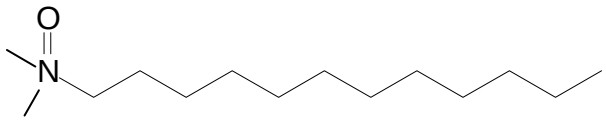
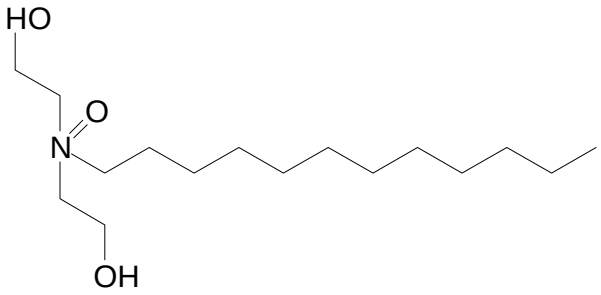
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	1643-20-5	1-Dodecanamine, N,N-dimethyl-, N-oxide
	3332-27-2	1-Tetradecanamine, N,N-dimethyl-, N-oxide
	70592-80-2	Amines, C10-16-alkyldimethyl, N-oxides
	68955-55-5	Amines, C12-18-alkyldimethyl, N-oxides
	2605-79-0	Decanamine, N,N-dimethyl-, N-oxide
	7128-91-8	Hexadecanamine, N,N-dimethyl-, N-oxide
	2571-88-2	Octadecanamine, N,N-dimethyl-, N-oxide
	61788-90-7	Amine oxides, cocoalkyldimethyl
	85408-48-6	Amines, C10-18-alkyldimethyl, N-oxides
	85408-49-7	Amines, C12-16-alkyldimethyl, N-oxides
	61791-47-7	Ethanol, 2,2'-iminobis-, N-coco alkyl derivs., N-oxides
	2530-44-1	Ethanol, 2,2'-(dodecyloxidoimino)bis-
	14048-77-2	Ethanol, 2,2'-(octadecyloxidoimino)bis-
	61791-46-6	Ethanol, 2,2'-iminobis-, N-tallow alkyl derivs., N-oxides
	93962-62-0	Ethanol, 2,2'-[(9Z)-9-octadecenyloxidoimino]bis-
Chemical Category Name	Amine Oxides (AO)	
Structural Formula	Typical structures for amine oxides are as follows: C12 dimethyl amine oxide  C12 dihydroxyethyl amine oxide 	

SUMMARY CONCLUSIONS OF THE SIAR

Category Identification/Justification

The justification for grouping the amine oxides (AO) into a category is based on their structural and functional similarity. All of the substances in this category are surfactants, consisting of a polar "head" (the amine oxide) and a relatively inert, hydrophobic "tail" (the long alkyl substituent). The structural variations in the category are three-fold: 1) the nature of the second and third substituents on the amine are either methyl groups or hydroxyethyl groups; 2) the long alkyl chain ranges in length from 8 to 20 carbons; and 3) the long alkyl chain may contain one or two double bonds (i.e. unsaturation) as in C18:1 (oleyl) or C18:2 (linoleyl). Alkyl chain lengths range from 8 to 20 with 12 and 14 being predominant. Average chain lengths for the mixtures are 12.9 to 13.5, with the exception

of one tallow-derived compound. The presence of methyl- vs. hydroxyethyl-substituents affects the basicity of the nitrogen only marginally, and the hydroxyethyl group lends more bulk to the hydrophilic head-group of the surfactant. The length of the longest alkyl substituent does not alter the chemical reactivity of the molecule, but does affect its physical properties. The influence of unsaturation in the alkyl chain (as in CAS Nos. 93962-62-0 Ethanol, 2,2'-[(9Z)-9-octadecenyloxidoimino]bis- and 61791-46-6 Ethanol, 2,2'-iminobis-, N-tallow alkyl derivs., N-oxides) is expected to make the molecule prone to reactions as typical for unsaturated fatty alkyl chains. Nevertheless, their overall chemical behavior fits within that of the group of C8-18 alkyl dihydroxy ethyl amine oxides.

Human Health

Substantial data exist for mammalian toxicity by *in vitro* and *in vivo* testing. Amine oxides are produced, and transported in aqueous solutions that are 25-35% concentration and most tests were conducted with aqueous solutions in that concentration range. Sometimes aqueous formulations were tested where the AO was at lesser concentrations than 25-35%. Whatever concentration were tested, results are reported below for the active ingredient, amine oxide, in mg AO/kg bw for dermal and oral acute toxicity results and mg AO/kg bw/day for repeated dose studies.

Toxicokinetic and metabolism studies indicate AO's are extensively metabolized and readily excreted after oral administration. Amine oxide was readily absorbed dermally by rats, mice and rabbits after 24 to 72 hours of exposure. After 8 hours of dermal exposure, humans absorbed <1%.

In rat oral acute toxicity limit tests, no deaths occurred at single doses of 600 mg C_{10-16} AO/kg bw or less (for CAS No 70592-80-2). In multi-dose studies, acute oral LD_{50} values for rats ranged from 846 mg AO/kg bw to 3873 mg AO/kg bw (both values for CAS No 61788-90-7), with several other AO's having rat oral LD50's falling within this range. In single dose acute dermal toxicity limit tests, no deaths occurred at a dose of 520 mg AO/kg bw (CAS No 70592-80-2). This dose was equivalent to 2 mL/kg of a 30% formulation. There were no deaths observed in a rat acute inhalation study to aerosol droplets of a consumer product providing a dose of 0.016 mg AO/L.

In a series of studies on rabbits, AO's of varying chain length showed consistent results and all 1) were not irritating to the skin or eyes at low concentrations (1%), 2) were moderately irritating at 5%, and 3) more severely irritating when tested as produced (e.g., ~30% aqueous solutions). In studies that included rinsing, eye irritation effects diminished with rinsing after 30 seconds of exposure and were slight with rinsing after 4 seconds of exposure. In Draize rabbit eye irritation tests using ~30% AO solutions, rabbits experienced severe to moderate irritation. (The maximum concentration of AO is 10% active in consumer products.) Accidental eye exposure in manufacturing employee incidents and consumer incidents established that eye irritation effects of exposure during manufacturing and use of products containing AO and other surfactants are moderate, transient and reversible

There is no indication of skin sensitization for the AO category based on the available animal and human data.

In four repeated-dose studies with rats and mice exposed to AO via oral and dermal routes (all with CAS No 70592-80-2), three dermal studies were designed to assess the effect of repeated exposure on skin at maximum doses of 1.5 mg AO/kg-bw/day. Higher doses were tested in a 90-day dietary study with rabbits. No treatment-related clinical chemistry, hematology and histopathological changes were observed. In these studies, LOAELs ranged from 87 to 150 mg AO/kg bw/day with the highest oral NOAEL below the lowest LOAEL as 80 mg AO/kg bw/day. Signs of toxicity observed in the oral study included suppressed mean body weight gain, lenticular opacities and diarrhea; in the dermal studies, local dermal irritation was evident.

In five *in vitro* bacterial (*Salmonella*) mutagenicity studies, AO shows no evidence of mutagenicity either with or without S9 metabolic activation at concentrations up to 250 ug/plate (higher concentrations caused cytotoxicity). Three *in vivo* studies investigated clastogenic effects on a close structural analog of the category, 1-(methyldodecyl)dimethylamine-N-oxide including: a mouse micronucleus, a Chinese hamster micronucleus and a Chinese hamster cytogenetics study. These studies were all negative showing no increase in micronuclei or chromosome aberrations. An *in vivo* mouse dominant lethal assay showed no evidence of heritable effects. Two AOs (CAS No 1643-20-5 and CAS No 3332-27-2) were negative in an *in vitro* cell transformation assay tested at concentrations up to 20 ug/ml.

The carcinogenic potential of amine oxides has been thoroughly investigated in three carcinogenicity studies in rats or mice by dermal, dietary, or drinking water routes. In all cases the substances demonstrated no evidence of a

carcinogenic response.

No evidence of reproductive toxicity or fertility effects was observed in a study in which rats were given dietary doses of AO in the diet over two generations (CAS No 1643-20-5). No macroscopic or histopathological changes were attributable to treatment with the test substance. The maternal NOAEL from this reproductive study was >40 mg AO/kg bw/day, which was the highest dose tested. At all treatment levels, the rate of bodyweight gain for the F1 and F2 offspring was reduced during the lactation period, however, this reduction was not greater than 10%. This effect appeared to be dose-related, but was not statistically significant until after weaning in the mid and high dose levels. This was not considered an adverse effect since the body weight change only reached statistical significance when the rat pups were getting the majority of their calories from solid food (Developmental NOAEL >40 mg/kg bw/day). In three developmental toxicity studies via gavage in rats and rabbits (with CAS No 1643-20-5 & 70592-80-2), effects such as decreased fetal weight or delayed ossification, were most often observed only at maternally toxic doses and were associated with the irritation effects of AO on the gastrointestinal tract. No decreases in litter size, no changes in litter parameters, no malformations or significant differences in skeletal defects were observed at oral doses up to 25 mg/kg bw/day in rats (based on decreased fetal weight at 100 mg/kg bw/day) and >160 mg/kg bw/day in rabbits (the highest dose tested).

Environment

The chemicals of the amine oxides category do not exist as 'pure' substances, but are produced, transported and used as aqueous solutions, typically within a range of 25-35% AO/water. Experimental values for melting points of C10 to C16 amine oxides range from 125 to 136°C. Amine oxides undergo Cope elimination, i.e., the formation of an olefin and a hydroxylamine by pyrolysis of an amine oxide, in the temperature range 150-200°C, thus decomposition is likely to occur before the melting point is reached, and all boiling points are predicted to be far above the decomposition temperature. Amine oxides are not volatile: predicted vapor pressure values are < 4.6E-7 hPa. Amine oxides are highly water soluble – measured values for a C12.6 average chain length is ~410g/L. Although it is impossible to accurately measure an octanol-water partition coefficient for surface-active agents like amine oxides, an octanol-water partition coefficient (Log value) of < 2.7 has been calculated for amine oxides of chain length C14 and below. The predicted atmospheric oxidation half lives are of the order of 5 hours, indicating a relatively rapid atmospheric degradation potential.

Amine oxides are removed by conventional sewage treatment systems and biodegrade under aerobic and anaerobic conditions. Of the collected data, four amine oxides meet the "readily biodegradable" OECD criterion, two are "ultimately biodegradable," and two are "inherently biodegradable." These studies are conducted on complex mixtures with a high degree of alkyl chain length overlap. Further, biodegradation is not dependent on chain length. Removal of amine oxides in biological wastewater treatment has been studied in laboratory simulation studies (>99.8% removal, OECD 303A study) as well as through monitoring activities in different geographies; the main removal mechanism can be attributed to mineralization and an average removal number of 98% can be assumed as applicable for secondary activated sludge treatment. Level III fugacity modeling, using loading rates for air, soil, and water of 1000 kg/h for each media, shows water receiving compartment receiving 99.5%; the other compartments are negligible. The bioconcentration factor for amine oxides <C14, is predicted to be <87, based on log Kow data, indicating low potential for bioaccumulation in aquatic organisms.

Extensive aquatic toxicity data are available for commercially representative amine oxides (C10 to C18) that are single chain length as well as mixtures. Based on hazard data, freshwater green algae are considered the most sensitive species, for acute and chronic endpoints. Acute toxicity is affected by chain length for fish and invertebrates. Chain length affects hydrophobicity, wherein longer chain-lengths increase the rate of uptake and decrease depuration. All but four supporting AO's have been tested for acute toxicity in fish, daphnia, and algae. The range of acute $LC_{50}/EC_{50}/ErC_{50}$ values based on a review of the aquatic toxicity data on AO were 0.60-32 mg/L for fish, 0.50-10.8 mg/L for *Daphnia magna* and 0.010-5.30 mg/L for algae. Chronic toxicity data were normalized to a chain length of 12.9 carbon atoms, as this average chain length represents the largest volume product for North America (CAS No 70952-80-2). Chronic toxicity (NOEC, EC20) for an amine oxide of average chain length of C12.9 ranged as follows for the different trophic levels: 0.010-1.72 mg/L for algae, 0.28 mg/L for Daphnia (flow through) and 0.31 mg/L for fish (flow through). These are based on geometric mean values, and a dataset of 21 chronic toxicity studies. Based on a chronic periphyton microcosm bioassay that included 110 taxa of algae (most sensitive species), a NOEC value of 0.050 mg/L was derived when normalized for a C12.9 amine oxide.

Exposure

For the AO category as a whole, current production is approximately 26,000 metric tonnes in the US (sponsor country), 16,000 tonnes in Europe and 6,800 tonnes in Japan. In the production phase, manufacturing processes have been designed to maximize production yield and minimize potential releases. The potential for human exposure to AO is minimized by a water solubility of 409.5 g/L, having volatility below 4.6E-5 Pa and being produced in aqueous solutions. Engineering controls (e.g., closed system operations, exhaust ventilation, dust collection) and personal protective equipment (e.g., protective clothing, eyewear, and gloves) at manufacturing and formulation facilities further mitigate worker exposure. No special engineering controls or additional personal protective equipment are uniquely specified for AO. A limited amount of AO in aqueous solution may be released as a dilute solution from washing and rinsing operations in the manufacturing process and is discharged to wastewater treatment.

Labeling of consumer products containing AO and other surfactants include warnings of the potential for eye irritation and first aid instructions to rinse with water.

Amine oxides are amphoteric surfactants used at active concentrations between 0.1 and 10% in consumer cleaning and personal care products, usually in conjunction with other surfactants. They function as foam stabilizers, thickeners and emollients, emulsifying and conditioning agents in liquid dishwashing and laundry detergents, liquid hard surface cleaners, shampoos, hair conditioners, creams, moisturizers, bar soaps, cleansing and other personal care products. There are no known commercial uses or industrial process intermediate uses of the amine oxides.

Data suggest that inhalation of AO-containing products during use will be low. Spray cleaning products containing AO are designed to produce the large particle sizes needed for efficient delivery of the spray to the surface being cleaned. In laboratory simulations with six spray nozzles representing those used in spray cleaning products, less than 0.1% of the total volume sprayed consists of respirable particles (particles under 10 microns in diameter) and air concentrations in the breathing zone are in the 0.13-0.72 mg/m^3 range. Based on these data, it is expected that inhalation exposures to AO in respirable particles are low.

Results of environmental field monitoring in the United States and the Netherlands indicate that surface water concentrations downstream from sewage treatment plant mixing zones range from <0.1 to <1 µg/L. Results of a four season monitoring program in major urban rivers of Japan found concentrations ranging from non-detect (< 0.01 µg/L) to 0.34µg/L, with a median concentration of 0.04µg/L.

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

Human Health: This category is currently of low priority for further work. The chemicals in this category present properties indicating a hazard for human health (skin and eye irritation). However, these hazards do not warrant further work as they are related to reversible, transient and non-lasting effects. Nevertheless, these hazards should be noted by chemical safety professionals and users.

Environment: The chemicals in this category are candidates for further work. The chemicals in this category have properties indicating a hazard for the environment (aquatic toxicity <1 mg/L for fish, aquatic invertebrate and/or algae). This category is anticipated to biodegrade and has a limited potential for bioaccumulation. Member countries are invited to perform an exposure assessment and, if necessary, a risk assessment.