

SCREENING-LEVEL HAZARD CHARACTERIZATION Long Chain Alcohols Category

Sponsored Chemicals

1-Hexanol	CASRN 111-27-3
1-Octanol	CASRN 111-87-5
1-Decanol	CASRN 112-30-1
1-Undecanol	CASRN 112-42-5
1-Tridecanol	CASRN 112-70-9
1-Tetradecanol	CASRN 112-72-1
1-Pentadecanol	CASRN 629-76-5
1-Hexadecanol	CASRN 36653-82-4
9-Octadecen-1-ol, (9Z)-	CASRN 143-28-2
1-Eicosanol	CASRN 629-96-9
1-Docosanol	CASRN 661-19-8
Alcohols, C12-15	CASRN 63393-82-8
Alcohols, C9-11	CASRN 66455-17-2
Alcohols, C12-18	CASRN 67762-25-8
Alcohols, C16-18	CASRN 67762-27-0
Alcohols, C14-18	CASRN 67762-30-5
Alcohols, C10-16	CASRN 67762-41-8
Alcohols, C8-18	CASRN 68551-07-5
Alcohols, C16-18 and C18 (unsat'd)	CASRN 68002-94-8
Alcohols, C14-18 and C16-18 (unsat'd)	CASRN 68155-00-0
Alcohols, C14-16	CASRN 68333-80-2
Alcohols, C6-12	CASRN 68603-15-6
Alcohols, C12-13	CASRN 75782-86-4

The High Production Volume (HPV) Challenge Program¹ was conceived as a voluntary initiative aimed at developing and making publicly available screening-level health and environmental effects information on chemicals manufactured in or imported into the United States in quantities greater than one million pounds per year. In the Challenge Program, producers and importers of HPV chemicals voluntarily sponsored chemicals; sponsorship entailed the identification and initial assessment of the adequacy of existing toxicity data/information, conducting new testing if adequate data did not exist, and making both new and existing data and information available to the public. Each complete data submission contains data on 18 internationally agreed to “SIDS” (Screening Information Data Set^{1,2}) endpoints that are screening-level indicators of potential hazards (toxicity) for humans or the environment.

The Environmental Protection Agency’s Office of Pollution Prevention and Toxics (OPPT) is evaluating the data submitted in the HPV Challenge Program on approximately 1400 sponsored chemicals by developing hazard characterizations (HCs). These HCs consist of an evaluation of the quality and completeness of the data set provided in the Challenge Program submissions. They are not intended to be definitive statements regarding the possibility of unreasonable risk of injury to health or the environment.

The evaluation is performed according to established EPA guidance^{2,3} and is based primarily on hazard data provided by sponsors; however, in preparing the hazard characterization, EPA considered its own comments and public comments on the original submission as well as the sponsor’s responses to comments and revisions made to the submission. In order to determine whether any new hazard information was developed since the time of the HPV Challenge or OECD HPV submission, a search of the following databases was made from one year prior to the date of the HPV Challenge submission or the OECD HPV submission to the present: (ChemID to locate available data sources including Medline/PubMed, Toxline, HSDB, IRIS, NTP, ATSDR, IARC, EXTOXNET, EPA SRS, etc.), STN/CAS online databases (Registry file for locators, ChemAbs for toxicology data, RTECS, Merck, etc.) and Science Direct. OPPT’s focus on these specific sources is based on their being of high quality, highly relevant to hazard characterization, and publicly available.

OPPT does not develop HCs for those HPV chemicals which have already been assessed internationally through the HPV program of the Organization for Economic Cooperation and Development (OECD) and for which Screening Initial Data Set (SIDS) Initial Assessment Reports (SIAR) and SIDS Initial Assessment Profiles (SIAP) are available. These documents are presented in an international forum that involves review and endorsement by governmental authorities around the world. OPPT is an active participant in these meetings and accepts these documents as reliable screening-level hazard assessments.

These hazard characterizations are technical documents intended to inform subsequent decisions and actions by OPPT. Accordingly, the documents are not written with the goal of informing the general public. However, they do provide a vehicle for public access to a concise assessment of the raw technical data on HPV chemicals and provide information previously not readily available to the public.

¹ U.S. EPA. High Production Volume (HPV) Challenge Program; <http://www.epa.gov/chemrtk/index.htm>.

² U.S. EPA. HPV Challenge Program – Information Sources; <http://www.epa.gov/chemrtk/pubs/general/guidocs.htm>.

³ U.S. EPA. Risk Assessment Guidelines; <http://cfpub.epa.gov/ncea/raf/rafguid.cfm>.

Chemical Category Name	Long Chain Alcohols
Chemical Abstract Index Name	Chemical Abstract Service Registry Number (CASRN)
1-Hexanol	111-27-3
1-Octanol	111-87-5
1-Decanol	112-30-1
1-Undecanol	112-42-5
1-Tridecanol	112-70-9
1-Tetradecanol	112-72-1
1-Pentadecanol	629-76-5
1-Hexadecanol	36653-82-4
9-Octadecen-1-ol, (9Z)-	143-28-2
1-Eicosanol	629-96-9
1-Docosanol	661-19-8
Alcohols, C12-15	63393-82-8
Alcohols, C9-11	66455-17-2
Alcohols, C12-18	67762-25-8
Alcohols, C16-18	67762-27-0
Alcohols, C14-18	67762-30-5
Alcohols, C10-16	67762-41-8
Alcohols, C8-18	68551-07-5
Alcohols, C16-18 and C18 (unsaturated)	68002-94-8
Alcohols, C14-18 and C16-18 (unsaturated)	68155-00-0
Alcohols, C14-16	68333-80-2
Alcohols, C6-12	68603-15-6
Alcohols, C12-16	68855-56-1
Alcohols, C12-13	75782-86-4
Alcohols, C14-15	75782-87-5
Structural Formula	$\text{CH}_3(\text{CH}_2)_n\text{CH}_2\text{OH} \text{ (Linear: } n = 4 \text{ to } 20)$ $\begin{array}{c} \text{CH}_3(\text{CH}_2)_n\text{CHCH}_2\text{OH} \\ \\ (\text{CH}_2)_m\text{CH}_3 \end{array}$ (Essentially linear: $n + m = 3$ to 18) $\begin{array}{c} \text{CH}_3(\text{CH}_2)_n\text{CH}(\text{CH}_2)_m\text{OH} \\ \\ \text{CH}_3 \end{array}$ (Other methyl branching: $n + m = 9$ or 10 ; in Essentially linear Fischer-Tropsch alcohols) $\text{CH}_3(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_7\text{CH}_2\text{OH}$ (Unsaturated; 9-Z unsaturated components are

present in some commercial products)

Summary

The long chain alcohols category consists of both liquid and solid substances with a carbon chain length of C6-22. These substances have low to high water solubility and low to high vapor pressure. Both vapor pressure and solubility tend to decrease with increasing carbon chain length. The substances in the long chain alcohols category possess high to moderate mobility in soil; however, longer chain substances with a high degree of branching may possess low mobility. Measured data indicate that alcohols with chain lengths up to C18 are readily biodegradable. Biodegradation may be slower for alcohols possessing a high degree of branching. Long chain alcohols are expected to have low persistence (P1). Estimated bioaccumulation factors (BAF) suggest that bioaccumulation ranges from low (B1) to high (B3).

Human Health

Acute toxicity is low for category members following oral, dermal or inhalation exposure. A 13-week oral repeated-dose toxicity study shows no significant treatment-related effects in rats administered CASRN 111-27-3 (C6) via dietary exposure at 1127 mg/kg-bw/day (highest dose tested); however, mortality (4/5) and marked CNS effects (ataxia, tremors and narcosis) are noted in dogs following oral administration of gelatin capsules containing CASRN 111-27-3 at a concentration of 1000 mg/kg-bw/day. Local irritation of the gastrointestinal tract is the only treatment-related effect reported in a second group of dogs administered CASRN 111-27-3 via the diet for 13 weeks; the NOAEL for systemic toxicity is 370 mg/kg-bw/day (highest dose tested) for this portion of the study. Significant decreases in body weight gain (~10%) and food consumption (~17%) are reported in rats exposed to CASRN 36653-82-4 (C16) during a 13-week dietary study; the NOAEL for systemic toxicity is 750 mg/kg-bw/day. A repeated-dose toxicity study with CASRN 661-19-8 (C22) administration in rats and dogs indicates no effects on body weight or food consumption in animals treated via oral gavage during a 26-week study; the NOAELs for systemic toxicity are 1000 and 2000 mg/kg-day (highest dose tested) in rats and dogs, respectively.

A 28-day oral repeated-dose toxicity study with CASRN 67762-41-8 (C10-16) administration in rats shows decreased body weight gain (10%) in males and liver effects (increased alanine transaminase, alkaline phosphatase and cholesterol) in females at 1000 mg/kg-day. The NOAEL for systemic toxicity is 300 mg/kg-day. Decreased body weight (15%), elevated liver enzymes (alanine transaminase and alkaline phosphatase) and increased liver weight are reported in male rats following dietary exposure to CASRN 68333-80-2 (C14-C16) at 1000 mg/kg-bw/day during a 13-week oral repeated-dose toxicity study; the NOAEL for systemic toxicity is 200 mg/kg-bw/day. Decreased body weight (at 1000 mg/kg-day) is the only treatment-related effect reported in rats treated with the supporting chemical, CASRN 123-51-3 (C5) during a 17-week toxicity study. Increased liver weight, stomach inflammation and changes in clinical chemistry (decreased alkaline phosphatase, alanine transaminase, glucose and cholesterol) are reported in a 90-day oral repeated-dose study with the supporting chemical, CASRN 104-76-7; the NOAEL for systemic toxicity is 125 mg/kg-bw/day.

Overall, the available reproductive and developmental toxicity data for the long chain alcohols

indicate no developmental toxicity and minimal maternal toxicity with repeated exposure. No treatment-related effects on reproductive organs are noted in dogs or rats following 13 weeks of dietary exposure to CASRN 111-27-3 (C6); however, a developmental toxicity study with CASRN 111-27-3 shows significant decreases in maternal body weight gain in pregnant rats following oral gavage at 1000 mg/kg-day during days 6-15 of gestation. A developmental toxicity study with CASRN 111-87-5 (C8) shows dose-related increases in systemic toxicity (CNS depression, decreased bodyweight gain, pneumonia) in treated dams following oral gavage at 1300 mg/kg-day (highest dose tested), but no evidence of developmental toxicity; the NOAELs for maternal and developmental toxicity are 130 and 1300 mg/kg-day, respectively. No maternal or developmental effects are reported in rats administered CASRN 112-30-1 (C10) via vapor inhalation at 0.1 mg/L on days 1-19 of gestation. Maternal toxicity (decreased body weight gain) in the absence of developmental effects is noted in rats and rabbits following inhalation exposure with the supporting chemical, CASRN 123-51-3 (C5) at 10 mg/L on days 6-15 of gestation; the maternal NOAEC is 2.5 mg/L for both species. In a combined repeated-dose/reproductive/developmental toxicity study in rats and rabbits, CASRN 661-19-8 (C22) shows no effects on reproductive or developmental parameters (number of corpora lutea, implantation sites, resorptions, and viable fetuses) in animals treated via oral gavage; the NOAELs for reproductive and developmental toxicity are 1000 and 2000 mg/kg-day (highest dose tested) in rats and rabbits, respectively. A similar lack of reproductive effects is noted in two (one-generation) reproductive toxicity studies involving dietary exposure to the supporting chemicals, CASRN 112-53-8 (C12) or CASRN 112-92-5 (C18); the NOAEL for both studies is 2000 mg/kg-bw/day, based on no observed adverse effects at the highest dose tested.

No reproductive or developmental toxicity studies are available for the essentially linear alcohols; however, no effects on reproductive organs are noted in the 13-week oral repeated-dose toxicity studies described above. No effects on reproductive organs are reported following dietary exposure to CASRN 68333-80-2 (C14-16) during a 90-day repeated-dose toxicity study; the NOAEL is 200 mg/kg-bw/day. In addition, developmental toxicity studies in rats and rabbits involving inhalation exposure to the supporting chemical, CASRN 123-51-3 (100% branched) show maternal toxicity (decreased body weight gain), but no developmental effects in animals treated at 10 mg/L (highest dose tested); the maternal NOAEC is 2.5 mg/L for both species.

Several *in vitro* and *in vivo* mutagenicity studies are available for the long chain alcohols category. Evaluation of *in vitro* data shows a consistent lack of mutagenic potential for the entire range of carbon chain lengths represented in this category. Results for tested members, (CASRNs 112-53-8 (C12), 112-92-5 (C18) and 661-19-8 (C22)) are consistently negative in the *in vivo* mouse bone marrow micronucleus test. Further support for the lack of mutagenicity is provided by CASRN 71-36-3 (C4), a supporting chemical which is below the minimal chain length considered for this category, but is considered here as a “worst-case scenario” for human exposure due to its enhanced bioavailability. The available data for CASRN 71-36-3 shows no evidence of mutagenicity in bacterial cells *in vitro* and no evidence of chromosomal aberrations in mammalian cell cultures or a mouse micronucleus assay *in vivo*.

A representative number of essentially linear alcohols show a consistently negative response in the bacterial reverse gene mutation test (Ames assay). Other available data include negative results for CASRN 67762-41-8 (C10-16) in chromosomal aberrations tests in mammalian cells. In addition, the supporting chemical, CASRN 104-76-7 shows consistently negative results in a comprehensive data set covering *in vitro* (bacterial and mammalian cell gene mutation assays, a

chromosomal aberrations test and an Unscheduled DNA Synthesis assay) as well as *in vivo* (mouse micronucleus and a dominant lethal test) assays.

The available data indicate an inverse relationship between chain length and irritant effects for both linear and essentially linear alcohols represented in this category. Shorter chain length alcohols (C6-11) may induce varying degrees of skin or eye irritation depending on the test protocol used; however, severity generally becomes less pronounced with increasing chain length. Although a weakly positive result is reported for CASRN 112-30-1 (C10), the weight of evidence for this category indicates no potential for skin sensitization in guinea-pigs.

Environmental Effects

In general, the ranges of expected ecological characteristics of these toxicants could be described as follows:

- For the shorter chain length category members (\leq C11): high water 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.
- For the mid-range chain length category members (C11-13): low water 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.
- For the longer chain length category members (C14-15): low water 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 water solubility.
- For the longest chain length category members (\geq C16): low solubility limits the dissolved (bioavailable) concentration of the alcohol to the extent that neither acute nor chronic toxicity are likely to be exhibited.

Furthermore, some 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 LC₅₀): 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 the limit of water solubility for single chain lengths >C13-14 and for some multi-component substances.
- Acute effects in invertebrates (EC₅₀): from 0.13 mg/L (*48h estimated, C14-16 alcohols*) and 0.8-1.1 mg/L (*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_rC₅₀): 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_{repro} 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.

No Data gaps were identified for SIDS endpoints.

The sponsor country, the United Kingdom, presented the SIDS documents at the OECD SIAM 22 during April 18-21, 2006. The SIAR, SIAP and Dossier are in the process of being finalized by OECD (<http://cs3-hq.oecd.org/scripts/hpv/>). This hazard characterization includes EPA review of the SIDS documents and any relevant studies obtained through EPA's literature search.

NOTE: The OECD document upon which this hazard characterization is based was developed by the United Kingdom and represents long chain alcohols that are of commercial interest in that and other countries. Their analysis considers 30 sponsored chemicals and 11 supporting chemicals. Twenty-five (identified above) of the 41 chemicals were originally sponsored in the US HPV Challenge Program and are the subject of this hazard characterization.

Category Justification

The long chain alcohols category may be justified on the basis of similarities in structural, physicochemical, environmental and health parameters. Although a wide range of values exist for some of these properties, members of this category share common modes of degradation, biological action and use.

Long chain alcohols occur as a homologous series of increasing carbon chain lengths. Certain branched and unsaturated structures are considered to have similar properties that justify their inclusion in this category. Commercial products contain a range of alcohols, which in some products may include: unsaturated alcohol components and essentially linear (mono-alkyl branched) components, as well as linear alcohols. All components of the commercial products relevant to this category are primary alcohols. For the evaluation of human health effects, the category was divided into two subcategories: linear and essentially linear. The latter subcategory includes long chain alcohols with some branching. The composition of category members is described in more detail in section 1.1.2 of the SIAR available at the link provided above.

Due to limited data availability, appropriate supporting data have been included to assess the repeat-dose toxicity for the essentially linear subcategory of the long chain alcohols. A 17-week oral study with the supporting chemical CASRN 123-51-3 (C5), and mutagenicity studies with CASRN 71-36-3 (C4) have been selected for assessing toxicities at the lower end of the essentially linear alcohols. The supporting chemical CASRN 71-36-3 (C4), is below the minimal chain length considered for this category, but is considered here as a "worst-case scenario" for human exposure due to its enhanced bioavailability. In addition, CASRN 104-76-7 (a 100 % branched alcohol) may reasonably represent the branched components present in the C6-12 range of this subcategory.

Taken together, a comparison of the SIDS, irritation and sensitisation endpoints demonstrates that the toxicological properties of the linear and essentially linear subcategories are fully comparable and justify their consideration as a single category. There is a clear relationship between chain length and toxicological properties justifying read across for category members.

1. Chemical Identity

1.1 Identification and Purity

See identification and purity information at: <http://cs3-hq.oecd.org/scripts/hpv/>.

1.2 Physical-Chemical Properties

See physical-chemical properties at: <http://cs3-hq.oecd.org/scripts/hpv/>.

2. General Information on Exposure

2.1 Production Volume and Use Pattern

The Long Chain Alcohols category chemicals had an aggregated production and/or import volume in the United States between 803 million pounds and 2.98 billion pounds in calendar year 2005:

- CASRN 111-27-3: 10 to <50 million pounds;
- CASRN 111-87-5: 50 to <100 million pounds;
- CASRN 112-30-1: 50 to <100 million pounds;
- CASRN 112-42-5: 50 to <100 million pounds;
- CASRN 112-70-9: 50 to <100 million pounds;
- CASRN 112-72-1: 50 to <100 million pounds;
- CASRN 143-28-2: 1 to <10 million pounds;
- CASRN 629-76-5: 10 to <50 million pounds;
- CASRN 629-96-9: 10 to <50 million pounds;
- CASRN 661-19-8: 1 to <10 million pounds;
- CASRN 36653-82-4: 50 to <100 million pounds;
- CASRN 63393-82-8: 100 to <500 million pounds;
- CASRN 66455-17-2: 10 to <50 million pounds;
- CASRN 67762-27-0: 10 to <50 million pounds;
- CASRN 67762-30-5: 50 to <100 million pounds;
- CASRN 67762-41-8: 100 to <500 million pounds;
- CASRN 68603-15-6: <500,000 pounds;
- CASRN 68855-56-1: 1 to <10 million pounds;
- CASRN 75782-86-4: 100 to <500 million pounds; and
- CASRN 75782-87-5: 100 to <500 million pounds.

Chemicals under CASRNs 67762-25-8, 68002-94-8, 68155-00-0, 68333-80-2, 68551-07-5, are not reported in the 2006 IUR.

Non-confidential information in the IUR indicated that the industrial processing and uses of the long chain alcohols category include intermediates, odor agents, solvent (for cleaning or degreasing), solvents (which become part of product formulation or mixture), surface active agents, flotation agents, fuels, lubricants, agricultural chemicals (non-pesticidal), processing aids, not otherwise listed, stabilizers, and other. For chemicals under CASRNs 112-42-5, 112-70-9, 629-76-5, 66455-17-2, 67762-27-0, 75782-86-4 and 75782-87-5, the sole reported non-confidential industrial processing and use is as an intermediate. CASRN 68855-56-1 is only

reported for use as a surface active agent. Non-confidential industrial processing and use information for CASRN 143-28-2 is not readily obtainable. No industrial processing and use information was reported for CASRN 68603-15-6.

Non-confidential information in the IUR indicated that the commercial and consumer uses of the long chain alcohols category include adhesives and sealants, electrical and electronic products, fabrics, textiles, and apparel, lawn and garden products (non-pesticidal), lubricants, greases, and fuel additives, metal products, paints and coatings, paper products, polishes and sanitation goods, photographic supplies, rubber and plastic products, soaps and detergents, wood and wood furniture, and other. Non-confidential commercial and consumer use information for CASRN 143-28-2 is not readily obtainable. No commercial and consumer uses were reported in the 2006 IUR for CASRNs 112-42-5, 112-70-9, 629-76-5, 63393-82-8, 66455-17-2, 67762-27-0, 67762-30-5, 67762-41-8, 68603-15-6, 75782-86-4 or 75782-87-5.

2.2 Environmental Exposure and Fate

See environmental exposure and fate data at: <http://cs3-hq.oecd.org/scripts/hpv/>.

3. Human Health Hazard

See human health hazard data at: <http://cs3-hq.oecd.org/scripts/hpv/>.

4. Hazard to the Environment

See environmental hazard data at: <http://cs3-hq.oecd.org/scripts/hpv/>.