

**SIDS INITIAL ASSESSMENT PROFILE**

Chemical Category Name	Long Chain Alcohols (C6-22 primary aliphatic alcohols)			
CAS Nos	<b>Chemical name</b>	<b>CAS no.</b>	<b>Chemical name</b>	<b>CAS no.</b>
	1-Hexanol	111-27-3	Alcohols, C16-18	67762-27-0
	1-Octanol	111-87-5	Alcohols, C14-18	67762-30-5
	1-Decanol	112-30-1	Alcohols, C10-16	67762-41-8
	1-Undecanol	112-42-5	Alcohols, C8-18	68551-07-5
	1-Tridecanol	112-70-9	Alcohols, C14-16	68333-80-2
	1-Tetradecanol	112-72-1	Alcohols, C6-12	68603-15-6
	1-Pentadecanol	629-76-5	Alcohols, C12-16	68855-56-1
	1-Hexadecanol	36653-82-4	Alcohols, C12-13	75782-86-4
	1-Eicosanol	629-96-9	Alcohols, C14-15	75782-87-5
	1-Docosanol	661-19-8	Alcohols, C12-14	80206-82-2
	Alcohols, C12-15	63393-82-8	Alcohols, C8-10	85566-12-7
	Alcohols, C9-11	66455-17-2	Alcohols, C10-12	85665-26-5
	Alcohols, C12-18	67762-25-8	Alcohols, C18-22	97552-91-5
	9-Octadecen-1-ol (9Z)-	143-28-2	Alcohols, C14-18. & C16-18-unsatd	68155-00-0
	Alcohols, C16-18 & C18 Unsaturated	68002-94-8	Tridecanol, branched & linear	90583-91-8
Structural Formula	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>n</sub> CH <sub>2</sub> OH		Linear n = 4 to 20	
	$\begin{array}{c} \text{CH}_3(\text{CH}_2)_n\text{CHCH}_2\text{OH} \\   \\ (\text{CH}_2)_m\text{CH}_3 \end{array}$		2-Alkyl branched n + m = 3 to 18, and m is predominantly = 0. Present in essentially-linear alcohols	
	$\begin{array}{c} \text{CH}_3(\text{CH}_2)_n\text{CH}(\text{CH}_2)_m\text{OH} \\   \\ \text{CH}_3 \end{array}$		Other-methyl branching n + m = 9 or 10 Present in essentially-linear Fischer-Tropsch derived alcohols	
	$\begin{array}{c} \text{CH}_3(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_7\text{CH}_2\text{O} \\ \text{H} \end{array}$		Unsaturated 9-Z unsaturated components are present in some commercial products.	

**SUMMARY CONCLUSIONS OF THE SIAR****Category Rationale**

This category covers a family of 30 primary aliphatic alcohols within a carbon chain length range of C6-C22. Commercial products generally include several aliphatic alcohol components, with a range of carbon chain lengths

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present. The family consists of alcohols with varying compositions and structures. Composition depends on the route to manufacture and the related feedstocks. Most of the alcohols have linear carbon chains but certain manufacturing processes create branched structures. Data are also available for eleven other similar substances, which support the category. Non-sponsored alcohols may not be HPV or may not be produced by members of the consortium, but have structures similar to sponsored linear alcohols.

Key points are that the members share:

- The same structural features
- Similar metabolic pathways
- Common mode of ecotoxicological action
- Common levels and mode of human health related effects.

This allows multi-component reaction products to be considered within the Category by the application of validated models of exposure and effects, on the basis of detailed knowledge of the composition. For the environmental end points, this has been done in two ways:

Read-across: this applies to biodegradability, for which sufficient data are available to allow read across from the pattern of degradation across the entire category to fill data gaps directly. For algae, read-across-based expert judgement was applied, taking into account measured and predicted effects in daphnids and fish for the substance of interest.

Modelling: a model of the ideal solubility of the components of the substances has been set up, which allows component and total solubility at any loading rate to be calculated. By use of knowledge of the properties of each component, ecotoxicological effects have been predicted.

### **Human Health**

Considering the manufacturing processes two sub-categories of aliphatic alcohols can be distinguished:

- Linear alcohols: Saturated or unsaturated primary -non-branched- aliphatic alcohols containing an even number of carbon atoms.
- Essentially linear alcohols: Saturated, primary linear aliphatic alcohols and their saturated, mono branched primary alcohol isomers of corresponding carbon chain length

A detailed assessment of the toxicological database of both sub-categories shows that the linear and the essentially linear alcohols are of a low order of toxicity following acute and repeated exposures. The endpoints of skin and eye irritation show a trend within each of the sub-categories with the lower members of the category displaying a more pronounced response than the longer-chained-alcohols. The overall toxicological profile of the sub-categories of linear and essentially linear alcohols is qualitatively and quantitatively similar for all end points assessed. The observed relationship between chain length and toxicological properties is equally present for both sub-categories. Moreover, the mammalian metabolism of the aliphatic alcohols is highly efficient and proceeds similarly for each of the sub-categories. The first step of the biotransformation the alcohols are oxidised to the corresponding carboxylic acids, followed by a stepwise elimination of C2 units in the mitochondrial  $\beta$ -oxidation process. The metabolic breakdown of mono-branched alcohol isomers is also highly efficient and involves processes that are identical to that of the linear aliphatic alcohols. The presence of a side chain does not terminate the  $\beta$ -oxidation process, however in some cases a single Carbon unit is removed before the C2 elimination can proceed.

Surrogate and supporting substances have been assessed for this category in order to address potential concerns associated with differing degrees of branching and to justify the read-across within the sub-category of the essentially linear alcohols.

Aliphatic alcohols are absorbed by all common routes of exposure, widely distributed within the body and efficiently eliminated. There is a limited potential for retention or bioaccumulation for the parent alcohols and their biotransformation products.

The category of the long-chain aliphatic alcohols as a whole is of a low order of acute toxicity upon inhalational, oral or dermal exposure. The members of this category are generally of a low volatility and the acute lethal

concentration exceeds the saturated vapour pressure. In most cases the acute oral and dermal LD50 values exceed the highest dose tested and, depending on the test protocol, range from >2000 to >10,000 mg/kg.

Overall, the toxicology database shows an inverse relationship between chain length and toxicity. The shorter chain alcohols tend to induce more pronounced effects when compared to materials with a longer chain length. This is illustrated most clearly by the degree of irritation in skin and eye irritation studies in laboratory animal studies. For the aliphatic alcohols in the range C6 – C11 a potential for skin and eye irritation exists, without concerns for tissue destruction or irreversible changes. Aliphatic alcohols in the range C12 – C16 have a low degree of skin irritation potential; alcohols with chain lengths of C18 and above are non-irritant to skin. The eye irritation potential for alcohols with a chain length of C12 and above has been shown to be minimal.

Aliphatic alcohols have no skin sensitisation potential.

Repeated exposure to aliphatic alcohols is generally without significant systemic toxicological findings and this category is therefore regarded to be of a low order of toxicity upon repeated exposure. At the lower end, members of this category induce local irritation at the site of first contact. Other notable findings observed for several members within this group suggest mild changes consistent with low-grade liver effects with the changes in essentially linear alcohols being slightly more pronounced than in branched alcohols. Typical findings include: slightly increased liver weight, in some cases accompanied by clinical chemical changes but generally without concurrent histopathological effects. Special studies demonstrated that this category does not have a potential for peroxisome proliferation. CNS effects were absent upon inhalation or dietary administration, however 1-hexanol and 1-octanol showed a potential for CNS depression upon repeated administration of a bolus dose. Similarly, 1-hexanol and 1-octanol induced respiratory distress upon repeated administration of a bolus dose. Aliphatic alcohols do not have a potential for peripheral neuropathy. Typical NOAEL's recorded for this category range between *ca.* 200 mg/kg/day to 1000 mg/kg/day in the rat upon sub-chronic administration via the diet.

Several members of the long chain aliphatic alcohol category were used as a vehicle or solvent in chronic skin painting studies. Although the validity of such experiments is limited, there was no evidence of a carcinogenic potential for this category. Long chain aliphatic alcohols do not contain structural elements of concern for potential interaction with DNA and have been shown to be without mutagenic activity, primarily on the basis of Ames assays and mouse micronucleus assays.

On the basis of the lack of adverse findings in the reproductive organs in repeated dose toxicity studies and in screening studies for reproductive effects this category is considered without a potential for adverse effects on fertility and reproductive toxicity. Similarly, developmental toxicity studies in substances belonging to this category and aliphatic alcohols supporting this category studies have confirmed the lack of potential adverse effects on the developing foetus.

### Environment

The general trends in the data show properties that vary with carbon chain length in accordance with normal expectations. As carbon chain length increases melting point increases, boiling point increases and vapour pressure decreases; one consequence of this is that flash point temperatures increase at higher molecular weight. Water solubility decreases and the octanol-water partition coefficient increases with increasing carbon chain length.

Physicochemical properties vary, as described, across members of the Category. Ranges of key property values are:

- Melting point: from *ca.* -50°C (*measured; Hexanol*) to +72.5°C (*measured; Docosanol*)
- Boiling point: from 158°C (*measured; Hexanol*) to *ca.* 400°C (*upper limit of measured boiling range for C18-22 alcohols, supported by estimated value for Docosanol*)
- Density: from *ca.* 0.80 g/cm<sup>3</sup> to *ca.* 0.85 g/cm<sup>3</sup> (*measured; range across category*)
- Vapour pressure: from 8.2E-08 hPa (*estimated; Docosanol*) to 1.22 hPa (*measured; Hexanol*)
- Water solubility: from *ca.* 0.001 mg/l (*measured; Octadecanol*) to 5900 mg/l (*measured; Hexanol*)
- Partition coefficient: from 2.03 (*measured; Hexanol*) to >7 (*measured, Eicosanol*)

### Environmental Fate

Reliable measured data show that alcohols with chain lengths up to C18 are readily biodegradable (*measured; hexanol, octanol, decanol, dodecanol, tetradecanol, hexadecanol and octadecanol*). At carbon chain lengths up to C16, most tests showed that pass levels for ready biodegradation were reached within the 10-day window, with removal levels up to 100% over the timescale of the test. Chain lengths of C16-18 achieved ready test pass levels (62% to 76% in tests on single chain lengths) but not within the 10 day window. The one test on a single carbon chain length greater than C18 (docosanol) showed degradation of 37%. In additional studies conducted at environmentally realistic concentrations with radiolabelled substances (C12-16), very high rates of degradation have been measured (very rapid rate constants, with ca. 75-85% removed as CO<sub>2</sub> and metabolites). These rates accord with field data for measured concentrations in waste-water treatment plant influent and effluent showing greater than 99% removal for carbon numbers 12 to 18. This summary of degradation is applicable to both linear and branched components of substances in the category. Therefore, the whole category is considered to show very high levels of biodegradability. Rapid degradation is also indicated by the removal rates in the chronic aquatic toxicity tests for the lower solubility substances (C10 to C15), where rapid removal of the substance from the test medium was observed, most likely due to biodegradation by micro-organisms.

All of the alcohols in this group would be expected to be stable in respect of abiotic degradation in water. Photo-oxidation in aqueous systems will not be significant. Alcohols have no hydrolysable groups and are therefore not susceptible to hydrolysis. Oxidation would not be expected under normal environmental conditions.

The substances are susceptible to atmospheric degradation by hydroxyl radicals, with half-lives ranging between ca. 10-30 hours (based on measured and estimated rate constants, for a hydroxyl radical concentration of 5E+05 molecules/cm<sup>3</sup>). Longer chain lengths have shorter estimated half-lives within this range.

No reliable guideline-standard measured bioconcentration data are available. Bioconcentration factors (BCF) calculated on the basis of log Kow range from 7.0 for C6 to a maximum of 46000 for C16, reducing to 1100 for C22. For hexadecanol, the BCF (Q)SAR estimates a value of 45300 (recalculated from the parabolic Connell and Hawker equation), but a measured value of 56 and a range of values from 507-1550 from two unreliable studies exist; BCF data for alcohols similar to those in this family but with 2.1-2.9 branches per molecule also indicate that BCF (Q)SAR overestimate BCF. Log Kow-based BCF (Q)SAR predictions also take no account of biotransformation/metabolism of alcohols in living organisms, the natural mechanism for their removal. For these reasons it is expected that category members will have a low potential for bioaccumulation.

Fugacity modelling shows that the predicted fate of all of the Category members varies depending on the route of release into the environment. For chain lengths C10 and above, alcohol released to water is predicted to partition into sediment. When alcohols are released to air, for chain lengths C14 and above, less than half of alcohol ultimately present in the environment can be found in air.

The situation for modelling exposure of multi-component substances is complicated by the fact that, given a particular route of exposure, each component will behave independently on release to the environment.

#### *Effects on aquatic organisms*

Alcohols in this Category act by non-polar narcosis and demonstrate a similar order of magnitude of toxicity in fish, invertebrates and algae. For pure substances, as chain length increases, lipophilicity increases and aqueous solubility decreases. There is an associated increase in aquatic toxicity up to a limiting chain length, at which very low aqueous solubility limits the bioavailable concentration of the alcohol in the water, resulting in a concentration at which no effects are exerted (the cut-off). Consequently, longer chain lengths show no toxicity. For aquatic organisms the chain length cut-off for acute effects lies at C13 to C14 (depending on the test species). For chronic effects, the cut-off for effects in invertebrates is in the region of C15. [The cut-off for chronic effects is probably not a limitation due solely to solubility, but is due to a limitation of the concentration at the site of action. This is not an artefact of the protocol used for the studies].

Effect concentrations vary, as described, across members of the Category. Ranges of key property values, including lowest and highest measured data as well as lowest estimated values as appropriate, are:

- Acute effects in fish (96h LC<sub>50</sub>): from 0.48 mg/l (*estimated, C12-14 alcohols*) and 0.7-0.8 mg/l (*nominal, C6-12 alcohols*) to 97 mg/l (*measured, Hexanol*). No effects up to limit of water solubility for single chain lengths >C13-14 and for some multi-component substances.
- Acute effects in invertebrates (EC<sub>50</sub>): from 0.13 mg/l (*48h estimated, C14-16 alcohols*) and 0.8-1.1 mg/l

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(96 h nominal, 1-undecanol) to 200 mg/l (24h nominal, Hexanol). No effects likely up to the limit of water solubility for single chain lengths >C13 and for some multi-component substances.

- Acute growth rate effects in algae (72 h E<sub>r</sub>C<sub>50</sub>): from ca. 0.1 mg/l (nominal, C10-16 and C12-16 alcohols, and estimated for various substances) to 80 mg/l (measured, Hexanol). No effects likely up to the limit of water solubility for single chain lengths >C14 and for some multi-component substances.
- Chronic effects in invertebrates: 21-day NOEC<sub>repro</sub> from 0.0098 mg/l (measured, tetradecanol, based on mean measured initial concentration) to 1 mg/l (measured, octanol). No effects are expected for single chain lengths >C15 up to limit of aqueous solubility.

In this assessment, trends between aquatic toxicity and carbon chain length are based on normal (linear) alcohols, since data do not exist on single carbon chain length, essentially-linear, alcohols. However, the comparability of the toxicity of straight chain and essentially linear alcohols is shown by a comparison of commercial products. The data sets for essentially pure substances have been interpreted in terms of conventional (quantitative) structure-activity relationships ((Q)SARs), by correlation of the effect concentrations with octanol-water partition coefficients.

In summary, the ranges of expected environmental behaviours of these substances could be characterised as follows.

- For short chain category members ( $\leq$ C11): high solubility; acute toxicity to aquatic organisms in the range 1-100 mg/l, chronic toxicity to aquatic organisms in the range 0.1-1.0 mg/l; readily biodegradable;
- For mid-range chain length category members (C11-C13): low solubility; acute toxicity in the range 0.1-1.0 mg/l, well-characterised chronic toxicity to aquatic organisms in the range 0.1-<1.0 mg/l; very high biodegradability (readily biodegradable with extremely high removal in environmentally relevant concentrations);
- For longer chain length category members (C14-15): low solubility limits bioavailability and hence acute effects are unlikely to be expressed, well-characterised chronic toxicity to aquatic organisms in the range 0.01 mg/l – limit of solubility; very high biodegradability (readily biodegradable with extremely high removal in environmentally relevant concentrations);
- For the longest chain category members ( $\geq$ C16): low solubility limits the dissolved (and hence bioavailable) concentration of the alcohol to the extent that neither acute nor chronic toxicity are likely to be exhibited; also significantly biodegradable (considered equivalent to inherent biodegradation; very extensive removal seen under environmentally relevant conditions) but more adsorbing than the lower homologues.

## Exposure

Total global production of these long chain aliphatic alcohols by consortium members in 2002 was estimated as approximately 1580 thousand metric tonnes annually. Approximately 50% of the total production volume is used directly in final products (industrial/commercial products and various consumer/personal care products). The remainder is processed as an intermediate (with approximately 65% of the intermediate volume being site limited).

Exposure could arise in association with production, formulation and industrial use of these substances. Within commercial use, the substances are used principally as synthetic intermediates with low expected release levels. For the 50% of Category members intentionally used directly in industrial/commercial and consumer products, release to the environment can be anticipated (especially via waste water treatment plant effluent after disposal to drain). Monitoring data are available from wastewater treatment plant effluents in USA, Canada, UK, Netherlands, Spain, Italy and Germany. The 90th percentile for individual monitored effluent measurements worldwide, not accounting for treatment type and flow, is 2.121  $\mu$ g/L and the global average is 1.057  $\mu$ g/L. Modelled (SIMPLETREAT) mixing zone concentration is estimated at ~ 0.02  $\mu$ g/L from a manufacturing plant.

These substances are also produced naturally, in all living organisms, from bacteria to man, and thus are widely present throughout the natural world. It is clear that measurements of long chain alcohol in environmental matrices will reflect the combination of both natural and anthropogenic sources. An environmental exposure assessment is available in the Annex and: ([http://www.bangor.ac.uk/~oss034/Fatty\\_Alcohol\\_Natural\\_and\\_Anthropogenic\\_Sources.doc](http://www.bangor.ac.uk/~oss034/Fatty_Alcohol_Natural_and_Anthropogenic_Sources.doc)).

Occupational Exposure: As a rule aliphatic alcohols are manufactured and processed in established chemical

complexes in closed installations; these are usually operated at high temperature and pressure. At these sites standard personal protective equipment is routinely applied to prevent direct skin and eye contact. Generally, aliphatic alcohols are of a low volatility and as a rule engineering controls are available preventing the need for respiratory protection. For non-routine operations involving a break in enclosed systems a higher level of protection is applied. Operations with a potential for significant exposure require a permit to work system and a case-by-case assessment is made for appropriate protective measures. Exposure through the use of products in industry and commerce is mitigated by applying measures aimed to prevent direct skin and eye contact by following the recommendations in the material safety data sheet (MSDS).

Consumer Exposure: Aliphatic alcohols are formulated in consumer laundry, cleaning and personal care products. Product labels reflect the hazard potential of the chemical ingredients in these products and include first aid instructions in case of non-intentional exposure.

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

**Human Health:** The chemicals of the category of the long chain aliphatic alcohols are of low priority for further work. The members of this category are of a low order of toxicity by all common routes of exposure upon acute or repeated exposure. Overall, the toxicology database for this category shows an inverse relationship between chain length and toxicity. The key human health hazards identified for this category are the irritative properties for skin and eye of aliphatic alcohols with chain lengths of C11 or below. These hazards are well characterized and do not lead to tissue destruction or irreversible changes. They should nevertheless be noted by chemical safety professionals and users.

**Environment:** The category comprises a homologous series of linear and essentially linear C6 - 22 alcohols. Increasing carbon chain length leads to a predictable pattern in physico-chemical properties; this drives a distinct range of fate behaviours in the environment. Category members all have the same mode of ecotoxicological action. In addition, all of the category members are rapidly biodegradable especially at environmentally relevant concentrations. Alcohols are metabolised/biotransformed in living organisms; this biotransformation suggests that bioaccumulation potentials based on octanol-water partition coefficients may be overestimates. Measured BCF data on a related alcohols Category supports the concept that the bioaccumulation potential of these substances will be lower than estimated from log Kow.

Many of the substances in the category do not present a hazard for the environment (acute aquatic toxicity >100 mg/l, or above water solubility with no effects exhibited) and are of low priority for further work. These category members are CAS Numbers: 36653-82-4, 629-96-9, 661-19-8, 143-28-2, 67762-27-0, 67762-30-5, 97552-91-5, 68155-00-0.

Some of the substances in this category present a hazard for the environment (acute toxicity to fish, daphnids and algae in the range 1 - 100 mg/l). However all of these substances are readily biodegradable. Therefore these subgroup members are of low priority for further work. These subgroup members are CAS Numbers: 111-27-3, 111-87-5, 85566-12-7, 67762-25-8, 68002-94-8.

The remaining substances in the category present a greater hazard for the environment (high acute toxicity to fish, daphnids and algae, in the range 0.1 - 1 mg/l, and/or high chronic toxicity). The substances in this subgroup biodegrade rapidly and environmental monitoring data from seven countries indicates exposures to the environment is anticipated to be low and are included in an Annex to the SIAR. The chemicals in this subgroup that should be candidates for further work by member countries, who are invited to perform an exposure assessment and, if necessary, a risk assessment, are CAS Numbers: 112-30-1, 112-42-5, 90583-91-8, 112-70-9, 112-72-1, 629-76-5, 68603-15-6, 67762-41-8, 68855-56-1, 63393-82-8, 66455-17-2, 68333-80-2, 75782-86-4, 75782-87-5, 80206-82-2, 68551-07-5, 85665-26-5.