SIDS INITIAL ASSESSMENT PROFILE

CAS Nos.	68526-84-1	Alcohols C8-C10-iso, C9 rich
	27458-94-2	Isononyl alcohol
	68526-85-2	Alcohols C9-C11-iso, C10 rich
	25339-17-7	Isodecyl alcohol
	10042-59-8	2-Propylheptan-1-ol
	68526-86-3	Alcohols C11-C14-iso, C13 rich
	27458-92-0	Isotridecan-1-ol
Chemical Category Name	Oxo Alcohols C9 to C13	
Structural Formula	68526-84-1	CH_3-CH(CH_3)-(CH_2)$_6$-OH (based on a C9 alcohol; general structure; contains essentially methyl branching patterns)
	27458-94-2	CH_3-CH(CH_3)-(CH_2)$_6$-OH (general structure; contains various methyl and/or ethyl branching patterns)
	68526-85-2	CH_3-CH(CH_3)-(CH_2)$_7$-OH (based on a C10 alcohol; general structure; contains various methyl branching patterns)
	25339-17-7	CH_3-CH(CH_3)-(CH_2)$_7$-OH (general structure; contains various methyl branching patterns)
	10042-59-8	CH_3-(CH_2)$_4$-CH(CH_2-CH_2-CH_3)-CH_2-OH (based on a C10 alcohol general structure; may also contain methyl branching)
	68526-86-3	CH_3-CH(CH_3)-(CH_2)$_{10}$-OH (based on a C13 alcohol; general structure; contains various methyl branching patterns)
	27458-92-0	CH_3-CH(CH_3)-(CH_2)$_{10}$-OH(general structure; contains various methyl and/or ethyl branching patterns)

SUMMARY CONCLUSIONS OF THE SIAR

Category Justification

The Oxo Alcohols C9 to C13 Category is a family of saturated alcohols that are produced from olefins by the hydroformylation or "oxo" process. Hydroformylation is the reaction of an olefin with carbon monoxide and hydrogen to produce an aldehyde, and its subsequent hydrogenation to the alcohol. The number of carbon atoms in the category members ranges from 9 to 13. Category members contain predominantly branched alkyl groups. Each member is a multi-isomeric product, containing saturated primary alcohols of high purity, and having the following basic structure: CH_3-R-CH_2-OH, where R is a branched isomeric structure.

The justification for the Oxo Alcohols C9 to C13 Category is that the members have:

- similar chemical structures,
- similar physico-chemical properties,
- comparable environmental fate,
- the same mode of action.

In general, acute aquatic toxicity of aliphatic alcohols occurs by non-polar narcosis. The mode of action is disruption of biological membrane function. Mammalian metabolic pathways for both linear and branched n-primary alcohols are likely to include similar reactions for all category members and result in structurally similar metabolites.

The data demonstrate that the category is valid for the SIDS endpoints, and read across was applied where no data were available.
Analogue substances which have similar structure and properties of sufficient similarity are of value in supporting selected endpoints of the Category members. They are Alcohols, C7-11-branched and linear (CAS RN: 85566-14-9 - R length (C number) and structure: C7 to C11 Linear), Nonan-1-ol (CAS RN: 143-08-8; 28473-21-4 - R length (C number) and structure: C9 Linear) and Dodecan-1-ol (CAS RN: 112-53-8 - R length (C number) and structure: C12 Linear). As the analogues are not produced by consortium members, they are not included in this category.

Human Health

Linear and branched chain alcohols exhibit similar patterns of absorption, metabolism, and excretion. Both linear and branched aliphatic alcohols are absorbed through the gastrointestinal tract and are rapidly eliminated from the blood. Plasmatic half-lives are normally difficult to measure since many of the low molecular weight metabolites (e.g. aldehydes, carboxylic acids) are endogenous in humans. Linear and branched chain alcohols are initially oxidized to their corresponding aldehydes and further to their corresponding carboxylic acids by high capacity NAD+/NADH-dependent enzymes, which are then metabolized to carbon dioxide via the fatty acid pathways and the tricarboxylic acid cycle. Alcohol dehydrogenase (ADH) enzymes are the cytosolic enzymes that are primarily responsible for the oxidation of alcohols to their corresponding aldehydes. Alcohols also can be oxidized to aldehydes by non-ADH enzymes present in the microsomes and peroxisomes, but these are generally quantitatively less important than ADH. Aldehyde dehydrogenases (ALDH) oxidize aldehydes to their corresponding carboxylic acids. Branched-chain aliphatic alcohols and aldehydes have been shown to be excellent substrates for ADH and ALDH. As carbon chain length increases, the rates of ALDH-mediated oxidation also increase. The metabolism of branched-chain alcohols, aldehydes, and carboxylic acids containing one or more methyl substituents is determined primarily by the position of the methyl group on the branched-chain. Higher molecular weight homologues (> C10), may also undergo a combination of ω-, ω-1 and β-oxidation, and selective dehydrogenation and hydration to yield polar metabolites which are excreted as the glucuronic acid or sulfate conjugates in the urine and, to a lesser extent, in the feces. Thus, the principal metabolic pathways utilized for detoxification of these branched-chain substances are determined primarily by four structural characteristics: carbon chain length, and the position, number, and size of alkyl substituents. Most of the substances in the Oxo Alcohols C9 to C13 category are mixed branched-chain alcohols. Based on the similar metabolism of linear and branched-chain alcohols within this carbon number range, it can be concluded that the members of the Oxo Alcohols C9 to C13 category will undergo metabolism similar to those of the analogue linear substances mentioned above. No pharmacokinetic study was conducted on members of the category.

Members of the Oxo Alcohols C9 to C13 Category have a low order of toxicity by the oral, dermal, inhalation and intraperitoneal routes of exposure. Oral LD_{50}s ranged from > 2000 to 5400 mg/kg bw and dermal LD_{50}s ranged from > 2600 to 5010 mg/kg bw. Inhalation exposure studies conducted at saturated vapor pressures generally produced no deaths. Although the lighter C9 alcohols were an exception, the resulting LC_{50} was in excess of 3600 ppm. Members of the Oxo Alcohols C9 to C13 Category were moderately irritating to the skin of rabbits and generally irritating (range: non-irritating to severely irritating) to the eyes of rabbits. Additionally, the alcohols C9-C11-iso, C10 rich (CAS RN 68526-85-2) produced moderate upper airway sensory irritation in male mice exposed to vapor atmospheres up to the achievable limit. Based on limited data, there is no indication of skin sensitizing potential for the Oxo Alcohols C9 to C13 Category. No data are available to assess the potential for respiratory tract sensitisation in animals or humans.

Only one category member, 2-propylheptanol, was tested in a subchronic toxicity study. The 90-day study in rats showed the liver to be the main target organ, and resulted in a NOAEL of 150 mg/kg bw/day in males and 30 mg/kg bw/day in females (only one female showed peroxisome proliferation related effects). In 14-day *screening* studies in rats designed to evaluate the liver and testes, iso-nonanol, iso-decanol, and isotridecanol produced minimal or no effects on the liver, and no testicular effects at doses of 144, 168 and 184 mg/kg bw/day, respectively. The available data suggest that the members of the Oxo Alcohols C9 to C13 Category are likely to demonstrate a low order of subchronic toxicity.

Studies carried out on four members of the Oxo Alcohols C9 to C13 Category in accordance with OECD TG 471, using *Salmonella typhimurium* as well as *Escherichia coli* did not show genotoxic effects, either with or without metabolic activation. One category member, isodecanol, was also tested in an *in vitro* chromosomal aberration assay according to OECD TG 473, using V79 Chinese hamster lung fibroblasts, and no mutagenic effects were found with or without metabolic activation. *In vivo* assays were conducted with two category members and did not show genotoxic effects, although only limited experimental details were available. Additionally, an *in vivo* mouse

micronucleus assay was carried out with the analogue linear alcohol (1-dodecanol) and found no clastogenicity. Based on the lack of effects found in the limited studies available and based on data for similar linear alcohols used as analogues, the members of the Oxo Alcohols C9 to C13 Category are considered to have a low genotoxic potential. No chronic toxicity or carcinogenicity studies have been conducted on Oxo Alcohols C9 to C13 Category members. Based on the negative *in vitro* and *in vivo* genotoxicity data, and the absence of any structural alerts, members of the Oxo Alcohol C9 to C13 Category are unlikely to possess genotoxic carcinogenic potential.

Developmental toxicity studies conducted by the oral route on isononyl alcohols, isodecanol, 2-propylheptanol and isotridecanol demonstrated that these materials do not affect reproductive parameters. Although a slight increase in resorptions was observed in several of the studies, this only occurred in the highest dose group(s) and in the presence of overt maternal toxicity. NOAELs for developmental toxicity ranged from 144-1440 mg/kg bw/day. As supporting information, testing of 1-dodecanol in a combined repeated dose developmental /reproductive study showed no effects to parents or offspring at levels up to 2000 mg/kg bw/day. Furthermore, inhalation exposure to vapors, at levels of 150 and 100 mg/m^3 of respectively 1-nonanol and 1-decanol, did not induce any statistically significant changes in reproductive parameters. In the 14-day repeat dose studies of isononanol, isodecanol and isotridecanol, no changes in testicular weight were observed. These data support the conclusion that members of the Oxo Alcohols C9 to C13 category are not selective reproductive toxicants.

Environment

Members of the Oxo Alcohols C9 to C13 Category are liquid at 25°C. Most of their physico-chemical properties were obtained by direct measurement. Values that could not be measured were obtained via calculation using chemical structures that best characterize the range of constituent chemicals. The category members demonstrated relatively similar properties or progressive change across a range of values with melting point ranging from -117°C to -40°C, boiling point ranging from 202°C to 270°C (at 1,013 hPa), density ranging from 0.832g/cm^3 to 0.846 g/cm^3, vapour pressure ranging from 0.002 to 0.054 hPa at 25°C, water solubility values ranging from 2 mg/l to 240 mg/l, and log K_{ow} values cited as greater than 3.4 and ranging up to 5.5. Henry's Law Constant (HLC), a measure of the potential of a molecule to evaporate from open water, indicates that the category members will not volatilize at an appreciable rate, if released to water (HLCs range from 3.61 to 20.0 Pa.m^3/mol).

Results of the environmental distribution model, using a level III fugacity model, suggest a high environmental distribution into the water compartment for alcohols C8-C10-iso, C9 rich, isononanol, isodecyl alcohol, and 2-propyl heptan-1-ol. The model also predicts a high environmental distribution into the sediment compartment for alcohols C11-C14-iso, C13 rich and isotridecanol. Volatilization to the air from aqueous and terrestrial habitats will be negligible because Oxo Alcohols C9 to C13 have low vapor pressure (<0.06 hPa at 25° C). However, in the air, these substances have the potential to rapidly degrade through indirect photolytic processes mediated primarily by hydroxyl radicals ($^{\bullet}$OH) with a calculated degradation half-life ranging from approximately 6 to 9 hours (based on 12-hour day) and 18 to 33.6 hours (based on a 24-hour day). Although, Oxo Alcohols C9 to C13 have the potential to degrade at a significant rate in the atmosphere, it is unlikely that degradation in this compartment will occur to an appreciable extent because they have a low potential to partition to this compartment. Aqueous photolysis and hydrolysis will not contribute to the transformation of the Oxo Alcohols C9 to C13 in aquatic environments because they are not susceptible to these reactions.

Biodegradability of the Oxo Alcohols C9 to C13 Category members has been evaluated with standard test guidelines. The results from these studies suggest that the members of the Oxo Alcohols C9 to C13 Category are subject to microbial degradation in the aquatic environment under both aerobic and anaerobic conditions with biodegradation potentials of 60.6% to 90-100% in 28 days, and that they are either readily or inherently biodegradable. The inherently biodegradable materials, although exceeding the criteria of 60% biodegradation in 28 days, did not do so within the 10-day window necessary for a "readily biodegradable" designation. Therefore the predominant mechanism accounting for removal in a wastewater treatment facility is biodegradation, followed by partitioning to sludge, with volatilization accounting for the remaining loss.

Member substances of the Oxo Alcohols C9 to C13 Category have been shown to exhibit moderate to high acute aquatic toxicity, in various organisms covering the three trophic levels. Experimental acute toxicity values for fish and invertebrates range from 0.42 to 11 mg/L, and 0.39 to 17.1 mg/L, respectively. For algae, the experimental 72-hr EC_{50} range from 1.6 to 19.0 mg/L. Despite some variability, the acute aquatic toxicity data clearly shows that as carbon number increases from a C9 to a C13, toxicity increases as is expected for non-polar narcotics. Experimental chronic toxicity data for category members are not available. Chronic toxicity data for an analogue substance (dodecanol) indicate a low potential to produce chronic toxicity to aquatic invertebrates. The 21-day

NOEL for a daphnid was 1 mg/L. Calculated chronic toxicity values range from 0.03 to 11.1 mg/L for the three trophic levels.

Category members have a low potential to bioaccumulate in aquatic species based on biochemical evidence of biotransformation and on experimentally derived bioconcentration factors (BCF) in fish in the range of 15 to 60.
In the terrestrial environment, category members are expected to exhibit a low order of toxicity based on calculated 16-day earthworm LC_{50} values ranging from 128 to 374 mg/kg soil.

Exposure

Oxo Alcohols C9 to C13 Category substances are primarily used as chemical intermediates and additional applications can include uses such as co-solvents, anti-foaming agents, solvent extraction and flotation. Based on physical properties, the primary workplace exposure would be through inhalation and dermal contact. The majority of the applications do not contain free alcohols; therefore, minimal consumer exposure is foreseen, since the consumer is only indirectly exposed through the use of the applications and uptake is expected to be low. The SPIN database contains confidential data for category members, alcohols, C8-C10-iso, C9 rich, isononyl alcohol, and 2-propylheptanol. No consumer products are listed for isodecanol, isotridecanol, or alcohols, C11-C14-iso, C13 rich. For alcohols, C9-C11-iso, C10 rich 22 preparations are listed in Sweden and Denmark at 1.1 to 2.0 tonnes/ annum, including consumer products in Sweden used for lubricants and additives. Alcohols, C11-C14-iso, C13 rich is listed for approximately 80 preparations with tonnes/annum of 459, 8, 0.1, and 6.7 in Sweden, Norway, Finland and Denmark, respectively. Intended uses of the preparations include paints, lacquers, varnishes, construction applications, surface-active agents in cleaners, and intermediates in the manufacture of non-metallic mineral products. Isotridecanol has 18 products and 36 preparations listed with levels at or below 1.3 tonnes/ annum in Sweden, Norway and Denmark. These preparations and products have intended uses in paints, lacquers, and varnishes and primarily in the manufacture of textiles and also in the automobile sector. At least four uses listed are for antifoaming agents. Of the 36 preparations listed for isotridecanol, at least 21 list a zero tonnage (*i.e.*, not intentionally added to the preparation). European production capacities (in 2003) for category members are of 200000-500000 t/year.

At production sites, potential exposure to Oxo Alcohols C9 to C13 in the environment is low because there are no direct releases to the environment. There was no information on environmental concentrations for substances in the Oxo Alcohols C9 to C13 Category. Essentially, Oxo Alcohols C9 to C13 released during manufacture enter the wastewater treatment facility (WWTF) where they can be biodegraded rapidly or sorbed to sewage sludge, which in Europe is mainly incinerated and in the United States is either incinerated or landfilled. The latter severely hinders their further migration because oxo alcohols have a low potential to migrate through soil as suggested by their K_{oc} values. Process, storage, and handling operations are conducted in enclosed facilities. Over-spills are collected and treated (via WWTF), and air from production plants and pumping stations is collected and incinerated.

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

Human Health: The chemicals in the Oxo Alcohols C9 to C13 Category are of low priority for further work. They possess properties indicating a low hazard for human health, except for eye and skin irritation. These hazards do not warrant further work as they are related to reversible effects. They should nevertheless be noted by chemical safety professionals and users. Countries are invited to perform an exposure assessment for workers and consumers and if necessary a risk assessment.

Environment: The chemicals with chain lengths of C9 and C10 (CAS No 68526-84-1, 27458-94-2, 68526-85-2, 25339-17-7, 10042-59-8) have properties indicating a hazard for the environment (acute aquatic EC/LC_{50} values between 1 and 100 mg/l). However they are of low priority for further work for the environment because of their rapid biodegradation and their limited potential for bioaccumulation.
The chemicals with chain lengths of C13 (CAS No 68526-86-3, 27458-92-0) show acute aquatic effects at concentrations below 1 mg/l. Therefore, they should be candidates for further work. Furthermore, member countries are invited to perform an exposure assessment and if necessary a risk assessment.