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SIDS INITIAL ASSESSMENT PROFILES AGREED IN THE COURSE OF THE OECD COOPERATIVE CHEMICALS ASSESSMENT PROGRAMME IN 2014

Series on Testing & Assessment
No. 245

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IOMC
INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS
A cooperative agreement among FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD

Environment Directorate
ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT
Paris 2017

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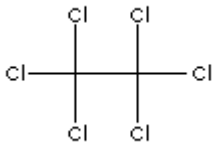
INITIAL TARGETED ASSESSMENT PROFILE

Category Name	Hexachloroethane
CAS No(s).	67-72-1
Structural Formula	

SUMMARY CONCLUSIONS OF THE TARGETED ASSESSMENT

NOTE: The present Initial Targeted Assessment Profile (ITAP) addresses the following human health endpoints: carcinogenicity and genotoxicity. It cannot be considered as a full SIDS Initial Assessment. Summary information on exposure is also reported here. Human health endpoints included in the Canadian screening assessment that have not been presented to OECD member countries are not included in this ITAP.

"The final screening assessment has been published under the responsibility of the Government of Canada. [http://www.ec.gc.ca/ese-ees/default.asp?lang=En&n=CD3BB2EB-1]"

Rationale for Targeting the Assessment

The Government of Canada "categorized" or prioritized all 23,000 chemical substances on its Domestic Substances List (DSL) from 1999 to September 2006, as required by its *Canadian Environmental Protection Act, 1999* (CEPA 1999). Using information from Canadian industry, academic research and other countries, Government of Canada scientists applied a set of rigorous tools to the 23,000 chemical substances on the DSL. They were categorized to identify those that were: **inherently toxic** to humans or to the environment and that might be **persistent** and/or **bioaccumulative**; and substances to which people might have **greatest potential for exposure**. During this priority-setting exercise, distinct approaches were taken for identifying substances of likely concern for human health and the environment, and subsequent assessment activities may have focused on either human health or ecological endpoints. Through categorization, the Government of Canada has identified approximately 4,000 of the 23,000 chemical substances on the DSL as priorities for further assessment, research and/or measures to control their use or release.

In Canada, the substance, hexachloroethane, was identified as an assessment priority because it was classified by other agencies as a possible carcinogen to humans and because it met the criteria for persistence, bioaccumulation and inherent toxicity to aquatic life.

Under the Canadian Environmental Protection Act (CEPA 1999), a screening assessment is conducted to determine whether a substance presents or may present a risk to the environment or to human health. For humans, this includes, but is not limited to, exposures from ambient and indoor air, drinking water, foodstuffs, and the use of consumer products. A conclusion under CEPA 1999 is not relevant to, nor does it preclude, an assessment against the hazard criteria specified in the Controlled Products Regulations, which is part of the regulatory framework for the Workplace Hazardous Materials Information System [WHMIS] for products intended for workplace use.

Physical-chemical Properties

The substance, hexachloroethane, is characterized by colourless crystals with camphor-like odour at ambient temperature, has a melting point of 185-188°C, boiling point of 185-187°C (sublimes without decomposition) and a vapour pressure of 28-29 Pa at 20°C (all measured values). The measured octanol-water partition coefficient (log K_{ow}) is 3.34-5.31, and the measured water solubility is 7.7 mg/L at 25°C. The measured organic carbon-water partition coefficient (log K_{oc}) is 2.24-4.3.

Human Health

The majority of the studies described here have been reviewed by the International Agency for Research on Cancer (IARC 1999) or the US EPA (2011).

Genotoxicity: A sufficient genotoxicity database was available.

- The chemical was negative for gene mutations in the majority of *S. typhimurium* (bacterial) and *S. cerevisiae* (ascomycetes fungi) mutation assays conducted with and without metabolic activation.
- Chromosomal aberrations were negative with and without activation, whereas induction of sister chromatid exchanges (SCEs) were negative in Chinese hamster cells without metabolic activation, but positive only with activation at doses that induce cell cycle delay..
- It was negative for micronuclei in human lymphoblastoid cells but equivocal for micronuclei induction in human blood cells.
- DNA damage was negative in cultured human lymphocyte but positive in isolated human lymphocytes with and without activation.
- DNA binding was positive in calf thymus DNA with microsomal activation, and rat and mice liver, kidney, lung and stomach tissue with activation, but DNA adducts were not identified.
- Other indicator tests such as mitotic gene conversion in *S. cerevisiae* (ascomycetes fungi), aneuploidy in *A. nidulans* (yeast cells), SOS induction and strand damage using *S. typhimurium* (bacterial), differential toxicity in *B. subtilis* (bacterial) and cell transformation in mouse BALB/c-3T3 mouse cells, were all negative.

Overall, ***in vitro*** mutagenicity, clastogenicity and DNA damage assays showed negative results. Although DNA binding was positive in mammalian cells, there was no clear evidence of adduct formation.

A limited number of *in vivo* studies showed:

- *D. melanogaster* showed equivocal results for somatic gene mutation. DNA, RNA and protein binding were positive in liver, lung, kidney, and stomach cells, after i.p. administration of hexachloroethane to rats and mice, but the adducts were not identified.
- A micronuclei assay in mice was negative in bone marrow (hexachloroethane administered i.p.).

In vivo genotoxicity studies were equivocal overall. The only positive results of potential significance were those in a single report in which DNA binding was reported *in vivo* and *in vitro*; however, there was no clear evidence of adduct formation.

Carcinogenicity potential was determined on the basis of long-term and initiation-promotion oral studies.

In an oral carcinogenicity bioassay in F344/N rats exposed by gavage to hexachloroethane, 50 males/group were exposed to doses of 0, 10, or 20 mg/kg-bw per day and 50 females/group were exposed to 0, 80, or 160 mg/kg-bw per day, 5 days per week for 2 years. A statistically significant ($p < 0.01$) increase in the combined incidence of renal adenomas or carcinomas (1/50, 2/50 and 7/50, respectively) was observed in high dose males. An increased incidence of pheochromocytomas of the adrenal gland (15/50, 28/45 and 21/49, respectively) was

observed in males at both doses, with the increase being statistically significant ($p < 0.01$) at the low dose. There was no increase in the incidence of tumours at any site in females. There was no significant difference in survival between any groups of either sex. Since the adrenal tumours did not follow a dose response trend, Benchmark Dose (BMD) calculations could not be performed. For renal adenoma or carcinoma (combined) in male F344 rats, the lowest calculated $BMDL_{10}$ (the lower bound on the exposure associated with a 10% extra cancer risk) is 8.53 mg/kg-bw per day.

In an oral carcinogenicity study in Osborne-Mendel rats, 50 animals/sex were exposed by gavage to hexachloroethane 5 days per week for 22 weeks followed by a cyclic pattern of dosing for 56 weeks (1 dose free week followed by 4 weeks of dosing) at time-weighted average doses of 212 or 423 mg/kg-bw per day over the 78 week period, which was then followed by a dose-free observation period of 33 or 34 weeks. Twenty animals/sex/group were exposed by gavage to vehicle (corn oil) or placed on test as untreated controls without intubation. A non-statistically significant increased incidence of kidney tubular cell adenomas (0/20, 0/20, 4/49 and 0/50 at 0 [naive], 0 [vehicle], 212 and 423 mg/kg-bw per day, respectively) was observed in low dose males. Survival of male rats at 90 weeks was 19/50 for the high dose, 24/50 for the low dose, 14/20 for controls and 11/20 for vehicle controls. High mortality may have precluded the observation of late-developing tumours.

In an oral carcinogencitiy study in B6C3F1 mice, 50 animals/sex were exposed by gavage to hexachloroethane 5 days per week at time-weighted average doses of 590 or 1179 mg/kg-bw per day for 78 weeks, followed by a dose-free observation period of 12 or 13 weeks. Twenty animals/sex/group were exposed by gavage to vehicle (corn oil) or placed on test as untreated controls without intubation. An increased incidence of hepatocellular carcinomas was observed in both sexes (1/18, 3/20, 15/50 and 31/49 in males and 0/18, 2/20, 20/50 and 15/49 in females at 0 [untreated], 0 [vehicle], 590 and 1179 mg/kg-bw per day, respectively). When compared to vehicle controls, the increase was statistically significant ($p < 0.001$) only at the high dose in males and the low dose in females.

To assess initiation potential, 10 male Osborne-Mendel rats received 500 mg/kg-bw hexachloroethane by gavage 24 hours after partial hepatectomy. Six days later, the animals received a 0.05% dietary exposure to the tumour promoter phenobarbital for 7 weeks. No increase in preneoplastic lesions (i.e., gamma glutamyltranspeptidase positive foci) was observed in the liver of rats. To assess promotion potential, 10 male rats/group were i.p. injected with 30 mg of the tumour initiator, diethylnitrosamine or given 5 mL/kg bw water 24 hours after partial hepatectomy. Six days later, the animals received 500 mg/kg-bw hexachloroethane by gavage, 5 days/week for 7 weeks. A significantly increased incidence increased ($p < 0.05$) of preneoplastic lesions (liver foci) was observed in the animals. In summary, results were negative in the initiation study and positive in the promotion study.

Potential Mode of Action for Oral Carcinogenicity

No studies have been identified that presented immunohistochemical evidence of the presence of alpha-2µ-globulin in hyaline droplets in the kidneys of male rats exposed to hexachloroethane. Although evidence for a role of alpha-2 µ -globulin nephropathy in the induction of renal tumours in male rats by hexachloroethane is suggestive, it is not conclusive. In addition, the US EPA (2011) examined the mode of action of the kidney tumours in male rats and similarly concluded that the evidence was insufficient to conclude that kidney tumours were consequential to alpha-2µ-globulin accumulation. Furthermore, the potential mode of induction of the liver tumours in mice or adrenal tumours in rats by hexachloroethane have not been investigated.

Although the mode of induction of tumours by hexachloroethane has not been well studied, the available data on genotoxicity is generally negative, suggesting that the mechanism of carcinogenicity in some target tissues may be non-genotoxic In the absence of information indicating otherwise, the kidney tumours in male rats and liver tumours in male and female mice are considered relevant to humans.

Carcinogenicity Potential in Humans

In a cohort study (n = 1880) of male workers at aluminum foundries and aluminum smelters in Sweden, no significant association (in excess or trend over duration of employment) was observed between exposure to

hexachloroethane (exposure levels were not available, so proxy exposure variables like type of casting technique applied, duration of employment and job title were used) and incidences of anorectal, liver or lung cancer or malignant lymphoma. Confounding influences by co-exposures to agents such as polycyclic aromatic hydrocarbons or silica dust cannot be ruled out, and the power of the study was low.

Based on the available human and animal and in vitro data, the International Agency for Research on Cancer (IARC 1999), proposed that hexachloroethane was *possibly carcinogenic to humans* (Group 2B), based on *sufficient evidence* in experimental animals and *inadequate evidence* in humans. Similarly,the U.S. EPA (2011) updated the Integrated Risk Information system and concluded that hexachloroethane was *likely to be carcinogenic to humans* by all routes of exposure.

Hexachloroethane possesses properties indicating a hazard for the one human health endpoint, carcinogenicity (kidney tumours and liver tumours via the oral route) targeted in this assessment.

Exposure Summary Information

Hexachloroethane is currently imported into Canada (sponsor country) for use as a degassing agent for oxides and hydrogen elimination from aluminum alloys during die casting at a quantity of less than 2000 kg per year. It was previously reported to be used in Canada as a chemical intermediate, as a flux agent for grain refining and degassing of aluminum alloys, and as a flame retardant in industrial laminating resins. It is no longer used in military smoke ammunition in Canada, and no evidence has been found for its current use as a flame retardant. Global uses of hexachloroethane noted in earlier scientific and technical literature were in military pyrotechnics, in the metallurgical industry, as a plasticizer, as an ignition suppressant, as a processing aid in various industrial processes, as a component of fungicidal and insecticidal formulations, and (formerly) as an anthelmintic in veterinary medicine. The production and uses of hexachloroethane are being phased out internationally. The European Commission prohibits the use of hexachloroethane in the manufacturing or processing of nonferrous metals. In the United States (US), there has been a trend away from using hexachloroethane flux in the secondary aluminum industry. Similarly, representatives of the aluminum industry in the US report that hexachloroethane is no longer used in most primary aluminum degassing.

Based on the most recent survey for this compound, approximately 150 tonnes of hexachloroethane were manufactured and 10–100 tonnes were imported in Canada during the 2000 calendar year. Although it is not manufactured for commercial distribution, hexachloroethane is formed during other processes in the chlorinated chemical industry; for example, this chemical is a by-product resulting from the 1,2-dichloroethane manufacturing process. Hexachloroethane can also be produced as a by-product of the chlorination of water and sewage and the incineration of chlorinated hydrocarbons.

Hexachloroethane can also be produced naturally by Rhodophyta algae. The halogenating capacity of the algae was established through incubation experiments.

Current Canadian sources of releases to the environment are minor but potentially numerous. They include possible releases from industrial facilities during manufacturing and processing, from the chlorination of water and sewage, from the incineration of chlorinated hydrocarbons, from municipal and industrial landfills by leaching and from the use of contaminated solvents (e.g., tetrachloroethylene).

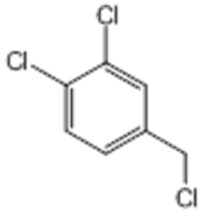
Releases of hexachloroethane reported by Canadian industries to the National Pollutant Release Inventory indicated that there have been no releases at reporting thresholds since 2006, and prior to that year, all releases occurred to air and off-site disposal. From 1999 to 2005, on-site releases ranged from 0.001 to 0.012 tonne per year, and 0.004–19 tonnes per year were released to off-site disposal. Hexachloroethane is expected to be released by users (rather than producers) mostly to air, with smaller releases to water and soil. Releases of hexachloroethane associated with the die casting of aluminum products are expected to be minimal given the nominal amounts being used and the manner of processing.

According to the US Toxics Release Inventory, 467.2 kg of hexachloroethane were emitted to the atmosphere, 75.7 kg injected to underground wells, 164.6 kg to on site and off site landfills and 644.1 kg were released to other off site management facilities in the US in 2011.

Hexachloroethane has not been identified in consumer products in Canada and exposure from these sources are expected to be limited, as its use is being phased out or restricted in many countries.

Note: This document may only be reproduced integrally. The conclusions in this document are intended to be mutually supportive, and should be understood and interpreted together.

INITIAL TARGETED ASSESSMENT PROFILE

CAS No.	102-47-6
Chemical Name	**1,2-Dichloro-4-(chloromethyl)benzene**
Structural Formula	

SUMMARY CONCLUSIONS OF THE TARGETED ASSESSMENT

NOTE: The present assessment was targeted to address only the following endpoint(s): Human Health: repeated dose toxicity and *in vitro* mutagenicity. It cannot be considered as a full SIDS Initial Assessment. Summary information on exposure is also reported here. Other endpoints for human health and the environment have not been presented to OECD member countries, and thus are not included in this profile.

Rationale for targeting the assessment

Under the Japanese Chemical Substances Control Law (CSCL), risk assessment of existing chemical substances has been conducted by the government. The CSCL was amended in 2010 and 2011 and shifted toward risk-based management from hazard-based management. Chemical substances are classified as follows from April 1, 2011: (1) Class I Specified Chemical Substances (persistent, highly bioaccumulative, has long-term toxicity for humans or long-term toxicity predator animals at higher trophic level), (2) Class II Specified Chemical Substances (has long-term toxicity for humans or flora and fauna in the human living environment, has risk), (3) Monitoring Chemical Substances (persistent, highly bioaccumulative, long-term toxicity unknown), (4) Priority Assessment Chemical Substances (suspected long-term toxicity for humans or flora and fauna in the human living environment, suspected risk) and (5) General Chemical Substances (risk to humans or flora and fauna in the human living environment is sufficiently low).

1,2-Dichloro-4-(chloromethyl)benzene is classified as a General Chemical Substance based on degrees of hazard intensity and exposure estimates at the priority assessment meeting.

This targeted assessment document was originally based on the material of the priority assessment meeting provided from the chemical assessment council of Ministry of Health, Labour and Welfare (MHLW), Japan, and the toxicological profile was re-assessed for the OECD Cooperative Chemicals Assessment Programme.

Physical-Chemical Properties

1,2-Dichloro-4-(chloromethyl)benzene is solid at room temperature. Melting point is 37.5 °C, and boiling point is 241 °C. Partition coefficient between octanol and water (log K_{ow}) is estimated to be 4.08 by KOWWIN. Vapour pressure is estimated to be 9.59 Pa at 25 °C. Values of water solubility are estimated to be 15.0 mg/L and 13.0 mg/L at 25 °C by WSKOWWIN and WATERNTWIN respectively.

Human Health

A 28-day repeated dose toxicity study was conducted in rats according to the Japanese guideline and OECD Guideline 407 under GLP. Rats were administered 1,2-dichloro-4-(chloromethyl)benzene by gavage at 0 (vehicle control: 0.5% Sodium carboxymethyl cellulose), 10, 30, 100, and 300 mg/kg bw/day. At 300 mg/kg bw/day, one female died during the treatment period. At the end of the administration period, relative and absolute weights of the liver and kidney were significantly increased in males and females at 300 mg/kg bw/day. In urinalysis, urine volume and casts in urinary sediments in males and epithelium in urinary sediments in males and females increased at 300 mg/kg bw/day. In the histopathological findings, in the forestomach, hyperkeratosis was observed in males at 10 mg/kg bw/day and higher, and in females at 30 mg/kg bw/day and higher, hyperplasia of the squamous epithelium was observed in males at 30 mg/kg bw/day and higher, and in females at 10 mg/kg bw/day and higher, and edema and cellular infiltration were observed in males and females at 10 mg/kg bw/day and higher, and erosion was observed in males at 300 mg/kg bw/day. In the kidney, hyaline droplet in the tubular epithelium was observed in males of the 100 mg/kg bw/day and higher, and increased basophilic tubular epithelium, dilatation of the tubules, degeneration of the tubular epithelium, and fibrosis of the interstitium in males and females, and necrosis of the tubules and interstitial cellular infiltration in females were observed at 300 mg/kg bw/day. Increased relative weights of the liver and kidney, hyperplasia of the squamous epithelium in the forestomach, and , basophilic tubular epithelium, dilatation of the tubules, and interstitial cellular infiltration in the kidney, remained at the end of recovery period. Based on these findings at 10 mg/kg bw/day in males and females, the LOAEL of this study was considered to be 10 mg/kg bw/day.

In a bacterial mutation study using *Salmonella typhimurium* and *Escherichia coli* (OECD TG 471), 1,2-dichloro-4-(chloromethyl)benzene was negative in all *Salmonella* strains and *E.coli* with and without metabolic activation. In an *in vitro* chromosome aberration test using CHL/IU cells (OECD TG 473), 1,2-dichloro-4-(chloromethyl)benzene did not induce structural chromosomal aberrations or polyploidy with and without metabolic activation. No *in vivo* mutagenicity data are available. Based on these results, 1,2-dichloro-4-(chloromethyl)benzene is considered to be non genotoxic *in vitro*.

Agreed Hazard Conclusions

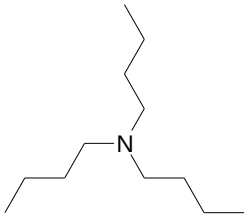
This chemical possesses properties indicating a hazard for one human health endpoint (repeated dose toxicity) targeted in this assessment.

Available Exposure

Production and import volume of 1,2-dichloro-4-(chloromethyl)benzene in Japan was not reported. However volume of production and import for the total of mono- and di-chlorobenzylchlorides in Japan was reported to be 3,000 - 4,000 tones in fiscal year 2010. Production volume in other countries is not available. 1,2-Dichloro-4-(chloromethyl)benzene is used as an intermediate for agricultural chemicals and pharmaceutical

products.

SIDS INITIAL ASSESSMENT PROFILE

CAS No(s).	102-82-9
Chemical Name(s)	TRIBUTYLAMINE (**TBA**)
Structural Formula(s)	

SUMMARY CONCLUSIONS OF THE SIAR

Analogue Rationale

Toxicokinetic data were not located for **TBA.** However, data were located for tributylammonium chloride (CAS No. 6309-30-4), a salt of TBA. In this case, testing the salt of TBA avoids damage to the gastrointestinal tract following gavage administration due to the caustic mode of action. Repeated-dose toxicity data for **TBA** are limited. In addition, reproductive toxicity data were not located. Therefore, read-across to di-n-butylamine (DBA; CAS No 111-92-2) for repeated dose and reproductive (fertility) toxicity endpoints is appropriate because both compounds have similar chemical structures and because **TBA** is partially deaminated to DBA derivatives *in vivo* and is excreted in the urine. Furthermore, for both compounds, the acute and repeated-dose inhalation effects are generally related to local effects. Although the water solubilities of TBA and DBA are different (0.08 and 3.8 g/L, respectively), the acute oral LD50 values are in the same range (420 and 550 mg/kg bw, respectively, for male rats). For ecotoxicity purposes, dibutylamino ethanol (CASRN 102-81-8) is used as an analogue to support the TBA data for acute fish and algae toxicity endpoints; data for acute and chronic invertebrates are also presented for comparative purposes. This approach is appropriate because both compounds have similar chemical structures (i.e., both classified as tertiary amines with a central nitrogen atom bearing an unshared pair of electrons that underlies their similar chemical behavior) and physico-chemical properties. According to the acute aquatic toxicity classification of OASIS (MOA profiler in QSAR Toolbox) for the mode of action, both TBA and dibutylaminoethanol are considered to be narcotic amines.

Read Across Strategy

Mammalian toxicity			Ecotoxicity
Toxicokinetics	Repeated dose	Reproductive toxicity	Acute and chronic aquatic toxicity
TRIBUTYLAMMONIUM CHLORIDE	DBA	DBA	DIBUTYLAMINOETHANOL

Physical-chemical Properties

TBA is a liquid with a measured melting point of $\leq$- 90 °C, a measured boiling point of 208 °C at 1013 hPa and a measured vapour pressure of 0.18 hPa at 20 °C. The measured octanol-water partition coefficient (log K_{ow}) is 3.34 at 20 °C, the estimated log K_{oc} (25°C) is 1860 and 18900 for the neutral and for the ionized molecule (pH 7) respectively, and the water solubility is 0.08 g/L at 20 °C. A pH of 10.2 was measured at 0.1 g/L and 25 °C.

The pKa value of the conjugate acid of **TBA** in water is 10.89 (measured). The pKa value of dibutylamino

ethanol is 10.3 (measured).

Human Health

TBA is expected to be absorbed by the dermal, oral and inhalation routes of exposure. Following oral exposure to tributylammonium chloride, a salt of **TBA**, the majority of excretion is expected in the urine; urinary metabolites identified were chain hydroxylation (60%), deamination to di-n-butylamine derivatives (ca. 33%), in addition to unchanged (10%) and unidentified (14%) of the administered dose.

The acute 4 hour inhalation LC50 of **TBA** in rats is 0.5 – 0.69 mg/L [similar/same as OECD TG 403 or a standard acute inhalation study design]. Clinical signs of toxicity included irritation (not specified), abnormal respiration and rales, restlessness, symptoms of respiratory tract irritation, closed eyelids, excessive salivation, tremor and convulsions. The acute dermal LD50 of **TBA** was 195 mg/kg bw (rabbits; use of vehicle not specified) to > 2000 mg/kg bw (rats; 40% in vehicle) [similar to OECD TG 402 or a standard acute dermal study design]. Clinical signs of toxicity included slight edema and erythema at the application site and transient convulsions, spastic gait, dyspnea, apathy and poor general state. Each of the acute oral studies have some limitations and are considered reliability 4; a weight-of-evidence analysis is applied to these and all results are reported. The acute oral LD50 of **TBA** in rats ranged from 420 - 780 mg/kg bw [similar to OECD TG 401 or a standard acute oral study design]. Clinical signs of toxicity included salivation, rapid respiration, lethargy, slight staggering, ataxia, tremor, twitching, seizures, lateral or abdominal position, imbalance, dyspnea and dilated pupils. These clinical effects were signs of animal suffering at high doses/concentrations of the corrosive chemical. The acute oral LD50s in other species are >39 mg/kg bw (cat, sex not reported), >390-<708 mg/kg bw (rabbit, sex not reported), 615 mg/kg bw (rabbit, male and female), 114 mg/kg bw (mouse, male and female), 888 mg/kg bw (mouse, sex not reported), and 350 mg/kg bw (guinea pig, male and female) (no guideline specified). **TBA** was corrosive to rabbit skin in a short term patch test (no guideline specified). Although **TBA** was not irritating to the rabbit eye in an OECD TG 405 study, vapour concentrations did likely cause eye irritation in an acute inhalation toxicity study. **TBA** is a respiratory tract irritant in acute inhalation studies in rats [similar to OECD TG 403 or a standard acute inhalation study design]. **TBA** was negative for skin sensitization in a Buehler Test with guinea pigs [similar to OECD TG 406].

Repeated-dose toxicity data were limited for **TBA** to a single inhalation toxicity study. Rats were exposed to **TBA** via inhalation (whole-body) at concentrations up to 0.923 mg/L 6 h/day, 5 days/wk for a total of 19 exposures (RL=4, no guideline specified). These animals exhibited nasal irritation, some loss of muscular control, lethargy, tremors and lack of weight gain. In a study similar to OECD TG 413, repeated nose-only inhalation study, rats were exposed to the analogue substance DBA at 0.051, 0.142, and 0.448 mg/L for 6 h/day, 5 days/wk for 90 days. At the highest dose, convulsions were seen in some rats within the first three days, and a decrease in body weight and food consumption was also observed. At 0.448 mg/L, nasal irritation and hyperplasia, hemorrhage and inflammatory cell infiltration were most pronounced during the first three days, indicating that some adaptation occurred. Mucous cell hyperplasia was also observed at the two lower doses. Some hyperplasia of lymphoid tissues surrounding the respiratory tract was seen at all doses, without statistical significance. The Lowest Observed Adverse Effect Concentration (LOAEC) for local irritation following 90 day repeated dose inhalation exposure to DBA was 0.051 mg/L; this LOAEC is considered applicable to **TBA**.

TBA did not induce mutations in a bacterial reverse mutation assay [similar to OECD TG 471] or an in vitro mammalian gene mutation assay at the HPRT locus in mouse lymphoma L5178Y cells [OECD TG 476]. In addition, **TBA** did not induce micronuclei in bone marrow of mice at 150 mg/kg bw [OECD TG 474]. Based on these studies, there is no evidence that **TBA** is genotoxic.

No data are available for the carcinogenicity of **TBA**.

Effects on fertility data were not located for **TBA*;*** read across to analogue substance DBA is used to fill this endpoint. Test substance-related microscopic changes were not observed in the reproductive organs of either males or female rats exposed by inhalation for 91 days (similar to OECD TG 413) to analogue substance DBA at concentrations up to 0.448 mg/L (highest concentration tested); a similar lack of effect on reproductive oragns is expected for **TBA**. For developmental toxicity of **TBA**, when administered to 20 pregnant rats by oral gavage on gestation days 6-15 at doses of 0, 15, 45 and 135 mg/kg bw/day [OECD TG 414], **TBA** caused systemic

toxicity (mortality, transient reductions in body weight gain) at 135 mg/kg bw/day resulting in a maternal NOAEL of 45 mg/kg bw/day; the developmental NOAEL was 135 mg/kg bw/day (the highest dose tested). There were no embryotoxic or fetotoxic effects except a slight and dose-related increase in fetal body weight gain, which was significant at the highest dose. The treatment did not produce malformations.

TBA possesses properties indicating a hazard for human health [acute and repeated-dose toxicity, skin corrosion, respiratory tract irritation andpotential for eye irritation]. Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Environment

TBA is expected to be hydrolytically stable in the natural environment and to exist as a cation in water at environmentally relevant pH. It should be noted, however, that EPISuite predicts certain environmental fate endpoints in their neutral forms (Phototransformation in air, adsorption/desorption and Level III fugacity model). Therefore, there will be some differences between predicted and actual results.

A standard hydrolysis study was not located for **TBA**; due to the structural properties of the substance, hydrolysis is not expected under environmental conditions.

In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of 1.2 hours. Two OECD TG 301B studies with **TBA** resulted in ≥80% biodegradation after 28 days (readily biodegradable) and an OECD TG 302 B (activated sludge from industrial WWTP) resulted in 98% biodegradation in 15 days (6% after 3 h) (inherently biodegradable). Based on TOC measurements in a screening test, **TBA** has been found to be stable for 28 days in test solutions (no significant loss, nearly 100%) in an abiotic elimination control according to OECD TG 301B. Considering the tests in total, **TBA** is readily biodegradable under aerobic conditions.

A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that **TBA** (in the neutral form), will distribute mainly to the soil (75%) and water (24%) compartments with minor distribution to the air (0.5%) and sediment compartments (1%). However, as the model does not take into account the charged form of the molecule at environmental relevant pH-values (pH 5-9), the model may underestimate distribution of **TBA** into water. An estimated pH-corrected Henry's law constant (pH 7.0; charged molecule) of 0.006 $Pa.m^3$/mole at 25 °C suggests that volatilization of **TBA** from the water phase is not expected to be high.

TBA is not expected to bioaccumulate in the aquatic environment based on a measured bioconcentration factor of 3.2-47 (10 µg/L); 7.3 (100 µg/L) [OECD TG 305C; test species: *Cyprinus carpio*]. The analogue chemical dibutylamino ethanol (CASRN 102-81-8) is also not expected to bioaccumulate in the aquatic environment based on a measured bioconcentration factor of < 5 (0.2 mg/L); < 39 (0.02 mg/L) [OECD TG 305C; test species: *Cyprinus carpio*].

Acute ecotoxicity data with dibutylamino ethanol is used to support the TBA data for the fish and algae acute toxicity endpoint; data for invertebrates are also presented for comparative purposes, as not all tests for **TBA** include measurements of stability. It is demonstrated that the toxicity of **TBA** and dibutylamino ethanol are in the same range, however, **TBA** seems to be slightly more toxic than dibutylamino ethanol. Based on TOC measurements in a screening test, **TBA** has been found to be stable in test solutions (>80% for 96 and 48 hours, respectively) according to OECD TG 201 and 202 (without organisms). The following acute toxicity test results have been determined for aquatic species, e.g.:

Fish
TBA:
Danio rerio 28 d LC_{50} >10 mg/L (nominal; semi-static; not neutralized, pH 7.1-8.3) [OECD TG 204]
Oryzias latipes 96 h LC_{50} = 16.3 mg/L (nominal; semi-static; not neutralized, pH 8.1 - 8.7) [OECD TG 203]

Dibutylamino ethanol:
Oryzias latipes 96 h LC_{50} = 29.2 mg/L (measured; semi-static; pH 7.4-8.9) [OECD TG 203]
Leuciscus idus 96 h LC_{50} = 31.6 mg/L (nominal; not neutralized pH 7.3 to 9.6, geometric mean; static); > 100

–< 500 mg/L (neutralized; pH 7.3-7.7; nominal; static) [DIN 38412, part 15]

Invertebrate
TBA:
Daphnia magna 48 h EC_{50} = 8 mg/L (measured; semi-static; not neutralized, pH 7.9-8.0) [OECD TG 202]
Daphnia sp. 24 h EC_{50} = 18 mg/L (not specifed, static; not neutralized, pH not reported) [DIN 38412, part 11]

Dibutylamino ethanol:
48 h EC_{50} = 81.7 (nominal; semi-static; not neutralized, pH 7.8 to 8.0 (highest concentration)) [similar to OECD TG 202]
48 h EC_{50} > 108 mg/L (measured; pH 7.9-9.6) [OECD TG 202]

Algae
TBA:
[*Desmodesmus subspicatus*] 72 h EbC_{50} = 3.6 mg/L; 72 h EbC_{10} = 1.5 mg/L (not specified; static; not neutralized, pH not reported);
72 h EbC_{50} = 8.2 mg/L; 72 h EbC_{10} = 1.4 mg/L (not specified; neutralized, pH not reported) [DIN 38412, part 9]

Dibutylamino ethanol:
[*Pseudokirchnerella subcapitata*] 72-h EbC_{50} = 9 mg/L; 72-h $NOEbC_{50}$ = 1.65 mg/L (measured; static; not neutralized, pH 7.8 - 10.2);
72-h ErC_{50} = 21 mg/L; 72-h $NOErC_{50}$ = 3.2 mg/L (measured; static; not neutralized, pH 7.8 - 10.2)

In a chronic aquatic toxicity study in *Daphnia magna* with dibutylamino ethanol, the 21-d EC_{50} for reproduction = 9 mg/L (21-d NOEC for reproduction = 4.4 mg/L) (measured; not neutralized, pH 7.4 - 9.5) .

TBA possesses properties indicating a hazard for the environment (acute aquatic toxicity values between 1 and 100 mg/L). TBA is readily biodegradable and has a low bioaccumulation potential. Adequate screening-level data are available to characterize the hazard to the environment for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Exposure

TBA is commercially produced with an annual production volume of 454 < 4,536 tonnes in the United States [sponsor country]. Global production volume was also estimated to be approximately 454-4536 tonnes/year in year 2010. These values are provided as ranges to protect confidential business information.

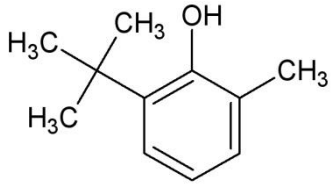
TBA is used as a proton scavenger in a variety of chemical processes and to produce quaternary ammonium compounds (e.g. tributylmethyl and tetrabutyl ammonium bromide, chloride or bisulphate) which are used as phase transfer catalysts, and to produce phosphonium salts. **TBA** is also used commercially as an acid acceptor and used as directly as a catalyst in phenolic resins, polycarbonates, polyesters, and engineered plastics.

TBA is produced in closed systems by producer sponsor companies. It is not known whether other producers might use other (e.g., open) systems of manufacturing. Inhalation and dermal exposure may be possible during occupational use. Procedures are recommended for ensuring that emissions and exposures are well controlled during production and use. In production, **TBA** is handled in closed systems by ACC Amines panel producers. Necessary engineering controls during production include proper ventilation, containment, safety equipment and actual hardware designed to minimize exposure through splashing or exposure to the air. Transfer of these materials is in closed pipe systems rather than in open systems to minimize loss. There may be low level losses in process waters, which are discharged to a waste water treatment system. Limited potential exists for release of material to a publicly-owned treatment works (POTW) or a body of water after primary biological

treatment on site. **TBA** is stored in closed tanks and transported in tank cars and tank trucks, and smaller amounts are transported in drums or Intermediate Bulk Containers (IBCs).

Consumer exposures have not been reported for **TBA**.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	2219-82-1
Chemical Name	2-Methyl-6-*tert*-butylphenol
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Physical and Chemical Properties

2-Methyl-6-*tert*-butylphenol is a yellow liquid or solid with a melting point of 24-31 °C and a boiling point of 230 °C. Density is 0.924 g/cm^3 at 80 °C and vapour pressure is 3.96 Pa at 25 °C (estimated). The calculated octanol-water partition coefficient (log K_{ow}) is 3.97 and the estimated water solubility is 101.3 mg/L at 25 °C.

Human Health

No specific studies were available on the absorption, distribution, metabolism, or excretion of 2-methyl-6-*tert*-butylphenol. In a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test, oral repeated doses of 2-methyl-6-*tert*-butylphenol caused anemia due to decreased erythrocyte count and hemoglobin concentration. Also, the test substance had effects on hepatic function and increased extramedullary hematopoiesis and hemosiderin deposition in spleen of rats. These results suggested the possibility of absorption of 2-methyl-6-*tert*-butylphenol and distribution in spleen, liver and stomach.

In the acute toxic class method study, LD_{50} cut-off value was considered to be 500 mg/kg bw for female rats [OECD TG 423]. All animals at 2,000 (1st step) mg/kg bw died. At 300 (2nd and 3rd steps) mg/kg bw no death was observed and body weight was normally increased in all animals. Inanimation, prone position, loss of locomotor activity and moribund state were observed after the administration of the test substance at 2,000 mg/kg bw.

The acute dermal LD_{50} value was greater than 2,000 mg/kg bw for male and female rats [OECD TG 402]. Exfoliation was temporarily observed for 5 males and 1 female. No mortality, gross pathology and body weight change were observed.

2-Methyl-6-*tert*-butylphenol was considered to cause skin corrosion in 1 male rabbit [OECD TG 404]. No irritation or corrosion response was observed following 3 minutes and 1 hour exposures. But skin corrosion with skin necrosis, discoloration, erythema (score 3) and edema (score 4) were observed after the 4-hour exposure.

2-Methyl-6-*tert*-butylphenol was tested for eye irritation in three male rabbits according to OECD TG 405. In the initial and confirmatory tests, congestion of the iris (score 1), redness of the conjunctivae (score 1-2), chemosis of the conjunctivae (score 1-2) and discharge (score 3) were temporarily observed. Also, signs of pain, distress, excessive blinking and excessive tearing were observed after the application of the test substance. The maximum mean total score (MMTS) was 17.0. Based on the results, 2-methyl-6-*tert*-butylphenol was considered to cause eye irritation in rabbits under the conditions of this study

In a repeated dose oral toxicity study in rats following OECD TG 422, 2-methyl-6-*tert*-butylphenol was administered via gavage to 12 animals/sex/dose at 0, 8, 40 and 200 mg/kg bw/day. Male rats were treated from 14 days before mating to the day before necropsy (42 days), and female rats were treated from 14 days before mating to day 4 of lactation (42-50 days). As a recovery group, 5/12 males at 0 and 200 mg/kg bw/day were observed for 14 days after the administration period. Additional 5 females at 0 and 200 mg/kg bw/day were treated for 42 days without mating and observed for 14 days as a satellite group. No death was observed in

either sex. Observed clinical signs were prone position, a decrease in locomotor activity, abnormal gait, and irregular respiration in one female of the 200 mg/kg group before mating. Body weight was decreased in females of the 200 mg/kg bw/day group throughout the gestation and lactation periods and in males of the 200 mg/kg bw/day group after day 22. During the recovery period, body weight was also decreased in males of the 200 mg/kg bw/day group. Although body weight gain was suppressed in males on day 22 and females on day 0 of gestation, the body weight gain was comparable to or higher than the control group afterward. Anemic changes were noted in both sexes of the 200 mg/kg bw/day group and increased spleen weight was observed in females of the 200 mg/kg bw/day group. In the spleen, an increase in extramedullary hematopoiesis was noted. After the recovery period, the following changes were noted in the 200 mg/kg bw/day group: anemic findings, increased spleen weight in males, an increase in extramedullary hematopoiesis in one male, an increase in hemosiderin deposition in both sexes. In blood chemistry, high γ-glutamyltransferase and an increasing tendency in aspartate aminotransferase, alanine aminotransferase, and triglyceride were noted in males of the 200 mg/kg bw/day group. Total cholesterol was increased in both sexes of the 200 mg/kg bw/day group. In the liver, the organ weight was increased in both sexes of the 40 and 200 mg/kg bw/day groups and centrolobular hypertrophy of the hepatocytes was seen in both sexes of the 200 mg/kg bw/day group. Other changes in liver disappeared after the recovery period except that an increased liver weight remained in females of the 200 mg/kg bw/day group. Furthermore, treatment-related hyperplasia of squamous limiting ridge in the forestomach was noted in males of the 200 mg/kg bw/day group. Moreover, eosinophil cell infiltration of the glandular stomach and an increase in globule leukocyte were noted in one male of the 200 mg/kg bw/day group. These changes recovered or tended to recover by the end of the recovery period. There were no changes related to the test substance in behavior test, functional test, motor activity, food consumption, urinalysis of males, or necropsy findings. Based on the effects on the anemic changes and liver function noted in both sexes of the 200 mg/kg bw/day group, the NOAEL for repeated dose oral toxicity was considered to be 40 mg/kg bw/day.

In an Ames test with *Salmonella typhimurium* TA98, TA100, TA1535, TA1537 and *Escherichia coli* WP2*uvr*A [OECD TG 471], 2-methyl-6-*tert*-butylphenol did not induce gene mutation in bacteria *in vitro* both with and without metabolic activation. In an *in vitro* chromosomal aberration test [OECD TG 473] using Chinese hamster lung cells, 2-methyl-6-*tert*-butylphenol did not show the structural or numerical chromosome aberrations regardless of application of metabolic activation. Based on these results, 2-methyl-6-*tert*-butylphenol is considered to be non genotoxic *in vitro*.

No reliable studies were available for the carcinogenicity of 2-methyl-6-*tert*-butylphenol.

2-methyl-6-*tert*-butylphenol has been investigated in a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test in rats [OECD TG 422]. 2-Methyl-6-*tert*-butylphenol was administered by oral gavage to 12 animals/sex/dose at 0, 8, 40 and 200 mg/kg bw/day. See the repeated dose section for the dosing regime. During the observation period, gestation length was prolonged at 200 mg/kg bw/day. No abnormality was found in the reproductive organs of either sex. There were no changes in the number of corpora lutea or implantations, implantation index, gestation index, or delivery index, which was considered to have no effect on the implantation or maintenance of the pregnancy. No abnormal findings ascribable to the test substance were found in estrous cycle, mating index, fertility index, sex ratio, external features, or necropsy of the offspring. No effects on body weight of pups were evident in any dose group. The number of live offspring at birth and on day 4, live birth index, and viability index on day 4 were low at 200 mg/kg bw/day. Therefore, the NOAEL for reproduction and developmental toxicity was 40 mg/kg bw/day, respectively.

2-Methyl-6-*tert*-butylphenol possesses properties indicating a hazard for human health (skin corrosion, eye irritation, repeated dose toxicity and reproduction/developmental toxicity via gavage). Adequate screening-level data are available to characterize the human health hazard for the purposes of the Cooperative Chemicals Assessment Programme.

Environment

2-Methyl-6-*tert*-butylphenol does not possess a molecular structure that contains functional groups subject to hydrolysis under neutral ambient conditions. In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of 0.2 day by AOPWIN ver. 1.92. A test for ready biodegradability was conducted with 2-methyl-6-*tert*-butylphenol with activated sludge for 28 days [OECD TG 301C]. The concentration of the test substance was 100 mg/L and the concentration of the activated sludge was 30 mg/L as suspended solid matter. The test results showed 9% degradation by BOD. The DOC and test substance loss was 81% and 98%, respectively. The relevance of the decrease in DOC is unknown. QSAR

estimates support the test result of not ready biodegradability (BIOWIN 4.10). Therefore, 2-methyl-6-*tert*-butylphenol was considered to be not readily biodegradable.

A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that 2-methyl-6-*tert*-butylphenol is mainly distributed to the soil (80.1%) and water (17.5%) compartments with a minor distribution to the sediments compartment (2.13%) and a negligible amount in the air compartment. If released only to the soil compartment, 2-methyl-6-*tert*-butylphenol stays in the soil compartment (99.7%) with negligible amounts in other compartments. A Henry's law constant of 0.162 Pa-m^3/mole (6.34×10^{-5} atm-m^3/mole) at 25°C suggests that volatility of 2-methyl-6-*tert*-butylphenol from the water phase is not expected to be high. A log K_{oc} of 3.33 was estimated based on the MCI method, indicating a moderate potential for accumulation in soil.

In 28 days exposure to *Cyprinus carpio*, bioconcentration factor (BCF) of 34~114 and 28~59 were obtained at 0.2 mg/L and 0.02 mg/L, respectively. Using an octanol-water partition coefficient (log K_{ow}) of 3.97, a bio-concentration factor (BCF) of 115.9 was estimated based on regression method with BCFBAF ver. 3.01. Therefore, this chemical has a low potential of bioaccumulation.

The following acute toxicity test results have been determined for aquatic species:

Fish [*Oryzias latipes*, OECD TG 203]	96 h LC_{50}=5.1 mg/L (measured; semi-static)
[*Oryzias latipes*, Japan CSCL]	96 h LC_{50}=4.32 mg/L (measured; semi-static)
Invertebrate [*Daphnia magna*, OECD TG 202]	48 h EC_{50}=3.08 mg/L (measured; static)
[*Daphnia magna*, Japan CSCL]	48 h EC_{50}=5.25 mg/L (measured; static)

Algae [*Pseudokirchneriella subcapitata*, Japan CSCL] 72 h ErC_{50}=6.31 mg/L (growth rate, measured; static)

2-Methyl-6-*tert*-butylphenol possesses properties indicating a hazard for the environment (acute aquatic toxicity between 1 and 10 mg/L for fish, invertebrate and algae). The chemical has a low bioaccumulation potential and is not readily biodegradable. Adequate screening-level data are available to characterize the environmental hazard for the purpose of the Cooperative Chemicals Assessment Programme.

Exposure

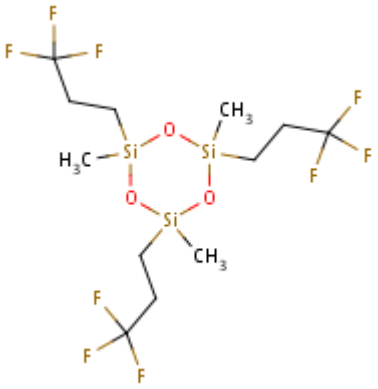
In the Republic of Korea (sponsor country), the production, use and import volumes of 2-methyl-6-*tert*-butylphenol were 2,889, 3,099 and 200 tonnes in 2006, respectively. And the production and use volumes were 168 and 8 tonnes in 2010, respectively.

2-Methyl-6-*tert*-butylphenol is used as an antioxidant, stabilizing agent, or in synthetic materials. In the sponsor country, 2-methyl-6-*tert*-butylphenol is mainly used as an antioxidant. The industrial manufacture process of antioxidants is as follows: the raw material, o-cresol, is alkylated with isobutylene. The product is purified by hot filtration.

In the sponsor country, 2-methyl-6-*tert*-butylphenol is manufactured and used in closed systems. Workplaces are under control in accordance with the MSDS. Occupational exposure is managed by local ventilation system and wastewater in the process is well controlled by physical and chemical treatment. Since worker exposure may include inhalation exposure, workers are equipped with personal protective equipment such as gas masks, safety cap, rubber gloves, rubber boots and goggles. Occupational exposure is considered to be properly controlled in the sponsor country.

2-methyl-6-*tert*-butylphenol is used only industrially in the Republic of Korea. Therefore, consumer exposure is not expected in the sponsor country.

SIDS INITIAL ASSESSMENT PROFILE

CAS No(s).	2374-14-3
Chemical Name(s)	2,4,6-trimethyl-2,4,6-tris(3,3,3-trifluoropropyl)cyclotrisiloxane (Fluorosilicone trimer)
Structural Formula(s)	

SUMMARY CONCLUSIONS OF THE SIAR

Physical-chemical Properties

Fluorosilicone trimer is a cyclotrisiloxane comprised of a six-membered siloxane ring having alternating silicon and oxygen atoms (three each). Each silicon atom is bonded to two pendant groups: one methyl group ($A=CH_3$) and one 3,3,3-trifluoropropyl group ($B=CH_2CH_2CF_3$). The fluorosilicone trimer can exist as two distinct configurational isomers, referred to as the cis- and trans- forms. In the cis- form, all identical pendant groups lie on the same side of the siloxane ring (i.e. AAA and BBB), whereas in the trans- form, one of the pendant groups is different on each side (AAB and BBA). Fluorosilicone trimer is a liquid containing suspended solids[1] with a measured melting point range of -1.9°C (cis- isomer) to 35°C (trans- isomer), a measured boiling point range of 239°C (cis- isomer) to 242°C (trans- isomer), and a vapour pressure of 0.88 hPa at 25 °C (extrapolated from measured data). The calculated octanol-water partition coefficient (log K_{ow}) is 9.84 at 25 °C and the calculated water solubility is 4.7E-07 mg/L at 25 °C (both values RL=4[2]).

Human Health

Although no toxicokinetic studies are available for Fluorosilicone trimer, the treatment-related adverse health effects observed with oral and dermal exposure imply some level of bioavailability with exposure by these routes.

The acute oral LD50 values of Fluorosilicone trimer are 4659 (50% in maize oil; according to OECD TG 401), 10,000 (undiluted), 3750 (50% in corn oil), and 252 (5% in corn oil) mg/kg bw in rats (no guideline specified); sluggishness, piloerection and coma, reduced body weight gain and/or body weight loss, and bloody nasal discharge were observed. Adverse effects were noted at necropsy in the stomach, intestines, liver and kidneys. The acute dermal LD50 was 25,400 mg/kg bw in rabbits; decreased activity, lacrimation, nasal discharge, transient erythema and reduced body weight gain were observed (similar to OECD TG 402). Adverse effects were noted at necropsy in the kidneys, liver, gastrointestinal tract, thymus and lungs. No acute inhalation studies are available.

[1] The solid is one of the two stereoisomers that comprise the sponsored substance, which can have a melting transition above room temperature. The lower and upper melting transitions depend on the isomer composition of the mixture.

[2] Not all programs within EPI Suite have been validated for chemicals that contain the element Si, but recent upgrades to the Kow and water solubility modules, found in the current version of EPI Suite (v4.11), give reasonable estimates for silanes and siloxanes.

The substance is not considered irritating to the skin or eye of rabbits (OECD TG 404 and 405), and is not considered a skin sensitizer in guinea pigs (OECD TG 406).

In a 21 day dermal repeated dose study, male and female rabbits (no guideline specified) were administered the test substance (99.7% purity) under occlusive cover for 6 hours per day, five days per week at doses of 0, 40, 200 and 400 mg/kg/day. Five rabbits in the 400 mg/kg bw dose group died. A single female died at 200 mg/kg bw, but this death was not considered treatment related (pneumonia). A reduced rate of weight gain, lower food consumption, and decreased serum alkaline phosphatase activity was observed at 200 and 400 mg/kg bw. Significant increases in serum glutamic-pyruvic transaminase and glutamic oxalacetic transaminase activities were observed in male animals at 200 and 400 mg/kg bw. In females, serum glutamic oxalacetic transaminase activity was increased in the 200 mg/kg bw group. Relative liver weights were decreased in all female treated groups; in males, the relative liver weights were decreased only in 200 mg/kg bw group. Gross and microscopic pathologic examination revealed no treatment-related effects. The NOAEL was considered to be 40 mg/kg bw/day for male and female rabbits when applied dermally, based on the correlation of decreased liver weights and changes in serum enzymes, suggesting effects on the liver at 200 and 400 mg/kg bw.

In a 90-day gavage study, male and female rats (EPA OPPTS 870.3100, similar to OECD TG 408) were administered the test substance (98.3 %; in sesame oil) by gavage at doses of 0.8, 4, 20 and 50 mg/kg bw/day for 90 days. There were an additional ten rats/sex included as recovery groups in the control and high dose groups; due to excessive mortality in the high dose group, the recovery period was not conducted. After severe toxicity was noted during the first week of dosing, the dose level was reduced from 50 to 35 mg/kg bw/day and the high dose group was relabelled as 50/35 mg/kg bw/day. Eighteen of twenty animals (eight male/ten female) died in the 50/35 mg/kg bw/day group, two 20 mg/kg bw/day group females died, and two control group males died. Clinical findings were consistent with indications of skeletal muscle toxicity, were observed predominantly in the 50/35 mg/kg bw/day group females. Clinical signs for the 20 mg/kg bw/day group females and 50/35 mg/kg bw/day group males and females also included prostration, lethargy, piloerection, biting of cage bottom, head bobbing and hyperactivity. Increased salivation and wet and/or dried red or yellow material on various body surfaces were noted in the 20 and 50/35 mg/kg bw/day groups. Test article-related decreases in mean body weights were noted in the 20 mg/kg bw/day group males and the 50/35 mg/kg bw/day group males and females. Slight decreases in food consumption were also noted in the 50/35 mg/kg bw/day group males and females. Test article-related increases in urea nitrogen, phosphorus and potassium and decreased cholesterol were noted at the 20 and 50/35 mg/kg bw/day dose levels. Increased mean liver weights correlated with periportal hepatocellular vacuolar changes and were noted in the 20 and 50/35 mg/kg bw/day groups. Decreased mean seminal vesicle and prostate weights group (20 and 50/35 mg/kg bw/day), were not considered adverse due to the lack of correlating histological findings in these tissues or in the testes and epididymides. Periportal vacuolar change was noted for males and females in all treated groups, but there was no indication of impaired liver function based on serum chemistry results and these changes were not considered adverse. In the skeletal muscle (rectus femoris), minimal to moderate degeneration was noted in the 20 and 50/35 mg/kg bw/day groups; this finding is consistent with the clinical findings of skeletal muscle toxicity. In the heart, treatment-related cardiomyopathy (subacute or chronic) was noted in the 4, 20 and 50/35 mg/kg bw/day group males and females; the findings were significant at 20 and 50/35 mg/kg bw/day. The NOAEL was 0.8 mg/kg bw based on effects on the heart, skeletal muscle and liver at 20 mg/kg bw/day and above.

In a 28-day gavage range-finding study groups of five male and female rats were administered the test substance (>98%, in sesame oil) by gavage for 28 days at doses of 0.2, 1.0, 5.0, 31.25, 62.5, 125 and 250 mg/kg bw/day. Two additional high concentration gavage dose groups, 125 and 250 mg/kg bw/day, were evaluated using five males per dose level and one to two females (respectively) per dose level. All animals dosed with either 125 or 250 mg/kg bw/day and three males dosed with 62.5 mg/kg bw/day died.One male died at 31.25 mg/kg bw/day (gavage error). Clinical signs of toxicity preceding death included the inability to use hind legs, tremors, loss of righting reflex, lethargy, decreased body temperature, tremors, fecal soiling or bleeding from the penis. Clinical signs in animals that survived to necropsy included an inability to use hind legs, tremors and lethargy. There was a reduction in mean male body weights at 31.25 mg/kg bw/day. After adjusting for the body weight, there were also significant decreases in mean ventral prostate and seminal vesicle weights at 31.25 mg/kg bw/day and a significant increase in liver weight at 62.5 mg/kg bw. Generally, increases in female liver weights were also observed up to 62.5 mg/kg bw/day. Severe diffuse inflammation and hyperplasia of the urinary bladder mucosa and renal pelvis and slight hyperplasia of the urinary bladder epithelium were noted in two animals in the 31.25

mg/kg bw/day group. The NOAEL for male and female rats was 5 mg/kg bw/day, based on urinary bladder hyperplasia seen at 31.25 mg/kg bw/day and above.

Fluorosilicone trimer was negative for gene mutations (*S. typhimurium* TA 1535, TA 1537, TA 98 and TA 100 and *E. coli* WP2 uvr A) in vitro (similar to OECD TG 471), mammalian cell transformation (no guideline specified) in vitro, and chromosome aberration in vivo (OECD TG 474). The substance is not considered to be genotoxic.

No data are available for the carcinogenicity of Fluorosilicone trimer.

In an OECD Guideline 415 (One-Generation Reproduction Toxicity Study), groups of twenty-five rats/sex were administered the test substance (98.3%) in sesame oil by gavage at doses of 0, 0.8, 4, 20, and 50 mg/kg bw/day. The test substance was administered daily for a minimum of 70 days prior to mating. Treatment of the F(0) males continued throughout mating and continuing until one day prior to euthanasia. Treatment of the F(0) females continued throughout mating, gestation, and through lactation day 20. The high dose group was labeled as 50/35 mg/kg bw/day due to a reduction in dose level from 50 to 35 mg/kg bw/day after severe toxicity was noted during the first week of dosing. Clinical signs noted in dams were predominantly in the 50/35 mg/kg bw/day group included impaired use of the hindlimbs, reduced hindlimb resistance, a hunched appearance, and rocking, lurching, or swaying while walking. The most frequently observed clinical findings, noted in the 20 and 50/35 mg/kg bw/day groups and considered to be exposure-related, included red and yellow material on various body surfaces and exophthalmus. Mean absolute prostate gland and pituitary gland weights were reduced in the 20 and 50/35 mg/kg bw/day group males, and mean absolute seminal vesicle, epididymal and testicular weights were reduced in the 50/35 mg/kg bw/day group. The decrease in prostate and pituitary gland weights appear to be at least partly related to decreased body weight. The effect on organ weight was without microscopic correlates and male reproductive performance was unaffected by treatment. As such, the modest decrease in prostate and pituitary gland weight is not considered to represent an adverse effect. There were four and five unscheduled deaths within the period from G20 to PND 3 for the 20 and 50/35 mg/kg bw/day dose group females. Of these, one of the deaths in the 50/35 mg/kg bw/day dose group females was considered possibly related to dystocia. Several unscheduled deaths occurred in both groups both prior to (2 at 20 mg/kg bw/day; 4 at 50/35 mg/kg bw/day) and after (5 in the 20 mg/kg bw/day and 4 in the 50/35 mg/kg bw/daydose groups) the G20 – PND 3 period. Significant mortality was also present in the 20 and 50/35 mg/kg bw/day dose group males, 5 and 10 respectively. Treatment related mortality is considered to represent maternal systemic toxicity unrelated to parturition. Mean body weight gains and food consumption were reduced in the 50/35 mg/kg bw/day group (males and females) early in the pre-breeding period. Mean body weight gain in the 50/35 mg/kg bw/day group females was reduced late in gestation, and mean body weights and food consumption were reduced in these females throughout lactation. Mean body weights in the 20 mg/kg bw/day group males were reduced from week 5 through the remainder of the study, while food consumption in the females in this group was reduced throughout lactation. In the 50/35 mg/kg bw/day group F0 females, the mean number of implantation sites was reduced, and the mean calculated difference between the number of pups born and the number of implantation sites was increased. For dams that delivered and were evaluated at scheduled necropsy on lactation day 21, in the 50/35 mg/kg bw/day group, a statistically significant ($p<0.01$) reduction was observed in the mean number of implantation sites, and a statistically significant ($p<0.01$) increase was observed in the mean calculated difference between the number of pups born and the number of implantation sites counted at necropsy. Total litter losses between lactational days 0 and 4 occurred in three females in the 50/35 mg/kg bw/day group. Mean postnatal survival was reduced at 50/35 and 20 mg/kg bw/day from birth to PND 4 and from PND 4 to PND 21, but was statistically significant in only the 50/35 mg/kg bw/day group. Mean male and female pup body weights in the 20 and 50/35 mg/kg bw/day groups were generally reduced during the entire postnatal period. There was a dose-related decrease in mean postnatal survival from birth-PND4 and PND 4-21 in the 20 mg/kg bw/day and 50/35 mg/kg bw/day groups (statistically significant only in the 50/35 mg/kg/day group). There were no gross findings for the pups. Based on an increase in the mean number of days between pairing and coitus and an increase in mean gestation length, the NOAEL for reproductive toxicity was 20 mg/kg bw/day. Based on mortality and clinical signs of skeletal muscle pathology, the NOAEL for parental toxicity in rats was 4 mg/kg bw/day. Based on dose-related effects at 20 and 50/35 mg/kg bw/day during the postnatal period, the NOAEL for developmental toxicity of rats was 4 mg/kg bw/day.

In a rat uterotropic assay, using the ovariectomized rat model (no guideline specified), Fluorosilicone trimer did not produce estrogenic activity at doses up to 500 mg/kg bw.

2,4,6-trimethyl-2,4,6-tris(3,3,3-trifluoropropyl)cyclotrisiloxane (Fluorosilicone trimer) possesses properties indicating a hazard for human health (repeated dose toxicity, reproductive toxicity). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Environment

Not all programs within EPI Suite have been validated for chemicals that contain the element Si, but recent upgrades to the Kow and water solubility modules, found in the current version of EPI Suite (v4.11), give reasonable estimates for silanes and siloxanes. For example, KOWWIN (v1.68 in EPI v4.11) has 32 chemicals containing Si in its combined training and validation sets. The water solubility programs WSKOWWIN and WATERNT have 0 and 19 combined training/validation chemicals with Si, respectively.

A modified OECD TG 111 (Hydrolysis as a Function of pH) study was conducted for Fluorosilicone trimer; to improve solubility, a much higher concentration of co-solvent was used (20 %v/v acetonitrile) than specified by the guideline (1 %v/v). Because of the effect that the co-solvent could have on the siloxane hydrolysis kinetics, the study was actually conducted as a comparative assessment using hexamethylcyclotrisiloxane (D3; CAS 541-05-9, available for review at http://www.oecd.org/env/hazard/data) as a reference substance. D3 was selected for its structural similarity to the Fluorosilicone trimer, and the fact that a OECD TG 111 hydrolysis study was conducted with D3. D3 half-lives were 2.5 to 60 times longer (depending on pH) in the presence of greater co-solvent concentration. This implies that the hydrolysis rates of the Fluorosilicone trimer are expected to be greater (i.e., shorter half-life) in fully aqueous solution. The $t_{1/2}$ (half-time) of Fluorosilicone trimer in 20% acetonitrile/80% aqueous buffer was >7.5 days, 6 days and 11 minutes at pH 5, 7 and 9 and at 25°C. The final hydrolysis product was identified as methylbis(3,3,3-trifluoropropyl)silanediol, although the kinetics of product formation were not determined.

In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of 2.4 days. In an OECD TG 301 B (Ready Biodegradability: CO2 Evolution Test), Fluorosilicone trimer degraded -3.33% in 28 days; it was not "readily biodegradable".

Level III fugacity modelling, using loading rates of 1000 kg/h each for air, soil and water, shows the following percent distribution when it is released simultaneously to all three compartments: Air = 11.7%, Water = 22.1%, Soil = 23.7%, and Sediment = 42.5%. A Henry's law constant of 1.72E+07 Pa-m3/mole at 25 ºC; the fluorosilicone trimer is a large molecule having low diffusivity in water, so that it is slow to cross the air-water interface. The log KAW value of 3.84 at 25 ^{o}C. Test data for bioaccumulation is not available. For very hydrophobic substances uptake through the diet is likely to exceed uptake through water. Therefore, test data and modelling approaches based on aqueous exposure may not be adequate to characterize the bioaccumulation potential for the substance. The biotransformation rate in fish is estimated to be very slow (BCFBAF, v3.01) and therefore, the substance is predicted to accumulate if taken up by fish. However, the combination of very low water solubility and the ability to hydrolyze may significantly limit the presence of the dissolved substance in the aquatic environment. In conclusion, fluorosilicone trimer is estimated to have the potential to bioaccumulate in the aquatic environment but a quantitative measure cannot be provided based on currently available information.

Acute aquatic toxicity studies were not conducted due to the very low water solubility of the substance. However, a chronic Daphnia test performed at the limit of functional water solubility showed no acute effects. The following acute toxicity results were estimated for aquatic species:

Species	Estimated values (ECOSAR Program (v1.11) (mg/L)	Comments
Fish	96 hour LC_{50} = 3.52E-005	Neutral Organics SAR
Daphnid	48 hour LC_{50} = 4.13E-005	Neutral Organics SAR
Green Algae	96-hour EC50 = 0.000612	Neutral Organics SAR; Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation are reported.

The chronic (21 d) flow through toxicity limit test (OECD TG 211) was performed with *Daphnia magna*. The nominal concentration was 20 µg/L (which is far above water solubility of 0.00047 µg/L). A solvent (acetone) was used, and a solvent control was included in the study. The measured concentrations at days 0, 7, 14, and 21 were 0.51, 6.1, 0.79, and 3.1 µg/L with a geometric mean of 1.7 µg/L. The NOEC (mortality, adult length) >= 1.7ug/L; the NOEC (reproduction, offspring/female) <1.7 ug/L and the LOEC for mortality and body length > 1.7 mg/L.

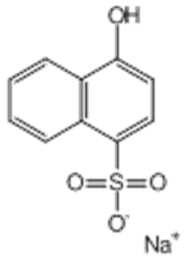
2,4,6-trimethyl-2,4,6-tris(3,3,3-trifluoropropyl)cyclotrisiloxane (Fluorosilicone trimer) possesses properties indicating a hazard for the environment at the limit of functional water solubility (chronic toxicity aquatic invertebrates <1 mg/L). Fluorosilicone trimer is not readily biodegradable. The fluorosilicone trimer has the potential to bioaccumulate. Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Exposure

In the United States, production volume in 2005 was ca. 227-1134 tonnes; in Japan production volume in 2005 was < 227 tonnes, and in Europe production volume in 2014 was 102 – 1016 tonnes. Ranges are provided to protect confidential business information. Fluorosilicone trimer is used in formulations up to 100% as a chemical intermediate in polymer production.

Fluorosilicone trimer is handled in closed systems, and transported from the production site as the parent chemical, and then intended to be consumed during use. Less than 0.1 % of the total annual production volume is sold. Transfer is in closed pipe, drums, or tanks rather than in open systems to minimize loss of this material (through hydrolysis). There are no intentional releases to the environment from manufacturing processes. Engineering controls include general and local ventilation, water scrubber devices and related equipment, and closed sampling systems. In additional, employees are required to use personal protective equipment including impermeable chemical resistant gloves, goggles, fire resistant clothing, safety shoes, hard hats, and respirators. Potential routes of exposure include inhalation and dermal exposure. There are no consumer uses of the substance.

INITIAL TARGETED ASSESSMENT PROFILE

CAS No.	6099-57-6
Chemical Name	1-Naphthol-4-sulfonic acid sodium salt
Structural Formula	

SUMMARY CONCLUSIONS OF THE TARGETED ASSESSMENT

NOTE: The present assessment was targeted to address only the following endpoint(s): Human Health: acute toxicity, repeated dose toxicity and *in vitro* mutagenicity. It cannot be considered as a full SIDS Initial Assessment. Summary information on exposure is also reported here. Other endpoints for human health and the environment have not been presented to OECD member countries, and thus are not included in this profile.

Rationale for targeting the assessment

Under the Japanese Chemical Substances Control Law (CSCL), risk assessment of existing chemical substances has been conducted by the government. The CSCL was amended in 2010 and 2011 and shifted toward risk-based management from hazard-based management. Chemical substances are classified as follows from April 1, 2011: (1) Class I Specified Chemical Substances (persistent, highly bioaccumulative, has long-term toxicity for humans or long-term toxicity for predator animals at higher trophic level), (2) Class II Specified Chemical Substances (has long-term toxicity for humans or flora and fauna in the human living environment, has risk), (3) Monitoring Chemical Substances (persistent, highly bioaccumulative, long-term toxicity unknown), (4) Priority Assessment Chemical Substances (suspected long-term toxicity for humans or flora and fauna in the human living environment, suspected risk) and (5) General Chemical Substances (risk to humans or flora and fauna in the human living environment is sufficiently low).

1-Naphthol-4-sulfonic acid sodium salt is classified as a General Chemical Substance based on degrees of hazard intensity and exposure estimates at the priority assessment meeting.

This targeted assessment document was originally based on the material of the priority assessment meeting provided from the chemical assessment council of Ministry of Health, Labour and Welfare (MHLW), Japan, and the toxicological profile was re-assessed for the OECD Cooperative Chemicals Assessment Programme.

Physical-Chemical Properties

1-Naphthol-4-sulfonic acid sodium salt is white powder at room temperature. As 1-naphthol-4-sulfonic acid sodium salt is a salt of an acid and sodium, 1-naphthol-4-sulfonic acid sodium salt completely dissociates with 1-naphthol-4-sulfonic acid anion and sodium cation in water. Physicochemical properties of 1-naphthol-4-sulfonic acid sodium salt are not available. As EPISUITE calculates the properties for 1-Naphthol-4-sulfonic acid after entering CAS No. 6099-57-6, physicochemical properties of 1-Naphthol-4-sulfonic acid sodium salt could not be estimated. Although no quantitative value is obtained for water solubility, it is expected to be high based on its molecular structure and the estimated value for the acid which is > 2.95×10^5 mg/L at 25 ℃.

Human Health

In a single dose oral toxicity test [OECD TG 401], 1-naphthol-4-sulfonic acid sodium salt was administered by gavage to male and female rats at 0 (vehicle control: water for injection) or 2000 mg/kg bw. In the 2000 mg/kg bw group, soft feces were observed in the early observation period, and the body weight of females was slightly lower than the control on days 8 and 11 after administration. Because no deaths were found in this study, the oral LD_{50} value was concluded to be greater than 2000 mg/kg bw.

A 28-day repeated dose toxicity study was conducted in accordance with the Japanese guideline (similar to OECD TG 407). In this study, 1-naphthol-4-sulfonic acid sodium salt was administered to male and female rats by gavage at 0 (vehicle control: water for injection listed in the Japanese Pharmacopoeia), 100, 300 or 1000 mg/kg bw/day. The test substance did not cause any changes in clinical signs, food consumption, body weight, hematological and blood biochemical parameters, or gross pathological and histopathological findings in any dose group. In the 1000 mg/kg bw/day group, the absolute weight of epididymis was increased by 16%, but this change was considered to be toxicologically insignificant because no changes were found in the gross pathological or histopathological findings in the epididymides. Therefore, the NOAEL for 1-naphthol-4-sulfonic acid sodium salt is considered to be 1000 mg/kg bw/day in this study.

The mutagenicity was evaluated in *Salmonella typhimurium* TA98, TA100, TA1535 and TA1537, and *Escherichia coli* WP2 *uvr*A according to the Japanese guideline (similar to OECD TG 471). In this study, 1-naphthol-4-sulfonic acid sodium salt was negative in all tested strains with and without metabolic activation. In an *in vitro* chromosome aberration test performed according to the Japanese guideline (similar to OECD TG 473), 1-naphthol-4-sulfonic acid sodium salt was negative for structural chromosomal aberration or polyploidy induction in Chinese hamster lung (CHL/IU) cells with and without metabolic activation. *In vivo* genotoxicity data are not available. Based on these results, 1-naphthol-4-sulfonic acid sodium salt is considered to be non genotoxic *in vitro*.

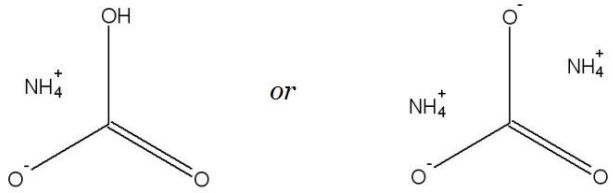
Agreed Hazard Conclusions

This chemical does not possess properties indicating a hazard for human health endpoints targeted in this assessment.

Available Exposure

Production and/or import volume of 1-naphthol-4-sulfonic acid sodium salt was reported to be less than 1,000 tones in fiscal year 2010 in Japan. Production volume in other countries is not available. 1-Naphthol-4-sulfonic acid sodium salt is used as an intermediate for dyes, such as Supramine Red B and Benzo Copper Blue.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	10361-29-2
Chemical Name	Ammonium carbonate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Ammonium carbonate, as described by CAS No. 10361-29-2, is an inorganic substance that consists of ammonium bicarbonate (CAS No. 1066-33-7) and diammonium carbonate (CAS No. 506-87-6), and their relative quantities are depending on the ratio of carbonic acid and ammonium salt. Ammonium carbonate may also exist as a mixture of ammonium bicarbonate and ammonium carbamate. Ammonium bicarbonate (NH_4HCO_3; CAS No. 1066-33-7) was assessed previously in the programme (SIAM 22, sponsor France/ICCA). This assessment covers the ammonium carbonate mixture, as described by CAS No. 10361-29-2, and uses test data for the following substances as indicated in the text.

- *Ammonium carbonate*: Carbonic acid, monoammonium salt, mixture with carbamic acid, monoammonium salt or mixture of Ammonium bicarbonate and ammonium carbamate
- *Ammonium carbonate (1:1)*: Carbonic acid, ammonium salt (1:1) or Ammonium bicarbonate, previously assessed in the programme
- *Ammonium carbonate (1:2)*: Carbonic acid, ammonium salt (1:2) or Diammonium carbonate

Physical and Chemical Properties

Ammonium carbonate is colourless, translucent or white, in the form of either crystals or powder. The substance has a strong odour of ammonia and sharp taste. Ammonium carbonate volatilizes at about 60 °C and decomposes before boiling and in hot water. The water solubility of ammonium carbonate is 320,000 mg/L at 20 °C. The dissociation constant is not applicable to an inorganic salt such as ammonium carbonate. *Ammonium carbonate (1:1):* The melting point is 107 °C and the density is 1.583 g/cm^3. It has water solubility of 174,000 mg/L at 20°C and measured vapour pressure of 7.85 kPa (dry ammonium carbonate) at 25.4 ^oC. The empirical value may represent decomposition of the substance into ammonia and carbon dioxide. This might explain the difference between measured and estimated values. The estimated log P_{ow} value for ammonium carbonate (1:1) is -3.08.

Ammonium carbonate (1:2): The melting point is 58 °C and water solubility is 100,000 mg/L at 15 °C. The estimated vapour pressure is 8.04×10^{-8} Pa at 25 ^oC. The estimated log P_{ow} value for ammonium carbonate (1:2) is -1.49.

Human Health

Toxicokinetics

No specific studies are available on the absorption, distribution, metabolism, or excretion of ammonium carbonate. Ammonia and ammonium ions are integral components of normal metabolic processes and play an essential role in the physiology of human and other species. The toxicological profile of the test substance is assumed to be due to the free ammonia rather than to the ionized form. Ammonia or ammonium ion can be absorbed by the inhalation and oral routes of exposure, but there is a less certainty regarding absorption through the skin. Most of the inhaled ammonia is retained in the upper respiratory tract and is subsequently eliminated in expired air. Ingested ammonium compounds are absorbed in the intestinal tract. Ammonia or ammonium ion is widely distributed to all body compartments although substantial first-pass metabolism occurs in the liver where it is transformed into urea and glutamine. Ammonia or ammonium ion absorbed into the tissues is taken up by glutamic acid, which participates in transamination and other reactions. Most of ammonia or ammonium ion is excreted in the urine as urea and minimal amounts are excreted in the faeces and in expired air.

Bicarbonate ions are integral components of normal metabolic processes and play an essential role in the physiology of

human and other species. Bicarbonate ion can be formed from CO_2 and H_2O and this equilibrium reaction acts as the major extracellular buffer system in blood and interstitial fluids of vertebrates. CO_2 from the tissues diffuses rapidly into red blood cells, where it is hydrated with water to form carbonic acid. This reaction is accelerated by carbonic anhydrase, an enzyme present in high concentrations in red blood cells. The carbonic acid formed dissociates into bicarbonate and hydrogen ions. Most of the bicarbonate ions diffuse into the plasma.

Acute Oral Toxicity

Ammonium carbonate was administered by oral gavage at 2,000 mg/kg bw to 3 rats in the first step and at 300 mg/kg bw to 3 rats in each of the second and third steps. All animals died at 2,000 mg/kg bw. At necropsy, small intestine was filled with red viscous fluid. The lung, trachea and bronchus filled with red foamy fluid and dark red spots were observed. Clinical signs included prone position, lying on side, convulsion, piloerection, salivation, staining around mouth, nasal discharge and dirty nose. No mortality or clinical signs were observed in rats treated with 300 mg/kg. LD_{50} cut-off value in female rats for ammonium carbonate was 500 mg/kg bw [OECD TG 423].

Ammonium carbonate (1:1) was administered by oral gavage at 215, 681, 1,470 and 2,150 mg/kg bw to 5 rats/sex. All animals died at 2,150 mg/kg bw and 3 of 5 female rats died at 1,470 mg/kg bw. Clinical signs included poor general state, apathy, abnormal position, dyspnea, staggering, tonic convulsions, exophthalmos and salivation Gross pathology revealed general congestion, glandular stomach and slightly reddened mucosa. The acute oral LD_{50} values of ammonium carbonate (1:1) for male and female rats were 1,470-2,150 mg/kg bw and ca. 1,470 mg/kg bw, respectively [OECD TG 401].

In another study, the acute oral LD_{50} values for male and female rats were ca. 2,000 mg/kg bw and <2,000 mg/kg bw, respectively [OECD TG 401]. All female rats and 2 of 5 male rats died at 2,000 mg/kg. Clinical signs included poor general state, dyspnoea, apathy, abdominal position, lateral position, atonia, tonic convulsions and exophthalmos. Also, gross pathology revealed general congestion, diffusely reddened glandular stomach, and liquid and slight bloody contents in small intestines.

Ammonium carbonate (1:2) was administered by oral gavage at 215, 681, 1,470 and 2,150 mg/kg bw to 5 male and 5 female rats in each dose. Mortalities were observed at 2,150 mg/kg bw in both male and female rats, and general congestion of stomach and small intestine was observed in dead animals. The acute oral LD_{50} values of ammonium carbonate (1:2) for male and female rats were 2,150 mg/kg bw and 1,800 mg/kg bw, respectively [OECD TG 401].

Acute Inhalation Toxicity

Acute inhalation toxicity tests are not available for ammonium bicarbonate. As an indication of the possible inhalation toxicity, data for ammonia is given (ammonia is the thermal decomposition products of ammomium bicarbonate).

In an acute inhalation study, twelve mice per dose were exposed to 0, 3,440, 4,220 and 4,860 ppm (equivalent to 0, 2.41, 2.95 or 3.40 mg NH_3/L air) of ammonia by whole-body exposure for one hour. 10 of 12 mice died at 4,860 ppm and 5 of 12 mice died at 4,220 ppm. Liver weight was significantly elevated in survivors at 4,220 and 4,860 ppm. Clinical signs included tremors, ataxia, convulsions, seizure, dyspnea and coma. Also, gross pathology revealed diffuse hemorrhage in lungs, and histology showed diffuse intra-alveolar hemorrhage and acute vascular congestion in lungs. In livers, acute congestion of hepatic sinusoids and blood vessels was observed. The calculated acute inhalation LC_{50} value of ammonium carbonate (1:1) for mice was ≥13.8 mg NH_4HCO_3/L air (equivalent to 2.96 mg NH_3/L air).

Acute Dermal Toxicity

The acute dermal LD_{50} value of ammonium carbonate was greater than 2,000 mg/kg bw for male and female rats [OECD TG 402, EU Method B.3 and EPA OPPTS 870.1200]. Ammonium carbonate was directly applied to the skin under an occlusive wrap of rats (5 males and 5 females) at the concentration of 2,000 mg/kg bw. The duration of exposure was 24 hours and the animals were observed for 14 days following a single treatment. No mortality and gross pathology findings were noted in animals during the study.

Skin Irritation

A study was performed following *In Vitro* Skin Irritation: Reconstructed Human Epidermis Test [OECD TG 439] to assess ammonium carbonate by a single application of 50 µL volume. For each treated tissue, optical density was calculated and the tissue viability was expressed as a % relative to negative control. Following exposure with ammonium carbonate, the mean treated skin value was 115%. Based on the result, ammonium carbonate was not skin irritating.

A study was performed under *In Vitro* Skin Corrosion: Human Skin Model Test [OECD TG 431] to assess ammonium carbonate (1:1) by a single topical application of 25 µL volume. In the corrosion test, the mean viability of the treated EpiDerm™ tissues was 105% after 3 minutes exposure and 36% after 1 hour exposure. In the irritation test, the mean viability of the treated EpiDerm™ tissues was 71% after 1 hour exposure with about 42 hours post-incubation. Based on the results, ammonium carbonate (1:1) was not skin irritating.

Eye Irritation

The acute eye irritation test was performed according to [OECD TG 405, EU Method B.5, EPA OPPTS 870.2400 and MAFF TG 12 Nousan No.8147]. Slight cornea opacity (score of 0.2), moderate conjunctival redness (score of 2) and slight

chemosis (score of 0.8) were observed at the 24- and 72-hours examinations. Based on these results, ammonium carbonate was not eye irritating to rabbits under the test conditions.

Skin sensitization

No data on skin sensitization is available.

Repeated Oral Toxicity

In a repeated dose oral toxicity study in rats [OECD TG 407], ammonium carbonate was administered via gavage to 5 animals/sex/dose at 0, 31.25, 125 and 500 mg/kg bw/day for 28 days. At the end of dosing, there were no statistically significant changes noted on haematology, clinical chemistry and organ weight. Mortality, general conditions and gross evidences of clinical signs and symptoms were examined in all animals throughout the study. Individual body weight of both sexes was measured once a week during the dosing period. Food consumption was recorded. Sensory activity, grip strength and motor activity, urinalysis, haematology, clinical chemistry, organ weights and histopathology were examined. Histopathology was evaluated only in the control, high dose groups, and the low dose group whose macroscopic lesions were observed. No death was observed in either sex. No treatment-related effects were observed in clinical signs, body weight, ophthalmological examination and urinalysis. The effects on haematology (increased eosinophils [44.4%] and neutrophils [37.3%] and decreased lymphocytes [8.8%]) and clinical chemistry (increased Cl and decreased K) were not considered to be treatment-related because the changes were within normal physiological range for rats of the strain and age used. The effects on organ weight (increased ovaries [22,6%] and pituitary gland [28,6%] weight, and decreased lung [8.7%] weight) were not supported by the pathological findings; these effects were considered to be an adaptive change. Therefore, the NOAEL for repeated dose oral toxicity was considered to be 500 mg/kg bw/day (highest dose tested).

Genotoxicity

In an Ames test [OECD TG 471] with multiple strains of *Salmonella typhimurium* TA1535, TA1537, TA98, TA100, and *Escherichia coli* WP2*uvr*A, ammonium carbonate did not induce gene mutation in bacteria *in vitro* both with and without metabolic activation. In an *in vitro* chromosomal aberration test using Chinese hamster ovary K1 cells, ammonium carbonate induced chromosomal aberrations at 2.5 mg/mL (49% of cell growth rate) with metabolic activation and did not induce chromosomal aberrations without metabolic activation. An *in vivo* micronucleus assay using mouse bone marrow cells [OECD TG 474] showed negative results up to 1,000 mg/kg bw. Based on these results, ammonium carbonate was not considered to be genotoxic.

No reliable data are available for the carcinogenicity of ammonium carbonate.

Reproduction and Developmental Toxicity

Ammonium carbonate has been investigated in a reproduction and developmental toxicity screening test in rats [OECD TG 421]. Ammonium carbonate was administered by oral gavage to 12 animals/sex at 0, 250, 500 or 1,000 mg/kg bw/day. Male rats were administered for 2 weeks prior to mating, during mating period and 2 weeks post mating period (at least 28 or more days), and female rats were administered from 2 weeks prior to mating to day 3 of lactation including the mating and gestation period. During the observation period, there were no dose-related effects on clinical signs, body weight, food consumption, mating, gestation, delivery, organ weights, necropsy and histopathology in parents. No dose-related changes in clinical signs, body weight, viability index, external malformations and sex ratios were noted in pups. This study found no indication of any reproduction toxicity in parent animals or developmental toxicity in pups at the highest dose of 1,000 mg/kg bw/day. Therefore, the NOAEL for reproduction and developmental toxicity was 1,000 mg/kg bw/day.

Ammonium carbonate does not present a hazard to human health due to its low hazard profile. Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD the Cooperative chemical assessment Programme.

Environment

Photodegradation is not applicable to inorganic substances such as ammonium carbonate. However, ammonium carbonate decomposes when exposed to air with loss of ammonia (NH_3) and carbon dioxide (CO_2) and is converted into ammonium bicarbonate. In the aquatic environment, ammonium carbonate dissociates into and releases NH_3/NH_4^+ and HCO_3^-/CO_3^{2-} depending on pH and temperature. The dissociated NH_4^+ is easily mineralized to nitrite ion (NO_2^-) by *Nitrosomonas*, and nitrite ion is oxidized to nitrate ion (NO_3^-) by *Nitrobactor*. Environmental fate analysis is based on log K_{ow} and log K_{oc}, and typical fugacity modelling is not applicable to ammonium carbonate as it is an inorganic compound. Ammonium carbonate is not expected to bioaccumulate in soil or aquatic organisms due to its high solubility in water. However, bioaccumulation of some ammonium compounds is closely related to nitrogen cycles in air, soil and water.

Ammonia aquatic toxicity depends on temperature, pH and ionic strength in the test water. A key factor is the speciation of ammonia: uninonzied ammonia (NH_3) and ammonium ion (NH_4^+). The speciation changed markedly with temperature and pH, and also with the test water ionic strength. The concentration of un-ionized ammonia increases with higher pH and temperature, and the un-ionized ammonia appeared to be much more toxic than ammonium ion. Because un-ionized ammonia is a neutral molecule and un-ionized ammonia is able to diffuse across the epithelial membranes of aquatic organisms much more readily than the charged ammonium ion.

The following acute toxicity test results have been determined for aquatic species. The values based on the ammonia concentration are also given on the table:

Species	Test guideline	Endpoints	Temperature (°C)	pH	Test substance
Fish [*Oryzias latipes*]	OECD TG 203	96 h, LC_{50} > 100 mg/L (nominal; semi-static) > 0.48-2.58 mg NH_3/L (estimated)	22.3-23.6	7.52-8.21	Ammonium carbonate
Fish [*Oncorhynchus mykiss*]	No data	96h, LC_{50} = 102.2 mg/L (measured; flow-through) = 18.1 mg/L (measured, total ammonia nitrogen)	13.9	8.10	Ammonium carbonate (1:1)
Fish [*Oncorhynchus mykiss*]	No data	96h, LC_{50} = 97.7 mg/L (measured; flow-through) = 17.3 mg/L (measured, total ammonia nitrogen)	13.6	8.12	Ammonium carbonate (1:1)
Invertebrate [*Daphnia magna*]	OECD TG 202	48h, EC_{50} > 100 mg/L (nominal; static) > 0.85-3.43 mg NH_3/L (estimated)	20.3-20.9	7.81-8.4	Ammonium carbonate
Algae [*Pseudokirchneriella subcapitata*]	OECD TG 201	72h, E_rC_{50} / E_yC_{50} > 100 mg/L (nominal; static) > 0.06-0.82 mg NH_3/L (estimated)	22.8	7.3-8.4	Ammonium carbonate
Algae [*Pseudokirchneriella subcapitata*]	OECD TG 201 EU C.3 EPA OPPTS 850.5400	72h, E_rC_{50} = 252.92 mg/L (growth rate; nominal; static)72h, E_yC_{50} = 122.46 mg/L (yield; nominal; static) 72h, E_bC_{50} = 141.44 mg/L (biomass; nominal; static) (un-ionized ammonia (NH_3) =4.8% of total ammonia at pH 8.01; 47.1% of total ammonia at pH 9.26)	23	8.01-9.26	Ammonium carbonate

The following chronic toxicity test results have been determined:

Atlantic Salmon 53d, NOEC < 168 mg/L (measured, ammonium carbonate (1:2), <0.07 mg NH_3/L, pH 6.74, 13°C)

In the aquatic environment, ammonium carbonate dissociates into and releases ammonium ion (NH_4^+) and bicarbonate ion (HCO_3^-). The dissociated NH_4^+ cation has a significant eutrophication potential due to nitrogen in form of ammonium ion. When ammonium ion increases in water, plant growth is enhanced, and dissolved oxygen is reduced when dead plant material decomposes, which eventually can cause organisms in water to die.

Ammonium carbonate has a low hazard profile for the environment. Adequate screening-level data are available to characterize the environmental hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme. The pH and temperature of water bodies can affect the concentration of un-charged ammonia derived from the assessed substance; ammonia is the toxicologically relevant form for aquatic toxicity. Ammonia also has indirect and long-term effects on ecosystems, e.g. eutrophication, groundwater pollution and soil acidification due to the nitrification of ammonia.

Exposure

Production

In the Republic Korea (sponsor country), the production, use and import volumes of ammonium carbonate were 60,448, 60,635 and 720 tonnes in 2010, respectively. For the volumes of ammonium carbonate, the production, use and import volume of ammonium carbonate (1:1) and ammonium carbonate (1:2) were 2,084, 1,479, 702 and 58,364, 59,154, 18 tonnes in 2010, respectively.

In the sponsor country, ammonium carbonate (1:1) is produced as a by-product in the process of manufacturing basic organic compounds. The production process is as follows: chemical reaction occurs among raw materials such as alkylbenzene, phthalic anhydride, urea, copper(I) chloride and ammonium molybdate, producing ammonia gas as a by-product, . Adding CO_2 to the ammonia gas, produces ammonium carbonate (1:1)

Reaction formula:

1. Initial reaction: $C_8H_4O_3 + CH_4N_2O \rightarrow C_9H_8N_2O_4 \rightarrow C_8H_5NO_2 + CO_2 + NH_3$
2. Decomposition: $NH_2 \cdot CONHCO \cdot NH_2 \rightarrow CO_2 + NH_3 + NH_2CN$
3. Ammonium carbonate solution (1:1): $CO_2 + NH_3 + H_2O \rightarrow NH_4HCO_3$

Use Pattern

In general, ammonium carbonate is used for baking powders, washing and defatting woollens, tanning, dyeing, manufacture of rubber articles, casein glues, casein colours, fire extinguishers and pharmaceutical aid. Ammonium carbonate (1:1) is used for fire extinguishers, manufacture of porous plastic and ceramics, dyes, pigments, fertilizers and defatting textile.

In the sponsor country, ammonium carbonate is mainly used for nitrogen oxide removal of cement, manufacture of hydroxylamine sulphate, and as food additives for chocolate and cocoa, intermediates, process regulators and reducing agents. Ammonium carbonate (1:1) is mainly used as process regulators, an ingredient of cosmetics, pH regulating agents and electroplating agents. Ammonium carbonate (1:2) is mainly used for electroplating, semiconductor and adhesive.

Occupational Exposure

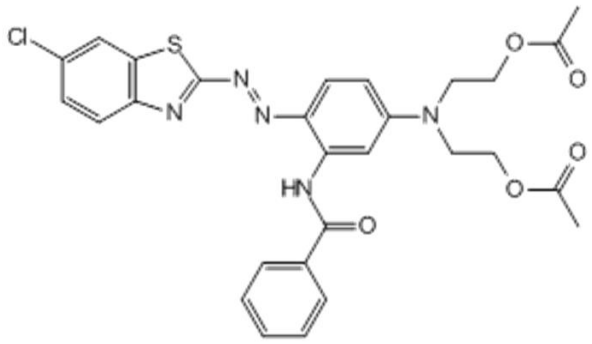
In production facilities of the sponsor country, ammonium carbonate (1:1) is produced as a by-product of basic organic compounds in closed systems. Workplaces are controlled according to in-house operation safety regulation. Waste gases generated in workplaces are controlled by Regenerative Thermal Oxidizer (R.O.T), and waste water is treated through treatment facilities and contract agencies. In workplaces, workers are equipped with personal protective equipment such as dust masks, gloves, clothes and boots. According to monitoring data, ammonium gases were estimated to be below detection limit in workplaces, and ammonium carbonate (1:1) generated was stored in tanks. Therefore, occupational exposure is considered to be negligible in the sponsor country.

In use facilities of the sponsor country, ammonium carbonate (1:2) is handled in closed systems. Workplaces are under control in accordance with the material safety data sheet. Occupational external exposure is managed by dust collector. To ensure workers safety during tank maintenance, workers are equipped with personal protective equipment such as safety helmet, rubber gloves, masks and goggles. Therefore, occupational exposure is considered to be negligible in the sponsor country.

Exposure of the general population

Ammonium carbonate is mainly used as a food additive in the sponsor country. According to Korean Food Additives Codex, it is used as alkali agents for chocolate, dry cocoa-sugar mixture, cocoa powders, nib, dust, mass and press cake. Also, it is used as raising agents for grain products for infants, fish sticks and fillets and as neutralizing agents for dietary casein products. Ammonium carbonate is an approved food additive.

INITIAL TARGETED ASSESSMENT PROFILE

CAS No.	26630-87-5
Chemical Name	N-[5-[Bis[2-(acetyloxy)ethyl]amino]-2-[(6-chlorobenzothiazol-2-yl) azo]phenyl]benzamide (hereafter mentioned as Disperse Red 206)
Structural Formula	

SUMMARY CONCLUSIONS OF THE TARGETED ASSESSMENT

NOTE: The present assessment was targeted to address only the following endpoint(s): Human Health: acute toxicity, repeated dose toxicity and *in vitro* mutagenicity. It cannot be considered as a full SIDS Initial Assessment. Summary information on exposure is also reported here. Other endpoints for human health and the environment have not been presented to OECD member countries, and thus are not included in this profile.

Rationale for targeting the assessment

Under the Japanese Chemical Substances Control Law (CSCL), risk assessment of existing chemical substances has been conducted by the government. The CSCL was amended in 2010 and 2011 and shifted toward risk-based management from hazard-based management. Chemical substances are classified as follows from April 1, 2011: (1) Class I Specified Chemical Substances (persistent, highly bioaccumulative, has long-term toxicity for humans or long-term toxicity predator animals at higher trophic level), (2) Class II Specified Chemical Substances (has long-term toxicity for humans or flora and fauna in the human living environment, has risk), (3) Monitoring Chemical Substances (persistent, highly bioaccumulative, long-term toxicity unknown), (4) Priority Assessment Chemical Substances (suspected long-term toxicity for humans or flora and fauna in the human living environment, suspected risk) and (5) General Chemical Substances (risk to humans or flora and fauna in the human living environment is sufficiently low).

Disperse Red 206 is classified as a General Chemical Substance based on degrees of hazard intensity and

exposure estimates at the priority assessment meeting.

This targeted assessment document was originally based on the material of the priority assessment meeting provided from the chemical assessment council of MHLW, and the toxicological profile was re-assessed for the OECD Cooperative Chemicals Assessment Programme.

Physical-Chemical Properties

Disperse Red 206 is yellow-brown powder at room temperature. Both melting point and boiling point are calculated to be 321 °C and 733 °C respectively by MPBVPWIN. However Disperse Red 206 may decompose before reaching these temperatures. Partition coefficient between octanol and water (log K_{ow}) is estimated to be 6.28 by KOWWIN. Vapour pressure is estimated to be 1.30×10^{-15} Pa at 25 °C with Modified Grain method by MPBVPWIN. Water solubility is estimated to be 3.48×10^{-4} mg/L at 25 °C by WSKOWWIN.

Human Health

The oral LD_{50} of Disperse Red 206 was greater than 2,000 mg/kg bw (OECD TG 401) in rats. The substance did not cause death or any clinical toxicity.

A 28-day repeated dose toxicity study was conducted in rats according to the Japanese test guideline (similar to OECD TG 407). Rats were administered Disperse Red 206 by gavage at 0 (vehicle control: 0.5 % methylcellulose solution), 250, 500, and 1,000 mg/kg bw/day. Liver weights were increased in males given 250 mg/kg bw/day or more, and in females receiving 1000 mg/kg bw/day. Thymus weights were decreased in males and females given 500 mg/kg bw/day and ovary weights were decreased in females given 1000 mg/kg bw/day. Significant low values of anemic parameters and γ-globulin fraction ratio as biochemical analysis were observed in males. These changes were not considered to be adverse effects because the changes were not dose-related and there were no accompanying histopathological changes in the related organs. Therefore, the NOAEL of this study was considered to be 1,000 mg/kg bw/day.

In a bacterial mutation study using *Salmonella typhimurium* and *Escherichia coli* (OECD TG 471), Disperse Red 206 was positive in TA98 with and without metabolic activation but negative in TA 1535, TA 1537, TA 98, TA 100 and WP2 uvr A. In an *in vitro* chromosome aberration test using CHL/IU cells (OECD TG 473), Disperse Red 206 induced structural chromosomal aberrations with metabolic activation and polyploidy with and without metabolic activation. No *in vivo* genotoxicity data are available. Based on these results, Disperse Red 206 is considered to be genotoxic *in vitro*.

Agreed Hazard Conclusions

This chemical presents a hazard for one human health endpoint (genotoxicity *in vitro*) targeted in this assessment.

Available Exposure

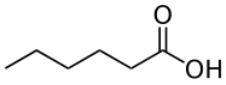
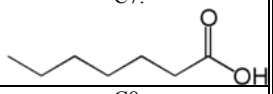
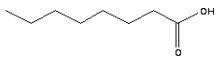
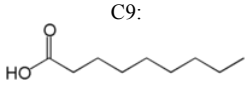
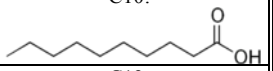
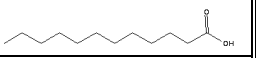
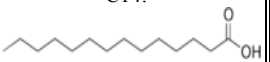
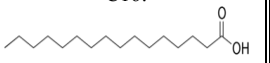
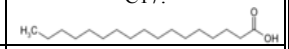
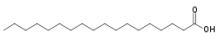
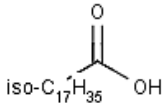
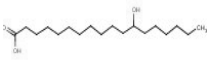
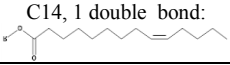
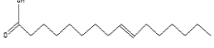
No information is available concerning the production volume of Disperse Red 206 in Japan. Production volume

in the world is also not available. Disperse Red 206 is used as a disperse dye.

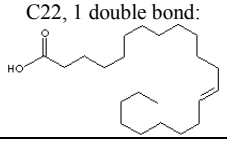
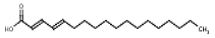
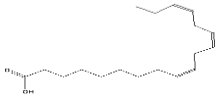
SIDS INITIAL ASSESSMENT PROFILE

Category name	Aliphatic Acids Category

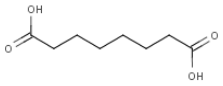
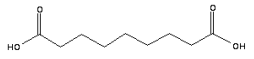
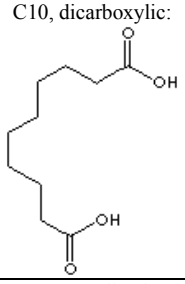
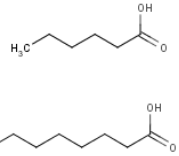
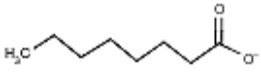
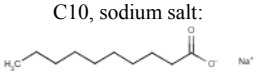
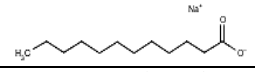
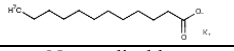
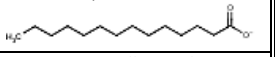
CAS No(s), Chemical name(s) and structural formula(s) [1]

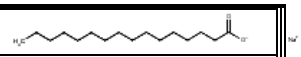
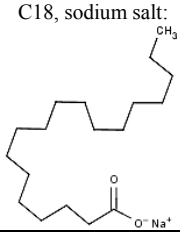
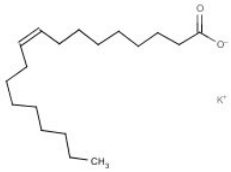
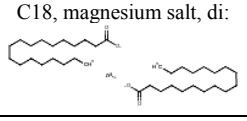
CAS No	IUPAC or CAS Name	Structural Formula
Single component – Saturated (12)		
142-62-1	Hexanoic acid	C6: 
111-14-8	Heptanoic acid	C7: 
124-07-2	Octanoic acid	C8: 
112-05-0	Nonanoic acid	C9: 
334-48-5	Decanoic acid	C10: 
143-07-7	Dodecanoic acid	C12: 
544-63-8	Tetradecanoic acid	C14: 
57-10-3	Hexadecanoic acid	C16: 
506-12-7	Heptadecanoic acid	C17: 
57-11-4	Octadecanoic acid	C18: 
30399-84-9	Isooctadecanoic acid	C18, methyl branched: 
106-14-9	12-Hydroxyoctadecanoic acid; 12-hydroxy-octadecanoic acid	C18, 1 hydroxyl group: 
Single component – Mono- unsaturated (4)		
544-64-9	(Z)-Tetradec-9-enoic acid; 9-Tetradecenoic acid, (Z)-	C14, 1 double bond: 
2091-29-4	9-Hexadecenoic acid, (Z)-	C16, 1 double bond: 
112-80-1	(Z)-Octadec-9-enoic acid; 9-Octadecenoic acid, (Z)-	C18, 1 double bond:

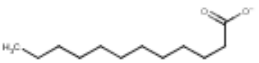
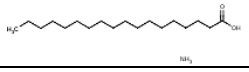
[1] The table is organized according to general aliphatic acid structure. Specifically, by increasing carbon chain length, with any structure variations (e.g., unsaturated, dicarboxylic, double bonds, hydroxyls, salts) appearing after the corresponding base structure.

		
112-86-7	(Z)-Docos-13-enoic acid; 13-Docosenoic acid, (Z)-	C22, 1 double bond: 
Single component - Di-unsaturated (2)		
60-33-3	(9Z,12Z)-Octadeca-9,12-dienoic acid; 9,12-Octadecadienoic acid	C18, 2 double bonds: 
121250-47-3	(8E,12E)-octadeca-8,12-dienoic acid; Octadecadienoic acid (Conjugated linoleic acid)	C18, 2 adjacent double bonds: 
Single component - Tri-unsaturated (1)		
463-40-1	(9Z,12Z,15Z)-Octadeca-9,12,15-trienoic acid; 9,12,15-Octadecatrienoic acid, (Z,Z,Z)	C18, 3 double bonds: 
Alkyl range sourced based (multi-component) – Saturated (13)		
68603-84-9[2]	Carboxylic acids, C5-9	Not Applicable
68937-74-6	Fatty acids, C6-10	Not Applicable
67762-36-1	Fatty acids, C6-12	Not Applicable
68937-75-7	Fatty acids, C8-10	Not Applicable
90990-08-2	Fatty acids, C8-18	C12-14
68002-90-4	Fatty acids, C10-16	Not Applicable
90990-10-6	Fatty acids, C12-14	Not Applicable
67701-01-3	Fatty acids, C12-18	Not Applicable
67701-02-4	Fatty acids, C14-18	Not Applicable
68424-37-3	Fatty acids, C14-22	Not Applicable
67701-03-5	Fatty acids, C16-18	Not Applicable
68937-76-8	Fatty acids, C16-20	Not Applicable
90990-11-7	Fatty acids, C18-22	Not Applicable
Alkyl range sourced based (multi-component) –Unsaturated (1)		
68648-24-8	Fatty acids, vegetable-oil, unsaturated	Not Applicable
Alkyl range sourced based (single or multi-component) – Mixture of saturated and unsaturated (16)		
68937-85-9	Fatty acids, coco, heavy fractions	Not Applicable
68938-15-8	Fatty acids, coco, hydrogenated	Not Applicable
61788-47-4	Fatty acids, coco	Not Applicable
67701-05-7	Fatty acids, C8-18 and C18-unsaturated	Not Applicable
68918-39-8	Soaps, stocks, C8-18 and C18 unsaturated alkyl, acidulated	Not Applicable
90990-15-1	Fatty acids, C12-18 and C18-unsaturated	Not Applicable
68334-03-2	Fatty acids, C12-20 and C12-20 unsaturated	Not Applicable
61790-38-3	Fatty acids, tallow, hydrogenated	Not Applicable
67701-06-8	Fatty acids, C14-18 and C16-18-unsaturated	Not Applicable

[2] Multi-component substances are presented in red text.

61790-37-2	Fatty acids, tallow	Not Applicable
68308-53-2	Fatty acids, C14-18 and C16-18-unsaturated, sodium salts	Not Applicable
68002-87-9	Fatty acids, C14-18 and C16-22-unsaturated	Not Applicable
68440-15-3	Fatty acids, palm-oil	Not Applicable
67701-07-9	Fatty acids, C16 and C18-unsaturated	Not Applicable
67701-08-0	Fatty acids, C16-18 and C18-unsaturated	Not Applicable
61789-45-5	Fatty acids, dehydrated castor-oil	Not Applicable
Dicarboxylic acids (single or multi-component) Saturated (4)		
68937-72-4	Carboxylic acids, di-, C4-11	C6-9, dicarboxylic 
123-99-9	Nonanedioic acid	C9, dicarboxylic: 
111-20-6	Decanedioic acid	C10, dicarboxylic: 
68937-70-2	Carboxylic acids, C6-18 and C8-15 di-	C9-18; C6-14, dicarboxylic: 
Sodium and potassium salts (single or multi-component) Saturated (10)		
67762-44-1	Fatty acids, C6-12, Na salts	Not applicable
1984-06-1	Sodium octanoate; Octanoic acid, sodium salt	C8, sodium salt: 
1002-62-6	Sodium decanoate; Decanoic acid, sodium salt	C10, sodium salt: 
629-25-4	Sodium dodecanoate; Dodecanoic acid, sodium salt	C12, sodium salt: 
10124-65-9	Potassium dodecanoate, Dodecanoic acid, potassium salt	C12, potassium salt: 
91032-12-1	Fatty acids, C12-18, sodium salts	Not applicable
822-12-8	Sodium tetradecanoate; Tetradecanoic acid, sodium salt	C14, sodium salt: 
408-35-5	Sodium hexadecanoate; Hexadecanoic acid, sodium	C16, sodium salt:

	salt	
68424-38-4	Fatty acids, C16-18, sodium salts	Not applicable
822-16-2	Sodium octadecanoate; Octadecanoic acid, sodium salt	C18, sodium salt: 
Sodium and potassium salts (single component) Mono-unsaturated (1)		
143-18-0	Potassium (Z)-octadec-9-enoate; 9-Octadecenoic acid, (Z)-, potassium salt	C18, 1 double bond, potassium salt: 
Sodium and potassium salts (multi-component) Mixture of saturated and unsaturated (9)		
61789-30-8	Fatty acids, coco, potassium salts	Not applicable
61789-31-9	Fatty acids, coco, sodium salts	Not applicable
67701-09-1	Fatty acids, C8-18 and C18-unsaturated, potassium salts	Not applicable
67701-10-4	Fatty acids, C8-18 and C18-unsaturated, sodium salts	Not applicable
68082-64-4	Fatty acids, vegetable-oil, sodium salts	Not applicable
67701-11-5	Fatty acids, C14-18 and C16-18-unsaturated, sodium salts	Not applicable
8052-48-0	Fatty acids, tallow, sodium salts; Fatty acids, tallow, sodium salts	Not applicable
61790-79-2	Fatty acids, palm-oil, sodium salts	Not applicable
68002-80-2	Fatty acids, C14-18 and C16-18-unsaturated, potassium salts	Not applicable
Magnesium and calcium salts (multi-component) - Mixture Saturated and Unsaturated (1)		
64755-01-7	Fatty acids, tallow, calcium salts	Not applicable
Magnesium and calcium salts (single component) Saturated (2)		
542-42-7	Calcium hexadecanoate; Hexadecanoic acid, calcium salt	C16, calcium salt
557-04-0	Magnesium octadecanoate; Octadecanoic acid, magnesium salt	C18, magnesium salt, di: 

Ammonium salts (single component) Saturated (2)		
2437-23-2	Azanium dodecanoate; Dodecanoic acid, ammonium salt	C12, ammonium salt: 
1002-89-7	Azanium octadecanoate; Octadecanoic acid, ammonium salt	C18, ammonium salt: 

SUMMARY CONCLUSIONS OF THE SIAR

Analogue/Category Rationale

The aliphatic acids category consists of 78 sponsored naturally derived (from plant or animal fats and oils) homologous aliphatic acids, 74 contain a carboxyl group at the polar end, while the nonpolar tail of the molecule consists of a hydrocarbon chain; an additional four (4) contain a carboxyl group at both ends and the non-polar hydrocarbon chain in the middle. Fatty acids are amphiphilic compounds; in other words, each molecule has a hydrophilic, polar part (the carboxyl group) and a hydrophobic, nonpolar part (the hydrocarbon tail). The aliphatic acids category consists of C4-C22 aliphatic acids, also called fatty acids, and their salts. All naturally occurring unsaturated fatty acids (plant and animal derived) are cis isomers; trans-unsaturated aliphatic acids are not included in the category. Substances that are source named are derived from the stipulated source material. For example, coco fatty acid means the source is coconut oil; tallow specifies animal fat, etc. The specific source for substances that are not source named (for example, **Fatty acids, C16-18 and C18-unsaturated**[3]) cannot be stipulated, but the source is plant or animal fats or oils. The sponsored substances may be saturated, unsaturated or a mixture of saturated and unsaturated aliphatic chains. The sponsored aliphatic acids include single carbon chain length substances (single component aliphatic acids), homologous mixtures of the single carbon chain length substances (multi-component aliphatic acids), homologous salts of the single and multi-component substances and single carbon chain length dicarboxylic acids, and di-acid salts of the single component substances. The single component substances include saturated compounds and mono-, di- or tri-unsaturated compounds. The multi-component substances include saturated, unsaturated and undefined mixtures of saturated and unsaturated carbon chains. The level of unsaturation cannot be described as these are naturally derived, not pure substances, and the substance descriptors do not allow for differentiation at the level of unsaturation. The sodium salts include single and multi-component saturated compounds and multi-component, mixture of saturated and unsaturated compounds. The potassium salts include saturated, single component mono-unsaturated and multi-component

[3] Sponsored substances are presented in **bold** text.

mixture of saturated and unsaturated compounds. The ammonium salts are single component saturated compounds. The magnesium or calcium di-acids are two single component saturated acid chains associated with one metal ion.

The general structure for aliphatic (mono) acids is:
RC(=O)OX, where:
R is a linear alkyl chain that may be saturated or unsaturated (with 1 to 3 double bonds) and;
X is a hydrogen ion; or X = the ammonium, sodium, potassium, magnesium or calcium ion for salts.
(Note: Salts of calcium and magnesium are "+2"; they can form salts with two carboxylic acid chains while sodium and potassium which are "+1", form salts with only a single acid chain.)

Notable structural features of individual category members that vary from the general structure above include a methyl branched substance, a hydroxyl group substituted substance, and the dicarboxylic acids.

A methyl-branched single component saturated aliphatic acid (**isooctadecanoic acid; CAS 30399-84-9**) is not a highly branched material, rather the branching is a minor variation on a long aliphatic acid chain, and the branching is not expected to affect the properties of the substance.

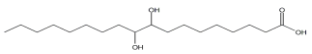
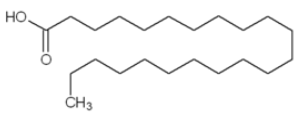
A single component saturated aliphatic acid contains a hydroxyl group (**12-hydroxy-octadecanoic acid, CAS 106-14-9**); this additional side chain is not a functional group on the molecule and is not expected to affect the properties of the substance.

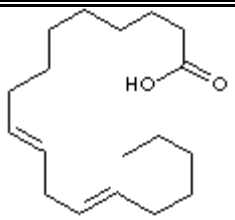
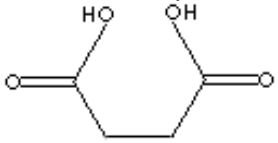
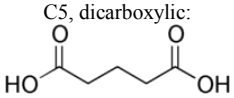
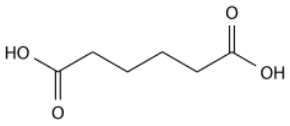
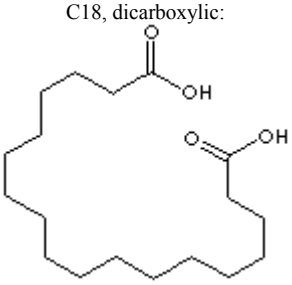
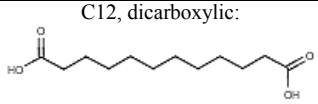
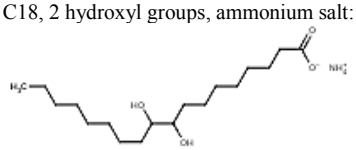
Sponsored substances also include single-chain length and multi-component chain length dicarboxylic acids; the dicarboxylic acids have no structural differences in functional groups.

Analogues: An additional fourteen (14) aliphatic acids are included as supporting substances and are distributed among the same subgroups as the sponsored substances.

Key points are that the sponsored and supporting substances share:
- The same structural features
- Similar metabolic pathways
- Common mode of ecotoxicological action
- Common levels and mode of human health related effects.

Identity of the supporting substances

CAS No	IUPAC or CAS Name	Molecular Formula [(a)]	Structural Formula	Molecular Weight [(1)]
Single component				
120-87-6	9,10-Dihydroxy-octadecanoic acid	C18-H36-O4	C18, 2 hydroxyl groups: 	316.49
112-85-6	Docosanoic acid	C22-H44-O2	C22: 	340.6
2197-37-7	(9Z,12Z)-octadeca-9,12-dienoic acid; 9,12-Octadecadienoic acid	C18-H32-O2	C18, 2 double bonds:	280.45

				
Alkyl ranges and sourced based				
95912-82-6	Fatty acids, C16-22 and C18-22 unsaturated	Not applicable	C16-22, unsaturated	Not applicable
61790-12-3	Fatty acids, tall-oil	Not applicable	C18, 1 double bond (predominately); C18-20	Not applicable
85711-54-2	Fatty acids, rape-oil	Not applicable	C18-22	Not applicable
68953-27-5	Fatty acids, sunflower, conjugated	Not applicable	C16-18, adjacent double bonds	Not applicable
Dicarboxylic acids				
110-15-6	Butanedioic acid	C4-H6-O4	C4, dicarboxylic: 	118.09
110-94-1	Pentanedioic acid	C5-H8-O4	C5, dicarboxylic: 	132.12
124-04-9	Hexanedioic acid	C6-H10-O4	C6, dicarboxylic: 	146.14
871-70-5	Octadecanedioic acid	C18-H34-O4	C18, dicarboxylic: 	314.47
693-23-2	Dodecanedioic acid	C12-H22-O4	C12, dicarboxylic: 	230.31
Sodium and potassium salts (2)				
68424-26-0	Fatty acids, C16-18 and C18-unsaturated, sodium salts	Not applicable	C16-22, unsaturated, sodium salts	Not applicable
Ammonium salts (2)				
84753-04-8	9,10-Dihydroxy-octadecanoic acid, ammonium salt	C18-H36-O4.H3-N	C18, 2 hydroxyl groups, ammonium salt: 	333.52

(1) Molecular formula not available for multi-component substances. Molecular weights provided for single chain length aliphatic acids.
(2) Sodium, potassium, magnesium, calcium and ammonium aliphatic acid salts contain the same chain length (or range) as a

corresponding single component or Alkyl range or source based sponsored substance. As such, read across to the corresponding sponsored substances or supporting substances is reasonable.

The supporting substances are used to supplement existing human health and environmental data for the sponsored substances.

Summary of supporting substance human health read across data

Substance	Irritation		Acute toxicity	Repeated dose toxicity	Mutagenicity	Fertility and Development
	Skin	Eye				
Single Component						
120-87-6	NO DATA	X	NO DATA	NO DATA	NO DATA	NO DATA
112-85-6	NO DATA	NO DATA	X	X	X	X
Alkyl Range Source based						
61790-12-3	NO DATA	NO DATA	X	X	X	X
85711-54-2	NO DATA	NO DATA	X	NO DATA	NO DATA	NO DATA
Dicarboxylic acids						
110-15-6	X	X	X	X	X	NO DATA
110-94-1	X	X	X	X	X	X
124-04-9	X	X	X	X	X	X
693-23-2	NO DATA	NO DATA	X	X	X	X
871-70-5	NO DATA	X	X	X	X	NO DATA
Sodium and Potassium salts						
68424-26-0	NO DATA	NO DATA	X	NO DATA	NO DATA	NO DATA
Ammonium salts						
84753-04-8	X	X	X	NO DATA	X	NO DATA

X= data available and used for read across

Summary of supporting substance environmental read across data

Substance	Biodegradation	Acute toxicity		
		Fish	Daphnia	Algae
Single Component				
120-87-6	NO DATA	X	NO DATA	NO DATA
Alkyl Range Source based				
95912-82-6	NO DATA	NO DATA	X	NO DATA
68953-27-5	NO DATA	X	NO DATA	NO DATA
Dicarboxylic acids				
110-15-6	NO DATA	NO DATA	X	NO DATA
124-04-9	NO DATA	X	X	NO DATA
693-23-2	NO DATA	NO DATA	NO DATA	X
871-70-5	NO DATA	X	X	X
Sodium and Potassium salts				
91302-02-9	X	NO DATA	NO DATA	NO DATA
68424-26-0	NO DATA	X	NO DATA	NO DATA

X= data available and used for read across

The aliphatic acids share a common degradation pathway in which they are metabolized to acetyl-CoA or other key metabolites in all living systems. Common biological pathways result in structurally similar breakdown products, and are, together with the physico-chemical properties, responsible for similar environmental behavior and essentially identical hazard profiles with regard to human health. Differences in metabolism or biodegradability of even and odd numbered carbon chain compounds or saturated/unsaturated compounds are not expected; even- and odd- numbered carbon chain compounds, and the saturated and unsaturated compounds are naturally occurring and are expected to be metabolized and biodegraded in the same manner.

The acid and alkali salt forms of the homologous aliphatic acid are expected to have many similar physicochemical and toxicological properties when they become bioavailable; therefore, data read across is used for those instances where data are available for the acid form but not the salt, and vice versa. In the gastrointestinal tract, acids and bases are absorbed in the undissociated (non-ionized) form by simple diffusion or by facilitated diffusion. It is expected that both the acids and the salts will be present in (or converted to) the acid form in the stomach. This means that for both aliphatic acid or aliphatic acid salt, the same compounds eventually enter the small intestine, where equilibrium, as a result of increased pH, will shift towards dissociation (ionized form). Hence, the situation will be similar for compounds originating from acids and therefore no differences in uptake are anticipated.

Given the large number of substances in this category, their closely related chemical structure, expected trends in physical chemical properties, and similarity of toxicokinetic properties, both mammalian and aquatic endpoints were filled using read-across to the closest structural analogue, and selecting the most conservative sponsored or supporting substance effect level (see Tables 1, 2 and 3 at the end of this document). Structure-activity relationships are not evident for the mammalian toxicity endpoints. That is, the low mammalian toxicity of this category of substances limits the ability to discern structural effects on biological activity. Regardless, the closest structural analogue with the most conservative effect value was selected for read across. Irritation is observed for chain lengths up to a "cut-off" at or near 12 carbons~~)~~. Structure-activity relationships based on carbon chain length are evident in the available data on the aquatic ecotoxicity of substances of this category (aquatic toxicity increases with increasing chain length up to a "cut-off" at or near 12 carbons). Read-across between the (sponsored and supporting) subgroups and the category as a whole was used for the human health and environmental endpoints. Read across can be made between all sponsored substances (without regard for subcategory), and the lowest effect value for the closest structural analogue is selected.

The closest structural analogue was identified, and this approach has been used as the basis for the read across for human health endpoints. The closest structural analogues were ordered for each subdivision (using ">" to indicate the order of read across used), and the most conservative effect value for the closest structural analogue was selected to fill data gaps. The order of closest structural analogue follows for each subdivision. Note that the saturation or unsaturation level is not a factor in the toxicity of these substances and is not a critical component of the read across process. Where possible, we have prioritized read across between similar states of saturation and unsaturation. Higher water solubility of the potassium, sodium and ammonium salts make these a lower ranked analogy for the (non-salt) aliphatic acids, while lower water solubility of the magnesium and calcium salts make these a lower ranked analogy for all other members of the category.

Single Component (saturated and unsaturated) is read across to any other Single component > Alkyl Range Source Based > Sodium, Potassium, and Ammonium salts> Dicarboxylic acids> Magnesium and calcium salts.
Alkyl Range Source Based (saturated and unsaturated) is read across to any other Alky Range Source Based >Single component > Sodium, Potassium, and Ammonium salts> Dicarboxylic acids> Magnesium and calcium salts.
Dicarboxylic acids (saturated) is read across to any other Dicarboxylic acids > Single component or Alkyl Range Source Based > Dicarboxylic acids> Magnesium and calcium salts.
Sodium and Potassium salts (saturated and unsaturated) is read across to any other Sodium and Potassium salts > Ammonium salts > Single component or Alkyl Range Source Based > Dicarboxylic acids> Magnesium and calcium salts.
Magnesium and calcium salts (saturated and unsaturated) is read across to any other Magnesium and calcium salts > Single component or Alkyl Range Source Based > Dicarboxylic acids > Sodium, Potassium, and Ammonium salts.
Ammonium salts (saturated) is read across to any other Ammonium salts > Sodium or Potassium salts> Single component or Alkyl Range Source Based > Dicarboxylic acids > Magnesium and calcium salts.

Determination of closest structural analogue for aquatic toxicity endpoints. Clear trends for water solubility were driven by carbon chain length and by type of salt (see carbon chain length/water solubility trend tables). Therefore, the closest structural analogue definition for aquatic toxicity took into account not only closest structural analogue as described above for human health, but also consideration of similarity of carbon chain length or salt (and thus corresponding water solubility), before selection of the most conservative effect value to fill data gaps. In cases where the corresponding carbon chain length substances did not have data, the closest chain

length was selected, using a conservative (lowest value) approach.

Higher water solubility of the potassium, sodium and ammonium salts make these a lower ranked analogy for the aquatic toxicity endpoints for the (non-salt) aliphatic acids (and vice versa), while lower water solubility of the magnesium and calcium salts make these a lower ranked analogy for all other members of the category.

Single Component (saturated and unsaturated) is read across based on carbon chain length to other Single components > Alkyl Range Source Based > Dicarboxylic acids > Sodium, Potassium, and Ammonium salts > Magnesium and calcium salts.
Alkyl Range Source Based (saturated and unsaturated) is read across based on carbon chain length of Alkyl Range Source Based >Single component using the lowest carbon chain length of the mixture > Dicarboxylic acids > Sodium, Potassium, and Ammonium salts > Magnesium and calcium salts.
Dicarboxylic acids (saturated) is read across to any other Dicarboxylic acids > based on carbon chain length to Single component > Alkyl Range Source Based > Sodium, Potassium, and Ammonium salts> Magnesium and calcium salts.
Sodium and Potassium salts (saturated and unsaturated) is read across to any other Sodium and Potassium salts > Ammonium salts > based on carbon chain length to Dicarboxylic acids > Single component or Alkyl Range Source Based > Magnesium and calcium salts.
Magnesium and calcium salts (saturated and unsaturated) is read across to any other Magnesium and calcium salts > based on carbon chain length to Single component or Alkyl Range Source Based > Dicarboxylic acids > Sodium, Potassium, and Ammonium salts.
Ammonium salts (saturated) is read across to any other Ammonium salts > Sodium or Potassium salts> based on carbon chain length to other Dicarboxylic acids > Single component or Alkyl Range Source Based > Magnesium and calcium salts.

Physical-chemical Properties

Sponsored substances include single chain length aliphatic acids and mixtures of defined chain length ranges of aliphatic acids. Physical-chemical property estimates are for a discrete chain length as the estimation technique is based on a relationship between a specific chemical structure and a measured or estimated property of that structure. A property of a mixture of aliphatic acids is therefore a function of that property for each of the discrete chain length components in the mixture.

With regard to the physical / chemical properties of the sponsored Aliphatic Acids, two predominant trends are clearly evident with increasing alkyl chain length and include: i) increasing melting point, boiling point, and partition coefficient, and ii) decreasing water solubility and vapour pressure. Within a given carbon chain length, melting point increases with increasing saturation and decreases with increasing unsaturation. For example, 9-Octadecenoic acid, (Z)- (CAS 112-80-1) is mono-unsaturated and is a liquid; **Octadecanoic acid (CAS 57-11-4)** is saturated and is a solid. These trends are clearest to identify within each subgroup of Aliphatic Acids (single component - saturated, single component - unsaturated; alkyl range sourced - saturated, etc.). Within a given subgroup, when these trends are not clear, it is due to the comparison between measured and modeled data. When the comparison is repeated to compare between modeled estimates, the trends observed with increasing carbon chain length remain applicable. The following text and tables are organized by subdivision and describe these trends in more detail.

- **Single component**: The noted general trends with increasing alkyl chain length are observed when the entire single component group (12 saturated, 4 mono-unsaturated, 2 di-unsaturated, and 1 tri-unsaturated substances) is evaluated together; that is, the degree of saturation or unsaturation does not alter the properties trend. The effect of mono-unsaturation (C14:1 to C22:1) appears to be a slight increase in water solubility and a slight decrease in the partition coefficient, as compared to the corresponding saturated substances; a similar trend is noted for the C18 di- or tri-unsaturated. Slight (although inconsistent) effects on the trend for decreasing vapor pressure are also are also observed with the mono-, di- and tri-unsaturated substances as compared to the corresponding saturated substances.
- **Alkyl range sourced**: When considering the properties of the individual (single chain length) components, the two predominant trends [i) increasing melting point, boiling point, and partition coefficient, and ii) decreasing water solubility and vapour pressure] are evident with increasing alkyl chain length. Also

apparent are the slight effects of unsaturation, as noted above for the single component substances.

- **Dicarboxylic acids**: Compared to their corresponding single acid substances (C8-10 single component, saturated), the dicarboxylic acids exhibit modestly higher melting / boiling points and water solubility, and lower partition coefficients and vapour pressures. The trends described above for changes in physical chemical properties with increasing carbon chain length apply.

- **Salts**: As expected, the salts differ in physical / chemical properties as compared to their homologous single component substances. However the trends described above for single components with regard to changes in physical chemical properties with increasing carbon chain length apply.

Physical Chemical Property Trend Analysis by Subcategory

SUMMARY SINGLE COMPONENT					
Increasing Carbon chain	Melting point (ºC)	Boiling point (ºC at 1013 hPa)	Partition coefficient (log Kow) (--)	Water Solubility (mg/L at 25ºC)	Vapor pressure (hPa at 25 ºC)
Single Component: Saturated (12)					
Increasing C chain, C6-18	Increases (-3 - 152.85)	Increases (205.2 - 414.8)	Increases (1.92 - 8.23)	Decreases (1E+4 - 10^{-3})	Decreases (10^{-3} - 10^{-9})
Single Component: Mono-Unsaturated (4)					
C14-22, mono-unsaturated	No pattern across measured & modeled; Increases across modeled (99.5 - 158.97)	Increases (339 - 432.03)	Increases (5.8 - 9.69)	Decreases (0.94 - 10^{-5})	Decreases (10^{-5} - 10^{-7})
Single Component: Di-Unsaturated (2)					
C18, di-unsaturated	Increases across measured / modeled (-8.5 - 132.4); Same modeled (132.4)	Similar across measured / modeled (365.2 - 389.2); Same modeled (389.2)	Similar across measured / modeled (7.05 - 7.51); Same modeled (7.51)	Same, both modeled (0.0377)	Increases across measured / modeled (10^{-6} - 10^{-5}); Same modeled (10^{-5})
Single Component: Tri-Unsaturated (1)					
C18, tri-unsaturated	-16.5	231	6.46	0.124	10^{-7}
SUMMARY Alkyl range sourced based					
Alkyl Range Sourced Based (Multi-Component): Saturated (13)					
C5-9 - C18-22	Increases (-3 - 81)	Increases (205.2 - 383)	Increases (1.92 - 9.91)	Decreases (10^{4} - 10^{-4})	Decreases (10^{-2} - 10^{-7})
Alkyl Range Sourced Based (Multi-Component): Unsaturated (1)					
C12-20, mono-unsaturated	Decreases across measured / modeled (88.3 – 23); Increases across modeled (88.3 – 149.21)	Increases (313.1-408.8)	Increases (4.78-8.71)	Decreases (9.12 - 10^{-4})	Decreases (10^{-4} – 10^{-6})
Alkyl Range Sourced Based (Multi-Component): Mixture of saturated and unsaturated (16)					
C8-20	Increases (16.3 - 75.4)	Increases (239-383)	Increases (3.05 - 9.29)	Decreases (789 - 10^{-4})	Decreases (10^{-3} - 10^{-9})
C18 – C22, mono-unsaturated (1)	Increases (13.4 - 33.5) (1)	Increases (360 - 432) (1)	Increases (7.64 - 9.69) (1)	Decreases (0.0115 – 10^{-5}) (1)	No pattern across measured & modeled; Decreases across modeled (10^{-5} - 10^{-6}) (1)
SUMMARY Dicarboxylic acids					
Increasing C chain	MP (ºC)	BP (ºC at 1013 hPa)	Partition coefficient (--)	Water Solubility (mg/L at 25ºC)	Vapor pressure (hPa at 25 ºC)
Dicarboxylic Acids (Single- or Multi-Component): Saturated (4)					
C8 - C10, di' (2)	No pattern across measured / modeled; Small increase across modeled (119.13 - 127.36) (2)	No pattern across measured / modeled; Small increase across modeled (336.56 - 360.05) (2)	Increases (1.21 - 2.19) (2)	Decreases (10^{4} - 1000) (2)	Decreases (10^{-7} - 10^{-8}) (2)
SUMMARY Sodium and potassium salts					
Sodium and Potassium Salts (Single- or Multi-Component): Saturated (10)					
C6-18	Increases (172.6 - 286.5)	Increases (438.8 - 578.0)	Increases (-2.17 - 4.13)	Decreases (10^{6} - 3.32)	Decreases (10^{-8} - 10^{-12})

Sodium and Potassium Salts (Single-Component): Unsaturated (1)					
C18, mono-unsaturated	250.71	581.6	3.9	4.19	1.04 E-12
Sodium and Potassium Salts (Multi-Component): Mixture of Saturated and Unsaturated (9)					
C8-18	Increases (188.0 - 249.0)	Increases (462 - 578)	Increases (-1.38 - 4.13)	Decreases (10^{5} - 3.32)	Decreases (10^{-9} - 10^{-12})
C18, mono- and di-unsaturated [3]	Increases (233.5 - 252.4) [3]	Small increase (581.6 - 585.2) [3]	Decreases (3.92 - 3.70) [3]	Increases (5.21 - 8.17) [3]	Decreases (10^{-12} - 10^{-13}) [3]
SUMMARY Magnesium and calcium salts					
Magnesium and Calcium Salts (Single- or Multi-Component): Saturated or Mixture Saturated and Unsaturated (3)					
C14-18, magnesium and calcium salts	Increases 231.9 - 287.83)	Increases (568.2 - 661.1)	Increases (10.41 - 14.34)	Decreases (10^{-7} - 10^{-10})	Decreases (10^{-12} - 10^{-15})
C18, mono-unsaturated, calcium salt	291.2	668.2	13.91	10^{-10}	10^{-15}
SUMMARY Ammonium salts					
Ammonium Salts (Single Component): Saturated (2)					
C12-18, ammonium salts	Increases across modeled (180.71 - 213.23)	Increases (491.71 - 501.4)	Increases (2.12 - 5.07)	Decreases (547.8 - 0.565)	Decreases ($4 \times 10^{-8} – 3 \times 10^{-8}$)

[1] Comparing across the mono-unsaturated CAS (C18:1, C20:1, and C22:1)
[2] Excluding **68937-70-2** which was not modeled as a dicarboxylic acid
[3] Carbon chain length the same; range reflects differing levels desaturation

The trends for water solubility were also examined by carbon chain length across the sponsored aliphatic acid subdivisions, and for the homologous salts. In general, the water solubility of single carbon chain length substances followed a pattern of decreasing solubility as carbon chain length increases, especially at C16 and higher. In addition, greater solubility is seen for dicarboxylic acids as compared to their homologous single acids:

Water Solubility Trend Analysis by Carbon Chain Length

Carbon chain length	Water solubility (mg/L)
C6, single and C8-10, di	>1000
C8-9	>100 - <1000
C10	>10 - <100
C12	>1 - <10
C14	>0.1 - <1
>=C16	<0.1 (as low as 10^{-5})

As expected, the potassium, sodium and ammonium salts exhibited higher water solubility as compared to the homologous acids, and the magnesium and calcium salts exhibited lower water solubility as compared to the homologous acids.

Water Solubility Trend Analysis by Carbon Chain Length – Salts

Carbon chain length (potassium or sodium salt)	Water solubility (mg/L)
C6 to C12	>1000
C14	>100 to <1000
C16	>10 to <100
C18	>1 to <10

Carbon chain length (ammonium salt)	Water solubility (mg/L)
C12	>100 to <1000
C18	>0.1 to < 1

Carbon chain length (magnesium, calcium salt)	Water solubility (mg/L)

C14 to C18	<0.1 (as low as 10^{-11})

Human Health

Tables 1 and 2 provide a summary of the data for mammalian endpoints as well as the read across approach for filling these endpoints.

Toxicokinetics

Short (<= 6 carbons) and medium (6-12 carbon) chain aliphatic acids are directly absorbed into blood from the intestines. Long (>12 carbon) chain aliphatic acids are absorbed in the intestine and distributed in the blood as chylomicrons. Aliphatic acids serve as a fuel for muscular contraction and general metabolism. They are consumed by mitochondria to produce ATP through beta oxidation. Fatty acid oxidation begins with activation of the molecule in the cytosol. In this reaction, a thioester bond is formed between the carboxylic group of the fatty acid and the thiol group of coenzyme A. The activated from of the fatty acid is an acyl-CoA, the exact nature of which depends on the nature of the fatty acid itself. The acyl-CoA can then cross into the mitochondria where beta-oxidation progressively shortens fatty acids two-carbons at a time as acetyl-CoA units are removed with each round of the cycle. Fatty acids that enter beta-oxidation with an even number of carbons are converted entirely to acetyl-CoA, with the last round producing two acetyl-CoA molecules from one four carbon fatty acid. The number of molecules of acetyl-CoA produced is equal to half the number of carbon atoms in the original fatty acid. For fatty acids that have an odd number of carbons, the last round of beta-oxidation with a five-carbon chain releases acetyl-CoA and the 3-carbon chain propionyl-CoA. Propionyl-CoA is converted to succinyl-CoA, an intermediate in the Kreb's cycle. Propionyl-carboxylation of propionyl-CoA as four carbons, so one of the first steps in this pathway is the carboxylation of propionyl-CoA with an input of energy from ATP. The saturation of a fatty acid has less of a bearing on the metabolism than the length of the fatty acid chain; the longer the chain, the more rounds of beta-oxidation necessary.

Acute inhalation toxicity

Single Component (sponsored substances):

The one hour LC50 for **octadecanoic acid, magnesium salt (CAS No 557-04-0)** in rats was > 2 mg/L and < 200 mg/L (no guideline specified).

Acute oral (gavage) toxicity The acute oral LD_{50} values in rats for both sponsored and supporting substances were greater than >2000 mg/kg bw (according to or similar to OECD TG 401). Clinical signs were generally associated with poor condition following administration of high doses (salivation, diarrhea, staining, piloerection and lethargy). There were no adverse effects on body weight in any study. In some studies, excess test substance and/or irritation in the gastrointestinal tract was observed at necropsy.

Single Component (sponsored substances):

In an OECD TG 401 study, a group of five rats/sex was administered **octanoic acid (CAS No 124-07-2)** at a dose of 2000 mg/kg bw. There were no deaths, clinical signs, or findings at gross necropsy. The LD50 was > 2000 mg/kg bw.

In a study conducted according to the Federal Hazardous Substance Act (FHSA), groups of five male rats were administered **decanoic acid (CAS No 334-48-5)** at doses up to 10,000 mg/kg bw. There were no deaths. There were no clinical signs observed at 464 or 1000 mg/kg bw; at 2150 mg/kg bw, transient clinical signs included wheezing, salivation, serum, blood and urine, and at 4640 and 10,000 mg/kg bw there was transient excessive salivation and diarrhea. Depression, depressed righting and placement reflexes, and unkempt fur was noted in the 10,000 mg/kg bw group. Gross necropsy findings were not reported. The LD50 was > 10,000 mg/kg bw.

In an OECD TG 401 study, a group of five rats/sex was administered **dodecanoic acid (CAS No 143-07-7)** at a dose of 5000 mg/kg bw. There were no deaths. Transient slight piloerection was observed. At necropsy, stomach mucous membrane appeared slightly reddened. The LD50 was > 5000 mg/kg bw.

In a study conducted according to the FHSA, groups of five male albino rats were administered **tetradecanoic acid (CAS No 544-63-8)** at doses up to 10,000 mg/kg bw. There were no deaths. There were no clinical signs at 464, 1000, 2150 mg/kg bw. Transient slight diarrhea and excessive salivation was observed at 4640 mg/kg bw. The majority of animals in the 10,000 mg/kg group showed slight depression, mucoid diarrhea, unkempt fur stained with diarrhea, and serum and blood discharge from the nose and eyes the first three days of dosing. There were no findings at gross necropsy. The LD50 was > 10,000 mg/kg bw.

In an OECD TG 401 study, a group of five rats/sex was administered **hexadecanoic acid (CAS No 57-10-3)** at a

dose of 5000 mg/kg bw. There was one death. Animals exhibited transient slight piloerection and reduced activity. At necropsy, animals exhibited swelling of the stomach mucous membranes. The LD50 was > 5000 mg/kg bw.

In an OECD TG 401 study, a group of five rats/sex was administered **octadecanoic acid (CAS No 57-11-4,** as a 50% suspension in DMSO) at a dose of 5000 mg/kg bw. There was one death. Animals exhibited transient piloerection, excessive salivation, and diminished activity. At necropsy, the male animal that died exhibited a stomach full of test substance; surviving animals showed remnants of test substance in the stomach with swelling of the mucous membrane. The LD50 was > 5000 mg/kg bw.

In an OECD TG 401 study, a group of five rats/sex was administered **isooctadecanoic acid (CAS No 30399-84-9)** at a dose of 2000 mg/kg bw. There were no clinical signs, deaths, or findings at necropsy. The LD50 was > 2000 mg/kg bw.

In an OECD TG 401 study, a group of five rats/sex was administered **9-octadecenoic acid, (Z)- (CAS No 112-80-1)** at a dose of 2000 mg/kg bw. There were no clinical signs, deaths, or findings at necropsy. The LD50 was > 2000 mg/kg bw.

Single Component (supporting substances):

In an OECD TG 401 study, a group of five rats/sex was administered docosanoic acid (CAS No 112-85-6) at a dose of 2000 mg/kg bw. There were no clinical signs, deaths, or findings at necropsy. The LD50 was > 2000 mg/kg bw.

Alkyl ranges and source based (sponsored substances):

In a study conducted similar to OECD TG 401, two male and two female rats were administered **fatty acids, C14-18 (CAS No 67701-02-4)** at a dose of 2000 mg/kg bw (as a 20% suspension in peanut oil;). There were no deaths, or findings at necropsy. The LD50 was > 2000 mg/kg bw.

In an OECD TG 401 study, a group of five rats/sex was administered **fatty acids, C18-22 (CAS No 90990-11-7)** (as a 50% suspension in DMSO) at a dose of 5000 mg/kg bw. There were no deaths. Animals exhibited transient piloerection and diminished activity. During necropsy, a foreign substance was found in the stomach. The mucous membranes of the stomachs appeared red and swollen. The LD50 was > 5000 mg/kg bw.

In an OECD TG 401 study, a group of five rats/sex was administered **fatty acids, C14-18 and C16-18-unsaturated (CAS No 67701-06-8)** (as a 25% suspension in water) at a dose of 5000 mg/kg bw. There were no clinical signs, deaths, or findings at necropsy. The LD50 was > 5000 mg/kg bw.

In an OECD TG 401 study, a group of five rats/sex was administered **Fatty acids, C16-18 and C18-unsaturated (CAS No 67701-08-0)** (as a 25% suspension in water) at a dose of 5000 mg/kg bw. There were no clinical signs, deaths, or findings at necropsy. The LD50 was > 5000 mg/kg bw.

Alkyl ranges and source based (supporting substances):

In a study similar to OECD TG 401, a group of five rats/sex was administered fatty acids, tall-oil (CAS No 61790-12-3) at a dose of 10,000 mg/kg bw. Transient piloerection was observed in one male and abnormal stance was observed in one male and one female. There were no other clinical signs, deaths, or findings at necropsy. The LD50 was > 10,000 mg/kg bw.

In an acute oral study (no guideline specified), a group of five rats/sex was administered fatty acids, rape-oil (CAS No 85711-54-2) (in 2% carboxymethylcellulose) at a dose of 2000 mg/kg bw. There were no clinical signs, deaths, or findings at necropsy. The LD50 was >2000 mg/kg bw.

Dicarboxylic acids (sponsored substances):

In a study conducted similar to OECD TG 401, a group of two male rats were administered **nonanedioic acid (CAS No 123-99-9)** at a dose of 5000 mg/kg bw. There were no deaths; information regarding clinical signs, effects on body weight or findings at gross necropsy was not located. The LD_{50} was > 5000 mg/kg bw.

In a study conducted similar to OECD TG 401, a group of five rats/sex was administered **Decanedioic acid (CAS No 111-20-6)** at doses up to 3200 mg/kg bw. Clinical signs of weakness and diarrhea were reported. There were no further details. The LD_{50} was 2260 mg/kg bw.

In a study conducted similar to OECD TG 401, a group of five rats/sex was administered **hexanedioic acid (CAS No 124-04-9)** (20% in corn oil) at doses up to 6310 mg/kg bw. Mortality ratios of 0/5, 2/5, 3/5, and 5/5 occurred at 3160, 3980, 5010, and 6310 mg/kg bw, respectively. Clinical signs included reduced appetite and activity. Necropsy findings on decedents included hemorrhagic lungs, discolored livers, and acute gastrointestinal inflammation; there were no findings in survivors. The LD_{50} was 5050 mg/kg bw.

Dicarboxylic acids (supporting substances):

In an acute oral (guideline not specified), a group of three or five rats/sex were administered butanedioic acid (CAS No 110-15-6) at a dose of 2000 mg/kg bw. There were no deaths, clinical signs, or findings at gross necropsy. The LD_{50} was > 2000 mg/kg bw.

In a study conducted similar to OECD TG 401, a group of five rats/sex was administered pentanedioic acid (CAS

No 110-94-1) (50% aqueous solution) at doses up to 3980 mg/kg bw. Mortality ratios were 0/5, 3/5, 3/5, and 5/5 for the 2000, 2510, 3160, and 3980 mg/kg groups, respectively. Tremors were observed in the first 2 hours. Other signs noted included salivation and diarrhea. Necropsy findings included inflammation of gastric mucosa and liver hyperemia. The LD_{50} was 2750 mg/kg bw.

In an OECD TG 401 study, a group of five rats/sex was administered octadecanedioic acid (CAS No 871-70-5) (in corn oil) at a dose of 5000 mg/kg bw. There were two deaths; clinical signs in these animals included loose stools, hypoactivity and piloerection. At necropsy, findings in the two animals that died included distended, red stomachs and gastrointestinal tracts. The gastrointestinal tracts also contained solid blockages that were likely solidified test substance. There were no deaths, clinical signs, or findings at gross necropsy in the remaining eight animals. The LD_{50} was > 5000 mg/kg bw.

Sodium and potassium salts (supporting substances):

In a study similar to OECD TG 401 study, a group of five rats/sex was administered Fatty acids, C16-18 and C18-unsaturated, sodium salts (CAS No 68424-26-0) (in carboxymethylcellulose) by gavage at a dose of 2000 mg/kg bw. There were no deaths or clinical signs. The LD_{50} was > 2000 mg/kg bw.

Magnesium and calcium salts (sponsored substances):

Groups of rats (number and sex not specified) were administered **octadecanoic acid, magnesium salt (CAS No 557-04-0)** at doses up to 1000 mg/kg bw. A test guideline was not specified. Mild diarrhea was observed in animals at the highest dose. The LD_{50} was > 10,000 mg/kg bw.

Magnesium and calcium salts (supporting substances):

In an OECD TG 401 study, a group of five rats/sex was administered 9,10-Dihydroxy-octadecanoic acid, ammonium salt (CAS No 84753-04-8) (50% in water) at a dose of 2000 mg/kg bw. There were no deaths; clinical signs were limited to severe emaciation in one animal. Findings at necropsy included fluid in the uterus in one female and evidence of cystitis (pyelonephritis), mucus in the urinary bladder, and a slight light brown discoloration of the spleen in another female. The LD_{50} was > 2000 mg/kg bw.

Acute dermal toxicity studies were not located.

Skin and eye irritation potential, with a few stated exceptions, is chain length dependent and decreases with increasing chain length (Table 2). The animal skin irritation studies (generally similar to OECD TG 404) indicate that the C6-10 aliphatic acids are severely irritating or corrosive, while the C12 aliphatic acid is irritating, and the C14-22 aliphatic acids generally are not irritating or mildly irritating. **CAS 30399-84-9**, which is a C18 methyl branched structure, is a skin irritant. The dicarboxylic acids (C4-C9) **CAS 123-99-9** and **111-20-6** and supporting CAS 110-15-6, 110-94-1, and 124-04-9) are not skin irritants. Studies in human volunteers, using up to ten sequential 24-hour occluded exposure periods, demonstrate that the C8-12 aliphatic acids are the most irritating, with the C14-18 aliphatic acids having lower irritation potential; C7 (**CAS 111-14-8**) was the only fatty acid not reported to cause an irritation response in this study. It was not possible to determine why this discrepancy occurred and **CAS 111-14-8** was considered severely irritating based on a category read across approach. Human skin irritation studies using more realistic exposures (30-minute, 1-hour or 24-hours) indicate that the aliphatic acids have sufficient, good or very good skin compatibility. Animal eye irritation studies (generally similar to OECD TG 405) indicate that among the sponsored aliphatic acids, the C8-12 aliphatic acids are irritating to the eye while the C14-22 aliphatic acids are not irritating. Eye irritation potential of the ammonium salts does not follow chain length dependence; the C18 ammonium salts are corrosive to the eyes. No sensitisation data were located.

Repeated dose toxicity studies by the oral (diet, gavage or drinking water) route (only) were located for the sponsored and supporting substances.

Repeated dose oral

Single component (Sponsored substances):

In a 90 day study (no guideline specified), groups of ten rats/sex/group were administered **9-octadecenoic acid, (Z)- (CAS No 112-80-1)** in the diet at 5, 10 and 25% (ca. 0, 3300, 6100, 14,000 mg/kg bw/day). Three animals (two controls and one mid-dose) died from the blood collection procedure. There were no clinical signs, adverse effects on body weight, urinalysis, clinical chemistry, or hematology. Food consumption among test animals was slightly lower than among the control animals. There were no significant differences in organ/body weight ratios except for kidneys, adrenal glands and brain; female animals showed a higher organ/body weight ratio than controls. In the absence of microscopic abnormalities in these organs, this effect was not considered adverse. The

NOAEL was = 25% (14,000 mg/kg bw/day).

A group of twenty male rats were administered **9,12-Octadecadienoic acid (CAS No 60-33-3)** in the diet at a dose of 1.5 % (ca. 467 - 1970 mg/kg bw/day) for 36 weeks. There were no adverse findings; the NOAEL was = 467 - 1970 mg/kg bw/day.

Single component (supporting substances):

In an OECD TG 422 study, groups of male and female rats (13/sex/group), were administered docosanoic acid, CAS No 112-85-6) by oral gavage at doses of 0, 100, 300, 1000 mg/kg/day. For males the exposure period was 42 days; for females the exposure period was from 14 days prior to mating to day 3 of lactation (minimum of 39 days of exposure). There were no deaths or changes in general condition, no changes in body weight gain or food consumption, and no adverse histopathological, hematological or biochemical effects. The NOAEL was 1000 mg/kg bw, the highest dose tested.

Alkyl ranges and source based (supporting substances):

In a study similar to OECD TG 407 study, groups of ten male and female were administered fatty acids, tall-oil, CAS No 61790-12-3 in the diet at doses of 5, 10, and 25% (approximately equivalent to 2500, 5000, and 12,500 mg/kg/day) for 90 days. Two control rats died during blood sampling. No other deaths occurred and no clinical signs were observed. Body weight and body weight gain were not affected by treatment, but food consumption was slightly decreased at 10 and 25%. No changes in hematology, clinical chemistry or urinalysis parameters occurred at any dose. At gross pathology, no treatment-related effects were noted at any dose. No consistent organ weight changes and no histopathological effects were reported at any dose. Based on these the NOEL was 5% (approximately 2,500 mg/kg/day).

Dicarboxylic acids (supporting substances):

Groups of ten rats/sex were administered butanedioic acid, CAS No 110-15-6 in drinking water at doses of 0, 0.3, 0.6, 1.25, 2.5, 5, 10% (0, 240, 480, 1000, 2000, 4000, 8000 mg/kg bw/day) for 13 weeks. A guideline was not specified. Severe suppression of body weight gain occurred in rats in the 10% group, and all of the rats died during the first four weeks of exposure. There were no other deaths. Suppression of body weight gain was observed at 2.5 and 5%. Drinking water consumption was reduced in all exposure groups. No dose-related changes were observed in the hematology and biochemistry. There were no histopathological findings in surviving rats. On the basis of body weight depression, the maximum tolerated dose of monosodium succinate was determined to be approximately 2-2.5% (1700-2100 mg/kg bw/day) when given in the drinking water.

In a study similar to OECD TG 408, groups of 15 rats/sex/dose were fed 0, 0.5, 1.0 or 2.0% (0, 400, 800 and 1200 mg/kg bw/day) pentanedioic acid, CAS No 110-94-1 in the diet for 90 days. There were no deaths. No effects were observed on food consumption, hematology, clinical chemistry, urinalysis, organ weights or histopathology. Based on reduced body weight gains, the NOAEL is 800 mg/kg bw. Twenty rats/group were fed 0, 0.1, 1.0, 3.0, 5.0% hexanedioic acid, CAS No 124-04-9 in diet (0, 47, 1500, 2700 mg/kg bw/day); the females were fed either 0% (10 animals) or 1.0% (19 animals; 63 mg/kg bw) for 2 years. Body weight gains for the males were reduced in the 3 and 5% dose groups and food consumption was lower in the 5% dose group; these effects were not considered adverse. There were no effects on mortality, clinical signs, gross pathology, organ weights or histopathology. There were no effects on mortality, clinical signs, weight gains, food consumption, organ weights, gross pathology or histopathology for the female rats. The NOAEL is 2700 mg/kg bw/day (males) and 63 mg/kg bw (females), the highest doses tested.

In an OECD TG 407, groups of male and female rats (5/sex/dose) were administered octadecanedioic acid, CAS No 871-70-5 via oral gavage to 0 or 1000 mg/kg bw/day of the test substance daily for 28 days. No effects were observed on mortality, clinical signs, body weights, food consumption, or organ weights. No toxicologically relevant effects were observed on haematology or clinical chemistry. The NOAEL is = 1000 mg/kg bw/day.

In an OECD TG 422 study groups of male and female rats were administered dodecanedioic acid, CAS No 693-23-2 at doses of 0, 100, 500 or 1000 mg/kg bw by oral gavage. The NOAEL for systemic toxicity was 1000 mg/kg bw (the highest dose tested; limit dose) for both male and female animals.

Magnesium and calcium salts (Sponsored substances):

In a study conducted similar to OECD TG 408, groups of twenty rats/sex/group were administered **octadecanoic acid, magnesium salt (CAS No 557-04-0)** in the diet at 0, 5, 10, 20% for 90 days (4000, 8000, 16,000 mg/kg bw/day). Four males in the 20% group died in the first 8 weeks. Necropsy revealed the presence stone formation in the lower urinary pathways which likely accounted for these deaths. In the 20% group, weight gain (males) was significantly decreased in the first 8 weeks of dosing; there was also a 33% reduction in food consumption (males and females). The amount of utilizable energy in the diet decreased as the amount of test substance increased due to the relative poor absorption of the material (15-20% absorption at the 20% dosage level). This might explain the depletion of glycogen and decreased liver weight. There was a reduction in packed cell volume in the 20% group

after 12 weeks and males from the 20% group exhibited a decrease in liver glycogen. The kidney to bodyweight ratio was significantly reduced in all dosage groups for the female animals, and in the 10% group for the male animals. The liver to body weight ratio was significantly reduced in all dosage groups for the male animals, and in the 20% group for the females. The reduction in the liver to body weight ratios are likely due to the reduced food intake of the animals (33% reduction in the 20% group). The high magnesium content of the diet containing 20% magnesium stearate is likely to be the cause of the stone formation and changes in the urinary tract. Animals from the 20% group exhibited a deposition of iron in the kidney and liver (both sexes). The NOAEL is 5% in the diet, corresponding to 4000 mg/kg bw/day.

Repeated dose oral (gavage or diet) exposure to the sponsored or supporting aliphatic acids did not result in systemic toxicity with NOAELs greater than the limit dose of 1000 mg/kg bw (similar to OCED TG 407, 408 or 422). Similar results are expected for all of the category members.

Mutagenicity

The sponsored and supporting aliphatic acids are not mutagenic or clastogenic in vitro and the supporting aliphatic acids are not mutagenic or clastogenic in vitro or in vivo. Studies were similar to OECD TG 471 and 473. One exception to these results was the positive finding in an in vitro transformation assay with BALB/3T3 cells exposed to CAS 110-94-1 in the presence and absence of metabolic activation. As the only single positive result in this category, the weight of evidence indicates that members of the aliphatic acids category are not anticipated to be genotoxic.

In vitro Studies - Gene mutation

Single component (Sponsored substances):

In an OECD TG, *S. typhimurium* TA 98, TA 100, TA 1535, and TA 1537 were exposed to **hexanoic acid (CAS No 142-62-1)** at concentrations up to 800 ug/plate (cytotoxic >= 800 ug/plate) in the presence and absence of metabolic activation (Aroclor 1254 induced rat liver S-9 mix). Positive, negative and solvent controls were included and valid. The test substance was not mutagenic.

In an OECD TG 471, *S. typhimurium* TA 97, TA 98, TA 100, TA 1535, and TA 1537 were exposed to **heptanoic acid (CAS No 111-14-8)** at concentrations up to 6666 ug/plate (up to 1666 ug/plate for TA 97) in the presence and absence of metabolic activation (rats and hamsters induced with 10% or 30% Aroclor). Positive and solvent controls were included. Solvent controls were valid; validity data were not located for positive controls. The test substance was not mutagenic.

In a study conducted similar to OECD TG 471, *Salmonella (S.) typhimurium* TA 98, TA 100, TA 1535, and TA 1537 were exposed to **octanoic acid (CAS No 124-07-2)** at concentrations up to 1250 ug/plate in the presence and absence of metabolic activation (Aroclor 1254 induced rat liver S-9 mix). There was no information regarding positive, negative and solvent controls. The test substance was not mutagenic.

In an OECD TG 471, *S. typhimurium* TA 98, TA 100, TA 1535, and TA 1537 were exposed to **isooctadecanoic acid (CAS No 30399-84-9)** at concentrations up to 5000 ug/plate in the presence and absence of metabolic activation (Aroclor 1254 induced rat liver S-9 mix). Positive, negative and solvent controls were included and valid. The test substance was not mutagenic.

In an Ames test (no guideline specified), *S. typhimurium* TA 98, TA 100, TA 1535, TA 1537 and TA 1538 were exposed to **12-hydroxy-octadecanoic acid (CAS No 106-14-9)** at concentrations up to 2500 ug/plate in the presence and absence of metabolic activation (Aroclor 1254 induced rat liver S-9 mix). Positive and negative controls were included but results of the controls were not located. The test substance was not mutagenic.

In a mouse lymphoma assay, mouse lymphoma L5178Y cells were exposed to **12-hydroxy-octadecanoic acid (CAS No 106-14-9)** at concentrations up to 250 ug/plate in the absence of metabolic activation and up to 100 ug/plate in the presence of metabolic activation (Aroclor-induced rat liver S-9). Positive and solvent controls were included and valid. The test substance was not mutagenic.

In a Bacterial Reverse Mutation Assay (no guideline specified), *S. typhimurium* TA 98, TA 100, TA 1535, and TA 1537 were exposed to **9-Octadecenoic acid, (Z)- (CAS No 112-80-1)** at concentrations up to 10,000 ug/plate in the presence and absence of metabolic activation (Aroclor 1254 induced rat or hamster liver S-9 mix). Positive, negative and solvent controls were included but results of the controls were not located. The test substance was not mutagenic.

In a study similar to OECD TG 471, *S. typhimurium* TA 98, TA 100, TA 1535, TA 1537 and/or TA 97 were exposed to **9,12-Octadecadienoic acid (CAS No 60-33-3)** (concentrations not specified) in the presence and absence of metabolic activation (Aroclor 1254 induced rat liver S-9 mix; Zeiger et al. , 1987). Positive and solvent

controls were included and valid. The test substance was not mutagenic.

Single component (supporting substances):

In an OECD TG 471, *S. typhimurium* TA 100, TA 1535, TA 98, TA 1537 and *E. coli* WP2 uvrA were exposed to docosanoic acid (CAS No 112-85-6) at concentrations up to 5000 ug/plate in the presence and absence of metabolic activation (liver, induced with phenobarbital and 5,6-benzoflavone). Negative and solvent controls were included and valid; there was no data located regarding positive controls. The test substance was not mutagenic.

Alkyl ranges and source based (supporting substances):

In a study similar to OECD TG 471, *S. typhimurium* TA 98, TA 100, TA 1535, TA 1537 and/or TA 97 were exposed to fatty acids, tall-oil (CAS No 61790-12-3) at concentrations up to 10,000 ug/plate in the presence and absence of metabolic activation (Aroclor 1254 induced rat liver S-9 mix). Positive controls were included but results of the controls were not located. The test substance was not mutagenic.

Dicarboxylic acids (Sponsored substances):

In an OECD TG 471, *S. typhimurium* TA 98, TA 100, TA 1535, TA 1537, TA 1538 were exposed to **Decanedioic acid (CAS No 111-20-6)** at concentrations up to 5000 ug/plate in the presence and absence of metabolic activation (Aroclor 1254 induced rat liver S-9 mix). Positive, negative and solvent controls were included but results of the controls were not located. The test substance was not mutagenic.

Dicarboxylic acids (Supporting substances):

In an Ames test, *S. typhimurium* TA 92, TA 1535, TA 100, TA 1537, TA 94, and TA 98 were exposed to butanedioic acid (CAS No 110-15-6) at concentrations up to 5000 ug/plate in the presence and absence of metabolic activation (biphenyl KC-400-treated rat liver S-9). The test substance was not mutagenic.

In an Ames test, *S. typhimurium* TA 98, TA 100, TA 1535, TA 1537, and TA 1538 were exposed to pentanedioic acid (CAS No 110-94-1) at concentrations up to 5000 ug/plate in the presence and absence of metabolic activation. Positive and negative controls were included but results of the controls were not located. The test substance was not mutagenic.

In a mouse lymphoma assay (conducted according to Clive and Spector, 1975), mouse lymphoma L5178Y cells were exposed to pentanedioic acid (CAS No 110-94-1) at concentrations of 156 - 8295 ug/ml in the presence of metabolic activation (Aroclor-induced rat liver S-9). Concurrent negative and positive controls were run. Positive and solvent controls were included and but results not located. The test substance was not mutagenic.

In an in vitro transformation assay, BALB/3T3 cells were exposed to pentanedioic acid (CAS No 110-94-1) at concentrations up 12.5 mg/mL in the absence of metabolic activation (rat liver microsomes) and up to 26.3 mg/mL in the presence of metabolic activation. Concurrent negative and positive controls were run. The substance induced a significant, dose-related number of transformed foci under non-activation (3.3-12.5 mg/mL) and activation (16.8 and 21 mg/mL) conditions. Therefore, the substance was considered to be active in the BALB/3T3 in vitro transformation assay in the absence and presence of an exogenous metabolic activation system.

In an OECD TG 471, *S. typhimurium* TA 98, TA 100, TA 102, TA 1535, and TA 1537 were exposed to octadecanedioic acid (CAS No 871-70-5) at concentrations up to 5000 ug/plate in the presence and absence of metabolic activation. Positive, negative and solvent controls were included and valid. The test substance was not mutagenic.

In an Ames test (no guideline specified), *S. typhimurium* TA 98, TA 100, TA 1535, and TA 1537 were exposed to dodecanedioic acid (CAS No 693-23-2) at concentrations up to 5000 ug/plate in the presence and absence of metabolic activation. There was no data located regarding controls. The test substance was not mutagenic.

In an in vitro Bacterial Reverse Mutation Assay (Ames et al. (1975), *S. typhimurium* TA 98, TA 100, TA 1535, TA 1537, TA 1538 and *Escherichia coli* strain WP2 were exposed to hexanedioic acid (CAS No 124-04-9) at concentrations up to 10,000 ug/plate in the presence and absence of metabolic activation (Aroclor®-induced rat liver S-9). Positive controls were included and valid. The test substance was not mutagenic.

In an OECD TG 471 (Bacterial Reverse Mutation Assay), *S. typhimurium* TA 98, TA 100, TA 102, TA 1535, and TA 1537 were exposed to octadecanedioic acid (CAS No 871-70-5) at concentrations up to 5000 ug/plate in the presence and absence of metabolic. Positive, negative and solvent controls were included and valid. The test substance was not mutagenic.

Magnesium and calcium salts (sponsored substances):

In a Bacterial Reverse Mutation Assay (no guideline specified), *S. typhimurium* TA 1535, TA 1537 and TA 1538 and *Saccharomyces cerevisae* D4 were exposed to **octadecanoic acid, magnesium salt (CAS No 557-04-0)** (concentrations not specified) in the presence and absence of metabolic activation (rat, mouse and monkey liver and lung; Busch, 1982). Further details were not located. The test substance was not mutagenic.

Ammonium salts (Supporting substances):

In an OECD TG 471, *S. typhimurium* TA 98, TA 100, TA 1535, TA 1537 and TA 1538 were exposed to 9,10-Dihydroxy-octadecanoic acid, ammonium salt (CAS No 84753-04-8) at concentrations up to 5000 ug/plate in the presence and absence of metabolic activation (Aroclor 1254 induced rat liver S-9 mix). Positive controls were included but results of the controls were not located. The test substance was not mutagenic.

In vitro studies - Chromosome aberration

Single component (Sponsored substances):

In a study similar to OECD TG 473, Chinese Hamster Ovary (CHO) cells were exposed to **12-hydroxy-octadecanoic acid (CAS No 106-14-9)** at concentrations up to 213 ug/ml in the presence and absence of metabolic activation (rat liver S-9 induced with Aroclor 1254). Solvent and positive controls fulfilled the requirements for a valid study. The test substance did not induce chromosomal aberrations in this study.

Single component (Supporting substances):

In an OECD TG 473 study, Chinese hamster lung fibroblasts (V79) were exposed to docosanoic acid (CAS No 112-85-6) in the presence and absence of metabolic activation (Rat liver, induced with phenobarbital and 5,6-benzoflavone), The concentrations for the 24 hour exposure were 0, 350, 700, 1400, 2800 µg/ml; for the 48 hour exposure the concentrations were 0, 288, 575, 1150, 2300 µg/ml. For the short term exposure the concentrations were 0, 875, 1750, 3500 µg/ml and for the long term exposure the concentrations were 0, 875, 1750, 3500 µg/ml. Positive and negative controls were included and valid. There were no further details. The test substance was not clastogenic.

Dicarboxylic acids (Supporting substances):

In a chromosome aberration test (guideline not specified), Chinese hamster fibroblasts were exposed to butanedioic acid, CAS No 110-15-6 at concentrations up to 1.0 mg/mL in the absence of metabolic activation. The cells were exposed to the test substance at three different doses for 24 and 48 hours. Solvent and negative controls were included but results of the controls were not located. The test substance did not induce chromosomal aberrations in this study.

In an in vitro cytogenetic study in anaphase cells (guideline not specified), human embryonic lung cell cultures (WI-38) were exposed to hexanedioic acid, CAS No 124-04-9 in the absence of metabolic activation at concentrations of 0, 2, 20 and 200 ug/mL (USFDA, 1974). Positive and negative controls were included but results of the controls were not located. The test substance did not induce any of the analyzed aberrations (bridges, pseudochiasmata, multipolar cells, and acentric fragments).

In an OECD TG 473 study, V79 cells were exposed to 1,18-octadecanedioic acid (CAS No 871-70-5) in the presence and absence of metabolic activation. In experiment I, concentrations were tested up to 50 µg/ml without metabolic activation and up to 52.5 µg/mL with metabolic activation. In experiment II, concentrations were tested up to 50 µg/mL without metabolic activation and up to 31.5 µg/mL with metabolic activation. Positive, negative and solvent controls were included and valid. The test substance was not clastogenic.

In vivo studies

Dicarboxylic acids (Supporting substances):

In an in vivo mouse micronucleus study (guideline not specified), groups of four mice/sex were administered pentanedioic acid, CAS No 110-94-1 by intraperitoneal injection 800 mg/kg bw and sacrificed at 30 or 48 hours. Two additional groups of animals were given two injections of 800 mg/kg bw at 0 and 24 hours and sacrificed at 48 or 72 hours, respectively, after the first dose. Similar groups, serving as the positive and negative control, were evaluated concurrently (results from controls not located). The test substance did not produce a statistically significant increase in micronuclei in any of the treated groups, and was determined to be negative in this assay.

In an in vivo Rat Cytogenetic Chromosomal Aberration Assay (guideline not specified), groups of male rats/group [(nine negative controls and five positive controls); five per dose group for the subacute study (three negative controls)] were administered hexanedioic acid, CAS No 124-04-9 by oral gavage. In the acute tests, animals were given a single dose of the test substance (Test I: 0, 3.75, 37.5, 375 mg/kg bw; Test II: 0, 5000 mg/kg bw) and killed 6, 24, or 48 hours after administration. For the subacute tests, animals were given 5 doses (Test I: 0, 3.75, 37.5, 375 mg/kg bw; Test II: 0, 2500 mg/kg bw) 24 hours apart and killed six hours after the last dose. Positive and negative controls were included and valid. The test substance was not mutagenic.

In an in vivo dominant lethal assay, groups of ten male rats were administered hexanedioic acid, CAS No 124-04-9 by gavage for five days at doses of 3.75-375 mg/kg (experiment I); 5000 mg/kg (experiment II) or 2500 mg/kg (experiment II). Following treatment, the males were sequentially mated to two females per week for eight weeks. Females were sacrificed 14 days after separating from the male, and at necropsy the uterus was examined for early deaths, late fetal deaths, and total implantations. The fertility index, preimplantation loss, and lethal effects on the embryos were determined. Positive and negative controls were included and valid. There was no effect of

treatment and the test substance was concluded to not induce dominant lethal mutations.

Carcinogenicity
No data were located for carcinogenicity of the sponsored substances.

Reproductive toxicity
No effects on fertility or on reproductive organs (similar to OECD TG 408 or 422), or developmental effects (similar to OECD TG 422 or 416) were observed in studies on the sponsored or supporting aliphatic acids and the NOAELs correspond to the maximum dose tested. The weight of evidence supports the lack of reproductive and developmental toxicity potential of the aliphatic acids category.

Effects on Fertility/Reproductive organs
Single component (Sponsored substances):
In a 90 day study (no guideline specified), groups of ten rats/sex/group were administered **9-Octadecenoic acid, (Z)- (CAS No 112-80-1)** in the diet at 0, 3300, 6100, 14,000 mg/kg bw/day. There were no effects on gonads weights, and no gross or histopathological findings for testes, seminal vesicle, ovary, uterus, or prostate. The NOAEL for reproductive effects was 14,000 mg/kg bw, the highest dose tested.
A group of twenty male 344 rats were administered **9,12-octadecadienoic acid (CAS No 60-33-3)** in the diet at a dose of ca. 467 - 1970 mg/kg bw/day for 36 weeks. There were no effects on testes weights, no findings at gross necropsy or histopathological findings in the testes; the NOAEL for male reproductive effects was = 467 - 1970 mg/kg bw/day, the highest dose tested.
Single component (Supporting substances):
In an OECD TG 422 study, rats (13/sex/dose) were exposed to 0, 100, 300, or 1000 mg/kg bw/day of docosanoic acid, CAS No 112-85-6 via oral gavage. For males the exposure period was 42 days; for females the exposure period was from 14 days prior to mating to day 3 of lactation (minimum of 39 days of exposure). There were no effects on gonadal function, mating behaviour, conception, development of the conceptus or parturition. The NOAEL for reproductive toxicity is >= 1000 mg/kg bw/day, the highest dose tested.
Alkyl ranges and source based (Supporting substances):
In a two generation study (similar to OECD TG 416; the initial treatment period was decreased to three weeks versus ten weeks), groups of rats (30 females/15 males/dose) were administered 0, 5 or 10% fatty acids, tall-oil, CAS No 61790-12-3 in the diet, (equivalent to approximately 0, 2500 or 5000 mg/kg bw/day). The parental (F0) generation began treatment at 80 days of age and were mated at 100 days of age. Treatment continued through the weaning of the first generation (F1). After weaning, 20 F1 males and 20 F1 females per group were maintained on the parental diet. At 100 days of age, these rats were mated and allowed to deliver pups (F2). Treatment did not affect the number of live born or stillborn F1 litters and pups, or F1 weaning weight. No treatment-related changes in fertility, viability, lactation, or gestation indices were measured. Hematology, clinical chemistry and urinalysis parameters were unchanged, and gross and microscopic pathology revealed no treatment-related effects. The NOAEL for reproductive toxicity is >= ca. 5000 mg/kg bw/day for rats exposed for two generations.
Dicarboxylic acids (Supporting substances):
Male rats (20/dose) were fed 0, 0.1, 1.0, 3.0 or 5.0% diet (0, 47, 1500, 2700 mg/kg bw/day) hexanedioic acid, CAS No 124-04-9 in the diet and females were fed either 0% (10 animals) or 1.0% (19 animals; 63 mg/kg bw) for 2 years. There were no effects on testes weight. There were no histopathological findings for testes, ovaries or uterus. The NOAEL for effects on reproductive endpoints was 2700 mg/kg bw/day (males) and 63 mg/kg bw (females), the highest doses tested.
In an OECD TG 422 study, groups of twelve rats/dose were exposed to 0, 100, 500, or 1000 mg/kg bw/day of dodecanedioic acid, CAS No 693-23-2 by oral gavage. There were no effects on reproductive endpoints (mating index, fertility index, gestation index, pups born alive, viability index, and litter survival). The NOAEL for reproductive toxicity is >= 1000 mg/kg bw/day, the highest dose tested.
Magnesium and calcium salts (Sponsored substances):
In a study conducted similar to OECD TG 408, groups of twenty rats/sex/group were administered the octadecanoic acid, magnesium salt (CAS No 557-04-0) in the diet at 4000, 8000, 16,000 mg/kg bw/day for 90 days. There were no effects on reproductive organ weight or at gross necropsy for the testes and ovaries, and no histopathological findings for the testes, ovaries or uterus. The NOAEL for reproductive effects was 4000 mg/kg bw, the highest dose tested.

Developmental Toxicity

Single component (Sponsored substances):
In a study following the Chernoff/Kavlock Developmental Toxicity Screen, groups of female mice (26-30/dose) were treated via oral gavage on gestation days 8-12 with 10,000 mg/kg bw/day of **9,12-octadecadienoic acid (CAS No 60-33-3)**. There were no effects on number of litters, number of resorptions, number of pups/litter, number of live and dead births, postnatal survival rates, pup weights at days 1 and 3 or external abnormalities among dead pups. The NOEL for developmental toxicity is >= 10,000 mg/kg bw/day for mice with exposure on gestation days 8-12.

Single component (Supporting substances):
In an OECD TG 422 study, groups of rats (13/sex/dose) were exposed to 0, 100, 300, or 1000 mg/kg bw/day of docosanoic acid, CAS No 112-85-6 the test substance via oral gavage. For males, the exposure period was 42 days; for females from 14 days prior to mating to day 3 of lactation (minimum of 39 days). The number of live and stillborn pups was noted as well as the number that died postpartum. On day 4 of lactation, pups were necropsied. There were no effects on developmental parameters. The NOAEL for developmental toxicity is >= 1000 mg/kg bw/day, the highest dose tested.

Alkyl ranges and source based (Supporting substances):
In a two generation study (similar to OECD TG 416; the initial treatment period was decreased to three weeks versus ten weeks), groups of rats (30 females/15 males/dose) were administered 0, 5 or 10% of fatty acids, tall-oil, CAS No 61790-12-3 in the diet, (equivalent to approximately 0, 2500 or 5000 mg/kg bw/day). The parental (F0) generation began treatment at 80 days of age and were mated at 100 days of age. Treatment continued through the weaning of the first generation (F1). After weaning, 20 F1 males and 20 F1 females per group were maintained on the parental diet. At 100 days of age, these rats were mated and allowed to deliver pups (F2). Treatment did not affect the number of live born or stillborn F1 litters and pups, or F1 weaning weight. No treatment-related changes in fertility, viability, lactation, or gestation indices were measured. Hematology, clinical chemistry and urinalysis parameters were unchanged, and gross and microscopic pathology revealed no treatment-related effects. The NOAEL for developmental toxicity is >= ca. 5000 mg/kg bw/day for rats exposed for two generations.

Dicarboxylic acids (Supporting substances):
In a standard developmental study (guideline not specified), groups of 25 female rats were exposed to 0, 125, 400 or 1300 mg/kg bw of pentadecanoic acid, CAS No 110-94-1 via oral gavage on gestation days 6-15 with caesarean section on day 20. There were two deaths at 1300 mg/kg bw. Mean body weight gains were decreased only in the 1300 mg/kg bw dose group (during the dosing period); mean body weight gains post-dosing (gestation days 15-20) were normal compared to control. Clinical signs observed at 1300 mg/kg bw included salivation, rales, nasal discharge, slight inactivity, labored breathing, decreased body temperature, soft stools, and staining around the mouth, nares, and anogenital area. At 400 mg/kg bw, clinical signs included salivation, rales, and nasal discharge. No adverse effects were observed on body weight, general appearance, or behavior of rats at 125 mg/kg bw. The NOAEL for maternal toxicity is 125 mg/kg bw/day for rats exposed on gestation days 6-15. No adverse effects on pregnancy or no teratogenic effects were observed. The NOAEL for developmental toxicity is >= 1300 mg/kg bw/day for rats exposed on gestation days 6-15.

Groups of female rats (24-25/dose) were exposed via oral gavage to 0, 2.9, 13, 62 and 288 mg/kg bw of hexanedioic acid, CAS No 124-04-9 on gestation days 6-15 with caesarean section on day 20 (guideline not specified). No adverse effects on pregnancy, and no embryotoxic or teratogenic effects were observed. The NOAEL for maternal and developmental toxicity is >= 288 mg/kg bw/day, the highest dose tested, for rats exposed on gestation days 6-15.

In an OECD TG 422 study, rats were exposed to 0, 100, 500, or 1000 mg/kg bw/day of dodecanedioic acid, CAS No 693-23-2. After 14 days of dosing, rats were mated within the treatment groups and allowed to produce litters. Dosing continued through mating, gestation and lactation until day 54. There were no effects on developmental parameters. The NOAEL for parental toxicity and developmental toxicity is >= 1000 mg/kg bw/day, the highest dose tested.

The Aliphatic Acids category members possess properties indicating a hazard for human health (severe skin irritation/corrosion for C6-C10 [except for the dicarboxylic acids which are not irritating], irritating to the skin for C12 and methyl branched C18, irritating to the eye for C8-C12 and dicarboxylic acids (based on read-across to supporting substances). Adequate screening-level data are available to characterize the hazard to human health for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Environment

The aliphatic acids of this category are of similar very weak acid strength (approximately pKa 5), i.e., partially dissociate in aqueous solution; the salts of the aliphatic acids are highly dissociated in water solution such that the anion is the same for homologous salts and acids.

OECD TG 111 studies have not been conducted for the aliphatic acids. Hydrolysis is not an important fate path in the environment due to the fact that the substances lack hydrolysable functional groups. Aliphatic acids are hydrolytically stable in aqueous solutions.

The aliphatic acids are subject to photodegradation in air. Modeled photodegradation rates (half-lives) using AopWin v1.92 (EPI Suite v4.10) are based on the hydroxyl radical reaction at 25ºC (12-hr day; 1.5E6 OH/cm^3). Estimated half-lives generally increase with decreasing chain length and range from 0.6 hours (**9,12,15-Octadecatrienoic acid, (Z,Z,Z), CAS No. 463-40-1**, C18) to 17.5 hours (**Octanoic acid, sodium salt, CAS No. 1984-06-1**, C8). Level III fugacity modelling using EPI Suite v4.10 indicates that the aliphatic acids will distribute primarily to soil and water, with lesser amounts to air and sediment. With increasing chain length, the percent distributions to soil and sediment generally increase and the percent distributions to water and air generally decrease.

Biodegradation studies or model estimations for single and multi-component aliphatic acids generally confirm that the extent of biodegradation observed in 28 days meets the ready biodegradability criterion (>60%). In some cases, insufficient sampling points were included in the tests to determine whether or not the 10-day window was met and thus are insufficient to demonstrate ready biodegradability. When the 10-day window was not met or less than 60% biodegradation was observed in 28 days, it is likely that the aliphatic acids tested were not fully in solution. **Fatty acids, C14-22, CAS 68424-37-3** was the only sponsored substance that did not reach 60% biodegradation in 28 days, and is likely due to its poor water solubility. Modeling results for the magnesium (**Octadecanoic acid, magnesium salt; CAS 557-04-0**) and calcium (**Hexadecanoic acid, calcium salt, CAS 542-42-7**) salts indicate these substances are not readily biodegradable, most likely due to the expected low water solubility of the substances. However, the BKH Environmental data review of soaps states that the available data indicate all fatty acid salt chain lengths up to and including C18 can be metabolised under aerobic conditions and can be considered to be biodegradable. Biodegradability did not appear to be influenced by even or odd chain length, degree of saturation or unsaturation or branching. For example, odd/even chain length: C8 and C9 are readily biodegradable; Saturation/unsaturation: C18 (saturated) and C18 (di-unsaturated) are biodegradable, while C18 (mono-unsaturated) are readily biodegradable; branching or hydroxylation: the C18 hydroxylated substance was readily biodegradable and the C18 methyl branched substance was biodegradable. The aliphatic acids also undergo biodegradation under anaerobic conditions.

Estimated bioconcentration factor values are calculated using EPI Suite v4.10. The aliphatic acids have BCF values less than 100, indicating a low potential for bioaccumulation.

Summary of modeled BCF

Substance	Modeled BCF
Single Component	3.16 – 56.2
Alkyl Ranges and Source Based	3.16 – 56.2
Dicarboxylic acids	3.16
Sodium and potassium salts	3.16 – 56.2
Magnesium and calcium salts	3.38-72
Ammonium salts	3.16-70.8

The following acute toxicity test results have been determined for aquatic species (key studies only):

Substance	**Species**	**Effect level**	**Study Design**
	Fish	**LC_{50} (mg/L), 96 hr**	
Single component			
Sponsored substances			
Hexanoic acid; 142-62-1	*Pimephales promelas*	320 (measured)	No guideline specified, flow through
Nonanoic acid; 112-05-0	*Pimephales promelas*	104 (measured)	No guideline specified, flow

			through
Decanoic acid; 334-48-5	*Oryzias latipes*	20 (freshwater, nominal, 48 hr) 31 (seawater, measured, 48 hr)	No guideline specified, semi-static
Dodecanoic acid; 143-07-7	*Danio rerio*	150 (nominal) exceeds water solubility	OECD TG 203, static
Tetradecanoic acid; 544-63-8	*Leuciscus idus*	>100 - <300 (nominal) exceeds water solubility	Similar to OECD TG 203, semi-static
Hexadecanoic acid; 57-10-3	*Danio rerio*	>1000 (nominal) exceeds water solubility	Similar to OECD TG 203, semi-static
Octadecanoic acid; 57-11-4	*Danio rerio*	>1000 (nominal) exceeds water solubility	OECD TG 203, static
Isooctadecanoic acid; 30399-84-9	*Cyprinus carpio*	13.4 (nominal, 48 hr) exceeds expected water solubility	Evaluation of water-endangering materials, determination of the acute fish toxicity, Ad-hoc-working group 1, static
9-Octadecenoic acid, (Z)-; 112-80-1	*Oncorhynchus mykiss*	>56 (nominal; highest concentration tested) exceeds expected water solubility	No guideline specified, semi-static
Supporting substances			
9,10-Dihydroxy-octadecanoic acid; 120-87-6	*Danio rerio*	> 10000 (nominal) exceeds expected water solubility	EU 92/69/EWG/ Semi-static
Alkyl ranges and source based			
Sponsored substances			
Fatty acids, C6-12; 67762-36-1	*Danio rerio*	38 (nominal) exceeds expected water solubility of some components	OECD TG 203, semi-static
Fatty acids, C16-18; 67701-03-5	*Leuciscus idus*	>1000 (nominal; 48 hr) exceeds expected water solubility	Similar to OECD TG 203, static
Fatty acids, C18-22; 90990-11-7	*Danio rerio*	>100 (nominal) exceeds expected water solubility	Similar to OECD TG 203, semi-static
Fatty acids, C14-18 and C16-18-unsaturated; 67701-06-8	*Danio rerio*	>1000 (nominal) exceeds expected water solubility	Similar to OECD TG 203, semi-static
Fatty acids, C16-18 and C18-unsaturated; 67701-08-0	*Danio rerio*	300 (nominal) exceeds expected water solubility	Similar to OECD TG 203, semi-static
Fatty acids, tallow; 61790-37-2	*Cyprinus carpio*	Not toxic at limit of solubility	OECD TG 203, static
Supporting substances			
Fatty acids, sunflower, conjugated; 68953-27-5	*Danio rerio*	110 (nominal) exceeds expected water solubility	Similar to OECD TG203/semi-static
Dicarboxylic acids			
Sponsored substances			
Nonanedioic acid; 123-99-9	*Leuciscus idus*	310 (nominal; 48 hr)	Similar to OECD TG 203, static
Decanedioic acid; 111-20-6	*Danio rerio*	>9.67 (measured; highest concentration tested)	OECD TG 203, static
Supporting substances			
Hexanedioic acid; 124-04-9	*Pimephales promelas*	97 (nominal)	No guideline specified, static
Octadecanedioic acid; 871-70-5	*Danio rerio*	>100 (nominal; exceeds expected water solubility); WAF = 0.14-0.22	OECD TG 203, semi-static
Sodium and potassium salts			
Sponsored substances			
Octanoic acid, sodium salt; 1984-06-1	*Oryzias latipes*	310 (nominal)	No guideline specified, semi-static
Decanoic acid, sodium salt; 1002-62-6	*Oryzias latipes*	54 (nominal; WAF)	No guideline specified, semi-static
Dodecanoic acid, sodium salt; 629-25-4	*Oryzias latipes*	11 (nominal; WAF)	No guideline specified, semi-static
Tetradecanoic acid, sodium salt; 822-12-8	*Oryzias latipes*	118 (nominal)	No guideline specified, semi-static
Hexadecanoic acid, sodium salt; 408-35-5	*Oryzias latipes*	150 (nominal) exceeds expected water solubility	No guideline specified, semi-static
Octadecanoic acid, sodium salt; 822-16-2	*Oryzias latipes*	125 (nominal) exceeds expected water solubility	No guideline specified, semi-static
9-Octadecenoic acid, (Z)-, potassium salt; 143-18-0	*Lepomis macrochirus*	23 (not specified) exceeds expected water solubility	No guideline specified, static

Supporting substances			
Fatty acids, C16-18 and C18-unsaturated, sodium salts; 68424-26-0	*Danio rerio*	54 (nominal) exceeds expected water solubility	Similar to OECD TG 203/semi-static
	Aquatic invertebrate	**EC_{50} (mg/L), 48 hr**	
Single component			
Sponsored substances			
Hexanoic acid; 142-62-1	*Hyale plumulosa*	235 (measured, 48 hr, saltwater)	No guideline specified, no further details
Octanoic acid; 124-07-2	*Hyale plumosa*	128 (measured)	No guideline specified, semi-static
Decanoic acid; 334-48-5	*Hyale plumosa*	41 (measured; Water Accommodated Fraction (WAF)	No guideline specified, semi-static
Dodecanoic acid; 143-07-7	*Hyale plumosa*	>5.6 (nominal, WAF, limit of solubility) exceeds water solubility	No guideline specified, semi-static
Tetradecanoic acid; 544-63-8	*Hyale plumosa*	No mortality at saturation in seawater	No guideline specified, semi-static
9-Octadecenoic acid, (Z)-; 112-80-1	*Daphnia magna*	EC_0 >=32 (nominal; highest concentration tested; WAF, water hardness of 54 or 215 mg/L) exceeds expected water solubility	EC Guideline C2, static
9,12-Octadecadienoic acid; 60-33-3	*Daphnia magna*	55 (nominal, WAF) exceeds expected water solubility	EU 92/69/EWG, static
Alkyl ranges and source based			
Sponsored substances			
Fatty acids, tallow, hydrogenated; 61790-38-3	*Daphnia magna*	EC_0 >100 (nominal) exceeds expected water solubility	Static Acute Freshwater Invertebrate Toxicity Study of P1943.01, R.D. Vashon, 2-28-85, based on "Method for acute toxicity tests with fish, macroinvertebrates and amphibians," (US EPA 1975), static
Supporting substances			
Fatty acids, C16-22 and C18-22 unsaturated; 95912-82-6	*Daphnia magna*	0.695 (WAF, measured)	EU 92/69/EWG, static
Dicarboxylic acids			
Sponsored substances			
Decanedioic acid; 111-20-6	*Daphnia magna*	>11.6 (nominal)	OECD TG 202, static
Supporting substances			
Butanedioic acid; 110-15-6	*Daphnia*	374.2 (nominal, 48 hrs)	EPA (1975), static
Hexanedioic acid; 124-04-9	*Daphnia magna*	Ec0 = 62.5, EC100 = 125 (not specified)	EG-Richtlinie 79/831/EWG, C.2 "Acute Toxicity for Daphnia", no further details
Octadecanedioic acid; 871-70-5	*Daphnia magna*	>100 (nominal) exceeds expected water solubility	OECD TG 202, static
	Aquatic plants	**EC_{50} (mg/L), 72 hr**	
Alkyl ranges and source based			
Sponsored substances			
Fatty acids, C14-22; 68424-37-3	*Desmodesmus subspicatus*	>100 (nominal) exceeds expected water solubility	DIN 38412/9
Fatty acids, C14-18 and C16-18-unsaturated; 67701-06-8	*Desmodesmus subspicatus*	51 (nominal; 96 hr) exceeds expected water solubility	DIN 38412/9
Dicarboxylic acids			
Sponsored substances			
Decanedioic acid; 111-20-6	*Desmodesmus subspicatus*	NOEC >=10; EbC50>10; 24 hour ErC50 >10 (nominal)	OECD TG 203
Supporting substances			
Hexanedioic acid; 124-04-9	*Desmodesmus subspicatus*	26.6 (96 hr; nominal/measured not specified)	Algentest in Anlehnung an UBA
Octadecanedioic acid; 871-70-5	*Desmodesmus subspicatus*	EbC50 and ErC50 > 100 (nominal; exceeds expected water solubility); WAF = 0.14-0.19 (measured; limit of expected water solubility)	OECD TG 203

Dodecanedioic acid; 693-23-2	*Desmodesmus subspicatus*	EC_0 >=5.8 (nominal; highest concentration tested) exceeds water solubility	Algentest in Anlehnung an UBA
Sodium and potassium salts			
Sponsored substances			
Fatty acids, C12-18, sodium salts; CAS 91032-12-1	*Desmodesmus subspicatus*	EbC50 = 25; ErC50 = 41 (nominal) exceeds expected water solubility	DIN 38412/9

The Aliphatic Acids category members possess properties indicating a hazard for the environment (acute toxicity to fish: between 1-100 mg/L for carbon chain lengths C6 through C12, and multi-component sodium or potassium salts C16-18; acute toxicity to aquatic invertebrates: between 1 and 100 mg/L for carbon chain lengths C6 through C9 (including sodium salts) and less than 1 mg/L for sodium salts single component aliphatic acids C18 and multi component sodium salt aliphatic acids with carbon chain lengths including C14 through C18; and, acute toxicity to aquatic plants: between 1-100 mg/L for carbon chain length C12, including sodium or ammonium salts). The weight of evidence indicates that the Aliphatic Acids category members are readily biodegradable and are not expected to bioaccumulate. Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Exposure

According to the HERA Project Assessment on Fatty Acid Salts (2003), the estimated annual tonnage of fatty acids salts produced for use in household cleaning products in Europe is 71,306 metric tons. This has been compiled from 4 of the 6 main formulator companies and is estimated to cover greater than 80% of the tonnage used in household cleaning products. The total use of fatty acid salts in Europe in 1994 was estimated to be 701,000 MT/year. The estimated regional production volumes of the sponsored category of aliphatic acids, based on a 2002 survey of Consortium member companies (unpublished), are 997,900 tonnes in Europe and 952,500 tonnes in North America.

The textile industry is one of the major industrial and commercial users of fatty acids and their derivatives. Beyond their wetting properties, as are used in neutral soaps, fatty acids are used in dyeing, as textile lubricating agents, and as resins. Fatty acids are also used in pharmaceuticals, lubrication oils, as protective coatings, in rubber manufacturing, mining, metal working and in leather softening.
Aliphatic acids and their salts (soap) are widely used in household cleaning products, cosmetics including many lotions, lipsticks, and cleansing creams, food and food packaging, and paints and coatings.

Environmental exposure could arise in association with production, formulation and industrial use of these substances. There would also be exposure from consumer uses. The majority of the aliphatic acid salt uses result in down the drain releases to the environment.

For routine occupational operations, including those involving a breach of the closed system, goggles or safety glasses, gloves, safety boots and helmets are worn. Aliphatic acids have a low volatility and as a rule engineering controls are available that prevent the need for respiratory protection. Major routes of consumer exposure to aliphatic acids are from the use of aliphatic acid salts (soaps) in bar soaps and in household cleaning products.

Annex 1

Table 1 Summary of Read Across Approach Mammalian Toxicity Data

Substance CAS#	Acute toxicity (oral and inhalation)	Repeated dose (oral)	Gene mutation *in vitro*	Chromosome aberration *in vitro*	Chromosome aberration *in vivo*	Effects on fertility and/or reproductive organs	Developmental toxicity (oral)
Single component – Saturated (12)							
142-62-1	RA to 124-07-2 LD50 oral > 2000	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	**Negative**	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative))	RA to CAS *112-85-6*, NOAEL = 1000 (M/F)	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
111-14-8	RA to 124-07-2	RA to	**Negative**	WOE Single	WOE	RA to CAS *112-85-*	RA to CAS

	LD50 oral > 2000	*CAS 112-85-6* NOAEL = 1000 (42d)		component saturated (negative)	Dicarboxylic acids (negative))	*6*, NOAEL = 1000 (M/F)	*112-85-6*, NOAEL = 1000 (maternal and developmental)
124-07-2	**LD50 oral > 2000, > 5000, > 14700**	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	**Negative**	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative))	RA to CAS *112-85-6*, NOAEL = 1000 (M/F)	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
112-05-0	RA to CAS 124-07-2 and *112-85-6*; >2000	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	WOE Single component saturated (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS *112-85-6*, NOAEL = 1000 (M/F)	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
334-48-5	**LD50 oral > 10000**	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	WOE Single component saturated (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS *112-85-6*, NOAEL = 1000 (M/F)	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
143-07-7	**LD50 oral > 5000, > 10000**	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	WOE Sponsored and Supporting (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS *112-85-6*, NOAEL = 1000 (M/F)	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
544-63-8	**LD50 oral > 10000**	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	WOE Single component saturated (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS *112-85-6*, NOAEL = 1000 (M/F)	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
57-10-3	**LD50 oral > 5000, > 10000**	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	WOE Single component saturated (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS *112-85-6*, NOAEL = 1000 (M/F)	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
506-12-7	RA to CAS 57-10-3; >5000	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	WOE Single component saturated (negative)	WOE Sponsored and Supporting (negative)	WOE Dicarboxylic acids (negative)	RA to CAS *112-85-6*, NOAEL = 1000 (M/F)	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
57-11-4	**LD50 oral > 5000, > 10000**	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	WOE Single component saturated (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS *112-85-6*, NOAEL = 1000 (M/F)	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
30399-84-9	**LD50 oral > 2000**	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	**Negative**	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS *112-85-6*, NOAEL = 1000 (M/F)	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
106-14-9	RA to CAS 30399-84-9; >2000	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	**Negative**	**Negative**	WOE Dicarboxylic acids (negative)	RA to CAS *112-85-6*, NOAEL = 1000 (M/F)	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
Supporting 112-85-6	***LD50 oral > 2000***	***NOAEL = 1000 (42d)***	***Negative***	***Negative***	*No data*	***NOAEL = 1000***	***NOAEL = 1000* (maternal**

							and developmental)
Single component – mono – unsaturated (4)							
544-64-9	RA to CAS 112-80-1; >2000	RA to CAS 112-80-1 NOAEL = 14000 (90d)	RA to 112-80-1 (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS 60-33-3, NOAEL = 467-1970 (M) and *112-85-6*, NOAEL = 1000 (M/F)	RA to CAS 60-33-3 NOEL = 10000
2091-29-4	RA to CAS 112-80-1; >2000	RA to CAS 112-80-1 NOAEL = 14000 (90d)	RA to 112-80-1 (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS 60-33-3, NOAEL = 467-1970 (M) and *112-85-6*, NOAEL = 1000 (M/F)	RA to CAS 60-33-3 NOEL = 10000
112-80-1	**LD50 oral > 2000, > 5000, > 19100**	**NOAEL = 14000 (90d)**	**Negative**	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS 60-33-3, NOAEL = 467-1970 (M) and *112-85-6*, NOAEL = 1000 (M/F)	RA to CAS 60-33-3 NOEL = 10000
112-86-7	**LD50 oral > 5000**	RA to CAS 112-80-1 NOAEL = 14000 (90d)	RA to 112-80-1 (negative)	WOE Single component saturated (negative)	WOE Supporting (negative)	RA to CAS 60-33-3, NOAEL = 467-1970 (M) and *112-85-6*, NOAEL = 1000 (M/F)	RA to CAS 60-33-3 NOEL = 10000
Single component – di – unsaturated (2)							
60-33-3	RA to CAS 112-80-1; >2000	**NOAEL = 467 – 1970 (M, 36wk)**	**Negative**	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	**NOAEL = 467-1970 (M)**	**NOEL = 10,000**
121250-47-3	RA to CAS 112-80-1; >2000	RA to CAS 60-33-3 NOAEL = 467 – 1970 (M, 36wk), and 112-80-1 NOAEL = 14000 (90d)	RA to 112-80-1 (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS 60-33-3, NOAEL = 467-1970 (M) and *112-85-6*, NOAEL = 1000 (M/F)	RA to CAS 60-33-3 NOEL = 10000
Single component – tri – unsaturated (1)							
463-40-1	RA to CAS 124-07-2 and *112-85-6*; >2000	RA to CAS 60-33-3 NOAEL = 467 – 1970 (M, 36wk), and 112-80-1 NOAEL = 14000 (90d)	RA to 112-80-1 (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS 60-33-3, NOAEL = 467-1970 (M) and *112-85-6*, NOAEL = 1000 (M/F)	RA to CAS 60-33-3 NOEL = 10000
Alkyl range sourced based (multi-component) – Saturated (13)							
68603-84-9	RA to CAS 67701-02-4; >2000	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	WOE Single component saturated (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS *112-85-6*, NOAEL = 1000 (M/F)	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
68937-74-6	RA to CAS 67701-02-4; >2000	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	WOE Single component saturated (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS *112-85-6*, NOAEL = 1000 (M/F)	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
67762-36-1	RA to CAS 67701-02-4; >2000	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	WOE Single component saturated (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS *112-85-6*, NOAEL = 1000 (M/F)	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
68937-75-7	RA to CAS 67701-02-4; >2000	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	WOE Single component saturated (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS *112-85-6*, NOAEL = 1000 (M/F)	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
90990-08-2	RA to CAS 90990-11-7; >5000	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	WOE Single component saturated (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS *112-85-6*, NOAEL = 1000 (M/F)	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
68002-90-4	RA to CAS 90990-11-7; >5000	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	WOE Single component saturated (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS *112-85-6*, NOAEL = 1000 (M/F)	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and

							developmental)
90990-10-6	RA to CAS 90990-11-7; >5000	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	WOE Single component saturated (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS *112-85-6*, NOAEL = 1000 (M/F)	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
67701-01-3	RA to CAS 90990-11-7; >5000	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	WOE Single component saturated (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS *112-85-6*, NOAEL = 1000 (M/F)	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
67701-02-4	**LD50 oral > 2000**	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	WOE Single component saturated (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS *112-85-6*, NOAEL = 1000 (M/F)	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
68424-37-3	RA to CAS 90990-11-7; >5000	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	WOE Single component saturated (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS *112-85-6*, NOAEL = 1000 (M/F)	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
67701-03-5	RA to CAS 67701-02-4 and *85711-54-2*; >2000	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	WOE Single component saturated (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS *112-85-6*, NOAEL = 1000 (M/F)	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
68937-76-8	RA to CAS 67701-02-4; >2000	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	WOE Single component saturated (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative))	RA to CAS *112-85-6*, NOAEL = 1000 (M/F)	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
90990-11-7	**LD50 oral > 5000**	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	WOE Single component saturated (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative))	RA to CAS *112-85-6*, NOAEL = 1000 (M/F)	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
Alkyl range sourced based (multi-component) – Unsaturated (1)							
68648-24-8	RA to CAS 67701-06-8; >5000	RA to CAS *61790-12-3* NOAEL = 2500 (90d)	RA to *61790-12-3* (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS *61790-12-3*, NOAEL = 5000 (F0,F1)	RA to CAS *61790-12-3* NOAEL = 5000
Alkyl range sourced based (multi-component) – Mixture of saturated and unsaturated (16)							
68937-85-9	RA to CAS 67701-06-8; >5000	RA to CAS *61790-12-3* NOAEL = 2500 (90d)	RA to *61790-12-3* (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative))	RA to CAS *61790-12-3*, NOAEL = 5000 (F0,F1)	RA to CAS *61790-12-3* NOAEL = 5000
68938-15-8	RA to CAS 67701-06-8; >5000	RA to CAS *61790-12-3* NOAEL = 2500 (90d)	RA to *61790-12-3* (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative))	RA to CAS *61790-12-3*, NOAEL = 5000 (F0,F1)	RA to CAS *61790-12-3* NOAEL = 5000
61788-47-4	RA to CAS 67701-06-8; >5000	RA to CAS *61790-12-3* NOAEL = 2500 (90d)	RA to *61790-12-3* (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS *61790-12-3*, NOAEL = 5000 (F0,F1)	RA to CAS *61790-12-3* NOAEL = 5000
67701-05-7	RA to CAS 67701-06-8; >5000	RA to CAS *61790-12-3* NOAEL = 2500 (90d)	RA to *61790-12-3* (negative)	WOE Sponsored and Supporting (negative)	WOE Dicarboxylic acids (negative)	RA to CAS *61790-12-3*, NOAEL = 5000 (F0,F1)	RA to CAS *61790-12-3* NOAEL = 5000
68918-39-8	RA to CAS 67701-06-8; >5000	RA to CAS *61790-12-3* NOAEL = 2500 (90d)	RA to *61790-12-3* (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS *61790-12-3*, NOAEL = 5000 (F0,F1)	RA to CAS *61790-12-3* NOAEL = 5000
90990-15-1	RA to CAS 67701-06-8; >5000	RA to CAS *61790-12-3* NOAEL = 2500 (90d)	RA to *61790-12-3* (negative)	WOE Sponsored and Supporting (negative)	WOE Dicarboxylic acids (negative)	RA to CAS *61790-12-3*, NOAEL = 5000 (F0,F1)	RA to CAS *61790-12-3* NOAEL = 5000
68334-03-2	RA to CAS 67701-06-8; >5000	RA to CAS *61790-12-3* NOAEL = 2500 (90d)	RA to *61790-12-3* (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS *61790-12-3*, NOAEL = 5000 (F0,F1)	RA to CAS *61790-12-3* NOAEL = 5000
61790-38-3	RA to CAS 67701-06-8; >5000	RA to CAS *61790-12-3* NOAEL = 2500 (90d)	RA to *61790-12-3* (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS *61790-12-3*, NOAEL = 5000 (F0,F1)	RA to CAS *61790-12-3* NOAEL = 5000
67701-06-8	**LD50 oral > 5000**	RA to CAS *61790-12-3*	RA to *61790-12-3* (negative)	WOE Single component	WOE Dicarboxylic	RA to CAS *61790-12-3*,	RA to CAS *61790-12-3*

		NOAEL = 2500 (90d)		saturated (negative)	acids (negative)	NOAEL = 5000 (F0,F1)	NOAEL = 5000
61790-37-2	RA to CAS 67701-06-8; >5000	RA to CAS *61790-12-3* NOAEL = 2500 (90d)	RA to *61790-12-3* (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS *61790-12-3*, NOAEL = 5000 (F0,F1)	RA to CAS *61790-12-3* NOAEL = 5000
68308-53-2	RA to CAS 67701-02-4 and *85711-54-2*; >2000	RA to CAS *61790-12-3* NOAEL = 2500 (90d)	RA to *61790-12-3* (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS *61790-12-3*, NOAEL = 5000 (F0,F1)	RA to CAS *61790-12-3* NOAEL = 5000
68002-87-9	RA to CAS 67701-06-8; >5000	RA to CAS *61790-12-3* NOAEL = 2500 (90d)	RA to *61790-12-3* (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS *61790-12-3*, NOAEL = 5000 (F0,F1)	RA to CAS *61790-12-3* NOAEL = 5000
68440-15-3	RA to CAS 67701-02-4 and *85711-54-2*; >2000	RA to CAS *61790-12-3* NOAEL = 2500 (90d)	RA to *61790-12-3* (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS *61790-12-3*, NOAEL = 5000 (F0,F1)	RA to CAS *61790-12-3* NOAEL = 5000
67701-07-9	RA to CAS 67701-06-8; >5000	RA to CAS *61790-12-3* NOAEL = 2500 (90d)	RA to *61790-12-3* (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS *61790-12-3*, NOAEL = 5000 (F0,F1)	RA to CAS *61790-12-3* NOAEL = 5000
67701-08-0	**LD50 oral > 5000**	RA to CAS *61790-12-3* NOAEL = 2500 (90d)	RA to *61790-12-3* (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS *61790-12-3*, NOAEL = 5000 (F0,F1)	RA to CAS *61790-12-3* NOAEL = 5000
61789-45-5	RA to CAS 67701-06-8; >5000	RA to CAS *61790-12-3* NOAEL = 2500 (90d)	RA to *61790-12-3* (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS *61790-12-3*, NOAEL = 5000 (F0,F1)	RA to CAS *61790-12-3* NOAEL = 5000
Supporting 61790-12-3	***LD50 oral > 10000***	***NOAEL = 2500 (90d)***	***Negative***	*No data*	*No data*	***NOAEL = 5000 (F0,F1)***	***NOAEL = 5000***
Supporting 85711-54-2	***LD50 oral > 2000***	*No data*	*No data*	*No data*	*No data*	*No data*	*No data*
Dicarboxylic acids (single or multi-component) - Saturated (4)							
Supporting 110-15-6	***LD50 oral = 2260***	***NOAEL = 1700-2100 (13wk)***	***Negative***	***Negative***	*No data*	*No data*	*No data*
Supporting 110-94-1	***LD50 oral = 2750***	***NOAEL = 800 (90d)***	***Negative***	*No data*	***In vivo mouse micronucleus/Negative***	*No data*	***NOAEL (maternal) = 125 Developmental = 1300***
Supporting 124-04-9	***LD50 oral = 5050***	***NOAEL = 2700(M) 63(F) (2yr)***	***Negative***	*No data*	***Negative***	***NOAEL = 2700 (M); 63 (F)***	***NOAEL > 288 (maternal and developmental)***
68937-72-4	RA to CAS 124-04-9; 5050	RA to CAS *110-94-1* NOAEL = 800 (90 d)	WOE Dicarboxylic acids (negative))	WOE Dicarboxylic acids (negative))	WOE Dicarboxylic acids (negative))	RA to CAS *124-04-9* NOAEL = 63 (F) and *693-23-2*, NOAEL = 1000 (M)	RA to CAS *110-94-1* NOAEL = (maternal) = 125 and *124-04-9* (developmental) >288
123-99-9	**LD50 oral > 5000**	RA to CAS *110-94-1* NOAEL = 800 (90 d)	WOE Dicarboxylic acids (negative))	RA to *110-15-6* (negative)	WOE Dicarboxylic acids (negative))	RA to CAS *124-04-9* NOAEL = 63 (F) and *693-23-2*, NOAEL = 1000 (M)	RA to CAS *110-94-1* NOAEL = (maternal) = 125 and *124-04-9* (developmental) >288
111-20-6	**LD50 oral > 2000**	RA to CAS *110-94-1* NOAEL = 800 (90 d)	**Negative**	WOE Dicarboxylic acids (negative))	WOE Dicarboxylic acids (negative))	RA to CAS *124-04-9* NOAEL = 63 (F) and *693-23-2*, NOAEL = 1000 (M)	RA to CAS *110-94-1* NOAEL = (maternal) = 125 and *124-04-9* (developmental) >288
68937-70-2	RA to CAS 111-20-6; >2000	RA to CAS *110-94-1* NOAEL = 800 (90 d)	WOE Dicarboxylic acids (negative))	WOE Dicarboxylic acids (negative))	WOE Dicarboxylic acids (negative))	RA to CAS *124-04-9* NOAEL = 63 (F) and *693-23-2*, NOAEL = 1000 (M)	RA to CAS *110-94-1* NOAEL = (maternal) = 125 and *124-04-9* (developmental) >288

Supporting 693-23-2	***LD50 oral > 3000, > 17000***	***NOAEL = 5000(14d rf), = 1000 (15d)***	***Negative***	*No data*	*No data*	***NOAEL = 1000***	***NOAEL = 1000 (parental and developmental)***
Supporting 871-70-5	***LD50 oral > 5000***	***NOAEL = 1000 (28d), = 1000(14d rf)***	***Negative***	***Negative***	*No data*	*No data*	*No data*
Sodium and potassium salts (single or multi-component) – Saturated (10)							
67762-44-1	RA to CAS 67701-02-4; >2000	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	WOE Single component saturated (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative))	RA to *CAS 112-85-6* NOAEL = 1000	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
1984-06-1	RA to CAS 67701-02-4; >2000	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	WOE Single component saturated (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative))	RA to *CAS 112-85-6* NOAEL = 1000	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
1002-62-6	RA to CAS 67701-02-4; >2000	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	WOE Single component saturated (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative))	RA to *CAS 112-85-6* NOAEL = 1000	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
629-25-4	RA to CAS 67701-02-4; >2000	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	WOE Single component saturated (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative))	RA to *CAS 112-85-6* NOAEL = 1000	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
10124-65-9	RA to CAS 67701-02-4; >2000	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	WOE Single component saturated (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative))	RA to *CAS 112-85-6* NOAEL = 1000	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
91032-12-1	RA to CAS 67701-02-4; >2000	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	WOE Single component saturated (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative))	RA to *CAS 112-85-6* NOAEL = 1000	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
822-12-8	RA to CAS 67701-02-4; >2000	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	WOE Single component saturated (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to *CAS 112-85-6* NOAEL = 1000	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
408-35-5	RA to CAS 67701-02-4; >2000	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	WOE Single component saturated (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to *CAS 112-85-6* NOAEL = 1000	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
68424-38-4	RA to CAS 67701-02-4; >2000	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	WOE Single component saturated (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to *CAS 112-85-6* NOAEL = 1000	RA to CAS Supporting 112-85-6 and 124-04-9
822-16-2	RA to CAS 67701-02-4; >2000	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	WOE Single component saturated (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to *CAS 112-85-6* NOAEL = 1000	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
Sodium and potassium salts (single component) Mono-unsaturated (1)							
143-18-0	RA to CAS 112-80-1; >2000	RA to CAS 112-80-1 NOAEL = 14000 (90d)	RA to 112-80-1 (negative)	WOE Sponsored and Supporting (negative)	WOE Dicarboxylic acids (negative)	RA to CAS 60-33-3, NOAEL = 467-1970 (M) and *112-85-6*, NOAEL = 1000 (M/F)	RA to CAS 60-33-3 NOEL = 10000
Sodium and potassium salts (multi-component) – Mixture of saturated and unsaturated (9)							
61789-30-8	RA to CAS *68424-26-0*; >2000	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	WOE Single component saturated and RA to *61790-12-3* (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS 60-33-3, NOAEL = 467-1970 (M); *112-85-6* and 693-*23-2* , NOAEL = 1000 (M/F)	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
61789-31-9	RA to CAS *68424-26-0*; >2000	RA to *CAS 112-85-6* NOAEL =	WOE Single component saturated and RA to *61790-12-3*	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS 60-33-3, NOAEL = 467-1970 (M); *112-85-6* and	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and

		1000 (42d)	(negative)			693-*23-2* , NOAEL = 1000 (M/F)	developmental)
67701-09-1	RA to CAS *68424-26-0*; >2000	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	WOE Single component saturated and RA to *61790-12-3* (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS 60-33-3, NOAEL = 467-1970 (M); *112-85-6* and 693-*23-2* , NOAEL = 1000 (M/F)	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
67701-10-4	RA to CAS *68424-26-0*; >2000	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	WOE Single component saturated and RA to *61790-12-3* (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS 60-33-3, NOAEL = 467-1970 (M); *112-85-6* and 693-*23-2* , NOAEL = 1000 (M/F)	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
68082-64-4	RA to CAS *68424-26-0*; >2000	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	WOE Single component saturated and RA to *61790-12-3* (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS 60-33-3, NOAEL = 467-1970 (M); *112-85-6* and 693-*23-2* , NOAEL = 1000 (M/F)	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
67701-11-5	RA to CAS *68424-26-0*; >2000	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	WOE Single component saturated and RA to *61790-12-3* (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS 60-33-3, NOAEL = 467-1970 (M); *112-85-6* and 693-*23-2* , NOAEL = 1000 (M/F)	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
8052-48-0	RA to CAS *68424-26-0*; >2000	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	WOE Single component saturated and RA to *61790-12-3* (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS 60-33-3, NOAEL = 467-1970 (M); *112-85-6* and 693-*23-2* , NOAEL = 1000 (M/F)	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
61790-79-2	RA to CAS *68424-26-0*; >2000	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	WOE Single component saturated and RA to *61790-12-3* (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS 60-33-3, NOAEL = 467-1970 (M); *112-85-6* and 693-*23-2* , NOAEL = 1000 (M/F)	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
68002-80-2	RA to CAS *68424-26-0*; >2000	RA to *CAS 112-85-6* NOAEL = 1000 (42d)	WOE Single component saturated and RA to *61790-12-3* (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS 60-33-3, NOAEL = 467-1970 (M); *112-85-6* and 693-*23-2* , NOAEL = 1000 (M/F)	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
Supporting 68424-26-0	***LD50 oral > 2000***	*No data*	*No data*	*No data*	*No data*	*No data*	*No data*
Magnesium and calcium salts (multi-component) - Mixture Saturated and Unsaturated (1)							
64755-01-7	RA to CAS 557-04-0, >10,000	RA to CAS 557-04-0 NOAEL = 4000 (90 d)	RA to CAS 557-04-0 (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS 557-04-0, NOAEL = 4000	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
Magnesium and calcium salts (single component) – Saturated (2)							
542-42-7	RA to CAS 557-04-0, >10,000	RA to CAS 557-04-0 NOAEL = 4000 (90 d)	RA to CAS 557-04-0 (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS 557-04-0, NOAEL = 4000	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
557-04-0	**LD50 oral > 10000 LC50 inh > 2 (60 min)**	**NOAEL = 4000 (90d)**	**Negative**	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	**NOAEL = 4000**	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
Ammonium salts (single component) Saturated (2)							
2437-23-2	RA to CAS *84753-04-8*; >2000	RA to	RA to CAS *84753-04-8* (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS *112-85-6*, NOAEL = 1000 (M/F)	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and

							developmental)
1002-89-7	RA to CAS *84753-04-8*; >2000	*CAS 112-85-6* NOAEL = 1000 (42d)	RA to *84753-04-8* (negative)	WOE Single component saturated (negative)	WOE Dicarboxylic acids (negative)	RA to CAS *112-85-6*, NOAEL = 1000 (M/F)	RA to CAS *112-85-6*, NOAEL = 1000 (maternal and developmental)
Supporting 84753-04-8	***LD50 oral > 2000***	*No data*	***Negative***	*No data*	*No data*	*No data*	*No data*

Multi-component substances presented in red text.

Table 2 Summary of Read Across Approach: Irritation

Substance CAS# (Carbon chain length)	Skin irritation	Eye irritation
Single component – Saturated (12)		
142-62-1 (C6)	**Corrosive**	RA to 124-07-2 Irritating
111-14-8 (C7)	**Irritating**	RA to 124-07-2 Irritating
124-07-2 (C8)	**Corrosive**	**Irritating**
112-05-0 (C9)	RA to 124-07-2 Corrosive	RA to 124-07-2 Irritating
334-48-5 (C10)	**Corrosive**	**Irritating**
143-07-7 (C12)	**Irritating**	**Irritating**
544-63-8 (C14)	**Not irritating**	**Not irritating**
57-10-3 (C16)	**Not irritating**	**Not irritating**
506-12-7 (C17)	RA to 57-10-3 Not irritating	RA to 57-10-3 Not irritating
57-11-4 (C18)	**Not irritating**	**Not irritating**
30399-84-9 (C18, Me branched)	**Irritating**	RA to 57-11-4 Not irritating
106-14-9 (C18 hydroxyl)	RA to 57-11-4 Not irritating	RA to 57-11-4 Not irritating
Supporting 120-87-6 (C18 hydroxyl)	*No data*	***Not irritating***
Single component – mono – unsaturated (4)		
544-64-9 (C14)	RA to 112-80-1 Not irritating	RA to 112-80-1 Not irritating
2091-29-4 (C16)	RA to 112-80-1 Not irritating	RA to 112-80-1 Not irritating
112-80-1 (C18)	**Not irritating**	**Not irritating**
112-86-7 (C22)	**Mildly irritating**	**Not irritating**
Single component – di – unsaturated (2)		
60-33-3 (C18)	RA to 112-80-1 Not irritating	RA to 112-80-1 Not irritating
121250-47-3 (C18)	RA to 112-80-1 Not irritating	RA to 112-80-1 Not irritating
Single component – tri – unsaturated (1)		
463-40-1 (C18)	RA to 112-80-1 Not irritating	RA to 112-80-1 Not irritating
Alkyl range sourced based (multi-component) – Saturated (13)		
68603-84-9 (NA)	RA to 124-07-2 Corrosive	RA to 124-07-2 Irritating
68937-74-6 (NA)	RA to 124-07-2 Corrosive	RA to 124-07-2 Irritating
67762-36-1 (NA)	RA to 124-07-2 Corrosive	RA to 124-07-2 Irritating
68937-75-7 (NA)	RA to 124-07-2 Corrosive	RA to 124-07-2 Irritating
90990-08-2 (NA)	RA to 124-07-2 Corrosive	RA to 124-07-2 Irritating
68002-90-4 (NA)	RA to 334-48-5 Corrosive	RA to 334-48-5 Irritating
90990-10-6 (NA)	RA to 143-07-7 Irritating	RA to 143-07-7 Irritating

67701-01-3 (NA)	RA to 143-07-7 Irritating	RA to 143-07-7 Irritating
67701-02-4 (NA)	RA to 544-63-8 Not irritating	RA to 544-63-8 Not irritating
68424-37-3 (NA)	RA to 544-63-8 Not irritating	RA to 544-63-8 Not irritating
67701-03-5 (NA)	RA to 57-10-3 Not irritating	RA to 57-10-3 Not irritating
68937-76-8 **(NA)**	RA to 57-10-3 Not irritating	RA to 57-10-3 Not irritating
90990-11-7 **(NA)**	RA to 57-11-4 Not irritating	RA to 57-11-4 Not irritating
Alkyl range sourced based (multi-component) – Unsaturated (1)		
68648-24-8 (NA)	RA to 143-07-7 Irritating	RA to 143-07-7 Irritating
Alkyl range sourced based (multi-component) – Mixture of saturated and unsaturated (16)		
68937-85-9 (NA)	RA to 124-07-2 Corrosive	RA to 124-07-2 Irritating
68938-15-8 (NA)	RA to 124-07-2 Corrosive	RA to 124-07-2 Irritating
61788-47-4 (NA)	RA to 124-07-2 Corrosive	RA to 124-07-2 Irritating
67701-05-7 (NA)	RA to 124-07-2 Corrosive	RA to 124-07-2 Irritating
68918-39-8 (NA)	RA to 124-07-2 Corrosive	RA to 124-07-2 Irritating
90990-15-1 (NA)	RA to 143-07-7 Irritating	RA to 143-07-7 Irritating
68334-03-2 (NA)	RA to 143-07-7 Irritating	RA to 143-07-7 Irritating
61790-38-3 (NA)	RA to 544-63-8 Not irritating	RA to 544-63-8 Not irritating
67701-06-8 (NA)	RA to 544-63-8 Not irritating	RA to 544-63-8 Not irritating
61790-37-2 (NA)	RA to 544-63-8 Not irritating	RA to 544-63-8 Not irritating
68308-53-2 (NA)	RA to 544-63-8 Not irritating	RA to 544-63-8 Not irritating
68002-87-9 (NA)	RA to 544-63-8 Not irritating	RA to 544-63-8 Not irritating
68440-15-3 (NA)	RA to 544-63-8 Not irritating	RA to 544-63-8 Not irritating
67701-07-9 (NA)	RA to 57-10-3 Not irritating	RA to 57-10-3 Not irritating
67701-08-0 (NA)	**Not irritating**	**Not irritating**
61789-45-5 (NA)	RA to 57-11-4 Not irritating	RA to 57-11-4 Not irritating
Dicarboxylic acids (single or multi-component) – Saturated (4)		
Supporting 110-15-6 (C4)	RA to 110-94-1 Not irritating	**Severe irritant**
Supporting 110-94-1 (C5)	**Not irritating**	**Irritating**
Supporting 124-04-9 (C6)	**Not irritating**	**Irritating**
68937-72-4 (NA)	RA to 110-94-1 Not irritating	RA to 110-15-6 Severe irritant
123-99-9 (C9)	**Not irritating**	RA to 124-04-9 Irritating
111-20-6 (C10)	RA to 123-99-9 Not irritating	RA to 124-04-9 Irritating
68937-70-2 (NA)	RA to 124-04-9 Not irritating	RA to 124-04-9 Irritating
Supporting 871-70-5 (C18)	*No data*	***Irritating***
Sodium and potassium salts (single or multi-component) – Saturated (10)		
67762-44-1 (NA)	RA to 124-07-2 Corrosive	RA to 124-07-2 Irritating
1984-06-1 (C8)	RA to 124-07-2 Corrosive	RA to 124-07-2 Irritating
1002-62-6 (C10)	RA to 334-48-5 Corrosive	RA to 334-48-5 Irritating
629-25-4 (C12)	RA to 143-07-7 Irritating	RA to 143-07-7 Irritating

10124-65-9 (C12)	RA to 143-07-7 Irritating	RA to 143-07-7 Irritating
91032-12-1 (NA)	RA to 143-07-7 Irritating	RA to 143-07-7 Irritating
822-12-8 (C14)	RA to 544-63-8 Not irritating	RA to 544-63-8 Not irritating
408-35-5 (C16)	RA to 57-10-3 Not irritating	RA to 57-10-3 Not irritating
68424-38-4 (NA)	RA to 57-10-3 Not irritating	RA to 57-10-3 Not irritating
822-16-2 (C18)	RA to 57-11-4 Not irritating	RA to 57-11-4 Not irritating
Sodium and potassium salts (single component) Mono-unsaturated (1)		
143-18-0 (C18)	RA to 57-11-4 Not irritating	RA to 57-11-4 Not irritating
Sodium and potassium salts (multi-component) – Mixture of saturated and unsaturated (9)		
61789-30-8 (NA)	RA to 124-07-2 Corrosive	RA to 124-07-2 Irritating
61789-31-9 (NA)	RA to 124-07-2 Corrosive	RA to 124-07-2 Irritating
67701-09-1 (NA)	RA to 124-07-2 Corrosive	RA to 124-07-2 Irritating
67701-10-4 (NA)	RA to 124-07-2 Corrosive	RA to 124-07-2 Irritating
68082-64-4 (NA)	RA to 124-07-2 Corrosive	RA to 124-07-2 Irritating
67701-11-5 (NA)	RA to 544-63-8 Not irritating	RA to 544-63-8 Not irritating
8052-48-0 (NA)	RA to 544-63-8 Not irritating	RA to 544-63-8 Not irritating
61790-79-2 (NA)	RA to 544-63-8 Not irritating	RA to 544-63-8 Not irritating
68002-80-2 (NA)	RA to 544-63-8 Not irritating	RA to 544-63-8 Not irritating
Magnesium and calcium salts (multi-component) - Mixture Saturated and Unsaturated (1)		
64755-01-7 (NA)	RA to 544-63-8 Not irritating	RA to 544-63-8 Not irritating
Magnesium and calcium salts (single component) – Saturated (2)		
542-42-7 (C16)	RA to 557-04-0 Not irritating	RA to 557-04-0 Not irritating
557-04-0 (C18)	**Not irritating**	**Not irritating**
Ammonium salts (single component) Saturated (2)		
2437-23-2 (C12)	RA to 143-07-7 Irritating	RA to 84753-04-8 Corrosive
1002-89-7 (C18)	RA to 84753-04-8 Not irritating	RA to 84753-04-8 Corrosive
Supporting 84753-04-8 (C18)	***Not irritating***	***Corrosive***

Multi-component substances presented in red text.

Table 3 Summary of Read Across Approach: Biodegradation and Aquatic Toxicity

Substance CAS#	**Water Solubility (mg/L at 25 °C)**	**Biodegradation**	**Fish mg/L (96 h LC50)** [ECOSAR]	**Daphnia mg/L (48 h EC50)** [ECOSAR]	**Algae mg/L (72 h EC50)** [ECOSAR]
Single component – Saturated (12)					
142-62-1	1.03+04 (measured)	RA to 124-07-2 (Readily biodegradable)	**320 (measured) (>100)**	RA to 124-04-9 85.7 (nominal)	RA to 111-20-6 24 h: >10 (nominal), maximum conc tested at limit of solubility; no effects (no hazard at the solubility limit of the test)
111-14-8	2820 (modeled)	RA to 124-07-2 (Readily biodegradable)	RA to 124-07-2 48 h: 57 (nominal)	RA to 124-04-9 85.7 (nominal)	RA to 111-20-6 24 h: >10 (nominal), maximum conc tested at limit of solubility; no effects

					(no hazard at the solubility limit of the test)
124-07-2	789 at 30°C (measured)	**Readily biodegradable**	**48 h: 57 (nominal)**	RA to 124-04-9 85.7 (nominal)	RA to 111-20-6 24 h: >10 (nominal), maximum conc tested at limit of solubility; no effects (no hazard at the solubility limit of the test)
112-05-0	284 at 20°C (measured)	**Readily biodegradable**	**104 (measured)**	RA to 124-04-9 85.7 (nominal)	RA to 111-20-6 24 h: >10 (nominal), maximum conc tested at limit of solubility; no effects (no hazard at the solubility limit of the test)
334-48-5	61.8 (measured)	RA to 112-05-0 (Readily biodegradable)	**48 h: 20 (nominal)**	RA to 111-20-6 >11.6 (measured) (15 nominal, maximum conc tested at limit of solubility; no effects) (no hazard at the solubility limit of test)	RA to 111-20-6 24 h: >10 (nominal), maximum conc tested at limit of solubility; no effects (no hazard at the solubility limit of the test)
143-07-7	4.81 (measured)	**Biodegradable**	**150* (nominal)**	**5.6 mg/L (measured) (WAF, single conc tested; prepared at a Loading Level of 10,000 mg/L**	RA to 693-23-2 EC0 > 5.8 (limit test: highest conc tested was at the WS limit for the test)
544-63-8	1.07 (measured)	RA to 143-07-7 (Biodegradable)	**>100 - < 300* (nominal)**	RA to 61790-38-3 EC0>100* (nominal)	RA to 68242-37-3 >100* (nominal)
57-10-3	0.04 (measured)	**Ultimately biodegradable**	**>1000* (nominal)**	RA to 61790-38-3 EC0>100* (nominal)	RA to 68242-37-3 >100* (nominal)
506-12-7	0.0195 (modeled)	RA to 57-11-4 (Biodegradable)	RA to 57-10-3 >1000* (nominal)	RA to 61790-38-3 EC0>100* (nominal)	RA to 68242-37-3 >100* (nominal)
57-11-4	0.597 (measured)	**Biodegradable**	**>1000* (nominal)**	RA to 112-80-1 EC_0>32* (nominal; no effect at highest conc tested	RA to 871-70-5 >100* (nominal WAF loading level of 100; WAF = 0.14-0.19 measured)
30399-84-9	0.007 (modeled)	**Biodegradable**	**48 h: 13.4* (nominal)**	RA to 112-80-1 EC_0>32* (nominal; no effect at highest conc tested	RA to 871-70-5 >100* (nominal WAF loading level of 100; WAF = 0.14-0.19 measured)
106-14-9	0.3315 (modeled)	**Readily biodegradable**	RA to 120-87-6 *>10000 (nominal)**	RA to 112-80-1 EC_0>32* (nominal; no effect at highest conc tested	RA to 871-70-5 >100* (nominal WAF loading level of 100; WAF = 0.14-0.19 measured)
Supporting 120-87-6	*0.7641 (modeled)*	*No data*	***>10000 (nominal)****	*No data*	*No data*
Single component – mono – unsaturated (4)					
544-64-9	0.94 (modeled)	WOE Single component – mono - unsaturated (readily biodegradable)	RA to 544-63-8 >100 - < 300* (nominal)	RA to 61790-38-3 EC0>100* (nominal)	RA to 68242-37-3 >100* (nominal)

2091-29-4	0.13 (modeled)	WOE Single component – mono - unsaturated (readily biodegradable)	RA to C16 (57-10-3) >1000* (nominal)	RA to 61790-38-3 EC0>100* (nominal)	RA to 68242-37-3 >100* (nominal)
112-80-1	0.01151 (modeled)	**Readily biodegradable**	**>56* (nominal)**	**EC_0>32* (nominal; no effect at highest conc tested**	RA to 871-70-5 >100* (nominal WAF loading level of 100; WAF = 0.14-0.19 measured)
112-86-7	9.491E-05 (modeled)	**Readily biodegradable**	RA to C18 (112-80-1) >56* (nominal)	RA to 112-80-1 EC_0>32* (nominal; no effect at highest conc tested	RA to 871-70-5 >100* (nominal WAF loading level of 100; WAF = 0.14-0.19 measured)
Single component – Di-unsaturated (2)					
60-33-3	C18, 2 double bond; 0.03771 (modeled)	**Biodegradable**	RA to C18 (112-80-1) >56* (nominal)	**55* (nominal, WAF that exceeded WS limit)**	RA to 871-70-5 >100* (nominal WAF loading level of 100; WAF = 0.14-0.19 measured)
121250-47-3	0.0377 (modeled)	RA to 60-33-3 (biodegradable)	RA to C18 (112-80-1) >56* (nominal)	RA to 60-33-3 55* (nominal, WAF that exceeded WS limit)	RA to 871-70-5 >100* (nominal WAF loading level of 100; WAF = 0.14-0.19 measured)
Single component – Tri-unsaturated (1)					
463-40-1	0.124 (modeled)	RA to 60-33-3 (biodegradable)	RA to C18 (112-80-1) >56* (nominal)	RA to 60-33-3 55* (nominal, WAF that exceeded WS limit)	RA to 871-70-5 >100* (nominal WAF loading level of 100; WAF = 0.14-0.19 measured)
Alkyl range sourced based (multi-component) – Saturated (13)					
68603-84-9	1.03E+04 (measured)	RA to 68424-37-3 (moderately biodegradable)	RA to 124-07-2 48 h: 57 (nominal)	RA to 124-04-9 85.7 (nominal)	RA to 111-20-6 24 h: >10 (nominal), maximum conc tested at limit of solubility; no effects
68937-74-6	C6: 1.03E+04 (measured) – C10: 61.8 (measured)	RA to 68424-37-3 (moderately biodegradable)	RA to 334-48-5 48 h: 20 (nominal)	RA to 124-04-9 85.7 (nominal)	RA to 111-20-6 24 h: >10 (nominal), maximum conc tested at limit of solubility; no effects
67762-36-1	C6: 1.03E+04 (measured) - C12: 4.81 (measured)	RA to 68424-37-3 (moderately biodegradable)	**38 (nominal)**	RA to 124-04-9 85.7 (nominal)	RA to 111-20-6 24 h: >10 (nominal), maximum conc tested at limit of solubility; no effects
68937-75-7	C8: 789 at 30 °C – C10: 61.8 (measured)	RA to 68424-37-3 (moderately biodegradable)	RA to 334-48-5 48 h: 20 (nominal)	RA to 111-20-6 >11.6 (measured) (15 nominal, maximum conc tested at limit of solubility; no effects)	RA to 111-20-6 24 h: >10 (nominal), maximum conc tested at limit of solubility; no effects
90990-08-2	C8: 789 at 30 °C – C18: 0.597 (measured)	RA to 68424-37-3 (moderately biodegradable)	RA to 334-48-5 48 h: 20 (nominal)	RA to 111-20-6 >11.6 (measured) (15 nominal, maximum conc tested at limit of solubility; no effects)	RA to 111-20-6 24 h: >10 (nominal), maximum conc tested at limit of solubility; no effects
68002-90-4	C10: 6.18 (measured) – C16: 0.04 (measured)	RA to 68424-37-3 (moderately biodegradable)	RA to 334-48-5 48 h: 20 (nominal)	RA to 111-20-6 >11.6 (measured) (15 nominal, maximum conc tested at limit of solubility; no effects)	RA to 111-20-6 24 h: >10 (nominal), maximum conc tested at limit of solubility; no effects
90990-10-6	C12: 4.81 (measured) – C14: 1.07 (measured)	RA to 68424-37-3 (moderately biodegradable)	RA to 143-07-7 150* (nominal)	RA to 143-07-7 5.6 mg/L (measured) (WAF, single conc tested; prepared at a Loading Level of 10,000	RA to 693-23-2 EC0 > 5.8 (limit test: highest conc tested was at the WS limit for the

				mg/L	test)
67701-01-3	C12: 4.81 – C18: 0.597 (measured)	RA to 68424-37-3 (moderately biodegradable)	RA to 143-07-7 150* (nominal) (>100)	RA to 143-07-7 5.6 mg/L (measured) (WAF, single conc tested; prepared at a Loading Level of 10,000 mg/L	RA to 693-23-2 EC0 > 5.8 (limit test: highest conc tested was at the WS limit for the test)
67701-02-4	C14: 1.07 – C18: 0.597 (measured)	RA to 68424-37-3 (moderately biodegradable)	RA to 544-63-8 >100 - < 300* (nominal)	RA to 61790-38-3 EC0>100* (nominal)	RA to 67701-06-8 96 h: 51* (nominal)
68424-37-3	C14: 1.07 (measured) – C22: 0.016 (modeled)	**Moderately biodegradable**	RA to 544-63-8 >100 - < 300* (nominal)	RA to 61790-38-3 EC0>100* (nominal)	**>100* (nominal)**
67701-03-5	C16: 0.04 (measured) – C18: 0.597 (measured)	RA to 68424-37-3 (moderately biodegradable)	**48 h: >1000* (nominal)**	RA to 95912-82-6 >0.695 (measured WAF; corresponds to 1020 mg/L nominal)	RA to 67701-06-8 96 h: 51* (nominal)
68937-76-8	C16: 0.04 (measured) – C20 3E-04 (modeled)	RA to 68424-37-3 (moderately biodegradable)	RA to 67701-03-5 48 h: >1000* (nominal)	RA to 95912-82-6 >0.695 (measured WAF; corresponds to 1020 mg/L nominal)	RA to 67701-06-8 96 h: 51* (nominal)
90990-11-7	C18: 0.597 (measured) – C22 0.016 (modeled)	RA to 68424-37-3 (moderately biodegradable)	**>100* (nominal)**	RA to 60-33-3 55* (nominal, WAF that exceeded WS limit)	RA to 68424-37-3 >100* (nominal)
Alkyl range sourced based (multi-component) – Unsaturated (1)					
68648-24-8	C12:1 9.12 – C20:1 9.61 E-04 (modeled)	RA 68424-37-3 (moderately biodegradable)	RA to 143-07-7 150* (nominal)	RA to 143-07-7 5.6 mg/L (measured) (WAF, single conc tested; prepared at a Loading Level of 10,000 mg/L	RA to 693-23-2 EC0 > 5.8 (limit test: highest conc tested was at the WS limit for the test)
Alkyl range sourced based (multi-component) – Mixture of saturated and unsaturated (16)					
68937-85-9	C8: 789 at 30 °C – C12: 4.81 (measured)	RA to 143-07-7 (biodegradable)	RA to 334-48-5 48 h: 20 (nominal)	RA to 111-20-6 >11.6 (measured) (15 nominal, maximum conc tested at limit of solubility; no effects)	RA to RA to 111-20-6 24 h: >10 (nominal), maximum conc tested at limit of solubility; no effects
68938-15-8	C8: 789 at 30 °C – C12: 4.81 (measured)	RA to 143-07-7 (biodegradable)	RA to 334-48-5 48 h: 20 (nominal)	RA to 111-20-6 >11.6 (measured) (15 nominal, maximum conc tested at limit of solubility; no effects)	RA to 111-20-6 24 h: >10 (nominal), maximum conc tested at limit of solubility; no effects
61788-47-4	C8: 789 at 30 °C – C12: 4.81 (measured)	RA to 143-07-7 (biodegradable)	RA to 334-48-5 48 h: 20 (nominal)	RA to 111-20-6 >11.6 (measured) (15 nominal, maximum conc tested at limit of solubility; no effects)	RA to 111-20-6 24 h: >10 (nominal), maximum conc tested at limit of solubility; no effects
67701-05-7	C8: 789 at 30 °C – C18: 0.597 (measured) C18:1 0.0115 C18:2a 0.0377 C18:2b 0.0377 C18:3 0.124 (modeled)	RA to 57-11-4 (biodegradable)	RA to 334-48-5 48 h: 20 (nominal)	RA to 111-20-6 >11.6 (measured) (15 nominal, maximum conc tested at limit of solubility; no effects)	RA to 111-20-6 24 h: >10 (nominal), maximum conc tested at limit of solubility; no effects
68918-39-8	C8: 789 at 30 °C – C18: 0.597 (measured) C18:1 0.0115 C18:2a 0.0377 C18:2b 0.0377 C18:3 0.124 (modeled)	RA to 57-11-4 (biodegradable)	RA to 334-48-5 48 h: 20 (nominal)	RA to 111-20-6 >11.6 (measured) (15 nominal, maximum conc tested at limit of solubility; no effects)	RA to 111-20-6 24 h: >10 (nominal), maximum conc tested at limit of solubility; no effects
90990-15-1	C12: 4.81 –C18: 0.597 (measured) C18:1 0.0115 C18:2 8.17	RA to 143-07-7 (biodegradable)	RA to 143-07-7 150* (nominal)	RA to 143-07-7 5.6 mg/L (measured) (WAF, single conc tested; prepared at a	RA to 693-23-2 EC0 > 5.8 (limit test: highest conc tested was at the

	C18:2a 0.0377 C18:2b 0.0377 C18:3 0.124 (modeled)			Loading Level of 10,000 mg/L	WS limit for the test)
68334-03-2	C12: 4.81 (measured) – C20: 3E-04 (modeled) C12:1 9.12 - C20:1 9.611E-04 (modeled)	RA to 143-07-7 (biodegradable)	RA to 143-07-7 150* (nominal)	RA to 143-07-7 5.6 mg/L (measured) (WAF, single conc tested; prepared at a Loading Level of 10,000 mg/L	RA to 693-23-2 EC0 > 5.8 (limit test: highest conc tested was at the WS limit for the test)
61790-38-3	C14: 1.07 – C18 0.597 (measured)	RA to 61790-37-2 (biodegradable)	RA to 61790-37-2 >100* (nominal)	**EC0>100* (nominal)**	RA to 67701-06-8 96 h: 51* (nominal)
67701-06-8	C14: 1.07 – C18: 0.597 (measured) C18:1 0.0115 C18:2a 0.0377 C18:2b 0.0377 C18:3 0.124 (modeled)	**Readily biodegradable**	**>1000* (nominal)**	RA to 61790-38-3 EC0>100* (nominal)	**96 h: 51* (nominal)**
61790-37-2	C14: 1.07 – C18: 0.597 (measured) C16:1 0.133 C18:1 0.0115 C18:2a 0.0377 C18:2b 0.0377 C18:3 0.124 (modeled)	**Biodegradable**	**>100* (nominal)**	RA to 61790-38-3 EC0>100* (nominal)	RA to 67701-06-8 96 h: 51* (nominal)
68308-53-2	C14: 1.07 – C18: 0.597 (measured) C18:1 0.0115 C18:2a 0.0377 C18:2b 0.0377 C18:3 0.124 (modeled)	RA to 61790-37-2 (biodegradable)	RA to 61790-37-2 >100* (nominal)	RA to 61790-38-3 EC0>100* (nominal)	RA to 67701-06-8 96 h: 51* (nominal)
68002-87-9	C14: 1.07 (measured) – C22: 9.491E-05 (modeled)	RA to 61790-37-2 (biodegradable)	RA to 61790-37-2 >100* (nominal)	RA to 61790-38-3 EC0>100* (nominal)	RA to 68242-37-3 >100* (nominal)
68440-15-3	C14: 1.07 – C18: 0.597 (measured) C18:1 0.0115 C18:2a 0.0377 C18:2b 0.0377 (modeled)	RA to 61790-37-2 (biodegradable)	RA to 61790-37-2 >100* (nominal)	RA to 61790-38-3 EC0>100* (nominal)	RA to 67701-06-8 96 h: 51* (nominal)
67701-07-9	C16: 0.04 (measured) – C18:1 0.0115 C18:2a 0.0377 C18:2b 0.0377 C18:3 0.124 (modeled)	RA to 61790-37-2 (biodegradable)	RA to 67701-08-0 300* (nominal)	RA to 95912-82-6 >0.695 (measured WAF; corresponds to 1020 mg/L nominal)	RA to 67701-06-8 96 h: 51* (nominal)
67701-08-0	C16: 0.04 (measured) – C18: 0.597 (measured) C18:1 0.0115 C18:2a 0.0377 C18:2b 0.0377 C18:3 0.124 (modeled)	RA to 61790-37-2 (biodegradable)	**300* (nominal)**	RA to 95912-82-6 >0.695 (measured WAF; corresponds to 1020 mg/L nominal)	RA to 67701-06-8 96 h: 51* (nominal)
61789-45-5	C18: 1 0.0115 C18:2a 0.0377 C18:2b 0.0377 (modeled)	RA to 57-11-4 (biodegradable)	RA to C18 (112-80-1) >56* (nominal)	RA to 112-80-1 EC_0>32* (nominal; no effect at highest conc tested	RA to 871-70-5 >100* (nominal WAF loading level of 100; WAF = 0.14-0.19 measured)
Supporting 95912-82-6	*Poorly soluble*	*No data*	*No data*	***>0.695 (measured WAF; corresponds to 1020 mg/L nominal)***	*No data*
Supporting 61790-12-3	*0.01151 (estimated)*	*No data*	*No data*	*No data*	*No data*
Supporting 85711-54-2	*9.491E-5 (estimated)*	*No data*	*No data*	*No data*	*No data*
Supporting 68953-27-5	*.01513 (estimated)*	*No data*	***110 (nominal)***	*No data*	*No data*
Dicarboxylic acids (single or multi-component) – Saturated (4)					
Supporting 110-15-6	*8.079E5 (measured, Epi EDB)*	*No data*	*No data*	**374.2 (nominal)**	*No data*
Supporting 124-04-9	*3.08E4 (measured, Epi EDB)*	*No data*	***97 (nominal)***	***85.7 (nominal)***	*No data*
68937-72-4	1.19E + 04 (measured)	**Readily biodegradable**	*RA to 124-04-9 97 (nominal)*	RA to 110-15-6 374.2 (nominal)	RA to 111-20-6 24 h: >10 (nominal), maximum conc tested at limit of solubility; no effects

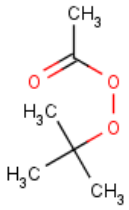
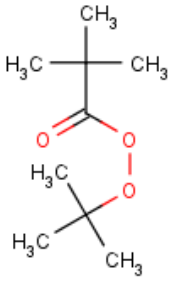
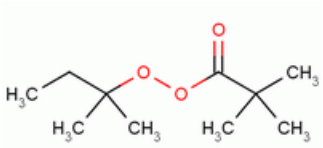
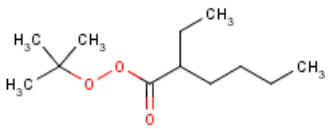
123-99-9	2400 at 20 °C (measured)	**Readily biodegradable**	*RA to 124-04-9 97 (nominal)*	RA to 124-04-9 85.7 (nominal)	RA to 111-20-6 24 h: >10 (nominal), maximum conc tested at limit of solubility; no effects
111-20-6	1000 at 20 °C (measured)	**Readily biodegradable**	**>9.7 (measured) (15 nominal, maximum conc tested at limit of solubility; no effects)**	**>11.6 (measured) (15 nominal, maximum conc tested at limit of solubility; no effects)**	**24 h: >10 (nominal), maximum conc tested at limit of solubility; no effects**
68937-70-2	1.03 E+04 (measured)	**Readily biodegradable**	*RA to 124-04-9 97 (nominal)*	RA to 124-04-9 85.7 (nominal)	RA to 111-20-6 24 h: >10 (nominal), maximum conc tested at limit of solubility; no effects
Supporting 693-23-2	*40 (measured)*	*No data*	*No data*	*No data*	***$EC_0 \geq$ 5.8 (limit test: highest conc tested was at the WS limit for the test)***
Supporting 871-70-5	*0.1485 (modeled)*	*No data*	***> 100* (nominal, WAF loading level of 100; WAF 0.14-0.22, measured)***	***>100* (nominal)***	***>100* (nominal WAF loading level of 100; WAF = 0.14-0.19 measured)***
Sodium and potassium salts (single or multi-component) – Saturated (10)					
67762-44-1	C6 1E+06 - C12 3244 (modeled)	RA to 68424-37-3 (moderately biodegradable)	RA to 1984-06-1 310 (nominal)	RA to 124-04-9 85.7 (nominal)	RA to 111-20-6 24 h: >10 (nominal), maximum conc tested at limit of solubility; no effects
1984-06-1	9.7 E+05 (modeled)	RA 124-07-2 (readily biodegradable)	**310 (nominal)**	RA to 124-04-9 85.7 (nominal)	RA to 111-20-6 24 h: >10 (nominal), maximum conc tested at limit of solubility; no effects
1002-62-6	3.13 E+04 (modeled)	RA 112-05-0 (readily biodegradable)	**54 (nominal; WAF used to test conc <u>above</u> WS limit)**	*RA to 111-20-6* >11.6 (measured) (15 nominal, maximum conc tested at limit of solubility; no effects)	RA to 111-20-6 24 h: >10 (nominal), maximum conc tested at limit of solubility; no effects
629-25-4	3244 (modeled)	RA to 143-07-7 (biodegradable)	**11 (nominal; WAF used to test conc <u>above</u> WS limit)**	*RA to 111-20-6* >11.6 (measured) (15 nominal, maximum conc tested at limit of solubility; no effects)	RA to 91032-12-1 EbC50 = 25; ErC50 = 41 (nominal)
10124-65-9	2656 (modeled)	RA to 143-07-7 (biodegradable)	RA to 629-25-4 11 (nominal; WAF used to test conc above WS limit)	*RA to 111-20-6* >11.6 (measured) (15 nominal, maximum conc tested at limit of solubility; no effects)	RA to 91032-12-1 EbC50 = 25; ErC50 = 41 (nominal)
91032-12-1	C12 3244-C18 3.32	RA *to 91032-09* (readily biodegradable)	RA to 629-25-4 11 (nominal; WAF used to test conc above WS limit)	*RA to 111-20-6* >11.6 (measured) (15 nominal, maximum conc tested at limit of solubility; no effects)	**EbC50 = 25; ErC50 = 41 (nominal)**
Supporting 91032-02-9	**C12-18, potassium**	**Readily biodegradable**	*No data*	*No data*	*No data*
822-12-8	330.8 (modeled)	RA to 143-07-7 (biodegradable)	**118 (nominal)**	*RA to 111-20-6* >11.6 (measured) (15 nominal, maximum conc tested at limit of solubility; no effects)	RA to 693-23-2 EC0 > 5.8 (limit test: highest conc tested was at the WS limit for the test)

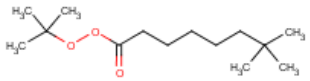
408-35-5	33.3 (modeled)	**Anaerobically biodegradable**	**150* (nominal)**	*RA to 111-20-6* >11.6 (measured) (15 nominal, maximum conc tested at limit of solubility; no effects)	RA to 693-23-2 EC0 > 5.8 (limit test: highest conc tested was at the WS limit for the test)
68424-38-4	C16 33.3 - C18 3.32 (modeled)	RA to 408-35-5 (Anaerobically biodegradable)	RA to 822-16-2 125* (nominal)	RA to 822-16-2 0.57 (nominal)	RA to 871-70-5 >100* (nominal WAF loading level of 100; WAF = 0.14-0.19 measured)
822-16-2	3.32 (modeled)	RA to 57-11-4 (biodegradable)	**125* (nominal)**	RA to 143-18-0 0.57 (nominal)	RA to 871-70-5 >100* (nominal WAF loading level of 100; WAF = 0.14-0.19 measured)
Sodium and potassium salts (single component) - mono-Unsaturated (1)					
143-18-0	4.19 (modeled)	RA to 112-80-1 (readily biodegradable)	**23 (not specified)**	**0.57 (nominal)**	RA to 871-70-5 >100* (nominal WAF loading level of 100; WAF = 0.14-0.19 measured)
Sodium and potassium salts (multi-component) – Mixture of saturated and unsaturated (9)					
61789-30-8	C8 2.48E+05 - C12 2656 (modeled)	RA to 143-07-7 (biodegradable)	RA to 629-25-4 11 (nominal; WAF used to test conc above WS limit)	RA to 124-04-9 85.7 (nominal)	RA to 91032-12-1 EbC50 = 25; ErC50 = 41 (nominal)
61789-31-9	C8 9.67E+05 - C12 3244 (modeled)	RA to 143-07-7 (biodegradable)	RA to 629-25-4 11 (nominal; WAF used to test conc above WS limit)	RA to 124-04-9 85.7 (nominal)	RA to 91032-12-1 EbC50 = 25; ErC50 = 41 (nominal)
67701-09-1	C8 2.48E+05 - C18 2.67 C18:1 4.19 (modeled)	RA to 57-11-4 (biodegradable)	RA to 629-25-4 11 (nominal; WAF used to test conc above WS limit)	RA to 124-04-9 85.7 (nominal)	RA to 91032-12-1 EbC50 = 25; ErC50 = 41 (nominal)
67701-10-4	C8 9.67E+05- C18 3.32 C18:1 5.21 (modeled) C18:2 8.17	RA to 57-11-4 (biodegradable)	RA to 629-25-4 11 (nominal; WAF used to test conc above WS limit)	RA to 124-04-9 85.7 (nominal)	RA to 91032-12-1 EbC50 = 25; ErC50 = 41 (nominal)
68082-64-4	C8 9.67E+05 - C18 3.32 C18:1 5.21 (modeled) C18:2 8.17	RA to 57-11-4 (biodegradable)	RA to 629-25-4 11 (nominal; WAF used to test conc above WS limit)	RA to 124-04-9 85.7 (nominal)	RA to 91032-12-1 EbC50 = 25; ErC50 = 41 (nominal)
67701-11-5	C14 331- C18 3.32 C18:1 5.21 (modeled) C18:2 8.17	RA to 61790-37-2 (biodegradable)	RA to 822-12-8 118 (nominal)	RA to 143-18-0 0.57 (nominal)	RA to 67701-06-8 96 h: 51* (nominal)
8052-48-0	C14 331- C18 3.32 C18:1 5.21 C18:2 8.17 (modeled)	RA to 61790-37-2 (biodegradable)	RA to 822-12-8 118 (nominal)	RA to 143-18-0 0.57 (nominal)	RA to 67701-06-8 96 h: 51* (nominal)
61790-79-2	C14 331- C18 3.32 C18:1 5.21 C18:2 8.17 (modeled)	RA to 61790-37-2 (biodegradable)	RA to 822-12-8 118 (nominal)	RA to 143-18-0 0.57 (nominal)	RA to 67701-06-8 96 h: 51* (nominal)
68002-80-2	C16 26.9- C18 2.67 C18:1 4.19 (modeled)	RA to 68424-37-3 (moderately biodegradable)	*RA to 68424-26-0 54 (nominal)*	RA to 143-18-0 0.57 (nominal)	RA to 871-70-5 >100* (nominal WAF loading level of 100; WAF = 0.14-0.19 measured)
Supporting 68424-26-0	*Likely very soluble*	*No data*	***54 (nominal)***	*No data*	*No data*
Magnesium and calcium salts (Multi-component, Mixture saturated and unsaturated) (1)					

64755-01-7	C14: 9.97E-07 (modeled) - C18: 2.00 at 35°C (measured) C18:1 2.04E-10 (modeled)	RA to 61790-37-2 (biodegradable)	RA to 544-63-8 >100 - < 300* (nominal)	RA to 61790-38-3 EC0>100* (nominal)	RA to 871-70-5 >100* (nominal WAF loading level of 100; WAF = 0.14-0.19 measured)
Magnesium and calcium salts (single component) – Saturated (2)					
542-42-7	9.1 E-09 (modeled)	RA to 57-10-3 (Ultimately biodegradable)	RA to 57-10-3 >1000* (nominal)	RA to 61790-38-3 EC0>100* (nominal)	RA to 871-70-5 >100* (nominal WAF loading level of 100; WAF = 0.14-0.19 measured)
557-04-0	1.045 E-10 (modeled)	RA to 57-11-4 (Biodegradable)	RA TO 30399-84-9 48 h: 13.4* (nominal)	RA to 112-80-1 EC_0>32* (nominal; no effect at highest conc tested	RA to 871-70-5 >100* (nominal WAF loading level of 100; WAF = 0.14-0.19 measured)
Ammonium salts (single component) – Saturated (2)					
2437-23-2	163.1 (modeled)	143-07-7 (Biodegradable)	RA to 629-25-4 11 (nominal; WAF used to test conc above WS limit)	RA to 143-07-7 >11.6 (measured) (15 nominal, maximum conc tested at limit of solubility; no effects)	RA to 91032-12-1 EbC50 = 25; ErC50 = 41 (nominal)
1002-89-7	0.565 (modeled)	RA to 57-11-4 (Biodegradable)	RA to 822-16-6 125* (nominal)	RA to 112-80-1 EC_0>32* (nominal; no effect at highest conc tested	RA to 871-70-5 >100* (nominal WAF loading level of 100; WAF = 0.14-0.19 measured)

Multi-component substances presented in red text.

SIDS INITIAL ASSESSMENT PROFILE

Category name	t-Butyl and t-Amyl Derived Alkyl Peroxyesters
CAS No(s). and Chemical Name(s)	CAS No. 107-71-1 t-Butyl peroxyacetate (**TBPA**) CAS No. 927-07-1 t-Butyl peroxypivalate (**TBPP**) CAS No. 29240-17-3 t-Amyl peroxypivalate (**TAPP**) CAS No. 3006-82-4 t-Butylperoxy-2-ethylhexanoate (**TBPEH**) CAS No. 26748-41-4 Neodecaneperoxoic acid, 1,1-dimethylethyl ester (tert-Butyl peroxyneodecanoate, **TBPN**)
Structural Formula(s)	 **TBPA**  **TBPP**  **TAPP**  **TBPEH**



TBPN

SUMMARY CONCLUSIONS OF THE SIAR

Category rationale

In the t-Butyl and t-Amyl Derived Alkyl Peroxyesters category there are five sponsored substances which are alkyl substituted peroxyesters (derivatives of t-butyl hydroperoxide or t-amyl hydroperoxide with aliphatic structure, the general molecular formula RC(=O)OOR'). The basis of the category is that the category members are structurally similar; the common functional characteristic is the peroxy moiety, The peroxy moiety is expected to define the toxicity of the category members due to its reactivity together with the overall size of the molecule. Trends in physical-chemical properties/reactivity follow structure. The toxicological pattern follows reactivity as well as branching and size of the alkyl groups. Expected trends in ecotoxicity that follow structure are demonstrated.

Table 1. Identification of Alkyl Substitutions

Alkyl Substituted Peroxyesters	R	R'	R Group Characteristi
TBPA	CH_3	$(CH_3)_3C$	aliphatic
TBPP	$(CH_3)_3C$	$(CH_3)_3C$	aliphatic
TAPP	$(CH_3)_3C$	$CH_3CH_2(CH_3)_2C$	aliphatic
TBPEH	C_7H_{15}	$(CH_3)_3C$	aliphatic
TBPN	C_9H_{19}	$(CH_3)_3C$	aliphatic

As mentioned before, this category consists of five substances[1], and not chemicals. Some of these substances require the presence of a diluent to remain stable (a diluent is an ingredient used to reduce the concentration of an active ingredient to achieve the desired effect of keeping the temperature down, and may also be referred to as a heat sink, which is a reservoir that absorbs heat as energy). The maximum concentration of organic peroxide with the minimum amount of diluent needed for transport would be considered a substance. Any further dilution would be considered a formulation.

Data for the sponsored substances including diluents are used to fill physical chemical, fate, mammalian and aquatic toxicity endpoints. **TBPEH** is stable as an isolated substance and has been tested without diluent. **TBPN** can be produced and used as both an isolated substance or with diluent. It is very thermally sensitive but not high in energy due to the large molecular size. **TBPN** was tested with and without diluent.

Typically, the highest concentration possible or commercially available would be tested, unless otherwise specified.

- **TBPA** – 50%
- **TBPP** – 75%
- **TAPP** –75%
- **TBPEH** – 98-100%

[1] **Substance:** A chemical element and its compounds, either in its natural state or obtained by any manufacturing process, including any additive necessary to preserve its stability and any impurity deriving from the process used, but excluding any diluent which may be separated without affecting the stability of the substance or changing its composition.

- **TBPN** – 98-100% (as UVCB)

It is impracticable to test all category members with all diluents for all endpoints. The effect of the diluent on the physical chemical, fate, mammalian and aquatic toxicity endpoints is not known. In most cases the diluent does not appear to significantly influence the results when compared to sponsored substances tested in the absence of diluent. Therefore the available information is considered representative for all category members, which are considered more like substances (with all belonging additives and impurities) than pure chemicals.

Identification of Diluents used for Testing

Substance	Physical chemical	Human health	Fate	Environmental toxicity
TBPA (50% in diluent)	Partition coefficient: isododecane[a]	Skin sensitization & OECD 422: isododecane. Acute and repeated dose inhalation: Shellsol T[c]. In vivo micronucleus: aliphatic hydrocarbon diluent[b]	Biodegradation: isododecane	No data located
TBPP (75% in diluent)	Vapor pressure: diluent not specified but likely isododecane.	Eye irritation: Shellsol T. Skin irritation: Shellsol T or isodecane. Skin sensitization: isododecane. Ames: isododecane. OECD 422: 75% isododecane.	Biodegradation: isododecane	Activated sludge and fish: isododecane
TAPP (75% in diluent)	Water solubility: diluent not specified but likely isododecane.	Eye & skin irritation, acute oral & inhalation toxicity: diluent not specified but likely Shellsol T or isododecane. Ames & in vivo micronucleus: aliphatic hydrocarbon diluent[b]	Biodegradation: isododecane	No data located
TBPEH (100%)	No diluent	No diluent	No diluent	No diluent
TBPN (75% in diluent)	Partition coefficient & Vapor pressure: 100% (no diluent)	Eye irritation & acute oral: Shellsol T. Skin irritation: Shellsol T or isododecane. Skin sensitization & Ames: diluent not specified but likely isododecane. In vivo micronucleus: isododecane.	Biodegradation: isododecane	Acute daphnia: isododecane. Chronic daphnia: 100% (no diluent)

a CAS 31807-55-3 or 93685-81-5

b CAS 64742-48-9; (Napththa (petroleum) heavy, or C10 -12 alkane/cycloalkane)

c CAS 64741-65-7; (Napththa (petroleum) heavy alkylate, if it contains >0.1% w/w benzene

The data as presented herein is considered indicative for the organic peroxides in the diluent as tested. Additionally, the data is considered indicative for the organic peroxides in alternate diluents that are not more hazardous than the tested diluent.

Reactivity and thermal decomposition

Organic peroxides contain an unstable O-O bond, and as such these substances are used as free radical formers to initiate reactions (opening of vinylic bonds, abstraction of hydrogen, etc.). Most organic peroxides are used at levels of less than 1% in an industrial setting. Formation of free radicals through the cleavage of the O-O bond is typically accomplished by increasing the temperature. Peroxyesters are a class of organic peroxides that are relatively unstable under basic or acidic conditions in the presence of water, which catalyzes the cleavage of the peroxyester molecule to form an organic acid and conjugate hydroperoxide.

TBPA, **TBPP**, and **TAPP** are unstable at room temperature (subject to thermal decomposition) and cannot be manufactured in the absence of diluent (which serves as a heat sink, and can be described as a reservoir that absorbs heat as energy). For example, **TBPA** violently decomposes (explodes) in an almost instantaneous chain reaction when its temperature is raised rapidly. However, the rates of thermal decomposition at low concentration at room temperature are slow when considering factors critical for rates of disappearance. When products are diluted, the same

heat of decomposition results in lower temperature rises, which moderates the rate of reaction. These same explosive properties can be expected for **TBPP** and **TAPP**. In diluent, **TBPA**[2], **TBPP**, and **TAPP** are stable and not expected to be reactive. **TBPEH** is stable and can be produced in the absence of diluent. **TBPN** is very thermally sensitive but not high in energy due to the large molecule; it is produced and used with and without diluents.
Thermal decomposition proceeds via a radical mechanism:

R-C(=O)OOR' → R(.) (radical) + CO2 + R'O(.) (radical)

This reaction is integral to how these peroxyesters are used. The rate at which thermal degradation occurs varies with the stability of the corresponding radical products. The radicals formed initiate other reactions with whatever chemicals (or biomolecules) are in the immediate vicinity. Commonly, radicals will abstract a hydrogen atom and form the stable organic R-H and R'O-H compounds as by-products.

Chemical/physical properties

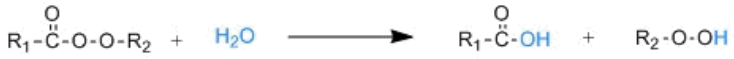
Water solubility and partition coefficients of the category members follow an expected trend associated with size of the alkyl substitution. That is, water solubility decreases and log K_{ow} increases from the smallest category member (**TBPA**) to the largest category member (**TBPN**).

	TBPA	**TBPP**	**TAPP**	**TBPEH**	**TBPN**
Log Kow	1.6	3.17	3.3	4.79	5.1 – 5.4
WS (mg/L)	20000	1490	815	46.3	9

All of the category members decompose (via thermal reaction), are volatile (based on estimated and extrapolated vapour pressures and estimated Henry's Law constants) and hydrolyze in water (or, are expected to hydrolyze in water).

Peroxyesters are a class of organic peroxides that are relatively unstable under basic or acidic conditions in the presence of water, which catalyzes the cleavage of the peroxyester molecule to form an organic acid and conjugate hydroperoxide.

The t-Butyl and t-Amyl Derived Alkyl Peroxyesters are expected to hydrolyze in the same manner. A general hydrolysis reaction scheme of a peroxyester is shown below.



The respective acids and hydroperoxides expected to be formed from hydrolysis of each of the category members follow:

Substance	**Expected Acid hydrolysis product**	**Expected Hydroperoxide hydrolysis product**
TBPA	Acetic (CAS No. 64-19-7) (1)	tert-Butyl hydroperoxide (CAS No. 75-91-2)
TBPP (75% in aliphatic diluent)	Pivalic (CAS No. 75-98-9)	tert-Butyl hydroperoxide (CAS No. 75-91-2)
TAPP	Pivalic (CAS No. 75-98-9) (1)	tert-Amyl hydroperoxide (CAS No. 3425-61-4)
TBPEH (technically pure)	2-ethyl hexanoic (CAS No. 149-57-5) (1)	tert-Butyl hydroperoxide (CAS No. 75-91-2)
TBPN (technically pure)	Neodecanoic (CAS No. 26896-20-8) (1)	tert-Butyl hydroperoxide (CAS No. 75-91-2)

(1) Data for the acid hydrolysis products are available. Acetic acid has been assessed in the U.S. HPV Challenge Program

[2] TBPA has a high concentration of active oxygen due to the small molecule size. The heat of decomposition is related to the central O-O bond. With a small molecule such as TBPA, the heat of decomposition results in higher temperatures, which leads to more rapid rates, and behaving like the other substances in the absence of diluent.

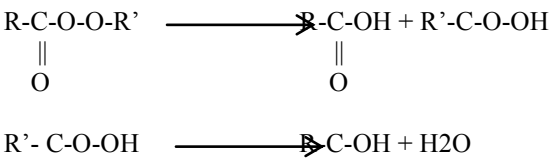
http://www.epa.gov/hpv/pubs/summaries/acetisalt/c13102tp.pdf. 2-Ethylhexanoic acid has previously been assessed in the OECD HPV Program. The SIDS Dossier for 2-Ethylhexanoic acid will be available for review on the UNEP website when published. Pivalic and neodecanoic acid have been assessed as part of the NeoAcids C5-C28 category in the U.S. HPV Challenge Program (http://www.epa.gov/hpvis/hazchar/Category_C5-C28%20%20Neoacids_HC_August%202007.pdf). The Hydroperoxides Category (Cumyl hydroperoxide (CHP) 80-15-9 and t-Amyl hydroperoxide (TAHP) 3425-61-4; was discussed and agreed at SIAM 27 http://webnet.oecd.org/Hpv/ui/handler.axd?id=9d4c8a7a-3ef6-467e-a05d-523c348371c3). t-Butyl hydroperoxide (TBHP) 75-91-2 was used as an analogue substance for the Hydroperoxides Category and was presented and agreed upon at SIAM 1; full documentation can be accessed at http://www.inchem.org/pages/sids.html.

Peroxidase activity

Peroxidases are enzymes that act as catalysts to promote the oxidation of substances. Peroxidases act on naturally occurring peroxides (such as hydrogen peroxide) forming an acid, alcohol and water as shown below.

ROOR' + electron donor (2 e-) + 2H+ → ROH + R'OH

For peroxyesters:



Peroxidases are commonly found in plants and animals, including humans. The category members are expected to be oxidized by naturally occurring peroxidases, resulting in the cleavage of the O-O bond. The expected metabolic products of the t-Butyl and t-Amyl Derived Alkyl Peroxyesters are the aliphatic acids (acetic, for **TBPA**; pivalic, for both **TBPP** and **TAPP**; 2-ethylhexanoic, for **TBPEH** and neodecanoic, for **TBPN**) and the corresponding hydroperoxide (t-butyl or t-amyl hydroperoxide). The peroxidase will also cleave the O-O bond of the hydroperoxide to form water and the corresponding alcohol (butanol or t-amyl alcohol).

Toxicological Properties

Toxicological mode of action of the category members is very complex due to their reactivity, differences in size and branching, multiple mechanisms involved in kinetics, and presence or absence of diluents.

Therefore, the toxicological pattern is not always consistent for irritation (all compounds produce some degree of skin irritation but not eye irritation; TBPA did not produce enough irritation to consider it a skin irritant but was irritating to the eye).

Effects observed in repeated dose toxicity studies reflect the levels of oxidative/corrosive damage that follows the structure. That is, as the branching of the alkyl group increases, the reactivity of the molecule decreases (shielding effect). TBPA is expected to be the most reactive substance in the category, and results of repeated oral exposure illustrate this effect, with observations of unspecific oxidative damage through the GI tract. The size of the alkyl groups is expected to influence systemic toxicity. The smallest substance (TBPA) is least toxic to kidney (only increased kidney weights were observed; as the size of the alkyl groups increase, more severe kidney toxicity is observed (for example, with TBPN).

Mutagenicity tests showed mixed or inconclusive results. Therefore, the closest analog approach was used for read across. The category members are all reproductive toxicants (effects on fertility and developmental effects).

As this is data rich category, there is enough information to fill in data gaps (Repeated dose and reproductive toxicity for TAPP and mutagenicity for TBPA).

Thermal decomposition with free radical formation is not expected to play role in mechanism of toxicity. The anticipated routes in the body are enzymatic and hydrolytic. Therefore, living organisms will be exposed to a mixture of parent compound, hydrolysis products and oxidation (peroxidases) metabolites.

Environmental Fate and Effects

The acute aquatic toxicity and estimated bioconcentration factors of the t-Butyl and t-Amyl Derived Alkyl Peroxyesters increase with decreasing water solubility and increasing partition coefficient. The category members are not readily biodegradable.

Read Across Strategy

The read across strategy is presented below. Taking a precautionary approach, category members without toxicity or environmental fate data are regarded the same as the closest analogue. For hydrolysis, estimations from EPIWIN were also taken into account for the proposal of the half-life time value.

Read Across Strategy

Substance		Endpoint						
	Hydrolysis	**Fish**	**Aquatic invertebrates**	**Algae**	**Skin and eye irritation**	**Repeated dose**	***In vitro* gene mutation**	**Repro. toxicity**
TBPA[(1)]	READ ACROSS FROM **TBPP**	READ ACROSS FROM **TBPP**	READ ACROSS FROM **TBPP**	X	READ ACROSS FROM **TBPP**	X (in aliphatic diluent)	READ ACROSS FROM **TBPP**	X (in aliphatic diluent)
TBPP	X (in aliphatic diluent)	X (in aliphatic diluent)	X (in aliphatic diluent)	X (in aliphatic diluent)	X (in aliphatic diluent)	X (in aliphatic diluent)	X (in aliphatic diluent)	X (in aliphatic diluent)
TAPP[(2)]	READ ACROSS FROM **TBPP**	READ ACROSS FROM **TBPP**	READ ACROSS FROM **TBPP**	READ ACROSS FROM **TBPP**	X (in aliphatic diluent)	READ ACROSS FROM **TBPP**	X (in aliphatic diluent)	READ ACROSS FROM **TBPP**
TBPEH	X (technically pure)	X (technically pure)	X (technically pure)	X (technically pure)	X (technically pure)	X (technically pure)	X (technically pure)	X(technically pure)
TBPN	X (technically pure)	X (technically pure)	X (in aliphatic diluent)	X (technically pure)	X (in aliphatic diluent)	X (technically pure)	X (in aliphatic diluent)	X (technically pure)

X = data available

[(1)]No data were available for TBPA. Taking into account physical-chemical properties (log Kow, water solubility and Vp) and the structural similarities, the closest analogue for read-across is TBPP.

[(2)]No data were available for TAPP. Taking into account physical-chemical properties (log Kow, water solubility and Vp) and the structural similarities, the closest analogue for read-across is TBPP.

Physical-chemical Properties

The t-Butyl and t-Amyl Derived Alkyl Peroxyesters are liquids, with measured melting points of <-22 ^{o}C for **TBPA** (75% in aliphatic diluent), -20 ^{o}C (measured/estimated not specified) for **TBPP** (75% in aliphatic diluent), <-25 ^{o}C (measured/estimated not specified) for **TAPP** (75% in aliphatic diluent), -67.6 to -66.2 ^{o}C for **TBPEH** (technically pure) and <-25 ^{o}C for **TBPN** (technically pure). A measured boiling point was located for **TBPA** (50-51°C, 50% in aliphatic diluent); the remaining category members decompose. Measured vapor pressures are 5.2 hPa at 21.2 ^{o}C for **TBPA** (75% in aliphatic diluent), 18 hPa at 18 ^{o}C (measured/estimated not specified) for **TBPP** (pure or in diluent not specified), 4.13 hPa at 10 ^{o}C for TAPP (75% in aliphatic diluent), and 0.02 hPa at 20 ^{o}C (for **TBPEH (**technically pure); **TBPP** and **TBPN** form thermal decomposition products at room temperature. Measured water solubility correlates well with structure (the longest chains result in the lowest water solubility values): 20,000 mg/L at 25^{o}C for **TBPA** (75% in aliphatic diluent), 1490 mg/L for **TBPP** (75% in aliphatic diluent), 815 mg/L for **TAPP** (75% in isododecane), 46.3 mg/L at 20 ^{o}C for **TBPEH** (technically pure) and 9 mg/L at ^{o}C for **TBPN** (technically pure). Measured data on the log Kow are available for all members. The log Kow values are 1.6 (temperature not specified) for **TBPA** (51% in aliphatic diluent), 3.17 (temperature not specified) for **TBPP** (75% in aliphatic diluent), 3.3 (temperature not specified) for **TAPP** (75% in aliphatic diluent), 4.79 at 25°C for **TBPEH** (technically pure) and 5.1 - 5.4 at 25°C for **TBPN** (technically pure).

Human Health

In many cases, and, consistent with standard procedures for acute toxicity studies, concentrations or doses used in these studies were not analytically verified (or it is unknown whether they were measured). In addition, these compounds have moderate to significant volatility, may thermally decompose (sometimes at room temperature), and may hydrolyze to some degree. Therefore, actual concentrations or doses that the animals were exposed to may be lower than those reported.

Toxicokinetics data are not available.

Peroxyesters are a class of organic peroxides that are relatively unstable under basic or acidic conditions in the presence of water, catalyses the cleavage of the peroxyester molecule to form an organic acid and conjugate hydroperoxide. The category members are also expected to be oxidized by naturally occurring peroxidases, resulting in the cleavage of the O-O bond.

Acute toxicity

Acute inhalation toxicity studies were located for all category members. Male and female rats were exposed to **TBPA** (75% in mineral spirits) by whole body aerosol/vapor inhalation exposure for four hours. Damage of the eyes and upper respiratory tract irritation were noted, and effects on the lungs were observed at necropsy. The 4 hour LC_{50} was 6.1 mg/L.
Male and female rats were exposed to **TBPP** (75% in mineral spirits) by whole body aerosol inhalation for four hours. Upper respiratory tract irritation was observed, and effects on the lung and liver were noted at necropsy. The 4 hour LC_{50} was 7.79 mg/L.
Male and female rats were exposed to **TAPP** (75% in mineral spirits) by whole body aerosol inhalation exposure for four hours. Upper respiratory tract irritation was noted. The 4 hour LC_{50} was > 9.5 mg/L.
Male and female rats were exposed to **TBPEH** (technically pure) by whole body aerosol inhalation for four hours. Clinical signs of skin and upper respiratory tract irritation were noted, and effects on the lungs were noted at necropsy. The 4 hour LC_{50} was 42.2 mg/L.
Male and female rats were exposed to **TBPN** (75% in mineral spirits) by whole body inhalation exposure for four hours. Clinical signs of eye and upper respiratory tract irritation and neurological effects were noted, and effects on the lung and liver were noted at necropsy. The 4-hour LC_{50} was 40.6 mg/L in males and 64.8 mg/L in females. The combined LC_{50} for both sexes was 50 mg/L.

The acute dermal LD_{50}s [similar to OECD TG 402] for rabbits were > 2000 mg/kg bw for **TBPP** and **TAPP** (both in aliphatic diluent)**.** Dermal irritation and necrosis were observed at the site of contact for **TBPP**; poor condition, body weight loss were noted for **TAPP**.

The acute oral LD_{50}s [similar to OECD TG 401] for rats were > 2000 mg/kg bw of **TAPP**, **TBPEH**, and **TBPN** (all in aliphatic diluent) and technically pure **TBPEH.** Signs of toxicity reported for **TAPP** and **TBPN** were generally associated with poor condition (decreased activity, ataxia, diarrhea, lacrimation, urinary incontinence, discharge around eyes and/or nose and salivation). Additional information (signs of toxicity) for **TBPEH** was not located in the study report.

Irritation

TBPP (75% in diluent), **TAPP** (purity not specified), **TBPEH** (technically pure), and **TBPN** (75% dilution in Shellsol T) are irritating to rabbit skin [similar to OECD TG 404], although **TBPA** (75% in diluent) was not irritating to the skin.
TBPP (75% in diluent), **TAPP** (purity not specified), **TBPN** (75% dilution in Shellsol T), and **TBPEH** (technically pure) are not eye irritants [similar to OECD TG 405]. **TBPA** (75% in diluent) was found to be an eye irritant.
It should be noted that acute inhalation studies indicate that eye irritation may be expected from a continuous airborne exposure to peroxyesters.
Acute inhalation toxicity studies [similar to OECD TG 403] suggest **TBPA**, **TBPP**, and **TBPN** (in aliphatic hydrocarbon diluent) are respiratory irritants in rats, while **TAPP** is not a respiratory irritant at the concentrations tested. The results would indicate that technically pure TBPEH is a respiratory irritant in rats. .

Skin Sensitization

TBPA (50% in Aromatic Free Mineral Spirits), **TBPP** (75% in Aromatic Free Mineral Spirits), **TAPP** (75% in isododecane), **TBPN** (75% in unspecified diluent), were all positive in a guinea pig maximization study (OECD TG 406). **TBPEH** (technically pure) was positive in a Buehler test. Therefore, all category members are considered skin sensitizers.

Repeated Dose Toxicity

In a Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OECD TG 422), rats received 0, 100, 300 and 1000 mg/kg bw/day of **TBPA** (in aliphatic diluent) via oral gavage. Three male animals died at 1000 mg/kg bw/day. Mean food consumption and body weights were decreased at various points of the study in all **TBPA**-exposure groups. Clinical chemistry changes included an increase total leukocyte count, increase of absolute and relative neutrophils, and increase of platelets in males at 1000 mg/kg bw/day.
At 1000 mg/kg bw/day, the liver, brain, heart, kidneys, adrenals, and spleen, testes and thymus weights were increased, and epididymides weights were decreased. At 300 mg/kg bw the relative liver and testes weight was increased.
Findings at necropsy for males in the 1000 mg/kg bw/day group included a thickened mucosa of the forestomach, a dilated duodenum, reddish discoloured mesenteric lymph nodes, or a thymus reduced in size. In females at 1000 mg/kg bw/day, fibrin-like coated or enlarged spleen, the forestomach with a red brown mucosa, thickened mucosa of duodenum and jejunum, discolouration of mesenteric lymph node and diaphragm adherent to the stomach were observed. Microscopic changes were observed in the stomach, duodenum, jejunum, ileum (males), liver, bone marrow, spleen, lymphatic organs and reproductive organs (males) at 1000 mg/kg bw. The stomach was also affected in animals at 100 and 300 mg/kg bw/day, the duodenum and jejunum at 1000 mg/kg bw/day, and in females the duodenum was affected at 1000 mg/kg bw/day.
The No Observed Adverse Effect Level (NOAEL, systemic, based on liver weight changes) for **TBPA** was 300 mg/kg bw. The Lowest Observed Adverse Effect Level (LOAEL, local, based on histopathological findings in the gastrointestinal tract) for parental animals was 100 mg/kg bw.

In a Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OECD TG 422), rats received 0, 50, 150, and 310 mg/kg bw/day of **TBPP** (75% in isododecane, sunflower oil used as vehicle) via oral gavage. There were no deaths. Salivation was observed in the 310 and 150 mg/kg bw/day groups. Body weight gain was reduced at 310 mg/kg bw/day. The mean daily food consumption was reduced at 310 and 150 mg/kg bw/day doses. There were no effects on hematology or clinical chemistry parameters in male animals. In the female animals treated with 310 mg/kg bw/day, the glucose concentration was significantly reduced. There were no macroscopic or microscopic findings. Mean kidney weights (absolute and relative to body and brain weights) were slightly increased in male animals at 310 mg/kg bw/day. The NOAEL for male and female rats for **TBPP** was 150 mg/kg bw/day based on increased kidney weights in males (with minimal decreased body weight) as well as decreased body weight and glucose levels in females.

In a Repeated Dose 28-Day Oral Toxicity in Rodents (OECD TG 407), rats received technically pure **TBPEH** (in corn oil) at 0, 100, 316, 1000 mg kg/bw/day. High dose and control recovery group animals were included in the study design. There were no deaths, clinical signs, or effects on body weights, food or water consumption. There was a decrease in the number of platelets in the blood of the mid- and the high-dose females, and an increase in alkaline phosphatase levels in the high-dose females (including recovery animals). Increased liver weights (absolute and relative to body or brain weights) were observed for male and female high dose animals; this finding was not noted in the recovery group animals. Increased kidney weights were observed in high dose males (relative to brain weight) and high dose females (relative to body weight); this finding was not noted in the recovery group animals. There were no gross or histopathological findings. The NOAEL for **TBPEH** is 316 mg/kg bw/day (males, based on increased liver and kidney weights) and 100 mg/kg bw/day (females, based on decreased platelet counts).

In a Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OECD TG 422), rats received technically pure **TBPN** by oral gavage at 0, 60, 200, and 600 mg/kg bw/day (sunflower oil used as vehicle). There were no deaths. Salivation was seen at all doses. Reduced body weight gain and reduced body weight was observed at 200 and 600 mg/kg bw, and decreased food consumption was observed at 600 mg/kg bw. At 600 mg/kg bw/d, females exhibited decreased hemoglobin concentration and hematocrit, increased reticulocytes; in males, clinical chemistry changes included increased alanine aminotransferase activity, increased creatinine concentration, inorganic phosphorous, potassium, and lower aspartate aminotransferase activity and lower concentrations of total bilirubin and calcium. Females exhibited higher activities of alanine aminotransferase and alkaline phosphatase, as well as higher urea and potassium concentrations. At 200 mg/kg bw, increased percentage of reticulocytes, higher mean activity of alanine aminotransferase and higher mean serum levels of urea was observed in females. At 60 mg/kg bw, an increased percentage of reticulocytes, and lower activity of aspartate aminotransferase and total bilirubin (males) were seen. At 600 mg/kg bw, liver weights, both absolute and relative, were higher in both sexes. Males also had higher absolute and relative kidney weights and relative testes weights, as well as decreased

thymus and adrenal weights (both absolute and relative). Females had decreased relative brain, kidney and heart weights. At 200 mg/kg bw, increased kidney weights and hyaline droplet nephropathy of male rats, increased liver weights in female animals were observed. Both sexes had higher absolute and relative liver weights. Males also had higher relative and absolute kidney weights and higher relative testes and spleen weights. Females also had decreased relative brain and kidney weights. At 60 mg/kg bw, increased liver weight in female animals was observed. Enlarged and pale kidneys were seen in males at 600 mg/kg bw. Histopathological evaluation of males at all doses revealed hyaline-like droplets in epithelial cells of proximal convoluted tubules, segmental tubular basophilia, and slight inter-tubular lymphocytic infiltration/dilation of tubuli in cortical – medullary region, with decreased frequency at lower doses. Minimal alveolar emphysema and mild hyperplasia of the bronchus associated lymphoid tissue were seen in some rats (both sexes).
Although it is possible that the kidney effects in males were due to α-2u globulin accumulation (a male rat specific effect), specific information was lacking on the identification of this particular protein. In addition, effects on total bilirubin and decreased aspartate aminotransferase were observed in males at this dose; due to these effects, no NOAEL could be established for males and the LOAEL is 60 mg/kg bw/day. For females, the NOAEL for **TBPN** is 60 mg/kg bw/day, based on effects on body weight, haematology, clinical chemistry and organ weights at 200 mg/kg bw/day.

A repeated dose study was not located for **TAPP**; the estimated repeated dose NOAEL is 150 mg/kg bw, based on the OECD TG 422 study with **TBPP**, considered to be the closest structural analogue.

Mutagenicity

Positive and negative results for gene mutation studies *in vitro* (bacterial and mammalian cells; similar to OECD TG 471 and 476, respectively) have been reported for the t-Butyl and t-Amyl Derived Alkyl Peroxyesters. *In vitro* studies were not located for **TBPA**.
TBPP was negative in one OECD TG 471 study (in aliphatic hydrocarbon diluent, % not specified), positive in a second OECD TG 471 study (75% in aliphatic diluent), and negative in an OECD TG 476 study (75% in aliphatic hydrocarbon diluent); based on weight of evidence (negative result in a mammalian gene mutation test) **TBPP** is considered to be a gene mutagen *in vitro*. **TAPP** (in aliphatic hydrocarbon diluent, % not specified) was positive in an OECD TG 471 study. **TBPEH** (technically pure) was positive in one OECD TG 471 study, negative in a second OECD TG 471 study and positive in an OECD TG 476 study. **TBPN** (74.7% in unspecified diluent) was positive in OECD TG 471 study and was negative in an OECD 476 study (technically pure). Based on read across from the closest analogue (**TBPP**), **TBPA** is considered to be a gene mutagen *in vitro*. The t-Butyl and t-Amyl Derived Alkyl Peroxyesters as a category may be considered to cause gene mutations *in vitro*.
TBPA, **TBPP**, **TAPP**, and **TBPEH** did not induce chromosome aberrations *in vivo* (similar to OECD TG 474, Mammalian Erythrocyte Micronucleus Test); in aliphatic hydrocarbon diluent or technically pure. An *in vivo* chromosome aberration study was not located for **TBPN**; based on read across from the other category members, **TBPN** is not considered clastogenic. The t-Butyl and t-Amyl Derived Alkyl Peroxyesters may be considered to be systemically non clastogenic *in vivo*.

Carcinogenicity
Carcinogenicity studies are not available for the category members.

Reproductive and developmental toxicity

Reproductive toxicity studies were located for **TBPA**, **TBPP**, **TBPEH**, and **TBPN**; no data were located for **TAPP**. Additional details on studies described below are presented under Repeated Dose Toxicity section.

In a Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OECD TG 422), rats received 0, 100, 300 and 1000 mg/kg bw/day of **TBPA** (in aliphatic hydrocarbon diluent) via oral gavage. The No Observed Adverse Effect Level (NOAEL, systemic, based on liver weight changes) and the Lowest Observed Adverse Effect Level (LOAEL, local, based on histopathological findings in the gastrointestinal tract) for parental animals was 100 mg/kg bw. At 1000 mg/kg bw/day, reduction of implantations was observed, together with a smaller number of live pups/dam at birth and at day 4 of lactation, smaller litter weight and slightly smaller pup weight. Therefore, the NOAEL for reproductive and developmental effects for **TBPA** is 300 mg/kg bw/day.

In a Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OECD TG 422), rats received 0, 50, 150 and 310 mg/kg bw/day of **TBPP** (75% in isododecane) via oral gavage. The NOAEL for systemic toxicity (parental) is 150 mg/kg bw/day based on increased kidney weights in males (with minimal decreased body weight) and decreased body weight and glucose levels in females at 300 mg/kg bw/day. Based on the absence of reproductive effects, the NOAEL for reproductive performance is 310 mg/kg bw/day (the highest dose tested); and the NOAEL for developmental effects for **TBPP** is 150 mg/kg bw/day based on mortality and reduced pup weights at 310 mg/kg bw/day.

In a Reproduction/Developmental Toxicity Screening Test (OECD TG 421), rats received 0, 100, 300, or 1000 mg/kg bw/day technically pure **TBPEH** via oral gavage. Treatment at 1000 mg/kg bw/day was associated with an increase of pre-implantation and post-implantation loss. There was a reduction in the number of live pups and their mean body weights at 1000 mg/kg bw/day The NOAEL for **TBPEH** is 300 mg/kg bw/day for parental systemic toxicity (based on clinical signs and body weight losses at 1000 mg/kg bw/day) and reproductive and developmental toxicity (based on the pre- and post-implantation losses, and reduction in the number of live pups and their mean body weights at 1000 mg/kg bw/day).

In a Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OECD TG 422), rats received 0, 60, 200, and 600 mg/kg bw/day technically pure **TBPN** via oral gavage. The NOAEL for maternal toxicity is 60 mg/kg bw/day (based on effects on body weight, hematology, clinical chemistry and organ weights at 200 mg/kg bw/day), with a paternal LOAEL of 60 mg/kg bw/day (based on effects on total bilirubin and decreased aspartate amino-transferase at all doses). The NOAEL for reproductive performance of the male and female rats for **TBPN** is 200 mg/kg bw/day (based on a higher percentage of post-implantation loss and stillborns and higher numbers of dams with prolonged duration of pregnancy at 600 mg/kg bw/day) and the NOAEL for developmental effects is 60 mg/kg bw/day (based on increased mortality and decreased pup weights at 200 and 600 mg/kg bw/day).

Taking into account effects observed in the closest structural analogue, **TBPP, TAPP** is also regarded as a reproductive and potential developmental toxicant when administered by the oral route. Using a precautionary approach, a NOAEL of 310 mg/kg bw/day is proposed for **TAPP** for reproductive toxicity and an NOAEL of 150 mg/kg bw/day for developmental toxicity.

TBPA, **TAPP**, **TBPEH**, and **TBPN** are toxic to reproduction, while **TBPP** had no effects on reproduction at the tested dose levels. The t-Butyl and t-Amyl Derived Alkyl Peroxyesters category members are potential developmental toxicants in the presence of parental toxicity.

The t-Butyl and t-Amyl Derived Alkyl Peroxyesters category members possess properties indicating a hazard for human health (acute toxicity; skin (TBPP, TAPP and TBPN), eye (TBPA) and respiratory irritation; skin sensitization; mutagenicity (gene mutations *in vitro*); repeated dose toxicity; and reproductive and potential developmental toxicity). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Environment

The EPIWIN modeling results presented here should be interpreted with caution as the library of reference peroxide substances used in EPIWIN is very limited in number.

The t-Butyl and t-Amyl Derived Alkyl Peroxyesters are hydrolytically unstable; OECD TG 111 studies were conducted with **TBPP**, **TBPEH** and **TBPN**. Half-lives at pH 7 and 25^{o}C were 9 hours for technically pure **TBPN** and 6 days for **TBPP**, 75% in aliphatic diluent. For technically pure **TBPEH**, the measured half-life at pH 7 and 15 ^{o}C was 86 hours, and at pH 7 and 37 ^{o}C it was 2.5 days. A hydrolysis study was not located for **TBPA**; based on the closest structural analogy, the hydrolysis half-life (6 days at pH 7 and 25^{o}C) is read across from **TBPP**.

In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to decrease with increasing molecular size (half-life = 1.4 days for **TBPN** up to 19.7 days for **TBPA**). EPIWIN Level III fugacity modelling predicts that, when distributed equally to air, water and soil, **TBPA**, **TBPEH** and **TBPN** will partition primarily to soil, **TAPP** will partition primarily to air and water, and **TBPP** will partition almost equally among the air, water and soil compartments. It should be considered that partitioning will be different for the products sold as formulations. The measured adsorption coefficient (log Koc) for **TBPN** was 3.64 and for **TBPP** was 1.59. The

estimated log Koc for **TBPEH** was 3.080 and 2.594 for the Kow method and MCI method, respectively.

Valid biodegradation data [OECD TG 301D] are available for all of the category members. **TBPA** (in aliphatic hydrocarbon diluent; no degradation in 28 days), **TBPP** (in aliphatic hydrocarbon diluent; 15% in 71 days), **TBPEH** (technically pure; 55% in 28 days) and **TBPN** (technically pure; 26% in 28 days) were found not readily biodegradable when tested in OECD TG 301D. **TAPP** was inherently biodegradable (32% in 28 days; 82% in 60 days). The t-Butyl and t-Amyl Derived Alkyl Peroxyesters were not readily biodegradable.
Bioaccumulation studies have not been conducted with the t-Butyl and t-Amyl Derived Alkyl Peroxyesters. Predicted BCF values, from BCFBAF Program v3.01 in EPIWIN v4.11, are 5.3 (**TBPA**), 57.4 (**TBPP**), 68.7 (**TAPP**), 672 (**TBPEH**) and 1352 (**TBPN**) L/kg wet-wt; these results indicate that TBPEH and **TBPN** may have the highest potential for bioconcentration in the category. Hydrolysis half-lives range from 10 hours to a few days and the reactivity of the category members will probably limit their bioaccumulation potential. The predicted BCF values for the hydrolysis products of the category members indicate low bioaccumulation potential.
The BCF value for the most commonly used diluent, isododecane, is 228 l/kg wt wg, indicating a low bioaccumulation potential. However, other diluants containing branched or cyclic alkyl compounds may have bioaccumulation potential.

Modeling results should be interpreted with caution as the library of reference peroxide substances used in EPIWIN is very limited in number, and the kM module (whole body primary biotransformation half-lives rate constant) does not contain peroxyester fragment.

Aquatic toxicity
ECOSAR predictions have not been used to support the read-across, as according to ECOSAR Help file predictions for Peroxy Esters are of low reliability. The SAR equations are based on very low number of experimental data.

No data for fish and Daphnia were available for **TBPA** and no acute aquatic toxicity data were available for **TAPP**. As noted previously, taking into account physical-chemical properties (log Kow, water solubility and Vp) and structural similarities, the closest analogue for read-across for both **TBPA** and **TAPP** is **TBPP**. It should be noted that only one diluent used in aquatic toxicity testing is isododecane.

The following acute toxicity test results have been determined for aquatic species:

Substance	**Species**	**Effect level**	**Comments**
Fish		**LC_{50} (mg/L), 96 hr**	
TBPA	-	No data located	Read across from **TBPP** = 18.85 mg/L
TBPP (75% in isodecane)	*Danio rerio*	18.85	OECD TG 203, semi-static, actual adjusted according to similarly performed *Daphnia magna* test
TAPP	Fish	No data located	Read across from **TBPP** = 18.85 mg/L
TBPEH (technically pure)	*Poecilia reticulate*	8.66	OECD TG 203, semi-static, nominal
TBPN (technically pure)	*Danio rerio*	0.33	OECD TG 203, semi-static, measured
Aquatic invertebrate		**EC_{50} (mg/L), 48 hr**	
TBPA	Daphnid	No data located	Read across from **TBPP**; 48 hour EC_{50} = 6.99 mg/L
TBPP (75% in unspecified diluent)	*Daphnia magna*	6.99	OECD TG 202, semi-static, measured
TAPP	Daphnid	No data located	Read across from **TBPP** = 6.99 mg/L
TBPEH (technically pure)	*Daphnia magna*	7.5	OECD TG 202, static, measured
TBPN (75% in isododecane)	*Daphnia magna*	0.79	OECD TG 202, static, nominal
Aquatic plants		**EC_{50} (mg/L), 72 hr**	

TBPA (51% in isodecane)	*Pseudokirchnerella subcapitata*	ErC_{50} = 3.2 EyC_{50} = 1.5 NOEC=0.993	OECD TG 201, measured
TBPP (75% in unspecified diluent)	*Pseudokirchnerella subcapitata*	ErC_{50} = 1.417 EyC_{50} = 0.422 NOEC = 1.417	OECD TG 201, measured
TAPP	Green Algae	No data located	Read across from **TBPP**; ErC_{50} = 1.417 mg/L EyC_{50} = 0.422 mg/L NOEC = 1.417
TBPEH (technically pure)	*Pseudokirchnerella subcapitata*	EbC_{50} = 0.1567 ErC_{50} = 0.4394 EyC_{50} = 0.1252 NOEC=0.018	OECD TG 201, measured
TBPN (technically pure)	*Pseudokirchnerella subcapitata*	ErC_{50} = 0.48 EyC_{50} = 0.09 NOEC=0.03	OECD TG 201, measured

The following chronic toxicity test results have been determined (OECD TG 211) with technically pure **TBPN**: [*Daphnia magna*] 21 d, NOEC = 0.049 mg/L (measured; semi-static).

The t-Butyl and t-Amyl Derived Alkyl Peroxyesters category members possesses properties indicating a hazard for the environment (acute toxicity from <1 to 100 mg/L; chronic toxicity to aquatic invertebrates and aquatic plants < 0.1 mg/L). The peroxyesters are not readily biodegradable but are not expected to bioaccumulate. Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Exposure

Based on the 2006 Inventory Reporting Rule, production volumes for pure chemicals without diluents in the United States are:

Substance	2006 Production Volume (tonnes)
TBPA	453 to < 4536
TBPP	453 to < 4536
TAPP	< 227
TBPEH	453 to < 4536
TBPN	453 to < 4536

According to ECHA registration dossier, EU production of t-Butyl and t-Amyl Derived **Alkyl Peroxyesters category members** for pure chemicals without diluents **is as follow:** (from http://echa.europa.eu/information-on-chemicals/registered-substances, last accessed August 5, 2014):

Substance	EU production in 2014 (tonnes)
TBPA	not available
TBPP	1,000 - 10,000
TAPP	not available
TBPEH	1,000 - 10,000
TBPN	100 - 1,000

TBPA is sold as a nominal maximum of 50% solution in aliphatics and is used as an initiator in the production of polyolefins, crosslinking rubber, curing unsaturated resins, styrenics and acrylics. **TBPP** is sold as a $\leq$ 75% solution in aliphatics. **TBPP** is used as an initiator to make polyvinylchloride (PVC) and polyolefins. **TAPP** is sold as a nominal maximum of 75% solution in aliphatics. **TAPP** is used as an initiator to make PVC and polyolefins. Only **TBPEH** and **TBPN** can be manufactured and distributed without diluents (technically pure). **TBPEH** is a basic industrial chemical used as initiator to start chain reactions in the synthesis of polymers. **TBPN** can also be sold as a nominal maximum of 75% solution in aliphatics, and is primarily used as a polymerization initiator in the production of low-density polyethylene and poly(vinyl chloride).

During manufacture, the t-Butyl and t-Amyl Derived Alkyl Peroxyesters are handled in closed systems with the exception of packing processes, where engineering measures (local ventilation) would be used. Personal protective equipment includes chemical goggles, and if any lines are opened, chemical gloves. Inhalation and dermal would be the most likely routes of exposure. At the industrial level, the peroxyesters are used in bulk in dilute solution in closed systems. Engineering measures (local ventilation) are used. Inhalation and dermal would be the most likely routes of exposure. When used in more concentrated forms, the containers are 7.5 gallons (ca. 30 L) or less. Personal protective equipment includes chemical goggles, and if any lines are opened, chemical gloves. There are no consumer uses of the t-Butyl and t-Amyl Derived Alkyl Peroxyesters. Peroxyesters are expected to be completely consumed during resin manufacture and polymer article production, are therefore not expected to be present as residuals in consumer products.

Annex I: Overview of toxicological data (reliable study results) for substances in the t-Butyl and t-Amyl Derived Alkyl Peroxyesters category and use of analogous substance data

Endpoint	t-Butyl peroxyacetate (**TBPA**) CAS No. 107-71-1	t-Butyl peroxypivalate (**TBPP**) CAS No. 927-07-1	t-Amyl peroxypivalate (**TAPP**) CAS No. 29240-17-3	t-Butylperoxy-2-ethylhexanoate (**TBPEH**) CAS No. 3006-82-4	Neodecaneperoxoic acid, 1,1-dimethylethyl ester (**TBPN**) CAS No. 26748-41-4
LC50 inhalation, mg/L	6.1	7.79	>9.5	42.2	50
acute dermal LD_{50}s for rabbits, mg/kg bw	No data located, proposed > 2000 mg/kg bw	> 2000 mg/kg bw	> 2000	No data located, proposed > 2000 mg/kg bw	No data located , proposed > 2000 mg/kg bw
acute oral LD_{50}s for rats, mg/kg bw	No data located, proposed > 2000 mg/kg bw	No data located, proposed > 2000 mg/kg bw	> 2000	> 2000	> 2000
Skin irritation	not irritating	irritating	irritating	irritating	irritating
Eye irritation	irritating	Not irritating	Not irritating	Not irritating	Not irritating
Respiratory irritant	irritating	irritating	Not irritating	irritating	irritating
Skin sensitization	Sensitizer	Sensitizer	Sensitizer	Sensitizer	Sensitizer
Repeated dose Oral NOAEL for rats mg/kg/day	NOAEL (systemic) 300 LOAEL (local) 100	150	*150, based on read across from* TBPP	316 (males) and 100 (females)	LOAEL(males) 60; NOAEL (females) 60
In vitro gene mutation	Positive, based on read across from closest analogue, **TBPP**	OECD TG 471/ positive and negative; OECD TG 476/negative Overall: positive based on weight of evidence	OECD TG 471/positive	OECD TG 471/ positive and negative; OECD TG 476/positive	OECD TG 471/positive OECD TG 476/negative
In vivo chromosome aberrations	OECD TG 474 /negative	OECD TG 474 /negative	OECD TG 474 /negative	Similar to OECD TG 474 /negative	negative, based on read across from category members
Reproductive toxicity NOAEL for rats mg/kg bw/day	300	310 (the highest dose tested).	310, based on read across from **TBPP**	300	200
Developmental toxicity	300	150	150, based on read across from closest	300	60

NOAEL for rats mg/kg bw/day			analogue, **TBPP**		

Note: This document may only be reproduced integrally. The conclusions in this document are intended to be mutually supportive, and should be understood and interpreted together.

SIDS INITIAL ASSESSMENT PROFILE

Category Name	Copper and copper compounds
CAS No(s) and chemical name	CAS 7440-50-8 (copper powder and massive[1]) CAS 7758-99-8 (copper sulphate pentahydrate) CAS 1317-38-0 (copper oxide) CAS 1317-39-1 (dicopper oxide) CAS 1332-65-6 (dicopper chloride trihydroxide)
Chemical Formula(s)	Cu $CuSO_4.5\ H_2O$ CuO Cu_2O $Cu_2Cl(OH)_3$

SUMMARY CONCLUSIONS OF THE SIAR

This document covers the category assessments for copper metal, massive and powder, coated copper flakes and several copper compounds, assessed under the EU Risk Assessment. Substance specific aspects are provided where relevant.

The SIAR is based on the EU Risk Assessment of copper and various copper compounds used as general chemicals, under the Existing Substance Regulation, completed in 2008 as an industry initiative. The copper risk assessment report and opinions from EU technical and scientific committees are available from *http://echa.europa.eu/copper-voluntary-risk-assessment-reports.* Considering the comments from the EU technical and scientific committees and additional information obtained from industry, updates were done for the 2010-2013 REACH registrations and this SIAR. Nevertheless, a limitation of this SIAR is the small number of recent open literature data (beyond 2006).

Rationale for copper category approach

The category includes a group of commonly used copper substances whose ecotoxicological and systemic human hazard profiles are related to the release of copper-ions. Nanoform copper substances are excluded from this assessment because the biological effects of nanoform metals can differ from the ionic forms.

The category includes five substances: soluble copper sulphate pentahydrate and dicopper chloride trihydroxide, less soluble CuO and Cu_2O, and three forms of zero valent copper materials (Cu°): copper massive, copper powder and coated copper flakes[2,3]. Coated copper flakes are added to the category because human health haz-

[1] Includes copper flakes, coated with aliphatic acid, because the toxicity data on this material is used to read across to copper powders and massives. The same CAS number is thus used to cover three different forms of copper in this assessment (massive, powder and coated flakes).

[2] Aliphatic acids are added for the production of coated copper flakes, to stabilise the copper flake in small particle sizes with higher surface area (needed for specific niche applications – biocides and pigments).

ards are available for these coated copper flakes. Where relevant for read-across purposes, information from other copper compounds is included in the assessment.

For the environmental endpoints and systemic health endpoints, the copper ion is considered as the reactive functional group within the category. The counter-ions of the copper salts (i.e. oxygen, sulphate, chloride and hydroxide), are due to their ubiquitous presence in environmental media and human fluids not considered to contribute to the environmental nor systemic human toxicity of copper salts.

The category implies that the effects assessment is expressed as Cu-ions and that further read-across to other copper compounds, not assessed in this SIAR, is possible on condition that the copper ions are driving the toxicity.

Copper is an essential nutrient for humans and non-human organisms and, therefore, low concentrations may lead to deficiency while high concentrations of copper ions may lead to copper toxicity.

Once released to the environment, copper ions have more than one oxidation state. The principal ionic forms are cuprous (Cu(I), Cu^{+}) and cupric (Cu(II), Cu^{2+}). The trivalent form (Cu(III), Cu^{3+}) occurs but is relatively unimportant in physical and biological systems. Cu^{+} is unstable in aqueous media and Cu^{1+}-ions readily transform into Cu^{2+}-ions. Depending on the chemistry of the receiving environment, soluble and/or insoluble copper compounds are formed. Hence Cu^{1+}-ions are, due to their instability, considered as a source of Cu^{2+} ions for environmental and systemic toxicity.

Environment:

The assessment aims at defining the basic hazards profile of soluble and sparingly soluble compounds, copper metal (powder and massive forms) and coated copper flakes.

Human health:

The human health hazard assessment addresses a large variety of effects and different administration routes. In assessing the human health effects of copper and copper compounds, the essentiality and homeostatic mechanisms have to be considered.

Acute effects are based on tests with the individual substances. Short term and long term systemic effects are based on tests with the individual soluble substances belonging to the category and/or read-across where such data are not available

Physical-chemical properties

Physico-chemical properties that are important for the human health and environmental hazard profiles are granulometry and solubility.

- Copper metal (Cu°) is insoluble and needs to be transformed to Cu(I) or Cu(II) to become bio-available/bio-accessible. Typical copper powders have a diameter of around 100 µm but small production volumes of fine powders are also reported. The surface area of fine powders (10-50 µm) is 67-107 mm^2/mg. The surface area of a massive copper material (sphere of 1 mm) is 0.67 mm^2/mg. The melting point of copper metal is 1059 - 1069°C. Its boiling point has not been determined in view of the high melting point.

[3] The same CAS number is used to cover three forms of zero valence copper materials : massive, powders and coated copper flakes.

- Copper flakes, coated with aliphatic acids have a particle size of 8 – 11 µm and surface area of 2,900 mm^2/mg. Cu is in the form of Cu° and therefore needs to be transformed to Cu(I) or Cu(II) to become bio-available/bio-accessible. The melting point of coated copper flakes is 1057 - 1058°C. Its boiling point has not been determined in view of the high melting point.

- Copper sulphate pentahydrate is a blue crystalline powder. Its water solubility at 25°C is 220 g/L. Copper sulphate pentahydrate decomposes at 110°C without melting or boiling.

- Dicopper oxide is an orange-red powder. The water solubility at 20°C is ≥ 28.6 g/L at pH 4.0, 6.39×10^{-4} g/L at pH 6.5 - 6.6, and < 5.39×10^{-4} g/L at pH 9.8. The melting point of dicopper oxide is in excess of 400°C (the maximum temperature tested). Its boiling point has not been determined in view of the high melting point.

- Copper oxide is a dark grey powder. The water solubility at 20°C is > 0.23 g/L at pH 5.1 - 5.5, 3.94×10^{-4} g/L at pH 6 and < 1.0×10^{-5} g/L at pH 9. The melting point of copper oxide is 1326°C. Its boiling point has not been determined in view of the high melting point.

- Dicopper chloride trihydroxide is a light green powder. The water solubility at 20°C is > 101 g/L at pH 3.1, 1.19×10^{-3} g/L at pH 6.5 and ≤ 5.25×10^{-4} g/L at pH 10. Dicopper chloride trihydroxide decomposes from 240°C without melting or boiling.

Remark 1: The octanol-water partition coefficient (log K_{ow}) is not relevant (the mechanisms of absorption of Cu^{2+} into organic matter and living cells are different from those traditionally attributed to carbon-based substances and the parameter therefore has little relevance to ionic copper). pKa is also not considered a relevant parameter and is thus not mentioned above.

Remark 2: Data on vapour pressure are only relevant for coated copper flakes (7.5e-9 Pa (20°C), they are negligible for Cu-compounds and Cu-metal. Vapour pressure is therefore considered as not relevant to the category members

Essentiality

Copper is an essential micronutrient, needed for optimal growth and development of micro-organisms, plants, animals and humans.

Human Health

Toxicokinetics (absorption, metabolism, distribution and elimination)

Introduction

The toxicokinetics of essential elements such as copper are regulated to a large degree by homeostatic mechanisms. Homeostasis can be described as the maintenance of a constant internal environment in response to changes in internal and external environments. Homeostatic maintenance requires the tightly coordinated control of copper uptake, distribution and efflux in cells and the organism as a whole. As a result of the presence of a homeostatic mechanism for copper, rat and human metabolism of copper are very similar and are therefore discussed together in the following sections.

Essentiality

Copper is an essential metal present in human body tissues and fluids at concentrations of parts per million or parts per billion. In common with other trace metals, copper has a number of physiological roles that may be classified as regulatory, structural and/or protective. In the regulatory role they are an essential part of metal-

loenzymes, acting either as electron donors or acceptors at the active site, or by shaping the enzyme to the configuration necessary for its activity. The structural functions of trace metals may be in, for example, membrane integrity or bone structure, and the protective function may involve antioxidant defence or the immune system. Copper is involved in the reactions and functions of many enzymes, including angiogenesis, neurohormone release, oxygen transport and regulation of genetic expression. Copper is an allosteric component of several enzymes that have oxidation and reduction activity, functioning as an electron transfer intermediate in redox reactions.

Absorption

Oral

A large quantity of oral absorption data are available for animals, specifically rats, and humans. These data enable an estimation of true absorption at the relatively high copper intakes used in toxicity studies.

True absorption was determined as there is a large quantity of data available on the absorption of copper in animals and humans, predominantly relating to oral exposure. In these studies, quantitative data on the absorption of copper have been based on faecal monitoring, as faecal excretion is the main excretory route for copper. In several of these studies, the amount absorbed has been determined as the difference between oral intake and faecal excretion. This absorption value represents a measure of *apparent absorption* only, as faecal copper does not distinguish between unabsorbed copper and endogenous copper losses. Endogenous copper losses may occur from (1) biliary excretion of systemically-absorbed copper that mixes with the endogenous pool and is subsequently excreted, and (2) the fraction absorbed by intestinal mucosa and subsequently eliminated into the GI tract as cells are sloughed off (i.e. without systemic absorption). *Apparent absorption* thus represents a somewhat crude measure of copper absorption. In order to measure *true absorption*, which provides a more accurate measure of copper absorption following oral exposure, the percentage of copper intake recovered in the faeces was corrected for endogenous copper losses.

Based on these absorption data, an absorption factor of 25% is taken to be the best estimate of true absorption in rats at the high copper intakes.

The most reliable human data currently available on copper absorption following oral exposure come from volunteer studies. Based on the available true absorption data, oral absorption rates in humans have been derived.The available data have been fitted to two functions giving a continuous distribution with mostly similar results:

Equation 1: oral absorption% = -15.0 ln(x) + 63.2777

Equation 2: oral absorption% =72.287 $e^{-0.1167x}$

x= copper intake (mg/day)

For a given dose in the GIT, absorption in humans is calculated based on the mean result for these two functions. In humans, this method of calculation is applied to the sum of the oral intake and copper arising from inhalation exposure and subsequently translocated to the GIT. The minimum oral absorption is set to 20%.

Oral absorption data for humans and rats show qualitative and quantitative similarities between the two species. In both species, absorption of copper over the range of intakes studied is inversely related to copper intake, illustrating the important role of absorption in copper homeostasis. In both species, true absorption of copper from diets containing what are considered as adequate levels of copper (1-10 mg/day in humans; 0.3-0.6 mg/kg bw/day in animals) is in the 30-60% range. The above oral absorption data, and corresponding functions, are based on copper sulphate. Assuming that orally-administered copper will occur in the GIT, at least in part, in the ionic form and therefore be available for absorption, and in view of the solubility of copper sulphate, it is considered appropriate to adopt a conservative approach and to use the oral absorption data for cop-

per sulphate for other less soluble copper species.

Dermal absorption and penetration

In the two reviewed studies, the copper compounds were applied in an aqueous medium (suspension). There is uncertainty about the applicability of these absorption data to exposures of dry copper compounds as encountered in occupational exposure scenarios. However, in view of the limitations of the studies on which this dermal absorption factor is based (absence of mass balance data and large standard deviations); the value of 0.3% is considered to represent the best estimate based on data currently available.

Given the available studies provide no consistent evidence that dermal absorption is greater for soluble than for insoluble copper substances, a dermal absorption factor of 0.3% is also proposed for both soluble and insoluble copper substances.

For dry exposure scenarios, a 10-fold lower dermal absorption value is proposed (0.03%), consistent with the approach used in the OECD Cooperative Chemicals Assessment of Zinc (and EU risk assessment).

Distribution

On entering interstitial fluid and blood plasma, absorbed copper initially becomes bound to two proteins, albumin and transcuprein. Most of the copper bound to albumin and transcuprein is rapidly transported via portal blood to the liver. Once in the liver, copper is incorporated into ceruloplasmin, which is subsequently released into the systemic circulation for delivery to other tissues.

Excretion

Quantitative data on excretion were reported in a bioequivalence study. The fate of excess copper was examined in bile-cannulated male Sprague Dawley rats (five per group) following oral administration of a single dose of copper (nominal dose 20 mg Cu/kg bw; actual dose 22-24 mg Cu/kg bw). Six inorganic copper salts were investigated including three category members. Copper levels in excreta during the 24-h period after dosing were as follows: bile 1.54-2.48% of dose; urine 0.20-0.39% of dose; faeces 64-76% of dose (although it is noted that faecal copper will also comprise some absorbed copper). Values were found to be similar for all six substances tested. The results showed faecal excretion to be the main route of elimination for orally-administered copper, with urinary excretion as a relatively minor route.

Comparative bioavailability

In mammalian toxicity, it is also considered that the most toxic form of any copper salt is the Cu^{2+} ion. This can be shown through the comparison of the most soluble (e.g. copper sulphate pentahydrate, copper nitrate) and relatively insoluble copper salts, where the solubility, bioavailability and hence toxicity of these salts can vary – with copper sulphate pentahydrate representing the worst-case scenario. As all suitable short- to long-term available animal copper toxicity studies are derived from oral administration, the use of copper sulphate pentahydrate data would represent a worst case scenario for the determination of the effect of relatively insoluble copper compounds in mammalian toxicity. In addition, the use of copper sulphate pentahydrate data would minimise the number of animal studies.

In vivo bioavailability

For the oral exposure route, in a series of bioavailability studies, conducted by several authors the bioavailability of copper sulphate to other relatively insoluble copper salts including copper oxide was compared. Although the species tested are not usual species used in regulatory guidelines, the results are consistent when evaluating a number of studies and appear to be reproducible. In addition, the studies have measured copper levels in the most important organ and body fluid in determining copper absorption from the gastro-intestinal tract, namely the liver and bile.

Relative bioavailability of supplemental copper sources

Source of copper	Species		
	Poul-try	Swine	Cattle
Copper sulphate	100	100	100
Copper oxide	0 (3)	30 (4)	15 (2)

Average numbers rounded to the nearest '5' and expressed relative to response obtained with copper sulphate. Number of studies or samples involved indicated within parenthesis.

The low bioavailability of copper in copper oxide, relative to that of copper in the sulphate salt, was also demonstrated in the rat following administration at adequate dietary levels.

In vitro bioavailability

Several studies assessed the release/dissolution of metal ions from metal bearing materials (minerals, soils, substances) in simulated biological fluids.

The release/dissolution of copper ions from copper materials and copper compounds was assessed from *in vitro* tests using biological fluids simulating oral exposure. The *in vitro* tests follow the ASTM D 5517-07 protocol, using HCl 0.07N (pH 1.5) as a gastric mimetic fluid. The copper materials tested include: copper wires (representing massive copper materials), copper powder (130 µm median diameter), biocidal and non-biocidal coated copper flakes (ca 8.5 µm), copper oxide, cuprous chloride and dicopper sulphide. Loading rates between 100 mg/L and 2 g/L were assessed. The results are expressed as % copper dissolved at the end of the bioelution test.

Copper, in the form of Cu°, is insoluble and needs to be transformed to Cu^{+} or Cu^{2+} to demonstrate solubility. Such transformation/dissolution takes place at the surface of the copper particles and therefore, for the copper massive, copper powder and coated copper flakes, the influence of surface area on bioaccessibility was also evaluated.

The results are summarized in the Table below. All copper present in $CuSO_4$ was solubilised (99.95%) in the gastric fluid while "massive" copper materials, tested as wires at different mass loadings (59 to 478 mg/L) and surface loadings (67 – 516 mm^2/L) consistently showed low solubility (0.1%).

Relative bio-accessibility of copper and copper compounds, assessed from the recovery of copper after bioelution tests in gastric fluids (pH 1.5, 2 hours) in accordance to ASTM D 5517-07.

Material Tested	Composition	Bioelution recovery (as % of Cu content)
Cu massive	>99.9% Cu	0.096 – 0.105
Cu powder	99.7% Cu, 0.3% Cu_2O	1.1 – (7.3*)
Dicopper sulphide	79.9% Cu	3.3

Cu flake – biocidal product	93.7% Cu, 2.6% Cu_2O, 3.89% LOI**	42 – 71
Cu flake – non-biocidal product	96.3% Cu, 1% Cu_2O, 2.8% LOI**	44 – 60
CuCl	63.78% Cu	77 – 94
CuO	80% Cu	68-84%
$CuSO_4$	25.45% Cu	100

*The results at the higher loading rate show unacceptably high variability (CV of 66%), possibly related to abrasion of the particles during the test. The results of this test are therefore not considered as reliable.
** Loss if ignition, as a measure of the organic content (coating by aliphatic acid).

For the Cu° materials, the relation between the release of Cu-ions and the surface area exposed is well described by a power function:

Bioaccessible copper ions = 1.94 surface loading (mm^2/L) $^{0.84}$

In conclusion, the *in vitro* gastric bioelution tests with various copper-bearing materials demonstrate important differences in bio-accessibility in gastric fluids: $CuS0_4.5H_20$ (100%) > CuCl > CuO > coated copper flakes > Cu_2S > copper powder > copper massive (0.1%).

The data also show that bio-accessibility of Cu° is related to surface area, described by the power function. Measured and modelled (from the power function) bio-soluble copper concentrations released from 200 mg copper powders/L are respectively 1.1% and 2.8% for a typical copper powder (0.024 m^2/g) and reasonable worst case 10 µm powder (of 0.067 m^2/g). Using the coated copper flakes as reference substance (with average bio-accessibility of 57%), the relative bio-accessibility of a typical copper powder (0.024 m^2/g) and reasonable worst case 10µm powder (of 0.067 m^2/g) are therefore respectively 1.9% and 4.9%.

These data can be used to predict the acute oral toxicity of copper massive and copper powder using available toxicity studies on other forms of copper and copper compounds and this is presented below in the acute toxicity section.

Acute toxicity

Available key study data for acute toxicity:

Key studies for acute toxicity by inhalation, dermal and oral exposure route

Route of administration / endpoint / test guideline	**Test substance**	**Clinical effects**	**Endpoint value**
Inhalation (US 173.132)			
LC_{50}, rat (m/f) – nose only	Dicopper chloride trihydroxide		>11.4 mg/L air (m/f)
Inhalation (OECD 403)			
LC_{50}, rat (m/f) – nose only	Dicopper chloride trihydroxide		2.83 mg/L air (m) > 2.77 mg/L air (f) 4.74 mg/L air (m/f)

LC_{50}, rat (m/f)	Dicopper oxide	Lung abnormalities, wet fur, staining, hunched posture, piloerection, ptosis, altered respiration.	2.92 mg/L air (m) 3.69 mg/L air (f) 3.34 mg/L air (m/f)
LC_{50}, rat (m/f)	Dicopper oxide	Respiratory depression, discolored lungs.	5.36 mg/L air (m/f)
LC_{50}, rat (m/f)	Dicopper oxide	Apathy, sedation, difficult respiration, squat position, reduced reflexes, tremors, disturbed coordination.	> 30 mg/L air (m/f)
LC_{50}, rat (m/f)	Dicopper oxide		> 5 mg/L air (m/f)
LC_{50}, rat (m/f)	Dicopper oxide	Respiratory reduction, enlarged lungs, subdued, hunched posture, piloerection, hypothermia, ataxia, staining of the fur, discoloration perianal region, slightly emaciated and unkempt condition. reduced weight gain.	ca. 5 mg/L air (m/f)
Inhalation (OECD 436)			
LC_{50}, rat (m/f)	Coated copper flakes	Ataxia, tremor, dyspnoe, reduced motility, reduced body weight gain. Grey-stained discolored lungs.	> 5.11 mg/L air (nose only-dry aerosol)
LC_{50}, rat (m/f)	Coated copper flakes	Decreased respiratory rate, laboured respiration, noisy respiration, hunched posture, piloerection	Males 0.733 mg/L Female 1.67 mg/L
Dermal (OECD 402)			
LD_{50}, dermal, rat (m/f)	Coated copper flakes		> 2,000 mg/kg bw
LD_{50}, dermal, rat (m/f)	Copper oxide	None	> 2,000 mg/kg bw
LD_{50}, dermal, rat (m/f)	Copper sulphate pentahydrate pentahydrate		> 2,000 mg/kg bw
LD_{50}, dermal, rat (m/f)	Dicopper chloride trihydroxide		> 2,000 mg/kg bw
LD_{50}, dermal, rat (m/f)	Dicopper oxide	None	> 2,000 mg/kg bw
LD_{50}, dermal, rabbit (m/f)	Dicopper chloride trihydroxide		> 2,000 mg/kg bw
Dermal (EPA OPP 81-2) equivalent to OECD 402			
LD_{50}, dermal, rabbit	Dicopper oxide	Reddened skin, weight	> 2,000 mg/kg bw

(m/f)		gain, liver lesion	
LD_{50}, dermal, rabbit (m/f)	Dicopper chloride trihydroxide		> 2,000 mg/kg bw
Oral (EPA OPP 81-1)			
LD_{50}, oral, rat (m/f)	Dicopper chloride trihydroxide		1,200 mg/kg bw (m) 950 mg/kg bw (f)
Oral (OECD 423)			
LD_{50}, oral, rat (m)	Copper oxide		> 2,000 mg/kg bw
LD_{50}, oral, rat (m/f)	Coated copper flakes		300-500 mg/kg bw
Oral (OECD 401)			
LD_{50}, oral, mice (m/f)	Dicopper chloride trihydroxide		299 mg/kg bw
LD_{50}, oral, rat (m/f)	Copper sulphate pentahydrate		481 mg/kg bw
LD_{50}, oral, rat (m/f)	Copper sulphate pentahydrate	Lethargy, prostate posture, green coloured diarrhea, voiding few faeces and moribundity	482 mg/kg bw
LD_{50}, oral, rat (m/f)	Dicopper oxide	Piloerection, hunched posture, lethargy, decreased respiratory rate and diarrhea.	1,625 mg/kg bw (m) 928-2,000 mg/kg dw (f) 1,340 mg/kg bw (m/f)
LD_{50}, oral, rat (m/f)	Dicopper chloride trihydroxide		1,796 mg/kg bw (m) 2,006 mg/kg bw (f) 1,862 mg/kg bw (m/f)
LD_{50}, oral, rat (m/f)	Dicopper chloride trihydroxide		1,083 mg/kg bw (m) 1,854 mg/kg bw (f) 1,398 mg/kg bw (m/f)

Read across and bridging for acute oral toxicity

For copper massive and uncoated copper powder, the acute oral toxicity can be predicted using *in vitro* studies and available toxicity studies on other forms of copper and copper compounds. *In vivo* acute oral toxicity tests are available for several copper bearing materials. The results of the appropriate oral toxicity studies are summarised below. These include data on 2 substances, dicopper chloride and dicopper sulphide, which are not included in this OECD CoCam review programme.

- The acute oral effects - LD_{50} - observed for coated copper flakes are between 300 and 500 mg/kg.
- The acute oral effects - LD_{50} - observed for copper sulphate pentahydrate: 481 mg/kg.
- The acute oral lethal effects - LD_{50} - observed for copper chloride: 336 mg/kg.
- The acute oral lethal effects - LD_{50} - observed for copper oxide is >2000 mg/kg
- The acute oral lethal effects - LD_{50} - observed for dicopper sulphide is >2000 mg/kg

The acute oral data indicate the importance of bio-availability/bio-accessibility: *in vivo* exposure to highly bio-accessible copper compounds (coated copper flakes, copper sulphate pentahydrate and copper chloride) results in a higher acute toxicity than *in vivo* exposure to less bioaccessible/bioavailable copper oxide and dicopper sulphide. As read-across approach, the measured LD_{50} values of the all source materials (coated flakes, $CuS0_4.5H_2O$ and CuCl) were expressed as mg bio-accessible Cu/kg bw and combined with the % bio-accessible Cu released from the various copper bearing materials to predict the LD_{50} values. The results are given below.

Oral LD50 values for the various copper materials

Cu Material	**Copper content %**	**Bio-accessible/ bio-availability Cu %(1)**	**LD_{50} as bio-accessible Cu (mg Cu/kg bw) (2)**	**Measured LD_{50} LD_{50} (mg sub-stance/kg bw)**	**Calculated LD_{50} LD_{50} (mg sub-stance/kg bw) (3)**
Coated flakes (2.9m2/g)	99.7	57	227	**400 (mid value of 300 -500 mg/kg)**	215-401
$CuSO_4.5H_20$	25.4	25	122	**481**	480-894
CuCl	63.78	51	173	**336**	232-442
CuO*	80	15-76		**>2000**	160-1513
Cu_2S	78.9	2.7		**>2000**	4685-8718
Copper powder (0.024m2/g)	100	1.1			**11091-20636**
10 µm copper powder (0.067m2/g)	100	2.8			**4357-8107**

(1) Obtained from bioelution test or *in vivo* bioavailability test
(2) Measured LD_{50} / (1)
(3) Min-Max range (2) / (1)

The above Table shows comparable bioavailable/bioaccessible LD_{50} values for the 3 substances with bound LD_{50} data (122 to 227 mg bio-available mg Cu/kg bw). The calculated LD_{50} values for these materials (copper coated flakes, $CuSO_4.5H_20$ and CuCl) correspond to the measured hazard profile of these materials (LD_{50} < 2,000 mg/kg and > 200 mg/kg bw). Correct predictions are also observed for Cu_2S (i.e. LD_{50} > 2,000 mg/kg). For CuO, the predicted LD_{50} values are below the observed LD_{50} and therefore, calculations are conservative.
The data therefore support the concept that bio-available copper ions are responsible for the observed acute toxicity profiles of $CuSO_4.5H_20$, CuCl, Coated copper flakes CuO and Cu_2S and that *in vitro* bioaccessibility data can be used as read-across parameter.
Therefore, following the read-across approach, the *in vivo* toxicity of coated copper flakes and copper compounds were combined with the relative bio-accessibility of copper powders and massive to derive the classification of copper powders/massive. From the assessment it was concluded that copper powder (typical powder and worst case 10µm powder) and therefore also copper massive follow the same hazard profile as CuO and Cu_2S (LD_{50} > 2,000 mg/kg) : they do not merit acute oral classification.
Consideration of available acute oral toxicity data leads to the conclusion that coated copper flakes have the same hazard as the soluble copper compounds ($CuSO_4.5H_20$ and CuCl). CuO and Cu_2S and copper powder/massive do not present a hazard by the oral route.
Conclusion on the acute oral, dermal and inhalation routes

- Oral: the release of copper ions drive the acute oral toxicity. Dicopper oxide, copper sulphate pentahydrate, dicopper chloride hydroxide and coated copper flakes present a hazard by the oral route. Copper oxide, copper powder and copper massive are not hazardous by the oral route.

- Dermal: all tested substances within the category are not hazardous by the dermal route. Considering the lower solubility and bioaccessability of copper powders/massives compared to the tested copper

substances, copper powders/massive forms do not present a hazard by the dermal route.

- Inhalation: Dicopper oxide, dicopper chloride hydroxide and copper flakes are considered hazardous by the inhalation route. Copper sulphate pentahydrate, copper oxide and copper powder/massive are not hazardous by inhalation route

Skin, eye and respiratory irritation

Available key study data for irritation (skin, eye and respiratory tract):

Test substance	**Guideline**	**Result**	**Symptoms**
Dicopper oxide	OECD 404, rabbit	Not skin irritant	Very slight erythema and very slight oedema observed in the abraded skin
	OECD 405, rabbit	Eye irritant	Ocular irritation
	OECD 405, rabbit	Not eye irritant	/
	EPA OPP 81.4, rabbit	Not eye irritant	Conjunctival redness and chemosis
Copper oxide	OECD 404, rabbit	Not skin irritant	/
	OECD 405, rabbit	Not eye irritant	Scattered or diffuse corneal opacity, iridial inflammation
Dicopper chloride trihydroxide	OECD 404, rabbit	Not skin irritant	/
	EPA OPP 81.5, rabbit	Not skin irritant	/
	OECD 405, rabbit	Not eye irritant	Corneal effects
	EPA OPP 81.4, rabbit	Not eye irritant	Corneal and conjunctival effects
	OECD 405, rabbit	Not an eye iritant	Conjunctival effects
	OECD 405, rabbit	Not an eye irritant	/
Copper sulphate pentahydrate	OECD 404, rabbit	Not skin irritant	/
	OECD 405, rabbit	Severe eye irritant	Lesions
Coated copper flakes	OECD 404, rabbit	Not skin irritant	/
Coated copper flakes	OECD 405, rabbit	Slight eye irritation	corneal and conjunctival effects

Of the category substances, dicopper oxide, copper sulphate pentahydrate and coated copper flakes are considered an eye irritation hazard. Copper oxides and dicopper chloride hydroxide do not present a hazard for eye irritation. No data are available for copper powders.

None of the category substances are considered a skin irritation hazard.

Skin sensitization

Available key study data for skin sensitization:

Test substance	**Guideline**	**Result**	**Symptoms**
Dicopper oxide	OECD 406, guinea pig	Not sensitizing	No skin response after challenge.

Copper oxide	OECD 406, guinea pig	Not sensitizing	Mild skin response: 10% w/w: discrete or patchy erythrema at challenge sites in 4/10 animals) at 24h; no skin reaction at 48h. 5% w/w: discrete or patchy erythrema at challenge sites in 2/10 animals) at 24h; no skin reaction at 48h.
Dicopper chloride trihydroxide	OECD 406, guinea pig	Not sensitizing	No skin response after challenge.
	EU B.6, guinea pig	Not sensitizing	No skin response after challenge.
Copper sulphate pentahydrate	OECD 406, guinea pig	Not sensitizing	Slight erythema in 1/20 animals at 24h observation only.
Coated copper flakes	OECD 406, guinea pig	Not sensitizing	No skin response after challenge.

The available animal data suggest the chemicals are of low hazard

Repeated dose toxicity

Available key study data for repeated dose:

Test substance	**Toxicity**	**Method and study type details**	**Symptoms**	**NOAEL / LOAEL**
Copper sulphate pentahydrate	Oral	B.26 Rat m/f subchronic Dose: 0, 8, 17, 34, 67 or 138 mg Cu/kg bw/day, for 92 days for 7d/week, administrated in the feed	hyperplasia of the squamous, liver inflammation, altered clinical chemistry and urinary parameters, increased cytoplasmic droplets	NOAEL: 16.7 mgCu/kg bw/day
Copper sulphate pentahydrate	Oral	B.26 Mice m/f subchronic Dose: 0, 44, 97, 187, 398 and 815 mg Cu/kg bw/day in males, and 0, 52, 126, 267, 536 and 1058 mg Cu/kg bw/day in females for 92 days for 7d/week, administrated in the feed	hyperplasia of the squamous, liver inflammation, altered clinical chemistry and urinary parameters, increased cytoplasmic droplets	NOAEL: 97.2 mgCu/kg bw/day (m) 125.7 mgCu/kg bw/day (f)
Dicopper oxide (Cu^{2+})	Inhalation	OECD 412 Rat m/f 0.21, 0.41, 0.8, 2.0 mg/m^3 (analytical conc.) Vehicle: air Exposure: 28 days, 6 hours per	macrophages in the lung, increase in neutrophil number in BALF and blood, increase in LDH and protein levels in the BALF. Neutro-	NOAEC: >= 2 mg dicopper oxide/m^3 air

		day (5 days per week.)	phil-dominated inflammation in the lung. Most test substance-related effects at 2.0 mg/m^3 appeared to show a peak in the effect prior to completion of exposure. Decreased wet/dry lung weight ratio (highest exposure level only)	

Studies have shown that copper and copper compounds are considered equally or less bioavailable to a number of animal species when compared to copper sulphate, therefore the use of copper sulphate studies is justified on scientific grounds. The copper sulphate studies indicate that there is no evidence to indicate that copper or copper compounds present a hazard for repeat dose oral toxicity.

The inhalation study on dicopper oxide in the rat performed to a standard guideline is considered the most relevant. In this study, no serious adverse effects were observed up to the maximum test concentration (2 mg Cu/m^3 as dicopper oxide). Therefore dicopper oxide does not present a hazard for repeated dose inhalation toxicity.

Genotoxicity

Available key study data for genotoxicity:

Test substance	**Method and study type details**	**Test results**	**Evaluation of results**
Copper sulphate pentahydrate	OECD 471 *In vitro* Bacterial reverse mutation assay Salmonella typhimurium Doses: 1.6, 8, 40, 200, 1000 µg/plate (exp. 1) and 50, 100, 200, 400, 800 µg/plate (exp. 2)	Negative for Salmonella typhimurium Strains TA98, TA100, TA1535, TA1537, TA102 (all strains/cell types tested); metabolic activation: with and without; Cytotoxicity: yes	Negative
Copper sulphate pentahydrate	EU B.12 *In vivo* micronucleus assay mouse	Genotoxicity: negative	Negative
Copper sulphate pentahydrate	OECD 486 *In vivo* Oral: gavage unscheduled DNA synthesis rat	Genotoxicity: negative (m)	Negative

There is no human data available on the genotoxic potential of copper and copper compounds in humans. Copper and copper compounds are not genotoxic.

Carcinogenicity

Dietary copper/copper compounds have been administered orally to rats in long-term studies. None of the studies presented below meets exactly the requirements of the International Guidelines, but they do show conclusively that copper has no carcinogenic activity.

Two types of studies have been performed:

- Investigative toxicity studies demonstrating no tumor formation or long term effects even at very high dose levels.
- Co-administration with known carcinogens to demonstrate that copper is effective at reducing the incidence and delaying the onset of tumours.

Toxicity to reproductive organs and fertility and developmental toxicity

Available key study data for toxicity to reproductive organs and fertility:

Test substance	**Method and study type details**	**NOAEL**
Copper hydroxide	OECD 414 Teratogenicity Rabbit, f Oral: gavage Day 7-28 of gestation Dose: 0, 6, 9, 18 mg Cu/kg bw/day	Maternal toxicity reported at 9 mg/kg bw/d (inappetance and initial weight loss) and 18 mg/kg bw/d (deaths, weight loss). Effects on foetus (increased incidence of some common skeletal variants and 9 and 18 mg/kg d. NOAEL maternal toxicity 6 mg/kg bw/day NOAEL teratogenicity 6 mg/kg bw/day
Copper sulphate pentahydrate	OECD 416 Multi-generation Rat m/f 0, 100, 500, 1000, 1500 ppm in diet Two-generation study Exposure >= 70d before mating	1500 ppm or 23.6 mg Cu/kg bw/day (m) (P) 1000 ppm (F1 and F2) or 26.7 mg Cu/kg bw/day – reduced spleen weight (f)
Dicopper chloride	OECD 422 Rat m/f 0, 0.8, 3.2, 12.9, 51.7 mgCu/kg bw/day Reprotoxcity/developmental toxicity screening test	12.9 mg Cu/kg bw/day based on systemic and reprotoxic effects

In the teratogenicity study, maternal toxicity was represented by initial weight loss. These effects are considered to be local effects on the stomach in rabbits which result from gavage administration of copper hydroxide. Consequently, it is considered inappropriate to use data on maternal toxicity from this study as the basis of a repeat-dose NOAEL for copper. The spleen effect cannot be considered a reproductive effect. The existing toxicology data therefore supports the conclusion that copper has no reproductive or developmental toxicity potential.

The results of multi-generation study indicates that under the conditions of this study, the no-observed-adverse-effect level (NOAEL) for reproductive toxicity was 1500 ppm (23.6 mg Cu/kg bw/day), the highest concentration tested. The NOAEL for P1 and F1 rats and F1 and F2 offspring during lactation was 1000 ppm, based on reduced spleen weight in P1 adult females, and F1 and F2 male and female weanlings at 1500 ppm however

the transient reduced spleen weights are not considered a reproductive endpoint as it did not affect growth or fertility.

Three of the substances and one form of zero valent copper in this category present a hazard for human health, based notably on the release/bioaccessibility of copper ions.

- **Copper sulphate pentahydrate: severe eye irritation and acute hazard by the oral route.**
- **Dicopper oxide: severe eye irritation, acute hazard by the oral and inhalation routes.**
- **Dicopper chloride hydroxide: acute hazard by the oral and inhalation route.**
- **Coated copper flakes: eye irritation, acute hazard by the oral and inhalation routes.**

Copper oxide, copper powder and copper massive do not pose a hazard to human health. In addition, the currently available evidence on the substances in the category do not cause concern for repeated dose toxicity, genotoxicity, reprotoxicity and carcinogenicity.

Adequate screening-level data are available to characterize the human health hazard for the purposes of the Cooperative Chemicals Assessment Programme.
Note: A voluntary risk assessment of copper and copper compounds was performed in the context of the EU Existing Substances Regulation

Environment

Essentiality and copper background level

Copper is an essential micronutrient, needed for optimal growth and development of micro-organisms, plants, animals and humans. Copper deficiency and copper toxicity was experimentally observed in freshwater, marine water and soil organisms.

Considering that copper is a natural element, essential for all life forms, the safe upper threshold levels need to be compared with copper background levels, the optimal concentration ranges and essentiality levels. As an example, typical copper ambient background levels, reported for European surface waters, range between 0.1 and 14 µg Cu/L with an EU-wide median value of 0.9 µg Cu/L. Some studies demonstrated copper deficiency for freshwater organisms at levels ranging between < 1 and 10 µg dissolved Cu/L.

Environmental fate properties

Copper is a natural element and transition metal. The release of copper ions (eg Cu(II)) depends on the substance, particle size and characteristics of the receiving medium. The solubility of Cu_2O and CuO is dependent on pH. Data on solubility and/or transformation/dissolution (OECD 29) indicate that copper sulphate pentahydrate, dicopper chloride hydroxide and Cu_2O have higher solubility than CuO (Annex 1). Copper metal (Cu°) needs to be transformed to its ionic forms (Cu+/Cu2+) to dissolve copper-ions. Copper metal (Cu°) transformation/dissolution to ionic copper (Cu^{+}/Cu^{2+}) takes place at the surface of the copper particles and is related to the pH and surface area exposed.

Transformation/dissolution tests (OECD 29) on CuO and Cu°, demonstrate important pH dependent copper release rates of ionic copper. At pH 6, 7days transformation/dissolution of CuO releases more than 10 times more copper ions than at pH 7. Similarly, at pH 6, 7 days transformation/dissolution of Cu° releases 5 times more copper ions than at pH 7. The results from the transformation/dissolution tests of CuO, copper massive materials (spheres of 1-1.5 mm diameter), copper powders and coated copper flakes are summarised in the table below.

Transformation/dissolution of CuO and Cu° materials, in accordance to OECD 29

Material	pH	Mass load-	Surface loading	µg soluble Cu/L

		ing (mg/L)	(mm^2/L)	7 days	28 days
CuO	6 7 8	1		49 5 0	210 9 1
Copper massive - wire and epoxy mounted (1.5 mm)	6	100	43-47	6-19	
Copper massive (1 mm) - read-across from wire and epoxy-mounted	6 6 6	1 10 100	0.67 6.7 67	<1 1-3 9-27	
Copper massive (1 mm) (epoxy mounted)	6	1	0.67	1	3
Fine Copper powders (10-50µm) - read-across from wire and epoxy-mounted	6	1	67-107	9-44	37-176*
Coated copper flakes	6 7	1 1	2900 2900	72 1 36 3	773 639

*From linear extrapolation of the7 days transformation/dissolution data

In conclusion, the information from solubility (see physico-chemistry) and transformation/dissolution tests with various copper-bearing materials demonstrate important differences in solubilisation properties ranging from fully soluble $CuSO_4.5H_2O$ to copper massive granules (1 mm diameter), with only 0.3% transformed/dissolved in 28 days at pH 6.
Hydrolysis, biodegradation and phototransformation are not applicable endpoints for copper and the inorganic copper salts.
The occurrence of various copper species will depend on the characteristics of the receiving environment. After being released into the environment, the Cu(II) ions typically bind to inorganic and organic ligands contained within water, soil and sediments. In water, Cu(II) binds to dissolved organic matter (e.g., humic or fulvic acids). The Cu(II) ion forms stable complexes with $-NH_2$, -SH, and, to a lesser extent, -OH groups in these organic acids. Cu(II) will also bind with varying affinities to inorganic and organic components in sediments and soils. For example, Cu(II) binds strongly to sulphides in sediments and to hydrous manganese and iron oxides in clay, and to humic acids, but much less strongly to aluminosilicates in sand. In all environmental compartments (water, sediment, soil), the binding affinities of Cu(II) with inorganic and organic matter is dependent on pH, the oxidation-reduction potential in the local environment, and the presence of competing metal ions and inorganic anions. The results of comparing the bio-availability of the Cu-ions in the receiving compartment must therefore be integrated in effects and risk characterisations.
Typical Kd-values for copper to freshwater suspended matter, freshwater sediment and soil are 30,246, 24,409 and 2,120 L/kg, respectively. Typical Kd-values for copper to marine and estuarine suspended matter are 131,826 and 56,234 L/kg, respectively. Typical Kd values correspond to 50^{th} percentiles of distribution of values from available monitoring data.

Scientific information on copper bioaccumulation factors (BCF, BAF, TTF) does not support the use of BAF or BCF values when they are used as traditional generic threshold criteria for the hazard potential since they are not an intrinsic property for copper. Therefore, for inorganic copper compounds, bioaccumulation factors should be used with caution (*Document ENV/JM/MONO(2001)*.

Indeed, for copper, acclimation and homeostatic regulation mechanisms are induced after longer exposure times. Furthermore, some organisms accumulate copper in a non-bioavailable form by using copper binding

and sequestrations mechanisms as regulation system. These adaptation and regulation systems play a role in the copper essentiality/toxicity profile and therefore, the BCF/BAF is not independent of exposure concentration and has no meaning for a hazard assessment.

Aquatic toxicity according to standard species/protocols

Different metal species are used as test substances in various ecotoxicity tests (e.g. $CuSO_4.5H_20$, $CuCl_2$, CuO). The metal ion (Cu^{2+}) drives the aquatic ecotoxicity and therefore, only tests with soluble inorganic copper compounds are retained. Acute and chronic toxicity data from the various soluble compounds (e.g. $CuSO_4.5H_20$, $CuCl_2$) were combined and expressed as soluble metal ion concentrations (µg dissolved Cu/L) causing a specific effect. To derive a reliable baseline data-set, the high quality measured toxicity values (µg dissolved Cu/L), obtained from the standard OECD test species and endpoints were retained.
High quality, acute $L(E)C_{50}$ values were retained from short term standard freshwater tests for 10 standard fish, invertebrate and algae test species (*Pseudokirchneriella subcapitata, Chlamydomonas reinhardtii, Chlorella vulgaris, Ceriodaphnia dubia, Daphnia magna, Oncorhynchus mykiss, Pimephales promelas, Lepomis macrochirus, Brachydanio rerio* and *Cyprinus carpio)*. Reliable values range between 3 and 9,150 µg Cu/L. The variability has been attributed to species-specific differences in sensitivity as well as water-characteristics such as pH, DOC and hardness. Species-specific geometric mean values range between 34 µg Cu/L (*Ceriodaphnia dubia*) and 2837 µg Cu/L (*Lepomis macrochirus*).

High quality, chronic NOEC(s) / EC_{10} values were retained from standard freshwater tests for 9 standard fish, invertebrate and aquatic plant test species (*Pseudokirchneriella subcapitata, Chlorella vulgaris, Chlamydomonas reinhardti* and *Lemna minor, Ceriodaphnia dubia, Daphnia magna, Oncorhynchus mykiss, Pimephales promelas* and *Salvelinus fontinalis*). Reliable values range between 2 and 337 µg Cu/L. The variability has been attributed to species and endpoint specific differences in sensitivity as well water-characteristics such as pH, DOC and hardness. Species-specific geometric mean values range between 12 µg Cu/L (*Ceriodaphnia dubia and Oncorhynchus mykiss*) and 137 µg Cu/L (*Chlorella vulgaris*). The information further indicates:

- The cellular mechanism of copper toxicity/deficiency, as well as the cellular mechanisms of copper homeostasis, has been largely preserved through evolution.
- The key indicator of copper toxicity is disturbance of the sodium homeostasis. The key target tissue for copper toxicity is therefore the water/organism interface, with cell wall and gill-like surfaces acting as target biotic ligands in all species investigated.
- The information on the ecotoxicity following exposures, through water and/or food and the information on metal bio-accumulation and homeostasis explain the observed small ratios between mortality and sub-lethal endpoints (typically a factor of 1 to 3).
- Large intra-species variability is observed and has been related to differences in copper species formed and different bio-availability in the various test media.

The hazard assessment of the substances in the category, derived from the acute $L(E)C_{50}$ or chronic NOEC(s) / EC_{10} values (µg dissolved Cu/L) and a molecular weight translation or the results from transformation/dissolution tests, shows that the copper compounds and the fine copper powders do pose a hazard to the environment. Coarse granules and massive copper materials release less copper ions and therefore pose less or no hazard to the environment under typical conditions.

Deriving the $HC_{5,50\%}$ from Species Sensitivity Distributions for freshwaters, marine waters and soils.

Several phenomena on the ecotoxicity of copper were considered for deriving $HC_{5,50\%}$ for freshwater, marine and soil compartments:

- The toxicity response is species-specific
- The toxicity response is dependent on the receiving environment
- The toxicity response is dependent on background levels

- The toxicity response is changing with time : e.g. ageing of copper in soils.

Freshwater

To derive a $HC_{5,50\%}$ value for the freshwater compartment, the standard chronic toxicity database was extended to include standard and non-standard species/protocols/endpoints**.** This resulted in a single-species chronic toxicity data–base of more than 200 NOEC/L(E)C_{10} values and 3 high quality, multi-species mesocosm studies. The observed single species NOEC/L(E)C_{10} values range between 2 and 510 µg Cu/L. The observed mesocosm NOEAECs[4] and LOEAEC [5] values were, respectively, 4 to 20 µg Cu/L and 9 to 40 µg Cu/L.

Accounting for species –specific differences : The copper aquatic effects database contains high quality, single-species chronic NOEC/L(E)C_{10} values for 27 species, representing algae, invertebrates (cladocerans, rotifer, molluscs, insects and amphipods), fish and higher plants. Species-specific geometric mean values range between 6 µg Cu/L (*Juga plicifera)*) and 137 µg Cu/L (*Chlorella vulgaris*). Considering the large number of species assessed, the statistical extrapolation method, applied to all NOEC/L(E)C_{10} values, is used to derive the $HC_{5,50\%}$.. Such Species Sensitivity Distribution was constructed using the non-normalised species-mean NOEC values for the most sensitive endpoints and resulted in a log normal $HC_{5,50\%}$ of 6 µg Cu/L.

Accounting for dependence on the water type: The species-specific NOECs observed are often characterised by large variability because Cu bioavailability and toxicity to aquatic organisms is influenced by abiotic parameters, such as pH, hardness and dissolved organic carbon (DOC). This raised the need to develop/use a bioavailability normalisation process for the $HC_{5,50\%}$ derivation. Chronic Biotic Ligand Models were developed for *Pseudokirchneriella subcapitata, Daphnia magna*, *Pimephales promelas* and *Oncorhynchus mykiss* in order to provide a mechanistic basis for understanding and predicting bioavailability through integration of chemical parameters (e.g. pH, hardness, DOC) and biological parameters (receptor sites on organism, mode of action).

The BLM models developed were further validated to represent the three basic trophic levels (algae, invertebrates and fish):
(1) a unified chronic model for the algae (*Pseudokirchneriella subcapitata, Chlamydomonas reinhardtii* and *Chlorella vulgaris*). The applicability of the model for predicting higher plant ecotoxicity (hydrocultures of barley) was demonstrated
(2) a chronic BLM for invertebrates (*Daphnia magna*). The capacity of the BLM for predicting copper toxicity to other invertebrates was demonstrated from copper toxicity studies with *Brachionus calyciflorus, Lampilis siliquoidea, Hyridella depressa* and *Hyalella azteca*
(3) a unified chronic model for 2 fish species (*Pimephales promelas and Oncorhynchus mykiss*).

The boundaries of the BLM applicability across species have been defined for pH (6-8.5), hardness (12-360 mg $CaCO_3$/L), dissolved organic carbon (DOC) (0-20 mg/L). The database showed under prediction for one field water with high Fe and Al and therefore boundaries were set as 332 µg dissolved Al/L and 332 µg dissolved Fe/L.

The BLMs developed for chronic fish (*P. promelas* and *O. mykiss*), invertebrates (*D. magna*) and algae (*P. subcapitata*) were used for normalising all retained chronic NOEC values of respectively fish, invertebrates and algae/plant species. Briefly, the bioavailability normalisation process normalises the NOEC/(L(E)C_{10} values to site-specific physicochemical conditions (i.e. pH, hardness and DOC).

The BLM normalised NOEC/(L(E)C_{10} values were used to construct Species Sensitivity Distributions for a range of physico-chemical conditions in European surface waters. Typical $HC_{5,50\%}$ s range between 7 and 30 µg Cu/L.

[4] NOEAEC : No Observed Ecological Adverse Effects Concentration
[5] LOEAEC : Lowest Observed Ecological Adverse Effects Concentration

Validation of the $HC_{5,50\%}$ derivation for multi-species systems: Species-specific NOECs and mesocosm specific NOEAECs / LOEAEC, protective of ecosystem structures and functions, are obtained from three distinct, high quality mesocosm studies, representing lentic and lotic system. Detailed comparisons between the BLM predicted and observed mesocosm effects, demonstrate that BLM could adequately predict the mesocosm sensitivity within a factor of 2.

Marine

The differences in physiology between freshwater and marine organisms, and the related differences in ecotoxic behaviour, led to the derivation of a separate $HC_{5,50\%}$ value for freshwater and marine environments. The estuarine compartment is not covered in this assessment.

The copper marine effects database contains more than 50 high quality, chronic NOECs/EC_{10}s values varying between 3 µg/L (*Phaeodactylum tricornutum*) and 145 µg/L (*Penaeus monodon*).

Accounting for species –specific differences: The copper marine effects database contains high quality, chronic NOECs/EC_{10}s values for 24 species. Species-specific geometric mean values range between 4 µg/*L (Phaeodactylum tricornutum*) and 145 µg/L (*Penaeus monodon*).

A Species Sensitivity Distribution was constructed using the species-specific NOECs and resulted in an $HC_{5,50\%}$ of 5 µg Cu/L.

Accounting for the characteristics of the marine water: Marine waters are characterised by high pH (typically around 8.3), high salinity (35‰) and high ionic strength. Unlike the inorganic composition of marine waters, DOC levels may vary considerable between marine water bodies. Open ocean waters usually have lower DOC, ranging between 0.5 and 1.8 mg/L. As for the freshwater system, Cu-availability and toxicity to marine organisms is therefore influenced by the strong binding of copper to the dissolved organic carbon (DOC). This raised the need to use an availability normalisation process.

A relationship between the EC_{50}s or NOEC/EC_{10}, values and the DOC levels were assessed for 6 species: *Fucus vesiculosus*, *Crassostreas gigas*, *Mytilus galloprovincialis*, *Dendraster excentricus*, *Strongylocentrotus purpuratu*s. Since the six data sets are statistically equivalent, these were combined for deriving an overall descriptor of the protective effects of DOC. This equation was used to translate all NOEC data to standard DOC levels of 2 mg DOC/L for coastal waters and 0.2 mg DOC/L for the open sea.

An organic carbon normalisation was carried out and the $HC_{5,50\%}$ was derived at a DOC levels representative of coastal and open ocean areas (2 and 0.2 mg/L). From the high quality data, $HC_{5,50\%}$ values of respectively 5.2 and 1.3 µg Cu/l, were derived.

Validation of the $HC_{5,50\%}$ derivation for a marine mesocosm: A marine mesocosm study resulted in NOEAEC and LOEAEC values of respectively 5.7 and 9.9 µg dissolved Cu/L. The mesocosm study therefore supports the $HC_{5,50\%}$ obtained from the single-species study. The assessment also confirmed that the DOC- normalised single species $HC_{5,50\%}$ is protective to the ecosystem structure and function.

Accounting for acclimation: copper deficiency is a well known phenomenon in open ocean but occurs at levels below the derived $HC_{5,50\%}$ for open oceans.

Terrestrial

The copper terrestrial effects database contains more than 250 high quality, chronic NOEC/EC_{10} values. The chronic NOECs/EC_{10}s vary between 8.4 mg/kg for *Eisenia andrei (*cocoon production) and 2,402 mg/kg (maize respiration). The lowest value is actually below the limit for essentiality for the species.

Information on 8 single species studies, in field contaminated soils, and 5 multi-species studies (freshly spiked and field contaminated) were used as an additional weight of evidence for the terrestrial compartment.

Accounting for species –specific differences: The copper terrestrial effects database contains high quality,

chronic NOEC values for 19 species and 9 microbial functions.

***Accounting for bioavailability dependence on the soil characteristics*:** To normalise the bio-availability data for soil type, a total of seven regression models were derived to predict toxicity of copper to terrestrial organisms for a wide range of soil types. For plants, the *L. esculentum* model (endpoint yield) was applied only on data for tomatoes, while all other plant data were normalised using the *H. vulgare* root elongation model because this endpoint is the most sensitive for plants. For invertebrates, the *E. fetida* model was used to normalise all soft-bodied species, while the *F. candida* model was used to normalise all hard-bodied species. For the microbial processes, all NOEC values related to the N-cycle were normalised based on the CEC slope of the nitrifying micro-organisms. The maize respiration model was used for normalisation of all microbial processes using a natural substrate. All other microbial processes were normalised using the substrate induced respiration model.

Accounting for soil leaching and ageing : Observed differences in toxicity of copper to terrestrial organisms, between lab spiked soils and field contaminated soils, allowed for the derivation of a leaching-ageing factor of 2, based on the 25-percentile of the ecotoxicity database. This factor was further supported by the mechanistic research on ageing and ionic strength (leaching) effects.

Deriving $HC_{5,50\%}$ values: Considering bio-availability and ageing, information from a large monitoring database allows calculating four $HC_{5,50\%}$ values of copper for soil samples taken from grazing land in European countries. The $HC_{5,50\%}$ values range between 13 and 205 mg Cu/kg dry weight, depending on the soil chemistry. A reasonable worst case 10th percentile of 69.6 mg Cu/kg dry weight is retained for the grazing land. A reasonable worst case 10^{th} percentile of 59.5 mg Cu/kg dry weight is retained for the arable land. The overall soil median reasonable worst case value across the two land-types is 64.6 mg Cu/kg dry weight.

Copper and copper compounds may present a hazard for the environment depending on the release/bioaccessibility of copper ions and on the conditions of the receiving environment (pH, hardness, presence and type of organic matter, anions and competing cations). Adequate screening-level data are available to characterize the environmental hazard for the purposes of the Cooperative Chemicals Assessment Programme.

Note: A voluntary risk assessment of copper and copper compounds was performed in the context of the EU Existing Substances Regulation[6].

Exposure

Production and uses - copper - worldwide

The 2012 global production of copper was 25.7 million tonnes. Approximately 20.2 million tonnes was produced from mining (primary production) and the smelting/refining of complex, end of life materials (secondary production). Another 5.5 million tonnes, combing offcuts from the value chain and clean, end-of- life scrap, were recycled directly by the producers of semi-fabricated products.

Recognising the locations of today's copper mines, Latin American is the main exporting region. The major importers are Asia, (particularly China, India and Korea) and, to a lesser extent, Europe. North America is

[6] *http://echa.europa.eu/copper-voluntary-risk-assessment-reports*

reasonably balanced between production and demand.

Production and uses - copper – Europe

EU production volume in 2012 of copper has stabilised at around 1.5 million tonnes for smelting and 1.8 million tonnes for refining. Additionally, around 1.3 million tonnes of scrap (secondary recycled raw material) is used as feedstock material. Besides the production, about 0.6 million tonnes of refined copper are imported in the EU.

Copper massive forms account for +/- 99.6% of the market. Principal uses include copper wire, for power cables, building wire, electric motors and voltage transformers, copper tubes and fittings, for domestic water, gas distribution, water heating systems and air conditioning, strip for the electronics industry and sheets for roofing, gutters and down-pipes.

Extrapolating EU data, copper powders are estimated to account for +/- 0.4%. They are mainly used for friction materials such as for vehicle brake pads, carbon brushes for electrical motors and sintered parts for engineering components.
Coated copper flakes represent less than 0.1% and are used mainly as pigments and as an active ingredient in antifouling paints.

Copper oxide is used as wood preservative (biocidal/antimicrobial), catalyst, brake pads, industrial (glass, ceramics).
Dicopper oxide is used as antifouling (biocidal/antimicrobial), fungicide (agrochemical), catalyst, "hot" industrial processes.
Copper sulphate pentahydrate is used as algaecide (biocidal/antimicrobial), fertiliser, raw material use, general industrial uses (dyes, mineral flotation, ceramics, glass), animal feed and foodstuffs.
Dicopper chloride hydroxide is used as fungicide (agrochemical), fertiliser and industrial uses e.g. ceramics

EU- exposure

Sources

Copper is a naturally occurring element that can be found at background levels in water, sediment and soil. Total copper releases were dominated by agricultural uses (feed additives and fertilizers, 39%) and traffic (mainly brake pads, 43%). Massive copper uses (wear of overhead wires, corrosion of copper tubes, fittings and taps and external building applications (roofs, gutters, down pipes, facades)) contribute to 15% of the total anthropogenic EU emissions. The relative contribution from waste incineration plants and landfill facilities is minor (0.4%). Other minor copper releases, that have been observed include, among others, industry releases, domestic and industrial heating, fireworks and domestic wastewaters .

Monitoring

Background levels of copper in water, sediment and soil are reported in the EU FOREGS Geochemical Atlas (Forum of European Geological Surveys). Median natural background concentration levels in Europe are 0.88 µg dissolved Cu/L for surface water (rivers and lakes), 14 mg/kg dry weight for river and lake sediment and 12 mg/kg dry weight for topsoil. Region-specific dissolved Cu freshwater PEC values, derived for Austria, Belgium, Denmark, Finland Barentz area, Germany Elbe, Ireland, Portugal, The Netherlands, Sweden, England, Wales and Scotland ranged between 0.5 and 4.7 µg dissolved Cu/L with a median of 2.7 µg dissolved Cu/L. Measured PECs for the EU-15 are 67,5 mg/kg dw for sediment and 31 mg/kg dw for agricultural soil.

Humans exposed via the environment

The contribution to dietary intake (copper from anthropogenic origin in fruit and vegetables, locally grown, and other foodstuffs) in the local environment was rather low due to the impact of industrial air pollution control measures and the effective homeostatic control of copper uptake by plants. External exposure through inhalation is even more limited.

Occupational exposure

The sectors that have been identified for estimating local exposures include: Smelting and Refining, Wirerod & Cables production, Casting Billets and Plates, Production of semi-finished copper shapes, Production of Copper Powders and Copper Chemicals. For melting and casting of billets and further processing, respirable copper as a function of total copper ranges from 6-25% with a median value of 9%. For smelting a single value of 13% is given while for non-foundry operations in the manufacture of copper powders the single value of 4%.

Consumer exposure

Consumer exposure to copper may occur via dermal or oral routes or via inhalation. Dermal exposure occurs mainly through the use of toiletries and cosmetics face cream and hair care products, through coin handling or jewellery. Additional dermal exposure is possible from the use of special paints or from copper containing wood preservatives and pesticides. Oral exposure (other than from food and water) occurs in particular by ingestion of dietary supplements containing copper, inhalation exposure occurs mainly through cigarette smoke. Internal exposure may also occur with the use of intra-uterine devices. There are no known exposures of consumers to other copper compounds covered in this category.

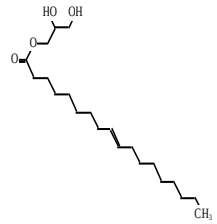
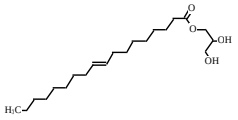
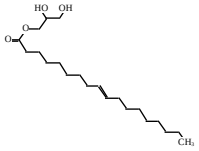
Limitations

The hazard profile is based on intensive literature searches and targeted research programs carried out for the European hazard classification and risk assessment regulation during the period 2000-2006. Recent findings are not included.

ANNEX 1: Standard OECD Solubility of copper compounds

Compound	pH range			
	5.5-6.5	**>6.5-7.5**	**>7.5-8.5**	**>8.5-10**
	Solubility (mg/L)			
$CuSO_4.5H_2O$	220000			
$Cu_2Cl(OH)_3$	1.19	-	-	0.525
Cu_2O	-	0.639	-	0.539
CuO	0.394	-	-	0.01

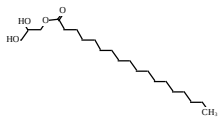
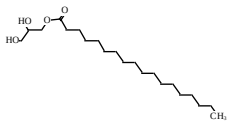
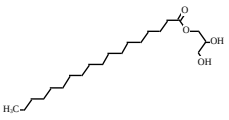
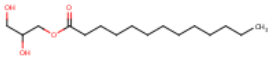
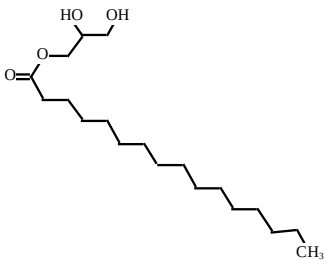
SIDS INITIAL ASSESSMENT PROFILE

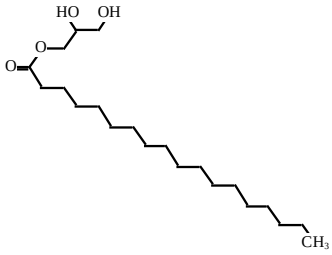
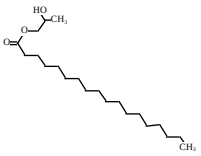
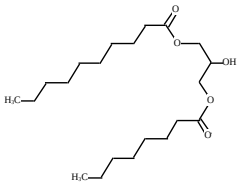
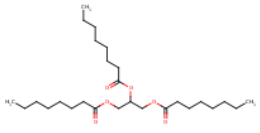
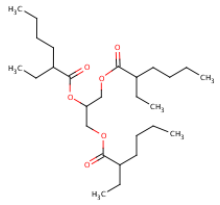
Category name	Glycerides Category		
CAS No(s), Chemical name(s) and structural formula(s) [1]	**CAS No [Class** [2] **]**	**IUPAC or CAS Name**	**Structural Formula**
	Monoglycerides		
	25496-72-4 [2]	Olein, mono-Octadecenoic acid, 1,2,3-propanetriol	
	37220-82-9 [2]	Glycerol oleate	
	68309-32-0 and 61790-12-3 [3] **[2]**	Glycerides,tall-oil	

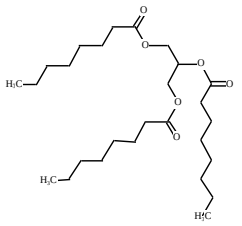
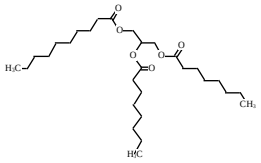
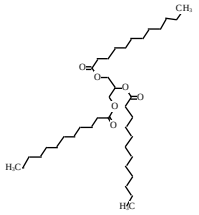
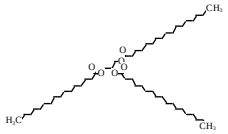
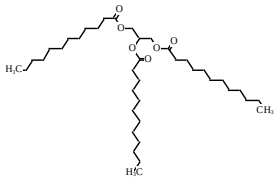
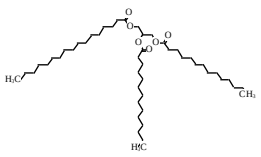
[1] Glycerides are commonly identified by industry and regulatory authorities as mono-, di-, tri, etc. and therefore the logical way to group the information in a manner that makes sense to the reader/reviewer is to provide subcategories (monoglycerides, diglycerides, triglycerides and mixtures of mono-, di- and triglycerides) and is consistent with the way these compounds are referenced in literature and regulatory references.

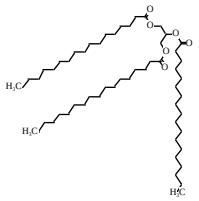
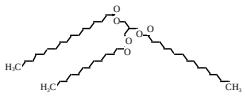
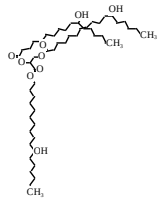
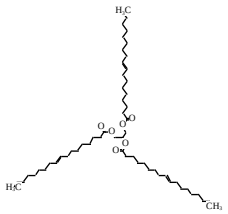
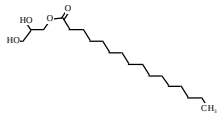
[2] Class 1 = single compounds composed of molecules with particular atoms arranged in a definite, known structure.
Class 2 = CHEMICAL SUBSTANCES OF UNKNOWN OR VARIABLE COMPOSITION, COMPLEX REACTION PRODUCTS AND BIOLOGICAL MATERIALS (UVCB)

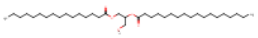
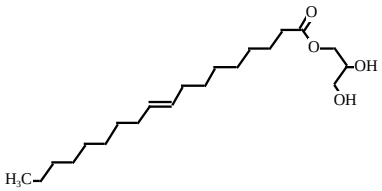
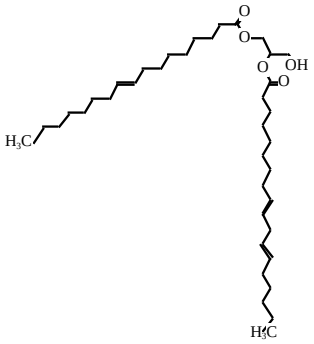
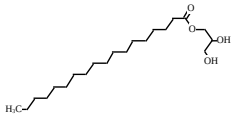
[3] The substances are analogues (the two CAS numbers describe the same substance).

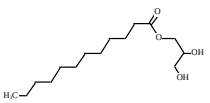
	31566-31-1 [2]	Octadecanoic acid, monoester with 1,2,3-propanetriol	
	61789-09-1 [2]	Monoglycerides, hydrogenated tallow	
	11099-07-3 and 67701-27-3[3] [2]	Glyceryl stearate	 and 
	91744-73-9 [2]	Glycerides, palm-oil mono-, hydrogenated	 and

		
	Diglycerides	
1323-39-3 **[2]**	Octadecanoic acid, 1,2-propanediol monoester	
65381-09-1 **[2]**	Decanoic acid, ester with 1,2,3-propanetriol octanoate	
	Triglycerides	
538-23-8 **[1]**	Octanoin, tri- (Octanoic acid, 1,2,3-propanetriyl ester; Tricaprylin)	
7360-38-5 **[1]**	Hexanoic acid, 2-ethyl-, 1,2,3-propanetriyl ester	

	85409-09-2 **[2]**	Glycerides, C8-10	
	73398-61-5 **[2]**	Glycerides, mixed decanoyl and octanoyl	
	8023-79-8 **[2]**	Oils, glyceridic, palm kernel	
	67701-28-4 **[2]**	Glycerides, C8-18 and C18-unsatd.	
	68334-28-1 **[2]**	Oils, vegetable, hydrogenated	
	67701-26-2 **[2]**	Glycerides, C12-18 (C14:C14:C18)	

	67701-30-8 **[2]**	Glycerides, C16-18 and C18-unsatd. (C18:C18:C18)	
	8030-12-4 **[2]**	Tallow, hydrogenated	
	8001-78-3 **[2]**	Castor oil, hydrogenated	
	122-32-7 **[2]**	Olein, tri - (Octadecenoic acid, 1,2,3-propanetriyl)	
	Mixtures of mono-, di- and triglycerides[1]		
	67701-33-1 **[2]**	Glycerides, C14-18 mono- and di-	
	68606-18-8 **[2]**	Glycerides, mixed coco, decanoyl and octanoyl	UVCB
	68424-61-3 **[2]**	Glycerides, C16-18 and C18-unsatd. mono- and di-	UVCB

	85251-77-0 [2]	Glycerides, C16-18 mono- and di-	
	97722-02-6 [2]	Glycerides, tall-oil mono-, di-, and tri-	 and 
	91744-20-6 [2]	Glycerides, C16-18 and C18-unsatd. mono-, di- and tri-	

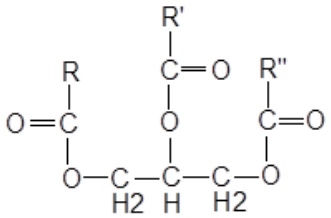
	68991-68-4 and **91052-53-8**[3] **[2]**	Coconut oil, transesterification products with decanoic acid mixed ester with glyceryl octanoate	

SUMMARY CONCLUSIONS OF THE SIAR

Category Rationale

The Glyceride Category contains thirty-one (31) sponsored glyceride substances which are defined as esters of monocarboxylic acids and glycerol bearing one (monoglycerides), two (diglycerides) or three (triglycerides) aliphatic chains, or, a mixture of mono-, di- and triglycerides, each ranging in number of carbons from 8 to 18. The C18 members of the group may be saturated or unsaturated with one carbon-carbon double bond. The glycerides grouping consists of both discrete chemicals with an incremental and constant change across its members (carbon chain length) and commercial mixtures that are composed of glycerides with a range of carbon chain lengths in its aliphatic side groups. The carbon chains do not contain any branching (they are all straight chains).

The chemical structure of the triglyceride members of this Glyceride Category is:



R, R1, and R2 are aliphatic chains containing from 8-18 carbon atoms, and two or three chains may be identical. The monoglycerides and diglycerides in this Glyceride Category have a similar structure except that glycerol is bonded to one and two aliphatic (fatty acid) chains, respectively, and have two and one free hydroxyl groups, respectively.

Glycerides are a group of lipids commonly called fats (solid at room temperature) and oils (liquid at room temperature). Due to the structural similarities of the glycerides, their physico-chemical properties are similar and

a clear correlation with chain length is observed. Melting point and boiling point increase with increasing chain length. The vapor pressures of the glycerides decrease with increasing carbon number and generally are low. Water solubility decreases and partition coefficient between octanol and water increase with increasing carbon number.

Fatty acids are generally ingested as triglycerides, which cannot be absorbed by the small intestine. When ingested, monoglycerides are readily absorbed through the duodenal mucosa and converted to triglycerides. In the small intestine, most triglycerides are split by pancreatic lipases into monoglycerides, free fatty acids, and glycerol, which can be absorbed by the intestinal mucosa. A small fraction of triglycerides are absorbed as free glycerol and as diglycerides. Once across the intestinal barrier, triglycerides are reformed. These resynthesized triglycerides collect into globules along with cholesterol and phospholipids and are encased in a protein coat as chylomicrons. Chylomicrons are transported in the lymph to the thoracic duct and eventually to the venous system. The chylomicrons are removed from the blood as they pass through the capillaries of adipose tissue. Fat is stored in adipose cells until it is transported to other tissues as free fatty acids which are used for cellular energy or incorporated into cell membranes.

Based on similarities in structural, physical chemical and toxicokinetic properties, read across among the sponsored substances is reasonable. The following table presents a summary of the read across approach (**bold text** indicates data are available; Read across is designated as "RA"). Read across results were selected based on the lowest available effects value or most conservative result.

Substance CAS#	**Acute toxicity (oral and inhalation)**	**Repeated dose (oral)**	**Gene mutation *in vitro***	**Chromosome aberration *in vitro***	**Chromosome aberration *in vivo***	**Effects on fertility and reproductive organs**	**Developmental toxicity (oral)**
Monoglycerides							
Olein, mono-Octadecenoic acid, 1,2,3-propanetriol **25496-72-4**	LD50 oral >2,000 (Read across (RA)	NOAEL = 2500 (90 day) (RA)	Negative (RA)	Negative (RA)	Negative (RA)	NOAEL = 5000 (M/F) (RA)	NOAEL = 5000 (RA)
Glycerol oleate **37220-82-9**	LD50 oral >2,000 (RA)	NOAEL = 2500 (90 day) (RA)	Negative (RA)	Negative (RA)	Negative (RA)	NOAEL = 5000 (M/F) (RA)	NOAEL = 5000 (RA)
Glycerides,tall-oil **68309-32-0** and **61790-12-3**	**LD50 oral >10,000**	**NOAEL = 12,500 (90 day)**	**Negative**	**Negative**	Negative (RA)	**NOAEL = 5000 (M/F)**	**NOAEL = 5000**
Octadecanoic acid, monoester with 1,2,3-propanetriol **31566-31-1**	LD50 oral >2,000 (RA)	NOAEL = 2500 (90 day) (RA)	**Negative**	Negative (RA)	Negative (RA)	NOAEL = 5000 (M/F) (RA)	NOAEL = 5000 (RA)
Monoglycerides, hydrogenated tallow **61789-09-1**	LD50 oral >2,000 (RA)	NOAEL = 2500 (90 day) (RA)	Negative (RA)	Negative (RA)	Negative (RA)	NOAEL = 5000 (M/F) (RA)	NOAEL = 5000 (RA)
Glyceryl stearate **11099-07-3** and **67701-27-3**	**LD50 oral >5,000**	NOAEL = 2500 (90 day) (RA)	Negative (RA)	Negative (RA)	Negative (RA)	NOAEL = 5000 (M/F) (RA)	NOAEL = 5000 (RA)
Diglycerides							
Octadecanoic acid, 1,2-propanediol monoester **1323-39-3**	**LD50 oral >5,000**	**NOAEL = 3760 (13 week)**	Negative (RA)	Negative (RA)	Negative (RA)	**NOAEL = 3760 (M/F)**	NOAEL = 5000 (RA)
Decanoic acid, ester with 1,2,3-propanetriol octanoate **65381-09-1**	**LD50 oral >5,000**	**NOAEL = 2500 (90 day)**	Negative (RA)	Negative (RA)	Negative (RA)	**NOAEL = 9800 (M/F)**	NOAEL = 5000 (RA)
Triglycerides							
Octanoin, tri-(Octanoic acid, 1,2,3-propanetriyl ester; Tricaprylin) **538-23-8**	**LD50 oral >5,000**	**NOAEL = 9500 (26 week)**	**Negative**	Negative (RA)	**Negative**	NOAEL = 5000 (M/F) (RA)	**NOAEL = 9500 (M/F)**

Hexanoic acid, 2-ethyl-, 1,2,3-propanetriyl ester **7360-38-5**	**LD50 oral >48,000**	NOAEL = 2500 (90 day) (RA)	**Positive**	Negative (RA)	**Negative**	NOAEL = 5000 (M/F) (RA)	NOAEL = 5000 (RA)
Glycerides, C8-10 **85409-09-2**	**LD50 oral >2,500**	**NOAEL = 2500 (90 day)**	Negative (RA)	Negative (RA)	Negative (RA)	**NOAEL = 9800 (M/F)**	NOAEL = 5000 (RA)
Glycerides, mixed decanoyl and octanoyl **73398-61-5**	**LD50 oral >5,000**	**NOAEL = 2500 (90 day)**	**Negative**	Negative (RA)	Negative (RA)	**NOAEL = 9800 (M/F)**	NOAEL = 5000 (RA)
Oils, glyceridic, palm kernel **8023-79-8**	**LD50 oral >5,000**	NOAEL = 2500 (90 day) (RA)	Negative (RA)	Negative (RA)	Negative (RA)	**NOAEL = 5000 (M/F)**	**NOAEL = 5000 (M/F)**
Glycerides, C8-18 and C18-unsatd. **67701-28-4**	LD50 oral >2,000 (RA)	NOAEL = 2500 (90 day) (RA)	Negative (RA)	Negative (RA)	Negative (RA)	NOAEL = 5000 (M/F) (RA)	NOAEL = 5000 (RA)
Oils, vegetable, hydrogenated **68334-28-1**	LD50 oral >2,000 (RA)	NOAEL = 2500 (90 day) (RA)	Negative (RA)	Negative (RA)	Negative (RA)	NOAEL = 5000 (M/F) (RA)	NOAEL = 5000 (RA)
Glycerides, C12-18 **67701-26-2**	**LD50 oral >10,000**	NOAEL = 2500 (90 day) (RA)	Negative (RA)	Negative (RA)	Negative (RA)	NOAEL = 5000 (M/F) (RA)	NOAEL = 5000 (RA)
Glycerides, C16-18 and C18-unsatd. **67701-30-8**	LD50 oral >2,000 (RA)	NOAEL = 2500 (90 day) (RA)	Negative (RA)	Negative (RA)	Negative (RA)	NOAEL = 5000 (M/F) (RA)	NOAEL = 5000 (RA)
Tallow, hydrogenated **8030-12-4**	LD50 oral >2,000 (RA)	NOAEL = 2500 (90 day) (RA)	Negative (RA)	Negative (RA)	Negative (RA)	NOAEL = 5000 (M/F) (RA)	NOAEL = 5000 (RA)
Castor oil, hydrogenated **8001-78-3**	LD50 oral >2,000 (RA)	NOAEL = 2500 (90 day) (RA)	**Negative**	Negative (RA)	Negative (RA)	NOAEL = 5000 (M/F) (RA)	NOAEL = 5000 (RA)
Olein, tri - (Octadecenoic acid, 1,2,3-propanetriyl) **122-32-7**	**LD50 oral >2,000**	NOAEL = 2500 (90 day) (RA)	**Negative**	Negative (RA)	Negative (RA)	NOAEL = 5000 (M/F) (RA)	NOAEL = 5000 (RA)
Mixtures of mono-, di- and triglycerides							
Glycerides, C14-18 mono- and di- **67701-33-1**	LD50 oral >2,000 (RA)	NOAEL = 2500 (90 day) (RA)	Negative (RA)	Negative (RA)	Negative (RA)	NOAEL = 5000 (M/F) (RA)	NOAEL = 5000 (RA)
Glycerides, mixed coco, decanoyl and octanoyl **68606-18-8**	LD50 oral >2,000 (RA)	NOAEL = 2500 (90 day) (RA)	Negative (RA)	Negative (RA)	Negative (RA)	NOAEL = 5000 (M/F) (RA)	NOAEL = 5000 (RA)
Glycerides, C16-18 mono- and di- **85251-77-0**	LD50 oral >2,000 (RA)	NOAEL = 2500 (90 day) (RA)	Negative (RA)	Negative (RA)	Negative (RA)	NOAEL = 5000 (M/F) (RA)	NOAEL = 5000 (RA)
Glycerides, tall-oil mono-, di-, and tri- **97722-02-6**	LD50 oral >2,000 (RA)	NOAEL = 2500 (90 day) (RA)	Negative (RA)	Negative (RA)	Negative (RA)	NOAEL = 5000 (M/F) (RA)	NOAEL = 5000 (RA)
Glycerides, C16-18 and C18-unsatd. mono-, di- and tri- **91744-20-6**	**LD50 oral >2,000**	NOAEL = 2500 (90 day) (RA)	**Negative**	Negative (RA)	Negative (RA)	NOAEL = 5000 (M/F) (RA)	NOAEL = 5000 (RA)
Coconut oil,transesterification products with decanoic acid mixed ester with glyceryl octanoate **68991-68-4** and **91052-53-8**	LD50 oral >2,000 (RA)	NOAEL = 2500 (90 day) (RA)	Negative (RA)	Negative (RA)	Negative (RA)	NOAEL = 5000 (M/F) (RA)	NOAEL = 5000 (RA)

Substance CAS#	Biodegradation	Acute aquatic toxicity (mg/L)		
		Fish 96 hr LC50	Aquatic invertebrate 48 hr EC50	Aquatic plants 72 hr EC50
Monoglycerides				
Olein, mono- Octadecenoic acid, 1,2,3-propanetriol **25496-72-4**	Readily biodegradable (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)
Glycerol oleate **37220-82-9**	Readily biodegradable (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)
Glycerides,tall-oil **68309-32-0** and **61790-12-3**	**Readily biodegradable**	**LL50* >1000 (nominal)**	**EL50* >1000 (nominal)**	**EbL50* = 854.9 (nominal), ErL50* >1000 (nominal)**
Octadecanoic acid, monoester with 1,2,3-propanetriol **31566-31-1**	**Readily biodegradable**	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)
Monoglycerides, hydrogenated tallow **61789-09-1**	Readily biodegradable (RA)	**>10,000 (nominal)**	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)
Glyceryl stearate **11099-07-3** and **67701-27-3**	Readily biodegradable (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)
Diglycerides				
Octadecanoic acid, 1,2-propanediol monoester **1323-39-3**	Readily biodegradable (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)
Decanoic acid, ester with 1,2,3-propanetriol octanoate **65381-09-1**	**Readily biodegradable**	**>10,000 (nominal)**	**EL50 >100 (nominal; 21 d)**	**EbL50, ErL50 >100 (nominal)**
Triglycerides				
Octanoin, tri- (Octanoic acid, 1,2,3-propanetriyl ester; Tricaprylin) **538-23-8**	Readily biodegradable (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)
Hexanoic acid, 2-ethyl-, 1,2,3-propanetriyl ester **7360-38-5**	**Readily biodegradable**	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)
Glycerides, C8-10 **85409-09-2**	**Readily biodegradable**	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)
Glycerides, mixed decanoyl and octanoyl **73398-61-5**	**Readily biodegradable**	**>53 (measured)**	**EL50 >100 (nominal)**	**EbL50, LLr50 > 1000 (nominal)**
Oils, glyceridic, palm kernel **8023-79-8**	Readily biodegradable (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)
Glycerides, C8-18 and C18-unsatd. **67701-28-4**	Readily biodegradable (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)
Oils, vegetable, hydrogenated **68334-28-1**	Readily biodegradable (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)
Glycerides, C12-18 **67701-26-2**	Readily biodegradable (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)
Glycerides, C16-18 and C18-unsatd. **67701-30-8**	**Readily biodegradable**	**>10,000 (nominal)**	**EL50 >100 (nominal; 21 d)**	**EbL50, ErL50 >100 (nominal)**
Tallow, hydrogenated **8030-12-4**	Readily biodegradable (RA)	>100 or exceeds water solubility (RA)	**EL50 >100 (nominal)**	**EbL50, ErL50 >100 (nominal)**
Castor oil, hydrogenated **8001-78-3**	**Readily biodegradable**	**>10,000 (nominal)**	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)
Olein, tri - (Octadecenoic acid, 1,2,3-propanetriyl) **122-32-7**	**Readily biodegradable**	>100 or exceeds water solubility (RA)	**EL50 >100 (nominal)**	>100 or exceeds water solubility (RA)
Mixtures of mono-, di- and triglycerides				
Glycerides, C14-18 mono- and di- **67701-33-1**	**Readily biodegradable**	**>10,000 (nominal)**	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)
Glycerides, mixed coco, decanoyl and octanoyl **68606-18-8**	Readily biodegradable (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)
Glycerides, C16-18 mono- and di- **85251-77-0**	Readily biodegradable (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)

Glycerides, tall-oil mono-, di-, and tri- **97722-02-6**	**Readily biodegradable**	**1700 (nominal)**	**EL50 >100 (nominal)**	**ECr50 = 13.88 (nominal; exceeds the estimated water solubility of the substance)**
Glycerides, C16-18 and C18-unsatd. mono-, di- and tri- **91744-20-6**	**Readily biodegradable**	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)
Coconut oil,transesterification products with decanoic acid mixed ester with glyceryl octanoate **68991-68-4** and **91052-53-8**	Readily biodegradable (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)

*WAF sample preparations are reported relative to a loading rate rather than a concentration [LL50 (fish); EL50 (daphnia); EbL50/ErL50 (algae)]

Physical-chemical Properties

The thirty-one (31) sponsored substances are solid or liquid glycerides and include i) two (2) substances composed of molecules with particular atoms arranged in a definite, known structure (defined chain length), and ii) twenty-nine (29) substances that are mixtures with a range of components. It is not possible to estimate values for mixtures with confidence and for the purposes of this assessment have been characterized by a representative chain length.

A property of a mixture of glycerides is therefore a function of that property for each of the discrete chain length components in the mixture. Melting point and boiling point increase with increasing chain length. Measured melting point values range from -32°C (**CAS 122-32-7;** triglyceride) to 85.4 °C (**CAS 8001-78-3,** triglyceride); for glycerides without measured data, estimated melting points range from 57-74 °C (**CAS 91744-20-6,** monoglyceride) to 349.8 °C (**CAS 67701-30-8,** triglyceride). Measured boiling point values range from 233°C at 1013 hPa (**CAS 538-23-8,** triglyceride) to 360-410 °C at 1013-1021 hPa (**CAS 7360-38-5,** triglyceride); for glycerides without measured data, estimated boiling points range from 378.7 °C (**CAS 68991-68-4 and 91052-53-8,** Mixtures of mono-, di- and triglycerides) to 893.4 °C (**CAS 8001-78-3,** triglyceride). Vapor pressure decreases with increasing carbon number and generally are low (5.09E-10 hPa at 25°C for **CAS 538-23-8,** triglyceride**,** measured; for glycerides without measured data, estimated values are <1E-05 hPa. Water solubility increases with decreasing carbon number; measured values range from <0.05 mg/L at 20°C (**CAS 8001-78-3**) to 3020 mg/L at 20 °C (**CAS 7360-38-5**, triglyceride); for glycerides without measured data, estimated values range from 6.52E-21 mg/L (**CAS 67701-30-8,** triglyceride) to 12.7 mg/L (**CAS 68991-68-4 and 91052-53-8,** Mixtures of mono-, di- and triglycerides). Measured partition coefficient values (log Kow) range from >3 at 20°C (**CAS 73398-61-5,** triglyceride) to >6.5 (**CAS 7360-38-5,** triglyceride); for glycerides without measured data, estimated values range from 3.7 (**CAS 68991-68-4 and 91052-53-8,** Mixtures of mono-, di- and triglycerides) to 23.9 (**CAS 67701-30-8,** triglyceride).

Human Health

Most of the available toxicokinetic data (animal and humans) relates to the absorption of triglycerides including **CAS 122-32-7**, **CAS 7360-38-5**, **CAS 8023-79-8** and **CAS 73398-61-5**, following oral administration, with limited data on its absorption after intravenous and dermal dosing. Toxicokinetic data are also available for **CAS 1323-39-3** (diglyceride), Data were not located for the inhalation route.

Glycerides are expected to be readily absorbed following ingestion, with rapid elimination from most tissues (possible exception of adipose, spleen). Glyceride metabolism and re-synthesis play a role in the absorption and distribution of ingested glycerides. Expiration is at least one route of elimination for ingested glycerides. These pathways are relevant for humans as well as other mammals.

Acute oral toxicity studies were located for twelve (12) Glyceride Category members (CAS **61790-12-3 and 11099-07-3** (monoglycerides)**, 1323-39-3 and 65381-09-1** (diglycerides)**, 538-23-8, 7360-38-5, 85409-09-2, 73398-61-5, 8023-79-8, 67701-26-2 and 122-32-7** (triglycerides) and, **91744-20-6** (mixtures of mono-, di- and triglycerides)). The oral LD50s for rats are > 2000 mg/kg bw (**CAS 122-32-7** (triglycerides) and **91744-20-6** (mixtures of mono-, di- and triglycerides)), and range up to > 48,000 mg/kg bw (**CAS 7360-38-5** (triglyceride) (OECD 401, Directive 84/449/EEC, B.1, or no guideline specified)). At doses consistent with recent testing standards (i.e., 2000 to 5000 mg/kg bw), there were no clinical signs, changes in body weight or findings at gross necropsy. Similar findings (LD50s and lack of toxicity) were reported for mice. Acute aerosol inhalation studies

were located for two glycerides (**CAS 85409-09-2** and **73398-61-5,** triglycerides); there were no adverse findings when rats or guinea pigs were exposed to 0.028 mg/L for six hours.

Skin and eye irritation studies were located for six (6) and five (5) members of the Glycerides Category, respectively. The Glycerides (**CAS 11099-07-3** (monoglyceride), **1323-39-3** (diglyceride), **7360-38-5, 73398-61-5** and **8023-79-8** (triglycerides) and **91744-20-6** (mixtures of mono-, di- and triglycerides) are not irritating to slightly irritating to the skin in standard irritation (Draize, OECD 405, FHSLA, or DOT) studies using rabbits. When a single occlusive patch containing an undiluted glyceride (**CAS 11099-07-3,** monoglyceride) was applied to human volunteer skin for 24 hours, no to slight irritation was noted. The Glycerides (**CAS 11099-07-3 (**monoglyceride**), 1323-39-3 (**diglyceride**), 73398-61-5** and **67701-26-2** (triglycerides) and **91744-20-6 (**mixtures of mono-, di- and triglycerides)) are not irritating to slightly irritating to the eyes in standard eye irritation (Draize or similar) studies using rabbits. The untested members of the Glyceride Category are expected to be not or slightly irritating to the skin and eyes. Clinical signs of respiratory tract irritation were not observed following 6 hour inhalation exposures to aerosols of two Glyceride Category members (**CAS 85409-09-2** and **73398-61-5,** triglycerides**)** at 0.028 mg/L.

Skin sensitization studies with guinea pigs and/or human volunteers were located for four (4) members of the Glycerides Category. In standard Magnusson and Kligman guinea pig maximization tests, the Glyceride Category members were not skin sensitizers. **CAS 73398-61-5,** triglyceride) was tested only in a guinea pig maximization test). In patch **(CAS 11099-07-3,** monoglyceride, and **7360-38-5,** triglyceride) or chamber studies with human volunteers (**CAS 122-32-7**, triglyceride), the Glyceride Category members were not skin sensitizers. The untested members of the Glyceride Category are expected to also not be skin sensitizers.

Repeated dose oral (gavage or diet studies) have been located for six (6) of the Glyceride Category members (**CAS 61790-12-3 (**monoglyceride**), 1323-39-3** and **65381-09-1 (**diglycerides**), 538-23-8, 85409-09-2** and **73398-61-5** (triglycerides). There were no adverse effects of treatment reported following repeated oral studies with rats, by either gavage or diet route. The NOAELs were =>2500 mg/kg bw, indicating the Glyceride Category members are not toxic. Although the studies do not conform to current, standard guidelines, the substances do not cause systemic toxicity. Similar results are expected for the Glyceride Category members that have not been tested.

In vitro and *in vivo* mutagenicity studies have been located for eight (8) and one (1) of the Glyceride Category members, respectively. The Glyceride Category members are negative for genotoxicity (*in vitro* bacterial reverse mutation assays (**CAS 68309-32-0** and **61790-12-3** and **31566-31-1 (**monoglycerides**), 538-23-8**, **73398-61-5, 8001-78-3** and **122-32-7 (**triglycerides**),** and **91744-20-6 (**mixtures of mono-, di- and triglycerides), *in vivo* host-mediated mutagenicity assay (**CAS 538-23-8,** triglyceride), in vitro (**CAS 68309-32-0** and **61790-12-3**, monoglycerides) or *in vivo* (**CAS 538-23-8,** triglyceride) chromosomal aberration, in vivo micronucleus assay (**CAS 538-23-8,** triglyceride), *in vivo* dominant lethal (**CAS 538-23-8**, triglyceride) and SCE (**CAS 538-23-8,** triglyceride and **CAS 7360-38-5**, triglyceride). One of the substances (CAS **7360-38-5**, triglyceride), was positive in an *in vivo* mouse spot test; the weight of evidence suggests this is not representative of the Glyceride Category members. A lack of genotoxicity is expected for those Glyceride Category members that have not been tested.

A carcinogenicity study has been located for Glyceride Category member **CAS 538-23-8 (**triglyceride**)**. In a two year gavage carcinogenicity study, there were significant dose-related increased incidences of pancreatic exocrine hyperplasia and adenoma, and proliferative lesions of the forestomach of rats administered **CAS 538-23-8 (**triglyceride**)**. Nephropathy and related severity were significantly decreased in high dose rats, and the incidence of mononuclear cell leukemia was decreased. A level of evidence of carcinogenicity was not assigned by NTP. A carcinogenicity study with tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) was conducted to test the transplacental carcinogenicity of NNK. Groups of pregnant hamsters were given subcutaneous (s.c.) injections of single or multiple doses of NNK (cumulative dose range, 50–300 mg/kg**),** on day 15 (last day of gestation) or on days 13, 14, and 15 of gestation, three s.c. injections of **CAS 7360-38-5** (triglyceride, 43 males, 40 females, last 3 days of gestation) and the offspring were evaluated for tumor development up to one year later. Within 1 year after treatment, up to 70% of the offspring developed tumors in various organs, including respiratory tract, nasal cavity, adrenal glands, pancreas, and liver. No tumors were found in the control hamsters treated with the vehicle (trioctanoin) alone. The overall tumor incidence was proportional to the cumulative dose. Females had a generally higher tumor incidence than males. **CAS 7360-38-5** (triglyceride) was negative in this study for transplacental carcinogenicity.

Effects on fertility and developmental toxicity studies were located for six (6) and five (5) Glyceride Category members, respectively. There were no effects on fertility (**CAS 61790-12-3** (monoglyceride)**, 1323-39-3** and **65381-09-1** (diglycerides), **85409-09-2, 73398-61-5** and **8023-79-8** (triglycerides**)** or developmental effects (**CAS 61790-12-3**, monoglyceride, **538-23-8, 7360-38-5** and **8023-79-8,** triglycerides**)** in rats, mice or hamsters in studies similar to OECD 416, FDA/WHO/DGHS safety evaluation protocol, 90 day studies examining reproductive organs, three–generation study or developmental studies with no protocol specified. In a developmental toxicity study in rats in which **CAS 538-23-8** was used as the vehicle control (9500 mg/kg bw) and water was used as the negative control, it was evident that the vehicle itself exerted a mild degree of developmental toxicity. There was a statistically significant 8% increase in total soft tissue malformations in the vehicle control group compared to 0% in the water control group. Maternal weight gain and fetal size were also lower in animals receiving **CAS 538-23-8** compared to the water controls, but these were not statistically significant." In a 3-generation study with **CAS 73398-61-5** (triglyceride), during lactation the volume of milk secreted by rats receiving the medium chain triglyceride in the diet at 9800 mg/kg bw was smaller and resulted in slower gain in body weight; after weaning, normal growth of the rats resumed. In this study, the LOAEL for developmental toxicity was 9800 mg/kg bw. Although the studies do not all conform to current, standard guidelines, the NOAELs were all greater than 2000 mg/kg bw. Similar results are expected for the Glyceride Category members which have not been tested.

The Glycerides Category members do not possess properties indicating a hazard for human health. Adequate screening-level data are available to characterize the hazard to human health for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Environment

Hydrolysis (OECD TG 111) studies have not been conducted for the glycerides. The ester group on the glycerides can be hydrolyzed to generate glycerin and the corresponding fatty acid. However, hydrolysis is expected to be very slow (>1 year) at room temperature, and the limited water solubility and steric hindrance of many of these substances will contribute to the lack of hydrolysis. If hydrolysis were to occur, the expected hydrolysis products (glycerin and the fatty acid) would not further hydrolyze, as there are no additional hydrolyzable groups for these substances.

The glycerides are subject to indirect photodegradation in air. Modeled photodegradation rates (half-lives) were estimated using AopWin v1.92 (EPI Suite v4.11). Estimated half-lives (hours; based on 12 hours of light per day; 1.5E+6 OH/cm^3) for hydroxyl radicals generally increase with decreasing chain length and range from ca. 0.5 hours (**CAS 122-32-7,** triglyceride) to 4.7 hours (**CAS 7360-38-5**, triglyceride). No ozone reaction was estimated for most of the glycerides (the model is only applicable to unsaturated molecules); for those Glyceride Category members for which an estimation was made, the half-lives (hours, 7E-11 mol/cm^3) for ozone reaction range from 0.46 to 2.1 hours (**CAS 25496-72-4, 37220-82-9, 68309-32-0** and **61790-12-3** (monoglycerides), **122-32-7** (triglyceride), **68424-61-3** and **97722-02-6** (mixtures of mono-, di- and triglycerides). Level III fugacity modelling using EPI Suite v4.11 indicates that the glycerides will distribute primarily to soil and water, with lesser amounts to air and sediment.

Biodegradation studies generally confirm that the extent of biodegradation observed in 28 days meets the ready biodegradability criterion (**CAS 68309-32-0** and **61790-12-3** (monoglycerides, 56-84% in 28 days)**, 31566-31-1** (monoglyceride, 108% in 51 days), **65381-09-1** (monoglyceride, 73 - 88% in 30 days), **7360-38-5** (triglyceride, >= 70.2 — <= 73.8 in 28 days), **85409-09-2** (triglyceride, 91.2 - 99.6% in 28 days), **73398-61-5** (triglyceride, 93% in 28 days), **67701-30-8** (triglyceride, 73 - 109% in 30 days)**, 8001-78-3** (triglyceride, 64% in 28 days)**, 122-32-7** (triglyceride, 77% in 28 days), **67701-33-1** (69 - 95% in 28 days; 68 - 73% in 30 days), **97722-02-6** (79% in 28 days)**,** and **91744-20-6** (mixtures of mono-, di- and triglycerides, 72% in 28 days)). In one study, biodegradation under anaerobic conditions was also demonstrated (CAS **122-32-7**; triglyceride, 63-106% in 51 days). Glyceride Category members that have not been tested are expected to be readily biodegradable based on read across to other Glyceride Category members.

Measured bioconcentration (BCF) factor data were not located for the Glycerides Category members. Estimated BCF values are calculated using BCFBAF v3.01 (EPI Suite v4.11). The Glyceride Category members have BCF values less than 500, indicating a low potential for bioaccumulation with the exception of **CAS 1323-39-3 (**diglyceride), with estimated BCF value of 1574. However, this value is very likely an overestimate of the substance's bioaccumulation potential since the influence of metabolism (via the common mechanism of β-

oxidation), which will be very high for substances in this category, is not fully represented. Overall, substances in the category have a low potential for bioaccumulation.

Due to the poorly soluble nature of many category members, it was difficult to distinguish whether the toxicity observed was due to the chemical toxicity or the physical presence of the test substance (particulates floating in and on the surface of the water, suds or film on the surface of the water) during aquatic toxicity testing. Therefore, two general strategies were used for testing these substances: (1) the use of a Water Accommodated Fraction (WAF) prepared at a maximum loading rate (i.e. concentrations of the test substance is significantly above its solubility limit) or (2) the use of a direct addition method in which the test substance was added directly to the test vessels, followed by shaking/stirring/use of a homogenizer for an extended period of time to allow for equilibrium. For both of these methods, it is more appropriate to report the nominal loading rate rather than a measured concentration, since the values greatly exceed the water solubility of the test substance. Acute toxicity test results are presented for aquatic species.

Fish

Name and CAS Number	Species/Test method	LC50 (mg/L), 96 hr	
Monoglycerides			
Olein, mono- Octadecenoic acid, 1,2,3-propanetriol **25496-72-4**	No data located		
Glycerol oleate **37220-82-9**	No data located		
Glycerides,tall-oil **68309-32-0** and **61790-12-3**	*Pimephales promelas*/ OECD 203/static	LL50* >1000 (nominal)	
Octadecanoic acid, monoester with 1,2,3-propanetriol **31566-31-1**	No data located		
Monoglycerides, hydrogenated tallow **61789-09-1**	No data located		
Glyceryl stearate **11099-07-3** and **67701-27-3**	No data located		
Glycerides, palm-oil mono-, hydrogenated **91744-73-9**	No data located		
Diglycerides			
Octadecanoic acid, 1,2-propanediol monoester **1323-39-3**	No data located		
Decanoic acid, ester with 1,2,3-propanetriol octanoate **65381-09-1**	*Danio rerio*/Similar to OECD 203/semi-static	>10,000 (nominal)	
Triglycerides			
Octanoin, tri- (Octanoic acid, 1,2,3-propanetriyl ester; Tricaprylin) **538-23-8**	No data located		
Hexanoic acid, 2-ethyl-, 1,2,3-propanetriyl ester **7360-38-5**	No data located		
Glycerides, C8-10 **85409-09-2**	No data located		
Glycerides, mixed decanoyl and octanoyl **73398-61-5**	*Danio rerio*/Directive 92/69/EEC, C.1/semi-static	>53 (measured)	
Oils, glyceridic, palm kernel **8023-79-8**	No data located		
Glycerides, C8-18 and C18-unsatd. **67701-28-4**	No data located		
Oils, vegetable, hydrogenated **68334-28-1**	No data located		
Glycerides, C12-18 **67701-26-2**	No data located		
Glycerides, C16-18 and C18-unsatd. **67701-30-8**	*Danio rerio*/Similar to OECD 203/semi-static daily renewal	>10,000 (nominal)	
Tallow, hydrogenated **8030-12-4**	No data located		
Castor oil, hydrogenated **8001-78-3**	*Danio rerio*/ ISO 7346/2/semi-static daily renewal	>10,000 (nominal)	

Olein, tri - (Octadecenoic acid, 1,2,3-propanetriyl) **122-32-7**	No data located		
Mixtures of mono-, di- and triglycerides			
Glycerides, C14-18 mono- and di- **67701-33-1**	*Danio rerio*/Similar to OECD 203/semi-static daily renewal	>10,000 (nominal)	
Glycerides, mixed coco, decanoyl and octanoyl **68606-18-8**	No data located		
Glycerides, C16-18 and C18-unsatd. mono- and di- **68424-61-3**	No data located		
Glycerides, C16-18 mono- and di- **85251-77-0**	No data located		
Glycerides, tall-oil mono-, di-, and tri- **97722-02-6**	*Danio rerio*/Similar to OECD 203/semi-static daily renewal	1700 (nominal)	
Glycerides, C16-18 and C18-unsatd. mono-, di- and tri- **91744-20-6**	No data located		
Coconut oil,transesterification products with decanoic acid mixed ester with glyceryl octanoate **68991-68-4** and **91052-53-8**	No data located		

Aquatic Invertebrates

Name and CAS Number	**Species/Test method**	**EC50 (mg/L) 48 hr**	
Monoglycerides			
Olein, mono- Octadecenoic acid, 1,2,3-propanetriol **25496-72-4**	No data located		
Glycerol oleate **37220-82-9**	No data located		
Glycerides,tall-oil **68309-32-0** and **61790-12-3**	*Daphnia magna*/OECD 202/static	EL50*>1000 (nominal)	
Octadecanoic acid, monoester with 1,2,3-propanetriol **31566-31-1**	No data located		
Monoglycerides, hydrogenated tallow **61789-09-1**	No data located		
Glyceryl stearate **11099-07-3** and **67701-27-3**	No data located		
Glycerides, palm-oil mono-, hydrogenated **91744-73-9**	No data located		
Diglycerides			
Octadecanoic acid, 1,2-propanediol monoester **1323-39-3**	No data located		
Decanoic acid, ester with 1,2,3-propanetriol octanoate **65381-09-1**	*Daphnia magna*/OECD 202/semi-static renewal every 2-3 days	EL50>100 (nominal; 21 d)	
Triglycerides			
Octanoin, tri- (Octanoic acid, 1,2,3-propanetriyl ester; Tricaprylin) **538-23-8**	No data located		
Hexanoic acid, 2-ethyl-, 1,2,3-propanetriyl ester **7360-38-5**	No data located		
Glycerides, C8-10 **85409-09-2**	No data located		
Glycerides, mixed decanoyl and octanoyl **73398-61-5**	*Daphnia magna*/EU Guideline 92/69/EWG/static	EL50>100 (nominal)	
	Daphnia magna/EU Guideline 92/69/EWG/static	EL50>100 (nominal)	
Oils, glyceridic, palm kernel **8023-79-8**	No data located		
Glycerides, C8-18 and C18-unsatd. **67701-28-4**	No data located		

Oils, vegetable, hydrogenated **68334-28-1**	No data located		
Glycerides, C12-18 **67701-26-2**	No data located		
Glycerides, C16-18 and C18-unsatd. **67701-30-8**	*Daphnia magna*/similar to OECD 202/semi-static renewal every 2-3 days	EL50>100 (nominal; 21 d)	
Tallow, hydrogenated **8030-12-4**	*Daphnia magna*/similar to OECD 202/static	EL50>100 (nominal)	
Castor oil, hydrogenated **8001-78-3**	No data located		
Olein, tri - (Octadecenoic acid, 1,2,3-propanetriyl) **122-32-7**	*Daphnia magna*/EU Guideline 92/69/EWG/static	EL50>100 (nominal)	
Mixtures of mono-, di- and triglycerides			
Glycerides, C14-18 mono- and di- **67701-33-1**	No data located		
Glycerides, mixed coco, decanoyl and octanoyl **68606-18-8**	No data located		
Glycerides, C16-18 and C18-unsatd. mono- and di- **68424-61-3**	No data located		
Glycerides, C16-18 mono- and di- **85251-77-0**	No data located		
Glycerides, tall-oil mono-, di-, and tri- **97722-02-6**	*Daphnia magna*/similar to OECD 202/static	EL50>100 (nominal)	
Glycerides, C16-18 and C18-unsatd. mono-, di- and tri- **91744-20-6**	No data located		
Coconut oil,transesterification products with decanoic acid mixed ester with glyceryl octanoate **68991-68-4** and **91052-53-8**	No data located		

Aquatic plants

Name and CAS Number	**Species/Test method**	**EC50 (mg/L), 72 hr**	
Monoglycerides			
Olein, mono- Octadecenoic acid, 1,2,3-propanetriol **25496-72-4**	No data located		
Glycerol oleate **37220-82-9**	No data located		
Glycerides,tall-oil **68309-32-0** and **61790-12-3**	*Pseudokirchnerella subcapitata*/ OECD 201/static	EbL50* = 854.9, ErL50 >1000 (nominal) NOELr = 500	
Octadecanoic acid, monoester with 1,2,3-propanetriol **31566-31-1**	No data located		
Monoglycerides, hydrogenated tallow **61789-09-1**	No data located		
Glyceryl stearate **11099-07-3** and **67701-27-3**	No data located		
Glycerides, palm-oil mono-, hydrogenated **91744-73-9**	No data located		
Diglycerides			
Octadecanoic acid, 1,2-propanediol monoester **1323-39-3**	No data located		
Decanoic acid, ester with 1,2,3-propanetriol octanoate **65381-09-1**	*Desmodesmus subspicatus*/ OECD 201/static	EbL50, ErL50 >100 (nominal), NOEL = 100	
Triglycerides			
Octanoin, tri- (Octanoic acid, 1,2,3-propanetriyl ester; Tricaprylin) **538-23-8**	No data located		

Hexanoic acid, 2-ethyl-, 1,2,3-propanetriyl ester **7360-38-5**	No data located		
Glycerides, C8-10 **85409-09-2**	No data located		
Glycerides, mixed decanoyl and octanoyl **73398-61-5**	*Desmodesmus subspicatus*/ OECD 201/static	EbL50, ErL50 >1000 (nominal loading), NOEC = 1000	
Oils, glyceridic, palm kernel **8023-79-8**	No data located		
Glycerides, C8-18 and C18-unsatd. **67701-28-4**	No data located		
Oils, vegetable, hydrogenated **68334-28-1**	No data located		
Glycerides, C12-18 **67701-26-2**	No data located		
Glycerides, C16-18 and C18-unsatd. **67701-30-8**	*Desmodesmus subspicatus*/ similar to OECD 201/static	EbL50, ErL50 >100 (nominal), NOEL =100	
Tallow, hydrogenated **8030-12-4**	*Desmodesmus subspicatus*/ similar to OECD 201/static	EbL50, ErL50 >100 (nominal), NOEL = 100	
Castor oil, hydrogenated **8001-78-3**	No data located		
Olein, tri - (Octadecenoic acid, 1,2,3-propanetriyl) **122-32-7**	No data located		
Mixtures of mono-, di- and triglycerides			
Glycerides, C14-18 mono- and di- **67701-33-1**	No data located		
Glycerides, mixed coco, decanoyl and octanoyl **68606-18-8**	No data located		
Glycerides, C16-18 and C18-unsatd. mono- and di- **68424-61-3**	No data located		
Glycerides, C16-18 mono- and di- **85251-77-0**	No data located		
Glycerides, tall-oil mono-, di-, and tri- **97722-02-6**	*Skeletonema costatum*/ ISO 10253 1995/static	ECr50 = 13.88 (nominal; exceeds the estimated water solubility of the substance)	
Glycerides, C16-18 and C18-unsatd. mono-, di- and tri- **91744-20-6**	No data located		
Coconut oil,transesterification products with decanoic acid mixed ester with glyceryl octanoate **68991-68-4** and **91052-53-8**	No data located		

*WAF sample preparations are reported relative to a loading rate rather than a concentration [LL50 (fish); EL50 (daphnia); EbL50/ErL50 (algae)]

There were no acute effects of the Glycerides Category members on fish, aquatic invertebrates or algae with LC50/LL50 or EC50/EL50 values less than the water solubility of the substance or that were less than 100 mg/L; similar results are expected for the Glycerides Category members that have not been tested.

There were no chronic reproductive effects of **CAS 65381-09-1** (diglyceride) or **67701-30-8** (triglyceride) on *Daphnia magna* (OECD 202), with NOEL (for reproduction) values > 100 mg/L; a concentration which exceeds the water solubility of the substances. Similar results are expected for the Glyceride Category members that have not been tested.

The Glycerides Category members do not possess properties indicating a hazard for the environment. Category members are rapidly biodegradable and have a low potential for bioaccumulation. Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the

OECD Cooperative Chemicals Assessment Programme.

Exposure

The 2012 production volumes reported by the US EPA (Chemical Data Reporting (CDR)) for the sponsored Glycerides in the United States is as follows:

Name and CAS Number	Production volume (Tonnes/year)
Monoglycerides	
Olein, mono- Octadecenoic acid, 1,2,3-propanetriol **25496-72-4**	454 – 4,536
Glycerol oleate **37220-82-9**	454 – 4,536
Glycerides,tall-oil **68309-32-0** and **61790-12-3**	1,076
Octadecanoic acid, monoester with 1,2,3-propanetriol **31566-31-1**	454 – 4,536
Monoglycerides, hydrogenated tallow **61789-09-1**	28
Glyceryl stearate **11099-07-3** and **67701-27-3**	31 and 423
Glycerides, palm-oil mono-, hydrogenated **91744-73-9**	(b)
Diglycerides	
Octadecanoic acid, 1,2-propanediol monoester **1323-39-3**	(b)
Decanoic acid, ester with 1,2,3-propanetriol octanoate **65381-09-1**	(c)
Triglycerides	
Octanoin, tri- (Octanoic acid, 1,2,3-propanetriyl ester; Tricaprylin) **538-23-8**	(b)
Hexanoic acid, 2-ethyl-, 1,2,3-propanetriyl ester **7360-38-5**	35
Glycerides, C8-10 **85409-09-2**	(b)
Glycerides, mixed decanoyl and octanoyl **73398-61-5**	454 – 4,536
Oils, glyceridic, palm kernel **8023-79-8**	22,680 -45,359
Glycerides, C8-18 and C18-unsatd. **67701-28-4**	113,398 - 226,796
Oils, vegetable, hydrogenated **68334-28-1**	454 – 4,536
Glycerides, C12-18 **67701-26-2**	Not listed on CDR
Glycerides, C16-18 and C18-unsatd. **67701-30-8**	(c)
Tallow, hydrogenated **8030-12-4**	17
Castor oil, hydrogenated **8001-78-3**	5885
Olein, tri - (Octadecenoic acid, 1,2,3-propanetriyl) **122-32-7**	45-227
Mixtures of mono-, di- and triglycerides	
Glycerides, C14-18 mono- and di- **67701-33-1**	4,536 - 22,680
Glycerides, mixed coco, decanoyl and octanoyl **68606-18-8**	(b)
Glycerides, C16-18 and C18-unsatd. mono- and di- **68424-61-3**	454- 4536
Glycerides, C16-18 mono- and di- **85251-77-0**	(c)
Glycerides, tall-oil mono-, di-, and tri- **97722-02-6**	445
Glycerides, C16-18 and C18-unsatd. mono-, di- and tri- **91744-20-6**	(b)
Coconut oil,transesterification products with decanoic acid mixed ester with glyceryl octanoate **68991-68-4** and **91052-53-8**	(b)

(b) No production volumes reported to the EPA either because the substance is not produced in the US or substance or manufacturers are exempt from reporting.
(c) Production Information withheld in order to maintain Confidential Business Information (CBI)

In U.S., the main applications are in personal care products, cosmetics, cleaning products, industrial intermediates and in pharmaceuticals.

Glycerides are naturally occurring substances. Exposures to those used in industry could arise in association with production, formulation and industrial use of these substances.

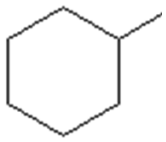
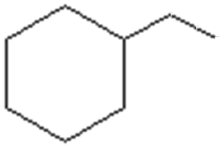
Glycerides are manufactured in established chemical manufacturing facilities that have standard engineering controls and procedures in place to ensure safe handling and use of chemicals. The precautions used includes corrosion-resistant vessels and piping of the type used for any quality-controlled chemical reaction. Glycerides have a low volatility and as a rule engineering controls are available that prevent the need for respiratory protection. For routine operations, including those involving a breach of the closed system, goggles or safety glasses, gloves, safety boots and helmets are worn, and a higher level of respiratory protection is applied and extra measures may be taken to prevent breathing of vapours, if (local) ventilation is inadequate. Formulation of large volumes of product occurs in a continuous process using a closed system; for smaller volumes, a batch process is used. Closed reactors and/or mixing tanks with closed charging systems are typically used for the formulation of

glycerides.

Exposure to glycerides through the use of formulated products in industry and commerce is mitigated by following the recommended use and precaution instructions detailed in the material safety data sheet (MSDS). MSDS' reflect the hazard potential of the chemical ingredients in the product and provide details on the precautions necessary when handling these products and the instructions for first aid in case of an accidental exposure.

Major routes of consumer exposure to glycerides are from the use of glycerides in personal care products and cosmetics. Indirect consumer exposure to glycerides may occur from exposures to residual levels of down-the-drain products in receiving waters from effluents of sewage treatment plants.

SIDS INITIAL ASSESSMENT PROFILE

Category Name	**Methyl･Ethylcyclohexane Category**
CAS No.	108-87-2 & 1678-91-7
Chemical Name	**Methylcyclohexane (CAS number: 108-87-2)** **&** **Ethylcyclohexane (CAS number: 1678-91-7)**
Structural Formula	**Methylcyclohexane**  **Ethylcyclohexane** 

SUMMARY CONCLUSIONS OF THE SIAR

Category rationale

The methyl･ethylcyclohexane category consists of two chemicals which are methylcyclohexane and ethylcyclohexane. Both of the chemicals have a cyclohexane-ring as a basic molecular structure, and either a methyl functional group ($-CH_3$) or an ethyl functional group ($-CH_2-CH_3$) is directly connected to this ring. Both chemicals are liquid at standard temperature and pressure. Based on the close similarity of molecular structures, all physical-chemical properties are similar.

There are a number of unifying considerations, which justify the inclusion of these two chemicals within the same category. These include:

1. Similarity of molecular structure and functional group

   These chemicals have a similar structure which is a direct connection of either methyl functional group ($-CH_3$) or an ethyl functional group ($-CH_2-CH_3$) to the cyclohexane ring.

2. Similarity of physical-chemical properties

   All physical-chemical properties, especially water solubility, vapour pressure and log K_{ow} are similar.

3. Similarity in health effects

   Toxicokinetic properties are similar.

   Target organs of repeated dose toxicity are the liver and kidney for both chemicals.

   Both chemicals show negative results of genotoxicity.

4. Similarity of environmental fate and distribution

   Both chemicals show the same or similar tendency in their environmental distribution, and biodegradation, which leads to the same behavior for these chemicals in the real environment.

5. Similarity of eco-toxicity

   Aquatic toxicity to fish (acute), daphnid (acute) and algae (acute and chronic) for both chemicals are very similar

Analogue rationale

Skin sensitization data of cyclohexane (CAS: 110-82-7) were used for the read across approach based on the similarity of structure. Cyclohexane is a basic molecular structure of methyl and ethylcyclohexenes.

Table 1 presents a summary of the read across (RA) approach for human health endpoints.

Table 1: summary of the read across (RA) approach

	Methylcyclohexane	**Ethylcyclohexane**
Toxicokinetics	**X**	**X**
Acute toxicity	**X**	**RA from methylcyclohexane**
Skin/eye irritation	**X**	**RA from methylcyclohexane**
Sensitization	**RA from cyclohexane**	**RA from cyclohexane**
Repeated dose toxicity	**X**	**X**
Genotoxicity	**X**	**X**
Carcinogenicity	**No data**	**No data**
Reproductive/developmental toxicity	**X**	**X**

X=data available

Physical-chemical properties

Physical-chemical properties of both methylcyclohexane and ethylcyclohexane are shown in Table 2. It is clearly demonstrated from this table that all of the physical-chemical properties for both chemicals are similar.

Table 2: Physical-chemical properties of both methylcyclohexane and ethylcyclohexane

Property	Methylcyclohexane	Ethylcyclohexane
Physical state/appearance	Colourless fragrant liquid	Colourless liquid
Odour	Faint, benzene-like odor	-
Melting point	-126.6 °C	-111.3 °C
Boiling point	100.9	131.8 °C
Density	0.769 g/cm^3 at 20 °C	0.788 g/cm^3 at 20 °C
Vapour pressure	6.13×10^3 Pa at 25 °C	1.71×10^3 Pa at 25 °C
Water solubility	14 mg/L at 25 °C	6.3 mg/L at 20 °C
Partition coefficient between octanol and water	log K_{ow} = 4.7 at 25 °C	log K_{ow} = 4.79 at 25 °C

Soil adsorption coefficient	log K_{oc} = 2.37 by KOCWIN	log K_{oc} = 2.65 by KOCWIN
Henry's Law constant	4.30×10^4 $Pa.m^3$/mole at 25 °C by vapour pressure divided by water solubility (K_{aw} = 17.3)	3.04×10^4 $Pa.m^3$/mole at 20-25 °C by vapour pressure divided by water solubility (K_{aw} = 12.3)
	3.43×10^4 $Pa.m^3$/mole at 25 °C by HENRYWIN (K_{aw} = 13.8)	4.56×10^4 $Pa.m^3$/mole at 25 °C by HENRYWIN (K_{aw} = 18.4)

Human Health

Toxicokinetics

Vapour inhalation exposure of methyl and ethylcyclohexanes to rats promptly distributed through systemic circulation to various organs, and elimination from the organs was rapid by withdrawal of the exposure except for fat tissue exposed to methylcyclohexane. After oral administration (rabbit study) methylcyclohexane was almost completely absorbed (82.4%) and excreted mainly via urine (65.4%) and expired air (5.6%). The main urinary metabolites were glucuronide conjugates of *trans*-4-methylcyclohexanol, *cis*-3-methylcyclohexanol and *trans*-3-methylcyclohexanol in rabbits. In the rats, orally administered with methyl and ethylcyclohexanes repeatedly, each six main urinary metabolites were identified (methylcyclohexane: cyclohexylmethanol, *trans*-3-methycyclohexanol, *trans*-4-methylcyclohexanol, 2c-hydroxy-4c-methylcyclohexanol, 2c-hydroxy-4t-methylcyclohexanol, and 2t-hydroxy-4c-methylcyclohexanol: ethylcyclohexane: 2c-hydroxy-4-ethylcyclohexanol, 2c-hydroxy-4t-ethylcyclohexanol, 2-hydroxy-4-ethylcyclohexane, *trans*-4-ethylcyclohexane, 2t-hydroxy-4t-ethylcyclohexanol, 2t-hydroxy-4c-ethylcyclohexanol). It was suggested that metabolism of the ring structure (dihydroxylation) was strongly favoured.

Acute toxicity

Three studies on single inhalation exposure with rats, mice, and dogs, and a study on subacute inhalation with rabbits were available for methylcyclohexane. In the rabbit study, all the animals died at 59.9 mg/L within 70 min after exposure initiation. LC_{50} was considered as between 39.6 and 59.9 mg/L. Signs of toxicity at 59.9 mg/L (70 min exposure) included severe convulsions, rapid narcosis, labored breathing, salivation, and conjunctival congestion. No deaths were observed in any other studies at one-hour emergency exposure limit concentrations of 16.3 mg/L (dogs) and 26.3 mg/L (rats and mice). Clinical signs observed in rats and mice included increased activity, hyperactivity, loss of coordination, and prostration. In the acute oral toxicity study with rabbits, minimum lethal dose was reported as 4000–4500 mg/kg bw. Clinical signs including CNS (central nervous system) depression in both routes and diarrhea in oral route were observed. No information was available for acute toxicity of ethylcyclohexane. Judging from very low level of acute toxicity of methylcyclohexane, acute toxicity of ethylcyclohexane was considered to be low in both inhalation and oral routes; however, effects on CNS was anticipated. No dermal studies were available.

It should also be noted that accidental aspiration of methyl and ethylcyclohexane may cause damage in the lung.

Irritation

In a primary skin irritation study for methylcyclohexane, no edema was observed, and very slight erythema reactions observed at 24 h post-application were reversible in rabbits. In an eye irritation study for methylcyclohexane (similar to OECD TG405), conjunctival redness observed at 1 h and 24 h post-instillation was fully reversible within 48 h in rabbits. Based on these results, the methylcyclohexane was concluded as not irritating to skin as well as eye. No information was available for skin and eye irritation of ethylcyclohexane. In consideration with negative results on skin and eye irritation of methylcyclohexane, ethylcyclohexane would not be irritating in the experimental animals. It should also be noted that prolonged or repeated exposure to methylcyclohexane or ethylcyclohexane can lead to severe irritant dermatitis due to defatting of the skin.

Sensitization

No information was available for sensitization of methyl and ethylcyclohexanes, but in two sensitization studies (OECD TG 406) conducted with cyclohexane, an analogue substance of methyl and ethylcyclohexanes, no sensitization was observed in guinea pigs. Methyl and ethylcyclohexanes were unlikely considered to be skin sensitizing.

Repeated dose toxicity

In a series of chronic vapour inhalation exposure studies (whole-body exposure for 12 months, 6 h/day, 5 days/week, and 12-month post-exposure at 1.6 and 8.0 mg/L) in rats, mice, dogs, and hamsters of methylcyclohexane, NOAECs in rats were 1.6 mg/L for males (based on slight increase in the incidence of renal tubular dilatation at the end of the exposure period, and significant increase in the incidence of medullary mineralization and hyperplasia of the renal papilla after the post-exposure period) and 8.0 mg/L for females (no effects), NOAEC in mice and dogs was 8.0 mg/L (no effects), and LOAEC in hamsters was 1.6 mg/L due to depressed body weight. In subacute (2–4 week: 11.35–39.55 mg/L) and subchronic (10 week: 0.948–4.57 mg/L) inhalation exposure studies with methylcyclohexane in rabbits, LOAEC of 11.35 mg/L (3 week) and NOAEC of 4.57 mg/L (10 week), respectively, were obtained due to microscopic effects on liver and kidney. Inhalation of ethylcyclohexane was expected to cause similar effects.

No reliable information is available for repeated dermal toxicity for the substances.

There are two oral repeated dose toxicity studies for methylcyclohexane. One is the combined repeated oral dose toxicity study with the reproduction/developmental toxicity screening test using rats (OECD TG 422). Males (12 animals/dose: 6 animals were treated as a recovery group) were dosed methylcyclohexane (0, 62.5, 250, and 1000 mg/kg bw/day) for 28 days including a 14 day pre-mating period and subsequent 14 day mating period. Females (12 animals/dose) were dosed for 42–47 days including 14 day pre-mating, mating, and gestation periods and days until day 4 of lactation. In addition, five or ten females/group was dosed for 28 days without mating (5 females at 0 and 1000 mg/kg bw/day were treated as recovery groups). Observed effects were related to liver function (increased liver weight, and non-reversible increased ALT and total cholesterol at 1000 mg/kg bw/day) and kidney (increased absolute and/or relative weights at 1000 mg/kg bw/day in both sexes, and slight bilateral hyaline droplet in the renal tubules at 250 mg/kg bw/day (4/6) and 1000 mg/kg bw/day (6/6) in males). In the immunohistochemical examination, α-2μ globulin positive reactions (+) were observed at similar level in male animals at 0 and 1000 mg/kg bw/day (3/3 and 3/3 respectively). Strong positive reactions (++) of the positive control samples were confirmed in this examination. Therefore, these effects in the kidney were considered to be independent of the α-2μ globulin accumulation. The NOAEL was determined as 62.5 mg/kg bw/day.
The other is the 28 day repeated oral dose toxicity study in rats (OECD TG 407). Methylcyclohexane was administered by gavage to groups of rats (5 per sex and dose) at 0 (vehicle: corn oil), 100, 300, and 1000 mg/kg bw/day, 7 days/week for 28 days. Satellite animals (5 animals/sex/dose) were concurrently administered at doses of 0 or 1000 mg/kg bw/day and set as the 14 day recovery test groups. The effects in the organ weights (increased absolute and relative liver weight at 1000 mg/kg bw/day) and histopathology (hypertrophy of hepatocytes for both sexes at 1000 mg/kg bw/day, and hyaline droplet formation for males (reversible) at 300 mg/kg bw/day and higher and females (non-reversible) at 1000 mg/kg bw/day) were observed. Thus, the NOAEL of methylcyclohexane in this study was 100 mg/kg bw/day in rats.

One reliable study report is available for repeated dose toxicity of ethylcyclohexane. In the 28 day oral repeated dose toxicity study in rats (OECD TG 407), rats (5 animals/sex/dose) were given ethylcyclohexane at doses of 0 (vehicle: olive oil), 40, 200, and 1000 mg/kg bw/day for 28 consecutive days. Satellite animals (5 animals/sex/dose) were concurrently administered at doses of 0 or 1000 mg/kg bw/day and set as the 14 day recovery test groups. The effects of ethylcyclohexane were found in some hematological parameters, increased gamma-GT activity (males only), and increased liver weight accompanied with centrilobular hypertrophy of hepatocytes at 1000 mg/kg bw/day. An increased relative and/or absolute weight of kidneys was observed at 200 mg/kg bw/day and higher in both sexes, and which was accompanied with hyaline droplets in the epithelium of renal proximal tubules in males. Appearance of eosinophilic bodies was found at 1000 mg/kg bw/day in males. Of these, only appearance of eosinophilic bodies was considered as a male rat-specific nephropathy as evidenced by α-2μ globulin positive reaction. The NOAEL for repeated dose toxicity was considered to be 40 mg/kg bw/day.

Genotoxicity

Methyl and ethylcyclohexanes did not induce gene mutation in bacterial in vitro tests (OECD TG 471 or 472). The substances did not induce chromosome aberrations in cultured Chinese hamster lung (CHL/IU) cells (OECD TG 473). Based on these results, methyl and ethylcyclohexanes are considered to be non-genotoxic *in vitro*.

Carcinogenicity

No guideline study for carcinogenicity was conducted.

Reproductive and developmental toxicity

As aforementioned combined repeated dose toxicity study with the reproduction/developmental toxicity screening test using rats for methylcyclohexane (OECD TG 422), reproductive parameters and developmental parameters were not affected up to 1000 mg/kg bw/day. Based on these results, NOAEL for reproductive/developmental toxicity of methylcyclohexane was considered to be 1000 mg/kg bw/day. In the 28 day repeated dose toxicity study, reproductive organs were not affected at 1000 mg/kg bw/day.

In a reproduction/developmental toxicity screening test (similar to TG 421), rats (12 animals/sex/dose) were treated with ethylcyclohexane by gavage at 0, 40, 200 and 1000 mg/kg bw/day. Male rats were dosed for 42 days, and female rats were dosed for 40-53 days (including 14 day pre-mating, mating, and gestation periods and days until day 3 of lactation). Reproductive parameters were not affected up to 1000 mg/kg bw/day. Although only viability index and body weight of pups on day 4 of lactation were tended to be decreased, these weak changes were not statistically significant. The NOAEL for reproductive/developmental toxicity of ethylcyclohexane was considered to be 1000 mg/kg bw/day.

Methyl- and ethylcyclohexanes possess properties indicating a hazard for human health (acute Central Nervous System depression, severe irritant dermatitis due to defatting with prolonged or repeated exposure). Adequate screening level data are available to characterize the human health hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Environment

Fugacity modelling (level III) for methylcyclohexane and ethylcyclohexane shows the very close patterns of the distribution because of their close physical-chemical properties. When equal and continuous release to air, water and soil is assumed, both of the chemicals are mainly distributed in air (22–25 %) and water (about 72 %) compartments.

Values of Henry's Law Constant suggest that both of the chemicals are volatile from water. Soil adsorption coefficients indicate that both of the chemicals have moderate adsorption to soil and sediment, and slow migration potential to groundwater.

Using AOPWIN, a calculated half-life time of 0.89 days and 1.06 days are obtained for methylcyclohexane and ethylcyclohexane respectively for the indirect photo-oxidation by reaction with hydroxyl radicals in air. Concentration of hydroxyl radicals of 1.5×10^6 OH/cm^3 and the time frame of hydroxyl radicals of 12 hours/day are assumed. It is thought that both of the chemicals are expected to rapidly photo-degrade in the atmosphere.

Because of the lack of hydrolysable functional groups in its molecular structure, both of methylcyclohexane and ethylcyclohexane are thought to be stable in water.

Biodegradation

Methylcyclohexane

A readily biodegradation test on methylcyclohexane was conducted with activated sludge based on OECD TG 301D. The concentration of methylcyclohexane was 10 mg/L, and 1 drop of the activated sludge from the waste-water treatment plant was put into the 1 L test solution with the cultivation period of four weeks. The test result showed 0 % degradation by BOD. Therefore, methylcyclohexane is not readily bio-degradable.

Ethylcyclohexane

A readily biodegradation test on ethylcyclohexane with activated sludge was conducted based on OECD TG 301C in compliance with GLP. The concentration of the ethylcyclohexane was 100 mg/L and the concentration of the activated sludge was 30 mg/L as suspended solid matters with the cultivation period of four weeks. The test result showed 0 % degradation by BOD and it was confirmed by the direct analysis with gas chromatography that more than 94 % of ethylcyclohexane remained after the cultivation period. Therefore, ethylcyclohexane is not readily bio-degradable.

Bioaccumulation

Methylcyclohexane

A study on methylcyclohexane according to OECD TG 305 with carp was performed in compliance with GLP. Bio-concentration factors of 95–321 and 134–237 were obtained for the test concentration of 100 µg/L and of 10 µg/L respectively for 8-week exposure period. Both of the test concentrations are well below the water solubility

of methylcyclohexane. Using a measured value of the octanol-water partition coefficient (log K_{ow}) of 4.7, a bio-concentration factor of 586 was calculated with BCFBAFWIN. Therefore, it is concluded that methylcyclohexane has a low potential for bioaccumulation.

Ethylcyclohexane

A study on ethylcyclohexane according to OECD TG 305 with carp was performed in compliance with GLP. Bio-concentration factors of 1,110–2,030 and 1,280–3,470 were obtained for the test concentration of 10 μg/L and of 1 μg/L respectively for 8-week exposure period. Both of the test concentrations are well below the water solubility of ethylcyclohexane. After the measurement of BCFs, test fish was transferred into the water without containing ethylcyclohexane, and concentrations of ethylcyclohexane in test fish were measured during 14 days. According to these measurements, a half-life time of the depuration of ethylcyclohexane from the fish body was calculated to be about 2–4 days. Using a measured value of the octanol-water partition coefficient (log K_{ow}) of 4.79, a bio-concentration factor of 672 was calculated with BCFBAFWIN. Therefore, it is concluded that ethylcyclohexane has a potential for bioaccumulation.

Acute aquatic toxicity test results are available for both methylcyclohexane and ethylcyclohexane.

Fish
Methylcyclohexane [*Oryzias latipes*]: 96 h LC_{50} = 2.1 mg/L (measured, semistatic), OECD TG 203
Ethylcyclohexane [*Oryzias latipes*]: 96 h LC_{50} = 0.75 mg/L (measured, semistatic), OECD TG 203
Daphnid
Methylcyclohexane [*Daphnia magna*]: 48 h EC_{50} = 0.33 mg/L (measured, semistatic), OECD TG 202
Ethylcyclohexane [*Daphnia magna*]: 48 h EC_{50} = 0.67 mg/L (measured, semistatic), OECD TG 202
Algae
Methylcyclohexane [*Pseudokirchneriella subcapitata*]:
72 h E_rC_{50} = 0.34* mg/L (measured, growth rate, static), OECD-TG 201
Ethylcyclohexane [*Pseudokirchneriella subcapitata*]:
72 h E_rC_{50} = 0.63 mg/L (measured, growth rate, static), OECD TG 201

The following chronic toxicity test results have been determined for aquatic species:
Algae
Methylcyclohexane [*Pseudokirchneriella subcapitata*]:
72 h NOE_rC = 0.067* mg/L (measured, growth rate, static), OECD TG 201
Ethylcyclohexane [*Pseudokirchneriella subcapitata*]:
72 h NOE_rC = 0.22 mg/L (measured, growth rate, static), OECD TG 201

*A large difference between nominal and measured concentrations was obtained in the test with *P. subcapitata* with methylcyclohexane. Derived NOEC and EC50 values should therefore be used with caution.

Methylcyclohexane and ethylcyclohexane possess properties indicating a hazard for the environment (acute aquatic toxicity values between 0.1 and 10 mg/L, chronic aquatic toxicity less than 0.1 mg/L). Both chemicals are not readily biodegradable. Methylcyclohexane has low potential for bioaccumulation and ethylcyclohexane has the potential to bioaccumulate. Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Exposure

Production volume

Methylcyclohexane

Total amounts of production and import of methylcyclohexane in Japan were 4,000 tonnes in the fiscal year 2012 and fiscal year 2011 according to the public information of Chemical Substances Control Law. In the United States, total amounts of production and/or import were reported to be 1 – 10 million pounds (454 to 4,540 tonnes) in 2006 according to Inventory Updated Reporting. Total amounts of production and import of methylcyclohexane in EU countries were reported to be 1,000 – 10,000 tonnes per year according to REACH registration information on the ECHA website. Production volume in the world is not available.

Ethylcyclohexane

Total amounts of production and import of ethylcyclohexane in Japan were reported to be < 600 tons in fiscal year 2011 and fiscal year 2012. In the United States, total amounts of production and/or import were reported to be < 0.5 million pounds (< 227 tonnes) in 2006 according to Inventory Updated Reporting. Production volume in the world is not available.

Production methods

Methylcyclohexane is separated by distillation from crude petroleum oils, or manufactured by hydrogenation of toluene and purified by distillation. Methylcyclohexane is also produced by the reaction of benzene with methane, or acidic hydrocracking of polycyclic aromatics.

Ethylcyclohexane is manufactured by hydrogenation of ethylbenzene and purified by distillation

Use pattern

Methylcyclohexane is used as a raw material in a variety of synthetic processes like pharmaceuticals and dyes, and used as a solvent. Methylcyclohexane is also used as a component of jet fuel. Another use of methylcyclohexane is as a component of cleaning solutions for printer.

Ethylcyclohexane is used for organic synthesis and used as a solvent. Ethylcyclohexane is used for specialized products, adhesive, paints, medicine, agricultural chemicals and additive for paints as thixotropic agents.

Occupational exposure

Concerning methylcyclohexane, Permissible Exposure Limits (PEL) are 500 ppm (8-hour time weighted average) according to OSHA and 400 ppm (8-hour time weighted average) according to NIOSH. Concerning ethylcyclohexane, no Permissible Exposure Limit is decided. Based on the high vapour pressure for both of the chemicals, inhalation may be the main potential exposure route.

Consumer exposure

As methylcyclohexane is used as a component of cleaning solutions for printers, consumers may be exposed to methylcyclohexane when cleaning printers with this type of cleaning solution.

As ethylcyclohexane is used as an additive for paints, consumers may be exposed by ethylcyclohexane when using this type of paints including ethylcyclohexane.

SIDS INITIAL ASSESSMENT PROFILE

Category Name	Soluble cobalt salts
Chemical Name(s) and CAS No(s).	Cobalt sulfate CAS 10124-43-3 (anhydrous) CAS 10026-24-1 (heptahydrate) Cobalt dinitrate CAS 10141-05-6 (anhydrous) CAS 10026-22-9 (hexahydrate) Cobalt dichloride CAS 7646-79-9 (anhydrous) CAS 7791-13-1 (hexahydrate) Cobalt diacetate CAS 71-48-7 (anhydrous) CAS 6147-53-1 (tetrahydrate)
Molecular Formula(s)	$CoSO_4$ $Co(NO_3)_2$ $CoCl_2$ $Co(C_2H_3O_2)_2$

SUMMARY CONCLUSIONS OF THE SIAR

RATIONALE FOR THE SOLUBLE COBALT SALTS CATEGORY

Category Assessments:

The category is based on a common moiety of concern, the divalent cobalt cation. All category members are potential contributors of this moiety. The counter ions of the cobalt salts (i.e. sulfate, nitrate, chloride, acetate), due to their ubiquitous presence in biota and/or their essential role in physiology, are not addressed further as they are not considered to contribute to toxicity of the cobalt salts.

In addition to the common moiety of concern (divalent cobalt cation), and toxicological inertness of the counter ion, the following inclusion criteria relevant to human health were applied: extreme water solubility (approx. 350-670 g/L) which is also reflected in the high bioaccessibility (>400 µg/mL) and significant oral bioavailability (approx. 30%). .

In the context of ecotoxicity, a read-across approach was adopted based on the assumption that the toxic agent released from the dissolution of the cobalt containing substances is the divalent cobalt cation. The cobalt salts included here are representative of substances that release divalent cobalt ions under environmentally relevant conditions. In order to provide a means to evaluate those substances for which little or no ecotoxicity information is available, and to reduce the need to test each individual substance, data were generated for category and non-category cobalt salts with a range of solubilities (from 146 g Co/L for Co dichloride to 2.6 mg Co/L for Co resinate) in order to validate this read-across approach. For the assessment of cobalt-containing substances that do not undergo complete and rapid dissolution, transformation/dissolution testing (TDp; OECD Method 29) is used to quantify the amount of dissolved cobalt ion generated, which allows the prediction of the toxicity of those substances that are not included in this category.

Substances Previously Assessed in the OECD Programme:

Initial targeted assessment profile (Human Health and Environment), SIAM 31, 20-22 October 2010, based on the 2011 Canadian Screening Assessment (CSA):

Sponsored Substances: Cobalt [Elemental cobalt]: CAS RN 7440-48-4; Cobalt chloride: CAS RN 7646-79-9; Sulfuric acid, cobalt (2+) salt (1:1) [Cobalt sulfate]: CAS RN 10124-43-3, CAS RN 10393-49-4

Supporting Substances: Nitric acid, cobalt salt [Cobalt nitrate]: CAS RN 14216-74-1*;* Acetic acid, cobalt salt [Cobalt acetate]: CAS RN 5931-89-5

Endpoints Targeted: Toxicokinetics, repeated dose toxicity, genetic toxicity, carcinogenicity, fertility.

PHYSICAL-CHEMICAL PROPERTIES

Cobalt sulfate is typically marketed as the heptahydrate, which is a rose, odourless, crystalline, inorganic solid. The relative density of cobalt sulfate is 3.71. Upon heating of the hydrated form, water of crystallisation is lost and the anhydrous form is formed. The melting point for the anhydrous cobalt sulfate is reported to be > 700°C. The water solubility of cobalt sulfate monohydrate at 20°C and 37°C is 376.7 g/L and 391.5 g/L (measured), respectively. The particle size distribution of a typical commercial sample of cobalt sulfate heptahydrate is characterised by a median diameter of D_{50} = 917.6µm.

Cobalt dinitrate is typically marketed as the hexahydrate, which is a red purple, flaked, inorganic solid. The relative density of cobalt dinitrate is 2.49. Cobalt dinitrate decomposes at 100-105 °C before melting. The water solubility of cobalt dinitrate hexahydrate at 20 °C is > 669.6 g/L (measured). The particle size distribution of a typical commercial sample of cobalt dinitrate hexahydrate is characterised by a median diameter of D_{50} = 993.68 µm.

Cobalt dichloride is typically marketed as the hexahydrate, which is a purple, odourless, crystalline, inorganic solid. The relative density of cobalt dichloride is 3.36-3.37. Upon heating of the hydrated form, water of crystallisation is lost and the anhydrous form is formed. The melting point for the anhydrous cobalt dichloride is reported to be between 735°C - 737°C, the boiling point is 1049°C. The water solubility of cobalt dichloride hexahydrate at room temperature is 585.8 g/L (measured). The particle size distribution of a typical commercial sample of cobalt dichloride hexahydrate is characterised by a median diameter of D_{50} approx. 570 µm.

Cobalt diacetate is typically marketed as the tetrahydrate, which is a red, crystalline inorganic solid with a relative density of 1.76 (measured at 21.4 °C). A decomposition temperature of cobalt diacetate tetrahydrate was determined at 370°C. Distinct melting or boiling points are not available. The water solubility of cobalt diacetate tetrahydrate at 20 °C is 348.04 g/L - 360 g/L (measured). The particle size distribution of a typical commercial sample of cobalt diacetate tetrahydrate is characterised by a median diameter of D_{50} = 219.04 µm.

Remark: Vapour pressure and Kow are not considered relevant parameters for the fate and effects assessment of inorganic chemicals.

HUMAN HEALTH

Toxicokinetics

Human data

Reliable human toxicokinetic data for soluble cobalt substances are scarce. Two toxicokinetic studies in human volunteers exist, which allow some quantitative conclusions:

- in a study in which cobalt chloride was administered once i.v. or orally, it is eliminated from blood rapidly (30% of dose within 24h p.a.), the liver initially retaining an estimated 20% of the dose.

- in a study with ten consecutive daily oral doses of cobalt chloride, increased blood and urine concentrations were observed, in comparison to the reference (non-exposed control subjects). The increases were 14-20-fold and 16-59-fold in males and females respectively.

Animal data

Absorption, oral route: in a reasonably well-described study, the oral absorption in rats following a single dose of cobalt chloride (33.3 mg Co/kg bw) is described. The oral absorption as judged by the extent of excretion via urine was 23.9 %

Absorption, inhalation route: Experimentally determined inhalation absorption rates have not been reported for any cobalt substance, which is why model predictions were performed (see in vitro data below). However, detailed lung clearance investigations have been conducted, which provide a basis for the assessment of the fate of inhaled cobalt particles: the clearance of soluble cobalt (as radioisotopic cobalt chloride) deposited intratracheally in the lungs of various species is rapid, with the mean fraction of ^{57}Co retained in lungs for >100 days accounting for merely 0.13-0.58% of dose. In a similar study in Sprague-Dawley rats involving head-only exposure to cobalt dichloride, a clearance half-time of 1.8h was reported.

Absorption, dermal route: there are no reliable in-vivo dermal absorption data in animals.

Metabolism: cobalt is not subject to any metabolism; regardless of its original chemical speciation, cobalt transforms to divalent cobalt cations, depending on its solubility in water and physiological media.

Distribution: cobalt is an essential metal (vitamin B12 component), and as such will be present as a low level, natural "background" in most tissues, such as muscle, lung, lymph nodes, heart, skin, bone, hair, stomach, brain, pancreatic juice, kidneys, plasma, urinary bladder, and highest in liver (0.5-1 µg/g). Laboratory animal studies in various species indicate that cobalt absorbed via the gastrointestinal tract is primarily retained in the liver.

Elimination: Ingested soluble cobalt substances are excreted primarily via faeces to ca. 70-83%, with urinary excretion accounting for the remainder of the dose. The overall elimination after systemic uptake is very rapid, with whole body retention rates of only ca. 1.5% 36 hours after administration of cobalt dichloride. The biliary excretion of cobalt (chloride) in rats has been reported in one study to be 2.6-7.3% of the dose within 24h p.a. In another study with cobalt chloride also in rats, total (faecal + urinary) excretion was relatively rapid (87.7% of dose in 4d), whereas biliary excretion in the first 2h p.a. ranged from 2.3-4.7% of dose.

There are no data suggesting that cobalt has any bioaccumulation potential.

In vitro data

In vitro bioaccessibility testing: The bioaccessibility of the cobalt category substances was investigated by measuring their solubility in seven different simulated physiological fluids. Soluble cobalt substances are readily soluble in water as well as in all tested physiological media, rendering them similarly highly bioaccessible under all relevant physiological circumstances. The in vitro bioaccessibility results are shown in the table below.

in vitro bioaccessibility data for the category substances

simulated physiological fluids	**Cobalt sulfate**	**Cobalt dichloride**	**Cobalt di(acetate)**	**Cobalt dinitrate**
	cobalt release concentration [µg Co/mL]			
Gastric	441.4[1]	432.1[1]	452.7[2]	393.2[2]
Alveolar	211.0[1]	256.7[1]	49.0[2]	64.4[2]
Intestinal	278.0[2]	397.4[1]	81.1[2]	119.4[2]
Lysosomal	330.8[1]	446.0[1]	362.9[2]	407.9[2]
Interstitial	292.5[1]	240.1[1]	45.9[2]	84.4[2]
Serum	3434.0[4]	4254.0[4]	445.5[3]	367.0[3]
Sweat (at 37°C)	386.5[2]	446.6[2]	457.6[2]	381.9[2]

[1]: incubation of 100 mg in 50 mL medium, measured cobalt concentration after 2 hrs.
[2]: incubation of 100 mg in 50 mL medium, measured cobalt concentration after 5 hrs.
[3]: incubation of 20 mg in 10 mL medium, measured cobalt concentration after 5 hrs.
[4]: incubation of 200 mg in 10 mL medium, measured cobalt concentration after 2 hrs.

In vitro dermal absorption data: The percutaneous absorption potential of cobalt chloride following topical application to human skin in vitro was investigated at two different application rates: ca. 100 µg/cm² and ca. 1000 µg/cm², exposure duration was 8h. For the two exposure concentrations, the corresponding absorbable doses corresponded to 0.38% and 1.08%, respectively, rendering dermal absorption of soluble cobalt substances as very low.

In vitro inhalation deposition/absorption model predictions: the uptake of different cobalt particles was predicted based upon their particle-size dependant respiratory tract deposition, coupled with their measured gastric bioaccessibility, and assuming at the same time conservatively that pulmonary deposition would involve complete dissolution/uptake. The thus predicted inhalation absorption factors for cobalt substances range from approx. 2% to 25%.

Acute Toxicity

Acute inhalation toxicity studies are not available for any of the soluble cobalt salts in this category due to a lack of technical feasibility

No information on the acute dermal toxicity of the category substances are available. Due to the poor dermal absorption of soluble cobalt salts, it can be concluded that the dermal route is not relevant for the acute systemic toxicity of soluble cobalt salts in this category.

All substances within the category show a moderate acute oral toxicity, with LD_{50} values between 300 and 2000 mg/kg body-weight as experimentally determined. Hence, cobalt diacetate, cobalt dichloride, cobalt dinitrate and cobalt sulfate are considered to be harmful if swallowed.

Available key study data for acute oral toxicity in rats

Test substance	**Study type**	**Result**	**Source**
Cobalt sulfate $CoSO_4$	Acute Oral Toxicity (OECD 401)	LD_{50}: 768 mg/kg bw (male/female) (cobalt sulfate heptahydrate) LD_{50}: 424 mg/kg bw (male/female) (cobalt sulfate) LD_{50}: 161 mg/kg bw (male/female) (cobalt)	Speijers, G.J.A. et al., 1982
		LD_{50}: 1330 mg/kg bw (male/female) (cobalt sulfate heptahydrate) LD_{50}: 279 mg/kg bw (male/female) (cobalt)	Llobet, J.M. & Domingo, J.L., 1983
Cobalt dinitrate $Co(NO_3)_2$	Acute Oral Toxicity (OECD 401)	LD_{50}: 691 mg/kg bw (male/female) (cobalt dinitrate hexahydrate) LD_{50}: 434 mg/kg bw (male/female) (cobalt dinitrate) LD_{50}: 140 mg/kg bw (male/female) (cobalt)	Speijers, G.J.A. et al., 1982
		LD_{50}: 978 mg/kg bw (male/female) (cobalt dinitrate hexahydrate) LD_{50}: 198 mg/kg bw (male/female) (cobalt)	Llobet, J.M. & Domingo, J.L., 1983
Cobalt dichloride $CoCl_2$	Acute Oral Toxicity (OECD 401)	LD_{50}: 537 mg/kg bw (male/female) (cobalt dichloride hexahydrate) LD_{50}: 133 mg/kg bw (male/female) (cobalt)	Llobet, J.M. & Domingo, J.L., 1983
		LD_{50}: 766 mg/kg bw (male/female) (cobalt dichloride hexahydrate) LD_{50}: 418 mg/kg bw (male/female) (cobalt dichloride) LD_{50}: 190 mg/kg bw (male/female) (cobalt)	Speijers, G.J.A. et al., 1982
Cobalt diacetate $Co(CH_3COO)_2$	Acute Oral Toxicity (OECD 401)	LD_{50}: 708 mg/kg bw (male/female) (cobalt diacetate tetrahydrate) LD_{50}: 503 mg/kg bw (male/female) (cobalt diacetate) LD_{50}: 168 mg/kg bw (male/female) (cobalt)	Speijers, G.J.A. et al., 1982
		LD_{50}: 819 mg/kg bw (male/female) (cobalt diacetate) LD_{50}: 273 mg/kg bw (male/female) (cobalt)	Llobet, J.M. & Domingo, J.L., 1983

The following clinical signs were predominantly observed in all studies: highest dose caused sedation and diarrhoea. tremors and convulsions prior to death, decrease in body temperature, increased heart rate, pilo erection. The temperature reductions were time- and dose-related. No macroscopic alterations were observed at the most significant organs. Most effects disappeared after 72 hours.

Skin, Eye and Respiratory Irritation

Available key study data for skin and eye irritation

Test substance	Study type	Result
Cobalt sulfate $CoSO_4$	Skin irritation, in vitro (OECD 439)	Not irritating
	Eye irritation, in vivo (OECD 405)	Reversible effects on the eye
Cobalt dinitrate $Co(NO_3)_2$	Skin irritation, in vivo (OECD 404)	Not irritating
	Eye irritation, in vivo (OECD 405)	Irreversible effects on the eye
Cobalt dichloride $CoCl_2$	Skin irritation, in vivo (OECD 404)	Not irritating
	Eye irritation, in vivo (OECD 405)	Irreversible effects on the eye
Cobalt diacetate $Co(CH_3COO)_2$	Skin irritation, in vivo (OECD 404)	Not irritating
	Eye irritation, in vivo (OECD 405)	Reversible effects on the eye

All substances of this category show minimal to mild skin effects, predominantly present as erythema formation. In all three tests, the values of erythema and oedema were below the threshold irritation score of ≥ 2.3 and the effects were fully reversible within 48 hours, thus would be considered as not irritating to the skin.

All cobalt substances within the category were shown to be irritating to eyes; however, whereas these effects were reversible with cobalt diacetate and cobalt sulfate, cobalt dichloride and cobalt dinitrate produce irreversible effects.

Five well-characterised exposure studies in two cobalt facilities producing cobalt substances support observations that worker exposures to inorganic cobalt substances (in the absence of other metal exposures) is associated with occupational asthma, being defined by clinically-compliant lung function testing. However, none of the studies were able to discriminate between individual cobalt substances and their specific potential to impair lung function, and also none of them indicated a high frequency of occurrence of occupational asthma among the worker population. An industry-wide questionnaire survey of industrial experience with occupational asthma did not indicate that the frequency of occupational asthma in workers is particularly high.

Skin Sensitisation

Cobalt dichloride and cobalt sulfate were identified as skin sensitisers in animal studies (guinea pig maximisation test and adjuvant and patch test, respectively) and cobalt dichloride was identified as a skin sensitiser in human observations (largely studies with volunteers). Based on similar bioaccessibility in artificial sweat, cobalt diacetate and cobalt dinitrate are also considered as skin sensitisers.

Repeated-Dose Toxicity

Oral: Oral 90-day animal studies for any of the cobalt substances within this category are not available[1]. However, as supportive information, data from 28-day oral repeated dose toxicity studies in rats with other cobalt substances are available (see Annex to this SIAP). The NOAELs identified in those studies cover a range of 5-1000 mg/kg bw/day (equivalent to approx. 0.5-700 mg Co/kg bw/day). In those cases where macroscopic and microscopic adverse effects were observed in those studies, they were consistently related to the gastrointestinal tract, described as degeneration/necrosis of mucosal epithelium, atrophy of villi and crypts, regeneration of mucosal epithelium and mucosal inflammation. Several human case reports exist on adverse effects in specific organs in humans potentially associated with cobalt exposure. These include cases of non-inflammatory cardiomyopathy (potentially associated with heavy consumption of beer containing cobalt as an additive), interferences with thyroid metabolism (under circumstances of oral Co supplementation or occupational exposure), effects on the haematopoietic system (manifesting itself as anaemia resulting from oral treatment with cobalt chloride), and neurotoxic effects characterised by progressive bilateral deafness with tinnitus and visual failure. The majority of these reports are insufficient for human health hazard assessment, since the persons were either exposed to other substances as well, or only single cases of overexposure with no further information on other confounding factors were reported. Consequently, no reliable causal or dose-response relationship to cobalt exposure can be established.

[1] At the time of finalisation of this document, a repeated dose oral toxicity study with cobalt chloride in rats according to OECD guideline 408 was ongoing, scheduled for finalisation in 2015.

Inhalation: 13-week repeated dose inhalation toxicity studies in rats and mice with cobalt sulfate were conducted primarily as range finders for corresponding 2-year inhalation carcinogenicity bioassays. For this reason, the full-range of histopathological investigations was not conducted. Animals were exposed to concentrations of 0, 0.3, 1, 3, 10, 30 mg/m³ which resulted primarily in necrotising injury to the respiratory tract. The larynx appeared to be the most sensitive tissue. Rats developed chronic inflammation of the larynx at concentrations of 1 mg/m³ and more severe effects in the nose, larynx, and lung at higher concentrations. Mice exhibited acute inflammation of the nose at concentrations of 1 mg/m³ and more severe effects in the nose, larynx, and lung at higher exposures. A NOAEC for local effects in the respiratory was not reached in these studies, as lesions, particularly in the larynx, were observed at the lowest concentration of 0.3 mg/m³ cobalt sulfate which represents the LOAEC.

Several epidemiological studies have been conducted in the past for the assessment of adverse health effects in particular on respiratory function in workers exposed to different concentrations of cobalt metal, oxides and salts under various occupational conditions. The reported effects of occupational inhalation exposure to inorganic cobalt compounds included reduced pulmonary function, increased frequencies of phlegm, cough, wheezing, and dyspnoea. No other clinical findings could be related to an exposure to cobalt substances. Based on cases of occupational asthma in workers exposed to cobalt compounds alone, no adverse effects were observed at cobalt exposures of up to 0.12 mg/m³ (min to max 0.02 -0.3 mg/m³). Effects on respiratory function were only observed at lower concentrations when co-exposure to irritant gases occurred. Acute responses of the lung to chemical injury are associated with irritant and inflammatory reactions that may cause changes in airway reactivity and pulmonary oedema. Chronic inflammatory reactions are likely threshold-based responses associated with lung tissue fibrosis, emphysema, asthma, and finally tumour formation. Persistent inflammatory processes may lead to unrestricted cell growth (lung tumours) by a cascade of mechanisms.

Dermal: No information on the repeated dose toxicity via dermal route of the category substances is available. Due to the poor dermal absorption of soluble cobalt salts, it can be concluded that the dermal route is not relevant for the repeated dose toxicity of soluble cobalt salts in this category.

Conclusion: An oral repeated-dose toxicity study is not available for the category substances. The hazard for repeated dose toxicity can be estimated by cross reference to non-category substance information, identifying the digestive tract as primary target organ. The repeated dose toxicity studies via inhalation with cobalt sulfate in rats and mice are not suitable for use in the hazard assessment of systemic effects (via route to route extrapolation). The respiratory tract of test animals is more susceptible to adverse effects by inhaled cobalt, showing an inflammatory response at concentrations at which systemic effects cannot be observed.

Genetic Toxicity

Bacterial test systems: Two published reports showing weak evidence for mutagenic activity of cobalt chloride and cobalt sulfate are available. Therefore, a series of GLP studies were performed using the bacterial strains that had shown evidence of potential mutagenic effects: cobalt chloride was tested in strain TA97a and cobalt sulfate was tested in strain TA100. The studies were performed in two different laboratories using an identical study design. In both laboratories, there was no evidence of any increases in revertant numbers with any of the test chemicals under any of the treatment conditions, and all 2 were appropriately concluded as negative. Overall there is no convincing evidence that soluble cobalt salts (tested as chloride and sulfate) are mutagenic in the bacterial reverse mutations test systems.

In-vitro mammalian mutagenicity: The only published reference from a mouse lymphoma tk assay with cobalt dichloride does not meet current recommendations. There are weak positive findings of induction of hprt mutations in 2 published studies with cobalt dichloride. However, a GLP study with cobalt sulfate has not confirmed hprt gene mutation activity tested to limits of toxicity, and over both 3 and 24 h incubation periods. The overall conclusion is that cobalt salts/compounds do not induce biologically relevant gene mutation responses in mammalian cells.

In-vitro clastogenicity: The in vitro clastogenicity of the cobalt salts within the category was investigated in numerous chromosomal aberration, micronucleus and tk mutation (small colony mutants) assays, indicating in vitro clastogenic effects.

In-vivo clastogenicity: There are two studies in the public domain which appear to suggest clastogenic and/or aneugenic effects in vivo, which however are either biologically implausible with respect to their time and or dose-dependency of effects, employ non-physiological routes of exposure or suffer from other deficiencies. These are however balanced by several reliable, negative in vivo bone marrow micronucleus and chromosomal aberration results with cobalt dichloride and cobalt sulfate. Further, a survey in workers occupationally exposed to cobalt,

inorganic cobalt substances did not detect significant increases of genotoxic effects (micronuclei and DNA damage in peripheral blood) in workers exposed to cobalt-containing dust at a mean level of 20 µg Co/m³.

In summary, soluble cobalt salts do not elicit any mutagenic activity either in bacterial or mammalian test systems. However they induce some genotoxic effects in vitro, mainly manifest as DNA strand or chromosome breaks, which are consistent with a reactive oxygen mechanism, as has been proposed by various authors. A weight-of-evidence approach was applied, considering positive as well as negative in vivo clastogenicity studies and the absence of such chromosome damage in humans that are occupationally exposed to inorganic cobalt substances. It was concluded that effective protective processes exist in vivo to prevent genetic toxicity with relevance for humans from the soluble cobalt salts category.

Carcinogenicity

Two 2-year inhalation carcinogenicity studies with cobalt sulfate heptahydrate in rats and mice are available, which are considered adequate to assess the carcinogenic potential. Following chronic inhalation exposure of cobalt sulfate in rats and mice at concentrations of 0, 0.3, 1 and 3 mg/m³. Respiratory tract tumours developed in rats and mice of both sexes at concentrations ≥ 0.3 mg/m³ cobalt sulfate hexahydrate (equivalent to ≥ 0.067 mg Co/m³), thus this concentration represents a LOAEC for inhalation carcinogenicity.

Taking into account the lack of a NOAEC in the concentration-response assessment of cobalt sulphate a benchmark dose (BMD) was calculated using the US EPA BMD software (Version 2.0) with the Gamma Model (Version 2.13). The numbers of alveolar/bronchiolar adenoma or carcinoma in the lung of rats and mice were selected as benchmark response. The 95% lower confidence limit of the BMD for a treatment-related increase in response of 10% was calculated (BMDL10). The lowest BMDL10 value was that for female rat tumours with 0.414 mg/m³ cobalt sulphate hexahydrate. There was also an increase in adrenal pheochromocytoma in female rats. It was uncertain whether a marginal increase in pheochromocytoma in mid-dose male rats was caused by cobalt sulfate. Limited epidemiological studies in workers of a cobalt producing plant in France did not find an increase in lung cancer risk among cobalt production workers. However, the significance of these studies was limited by the very small number of cases.

Based on the above information, all substances of the soluble cobalt salts category are considered as inhalation carcinogens.Reproductive Toxicity

A set of investigations of limited reliability exist in the public domain which nevertheless indicate an adverse impact on male reproductive function. These studies suffer from several shortcomings including a lack of a clear dose-response relationship, rendering them unreliable for the purposes of human health risk assessment. The above-mentioned studies also focus primarily on effects in males, so that there is a complete absence of adequate data allowing an assessment of effects on female fertility. Based on the above information, the soluble cobalt salt category substances are considered to impair male fertility.

No reliable data on developmental toxicity are currently available[2].

Conclusions

The soluble cobalt salts in this category present a hazard for human health, based on the significant bioaccessibility of cobalt ions (acute oral toxicity, respiratory and eye irritation, skin sensitisation, repeated dose toxicity, carcinogenicity and reproduction). Adequate screening-level data are available to characterize the human health hazard for the purposes of the Cooperative Chemicals Assessment Programme, except for developmental toxicity for which testing was ongoing at the time of finalisation of this document.

ENVIRONMENT

Essentiality and Cobalt Background Level

Cobalt is required to form vitamin B_{12}, which is essential for the growth of many aquatic organisms. Any detectable toxicity of cobalt in aquatic systems is most likely attributable to Co(II). Reported background concentrations of dissolved cobalt in European freshwaters are 0.333 ± 1.01 µg Co/L (median 0.16 µg Co/L) (Salminen, R. (ed.) 2005.

[2] At the time of finalisation of this document, repeated dose oral toxicity, reproduction and pre-natal developmental studies with cobalt chloride in rats were mandatory according to a Decision under the EU REACH Regulation. The repeated dose oral toxicity and pre-natal developmental studies were ongoing, scheduled for finalisation in 2015. The SIAP will be updated once these studies are finalised.

Geochemical Atlas of Europe. FOREGS database: http://www.gtk.fi/publ/foregsatlas/).

Environmental Fate Properties

In waters, cobalt has two common oxidation states, +2 and +3. Under most environmental conditions including natural waters, Co exists as the divalent cation Co(II) and is able to form strong complexes with organic ligands. The divalent cobalt species is highly soluble (with increased solubility at lower pH) and is readily available for uptake by organisms, while the trivalent cobalt species is relatively insoluble and usually found as insoluble oxides or hydroxides. Available data for Co(III) species are limited but do not suggest toxicity greater than that shown for Co(II) species; therefore, the limiting toxicity of cobalt in aquatic systems is most likely to be that of Co(II). In the absence of speciation data, ecotoxicity data derived for cobalt using soluble Co(II) compounds should provide a conservative estimate of the toxicity of other sparingly soluble cobalt compounds. With any cobalt salt, the transport and bioavailability of the cobalt cation and associated anion are determined by their solubility in environmental media (i.e., water, soils, sediments) and biological fluids (e.g., gastric fluid, blood), which is dictated by environmental parameters such as pH. Under most environmentally relevant conditions, cobalt salts will be present as the free metal and free anion. This is sufficient justification for the implementation of a "read-across strategy" using results obtained in tests conducted with soluble cobalt salts (e.g., cobalt dichloride), and this is applicable for all relevant environmental fate endpoints (e.g., adsorption/desorption coefficients and bioconcentration/ bioaccumulation factors).

Environmental Partitioning

Similar median values were obtained for the suspended particulate matter (SPM) distribution functions in freshwater (Log Kd of 4.59) and marine water (Log Kd of 4.94). The median Kd for sediment-seawater is one order of magnitude higher (Log Kd of 5.15), whereas the median Kd of sediment-freshwater and median Kd soil are more than one order of magnitude lower (Log Kd of 2.94 – 3.47) compared to the median Kd for suspended matter. An overview of derived 10^{th}, 50^{th} and 90^{th} percentiles of cobalt distribution coefficients in different environmental compartments, is presented below.

Summary of 10^{th}, 50^{th} and 90^{th} percentile of cobalt K_D values in different environmental compartments

	Suspended Particulate Matter		**Sediment**		
	Freshwater	**Seawater**	**Freshwater**	**Seawater**	**Soil**
10^{th} percentile	2.97	3.78	2.63 (Min)	3.28	1.10
50^{th} percentile	4.59	4.94	2.94	5.15	3.47
90^{th} percentile	6.25	6.05	3.60 (Max)	6.28	4.18

Bioconcentration

The state-of-the-science on metals bioconcentration/bioaccumulation factors (BCF, BAF) do not support the use of BAF or BCF values as a measure of environmental hazard for inorganic forms of cobalt since uptake is not an intrinsic property for cobalt. Cobalt is an essential element and therefore tissue levels are typically homeostatically controlled, thus elevated bioconcentration (BCF) values are commonly observed in waters containing suboptimal Co concentrations. Available data suggest that, as is the case with most metals, cobalt does not biomagnify (i.e., increase in cobalt concentration with increasing trophic level), but rather exhibits biodilution, particularly in upper levels of both aquatic and terrestrial food chains. For example, in marine water, the highest bioconcentration factor (BCF) was reported for phytoplankton (15,600) and plants (including moss and algae; 181-1485). A lower BCF was reported in marine invertebrates (11-156), while the lowest BCF was reported in marine fish (0.143-161).

Biodegradation

For the inorganic cobalt metal and cobalt salts in this dossier, biotic degradation is irrelevant, regardless of the environmental compartment: biotic processes may alter the speciation form of an element (e.g., binding dissolved organic carbon), but it will not eliminate the element from the aquatic compartment by degradation or transformation. Risk and hazard assessment of these compounds is based on the total elemental concentration in the environment, assuming that all cobalt is present as a dissolved cobalt species. This approach can be considered a worst-case approach for chemical assessment of cobalt.

Aquatic Toxicity According to Standard Protocols

Freshwater

A total of 13 acute toxicity tests were conducted using eleven species exposed to the test substance, cobalt dichloride hexahydrate. Although toxicity tests were not conducted using the other soluble cobalt salts in this category, these results are considered to be representative of the divalent cation released by other soluble cobalt salts. Further discussion of this read-across approach is detailed under the section titled Category Assessments. There was a significant concentration effect on juvenile and larval organism survival in all tests. Among the species assessed, acute toxicity values (LC_{50}, dissolved Co) differed from a low of 90.1 µg Co/L for duckweed, *Lemna minor*, to a high of 157,000 µg Co/L for the midge, *C. tentans*. The acute toxicity species sensitivity ranking, in order from most to least sensitive, was as follows: *L. minor* > *P. subcapitata* > *O. mykiss* > *C. dubia* > *D. magna* > *P. promelas* > *H. azteca* > *D. rerio* > *Aeolosoma* sp. > *L. stagnalis* > *C. tentans.* For the acute studies that included both larval and juvenile life stages of *P. promelas* and *D. rerio*, the larvae were more sensitive by factors of 18 and 5, respectively, with larval and juvenile LC_{50} of 3,090 and 54,100 µg Co/L, respectively, for *P. promelas* and 15,980 and 85,290 µg Co/L, respectively, for *D. rerio*. The $L(E)C_{50}$ for each species following acute cobalt exposure are summarised below.

Acute toxicity test results for organisms exposed to cobalt dichloride (µg dissolved Co/L)

Test species	**Common name**	**Life stage**	**$L(E)C_{50}$ (95% CI)**
Lemna minor	Duckweed		90.1 (69.9-116.1)
Pseudokirchneriella subcapitata	Algae		144 (118-176)
Oncorhynchus mykiss	Rainbow trout	Juvenile	1,512 (1,343 – 1,704)
Ceriodaphnia dubia	Water flea	Neonates	2,154 (1,566 - 2964)
Daphnia magna	Water flea	Juveniles	5,890 (5,680 – 6,100)
Pimephales promelas	Fathead minnow	Larval	3,090 (2,720 – 3,520)
		Juvenile	54,100 (45,500 – 64,300)
Hyalella azteca	Amphipod	Juveniles	3,290 (2,920 – 3,710)
Danio rerio	Zebrafish	Larval	15,980 (13,630 – 18,730)
		Juvenile	85,290 (72,300 – 100,700)
Aeolosoma sp.	Oligochaete	Neonates	42,700 (39,680 – 45,960)
Lymnaea stagnalis	Snail	1 month old	61,600 (44,100 – 86,100)
Chironomus tentans	Midge	2nd instar larvae	157,000 (116,000 – 211,000)

* NR - not reported

The chronic toxicity tests provided EC_{10}-NOEC values (dissolved Co) for 11 different freshwater organisms (*Lemna minor, Hyalella azteca, Ceriodaphnia dubia, Lymnaea stagnalis, Pseudokirchneriella subcapitata, Daphnia magna, Aeolosoma headleyi, Chironomus tentans, Pimephales promelas, Danio rerio, Oncorhynchus mykiss*) ranging from 4.9 µg Co/L (*Lemna minor*) to 2,171 µg Co/L (*Oncorhynchus mykiss*). The EC_{10} for each species following chronic cobalt exposure are summarised below.

Chronic species EC_{10} values (µg dissolved Co/L) for the most sensitive endpoint for all freshwater water-column dwelling organisms

Organism	**Common name**	**EC_{10} (95% CI)**
Lemna minor	Duckweed	4.9 (2.7-8.7)
Hyalella azteca	Amphipod	7.55 (4.00-14.27)
Ceriodaphnia dubia	Water flea	7.89 (0.72-86.37)
Lymnaea stagnalis	Snail	9.61 (3.65-25.24)
Pseudokirchneriella subcapitata	Algae	23.0 (14.1-37.5)
Daphnia magna	Water flea	32.36 (21.83-47.99)
Aeolosoma headleyi	Oligochaete	154.6 (124.9-191.5)
Chironomus tentans	Midge	167.1 (104.8-266.6)
Pimephales promelas	Fathead minnow	351.4 (210.6-586.5)
Danio rerio	Zebrafish	1,085 (569-2068)
Oncorhynchus mykiss	Rainbow trout	2,171 (1,658-2,842)

Marine

Marine organisms were exposed to the test substance, cobalt dichloride hexahydrate. Although toxicity tests were not conducted using the other soluble cobalt salts in this category, these results are considered to be representative of the divalent cation released by other soluble cobalt salts. Further discussion of this read-across approach is detailed under the section titled Category Assessments. The EC_{10}/NOEC values (dissolved Co) available for 10 different marine organisms (*Champia parvula, Neanthes arenaceodentata, Mysidopsis bahia, Skeletonema costatum, Dendraster, Mytilus* sp., *Strongylocentrotus purpuratus, Crassostrea* sp., *Dunaliella tertiolecta, Cyprinodon variegates*) ranged from 1.23 µg Co/L (*Champia parvula*) to 31,802 µg Co/L (*Cyprinodon variegates*). The EC_{10} for each species following chronic cobalt exposure are summarised below.

Species EC_{10}/NOEC values (µg dissolved Co/L) for the most sensitive endpoint for all marine organisms

Task	Endpoint	EC_{10} (95% CI)
Seaweed, *Champia parvula*	Cystocarp production	1.23 (0.5 – 2.9)
Marine annelid, *Neanthes arenaceodentata*	Reproduction	206.4 (98.4 – 432.9)
Mysid, *Mysidopsis bahia*	Reproduction	219 (24.6 – 1945)
Marine diatom, *Skeletonema costatum*	Growth rate	590.3 (377.5 – 922.8)
Sand dollar, *Dendraster excentricus*	Proportion normal	967.7 (820.5 – 1141)
Mussel, *Mytilus sp.*	Proportion normal	1656 (1580 – 1735)
Sea urchin, *Strongylocentrotus purpuratus*	Proportion normal	1786 (1733 – 1841)
Oyster, *Crassostrea sp.*	Proportion normal	2763 (2743 – 2783)
Marine flagellate, *Dunaliella tertiolecta*	Growth rate	11961 (10065 – 14214)
Sheepshead minnow, *Cyprinodon variegates*	Biomass	31802 (29938 – 33783)

Sediment

Sediment-dwelling organisms were exposed to the test substance, cobalt dichloride hexahydrate. Although toxicity tests were not conducted using the other soluble cobalt salts in this category, these results are considered to be representative of the divalent cation released by other soluble cobalt salts. Further discussion of this read-across approach is detailed under the section titled Category Assessments. The EC_{10}/NOEC values (total Co) available for cobalt for six different sediment-dwelling organisms (*Hyalella azteca, Ephoron virgo, Chironomus riparius, Gammarus pulex, Tubifex, Lumbriculus variegatu*) ranged from 86 mg Co/kg dry wt (*H. azteca*) to 2,170 mg Co/kg dry wt (*L. variegatus*). The EC_{10} for each species following chronic cobalt exposure are summarised below.

Species EC_{10}/NOEC values (total Co) for the most sensitive endpoint for all sediment dwelling organisms

Organism	Most sensitive endpoint	EC_{10}/NOEC (mg Co/kg dry wt)	Remark
Hyalella azteca	Growth	86 (50-144)	EC_{10}
Ephoron virgo	Growth	136 (96-192)	EC_{10}
Chironomus riparius	Emergence	148 (65-334)	EC_{10}
Gammarus pulex	Survival	273 (186-399)	EC_{10}
Tubifex	Reproduction	1176 (699-1978)	EC_{10}
Lumbriculus variegatus	Survival	2170	NOEC

Soil

A robust data set is available for evaluating the toxicity of cobalt to terrestrial organisms (plants, invertebrates, and microorganisms) and processes. A total of 141 individual toxicity studies were identified representing a total of 14 species; data are provided in the table below) In addition, toxicity data were identified from studies run in 15 separate

soils displaying a range of soil properties typical of those found throughout Europe.

Generic species/process mean values of EC_{10}/NOEC values for most sensitive endpoint for the 14 species and microbial processes (based on added cobalt concentrations).

Generic		Generic, aged	
Species/microbial process	**Species mean (mg Co/kg)**	**Species/microbial process**	**Species mean (mg Co/kg)**
Medicago sativa, shoot yield	3.2	*Medicago sativa*, shoot yield	4.2
Raphanus sativus, total yield	17.8	*Raphanus sativus*, total yield	23.7
Brassica napus, shoot yield	25.3	*Brassica napus*, shoot yield	40.0
Hordeum vulgare, root yield	33.8	*Hordeum vulgare*, root yield	45.0
Elymus lanceolatus, root yield	41.4	*Elymus lanceolatus*, root yield	79.4
Lycopersicon esculentum, root yield	46.7	*Lycopersicon esculentum*, shoot yield	85.1
Eisenia andrei, reproduction	54.8	*Eisenia andrei*, reproduction	105.1
Nitrification	77.2	Glucose induced respiration	124.9
Glucose induced respiration	78.1	Nitrification	127.6
Trifolium pratense, root length	90.1	*Trifolium pratense*, root length	172.9
Eisenia fetida, reproduction	144.4	*Eisenia fetida*, reproduction	238.6
Enchytraeus albidus, reproduction	176.0	*Enchytraeus albidus*, reproduction	319.4
Maize residue mineralisation	208.0	Maize residue mineralisation	343.7
Folsomia candida, reproduction	285.3	*Folsomia candida*, reproduction	466.3

Safe Threshold Values for Aquatic, Sediment, and Soil Compartments

The available chronic toxicity data were used for the construction of a site-specific Species Sensitivity Distribution (SSD) from which the median 5th percentile (HC_5) was derived. This value represents the $HC_{5,50\%}$ with 5%-95% confidence interval. The effects data set for cobalt with EC_{10} values is based on a range of algal, invertebrate and fish species, depending on the compartment, and ensures that the cobalt data set reflects organisms exposed to cobalt by a range of exposure pathways.

Employing a log-normal distribution function resulted in a calculated generic HC_5 value of 1.63 µg Co/L (95% CI 0.15-6.61) for the freshwater compartment, HC_5 value of 33.6 mg Co/kg dry wt (26.4-104.7 95%CI) for freshwater sediment, and HC_5 value of 7.09 µg Co/L (0.025 – 47.26; 95% CI) for the marine water compartment. No reliable acute or chronic toxicity data for the marine sediment compartment were identified in the open literature or in the grey literature; however, based on similar toxicity levels for freshwater versus marine water, it was assumed that the freshwater sediment values would be in the same range for the marine system. Comparison of the cobalt sensitivity of freshwater and marine water column dwelling organisms suggests that freshwater organisms are generally more sensitive to the effects of cobalt than marine organisms; therefore, the application of the freshwater sediment HC_5 to the marine environment should be both protective and conservative. An $HC_{5,50\%}$ of 7.7 mg/kg (5.3-10.7 mg/kg) was derived for the soil compartment by taking into account the effect of ageing, without consideration of the normalisation. The extant data for microorganisms are insufficient to perform a statistical extrapolation analysis (i.e., Species Sensitivity Distribution). A single study using an Activated Sludge Respiration Inhibition Test following OECD Method 209 that was conducted with cobalt dichloride resulted in estimated 30-minute EC_{10} and EC_{50} values for cobalt of 3.73 and 120 mg Co/L, respectively.

Site-specific Approach using the Biotic Ligand Model (BLM)

Cobalt chronic toxicity to aquatic organisms changes as a function of water quality parameters (e.g., Ca and Mg content, pH, dissolved organic carbon (DOC)); Co toxicity is principally affected by Ca and Mg concentration, with toxicity decreasing as a function of increasing Ca/Mg concentration. A biotic ligand model (BLM) was developed based upon extensive empirical data to predict cobalt chronic toxicity for several species including the algae (*P. subcapitata*), invertebrates (*Ceriodaphnia dubia* and *Daphnia magna*) and fathead minnows (*Pimephales promelas*) over a range of physicochemical conditions (i.e., pH, DOC, and hardness). Additionally, site-specific SSDs were developed for a series of European waters representing a range of water types. HC_5 values for each of the modelled locations ranged from 2.22 to 5.08 µg Co/L; a "reasonable worst case" scenario resulted in an HC_5 value of 1.88 µg Co/L.

Conclusion

Cobalt water soluble salts possess properties indicating a hazard for the environment (acute aquatic toxicity less than 1mg/L for two plant/algae species). The chemical has a low bioaccumulation potential. Adequate screening-level data are available to characterize the hazard to the environment for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Exposure

Production: The EU tonnage bands for all of the category substances is 1,000 – 5,000 tonnes per year. Main uses for the category substances range from corrosion inhibition, water treatment and oxygen scavenger, to passivation and plating agent in surface treatment, to nutrient in fertilisers and feed additives, in fermentation processes and biogas production, as catalyst in chemical processes, as intermediate in the production of batteries, as intermediate in the production of other cobalt substances as well as inorganic pigments, frits, glass, ceramic ware, and dyes.

Human exposure: Trace levels of cobalt are found in a wide variety of foods, and human exposure to cobalt may occur via the diet, drinking water, air and occupational as well as consumer exposure. Cobalt is present in nearly all foods in trace amounts. Furthermore, it should be noted that cobalt constitutes 4% by weight of vitamin B12 (cobalamin), an essential human nutrient.

Occupational exposure: Workers can be exposed to dusts of cobalt substances during their manufacture and use. Primary routes of exposure at the workplace are via inhalation and dermal contact.

A comprehensive assessment of occupational exposure during manufacture and each individual downstream use in Europe was recently conducted in the context of regulation EC 1907/2006 (REACH). Within this context monitoring data from manufacturers and downstream users have been collated and used to assess inhalation exposure during manufacture and downstream uses.

Dermal exposure has been assessed on a qualitative basis due to the sensitising effects of the cobalt substances. Workers are required to wear personal protective equipment as a precautionary measure to protect from any residual exposures unless exposure to the substance can be excluded.

Consumer exposure: Opportunities are low for consumer exposure to category substances. Out of the category consumer uses have been identified for cobalt diacetate, only. Cobalt diacetate is used as rubber adhesion agent in steel radial tires, were exposure can be neglected. Exposure associated with the use of recycled rubber in consumer applications, have been assessed to be negligible. Cobalt diacetate is used in the anodic oxidation of consumer goods, however, it will be transformed to cobalt dihydroxide during this process. Furthermore, cobalt diacetate is used as colouring agent in PET bottles allowed for use as food contact materials within the scope of Regulation (EC) 1935/2004, were specific migration limit (SML) for cobalt apply.

Environmental monitoring: Background levels of cobalt in water, sediment and soil are reported in the EU FOREGS Geochemical Atlas (Forum of European Geological Surveys). Typical (i.e. median) background concentration levels in Europe are 0.16 µg Co/L for surface water, 8.0 mg Co/kg dw for freshwater sediment, and 7.78 mg Co/kg dw for topsoil. An analysis of ambient total and dissolved Co-levels in water has been conducted for a limited number of countries. Country-specific reasonable worst-case (RWC) ambient levels were situated between 0.68 and 1.81 µg total Co/L (countries: Belgium, Spain, Sweden, United Kingdom). Dissolved RWC values were 0.07 and 1.32 µg Co/L for France and United Kingdom, respectively. The RWC ambient level represents the 90^{th} percentiles of ambient waters that are not directly affected by point source contamination (diffuse sources only). Cobalt monitoring data for the sediment compartment were identified for 5 countries (Belgium, Finland, France, Spain, Sweden), with the RWC ambient measured concentrations ranging from 16.4 to 29.4 mg Co/kg dry weight (FOREGS Geochemical Atlas).

ANNEX

Table: available key study data for repeated dose toxicity via oral route in rats related to non-category substances

Test substance	Study type	Key results
Cobalt sulfide Co content: 62.95%	OECD Guideline 422 (Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test) Dose: 0, 100, 300, 1000 mg/kg bw/day (actual ingested) Dose: 0, 63, 189, 630 mg Co/kg bw/day rat (Crl:CD (SD)) male/female	NOAEL: 1000 mg/kg bw/day (actual dose received) (male/female) based on: test mat. (The only treatment-related finding, not regarded as adverse, was piloerection noted in few male or female rats from a dose level of 100 mg cobalt sulphide/kg bw/day onwards.)
Tricobalt tetraoxide Co content: 73.4%	OECD Guideline 422 (Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test) Dose: 0, 100, 300, 1000 mg/kg bw/day (actual ingested) Dose: 0, 73, 220, 734 mg Co/kg bw/day rat (Crl:CD (SD)) male/female	NOAEL: 1000 mg/kg bw/day (actual dose received) (male/female) based on: test mat.
Cobalt (powder) Co content: 99.9%	OECD Guideline 422 (Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test) Dose: 0, 30, 100, 300, 1000 mg/kg bw/day (actual ingested) Dose: 0, 30, 100, 300, 1000 mg Co/kg bw/day rat (Crl:CD (SD)) male/female	NOAEL: 30 mg/kg bw/day (actual dose received) (male/female) based on: test mat. (Based on mortality, clinical signs of toxicity, effects on food consumption and macroscopic pathological changes observed at and above 100 mg cobalt powder/kg bw/day and reduced body weight at and above 300 mg cobalt powder/kg bw/day.)
cobalt(II) 4-oxopent-2-en-2-olate Co content: 20.32%	EU Method B.7 (Repeated Dose (28 Days) Toxicity (Oral)) Dose: 0, 15, 50, 150 mg/kg/day (actual ingested) Dose: 0, 3, 10, 30 mg Co/kg bw/day rat (Sprague-Dawley) male/female	NOEL: 15 mg/kg bw/day (actual dose received) (male/female) based on: test mat. based on reduced body weight gain, mean body weights and mean food consumption in male rats at 50 mg/kg bw/d.
Resin acids and Rosin acids, cobalt salts Co content: 7.77%	EU Method B.7 (Repeated Dose (28 Days) Toxicity (Oral)) Dose: 0, 15, 50, 150 mg/kg/day (actual ingested) Dose: 0, 1.2, 3.9, 11.7 mg Co/kg bw/day rat (Sprague-Dawley) male/female	NOAEL: 15 mg/kg bw/day (actual dose received) (male/female) based on: test mat. (Based on based on reduced body weight gain, mean body weights, in vivo and histopathology findings noted at 150 and 50 mg/kg/day, the No Observed Adverse Effect Level (NOAEL) was identified as 15 mg/kg/day.)
Cobalt, borate neodecanoate complexes Co content: 22.15%	OECD Guideline 422 (Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test) Dose: 0.5, 1.5, 5 mg/kg bw/day (actual ingested) Dose: 0.1,0.3, 1 mg Co/kg bw/day rat (Crj: CD(SD)) male/female	NOAEL: 5 mg/kg bw/day (nominal) (male/female) based on: test mat. (no endpoints e.g., body weights, feed consumption, clinical signs, behavioural tests, clinical chemistry, organ weights, histopathology, etc. which indicate any toxicity to the adults or offspring)
Stearic acid, cobalt salt Co content: 9.5%	OECD Guideline 422 (Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test) Dose: 0, 5, 15 and 100 mg/kg/day (females) (actual ingested) 0, 5, 15 and 40 mg/kg/day (males) (actual ingested) Dose: 0, 0.5, 1.5, 9.5 mg Co/kg/day (females) 0, 0.5, 1.5, 3.8 mg Co/kg/day (males) rat (Crj: CD(SD)) male/female	NOAEL: 5 mg/kg bw/day (actual dose received) (female) based on: test mat. (The NOAEL for systemic toxicity in P1 females was considered 5.0 mg/kg/day based on decreased body weight and food consumption, clinical signs of toxicity, mortality, and microscopic pathology effects.) NOAEL: 40 mg/kg bw/day (actual dose received) (male) based on: test mat.