal toxic doses). This hazard does not warrant further work as it is related to an effect which may only become evident at high exposure levels. It should nevertheless be noted by chemical safety professionals and users. In the Sponsor country, occupational exposure is controlled and adequate risk reduction measures are in place for consumers (classification and labelling). Member countries may desire to check their own risk management measures to find out whether there is a need for additional measures.

Environment:
The chemicals in this category are candidates for further work. Alkylamidopropyl betaines possess properties indicating a hazard for the environment (lowest acute aquatic toxicity values around 2 mg/l, high chronic toxicity to aquatic organisms). Therefore, an exposure assessment and, if then indicated, an environmental risk assessment is recommended.