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SIDS INITIAL ASSESSMENT PROFILES AGREED IN THE COURSE OF THE OECD COOPERATIVE CHEMICALS ASSESSMENT PROGRAMME IN 2013

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No. 244

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Series on Testing and Assessment

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SIDS INITIAL ASSESSMENT PROFILES AGREED IN THE COURSE OF THE OECD COOPERATIVE CHEMICALS ASSESSMENT PROGRAMME IN 2013

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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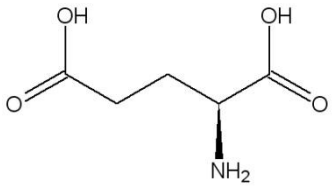
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	56-86-0
Chemical Name	L-Glutamic acid
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Physical and Chemical Properties

L-Glutamic acid is a white orthorhombic, disphenoidal crystal. Melting point is 160°C and sublimation point is 175°C. Density is 1.538 g/cm^3 at 20°C and vapour pressure is 2.27×10^{-6} Pa at 25°C (extrapolated data) and 1.46×10^{-4} Pa at 20°C (estimated data). Water solubility is measured as 8,640 mg/L at 25°C. L-Glutamic acid is insoluble in methanol, ethanol, ether, acetone, cold glacial acetic acid and common neutral solvents. The octanol-water partition coefficient (log K_{ow}) is -3.69 (experimental data) and -3.83 (estimated data). Dissociation constants are measured as $pK_1 = 2.13$, $pK_2 = 4.31$ and $pK_3 = 9.67$ at 25°C.

Human Health

L-Glutamic acid, commonly found in many foods, is an amino acid and a major excitatory neurotransmitter in the central nervous system. Most free L-glutamic acid in the brain is derived from local synthesis from L-glutamine and Kreb's cycle intermediates. It plays an important role in neuronal differentiation, migration and survival in the developing brain by facilitated Ca^{++} transport. L-Glutamic acid is metabolized by enterocytes in various routes. Most L-glutamic acid delivered to the intestine of healthy volunteers is removed by the splanchnic bed on the first pass. Since L-glutamic acid is oxidized in the epithelial cells of the small intestines, its concentration in blood is relatively low compared with other amino acids.

12-13 µc (10-11 mg) of L-Glutamic acid-2-C^{14} was administered to cecum of male albino rats and observed for four hours. Carcass and liver were autopsied to identify the distribution of ^{14}C of isolated glutamic acid. During the test period, 4-5 µc of $^{14}CO_2$ was exhaled, and the distribution of ^{14}C was 11.9-12.3 mµc/mmole in the carcass and 43.6-46.0 mµc/mmole in the liver. Also, carbon 2 of L-glutamic acid was converted into methyl carbon of acetate by intestinal flora.

The acute oral LD_{50} value was greater than 5,110 mg/kg bw for male and female rats [EC standard acute method]. No mortality and body weight changes were observed.

The acute dermal LD_{50} value 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]. Clinical signs included hromodacryorrhoea and scales. L-glutamic acid was non-irritant to rabbit skin [OECD TG 404 and EU Method B.4] and was not irritating to eyes in rabbits [OECD TG 405 and EU Method B.5]. L-glutamic acid was not a skin sensitizer [EU Method B.6].

The reliable repeated dose toxicity of L-glutamic acid has been investigated in 3 studies. In a repeated dose oral toxicity study in rats [OECD TG 407], L-glutamic acid was administered via gavage to 5 animals/sex/dose at 0, 62.5, 250 and 1,000 mg/kg bw/day for 7 days/week for 4 weeks. No death was observed in either sex. There were no treatment-related effects observed at any dose. Based on the results, the NOAEL for repeated dose oral toxicity was considered to be 1,000 mg/kg bw/day (the highest dose) in both sexes. In another repeated dose oral toxicity study in rats, L-glutamic acid was administered by the diet to 35-40 animals/sex/dose at 0, 0.1 and 0.4%

for 24 months. There was no evidence that L-glutamic acid caused any adverse effect on survival, weight increase, food intake, haematology or age-related pathological changes at either dose level in either sex. Motor activity and general behavioural patterns were not affected. Based on the results, L-glutamic acid did not show any toxic effects in this test condition. In the other oral repeated dose toxicity study in mice, L-glutamic acid was administered by the diet to 100 male animals/dose at 0, 1 and 4% w/w for 24 months. There were no treatment-related effects observed at any dose. L-Glutamic acid provided no evidence of toxic potential upon dietary administration.

In an Ames test with multiple strains of *Salmonella typhimurium* TA1535, TA1537, TA1538, TA98, TA100, TA97 and TA102 and/or *Saccharomyces cerevisiae*, L-glutamic acid 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, L-glutamic acid did not induce chromosomal aberrations with and without metabolic activation. An *in vivo* micronucleus assay using mouse bone marrow cells [OECD TG 474] showed negative results up to 2,000 mg/kg bw. Based on these results, L-glutamic acid is not considered to be genotoxic.

The carcinogenic potential of L-glutamic acid has been investigated in 2 studies. In an oral carcinogenicity study in rats, the test substance was administered by the diet to 35-40 animals/sex/dose at 0, 0.1 and 0.4% (equal to 0, 199 and 542 mg/kg bw/day for males, and 0, 125 and 348 mg/kg bw/day for females) for 2 years. There was no evidence that the test substance, at any dose levels, caused tumour in both sexes. Based on the result, L-glutamic acid is considered to have no carcinogenic potential. In another oral carcinogenicity study in mice, L-glutamic acid was administered by the diet to 100 males/dose at 0, 1 or 4% (w/w) for 2 years. There were no treatment-related effects observed at any dose. Based on the result, L-glutamic acid appeared to have no carcinogenic potential upon dietary administration.

L-Glutamic acid has been investigated in a reproduction and developmental toxicity screening test in rats [OECD TG 421]. L-Glutamic acid was administered by oral gavage to 14 animals/sex at 0, 250, 500 or 1,000 mg/kg bw/day. Male rats were administered for 2 weeks prior to mating, 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 reproductive 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.

In another reproduction study, 0.1 and 0.4% (equal to 199 and 542 mg/kg bw/day for males, and 125 and 348 mg/kg bw/day for females) L-glutamic acid were administered to Sprague-Dawley male and female rats aged 12 weeks for up to 2 years. There were no treatment-related changes in clinical signs, motor activity, food consumption, body weight, fertility, survival, organ weights or histopathological findings compared with the control group. Therefore, there were no reproductive toxicity effects of L-glutamic acid.

In a multigeneration and teratogenicity study, rats receiving 2% L-glutamic acid did not show any adverse effects such as skeletal malformations of fetuses.

In a neurotoxicity study, L-glutamic acid was administered by the diet to 6 male animals/dose at dose levels of 0 or 174,000 mg/kg bw/day for 5 weeks. Repeated oral administration of the test substance did not show specific neurological defects at 174,000 mg/kg bw/day in rats.

L-Glutamic acid does not present a hazard for 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 Cooperative Chemicals Assessment Programme.

Environment

In a stability in water test, L-glutamic acid was stable for 96 hours. In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of 0.261 day by AOPWIN ver. 1.92. A test for ready biodegradability was conducted with L-glutamic acid with activated sludge for 28 days [OECD TG 301E]. The concentration of the test substance was 50 mg/L corresponding to a carbon content of 20.4 mg C/L. The test result showed 97 % degradation by DOC removal. Based on this result, L-glutamic acid is considered

to be readily biodegradable.

A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that L-glutamic acid will be distributed mainly to the soil (73%) and water (26.9%) compartments with minor distribution to the sediments compartment (0.06%) and a negligible amount in the air compartment. A Henry's law constant of 1.49×10^{-9} Pa-m^3/mole (1.47×10^{-14} atm-m^3/mole) suggests that volatility of L-glutamic acid from the water phase is expected to be low. A soil adsorption coefficient of log K_{oc}=1.13 indicates that L-glutamic acid has negligible sorption to soil and sediment. Since the ionisation state of L-glutamic acid is sensitive to pH, the K_{oc} may vary with pH.

Using an octanol-water partition coefficient (log K_{ow}) of -3.69, a bioconcentration factor of 3.162 was calculated with BCFBAF, version 3.01. This chemical is not expected to bioaccumulate.

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

Fish [*Oryzias latipes*, OECD TG 203]	96 h LC_{50} >100 mg/L (nominal; static), >99.47 mg/L (measured; static)
Invertebrate [*Daphnia magna*, OECD TG 202]	48 h EC_{50} >83.14 mg/L (measured; static)
Algae [*Pseudokirchneriella subcapitata*, OECD TG 201]	
	72 h E_rC_{50} = 68.5 mg/L (growth rate, nominal; static)
	72 h E_yC_{50} = 54.4 mg/L (yield, nominal; static)

L-Glutamic acid possesses properties indicating a hazard for the environment (acute aquatic toxicity between 10 and 100 mg/L for algae). However, the substance is readily biodegradable and has a low bioaccumulation potential. 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 L-glutamic acid were 190, 2,382 and 2,494 tonnes in 2010, respectively. In Sweden estimated use volumes of L-glutamic acid were approximately 14, 9, 24 and 15 tonnes in 2007, 2008, 2009 and 2010, respectively. In the United States the estimated production volume of L-glutamic acid was below 225 tonnes in 2005.

L-Glutamic acid is used as a food additive and foodstuff condiment due to its flavour-enhancing properties. It is used as an intermediate in pharmaceuticals and synthetics, semiconductors, cosmetics and fertilisers. It is also used as a salt substitute, flavour enhancer, in nutrients, dietary supplements and fortified dietary supplements. In the sponsor country, L-glutamic acid is mainly used as additives of food and a foodstuff condiment, and is accepted for general use in food. According to JECFA no ADI is needed for L-glutamic acid, which is in agreement with the opinion of the sponsor country and Scientific Commitee for Food (SCF) of the European Commission. According to CODEX, for fortified dietary supplements of vegetable juice, Maximum Permitted Levels (MPL) is managed by Good Manufacturing Practice (GMP). Also, the use of fortified dietary supplements of infant milk formula is restricted to improving nutrient value for infants only. In addition, FCC reports that it is used as a salt substitute and in nutrients with no established MDL.

The industrial manufacture and use process of a condiment in a commercial formulation is as follows: L-glutamic acid is produced by adding sulfuric acid to raw sugar/molasses to remove inorganic matter and fermented using microorganisms. L-Glutamic acid produced by the above process is then separated by sulfuric acid or hydrochloric acid, and evaporated. Wet crystals are then dried and packed as an article.

In the sponsor country, L-glutamic acid is handled in closed systems, and workplaces are under control in accordance with the occupational safety and health acts. Occupational exposure is managed by sealed containers, filter facilities and personal protective equipment such as gas masks, waterproof clothes, rubber gloves, rubber boots and goggles in the workplace. Occupational exposure is considered to be negligible in the sponsor country. Exposure of humans via natural food and food additives was estimated to be up to approximately 3 g/day (International Food Information Council Foundation, 2011). Exposure through consumer products is expected to be negligible.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	74499-35-7 [also covers 57427-55-1, 121158-58-5, 210555-94-5 & 27193-86-8]
Chemical Name	Phenol, (tetrapropenyl) derivatives Tetrapropenyl phenol Phenol, dodecyl-, branched
Structural Formula	$HO\text{-}C_6H_4\text{-}(C_{10}H_{21}\text{-}C_{15}H_{31})$

SUMMARY CONCLUSIONS OF THE SIAR

Physico-chemical Properties

Tetrapropenyl phenol is a complex mixture of components. It is a liquid with a low measured water solubility (2.1 mg/L for the bulk material, with a large contribution from lower molecular weight components) and measured vapour pressure of 9.2×10^{-3} Pa at room temperature. The octanol-water partition coefficient for the main component is high (log K_{ow} 7.14, measured)

Human Health

There are no specific toxicokinetic data for tetrapropenyl phenol (TPP). Due to the high lipophilicity and the effects in rat repeated-dose toxicity studies, intestinal absorption and distribution in the body is anticipated. Tetrapropenyl phenol is not acutely toxic, with LD50s of around 2000 and 15000 mg/kg by the oral and dermal routes of exposure, respectively. Animal data indicate that this substance causes irritation to the eyes and skin, but it is not a skin sensitizer. The genotoxic potential of TPP has been well investigated, *in vitro* (bacterial and mammalian cell gene mutation) and *in vivo* (bone marrow cytogenetics), and negative results were obtained. Overall, TPP is not a genotoxicant. This substance causes adverse effects on organs and tissues in rats at dose levels that cause reductions in body weight gain. The NOAEL for repeated-dose toxicity in rodents is 5 mg/kg/day, as adrenal cortical hypertrophy was observed at doses of 20 mg/kg/day and above. It is noteworthy that similar changes were not observed in dogs administered up to 4000 ppm in the diet for 13 weeks.

In rats, tetrapropenyl phenol causes a reduction in the fertility of both sexes and a reduction in mean live litter size, in the presence of general toxicity, at a dose of ≥75 mg/kg/day. Effects on male and female reproductive organs were noted and some reduction in the growth rate of pups was observed during weaning at ≥25 mg/kg/day. This substance causes adverse developmental effects in rats (skeletal variations and malformations and external variations) at 300 mg/kg/day, the highest dose tested, but only in the presence of maternal toxicity. Overall, the NOAEL for toxicity to reproduction is 5 mg/kg/day. At present there is no direct evidence of endocrine disruption.

The chemical possesses properties indicating a potential hazard for human health (effects on fertility and developmental toxicity at doses that also cause maternal 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 log Kow (7.14) suggests a high bioaccumulation potential. An *in vivo* fish bioaccumulation study was conducted according to the OECD 305 guideline using carbon-14 radiolabelled tetrapropenyl phenol to explore

this. A steady-state whole body bioconcentration factor (BCF) of 823 was determined, indicating that TPP has a moderate potential to bioaccumulate (BCF >500).

TPP adsorbs strongly to laboratory glassware, and the Equilibrium Criterion (EQC Level 1) model indicates that this substance is likely to preferentially bind to the soil in the terrestrial environment and to sediment and suspended particles in the aquatic environment.

Tetrapropenyl phenol does not readily biodegrade, and is not inherently biodegradable. It does not undergo hydrolysis. An atmospheric half-life of 2.294 hours can be calculated based on hydroxyl radical interaction, but the low vapour pressure of this substance and its Henry's Law Constant indicate that partitioning into atmosphere will not be a significant pathway.

In aquatic ecotoxicity tests variable analytical results of test solution concentrations were observed due to the low water solubility and high adsorptive properties of TPP, although steps were taken to minimise the latter. Test results are quoted relative to averaged measured concentrations rather than nominal concentrations as, despite the variability in analysis, this better reflects what organisms were likely to have been exposed to.

Tetrapropenyl phenol is very toxic to *Daphnia* (48-hr EC_{50} = 0.017 mg/L (mean measured)) and algae (72-hr growth rate EC_{50} = 0.091 mg/L (geometric mean measured)). Although a reliable study on the acute toxicity of this substance to fish is lacking, it can be predicted that fish are not expected to be the most sensitive group of aquatic organisms using the ECOSAR Program in EPIWIN for the C12 homologue of tetrapropenyl phenol and bridging data from branched 4-nonylphenol. A 21-day reproduction NOEC of 0.002 mg/L (time-weighted mean measured) was obtained for *Daphnia*. This substance is not expected to inhibit wastewater treatment plant microorganisms at typical discharge rates (the 3-hr EC_{50} is greater than 1,000 mg/L (nominal) in activated sludge respiration inhibition tests).

The chemical possesses properties indicating a hazard for the environment (high aquatic toxicity and persistence). Adequate screening-level data are available to characterize the environmental hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Exposure

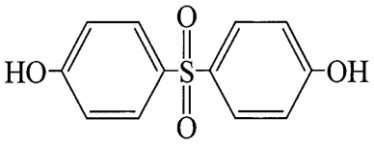
Tetrapropenyl phenol is produced in a closed process in France, Germany, Poland, Singapore, the United Kingdom and United States of America. The total global production volume is estimated to be around 115,000 tonnes/year.

Tetrapropenyl phenol is used almost exclusively (>99.7%) as a raw material by the lubricant additives industry to manufacture more chemically complex detergent and inhibitor additives for the oil and lubricants industry. Typical examples of lubricant additives made from tetrapropenyl phenol include alkylphenate sulfide detergents and anti-wear and anti-rust additives. Typical finished gasoline engine oil may contain 390 ppm of residual tetrapropenylphenol, and typical finished diesel engine oil may contain 1,520 ppm of residual tetrapropenyl phenol. During use of these engine oils, up to 95 % of the residual tetrapropenyl phenol is oxidized.

Occupational and consumer exposures to tetrapropenyl phenol are expected to be very low based on their physico-chemical properties, use and handling patterns. Potential releases of tetrapropenyl phenol to the environment may occur following production, use to make lubricant additives, blending lubricant additives into finished oils and use and disposal of used lubricants.

Note: A UK environmental risk assessment published in 2007 under the UK Coordinated Chemicals Risk Management Programme is available for this substance.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	80-09-1
Chemical Name	4,4'-Sulfonyldiphenol
Structural Formula	

SUMMARY CONCLUSION OF THE SIAR

Physical-chemical properties

4,4'-Sulfonyldiphenol is a white crystalline powder. Melting point is 240.5 °C. Boiling point is unmeasurable because the chemical decomposes at around 330 °C. An estimated value of boiling point is 422.5 °C. Density is 1.366 g/cm^3 at 15 °C. Measured value of vapour pressure is < 3.41×10^{-4} Pa at 80 °C, and calculated value is 6.29×10^{-8} Pa at 25 °C. Measured value of water solubility is 770 mg/L at 20 °C. Measured value of partition coefficient between octanol and water (log Kow) is 2.36 at 24.5 °C. Dissociation constant (pKa) of 7.02 at 25 °C shows that 4,4'-sulfonyldiphenol coexists as the neutral species and deprotonated phenolate anion in the aquatic environment.

Human Health

No specific studies are available on the absorption, distribution, metabolism, or excretion of 4,4'-sulfonyldiphenol. According to a 28-day repeat dose oral toxicity test of 4,4'-sulfonyldiphenol in rats, 2 males died in the 1000 mg/kg bw/day group. In pathological examinations, changes were observed in the cecum, liver, thymus, adrenal, spleen, bone marrow and kidney. Those findings suggest oral absorption and distribution to those organs in rats. In general human populations, 4,4'-sulfonyldiphenol (free plus conjugated) was found in 81% of 315 urine samples at concentrations ranging from below the LOQ (i.e.,0.02 ng/mL) to 21.0 ng/mL, with a mean value of 0.654 ng/mL (0.598 μg/g Cre).

Two limit dose studies estimated LD_{50}s >2000 mg/kg-bw (similar to OECD TG 401) and >5000 mg/kg-bw (OECD TG 401), and a standard study estimated an LD_{50} of 2830 mg/kg-bw (OECD TG 401) in rats. Clinical signs included diuresis, salivation, sedation, dyspnoea, lateral and prone positions, decreased body weight gain, bad general condition, exophthalmus, ruffled fur and curved body position.

4,4'-Sulfonyldiphenol was non-irritant to rabbit skin (OECD TG 404) and did not show skin irritation potential in the EpiDermTM skin corrosion/irritation test (OECD TG 431). 4,4'-Sulfonyldiphenol was not irritating to eyes in rabbits (OECD TG 405). 4,4'-Sulfonyldiphenol was not a skin sensitizer in an LLNA with mice (OECD TG 429).

A repeated dose toxicity study was conducted according to the Japanese Guideline (similar to OECD TG 407). 4,4'-Sulfonyldiphenol was administered to male and female rats (6 or 12 animals/sex/dose) at dose levels of 0 (control group: 0.5% carboxylmethyl cellulose solution), 40, 200 and 1000 mg/kg bw/day orally by gavage for 28 days. For the control, 200 and 1000 mg/kg bw/day groups, a 14-day recovery group was provided separately. Two males in the 1000 mg/kg bw/day group died. Females in the 200 mg/kg bw/day group and males and females in the 1000 mg/kg bw/day group showed significantly suppressed body weight gain and food consumption. The hematological examination revealed anemic changes at 1000 mg/kg bw/day in both sexes. In the blood chemistry examination, significant effects were observed as follows: decrease in total cholesterol (both

sexes), an increase in alkaline phosphatase and a decrease in lactate dehydrogenase (males), and increases in total protein, Ca and albumin (females) were observed at 1000 mg/kg bw/day. In urinalysis, significant increases in the incidence of rats with decreased pH and increased protein and urobilinogen were observed at 200 and 1000 mg/kg bw/day in males and/or females. In the histopathological examination, the hypertrophy of centrilobular hepatocytes and atrophy of the thymus were significantly increased at 1000 mg/kg bw/day in both sexes. In the adrenal, hypertrophy of cortical zona fasciculata cells was significantly increased in males at 1000 mg/kg bw/day. In the bone (femur), significantly increased spongy bone was observed in males and females in the 1000 mg/kg bw/day group. There were significant increases in mucosal hyperplasia and single cell necrosis in mucosal epithelium in the cecum in both sexes at 200 and 1000 mg/kg bw/day. Significantly increased weight of the kidney was observed in males in the 200 and 1000 mg/kg bw/day groups. In the recovery group, the changes in the kidney (weight of the kidney and urinary protein) and bone marrow (spongy cone) were still observed at 1000 mg/kg bw/day. In the spleen, a significant increase in extramedullary hematopoiesis was observed in the high-dose males and females at the end of recovery period. Based on suppressed body weight gain and effects in the kidney and cecum at 200 mg/kg bw/day, it was estimated that the NOAEL of 4,4'-sulfonyldiphenol was 40 mg/kg bw/day for both males and females.

Another study was conducted according to the OECD guideline (TG421) under GLP assurances as a preliminary reproduction toxicity screening test. 4,4'-Sulfonyldiphenol was administered by gavage at doses of 0, 10, 60 and 300 mg/kg bw/day to rats (12 animals/group/sex). Male rats were treated from 14 days before mating to the day before necropsy (including the mating period; 45 days in total) and female rats from 14 days before mating to day 3 of lactation (including the mating period, gestation period, and delivery; a total of 40 to 46 days). In the 300 mg/kg bw/day group, both males and females showed significantly suppressed body weight gain and food consumption. The relative weight of the pituitary was increased at 300 mg/kg bw/day. Males showed a significant increase in the relative weight of the liver, and both males and females showed hypertrophy of centrilobular hepatocytes in histopathological examination at 300 mg/kg bw/day. Cecum distension and diffuse hyperplasia of the mucosal epithelium were observed in both sexes of the 60 and 300 mg/kg bw/day groups although not all animals were examined histopathologically. Effects on the cecum were observed at lower doses in this test than in the repeated 28 day study due to the longer dosing period. Based on the effects on the cecum, the NOAEL for repeat dose toxicity is considered to be 10 mg/kg bw/day for both sexes.

4,4'-Sulfonyldiphenol did not induce gene mutation in bacterial reverse mutation tests in *Salmonella typhimurium* TA100, TA1535, TA98,TA1537 and TA1538 and *Escherichia coli* WP2 *uvrA* with or without exogenous metabolic action (OECD TG 471). 4,4'-sulfonyldiphenol was found to be negative in mammalian cell gene mutation tests (OECD TG 476) both with and without S9 mix. The test substance induced structural chromosome aberration of CHL/IU cells and CHO cells without exogenous metabolic activation (OECD TG 473). However, in two *in vivo* micronucleus assays in mice (OECD TG 474), 4,4'-sulfonyldiphenol showed no micronucleus inducibility up to 2000 mg/kg bw (single or twice gavage dose). Based on these results, 4,4'-sulfonyldiphenol is considered to be non genotoxic *in vivo*.

No data were available on the carcinogenicity of 4,4'-sulfonyldiphenol.

One study of reproductive and developmental toxicity was conducted according to the OECD guideline (OECD TG 421). 4,4'-Sulfonyldiphenol was administered by gavage to rats at doses of 0, 10, 60 and 300 mg/kg bw/day. Male rats were treated from 14 days before mating to the day before necropsy (including the mating period; 45 days in total) and female rats from 14 days before mating to day 3 of lactation (including the mating period, gestation period, and delivery; a total of 40 to 46 days). There were significant prolongation of estrous cycle and diestrus period, and a significant decrease in the implantation index at 300 mg/kg bw/day. A decrease in the fertility index was also observed at 300 mg/kg bw/day, although this effect was not statistically significant. In offspring in the 300 mg/kg bw/day group, the total number of offspring delivered, number of live offspring and the number of offspring alive on day 4 of lactation tended to be low, but these effects were considered to be due to decreased implantation index. The NOAEL of reproductive and developmental toxicity is considered to be 60 mg/kg bw/day based on prolongation of estrous cycle and diestrus period, decreased fertility index and decreased implantation index.

4,4'-Sulfonyldiphenol has uterotrophic potency in a *in vivo* uterotrophic assay. The number of in vitro studies indicated that 4,4'-sulfonyldiphenol can activate the estrogen receptor. In addition, significant prolongation of estrous cycle and diestrus period in the reproductive and developmental toxicity study (OECD TG 421)

suggested a potential endocrine mediated effect. According to these *in vivo* and *in vitro* studies, there is an indication that the substance has an endocrine modulating activity.

4,4'-sulfonyldiphenol possesses properties indicating a hazard for human health (repeated-dose toxicity, and reproductive toxicity, (potential endocrine modulating activity)). Adequate screening level data are available to characterize the human health hazard for the purpose of the Cooperative Chemicals Assessment Programme.

Environment

4,4'-Sulfonyldiphenol in the atmosphere is expected to be degraded by hydroxyl radicals. Using AOPWIN (ver. 1.92a), a calculated half-life time of 8.833 hours and a rate constant of 14.5×10^{-12} cm^3/molecule-sec are obtained for the indirect photo-oxidation of 4,4'-sulfonyldiphenol by reaction with hydroxyl radicals in air. It is assumed that the concentration of hydroxyl radicals in air is 1.5×10^6 OH/cm^3 and that the hydroxyl radicals are available to react with 4,4'-Sulfonyldiphenol for 12 hours/day. The results of the study of the photodegradation of 4,4'-sulfonyldiphenol in aqueous solutions showed that degradation of 4,4'-sulfonyldiphenol occurred under UV light.

A study according to OECD test-guideline 111 showed no hydrolysis of 4,4'-sulfonyldiphenol in water at pH 4, 7 and 9 at 50 °C after five days. 4,4'-Sulfonyldiphenol is not hydrolyzed due to the lack of hydrolysable functional groups.

An OECD test guideline 301C test was conducted with 4,4'-sulfonyldiphenol with activated sludge for four weeks. 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 result showed 0 % degradation by BOD. According to a research oriented study which is a kind of river-die-away method, the biodegradability of 4,4-sulphonyldiphenol was 0% after 22 days' incubation under aerobic conditions. BIOWIN (ver. 4.10) prediction indicates limited biodegradability of 4,4'-sulfonyldiphenol. According to these results, 4,4'-sulfonyldiphenol is considered to be not readily biodegradable.

In a study performed according to OECD test guideline 305 with carp exposed to 4,4'-sulfonyldiphenol, steady-state bioconcentration factors of ≤ 2.2 and ≤ 0.2 were obtained for the concentration of 50 µg/L and of 500 µg/L respectively for a 6-week exposure period. Using an octanol-water partition coefficient (log K_{ow}) of 2.36, a bioconcentration factor of 16.8 was calculated with BCFBAF (ver. 3.01). This chemical is not expected to bioaccumulative.

Fugacity level III calculations show that 4,4'-sulfonyldiphenol is mainly distributed in soil (83.0 %) and water (16.0 %) compartments if equally and continuously released to the air, soil and water. This is a result for only the neutral species of the chemical which is the dominant species at pH values below 6. At pH 8 and higher, deprotonated charged phenolate anions dominate. A Henry's law constant of 2.73×10^{-10} Pa.m^3/mole at 25 °C suggests that 4,4'-sulfonyldiphenol is non-volatile from water. A soil adsorption coefficient of log Koc = 3.26 indicates that 4,4'-sulfonyldiphenol has moderate adsorption potential to soil and sediment.

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

Fish [*Oryzias latipes*]:	96 h LC_{50} >100 mg/L (nominal, semistatic), OECD-TG 203
Daphnid [*Daphnia magna*]:	48 h EC_{50} = 100 mg/L (nominal, static), OECD-TG 202
Algae[*Pseudokirchneriella subcapitata*]:	72 h ErC_{50} = 65 mg/L (nominal, growth rate, static), OECD-TG 201
	72 h EbC_{50} = 16 mg/L (nominal, area method, static), OECD-TG 201

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

Daphnid [*Daphnia magna*]:	21 d LOEC = 8.8 mg/L (measured, semistatic), OECD-TG 211
	21 d NOEC = 2.7 mg/L (measured, semistatic), OECD-TG 211

Algae[*Pseudokirchneriella subcapitata*]:	72 h NOErC = 5 mg/L (nominal, growth rate, static), OECD-TG 201
	72 h NOEbC = 2.2 mg/L, (nominal, area method, static), OECD-TG 201

In the human health section, it is mentioned that the substance has a potential endocrine modulating activity. The relevance of this for the environment is unknown.

4,4'-sulfonyldiphenol possesses properties indicating a hazard for the environment (acute aquatic toxicity values between 10 and 100 mg/L for invertebrate and algae). This chemical is not 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

Total amounts of production and import of 4,4'-sulfonyldiphenol in Japan (the sponsor country) were reported to be 4,913, 4,222 and 2,962 tonnes in fiscal years 2005, 2006, 2007, respectively. In the 2010 fiscal year, production and import volumes of 4,4'-sulfonyldiphenol in Japan were reported to be 4,000 tonnes/year according to the notification of annual manufactured and/or imported quantities under the Chemical Substances Control Law. In the United States, the total amount of production and/or import was reported to be 1 - 10 million pounds (454 to 4,540 tonnes) in 2006. Production volume in the world is not available.

4,4'-Sulfonyldiphenol is manufactured by oxidation of 4,4’-thiodiphenol or dehydration reaction with phenol and sulfuric acid.

4,4'-Sulfonyldiphenol is manufactured in a closed system in Japan. Dusts generated during processing are collected by local exhaust ventilation system followed by appropriate treatment as industrial wastes. Therefore, release to the environment from industrial sites is considered to be negligible in Japan.

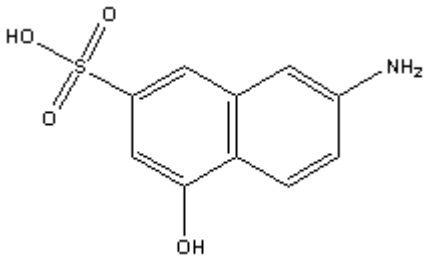
4,4'-Sulfonyldiphenol is used as an intermediate or used for product modification. 4,4’-Sulfonyldiphenol is reported to be used in thermal paper, such as cash register receipts and in can linings and plastics for food storage. The substance was identified in indoor dust and detected in urine samples from New York and seven Asian countries. In Japan, 4,4'-Sulfonyldiphenol is used as a raw material for vinyl chloride plastic, colour developer for thermal paper, dye fixative. 4,4'-Sulfonyldiphenol is also used as dyeing aid, flame retardant or raw materials for photographic coupler in Japan.

Occupational exposure through inhalation of dust and dermal route is anticipated when a worker handles this chemical directly.

4,4'-Sulfonyldiphenol is used as a raw material for industrial chemicals. On the other hand, 4,4'-sulfonyldiphenol is used in thermal paper, in can linings and plastics for food storage. The substance was identified in indoor dust and detected in urine samples in some countries. Therefore, it is consider that consumer exposure exists.

Note: Further test data for sub-chronic oral toxicity and developmental toxicity for this substance should become available in 2014.

INITIAL TARGETED ASSESSMENT PROFILE

CAS No.	87-02-5
Chemical Name	7-Amino-4-hydroxy-2-naphthalenesulphonic acid
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, hazard assessment of existing chemical substances via environmental exposure has been conducted. If a chemical substance is evaluated as "not biodegradable (persistent)" and "not highly bioaccumulative", at least, a 28-day repeated dose toxicity and two *in vitro* mutagenicity studies are required as screening studies for hazard evaluation regarding human health. If a chemical is evaluated as having potential of long-term toxicity for human health, the chemical is classified as a Type II Monitoring Chemical Substance. If not, the chemical is of low priority for further action. Type II Monitoring Chemical Substances undergo risk-based management; at first, annual production volumes of those substances are monitored.

7-Amino-4-hydroxy-2-naphthalenesulfonic acid was evaluated as "not biodegradable (persistent)" and "low bioaccumulative" by METI (Ministry of Economy, Trade and Industry, Japan). Biodegradation and bioaccumulation are not part of the targeted assessment and therefore not presented in ITAP. In order to determine whether this chemical is classified as a Type II monitoring chemical substance, the initial hazard assessment of 7-amino-4-hydroxy-2-naphthalenesulfonic acid was conducted for the acute toxicity, repeated dose toxicity and mutagenicity by MHLW (Ministry of Health, Labour and Welfare, Japan) in November 2005.

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

Physical-Chemical Properties

7-Amino-4-hydroxy-2-naphthalenesulphonic acid is an ash gray powder at room temperature. 7-Amino-4-hydroxy-2-naphthalenesulphonic acid decomposes at 180 - 200°C. Partition coefficient between octanol and water (log Kow) is calculated to be -1.39. Vapour pressure is calculated to be 3.27×10^{-9} Pa at 25 °C. Water solubility is 5,000 mg/L at 20 °C (this value is from Handbook of Environmental Data on Organic Chemicals, 5th edition). Density is 1.3811 g/cm^3 at 25 °C. Dissociation constants (pKa) are calculated to be 3.84 and 9.18

for the -NH_2 functional group and -OH functional group, respectively.

Human Health

No reliable information is available for oral acute toxicity. The oral LD50 of the substance is considered to be greater than 1000 mg/kg bw, as no toxicologically relevant effects were observed at this dose in the 28 day repeated dose toxicity study (see detailed data on the 28 day repeated dose toxicity study, next paragraph). The oral LD50 was reported to be 11500 mg /kg bw in rats as secondary information (supporting information).

A repeated dose oral toxicity study was conducted according to a Guideline for 28-Day Repeated Dose Toxicity Test in Mammalian Species (Chemical Substances Control Law of Japan). In this study, 7-amino-4-hydroxy-2-naphthalenesulfonic acid was administered to male and female rats daily via gavage at 0 (vehicle control: 5% gum arabic solution), 250, 500, or 1000 mg/kg bw/day for 28 days. The test substance did not cause any changes in clinical signs, body weights, food consumption, urinalysis, hematology, blood chemistry or organ weights. There were also no macroscopic or microscopic abnormalities that could be attributed to treatment with the test substance. Based on no toxicological effects, the NOAEL of 7-amino-4-hydroxy-2-naphthalenesulfonic acid was concluded to be 1000 mg/kg bw/day in rats (highest dose tested).

There are three bacterial mutation studies; two were conducted with *Salmonella typhimurium* TA98, TA100, TA1535 and TA1537, or with the foregoing four strains and TA1538 (similar to OECD TG 471), and one was conducted with four strains of *Salmonella typhimurium* and *Escherichia coli* WP2 *uvrA* (similar to OECD TG 471 and 472). 7-Amino-4-hydroxy-2-naphthalenesulfonic acid was positive with metabolic activation in all strains of *Salmonella typhimurium* in two out of three studies, but negative in *E.coli* with and without metabolic activation. In an *in vitro* chromosome aberration test using CHL/IU cells (similar to OECD TG473), 7-amino-4-hydroxy-2-naphthalenesulfonic acid did not induce structural chromosomal aberrations or polyploidy with and without metabolic activation up to concentrations of 1500 µg/mL (assay dissolution limit). However, structural chromosomal aberrations were observed in another study (similar to OECD TG 473), where 7-amino-4-hydroxy-2-naphthalenesulfonic acid was tested up to 4000 µg/mL (carboxymethylcellulose) with S9 mix in CHL cells. Based on these results, 7-amino-4-hydroxy-2-naphthalenesulfonic acid is considered to be genotoxic *in vitro*. No *in vivo* mutagenicity data are available.

Agreed Hazard Conclusions

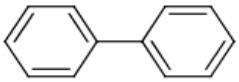
This chemical possesses properties indicating a hazard for one human health endpoint (*in vitro* genotoxicity) targeted in this assessment.

Available Exposure

Production and/or import volume of 7-amino-4-hydroxy-2-naphthalenesulphonic acid was reported to be 10 – 100 tonnes in the fiscal year 2007 in Japan (the sponsor country). Production volume in the world is not available.

7-Amino-4-hydroxy-2-naphthalenesulphonic acid is used as a feedstock for chemical synthesis and as an intermediate for azo dyes or other kinds of dyes in the sponsor country.

INITIAL TARGETED ASSESSMENT PROFILE

CAS No.	**92-52-4**
Chemical Name	**1,1'-Biphenyl** **(biphenyl)**
Structural Formula	

SUMMARY CONCLUSIONS OF THE TARGETED ASSESSMENT

NOTE: The present assessment is targeted to address the following human health endpoints: carcinogenicity/chronic toxicity and genotoxicity; and the following environment endpoints: stability in air, stability in water, biodegradation in water, bioaccumulation potential, and acute and chronic toxicity to aquatic organisms. 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 are included in the Canadian screening assessment but have not been presented to OECD member countries, and thus are not included in this profile.

The final screening assessment will be published under the responsibility of the Government of Canada.

Rationale for Targeting the Assessment

The Government of Canada "categorized" or prioritized all 23,000 chemical substances on its Domestic Substances List (DSL) by 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 to identify those that met the following criteria: **persistent** and/or **bioaccumulative** and **inherently toxic** to humans or to non-human organisms and/or having the **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. 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.

A screening assessment was undertaken on 1,1'-Biphenyl (biphenyl) on the basis that this compound was included in Canada's DSL pilot project implemented to develop and apply new approaches for screening assessments. At that time, biphenyl was identified as a substance likely to be prioritized on the basis of greatest potential for human exposure. However, during the categorization of the DSL, although biphenyl did meet the criteria for inherent toxicity to non-human organisms, it was not found to meet the ecological or human health categorization criteria.

Under 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

Biphenyl is a colourless solid at ambient temperature, and has a melting point of 69 °C, boiling point of 256.1 °C and vapour pressure of 1.19 Pa at 25°C (all measured values). The measured octanol-water partition coefficient (log K_{ow}) is 4.01, and the measured water solubility is 7.48 mg/L at 25 °C. The organic carbon-water partition coefficient (log K_{oc}) was estimated to be 3.71.

Human Health Targeted Endpoints

The majority of the studies described here have been reviewed by the World Health Organization (WHO 2006. Safety evaluation of certain food additives) and the International Programme on Chemical Safety (IPCS 1999. Biphenyl). However, additional or updated data relevant to the screening assessment are designated in square brackets.

Genotoxicity: Investigations of the genotoxicity potential of biphenyl in several *in vivo* and *in vitro* studies have provided mixed results.

- Biphenyl was not mutagenic in a number of *in vitro* bacterial gene mutation assays using multiple strains of *S. typhimurium* and two strains of *E. coli*, but showed mixed results in two strains of *S. cerevisiae*, and positive mutagenicity in mouse L51878Y and Chinese hamster cells with metabolic activation.

- Unscheduled DNA synthesis (UDS) was negative in human lung fibroblasts and rat hepatocytes *in vitro* with and without metabolic activation and *in vitro* DNA damage assays were negative in human fibroblasts with and without metabolic activation and bacterial cells (*E. coli* with and without activation, *B. subtilis* without activation) but were positive in mouse L51878Y cells with metabolic activation.

- Biphenyl induced chromosomal aberrations in human lymphocytes *in vitro* [additional data] and Chinese hamster cells *in vitro*, with metabolic activation, as well as induction of micronuclei and sister chromatid exchange (SCE) in human lymphocytes *in vitro* [additional data].

- In an *in vivo* comet assay, a single oral dose of 2000 mg/kg bw biphenyl caused significant DNA damage in various organs of male mice including stomach, liver, kidney, bladder, lung, brain and bone marrow 24 hours after exposure. In a subsequent comet assay in male mice, a single oral administration of 100 mg/kg bw of biphenyl caused DNA damage in the colon; however, damage to DNA in other tissues including stomach, liver, kidney, bladder, lung, brain, and bone marrow was observed 24 hours after exposure to 1000 or 2000 mg/kg bw of biphenyl [additional data].

- No evidence of chromosomal aberrations was reported in the bone marrow of rats exposed to biphenyl via inhalation to 320 mg/m³ biphenyl or via an unspecified route.

Based on the weight of evidence, 1,1'-biphenyl may have *in vivo* genotoxic potential.

Carcinogenic potential and Chronic Toxicity was determined on the basis of long-term oral studies.

In a carcinogenicity study, male and female SPF F344/DuCrj rats (n = 50/sex/dose) were administered 0, 500, 1500 or 4500 ppm (equivalent to 0, 25, 75, or 225 mg/kg bw per day, respectively) of biphenyl in diet for two years. A significant increase was reported in the incidence of papilloma or carcinoma of the bladder only in male rats in the high dose (225 mg/kg bw per day) group. Although calculi development and transitional cell hyperplasia (focal, nodular or papillary) were noted in the bladder of both sexes at the high dose, the incidences were much greater in males than in females. There was also a significant increase in hyperplasia and mineralization in renal pelvis in male and female rats in the high dose group. A lowest-observed-effect-level (LOEL) of 25 mg/kg bw per day was determined for non-cancer effects, including increase in serum enzymes (alkaline phosphatase, aspartate transaminase and alanine transaminase) and elevated blood urea nitrogen (BUN) levels in low-dose male and mid-dose female rats, which elevated with an increase in dose. Changes in haematological parameters (reduced haemoglobin and haematocrit) were also noted in mid and high-dose females and high-dose males.

Male and female Wistar rats (n = 50/sex/dose) were exposed to biphenyl at dietary concentrations of 0, 630 or 1250 ppm of biphenyl (0, 47, or 94 mg/kg bw per day, respectively) for 104-weeks. There was no evidence of urolithiasis or tumour formation. Dose-dependent effects, i.e., reduced body weight gain, alterations in serum enzymes (aspartate transaminase, alanine transaminase and lactate dehydrogenase) were noted at both doses. The LOAEL was 47 mg/kg bw per day (lowest dose tested).

Male and female Wistar rats (n = 50/sex/dose) were exposed to 0, 0.25 or 0.5% biphenyl in the diet (0, 188, or 375 mg/kg bw per day, respectively) for 75 weeks. There were dose-dependent increases in the presence of stones in the kidney, ureter and bladder in both sexes, but no evidence of carcinogenicity was observed. The LOAEL was 188 mg/kg bw/day based on these dose-dependent increases and hematuria, which developed as early as 16 weeks of exposure.

In an initiation/promotion study, male Wistar rats (n = 25/dose) were administered 0, 0.125 or 0.5% biphenyl in the diet (0, 94 or 375 mg/kg bw per day, respectively) for 34 weeks. Some rats in each dose group also received 0.1% *N*-ethyl-*N*-hydroxyethylnitrosamine (EHEN) for 2 weeks before exposure to biphenyl in diet. An increase was reported in the incidence of stones in the kidney, ureter and bladder in rats in the high dose group. No rats exposed to biphenyl alone developed tumours, and exposure to biphenyl did not enhance tumour development initiated by EHEN (incidences of 52, 54.5 and 28% at 0, 0.125 and 0.5% biphenyl, respectively). The NOAEL was 94 mg/kg bw per day.

In mice, the liver appears to be a target organ for toxicity of biphenyl. Male and female BDF_1 mice (n = 50/sex/dose) were administered 0, 667, 2000 or 6000 ppm biphenyl in the diet for 104 weeks (equal to 0, 97, 291, or 1050 mg/kg-bw per day in males and 0, 134, 414. or 1420 mg/kg-bw per day in females, respectively). Female mice had significant increases in the incidence of hepatocellular adenomas at 2000 and 6000 ppm (incidences of 2/50, 3/50, 12/50 and 10/49, respectively) and in hepatocellular carcinomas at 2000 ppm (incidences of 1/50, 5/50, 7/50 and 5/49, respectively). There were no increases in tumour incidences in male mice. Non-cancer effects observed were an increased incidence of basophilic cell foci in the liver of females at 2000 and 6000 ppm (incidences of 1/50, 1/50, 16/50, 14/50, respectively), and in the kidneys, increased incidences of necrotic desquamation of urothelium in the renal pelvis of males and females (significant at 6000 ppm only), as well as mineralization in the inner stripe of the outer medulla in females (significant at 2000 ppm and above). Significant increases in serum enzymes, blood urea nitrogen and calcium were noted at 2000 ppm and above in both sexes. The NOAEL was 97 mg/kg bw per day based on the non-neoplastic effects in the liver and kidney and increases in certain clinical chemistry parameters at the mid- and high doses [updated data].

Carcinogenicity Potential in Humans

The development of bladder tumour in rat has been proposed as the result of formation of urinary calculi (associated with elevated pH) which causes mechanical damage in the bladder and subsequent regenerative hyperplasia of the bladder epithelium. It is probable that the induction of tumours is secondary to the formation of bladder calculi, which in male rats results from the precipitation of the potassium salt of 4-hydroxybiphenyl-O-sulfate. These calculi then induce sustained mechanical damage, which in turn evokes haematuria and a regenerative response in the bladder epithelium. This is supported by the findings that bladder tumours occurred in close association with calculus formation and haematuria, and also supported by the observed sex differences in structure and composition of calculi and in occurrence of haematuria, which was absent in females. The postulated mechanism appears to be dose dependent, given the steep dose–response relationships found for the neoplastic and associated preneoplastic lesions. Bladder stones may form in humans; however, because of several anatomical or physiological differences (the bladder is vertical in humans versus horizontal in rodents, and humans will more easily lose calculi formed) and likely much lower exposures to such chemicals, the risk of bladder tumour development is considered very unlikely in humans.

In mice, biphenyl-induced hepatocarcinogenicity might be explained by peroxisome proliferation [additional data]. Exposure to peroxisome proliferators has been suggested to cause liver tumours via a non-genotoxic mechanism in mice and peroxisome proliferation is not considered as a relevant mode of action of tumour development in humans, but it has also been suggested that there is a lack of data to conclude that peroxisome proliferation is a relevant mode of action [additional data]. It has also been proposed that biphenyl-induced carcinogenicity of liver in mice may be associated with possible DNA damage by formation of reactive biphenyl metabolites, i.e., 2-HBP, 2,5-DHBP or 2-PBQ [additional data]. These metabolites do not appear to be significant in humans, based on studies in human liver and kidney slices. However, it is also proposed that

overall data are insufficient to establish a mode of action for the liver tumours in female mice.

1,1'-Biphenyl possesses properties indicating a hazard for human health (mixed results in both *in vitro* and *in vivo* studies for genotoxicity, potential carcinogenicity). The development of bladder tumours in male rats likely occurs subsequent to mechanical injury to urothelium at high doses and has limited relevance in humans. There is uncertainty with respect to the mode of action of biphenyl-induced tumours in the female mouse liver.

Environment

Environmental Fate

According to the results of Level III fugacity modelling (EQC 2003), biphenyl is expected to distribute mainly into air (98.4%) if only released into the atmospheric compartment. If only released into water, the substance is expected to mainly reside in water (88%), to some extent partition to air (2%) and also to be deposited to sediment (~10%). If only released to soil, the substance will entirely reside in this environmental compartment (100%). Based on Level III fugacity modelling, if released equally to air, water and soil, most of the substance will partition to the soil (~70%), followed by water (~25%), air (2%) and sediment (3%).

A measured Henry's Law Constant of 28 Pa•m^3/mole at 25 ^oC also indicates biphenyl volatilizes and may evaporate from the surface of water or moist soil. The modelled log K_{oc}, of 3.71(PCKOCWIN 2008) indicates a strong potential of the substance to accumulate in soil and sediment.

The characteristic travel distance (CTD) has been used as an indicator for long range transport potential. Based on its physical-chemical properties, a CTD for biphenyl has been calculated as 391 km (TaPL3 2000), and 394 km (using the OECD POPs Tool). The substance is considered to have a low potential for long-range transport in air (CTD < 700 km), which is in agreement with its rapid transformation in air from hydroxy radical attack resulting in a calculated half-life of 1.5 days. Biphenyl is not expected to react with other photo-oxidative species in the atmosphere, such as ozone, nor is it likely to degrade via direct photolysis.

In water, biphenyl can be considered both readily and inherently biodegradable, according to experimental results. A test for the ready biodegradability was conducted according to OECD test guideline 301 C (modified MITI test I), and found 66% Biological Oxygen Demand (BOD) after 14 days of incubation. In a study for inherent biodegradability (Sturm test (cfr. ASTM D5209-91)), monitoring of CO_2 evolution indicated that biphenyl is ultimately degraded by 88% after 43 days and around 69% after 28 days. These results are generally consistent with QSAR modelling of the ultimate degradability of the biphenyl structure (BIOWIN 2000, TOPKAT 2004), which suggests that biphenyl is readily biodegraded. However, the model thresholds for ready biodegradation are only just exceeded suggesting that biphenyl is still a fairly stable compound. All models except CATABOL (which suggests a very slow rate of biodegradation) agree on this point.

Estimated half-lives for the primary biodegradation of biphenyl in water range from 1.58 days (die-away test with river water) to 2.8 months (clean seawater). Biodegradation of biphenyl was also examined during 10 days in a natural lake water/sediment system with naturally present microorganisms. Analysis of trapped $^{14}CO_2$ indicates ultimate biodegradation of 37.8% in the low dose treatment (0.077 mg/L). The half-life of biphenyl was estimated to be 6-10 days in the lake water/sediment system. Given the low exposure duration (10 days), results of this test can be used in a weight-of-evidence approach. A sediment half-life of 333 days is reported in a 394-day mesocosm study with seawater, however this surface layer concentration decrease is attributed to partitioning rather than biodegradation. There is a lack of concentration decrease deeper in the sediment or in less contaminated sediment over the same time period.

In groundwater, calculated primary half-life values range from 3 to 14 days, using scientific judgement and based on the acclimated aqueous aerobic biodegradation half-life. In soil, the main removal process for biphenyl appears to be biodegradation, with a calculated primary biodegradation half-life value of 1.5 to 7 days, using scientific judgement and based on the acclimated aqueous aerobic biodegradation half-life.

Overall, available data suggest that biphenyl has a relatively fast rate of ultimate biodegradation and likely undergoes rapid primary transformations in the environment under aerobic conditions. A first-order

mineralization half-life of approximately 23 days for water is recommended based on the probability result from the TOPKAT model of 57% after 28 days. Rates of degradation are expected to be approximately the same in aerobic soils and sediments but slower under anaerobic conditions in these media.

At a log k_{ow} of ~4.0 biphenyl is expected to be bioavailable in water resulting in practically all uptake in aquatic biota directly occurring from water. Bioconcentration factors range from approximately 427 (BCFBAF model validation training set) to 1900 for rainbow trout (*Oncorhynchus mykiss*) and 2422 for the eastern oyster *Crassostrea virginaca* (both experimental BCFs). Biphenyl is therefore considered to have a potential to bioaccumulate in organisms (BCF > 500).

Aquatic Toxicity

Experimental data have been identified for biphenyl relating to acute and chronic toxicity of the substance to aquatic species across several taxa. Key endpoints for each are presented below:

Acute

- Algae *Pseudokirchneriella subcapitata*, 72 hour E_rC_{50} = 0.78 mg/L (growth rate, static, OECD Guideline 201); *Scenedesmus vacuolatus*, 24 h E_rC_{50} = 0.231 mg/L (growth rate, measured, static)
- Water flea (*Daphnia magna*), 24 hour LC_{50}= 1.3 mg/L, 48 hour LC_{50} = 0.36 mg/L, NOEC = 0.04 mg/L (measured, flow-through)
- Rainbow trout (*Oncorhynchus mykiss*), 96 hour LC_{50} = 1.5 mg/L (nominal, static)

Chronic

- Water flea (*Daphnia magna*), 21 day NOEC = 0.170 mg/L; 21 day LOEC of 0.32 mg/L, 21 day, MATC = 0.23 mg/L (measured, static)
- Rainbow trout (*Oncorhynchus mykiss*), 87 day NOEC = 0.229 mg/L, 87 day LOEC = 0.331 mg/L (measured, flow-through)

1,1'-Biphenyl possesses properties indicating hazard to the environment (acute and chronic aquatic toxicity below 1 mg/L). The substance is readily biodegradable but there is an indication of a long half-life in sediment. The substance has potential for bioaccumulation.

Exposure Summary Information

In Canada (sponsor country), biphenyl is mainly used in the chemical industry as an intermediate in the production of heat transfer fluids. High temperature heat transfer fluids are used in chemical manufacturing processes to heat or cool reaction mixtures. The total reported uses of biphenyl in Canada for the year 2000, were in the range of 10 000 to 100 000 kg.

Biphenyl has been used globally as a heat transfer agent, fungistat in packaging of citrus fruit, dyeing assistant for polyesters organic synthesis, and also for plant disease control and the manufacture of benzidine. Other uses identified were: antifreeze/coolant/de-icer, solvent/carrier, preservative, formulation component, functional fluid, i.e. hydraulic dielectric or other additives, catalyst/accelerator/initiator/activator; fragrance/perfume/deodorizer/flavouring agent; and finishing agent. With the exception of the heat transfer agent, these uses are historical in the sponsor country.

Biphenyl is known to be found both in nature and from anthropogenic sources. Biphenyl occurs naturally in coal tar (pitch), crude oil and natural gas. Leftover residue from coal tar distillation was identified in coal tar-based driveway sealants from local retail stores in Canada. Additionally, biphenyl has been detected in coal tar-derived creosotes.

Based on the most recent survey for this substance, no companies in Canada reported manufacturing biphenyl in a quantity greater than or equal to 10 000 kg for the 2000 calendar year. However, it was reported that it was

imported into Canada in the range of 10 000 to100 000 kg in the same year.

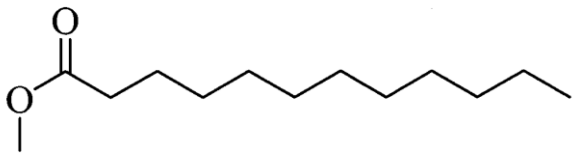
Biphenyl's release into the environment may occur from industrial processing of chemical intermediate, incomplete combustion of organic matter, such as from internal combustion engines, mineral oil and coal combustion, power generation, incinerators, burning of agricultural wastes and wood. Biphenyl is a by-product, notably in the manufacture of high octane motor and aviation fuels. It is also present in exhaust gas of vehicles, as well as emissions from residential heating and cigarette smoke. Fugitive emissions or venting during the handling, transport or storage of biphenyl could also be a source of biphenyl in ambient air.

Under Canada's National Pollutant Release Inventory (NPRI), industrial facilities in Canada reported a release of 4400 kg and 3800 kg of biphenyl, exclusively to air, in the years 2007 and 2008, respectively. On-site releases from the chemical industries sector accounted for 93% of the total emission and the rest was contributed from petroleum and coal products refining and manufacturers. Additional releases from other sources such as smaller industries and residential wood combustion are also expected to contribute to the total annual releases of biphenyl to the environment. It is estimated that a total of 110,000 kg of biphenyl are released to air through the domestic combustion of wood in Canada. These emissions and those from small industries across the country are not accounted for by the NPRI.

Industrial uses of biphenyl could result in releases to surface waters. However, most biphenyl in sewage treatment plant influent is removed and does end up in the sewage sludge. Biphenyl could end up in soil from the application of sewage sludge to agricultural land.

The general population exposure to biphenyl in the sponsor country is low from environmental media and food, as supported by monitoring data, and exposure from consumer products is expected to be negligible.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	111-82-0
Chemical Name	**METHYL LAURATE**
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Physical-chemical properties

Methyl laurate is a colourless clear liquid. Measured melting point and boiling point are 5.2 °C and 267 °C respectively. Vapour pressure at 25 °C extrapolated from the experimental value is 0.161 Pa. Water solubility is < 4.40 mg/L at 20 °C or calculated to be 1.39 mg/L at 25 °C. Measured value of partition coefficient between octanol and water (log Kow) is 6.5 at 25 °C. Soil adsorption coefficient (log Koc) is calculated to be 3.11.

Human Health

No experimental information is available for toxicokinetics, metabolism, and distribution of methyl laurate. However, general information for medium-length linear esters indicates that they are rapidly absorbed from the gastrointestinal tract, hydrolyzed to yield the corresponding alcohols and carboxylic acids and further oxidized to carbon dioxide via the fatty acid pathway and excreted via the urine.

In an acute inhalation toxicity study (OECD TG 436), no deaths or signs of toxicity were observed at 5 mg/L in rats. Therefore, the aerosol inhalation LC_{50} value of methyl laurate was concluded to be over 5 mg/L. In acute oral toxicity studies (OECD TG 401), no deaths or signs of toxicity were observed at 20000 mg/kg bw in rats. Thus, the oral LD_{50} value of methyl laurate was concluded to be over 20000 mg/kg bw in rats.

Methyl laurate caused slight to severe skin irritation to rabbit skin, but reversibility was observed within 14 days after application (OECD TG 405). Methyl laurate caused no skin irritation in humans. *In vitro* skin irritation studies with human cultured cells showed no irritation. In the eye irritation tests in rabbits, no abnormality was found by application of methyl laurate. No information is available regarding the respiratory tract irritancy of methyl laurate.

Negative skin sensitization to methyl laurate was reported in a guinea pig maximization test (OECD TG 406).

In the combined oral repeated dose toxicity study with the reproduction/developmental toxicity screening test using rats (OECD TG 422) at doses of 0 (vehicle: corn oil), 250, 500 and 1000 mg/kg bw/d, methyl laurate did not cause any treatment-related effects at the highest dose tested. The NOAEL for oral repeated dose toxicity was considered to be 1000 mg/kg bw/d.

Methyl laurate did not induce gene mutation in *Salmonella typhimurium* TA98 TA100, TA1535, TA1537 and *Escherichia coli* WP2 *uvrA in vitro* tests (OECD TG 471 or 472). The substance did not induce chromosome aberrations in both cultured Chinese hamster lung (CHL/IU) cells and human lymphocytes (OECD TG 473). Based on these results, methyl laurate is considered to be non-genotoxic *in vitro*.

No data are available for the carcinogenicity of methyl laurate.

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

Methyl laurate does not present a hazard for 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 Cooperative Chemicals Assessment Programme.

Environment

In the atmosphere, methyl laurate is expected to be degraded by hydroxyl radicals. A calculated half-life time of 0.811 days is obtained by AOPWIN (version 1.92a) for the indirect photo-oxidation by reaction with hydroxyl radicals in air.

In a study according to OECD test-guideline 111, methyl laurate was hydrolyzed at pH 9. Rate constant of 5.61×10^{-3} h^{-1} and half-life time of 5.14 days were measured at 25 °C at pH 9. No experimental data are available at pH 4 and pH 7. According to HYDROWIN (ver. 2.00), a half-life time for this chemical at pH 7 is calculated to be 7.28 years.

An OECD test guideline 301C test was conducted with methyl laurate with activated sludge for four weeks. The concentration of the test substance was 100 mg/L and the concentration of the activated sludge was 30 mg/L as suspended solid matters. The test result showed 78 % degradation by BOD. BIOWIN (version 4.10) prediction shows that methyl laurate is readily biodegradable. According to these results, methyl laurate is considered to be readily biodegradable.

No information was available on the bioconcentration on methyl laurate. Using an octanol-water partition coefficient (log K_{ow}) of 6.5, a bioconcentration factor of 381 was calculated with BCFBAF (version 3.01). This chemical has a low potential for bioaccumulation.

Fugacity level III calculations show that methyl laurate is mainly distributed in soil (71.8 %) and water (19.9 %) compartments if equally and continuously released to the air, soil and water. A Henry's law constant of 302 $Pa.m^3$/mole at 25 °C suggests that volatilization of methyl laurate from water is expected. A soil adsorption coefficient of log K_{oc} = 3.11 indicates methyl laurate has moderate potential for adsorption to soil and sediment.

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

Fish [*Oryzias latipes*]:	96 h LC_{50} > 0.52 mg/L (highest concentration, measured, flow-through), OECD-TG 203
Daphnid [*Daphnia magna*]:	48 h EC_{50} = 0.23 mg/L (measured, flow-through), OECD-TG 202
Algae [*Pseudokirchneriella subcapitata*]:	72 h ErC_{50} = 0.017 mg/L (measured, growth rate, static, closed), OECD-TG 201
	72 h EbC_{50} = 0.013 mg/L (measured, biomass*, static, closed), OECD-TG 201 * = area under growth curve

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

Daphnid [*Daphnia magna*]:	21 d LOEC = 0.21 mg/L (measured, flow-through), OECD-TG 211
	21 d NOEC = 0.081 mg/L (measured, flow-through), OECD-TG 211
Algae [*Pseudokirchneriella subcapitata*]:	72 h NOErC = 0.003 mg/L (measured, growth rate, static, closed), OECD-TG 201
	72 h NOEbC = 0.003 mg/L (measured, biomass, static, closed),

OECD-TG 201

Methyl laurate possesses properties indicating a hazard for the environment (acute aquatic toxicity values between 0.01 and 1.0 mg/L for invertebrate and algae and chronic toxicity less than 0.1 mg/L for invertebrate and algae). However this chemical is considered to be 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

Total amounts of production and import of methyl laurate in Japan (sponsor country) were reported to be 2,731 tonnes in the fiscal year 2010 according to the notification of annual manufactured and/or imported quantities of Priority Assessment Chemical Substances under Chemical Substances Control Law. In the United States, the total amount of production and/or import was reported to be 1 to 10 – 50 million pounds (4,540 to 22,680 tonnes) in 2006. Production volume in the world is not available.

Methyl laurate is manufactured by reaction of lauric acid with methanol in the presence of sulfuric acid. Methyl laurate is also produced as mixed fatty acid esters in Japan.

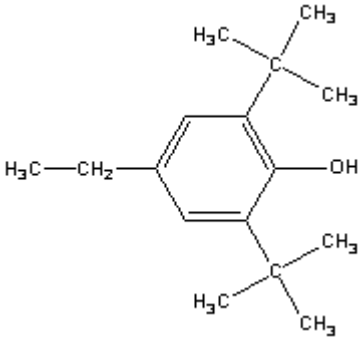
Methyl laurate is manufactured in closed system in Japan. Although small amounts of methyl laurate might be released into drains during cleaning of reaction vessels or packaging processes, the effluents are treated appropriately at sewage treatment facilities. As methyl laurate is readily biodegradable, release to the environment is small in Japan.

Methyl laurate is used as an industrial raw material such as an intermediate for emulsifiers, surface acting agents, or used as a paint additive in Japan. In the United States, methyl laurate is used as an intermediate according to Inventory Updated Reporting. Methyl laurate is also used as a food additive in Japan. In the Hazardous Substances Database, it is reported that methyl laurate is used as an intermediate for detergents, emulsifiers, wetting agents, stabilizers, lubricants, plasticizers, textiles, and flavouring agents. Methyl laurate is also used as a reference standard for gas chromatography and biochemical research. Methyl laurate is listed in the list of fragrance ingredients used in consumer goods published by the International Fragrance Association.

Occupational exposure through inhalation of vapour is anticipated when a worker handles this chemical directly. To prevent worker exposure to vapour, worker protection measures such as Local Exhaust ventilation or Personal Protective Equipment are necessary at production sites. Proper worker protection measures may be necessary at user sites as well.

As methyl laurate may be included in consumer products such as paints and fragrance or used as food additives, consumer exposure is anticipated. However, no detailed information was obtained for consumer exposure.

INITIAL TARGETED ASSESSMENT PROFILE

CAS No.	4130-42-1
Chemical Name	2,6-Di-*tert*-butyl-4-ethylphenol
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, hazard assessment of existing chemical substances via environmental exposure has been conducted. If a chemical substance is evaluated as "not biodegradable (persistent)" and "not highly bioaccumulative", at least, a 28-day repeated dose toxicity and two *in vitro* mutagenicity studies are required as screening studies for hazard evaluation regarding human health. If a chemical is evaluated as having potential of long-term toxicity for human health, the chemical is classified as a Type II Monitoring Chemical Substance. If not, the chemical is of low priority for further action. Type II Monitoring Chemical Substances undergo risk-based management; at first, annual production volumes of those substances are monitored.

2,6-Di-*tert*-butyl-4-ethylphenol was evaluated as "not biodegradable (persistent)" and "low bioaccumulative" by METI (Ministry of Economy, Trade and Industry, Japan). Biodegradation and bioaccumulation are not part of the targeted assessment and therefore not presented in ITAP. In order to determine whether this chemical is classified as a Type II monitoring chemical substance, the initial hazard assessment of 2,6-di-*tert*-butyl-4-ethylphenol was conducted for the acute toxicity, repeated dose toxicity and mutagenicity by MHLW (Ministry of Health, Labour and Welfare, Japan) in December 2007.

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

Physical-Chemical Properties

2,6-Di-*tert*-butyl-4-ethylphenol is a yellow solid at room temperature. Melting point and boiling point are 44 °C and 272 °C respectively (both values are from CRC Handbook of Chemistry and Physics, version 2008). Measured partition coefficient between octanol and water (log Kow) is ≥ 3.27. Vapour pressure is calculated to

be 0.29 Pa at 25 °C. Measured water solubility is 21 mg/L at 25 °C.

Human Health

No information is available for the acute toxicity of 2,6-di-*tert*-butyl-4-ethylphenol. In a dose-finding study, rats were daily dosed by gavage with 2,6-di-*tert*-butyl-4-ethylphenol at 0, 125, 250, 500 or 1000 mg/kg bw/day for 14 days. Neither deaths nor clinical signs were observed on day 1 of administration. A total of 4/5 males and 3/5 females died on day 7-13 of administration at 1000 mg/kg bw/day.

A repeated dose oral toxicity study was conducted following a Guideline for 28-Day Repeated Dose Toxicity Test in Mammalian Species (Chemical Substances Control Law of Japan) under the principles of GLP. In this study, 2,6-di-*tert*-butyl-4-ethylphenol was administered to rats via gavage at 0 (vehicle control: 0.5% methylcellulose solution), 15, 60, or 250 mg/kg bw/day for 28 days. No deaths or clinical signs of toxicity were observed, and no significant changes were found in terms of body weight and urinalysis in any group. In the hematological and blood chemical examination, the changes were observed in only 250 mg/kg bw/day group. Platelet, fibrinogen and APTT were increased in both sexes, and PT was increased in only males. There was increased total cholesterol and total protein in both sexes, and increased phospholipid in females.

A decrease in Cl was noted in 250 mg/kg bw/day females. The absolute and relative weights of the liver were increased at 60 and 250 mg/kg bw/day in both sexes. Histopathological examination revealed centrilobular hypertrophy of hepatocytes in both sexes given 60 mg/kg bw/day and 250 mg/kg bw/day and hypertrophy of follicular cells in the thyroid in both sexes given 250 mg/kg bw/day and in males given 60 mg/kg bw/day. After the 14-day recovery period, histopathological changes and an increase in organ weight of the liver and thyroid were recovered, however increased platelet and serum total cholesterol remained. Based on the hypertrophy in the liver and thyroid and increased liver weight in both sexes at 60 mg/kg bw/day, the NOAEL of 2,6-di-*tert*-butyl-4-ethylphenol was concluded to be 15 mg/kg bw/day in rats.

In a bacterial mutation study using *Salmonella typhimurium* TA98, TA100, TA1535 and TA1537, and *Escherichia coli* WP2 *uvrA* [OECD TG 471], 2,6-di-*tert*-butyl-4-ethylphenol was negative with or without metabolic activation. In an *in vitro* chromosome aberration test using CHL/IU cells [OECD TG 473], 2,6-di-*tert*-butyl-4-ethylphenol was positive with metabolic activation. Based on these results, 2,6-di-*tert*-butyl-4-ethylphenol is considered to be genotoxic *in vitro*.

Agreed Hazard Conclusions

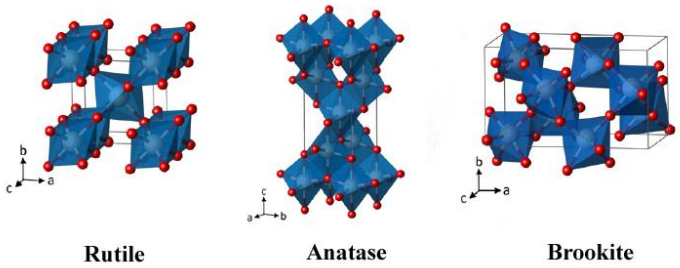
This chemical possesses properties indicating a hazard for human health endpoints (repeated dose toxicity and chromosomal aberrations *in vitro*) targeted in this assessment.

Available Exposure

Production and/or import volume of trialkyl (or alkenyl, C = 1 - 4) phenol, including 2,6-di-*tert*-butyl-4-ethylphenol, was reported to be 1,000 – 10,000 tonnes/year in the fiscal year 2007 in Japan (sponsor country). Specific Production and/or import volume of 2,6-di-*tert*-butyl-4-ethylphenol in the sponsor country is not available. Production and/or import volume of 2,6-di-*tert*-butyl-4-ethylphenol in the United States was 500,000 – 1,000,000 pounds (227 - 454 tonnes) according to 2006 Inventory Updated Reporting. Production volume in the world is not available.

2,6-Di-*tert*-butyl-4-ethylphenol is used as an antioxidant in the sponsor country. In 2006 Inventory Updated Reporting in the United States, it was reported that 2,6-di-*tert*-butyl-4-ethylphenol is used in rubber and plastic products.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	13463-67-7
Chemical Name	Titanium dioxide
Structural Formula	 Rutile Anatase Brookite

SUMMARY CONCLUSIONS OF THE SIAR

This report does not cover the nanoparticle form of titanium dioxide. The particle size of titanium dioxide assessed in this report is >100 nm.

Physical and Chemical Properties

Titanium dioxide exists in three different crystallographic structures: rutile, anatase and brookite. Common crystalline forms are anatase and rutile or a mixture of both forms. The crystal form is specified below if the information is available. Anatase forms brown tetragonal crystals, brookite forms white orthorhombic crystals, and rutile forms white tetragonal crystals. They have unit-cell parameters with *a*=b=4.5937 Å and *c*=2.9581 Å (rutile); *a*=*b*=3.7842 Å and *c*=9.5146 Å (anatase); *a*=9.16 Å, *b*=5.43 Å and *c*=513 Å (brookite). The melting points of titanium dioxide are 1560 °C (anatase) and 1,843 °C (rutile) and the boiling point is 2,500-3,000 °C. It has a density of 4.23 g/cm^3 (rutile), 3.90 g/cm^3 (anatase) and 4.13 g/cm^3 (brookite). Titanium dioxide is insoluble in water, hydrochloric acid, dilute sulphuric acid, nitric acid, and alcohol. It is soluble in hot concentrated sulphuric acid and hydrogen fluoride. Oxidation-reduction potential (E^o) is -0.502 V at 25 °C and 1 atm. Vapour pressure and partition coefficient are not applicable to metal-containing inorganic oxide substances. This inorganic substance does not contain relevant functional groups for which an assessment of the dissociation behaviour would be applicable.

Human Health

Toxicokinetics, Metabolism and Distribution

In an oral toxicokinetic study, the absorption, excretion and distribution of titanium dioxide in male and female rats were observed after exposure to diet containing platelet forms of thick and thin rutile and amorphous forms of rutile and anatase. The four forms of titanium dioxide were given orally at dose levels of 0 or 200 mg/kg (nominal, equivalent to approximately 30 mg/kg bw). These diets were administered to groups of three animals per sex per time-point for seven consecutive days and then were replaced by control diet for three days. After being fed with the treated diet, groups of animals were sacrificed at 1, 24, and 72 hours to analyze the titanium content in liver, kidneys, muscle, whole-blood, urine and feces. Feces was the main excretion route and the fecal excretion rate in all treated groups was similar. The mean total amounts of titanium in feces excreted in 72 hours after withdrawal from the treated diet ranged from 1.1-2.2 mg for male rats and from 1.1-1.3 mg for female rats. Urinary excretion and whole blood concentrations of titanium were below the limit of quantification (LOQ) and concentrations of titanium in liver, kidneys and muscle could not be detected for all tested groups. Based on the result from the urinary levels, this study was unable to detect differences in absorption among the four forms of titanium dioxide tested.

In an inhalation toxicokinetic study, male rats were exposed to anatase or rutile titanium dioxide aerosol for

7 hours. For anatase and rutile, the aerosol concentrations were 16.5±1.7 and 19.3±3.1 mg/m^3, and the Mass Median Aerodynamic Diameters (MMAD) were 1.0 and 0.83 µm, respectively. At days 1, 8, 27, and 132 after 7-hour exposure, 8-10 animals/group were analyzed to determine the retained amount of titanium dioxide in the lung. The initial deposition was estimated to be 136±14 µg anatase/lung and 151±30 µg rutile/lung at day 0 after exposure and 23±11 µg anatase/lung and 23±9 µg rutile/lung at day 132 post exposure. The retained amounts of anatase and rutile in the lung at days 1, 8, 27, and 132 were similar, and their clearance half-lives were 51 and 53 days, respectively. Statistically significant differences were not observed between anatase and rutile groups (p<0.05). In the lung lavage test, 6 males/group received by intratracheal instillation 0 (saline), 0.5 or 5.0 mg/rat anatase or rutile and 5 males received 1 mg/rat of PbO as a positive control. Twelve lung lavages/lung were performed on excised lungs 24 hours after dosing. There were no significant differences in cell counts or differentiation between the anatase and rutile groups. At 5.0 mg/rat, the polymorphonuclear leukocytes and peroxidase positive alveolar macrophages were increased in the lavages. The positive control showed higher values for almost all parameters measured.

Acute Toxicity

The acute oral LD_{50} value was greater than 5,000 mg/kg bw for male/female mice [OECD TG 420]. The results showed significant increase of titanium dioxide in the spleen and brain. Also, neuron vacuoles in the hippocampus and hydropic degeneration and spotty necrosis in liver cells were observed. In another study, the acute oral LD_{50} value was greater than 5,000 mg/kg bw for female rats [OECD TG 425, EPA OPPTS 870.1100]. No mortality and body weight changes were observed, and no gross lesions were present in all the animals at necropsy. But 1 rat dosed at 1,750 mg/kg bw and 3 rats dosed at 5,000 mg/kg bw temporarily exhibited grey coloured feces. In a limit test [OECD TG 401, EU Method B.1], the acute oral LD_{50} was greater than 2,000 mg/kg bw in both sexes of rats.

The acute inhalation LC_{50} values in male rats exposed to titanium dioxide powders were greater than 3.43 mg/L (particle size <3.5 µm was 56%, MMAD 3.2 µm) and greater than 5.09 mg/L(particle size <3.5 µm was 20%, MMAD 7.0 µm), respectively [OECD TG 403]. No mortality, body weight changes and clinical signs were observed. Gross pathology revealed mottled lungs in 2/5 males and 3/5 females exposed to titanium dioxide (particle size <3.5 µm was 56%), as well as pale lungs in 3/8 males and 1/5 females exposed to titanium dioxide (particle size <3.5 µm was 20%).

No acute dermal studies were available.

Irritation and Sensitization

Titanium dioxide was not skin irritating. No clinical signs of toxicity were observed in a skin irritation assay performed in 3 male rabbits [OECD TG 404]. Draize scores for erythema and edema were both "0". No dermal irritation in any of the rabbits was observed during the study. In another skin irritation assay performed in 3 rabbits/sex [equivalent to OECD TG 404], slight erythema occurred in 2/6 animals at 1 hour, 3/6 animals at 24 hours and 1/6 animals both at 48 and 72 hours. In addition, mild erythema occurred in 1/6 animals at 1 hour. No edema was observed. Titanium dioxide was considered to be a non-irritant in this study.

Acute eye irritation/corrosion test was performed according to OECD TG 405. Conjunctival redness (score of 1 or 2) observed at the 1- and 24-hour examinations. The treated eyes of three rabbits were normal by 24 or 48 hours after instillation of the test substance. Based on these results, titanium dioxide was not irritating to the eye of rabbits. In two other eye irritation studies performed under OECD TG 405, the results also showed that the test substance was not irritating to the eye of rabbits.

A Buehler test was performed with titanium dioxide using guinea pigs in accordance with OECD TG 406. Sensitization reactions were not observed in any of 20 animals treated with titanium dioxide for both 24 and 48 hours after the challenge application. No clinical signs of toxicity were observed. In a local lymph node assay [equivalent to OECD TG 429], titanium dioxide was applied to the ear of 5 female mice/group at concentrations of 0, 5, 25, 50 or 100% for three consecutive days. Stimulation indexes (SIs) of less than 3.0 were observed at all test concentrations. No clinical signs of toxicity were observed. Based on these results, titanium dioxide is not considered to be a dermal sensitizer.

In a non standard respiratory sensitization study, pregnant female mice received 50 µg/mouse intranasally of

titanium dioxide on day 14 of gestation and non-pregnant females received the same dose (9 mice in each group). On day 4 after birth, newborns from normal control females intraperitoneally received 0.1 mL of 50 µg/mL ovalbumin (OVA) with alum. On days 12 to 14 of life, these neonates were challenged three times with 3% OVA aerosol. Pregnant mice were shown to have a more significant level of respiratory sensitization than non-pregnant mice after titanium dioxide exposure. Neonates of mothers exposed to titanium dioxide showed increased allergic susceptibility. Offspring of mothers exposed to titanium dioxide showed increased airway hyperresponsiveness (AHR) and allergic inflammation (AI) with increased allergic susceptibility. Therefore, titanium dioxide may have the potential to be a respiratory sensitizer in mice.

Repeated Dose Toxicity

Repeated dose oral toxicity of titanium dioxide has been investigated in two studies. In a study following OECD TG 407, the test substance was administered via gavage to 5 rats/sex/dose at 0 (vehicle control, 1% methyl cellulose solution), 250, 500 or 1,000 mg/kg bw/day for 28 days. Additional recovery groups of 5 animals/sex were included in the control and high dose groups and observed for 14 days after treatment. No deaths were observed in either sex. Treatment related effects observed (compound-colored feces, effects on a few functional performance tests, some hematological and clinical chemistry parameters, liver and thymus weight changes) were not considered to be toxicologically significant. Therefore, the NOAEL was considered to be 1,000 mg/kg bw/day.

In another study conducted according to OECD TG 407, titanium dioxide was administered via gavage to 5 male rats/dose at 0 or 24,000 mg/kg bw/day for 28 days. No substance related effects were observed and the NOAEL was considered to be 24,000 mg/kg bw/day.

No dermal repeated dose toxicity studies are available.

In a repeated dose inhalation toxicity study, titanium dioxide (rutile) was administered via inhalation (whole body) to 80 rats/sex/concentration at 0, 10, 50 or 250 mg/m^3/day for 6 hours/day, 5 days/week for up to 2 years. Titanium dioxide particles showed a spherical configuration and a 1.5-1.7 µm MMAD. Approximately 84% of the dust particles were of respirable size (<13 µm MMAD). Exposure to titanium dioxide resulted in no excess mortality in any exposed group. Treatment related effects were observed as follows: increased haematocrit and haemoglobin in the 250 mg/m^3 treatment group, increased leukocyte and neutrophil count in all treatment groups, decreased lymphocyte count in all treatment groups, increased bilirubin content in females at 50 and 250 mg/m^3 treatment groups, decreased calcium concentrations in all treatment groups, increased lung and thymus weights in the 50 and 250 mg/m^3 treatment groups, increased incidences of pneumonia, tracheitis and rhinitis with squamous metaplasia of the anterior nasal cavity in all treatment groups. Based on the findings at 10 mg/m^3 (tracheitis, rhinitis with squamous metaplasia of the anterior nasal cavity, alveolar cell hyperplasia and broncho/bronchiolar pneumonia), the LOAEC for repeated dose inhalation toxicity was considered to be 10 mg/m^3.

In another repeated dose inhalation toxicity study (whole body), 65 female rats were exposed to 0, 10, 50 or 250 mg/m^3 of titanium dioxide (rutile) for 6 hours/day, 5 days/week for 13 weeks with recovery groups held for an additional 4, 13, 26 or 52 weeks post-exposure (MMAD: 1.44 µm, Geometric SD (GSD): 1.71, respirable fraction was not available). No deaths occurred during the exposure period. Lung and lung-associated lymph node burdens of titanium dioxide increased in a concentration-dependent manner. Pulmonary overload was achieved in rats at 50 and 250 mg/m^3. Inflammation was seen at 50 and 250 mg/m^3 by the evidence of increased numbers of macrophages and neutrophiles and incidences of soluble inflammation markers. Inflammatory responses remained elevated throughout the entire post-exposure recovery period at 250 mg/m^3. Pulmonary lesions with progressive epithelial and fibroproliferative changes were observed at 250 mg/m^3. These epithelial changes were also manifested in rats as evidenced by an increase in alveolar cell labeling at 250 mg/m^3 in cell proliferation studies. Based on these results, 10 mg/m^3 is considered as the NOAEC in this study.

In another inhalation study, male rats were exposed to aerosols of titanium dioxide (rutile) at concentrations of 0, 25 or 50 mg/m^3. Rats were exposed by whole-body inhalation 7 hours/day, 5 days/week (25 mg/m^3 exposure for 209 days, and 50 mg/m^3 for 118 days). The MMAD (GSD) for titanium dioxide was 2.1 µm (2.2). There were 6 time points and generally 12 animals/concentration were used. The lung burdens at the final exposure points were 24 and 17 mg/g for the high and low-dose groups, respectively. The mean lymph node burdens and number of polymorphonuclear cells (PMN) were raised with increasing exposure. The

higher levels of inflammation occurred concurrently with the higher lymph node burdens, after 69 and 139 days in the 50 and 25 mg/m^3 group. The predicted averages for percent PMN were, for the high and low-dose groups, respectively, 28% and 16%. The mean numbers of alveolar macrophages obtained did not change significantly compared to control animals. Titanium dioxide showed no significant fibrogenic activity. Therefore, the LOAEC for titanium dioxide was considered to be 25 mg/m³ based on the increased mean number of neutrophils with exposure-related lymph-node burdens.

In another study, female rats were exposed for 6 hours/day, 5 days/week for 4 weeks by nose-only inhalation to 0, 0.1, 1.0, or 10 mg/m^3 of titanium dioxide (MMAD: 1.3 µm , GSD: 2.6, respirable fraction was not available) and the lung burdens were determined at 1 week after the end of the exposure. The lungs were evaluated by analysis of bronchoalveolar lavage fluid (BALF) at 1, 8, and 24 weeks after the end of the exposure and by histopathology at 24 weeks. With lung burdens up to 420 µg/g lung, titanium dioxide elicited no changes in BALF parameters at any time after exposure, nor were any histopahological findings observed. Therefore, the NOAEC was considered to be 10 mg/m^3.

In another inhalation study following OECD TG 453, the test substance (rutile) was administered via inhalation (dry aerosol, whole body) to 50 rats/sex/concentration at 0 or 5 mg/m^3 for 6 hours/day, 5 days/week for 24 months. The MMAD (GSD) was 1.1 µm (1.6) and the respirable fraction was 78%, equivalent to 3.87±0.28 mg/m^3. A 5% incidence of lung fibrosis was seen in the titanium dioxide-exposed groups. After exposure, minor changes were observed in the cytologic pattern of the BALF. A lymphoid hyperplasia of the lung-associated lymph nodes was observed in the titanium dioxide-exposed group. Thus, the LOAEC was considered to be 5 mg/m^3 in rats.

A repeated dose inhalation study was conducted to examine burdens of titanium dioxide (rutile) in the lung and lung associated lymph nodes and selected lung responses in mice and hamster (73 females/concentration). Animals were exposed to 0, 10, 50 or 250 mg/m^3 pigmentary titanium dioxide for 6 hours/day, 5 days/week for 13 weeks with recovery groups held for an additional 4, 13, 26 or 52 weeks (46 weeks for hamster) post-exposure (MMAD: 1.39 µm in mice, 1.36 µm in hamster). Pulmonary parameters including inflammation, cytotoxicity, lung cell proliferation, and histopathologic alterations were assessed. Pigmentary titanium dioxide burdens in the lung and lymph nodes increased in a concentration-dependent manner. Inflammation was noted at 50 and 250 mg/m^3, as evidenced by increase in macrophage and neutrophil numbers and in soluble indices of inflammation in BALF. Based on the results, the NOAEC for mice and hamsters was 10 mg/m^3.

Mutagenicity

In an Ames test [OECD TG 471] with multiple strains of *Salmonella typhimurium*, and one strain of *Escherichia coli*, titanium dioxide did not induce gene mutations *in vitro* with and without metabolic activation. In a mammalian cell gene mutation assay [OECD TG 476] with mouse lymphoma L5178Y TK +/- cells, titanium dioxide was not mutagenic both with and without metabolic activation. Titanium dioxide did not induce chromosomal aberrations [OECD TG 473] in *in vitro* Chinese Hamster Ovary (CHO) cells and human lymphocytes with and without metabolic activation. In *in vitro* sister chromatid exchange (SCE) assays, titanium dioxide induced increasing SCE frequencies in CHO-K1 cells and human lymphocytes but did not induce any effects of SCE in CHO cells. In CHO-K5 cells, titanium dioxide did not induce micronucluses but induced it in CHO-K1 cells and human lymphocytes. In a recombination assay with *Bacillus subtilis* H17 (rec+) and M45 (rec-), titanium dioxide showed a negative result.

In an *in vivo* study [no guideline followed], titanium dioxide did not induce chromosome aberrations in mouse bone marrow cells and did not significantly elevate levels of micronuclei in the bone marrow cells of mice. However, it is not clear whether there was any exposure of the target tissues. In an *in vivo* sex-linked recessive lethal (SLRL) test with *Drosophila melanogaster*, it was suggested that titanium dioxide showed a negative result. In a non-standard *hprt* gene mutation assay, the *hprt* mutation frequency was significantly increased in alveolar type II cells of rats after *in vivo* exposure to titanium dioxide.

Based on the results from mutagenicity studies *in vitro*, the majority of the studies were negative (Ames, chromosome aberration and mammalian cell gene mutation tests). Positive results were observed in two micronucleus studies and two Sister Chromatid Exchange assays *in vitro* and were thought to be a consequence of oxidative stress mediated DNA damage. *In vivo* the results of somatic cell studies were negative, however it is not possible to conclude on the *in vivo* genotoxic potential of titanium dioxide due to

a positive result observed in a non-standard *in vivo* site of contact study in alveolar cells.

Table 1. Summary of genotoxicity results

Type of genotoxicity	**Type of study**	**Concentration range**	**Result**
In vitro			
Gene mutation assay	mouse lymphoma L5178Y TK +/- cells	31-500 µg/mL (±S9)	negative
	mouse lymphoma L5178Y cells, clone 3.7.2C	1.56-50 µg/mL (±S9)	negative
Bacterial reverse mutation assay (Ames test)	*Salmonella typhimurium* TA1535, TA1537, TA98 and TA100 and *Escherichia coli* WP2*uvr*A	100-5,000 µg/plate (±S9)	negative
	S. typhimurium strains TA1535, TA1537, TA98 and TA100 and *E. coli* strains WP2 and WP2*uvr*A	100-5,000 µg/plate (±S9)	negative
	Salmonella typhimurium TA1535, TA97, TA98 and TA100 and *Escherichia coli* WP2*uvr*A	100-10,000 µg/plate (±S9)	negative
Chromosomal aberration test	CHO cells	125-2,500 µg/mL (±S9)	negative
	CHO cells	1st trial: 68.72-800 µg/mL (-S9) and 167.8-800 µg/mL (+S9), 2nd trial: 167.8-800 µg/mL (+S9)	negative
	human lymphocytes	10-100 µg/mL (±S9)	negative
	CHO cells	15-25 µg/mL (±S9)	negative
Micronucleus test	human peripheral blood lymphocytes	1-10 µM	enhance oxidative stress-mediated DNA damage *in vitro*
	CHO-K1 cells	1-20 µM	positive
	CHO-K5 cells	0.025-10.0 µg/mL (-S9), 0.25-10.0 µg/mL (+S9)	negative
Sister chromatid exchange assay	CHO-K1 cells	1-5 µM	positive (1.59-fold to that of the control)
	CHO cells	2.5-25 µg/mL (±S9)	negative
	human peripheral blood lymphocytes	1-10 µM	enhance oxidative stress-mediated DNA damage *in vitro* (2-fold increase at 10 µM)
Bacillus subtilis recombination assay	*Bacillus subtilis* H17 (rec+), M45 (rec-)	0.005-0.5M	negative
In vivo			

Chromosomal aberration test	mouse bone marrow cells	625- 2,500 mg/kg	negative
Micronucleus test	mouse bone marrow cells	1st trial: 0-1,000 mg/kg bw 2nd trial: 0-1,500 mg/kg bw	negative
Sex-linked recessive lethal (SLRL) test	*Drosophila melanogaster*	Feeding: 1,500 ppm Injection: 5,680 ppm	negative
hprt *gene mutation assay*	alveolar type II cells in rats	10 and 100 mg/kg bw	positive

Carcinogenicity

In an oral carcinogenicity study, titanium dioxide was administered via the diet to 50 mice and 50 rats (per sex and per dose) at 0, 25,000 or 50,000 ppm (equivalent to 0, 3,250 and 6,500 mg/kg bw/day in the mice and 0, 1,250 and 2,500 mg/kg bw/day in rats) for 7 days/103 weeks. In mice, mortality results in female showed a significantly (p=0.001) positive dose-related trend. There was no effect on the mean body weight. No tumors occurred in dosed groups at incidences that were significantly higher than those for control groups. In rats, there was no excess mortality in any dosed groups and no effect on the mean body weight. Observed histopathological findings were not considered to be related to administration of titanium dioxide. Therefore, there was no evidence of carcinogenicity at any dose level in the oral studies.

There are three inhalation carcinogenicity studies of titanium dioxide in rats. In one study, the test substance was administered via inhalation (whole body) to 80 rats/sex/concentration at 0, 10, 50 or 250 mg/m^3/day for 6 hours/day for 5 days/week for up to 2 years. Titanium dioxide particle (rutile) was a spherical configuration and a 1.5-1.7 µm MMAD. Approximately 84% of the dust particles were of respirable size (<13 µm MMAD). No excess death was observed in either sex. Bronchioloalveolar adenomas, squamous metaplasias, pulmonary keratin cysts and squamous cell carcinomas were observed in the 250 mg/m^3 treatment group, while no compound-related lung tumors were found in rats exposed either to 10 or 50 mg/m^3. At 250 mg/m^3/day, the tumor findings are considered to be the result of prolonged inflammation and fibrogenesis as a result of particle overload of the clearance mechanism of the lung.

In another study following OECD TG 453, the test substance (99.5% rutile, MMAD: 1.1 µm, GSD: 1.6, respirable fraction was 78% which equivalent to 3.87±0.28 mg/m^3) was administered via inhalation (dry aerosol, whole body) to 50 rats/sex/concentration at 0 or 5 mg/m^3/day (limit test), for 6 hours/day and 5 days/week for up to 2 years. The incidence of primary lung tumors among the titanium dioxide-exposed rats (2/100; one adenoma and one adenocarcinoma) was comparable to the air-only controls (3/100; two adenoma and one adenocarcinoma).

In another study, groups of 50 male and 50 female rats were exposed by inhalation to 0 or 15.95 mg/m^3 titanium dioxide (99.9%, <0.5 µm) for 6 hour/day, 5 days/week for 12 weeks. At the end of the study, 78% of control and 88% of treated males and 90% of control and treated females survived. No significant differences in body weights or incidence of tumors were observed between control and treatment groups (lung and other respiratory tract tumors were benign; other neoplasms seen in the lung were metastases from tumors of other sites).

Based on the results from inhalation studies, the tumors observed in rats (such as bronchioloalveolar adenomas, squamous metaplasias, pulmonary keratin cysts and squamous cell carcinoma were observed in 250 mg/m^3), are thought to be secondary to particle overload. Therefore, titanium dioxide treated via inhalation was considered to have carcinogenic potential.

Titanium dioxide is classified by IARC (2010)as group 2B (Possibly carcinogenic to humans).

Reproductive and Developmental Toxicity

Titanium dioxide has been investigated in a reproductive and developmental toxicity screening test in rats [OECD TG 421]. Titanium dioxide was administered by oral gavage to 10 animals/sex at 0 or 1,000 mg/kg bw/day (limit test), to male rats from two weeks prior to mating, during the mating period and,

approximately, two weeks post mating, and to female rats from two weeks prior to mating, during the mating period, gestation period and 3 days after lactation. During the observation period, there were no dose related effects on clinical signs, body weights, food consumption, mating, gestation, delivery, organ weights, necropsy and histopathology in parents. No dose-related changes in clinical signs, body weights, viability index, external malformations and sex ratios were noted in pups. This study found no indication of any reproductive toxicity in parent animals or developmental toxicity in pups. Therefore, the NOAEL for reproductive and developmental toxicity was 1,000 mg/kg bw/day.

Titanium dioxide possesses properties indicating a hazard for human health (potential genotoxicity, repeated dose toxicity and carcinogenicity via inhalation). Adequate screening-level data are available to characterize the human health hazard for the purposes of the Cooperative Chemicals Assessment Programme.

Environment

Photodegradation is not applicable to metal-containing inorganic oxide substances that possess negligible vapour pressure such as titanium dioxide. Titanium dioxide is expected to be stable in water due to the absence of water-reactive functional groups, and due to its insolubility in water. Biodegradation, and environmental fate analysis based on log K_{ow} and log K_{oc}, are not applicable for inorganic substances such as titanium dioxide.

For the aquatic toxicity test, a water-accommodated fraction (WAF) was prepared with bulk titanium dioxide under OECD Series on Testing and Assessment Number 23. Test concentrations were expressed as a loading rate. The analysis results of the test substance in the test solution showed that the concentration was <LOQ of 0.1 mg/L for algae and <LOQ of 0.02 mg/L for fish and invertebrate.

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

Fish [*Oryzias latipes*, OECD TG 203]	96 h LL_{50}>100 mg/L (nominal; static)
Invertebrate [*Daphnia magna*, OECD TG 202]	48 h EL_{50}>100 mg/L (nominal; static)
	48 h EC_{50}>100, 48 h EC_{10}=91.2 mg/L (nominal; dispersion; static)
Algae [*Pseudokirchneriella subcapitata*, OECD TG 201]	
	72 h E_rL_{50} >100 mg/L (growth rate, nominal; static)
	72 h E_yL_{50} >100 mg/L (yield, nominal; static)

Titanium dioxide has a low hazard for the environment (acute aquatic toxicity > 100 mg/L). Adequate screening-level data are available to characterize the environmental hazard for the purposes of the Cooperative Chemicals Assessment Programme.

Exposure

In the Republic of Korea (sponsor country), the production, use and import volumes of titanium dioxide were 63,239, 227,446 and 126,748 tonnes in 2010, respectively. In Sweden, Denmark, Norway and Finland estimated use volumes of titanium dioxide were approx. 73,085, 148,816, 54,968, 49,855 and 75,988 tonnes in 2006, 2007, 2008, 2009 and 2010, respectively.

In the sponsor country, titanium dioxide is mainly used as a pigment in paints and paint additives. Titanium dioxide is used as a white pigment, opacifying agent in coatings, inks, adhesives, synthetic resins, plastic, rubber products and paper products. It is also used as a white colorant in foods, cosmetics and drugs, sunscreen, textiles and toothpaste.

For consumer exposure, the use of titanium dioxide is limited to a coloring agent in food and pharmaceuticals in the sponsor country. The general public may be exposed to small quantities of titanium dioxide by the

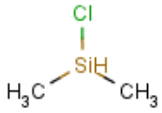
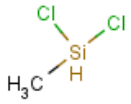
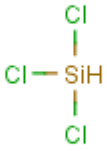
consumption of some food/foodstuff additives and intended use of products such as toothpastes (especially by children) and others. Titanium dioxide is acceptable for general food use with no established ADI. However, the US FDA suggests the quantity of titanium dioxide should not exceed 1 percent by weight of the food.

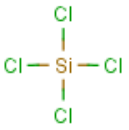
The most common industrial manufacturing process is as follows: ilmenite is treated using sulfuric acid and the titanium sulfate is further processed to titanium dioxide. The product is primarily the anatase form. Rutile is chlorinated and the titanium tetrachloride converted to the rutile form of titanium dioxide by vapour-phase oxidation.

In use facilities of the sponsor country, titanium dioxide is handled in closed systems and is used commercially as a powder. According to monitoring data, titanium dioxide was not detected in the workplace from 2009 to 2011. Occupational exposure is managed with personal protective equipment such as a gas mask with dustproof filter in the workplace.

Titanium dioxide may be released into water, the atmosphere and soil from the use and disposal of titanium dioxide containing products.

SIDS INITIAL ASSESSMENT PROFILE

Category Name	Monomeric Chlorosilanes
CAS No(s).	1066-35-9 75-54-7 10025-78-2 10026-04-7
Chemical Name(s)	Chlorodimethylsilane (**$ClMe_2SiH$**) Dichloromethylsilane (**Cl_2MeSiH**) Trichlorosilane (**Cl_3SiH**) Tetrachlorosilane (**Cl_4Si**)
Structural Formula(s)	 **$ClMe_2SiH$**  **Cl_2MeSiH**  **Cl_3SiH**



Cl_4Si

SUMMARY CONCLUSIONS OF THE SIAR

Analogue/Category Rationale

These chemicals can be represented by a similar general molecular formula:

$(Cl)_xSi(H)_y(Me)_z$

Where Cl = chlorine, x = 1, 2, 3, or 4;

Si = silicon [=1];

H = hydrogen, y = 0 or 1; if y = 0, then x = 4

Me = CH_3, z = 0, 1, or 2

Chlorosilanes react rapidly when exposed to moisture or polar reagents (those that contain a dissociable H^+), producing hydrogen chloride (HCl; CAS No. 7647-01-0) and the corresponding silanols (in general, siloxane oligomers and polymers). The half lives of the monomeric chlorosilanes are expected to be < 1 minute based on data from the structurally similar chlorosilanes dichloro(dimethyl)silane (Cl_2DMS) and trichloro(methyl)silane (Cl_3MS).

Data are not available on the hydrolysis of these compounds. However, the following is expected:

- **$ClMe_2SiH$** is expected to hydrolyze to form one mole each of HCl and dimethylsilanol (note that dimethylsilanol can hydrolyze to form dimethylsilanediol (DMSD) ultimately through hydrolysis of the SiH bond, which is pH dependent and occurs most rapidly under alkaline conditions).
- **Cl_2MeSiH** is expected to hydrolyze to form two moles of HCl and one mole of methylsilanediol (note that methylsilanediol can hydrolyze to form methylsilanetriol (MST) ultimately through hydrolysis of the SiH bond).
- **Cl_3SiH** is expected to hydrolyze to form three moles of HCl and one mole of silanetriol (note that silanetriol can hydrolyze to form silanetetrol ultimately through hydrolysis of the SiH bond).
- **Cl_4Si** is expected to hydrolyze to four moles of HCl and one mole of silanetetrol, which rapidly precipitates to insoluble silica (SiO_2) when the concentration is sufficiently high.

As noted, the silanols resulting from initial hydrolysis can condense spontaneously to form highly cross-linked polymeric gels in uncontrolled environments at concentrations greater than 500 mg/L. Because of these properties, they cannot be readily isolated without spontaneously forming highly cross-linked polymeric gels in uncontrolled environments and as such cannot be tested.

Hydrolysis Analogues. It is appropriate to use other chlorosilane data to estimate hydrolysis of the sponsored substances. Structurally similar chlorosilanes used for hydrolysis are dichloro(dimethyl)silane (Cl_2DMS) and trichloro(methyl)silane (Cl_3MS). These two analogous chlorosilanes were selected based on a hydrolysis study of

six chlorosilanes with varying substitutions. Despite the differences in substitution of these chlorosilanes, all the half-lives were < 17 seconds.

Human Health and Aquatic Toxicity Analogues. (1) All category members are expected to hydrolyze rapidly to form hydrogen chloride (HCl) as one of the products. Therefore, data for HCl can be used to represent the toxicity of the monomeric chlorosilanes.

(2) Trimethoxysilane rapidly hydrolyzes at pH 7 with $t_{1/2}$ <0.3 minutes at 2 ^{o}C to silanetriol as well as methanol. In aqueous environments, exposures to trimethoxysilane are likely to be transient and observed toxicity is likely due primarily to the hydrolysis products methanol, silanetriol, and condensed silanetriol materials. **Cl_3SiH** is expected to form the same silanol (silanetriol) upon hydrolysis. Therefore trimethoxysilane is used as a supporting substance, along with HCl. Reproductive toxicity data are not available for trimethoxysilane.

(3) Another previously assessed alkoxysilane, tetraethylorthosilicate (TEOS), rapidly hydrolyzes to ethanol and silanetetrol at pH 4, 7 and 9 with $t_{1/2}$ = 0.1, 4.4 and 0.2 hrs, respectively. In aqueous environments, exposures to TEOS are likely to be transient and observed toxicity is likely due primarily to the hydrolysis products ethanol, silanetetrol, and condensed silanol materials. Since TEOS hydrolyzes to the same silanol, it can be used as a supporting substance for **Cl_4Si**, along with HCl.

(4) A previously assessed alkylsilane, methyltrimethoxysilane (MTMS), rapidly hydrolyzes to methanol and methylsilanetriol at pH 4, 7 and 9 with $t_{1/2}$ = 0, 2.2 and 0.1 hrs, respectively. In aqueous environments, exposures to MTMS are likely to be transient and observed toxicity is likely due primarily to the hydrolysis products methanol, methylsilanetriol, and condensed silanetriol materials (high molecular weight polymers). Given the structural similarity between silanetriol and the supporting substance hydrolysis product methylsilanetriol, MTMS can be used as a supporting substance for **Cl_2MeSiH** and **Cl_3SiH**, along with HCl.

(5) For the supporting substances trimethoxysilane, TEOS, and MTMS, toxicity due to hydrolysis to methanol or ethanol is expected to be negligible.

(6) For the chromosome aberrations endpoint, data for supporting chlorosilane substance dichlorodimethylsilane (Cl_2DMS) are provided because this supporting substance hydrolyzes to the same silanol (and HCl) as sponsored substance, **Cl_2MeSiH**.

(7) A structurally similar silanol, dimethylsilanediol (DMSD) is stable, isolatable and as such has been tested in mammalian and aquatic systems. DMSD is closely related structurally to methylsilanediol (replacement of -H with -CH_3) and both substances have expected similar physicochemical properties, therefore the toxicological properties are expected to be similar and DMSD can be used as a supporting substance for **Cl_2MeSiH,** along with HCl.

(8) A structurally similar silanol, trimethylsilanol (TMS) is stable, isolatable and as such has been tested in mammalian and aquatic systems. TMS is closely related structurally to dimethylsilanol (replacement of -H with -CH_3) and both substances have similar physicochemical properties, therefore the toxicological properties are expected to be similar. This structural similarity suggests TMS can be used as a supporting substance for **$ClMe_2SiH$**, along with HCl.

HCl, trimethoxysilane, MTMS, TEOS, Cl_2DMS, and Cl_3MS were all presented and agreed under the OECD HPV Chemicals Programme (http://www.oecd.org/env/hazard/data). TMS and DMSD have both been used as analogues in the OECD HPV Chemicals Programme, most recently for chloroalkylchlorosilanes at CoCAM 3. Data for all can be found at http://www.oecd.org/ env/hazard/data.

The read-across strategy follows:

	Environmental fate	**Mammalian toxicity**			**Environmental effects**
Substance	**Hydrolysis**	**Eye irritation**	**Mutagenicity**	**Repeated dose toxicity, Reproductive toxicity**	**Acute aquatic toxicity**

$ClMe_2SiH$	Cl_2DMS	HCl	Cl_2DMS, **Cl_4Si,** HCl	TMS, HCl	TMS, DMSD, HCl
Cl_2MeSiH	Cl_2DMS	HCl	Cl_2DMS, **Cl_4Si,** HCl	DMSD, MTMS, HCl	DMSD, HCl
Cl_3SiH	Cl_3MS	HCl	**Cl_4Si,** HCl	Trimethoxysilane (1), MTMS, HCl	Trimethoxysilane, HCl
Cl_4Si	Cl_3MS	HCl	**Cl_4Si,** HCl	TEOS, HCl	TEOS, HCl

(1) Read across for repeated dose (inhalation) endpoint only

The toxicity of the category will be described by the most toxic category member or supporting chemical.

TMS and DMSD are not reactive like other supporting substances or HCl. Therefore, the data from TMS and DMSD should be evaluated along with data on HCl or other structurally similar/reactive compounds for a more complete understanding of the toxicity of the sponsored monomeric chlorosilanes.

Physical-chemical Properties

Not all programs within EPI Suite have been validated for chemicals that contain the element Si, but recent upgrades to the Kow module, found in the current version of EPI Suite (v4.10), may improve estimates for silanes and siloxanes for this endpoint. However, there is still uncertainty associated with the calculated values and they should be used with caution whenever they are reported. Inorganic substances (**Cl_3SiH** and **Cl_4Si**) are outside the applicability domain of EPI Suite.

The sponsored substances are liquids with measured melting points of -126.5 °C (**Cl_3SiH**) to -68.9 °C (**Cl_4Si**), measured boiling points of 31.5 °C (**Cl_3SiH**) to 56.9 °C (**Cl_4Si**) at 1013 hPa and vapour pressures of 292 hPa (**Cl_4Si**) to 721.8 hPa (**Cl_3SiH**) at 20°C. The calculated octanol-water partition coefficients (log K_{ow}) range from 1.46 (**Cl_3SiH**) to 1.93 (**$ClMe_2SiH$**), and the calculated water solubilities range from 3274 mg/L (**$ClMe_2SiH$**) to 9951 mg/L (**Cl_3SiH**) at 25 °C. The calculated water solubility and log K_{ow} values may not be accurate because the substances are hydrolytically unstable.

Human Health

No data are available on the toxicokinetics, metabolism and distribution of the monomeric chlorosilanes. However, these substances rapidly hydrolyze on contact with moisture. Dimethylsilanol, but not the remaining three silanol hydrolysis products (methylsilanediol, silanetriol, silanetetrol), may be absorbed across the skin or respiratory epithelium; as the size of the silanol hydrolysis products increase, absorption by the respiratory tract decreases and retention by respiratory mucus is expected to increase. Damage to membranes caused by the corrosive nature of HCl might enhance the uptake of the sponsored substances or the silanol hydrolysis products. Hydrogen and chloride ions will enter the body's natural homeostatic processes. HCl will rapidly dissociate and its effects are thought to be a result of pH change (local deposition of H^+). The low molecular weight and water solubility of the silanols suggest elimination via the kidneys in urine.

The attached Annex provides a summary of the read across values for mammalian toxicity.

The acute inhalation toxicity of the monomeric chlorosilanes is well characterized by the effects of HCl and is expected to result from HCl exposure. The 1-hour acute inhalation LC_{50}s (OECD 403) with rats for the monomeric chlorosilanes range from 8.4 (**Cl_2MeSiH**; nominal) to 17.3 mg/L (**$ClMe_2SiH$**; nominal). The acute inhalation hazard posed by a chlorosilane, as defined by an LC_{50} value, is directly proportional to its chlorine content and subsequently to the HCl that is liberated during hydrolysis. The principal clinical signs are expected to be indicative of respiratory and ocular effects resulting from HCl exposure. The acute inhalation LC_{50} of the supporting substance trimethoxysilane was ca. 0.3 mg/L. A 6-hour inhalation LC_{50} of >42 mg/L was reported for the supporting substance MTMS. Inhalation LC_{50} values for HCl were determined to be 4.2-4.7 mg/L for 1-hour exposures to rats. Dermal toxicity data were not located for the monomeric chlorosilanes. The oral LD_{50}s for the monomeric chlorosilanes when dosed diluted in oil were 3141 mg/kg bw (**Cl_2MeSiH**), 1030 mg/kg bw (**Cl_3SiH**) and 238 mg/kg bw (**Cl_4Si**). When dosed undiluted, **Cl_2MeSiH** resulted in an LD50 of <278 mg/kg-bw. Oral LD_{50} values of HCl were determined to be 238-277 mg/kg-bw for female rats.

The monomeric chlorosilanes rapidly hydrolyze to HCl and the associated silanol. Two of the sponsored

substances have been tested (**Cl_2MeSiH** and **$ClMe_2SiH$**) and are considered corrosive to the skin. Based on findings from acute oral and inhalation studies, the sponsored substances are expected to be respiratory and GI tract irritants. Eye irritation data are not available for the sponsored substances. HCl is corrosive and highly irritating to the skin, eyes and respiratory tract with no data reported to suggest as a sensitizer. Based on HCl formation, monomeric chlorosilanes possess properties indicating possible hazards for acute inhalation toxicity, skin, eye, and respiratory tract irritation.

No data regarding sensitization are available on the monomeric chlorosilanes.

Limited repeated dose toxicity data are available for the monomeric chlorosilanes with **Cl_3SiH** as the only tested material. Groups of rats (5/sex/concentration) were exposed in a nose-only exposure system to target concentrations of ca. 0.06 and 0.18 mg/L of **Cl_3SiH** or ca. 0.016 and 0.05 mg/L of **HCl**. Rats were exposed six hours per day, five days per week, for two weeks. There were no deaths, clinical signs, effects on body or organ weights and no findings at gross necropsy. Microscopic examination of animals exposed to **Cl_3SiH** showed mineralization in the kidneys of females; no other apparent treatment-related effects were observed. Data from supporting substances, trimethoxysilane, MTMS and TEOS, supporting hydrolysis products TMS and DMSD and hydrolysis product HCl are used to fill the repeated-dose toxicity endpoint for the monomeric chlorosilanes. Systemic effects following inhalation of TMS, trimethoxysilane, or MTMS (trimethoxysilane, and MTMS exposure likely as a mixture with silanol hydrolysis products) are well characterized. In the absence of adverse effects, in an OECD 422 study the NOAEC for TMS was ca. 2.2 mg/L (the highest concentration tested) in rats exposed for at least 28 days. Repeated inhalation exposure of rats to trimethoxysilane for 28 days at ca. 0.025 or 0.050 mg/L was lethal, with death likely a consequence of respiratory tract injury. Based on the body weight, organ weight, clinical pathology, histopathologic observations, and deaths, the NOAEC from this study appeared to be ca. 0.0025 mg/L. Exposure of rats to trimethoxysilane vapor ca. 0.0001, 0.0005, or 0.0025 mg/L for 90 days, followed by a 4-week recovery period produced no exposure-related effects in the biologic parameters monitored during this study. The NOEC for trimethoxysilane in a 90-day inhalation study with rats was determined to be at least ca. 0.0025 mg/L. Based on the increased incidence of grossly observed urinary bladder calculi along with the kidney dilation at the 2.2 mg/L/day exposure level, the NOAEC for repeated inhalation exposure (OECD 413) for MTMS was 0.56 mg/L and the LOAEC was 2.2 mg/L/day. By the inhalation route, during repeated dose toxicity studies, the local effects of irritation of HCl were observed in the groups of 0.015 mg/L and above in the 90-day inhalation study. The NOAEC for systemic toxicity for HCl, excluding the local effects of irritation, has been determined to be 0.030 mg/L for rats and mice.

Based on the observation of tubular nephropathy and associated clinical chemistry changes in male rats at 50 mg/kg-bw/day, the NOAEL for repeated oral exposure (at least 4 weeks) to TEOS was 10 mg/kg-bw/day and 50 mg/kg-bw/day in male and female rats, respectively (OECD 422). The NOAEL for repeated oral exposure (28 days) to TMS was 250 mg/kg-bw/day based on clinical signs, growth retardation, and changes in the liver (bile ducts) at 750 mg/kg-bw/day (OECD 407). The NOAEL for DMSD following repeated oral exposure (at least 28 days) was 250 mg/kg-bw/day based on liver porphyria in male rats and liver vacuolation in female rats (OECD 422). Based on liver effects (females), increased prothrombin time (males) and thyroid effects (both sexes), the NOAEL for repeated oral exposure (at least four weeks in an OECD TG 422 study) to MTMS was 50 mg/kg bw/day with a LOAEL of 250 mg/kg bw/day.

The sponsored substances did not induce gene mutations in *Salmonella typhimurium* bacterial cells (TA98, TA100, TA1535 and TA1537 for **$ClMe_3SiH$**, **Cl_3SiH**, or **Cl_4Si**, and TA1538 for **Cl_3SiH** and **Cl_4Si**) *in vitro* (OECD 471). The sponsored substance **Cl_4Si** did not cause chromosomal aberrations *in vitro* (OECD 476). The hydrolysis product HCl did not induce gene mutations in bacterial cells. Positive results in the *in vitro* chromosome aberration test with HCl were considered to be the effect of low pH. In *in vitro* chromosome aberration tests using mouse lymphoma cells **Cl_2DMS** was negative. Based on the available data, the monomeric chlorosilanes are not expected to be genotoxic.

No data are available for the carcinogenicity of the monomeric chlorosilanes.

No data are available on the reproductive toxicity of the monomeric chlorosilanes; data are available for the supporting substances MTMS, TEOS, TMS, and DMSD, and the hydrolysis product HCl. In a combined repeated-dose/reproductive/developmental toxicity screening test (OECD TG 422), TMS was administered via whole body vapor inhalation to 3 groups of rats, at nominal concentrations of 0, 60, 300 or 600 ppm (ca. 0, 0.22,

1.1, and 2.2 mg/L) for 6 hours/day, 7 days/week; each group consisted of 10 males, 10 toxicity phase females and 10 reproductive phase females. The NOAEC for reproductive, systemic and neonatal toxicity of TMS was ca. 2.2 mg/L when administered via whole-body inhalation exposure to rats. In a combined repeated-dose/reproductive/developmental toxicity screening test (OECD TG 422), rats (10/sex/dose) were administered DMSD at 0 (corn oil), 50, 250 or 500 mg/kg-bwkg-bw/day via oral gavage. No test article-related effects were observed in any of the effects on fertility or developmental parameters evaluated. The NOAEL for maternal toxicity is 250 mg/kg bw; the NOAEL for effects on fertility and developmental toxicity of DMSD in rats was 500 mg/kg-bwkg-bw/day (highest dose tested). The reproductive and developmental toxicity of MTMS has been investigated in a reproductive and developmental toxicity screening test in rats [OECD TG 422]. In this study, MTMS was administered via gavage to 10 rats/sex/dose at 0 (corn oil), 50, 250, and 1000 mg/kg-bw/day, for at least 28 days (males) and up to PND 4 (females). No adverse effects on reproductive or developmental parameters were observed up to the highest dose tested. Based on no adverse effects the NOAEL for reproductive and developmental toxicity was considered to be 1000 mg/kg-bw/day. In an OECD TG 422 with TEOS, no adverse effects on reproduction or development of rats were observed up to the highest dose tested. The NOAEL for fertility/developmental toxicity for TEOS was 100 mg/kg-bw/day in rats. The NOAEL for maternal toxicity was 50 mg/kg-bw/day. No reliable studies have been reported regarding toxicity to reproduction and development in animals after oral, dermal or inhalation exposure to hydrogen chloride/hydrochloric acid. Because proton and chloride ions are the normal constituents in the body fluid of animal species, lower concentration of hydrogen chloride gas/mist or solution does not seem to cause adverse effects to animals. In fact, the cells of gastric glands secretes hydrochloric acid into the cavity of stomach and orally administered sulfuric acid, which results in pH change as well, did not cause developmental toxicity to laboratory animals. These facts indicate that hydrogen chloride/hydrochloric acid is not expected to have developmental toxicity. In addition, no effects on the gonads were observed in a 90-day inhalation repeated-dose study up to concentrations of 0.073 mg/L. Based on data for the supporting substances, structurally similar silanols and the hydrolysis product, HCl, the monomeric chlorosilanes are not expected to be reproductive or developmental toxicants.

The monomeric chlorosilanes possess properties indicating a hazard for human health (lethality from acute oral and inhalation), corrosive and highly irritating to the skin, eyes (based on HCl), GI and respiratory tracts, repeated dose 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 module, found in the current version of EPI Suite (v4.10), may improve estimates for silanes and siloxanes for this endpoint. However, there is still uncertainty associated with the calculated values and they should be used with caution whenever they are reported.

The chlorine group is the most active functional group of these molecules and determines many aspects of the behaviour of the category members. The monomeric chlorosilanes are expected to undergo rapid hydrolysis in the presence of water to form one to three moles of HCl and one mole of mono-, di- or tri- silanol, depending on the parent substance. Hydrolysis is the primary reaction in aqueous systems. Hydrolysis studies were not conducted on the monomeric chlorosilanes. The momeric chlorosilanes hydrolyze rapidly; the half-lives are expected to be <1 minute based on data from two analogous substances, dichloro(dimethyl)silane (CAS No. 75-78-5) and trichloro(methyl)silane (CAS No. 75-79-6). Observed rates of hydrolysis were so rapid in all cases that it was not possible to distinguish among the different pH conditions.

The overall rate constants for reaction with OH radicals in the atmosphere due to indirect photolysis are 0.2992 x 10^{-12} and 0.1496 x 10^{-12} cm^3/molecule-sec for **$ClMe_2SiH$** and **Cl_2MeSiH**, respectively. The resulting half-lives due to indirect photolysis are 35.8 and 71.5 days for **$ClMe_2SiH$** and **Cl_2MeSiH**, respectively. **Cl_3SiH** and **Cl_4Si** are considered to be inorganic according to EPI Suite, and very few inorganic compounds were included in the training set for the methodology utilized in several EPI Suite programs. Therefore, inorganic compounds are considered to be outside the estimation domain. Any potential for photodegradation might be superseded by hydrolysis of the parent compound depending on the concentration of water vapor in the air. Biodegradation tests were not located for the sponsored substances. In an OECD 310, supporting hydrolysis product TMS showed 0% biodegradation over 28 days and based on studies of DMSD (^{14}C-dimethylsilanediol) in four soils at 25 ºC, the substance is not rapidly biodegradable. HCl is an inorganic compound and biodegradation tests are not applicable. Based on this information, **$ClMe_2SiH$** and **Cl_2MeSiH** are not expected to be readily biodegradable. **Cl_3SiH** and

Cl_4Si are considered to be inorganic compounds and biodegradation tests are not applicable. Due to rapid hydrolysis of the sponsored substances, any potential for biodegradation is likely to be of the hydrolysis products. Consequently, the only biodegradable materials in the test system will be silanols, and condensed silanol materials (high molecular weight polymers). At high concentrations, the silanols will condense to form highly cross linked, high molecular weight polymers that are water insoluble and effectively nonbiodegradable.

Fugacity modeling for inorganic substances (**Cl_3SiH** and **Cl_4Si**) is outside the applicability domain of EPI Suite. Fugacity modeling of HCl is not applicable. A Level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that the monomeric chlorosilanes will distribute mainly to the air (47.6 – 49%) and soil (ca. 46.2 - 47.6%) compartments, with minor distribution to water (ca. 5%) and negligible distribution to sediments (<0.1). Since the parent materials are not expected to be released to soil or water based on their uses and handling, a scenario of 100% emission to air is more realistic. When the monomeric chlorosilanes are released to air exclusively, the fugacity model predicts that 99.8% is reacted. The unreacted 0.2% remains in air (100%). The modeling results show that the environmental fate of the monomeric chlorosilanes is controlled by their high reactivity with water in all compartments. Level III fugacity modeling using equal loading rates of 1000 kg/h each for air, soil and water predicts that the hydrolysis products will distribute mainly to soil (62.8 – 75.2 %), with a smaller fraction to water (ca. 24.5 – 31.8 %) and negligible amounts to sediment and air. Based on the more realistic scenario of 100% release to air, the model predicts that dimethylsilanol will be distributed mainly in air (83.3%) and water (11.7%), and that the remaining three silanol hydrolysis products will be distributed mainly in soil (ca. 85-88%) and water (ca. 9-11%).

The bioaccumulation potential of the monomeric chlorosilanes was not measured due to rapid hydrolysis. The estimated BCF using the BCFBAF Program (v3.01) range from 4.3 L/kg wet-wt (**Cl_3SiH**) to 8.8 L/kg wet-wt (**$ClMe_2SiH$**), indicating the monomeric chlorosilanes are not expected to bioaccumulate. For the hydrolysis products, the estimated BCFs were all 3.2 L/kg wet-wt.

Acute aquatic toxicity data are not available for the monomeric chlorosilanes. The monomeric chlorosilanes are expected to undergo rapid hydrolysis, which occurs during testing; exposure to parent chlorosilane is likely to be transient and observed toxicity is likely due to its hydrolysis products, HCl and the respective silanol hydrolysis products. [The silanol hydrolysis product of **$ClMe_2SiH$** is structurally similar to both TMS and DMSD. The silanol hydrolysis product of **Cl_2MeSiH** is structurally similar to DMSD. The silanol hydrolysis product of **Cl_3SiH** is the same as the hydrolysis product of trimethoxysilane. The silanol hydrolysis product of **Cl_4Si** is the same as the hydrolysis product of TEOS.]

Test substance	Species	Result (mg/L)	Guideline; Test type
Fish, acute toxicity			
Supporting hydrolysis product for $ClMe_2SiH$			
TMS 1066-40-6	*Oncorhynchus mykiss*	96-hr LC_{50} = 271 (measured)	OECD TG 203; semi-static
Supporting hydrolysis product for $ClMe_2SiH$, Cl_2MeSiH			
DMSD 1066-42-8	*Oncorhynchus mykiss*	96-hr LC_{50} > 126 (measured)	OECD TG 203; static
Supporting substance for Cl_3SiH			
Trimethoxysilane 2487-90-3	*Oncorhynchus mykiss*	96-hr LC_{50} > 100 (nomimal)	OECD TG 203; static
Supporting substance for Cl_4Si			
TEOS 78-10-4	*Danio rerio*	96-hr LC_{50} > 245 (measured)	Directive 92/69/EEC, C.1; semi-static
Hydrolysis product for all category members			
HCl 7647-01-0	*Cyprinus carpio*	96-hr LC_{50} = pH 4.3 (4.92 mg/L)	OECD TG 203
Aquatic invertebrates, acute toxicity			
Supporting hydrolysis product for $ClMe_2SiH$			
TMS 1066-40-6	*Daphnia magna*	48-hr EC_{50} = 124 (measured)	OECD TG 202; semi-static
Supporting hydrolysis product for $ClMe_2SiH$, Cl_2MeSiH			

DMSD 1066-42-8	*Daphnia magna*	48-hr EC_{50} > 117 (measured)	OECD TG 202; static
Supporting substance for Cl_3SiH			
Trimethoxysilane 2487-90-3	*Daphnia magna*	48-hr EC_{50} > 100 (nominal)	OECD TG 202; static
Supporting substance for Cl_4Si			
TEOS 78-10-4	*Daphnia magna*	48-hr EC_{50} > 75 (measured)	OECD TG 202; flow-through
Hydrolysis product for all category members			
HCl 7647-01-0	*Daphnia magna*	48-hr EC_{50} = pH 5.3 (0.492 mg/L)	OECD TG 202
Aquatic plants toxicity			
Supporting hydrolysis product for $ClMe_2SiH$			
TMS 1066-40-6	*Pseudokirchneriella subcapitata*	72-hr EC_{50} > 750 (measured)	OECD TG 201
Supporting hydrolysis product for $ClMe_2SiH$, Cl_2MeSiH			
DMSD 1066-42-8	*Pseudokirchneriella subcapitata*	72-hr E_rC_{50} and E_bC_{50} > 118 (measured)	OECD TG 201
Supporting substance for Cl_3SiH			
Trimethoxysilane 2487-90-3	*Pseudokirchneriella subcapitata*	72-hr E_rC_{50} and E_bC_{50} >100	OECD TG 201
Supporting substance for Cl_4Si			
TEOS 78-10-4	*Pseudokirchneriella subcapitata*	72-hr E_rC_{50} and E_bC_{50} >100 (nominal)	OECD TG 201
	Scenedesmus subspicatus	E_bC_{50} = 889.2; E_bC_{50} >1039.3	Directive 87/302/EEC, part C, p. 89
Hydrolysis product for all category members			
HCl 7647-01-0	*Selenastrum capricornutum*	72-hr E_rC_{50} = pH 5.3 (0.492 mg/L)	OECD TG 201; static

The hazard of hydrochloric acid for the environment is caused by the proton (pH) effect. For this reason the effect of hydrogen chloride on the organisms depends on the buffer capacity of the aquatic ecosystem. Also the variation in acute toxicity for aquatic organisms can be explained to a significant extent by the variation in buffer capacity of the test medium. For example, LC_{50} values of acute fish toxicity tests varied from 4.92 to 282 mg/L. The toxicity values to *Selenastrum capricornutum* 72h-EC_{50} is 0.780 mg/L at pH 5.1 for biomass, 0.492 mg/L at pH 5.3 for growth rate, and the 72h-NOEC is 0.097 mg/L at pH 6.0 for biomass and growth rate. The 48h-EC50 for *Daphnia magna* is 0.492 mg/L at pH 5.3 based on immobilization.

Based on the properties of the hydrolysis product, HCl, the monomeric chlorosilanes possess properties indicating a hazard for the environment (acute toxicity to fish between 1 and 100 mg/L, acute toxicity to aquatic invertebrates and toxicity to algae < 1 mg/L). Toxic effects are expected primarily from the hydrolysis products (in particular hydrogen chloride, and depend on the buffering capacity of a particular aquatic environment. Therefore, the stated effect levels pertain to unbuffered systems and can be viewed as conservative). The monomeric chlorosilanes and their hydrolysis products are not expected to be readily biodegradable or to bioaccumulate. Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD HPV Programme.

Exposure

The estimated annual production volumes for the category members are:

Substance	Estimated United States 2010 Production (metric tonnes)	Estimated European 2010 production (metric tonnes)	Estimated Japanese 2010 production (metric tonnes)
$ClMe_2SiH$	2268 – 68,039	2268 – 68,039	113 (purchased)
Cl_2MeSiH	5359 – 362,874	5359 – 362,874	454 - 4536
Cl_3SiH	45,359 – 362,874	11,340 – 113,398 (a)	22,680 – 204,117
Cl_4Si	45,359 – 362,874	11340 - 90719 (b)	0

(a) Note: 88% of the reported volume produced in Europe is from 2008 data. The remaining 12% is from 2010 data.)

(b) Note: 64% of the reported volume produced in Europe is from 2008 data. The remaining 36% is from 2010 data.

100% of the monomeric chlorosilanes, by volume, are used as intermediates in the manufacture of commercial organosiloxanes. The monomeric chlorosilanes are reacted during use and lose their chemical identities.

The monomeric chlorosilanes are expected to be primarily produced and processed in closed systems. Due to the dynamic and exothermic nature of the processes incorporating chlorosilanes, many engineering controls are recommended to prevent occupational exposure such as local and general ventilation; ventilation system tied into scrubbers with nitrogen padding; ambient temperature; closed loop unloading; dry break connections; specific worker training; use of air emission abatement equipment such as incinerators, scrubbers and fabric filters is applicable as a best practice; treatment of effluent in waste water treatment plant. Production facility employees involved in chlorosilane production and application are required by the manufacturing facility to use personal protective equipment (PPE) such as respirators with organic vapor cartridges, full-face respirator with ABEK-filter; face shield and self-contained, positive pressure breathing apparatus (for prolonged or high exposure), slicker suit, rubber boots, Viton gloves/gauntlets (5-layer laminate of PE and EVOH (4H) or Butyl and Viton types recommended; nitrile gloves may also be used for short durations). For any situation (e.g. equipment maintenance and repair) where potential exposure to chlorosilanes is expected, the use of acid resistant protective equipment, respiratory equipment and face shield is recommended by the manufacturing facility because of their irritating or corrosive properties. Environmental exposure is expected to be low.

There are no consumer uses of the monomeric chlorosilanes.

ANNEX
Summary of Mammalian Toxicity Data Read Across Approach

Substance	Acute Toxicity (oral) (mg/kg)	Acute Toxicity (inhalation) (LC_{50} = mg/L)	Repeated Dose (oral) (mg/kg)	Repeated Dose (inhalation)	Gene Mutation *in vitro*	Chromosome Aberration *in vitro*	Effects on Fertility and Reproductive Organs (oral = mg/kg bw/day) (inhalation = mg/L)	Developmental Toxicity (oral = mg/kg bw/day) (inhalation = mg/L)
$ClMe_2SiH$	238 (RA)	**17.3 (60 min; nominal)**	NOAEL (systemic) = 250 (RA)	NOAEC = 0.03 (RA)	**Negative**	Negative (RA)	NOAEC (inh) = 0.073 (RA)	NOAEC (inh) = 2.2 (RA)
Supporting Substances								
Trimethylsilanol (TMS)	No used for read across	Not used for read across	**NOAEL (systemic) = 250**	**NOAEC = ca. 2.2 (hct)**	Not used for read across	Not used for read across	**NOAEC (inh) = 2.2 (hct)**	**NOAEC (inh)= 2.2 (hct)**
Cl_2DMS	Not used for read across	Not used for read across	Not used for read across	Not used for read across	Not used for read across	**Negative**	Not used for read across	Not used for read across
Cl_2MeSiH	**< 278 (undiluted)**	**8.4 (60 min; nominal)**	NOAEL (systemic) = 250 (RA)	NOAEC = 0.03 (RA)	Negative (RA)	Negative (RA)	NOAEC (inh) = 0.073 (RA) NOAEL (oral) = 500 (RA)	NOAEL (oral) = 500 (RA)
Supporting Substances								
DMSD	Not used for read across	Not used for read across	**NOAEL (systemic) = 250**	Not used for read across	Not used for read across	Not used for read across	NOAEL (oral) = 500	NOAEL (oral) = 500
MTMS	Not used for read across	Not used for read across	Not used for read across	**NOAEC = ca. 0.56 LOAEC = ca. 2.2**	Not used for read across	Not used for read across	NOAEL (oral) = 1000	NOAEL (oral) = 1000
Cl_2DMS	Not used for read across	Not used for read across	Not used for read across	Not used for read across	Not used for read across	**Negative**	Not used for read across	Not used for read across
Cl_3SiH	**1030 (10% dilution/ male)**	**15.0 (60 min; measured)**	NOAEL (systemic) = 50(RA)	NOAEC = ca. 0.0025 (RA)	**Negative**	Negative (RA)	NOAEC (inh) = 0.073 (RA) NOAEL (oral) = 1000 (RA)	NOAEL (oral) = 1000 (RA)
Supporting Substances								
Trimethoxysilane	Not used for read across	Not used for read across	No data	**NOAEC = ca. 0.0025**	Not used for read across	Not used for read across	Not used for read across	Not used for read across
MTMS	Not used for read across	Not used for read across	**NOAEL (systemic) = 50**	**NOAEC = ca. 0.56 LOAEC = ca. 2.2**	Not used for read across	Not used for read across	NOAEL (oral) = 1000	**NOAEL (oral) = 1000**
Cl_4Si	**238 (diluted)**	**9.1 (60 min; nominal)**	NOAEL (systemic) = 10 (males); 50 (females) (RA)	NOAEC = 0.030 (RA)	**Negative**	**Negative**	NOAEC (inh) = 0.073 (RA) NOAEL (oral) = 100 (RA)	NOAEL (oral) = 100 (RA)
Supporting Substances								
TEOS	Not used for read across	Not used for read across	**NOAEL = 10 (males) = 50 (females)**	Not used for read across	Not used for read across	Not used for read across	**NOAEL (oral) = 100**	**NOAEL (oral) = 100**
Supporting substance for all category members								
HCl	**238-277 mg/kg (female)**	**4.2-4.7 (60 min)**	No data	**NOAEC = 0.030**	**Negative**	**Positive (pH effect)**	**NOAEC (inh) = 0.073**	Not used for read across

RA = Read Across; hct = highest concentration tested

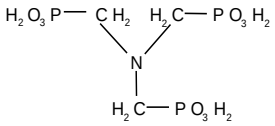
SIDS INITIAL ASSESSMENT PROFILE

Category Name	ATMP and salts (Phosphonic Acid Compounds Group 1) Amino tris(methylenephosphonic acid) and its sodium salts

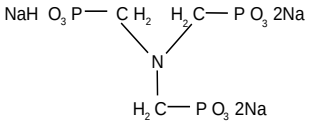
Chemical Names and CAS Numbers

Chemical name	CAS no.	Abbreviation
Amino tris(methylenephosphonic acid	6419-19-8	ATMP
Amino tris(methylenephosphonic acid), xNa Salt	20592-85-2	ATMP-xNa
Amino tris(methylenephosphonic acid), Na Salt	none found	ATMP-Na
Amino tris(methylenephosphonic acid), 2Na Salt	4105-01-5	ATMP-2Na
Amino tris(methylenephosphonic acid), 3Na Salt	7611-50-9	ATMP-3Na
Amino tris(methylenephosphonic acid), 4Na Salt	94021-23-5	ATMP-4Na
Amino tris(methylenephosphonic acid), 5Na Salt	2235-43-0	ATMP-5Na
Amino tris(methylenephosphonic acid), 6Na Salt	15505-05-2	ATMP-6Na

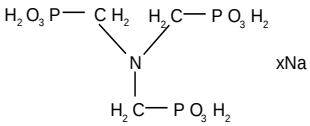
Structural Formula



Amino tris(methylenephosphonic acid)
CAS # 6419-19-8



Amino tris(methylenephosphonic acid), 5Na Salt
CAS # 2235-43-0



Amino tris(methylenephosphonic acid), xNa Salt
CAS # 20592-85-2

SUMMARY CONCLUSIONS OF THE SIAR

Category Rationale

This category covers a phosphonic acid and various sodium salts of that acid. The different salts are prepared by neutralising the acid to a specific pH. Data are available for the acid and some salts. The substances are commercially available as aqueous solutions only and in an environmental context the speciation will be the same. In the present context the effect of the counter-ion (sodium) will not be significant. The properties of the members of the category are consistent across all end points.

The category is expressed as Phosphonic Acid Compounds Group 1 because two other groups have been identified, with close structural analogy to the present one. Group 2 is 1-Hydroxy-1,1-ethane-diphosphonic acid (CAS 2809-21-4) and its sodium and potassium salts; Group 3 is Diethylene triamine penta(methylene phosphonic acid) (CAS 15827-60-8) and its sodium salts.

Human Health

In the rat, ATMP is poorly absorbed from the gut and rapidly eliminated after oral and i.v. administration. Elimination is primarily via the faeces following oral dosing with urine predominating after i.v. dosing. These

differences demonstrate clear differences in systemic disposition of ATMP after enteral or parenteral administration. Bone is the only tissue that exhibits deposition of test substance-derived radioactivity, however this is unlikely to occur to any biologically significant extent in view of the low level of uptake reported.

ATMP is of low acute toxicity in mammals. The acute oral LD_{50} is 2910 mg/kg while the dermal LD_{50} is >6310 mg/kg. The tetrasodium salt of ATMP was of lower toxicity with an oral LD_{50} of ~8610 mg/kg and a dermal LD_{50} of >5740 mg/kg. The pentasodium salt (20592-85-2) was of lower oral toxicity (7120 mg/kg) and dermal toxicity (>6320 mg/kg).

ATMP is a moderately severe eye irritant. The tetra- and pentasodium salts of ATMP are mildly irritating. ATMP can be considered to be non-irritating to the skin. The tetra- and pentasodium salts of ATMP induced very slight skin irritation responses. ATMP is not a skin sensitizer.

Repeated exposure in the diet to 500 mg/kg bw/day of the acid for 2 years resulted in no toxicological effects of concern. The systemic NOAEL for this good quality study conducted to OECD guideline 453 is therefore considered to be >500 mg/kg bw/day. Information available on the tetrasodium salt is less robust but similarly indicates that it is of low oral toxicity following repeat exposure with a NOAEL of >600 mg active acid/kg bw/day derived from a 28 day study or >175 mg/kg bw/d derived from a 90 day study.

Neither the acid nor a sodium salt induced gene mutations in bacteria. ATMP induced gene mutations in mouse lymphoma cells but this effect was not seen when a neutralized test solution was tested up to the solubility limit and is therefore considered to be an artefact of pH. The pentasodium salt of ATMP did not induce chromosome damage either *in vitro* or *in vivo*. Both the acid and the salts are therefore considered to lack genotoxic potential. This is confirmed by a carcinogenicity study. ATMP was not carcinogenic to rats treated with dose levels up to 500 mg/kg in the diet for 24 months.

ATMP is not selectively toxic to the male or female reproductive system, with a NOAEL of 275 mg/kg bw/day for males and 310 mg/kg bw/day for females. While no reproductive toxicity data were located for the salts, physico-chemical considerations suggest these will resemble those of the parent acid. ATMP and its salts are not fetotoxic or teratogenic in the rat or mouse with a consistent NOAEL of 1000 mg/kg body weight/day in both species.

Overall the NOAEL for ATMP is > 500 mg/kg bw/day, based on a chronic toxicity study.

Conclusion for Human Health

The chemicals in this category possess properties indicating a hazard for human health (ATMP is a moderately severe eye irritant). Although these hazards do not warrant further work as they are related to pH effects and chelation properties, they should nevertheless be noted by chemical safety professionals and users.

Environment

ATMP is a polyphosphonic acid of molecular weight 299. The phosphonic acid function is a strong acid, and it is frequently produced as a salt for reasons of ease of use. It can form stable complexes with polyvalent metal ions. As a consequence of the ionisation over typical pH ranges, it is of high water solubility (≥ 500 g/l) and low octanol-water partition coefficient (Log Kow = -3.53). Its vapour pressure is very low (1.9×10^{-10} Pa (estimated)). At pH 7, ATMP in water will be almost fully ionised four times, with a majority of the molecules ionised five times.

There is a possibility that the emission of a phosphonic acid could locally decrease the pH in the aquatic environment. In the normal use of these substances, their pH, concentration and water quality have to be monitored very carefully. Therefore, a significant decrease of the pH of the receiving water is not expected. Furthermore, the substances are usually used as salts with near-neutral pH, and their effects on pH are further buffered by the presence of metal ions. Generally the changes in pH of the receiving water should stay within the natural range of the pH, and for this reason, adverse effects on the aquatic environment are not expected due to release of the phosphonic acids.

ATMP and its salts may enter the environment via normal use in water treatment applications. It is predicted and has been shown to be adsorbed by inorganic matrices (measured Koc = 11740), and therefore adsorption to sewage sludge

and soil is strong. ATMP and its sodium salts are not readily or inherently biodegradable in laboratory studies carried out under standard conditions. Although these data suggest the potential for persistence, there is, however, evidence of partial degradation by abiotic processes in natural waters, and biodegradation following acclimation, or under conditions of low inorganic phosphate. In the presence of commonly found metal ions possessing redox properties, such as iron, metal-catalysed degradation and photodegradation can be rapid, which promotes further biodegradation. ATMP is not bioaccumulative (measured BCF <25).

As complexing agents, these substances could remobilise metals in the environment; however, their high degree of adsorption to sediments suggests that this is unlikely to occur.

ATMP and its salts are of low acute toxicity to fish, acute LC_{50} values determined in short-term and prolonged-term exposure tests are all equal to or in excess of 250 mg/l. ATMP also has low chronic toxicity to fish with a 60-day NOEC of 23 mg/l having been determined in an early-life stage test ATMP and its salts are of low to moderate acute toxicity to aquatic invertebrates. The lowest reliable acute toxic concentration determined for ATMP is a 48-h EC_{50} of 94 mg/l for the marine copepod *Acartia tonsa*. A sub-lethal test with the oyster, *Crassostrea virginica*, yielded a 96-hour EC50 for effects on shell growth of 201 mg/l and a chronic test with Daphnia magna yielded a 28-day NOEC of >25 mg/l, suggesting that ATMP has low chronic toxicity to aquatic invertebrates. A further chronic study in *Daphnia magna* of unassignable validity (Klimisch code 4) gave a 21-day NOEC of 3.0 mg/l and LOEC of 10 mg/l (based on nominal concentrations).

ATMP is of low acute toxicity to the marine sediment living amphipod *Corophium volutator* (10-day LC_{50}: >5000 mg/kg dw) and to sewage sludge micro-organisms (*Pseudomonas putida* 30-min EC_0: ≥500 mg/l).

The effects of ATMP observed in tests with algae are likely to be a consequence of nutrient limitation caused by complexation and not true toxicity. Thus, a 96-hour E_bC_{50} for *Selenastrum capricornutum*[1] of 12 mg/l and a 96-hour E_rC_{50} for *Skeletonema costatum* of 80 mg/l are likely to over-estimate the true toxicity. NOECs of ≤20 mg/l (most commonly in the range 10-20 mg/l), determined in studies for which reliability could not be assessed and which might also be subject to the effects of complexation, indicate that ATMP is likely to be of low chronic toxicity to algae.

ATMP is considered to be of low toxicity to terrestrial plants (*Avena sativa* 9-day EC_{50}: >1000 mg/l), although the reliability of the study on which this conclusion is based is uncertain. ATMP is also of low acute toxicity to birds when administered via the dietary exposure route (*Anas platyrhynchos* and *Colinus virginianus* 14-day LC_{50}: >565 mg/kg bw).

[1]Now known as *Pseudokirchneriella subcapitata*

Conclusion for the Environment

ATMP and its salts possess properties indicating a hazard for the environment (EC_{50} in the range 10 – 100 mg/l for algae). However these hazards do not warrant further work as they are related to acute toxicity, pH effects and metal chelation, which may become evident only at very high exposure levels. The substances are not readily biodegradable but have a low bioaccumulation potential.

Exposure

Current worldwide production of ATMP, HEDP and DTPMP (and their salts) is estimated to be in the range of 50,000 to 100,000 metric tonnes annually. The major uses of ATMP and its salts are as an additive in water treatment, where its ability to both complex with metal ions, and to prevent crystalline scale deposition in solution and onto surfaces through adsorption, are utilised. The substances are also used in detergent and cleaning applications, and in the paper, textiles and photographic industries, and also in off-shore oil well applications.

The major route of environmental exposure is expected to be release, often via wastewater treatment plants, to rivers. Agricultural land could be exposed via spreading of sewage sludge. Oil well use would lead to direct exposure of the marine environment. In rivers, they are expected to partition predominantly to sediment.

Human exposure in manufacturing and formulating is possible, but due to the use of personal protective equipment, limited to accidental situation. Where exposure can occur, dermal exposure is the most likely route of exposure. In

these cases PPE is recommended. The concentration of the substance in the product, together with PPE/engineering controls are important factors in the assessment of risk associated with the hazardous properties (mainly corrosivity/irritancy). Where concentrated solutions are handled, engineering controls and PPE are used to control exposure and reduce the risk from the corrosive/irritant properties. In downstream uses, where consumer exposure is possible, much more dilute concentrations are used, which significantly reduces or removes the likelihood of corrosivity/irritancy effects.

Consumer exposure is being assessed in more detail as part of the HERA project (HERA, in progress www.heraproject.com/).

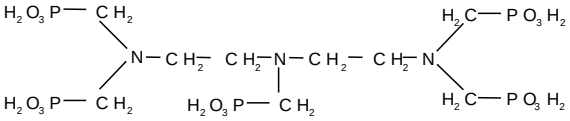
SIDS INITIAL ASSESSMENT PROFILE

Category Name	DTPMP and salts (Phosphonic Acid Compounds Group 3) Diethylene triamine penta(methylene phosphonic acid) and its sodium salts

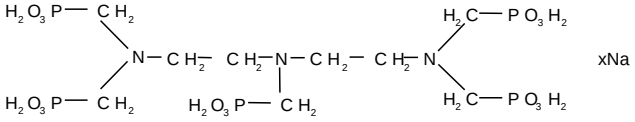
Chemical Names and CAS Numbers

Chemical name	CAS no.	Abbreviation
Diethylene triamine penta(methylene phosphonic acid)	15827-60-8	DTPMP
Diethylene triamine penta(methylene phosphonic acid), xNa Salt	22042-96-2	DTPMP-xNa
Diethylene triamine penta(methylene phosphonic acid), Na Salt	94987-76-5	DTPMP-Na
Diethylene triamine penta(methylene phosphonic acid), 2Na Salt	94987-75-4	DTPMP-2Na
Diethylene triamine penta(methylene phosphonic acid), 3Na Salt	95015-06-8	DTPMP-3Na
Diethylene triamine penta(methylene phosphonic acid), 4Na Salt	94987-77-6	DTPMP-4Na
Diethylene triamine penta(methylene phosphonic acid), 5Na Salt	61792-09-4	DTPMP-5Na
Diethylene triamine penta(methylene phosphonic acid), 6Na Salt	93841-74-8	DTPMP-6Na
Diethylene triamine penta(methylene phosphonic acid), 7Na Salt	68155-78-2	DTPMP-7Na
Diethylene triamine penta(methylene phosphonic acid), 8Na Salt	95183-54-3	DTPMP-8Na
Diethylene triamine penta(methylene phosphonic acid), 9Na Salt	93841-75-9	DTPMP-9Na
Diethylene triamine penta(methylene phosphonic acid), 10Na Salt	93841-76-0	DTPMP-10Na

Structural Formula



Diethylene triamine penta(methylenephosphonic acid)
CAS # 15827-60-8



Diethylene triamine penta(methylenephosphonic acid), xNa Salt
CAS # 22042-96-2

SUMMARY CONCLUSIONS OF THE SIAR

Category Rationale

This category covers a phosphonic acid and sodium salts of that acid. The different salts are prepared by neutralising the acid to a specific pH. Data are available for the acid and some salts. The substances are commercially available as aqueous solutions only and in an environmental context the speciation will be the same. In the present context the effect of the counter-ion (sodium) will not be significant. The properties of the members of the category are consistent across all end points.

The category is expressed as Phosphonic Acid Compounds Group 3 because two other groups have been identified, with close structural analogy to the present one. Group 1 is Amino tris(methylenephosphonic acid) (6419-19-8) and its sodium salts; Group 2 is 1-Hydroxy-1,1-ethane-diphosphonic acid (CAS 2809-21-4) and its sodium and potassium salts.

Human Health

Toxicokinetic data on DTPMP and its salts are limited. The available information, together with data for phosphonic acid compounds comprising Group 1 and Group2, suggest that only minor amounts of DTPMP and its salts would enter the body after ingestion or skin contact.

The DTPMP acid and salts are of low oral and dermal toxicity. The oral rat LD_{50} is 4164 mg/kg bw and the rabbit LD_{50} is higher (>4605 mg/kg bw). The acute rat oral LD50 of the heptasodium salt lies between 5838 and 8757 mg/kg bw. The dermal LD_{50} values for the salts are >5838 mg/kg bw for the rat. For the octasodium salt, the oral LD_{50} is >3870 mg/kg bw and the dermal LD_{50} >860mg/kg bw for the rabbit. There is sufficient information from studies performed to an adequate standard, plus additional information from non-key studies, to support these values.

There is evidence that DTPMP acid is an eye irritant, although different severities were reported in the two available assays (mild and severe). While both the formulations tested contained 10% HCl, which could contribute to the irritant response, it would however appear prudent to conclude that the anhydrous acid is a severe eye irritant. Evidence from three studies on DTPMP salts indicates these are only slightly irritating to the eye.

Several studies on DTPMP acid and its salts indicate they have a low skin irritation potential. Although these studies tested formulations and therefore the limit dose for the active acid or salts was not achieved, the presence of hydrochloric acid in the formulations would be expected to exacerbate the response obtained. Therefore, in view of the very limited responses obtained, it is considered likely that the pure acid or salt, if tested to a limit dose, would be, at most, mild skin irritants.

The salt of DTPMP has been studied in a good quality 90 day feeding study conforming to OECD guidelines. Repeated exposure to 842 mg/kg bw/d (males) and 903 mg/kg bw/d (females) resulted in perturbations of iron and calcium homeostasis (in the absence of any concurrent alteration of calcium plasma levels). Changes in some blood parameters and an increase in total bone density were seen at this dose. The NOAEL for this study was therefore 83 mg/kg bw/day based on the mid dose male group. There are a number of further studies available on the salt, covering durations from 90 days, one year or two years. In addition to effects on iron homeostasis and haematological effects, two of these studies have reported effects on liver pathology and NOAELs down to 4 mg/kg bw/d have been assigned. As these are secondary literature, where there is insufficient information for full evaluation, the findings are not considered to outweigh the recent GLP and OECD compliant 90 day study.

Neither the acid nor the salt induces mutations in well-conducted studies in bacteria. The evidence for mutagenic potential in mammalian cells is conflicting. The acid, even when neutralized, can induce mutations at the thymidine kinase locus in mouse lymphoma L5178Y cells in the presence of S9 mix. A negative response was seen when the salt (neutralized with NaOH) was tested. The difference in outcome between the tests on the acid when neutralized with NaOH and on the salt is difficult to rationalize since the species tested should be similar for both test substances and similar dose ranges were tested. It is probable the positive response for the acid does not reflect an ability to interact with DNA due to (1) lack of structural alerts for mutagenicity, (2) lack of evidence for gene mutation potential in sub-mammalian systems and (3) lack of potential to induce gene mutations in another well-conducted assay investigating mutations at the hprt locus in CHO cells. Perturbations of pH and osmolarity are considered to be unlikely causes of the positive response due to the low concentration at which a positive response on the acid was seen (0.73 mM) and because positive responses are only seen consistently in the presence of S9. A plausible alternative explanation is the test substance interacts with S9 resulting in the formation of oxidative species. Evidence for a lack of mutagenic potential of DTPMP in vitro is supported by a negative hprt locus test and in vivo is provided by a well-conducted chromosome aberration study in rat bone marrow following gavage with doses up to 1970 mg/kg bw. Consequently DTPMP and its salt are not considered to pose a genotoxic hazard.

The reproductive NOAEL for DTPMP in the rat is 294 mg/kg bw/day for parental males and 312 mg/kg bw/day for parental females. No histopathological changes were apparent in reproductive tissue from male or female rats following gavage administration of 850-900 mg/kg bw /day of the sodium DTPMP for up to 90 days. Results from a rat reproduction study provided evidence of equivocal fetotoxicity with a NOAEL of 100 mg/kg bw/day and a NOAEL of 312 mg/kg bw/day for teratogenicity of DTPMP in the rat, however these observations were not replicated in a developmental toxicity study on sodium DTPMP which provided a NOAEL of 1000 mg/kg bw/day for fetotoxicity and 2000 mg/kg bw/day for teratogenicity.

Conclusion for Human Health

The chemicals in this category possess properties indicating a hazard for human health (eye irritation, potential perturbations of iron and calcium homeostasis). Although these hazards do not warrant further work as they are related to pH effects and chelation properties, they should nevertheless be noted by chemical safety professionals and users.

Environment

DTPMP is a polyphosphonic acid of molecular weight 573. The phosphonic acid function is a strong acid, and it is frequently produced as a salt for reasons of ease of use. It can form stable complexes with polyvalent metal ions. As a consequence of the ionisation over typical pH ranges, it is of high water solubility ($\geq$ 500 g/l) and low octanol-water partition coefficient (Log Kow = -3.4). Its vapour pressure is very low (1.67×10^{-10} Pa (estimated)). At pH 7, DTPMP in water will be almost fully ionised five times, with a majority of the molecules ionised six times, and some seven or eight times.

There is a possibility that the emission of a phosphonic acid could locally decrease the pH in the aquatic environment. In the normal use of these substances, their pH, concentration and water quality have to be monitored very carefully. Therefore, a significant decrease of the pH of the receiving water is not expected. Furthermore, the substances are usually used as salts with near-neutral pH, and their effects on pH are further buffered by the presence of metal ions. Generally the changes in pH of the receiving water should stay within the natural range of the pH, and for this reason, adverse effects on the aquatic environment are not expected due to release of the phosphonic acids.

DTPMP and its salts may enter the environment via normal use in water treatment applications. It is predicted and has been shown to be adsorbed by inorganic matrices, and therefore adsorption to sewage sludge and soil is strong (measured Koc = 9748). They are not readily biodegradable in laboratory studies carried out under standard conditions. Although these data suggest the potential for persistence, there is, however, evidence of partial degradation by abiotic processes in natural waters, and biodegradation following acclimation, or under conditions of low inorganic phosphate. In the presence of commonly found metal ions possessing redox properties, such as iron, metal-catalysed photodegradation can be rapid, which promotes further biodegradation. DTPMP is not expected to be bioaccumulative, based on its low Log K_{ow} and read-across from the two related substances ATMP and HEDP.

As complexing agents, these substances could remobilise metals in the environment; however, their high degree of adsorption to sediments suggests that this is unlikely to occur.

DTPMP and its salts are of low acute toxicity to fish and aquatic invertebrates. The lowest reliable acute toxic concentrations determined for DTPMP are a 96-h LC_{50} for the rainbow trout, *Oncorhynchus mykiss*, that is in the range 180-252 mg/l and EC50 values determined in acute tests with aquatic invertebrates are all in excess of 150 mg/l. DTPMP is of low chronic toxicity to fish (*O. mykiss* 60-day NOEC: 25.6 mg/l). There are no chronic data for aquatic invertebrates but an acute sub-lethal test with the oyster, *Crassostrea virginica*, yielded a 96-hour EC_{50} for effects on shell growth of 155.8 mg/l and a NOEC of 55.5 mg/l.

The 2Na and 7Na salts of DTPMP are of low acute toxicity to the marine sediment living amphipod *Corophium volutator* (10-day LC_{50}: >2500 mg/kg dw). There are no reliable data describing the acute toxicity of DTPMP to sewage sludge micro-organisms.

The effects of DTPMP observed in tests with algae are likely to be a consequence of nutrient limitation caused by complexation and not true toxicity. Thus, a 95-hour E_rC_{50} for *Selenastrum capricornutum*[1] of 0.45 mg/l is likely to over-estimate the true toxicity. The true toxicity of DTPMP and its salts to algae is best represented by the 95 hour ErC_{50} value of >10 mg/l. This value was obtained in the only test where steps were taken to counter the effects of nutrient complexation and is therefore most likely to be indicative of true toxicity.

No data are available that describe the toxicity of DTPMP to terrestrial plants and invertebrates. DTPMP is of low acute toxicity to birds when administered via the dietary exposure route (*Anas platyrhynchos* and *Colinus virginianus* 14-day LC_{50}: >454 mg/kg bw).

[1]Now known as *Pseudokirchneriella subcapitata*

Conclusion for the Environment

DTPMP and its salts possess properties indicating a hazard for the environment (EC_{50} in the range 1 – 10 mg/l for algae). However these hazards do not warrant further work as they are related to acute toxicity, pH effects and metal chelation, which may become evident only at very high exposure levels. The substances are not readily biodegradable but have a low bioaccumulation potential.

Exposure

Current worldwide production of ATMP, HEDP and DTPMP (and their salts) is estimated to be in the range of 50,000 to 100,000 metric tonnes annually. The major uses of DTPMP and its salts are as an additive in water treatment, where its ability to both complex with metal ions, and to prevent crystalline scale deposition in solution and onto surfaces through adsorption, are utilised. The substances are also used in detergent and cleaning applications, and in the paper, textiles and photographic industries, and also in off-shore oil well applications.

The major route of environmental exposure is expected to be release, often via wastewater treatment plants, to rivers. Agricultural land could be exposed via spreading of sewage sludge. Oil well use would lead to direct exposure of the marine environment. In rivers, they are expected to partition predominantly to sediment.

Human exposure in manufacturing and formulating is possible, but due to the use of personal protective equipment, limited to accidental situation. Where exposure can occur, dermal exposure is the most likely route of exposure. In these cases PPE is recommended. The concentration of the substance in the product, together with PPE/engineering controls are important factors in the assessment of risk associated with the hazardous properties (mainly corrosivity/irritancy). Where concentrated solutions are handled, engineering controls and PPE are used to control exposure and reduce the risk from the corrosive/irritant properties. In downstream uses, where consumer exposure is possible, much more dilute concentrations are used, which significantly reduces or removes the likelihood of corrosivity/irritancy effects.

Consumer exposure is being assessed in more detail as part of the HERA project (HERA, in progress www.heraproject.com/).

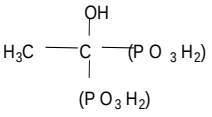
SIDS INITIAL ASSESSMENT PROFILE

Category Name	HEDP and salts (Phosphonic Acid Compounds Group 2) 1-Hydroxy-1,1-ethane-diphosphonic acid and its sodium and potassium salts

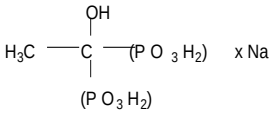
Chemical Names and CAS Numbers

Chemical name	CAS no	Abbreviation
1-Hydroxy-1,1-ethane-diphosphonic acid	2809-21-4	HEDP
1-Hydroxy-1,1-ethane-diphosphonic acid, xNa Salt	29329-71-3	HEDP-xNa
1-Hydroxy-1,1-ethane-diphosphonic acid, Na Salt	17721-68-5	HEDP-1Na
1-Hydroxy-1,1-ethane-diphosphonic acid, 2Na Salt	7414-83-7	HEDP-2Na
1-Hydroxy-1,1-ethane-diphosphonic acid, 3Na Salt	2666-14-0	HEDP-3Na
1-Hydroxy-1,1-ethane-diphosphonic acid, 4Na Salt	3794-83-0	HEDP-4Na
1-Hydroxy-1,1-ethane-diphosphonic acid, 5Na Salt	13710-39-9	HEDP-5Na
1-Hydroxy-1,1-ethane-diphosphonic acid, xK Salt	67953-76-8	HEDP-xK
1-Hydroxy-1,1-ethane-diphosphonic acid, K Salt	17721-72-1	HEDP-1K
1-Hydroxy-1,1-ethane-diphosphonic acid, 2K Salt	21089-06-5	HEDP-2K
1-Hydroxy-1,1-ethane-diphosphonic acid, 3K Salt	60376-08-1	HEDP-3K
1-Hydroxy-1,1-ethane-diphosphonic acid, 4K Salt	14860-53-8	HEDP-4K
1-Hydroxy-1,1-ethane-diphosphonic acid, 5K Salt	87977-58-0	HEDP-5K

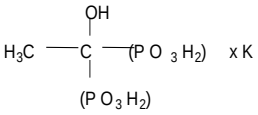
Structural Formula



1-Hydroxy-1,1-ethane-diphosphonic acid
CAS # 2809-21-4



1-Hydroxy-1,1-ethane-diphosphonic acid, xNa Salt
CAS # 29329-71-3



1-Hydroxy-1,1-ethane-diphosphonic acid, xK Salt
CAS # 67953-76-8

SUMMARY CONCLUSIONS OF THE SIAR

Category Rationale

This category covers a phosphonic acid and sodium salts of that acid. The different salts are prepared by neutralising the acid to a specific pH. Data are available for the acid and some salts. The substances are commercially available as aqueous solutions only and in an environmental context the speciation will be the same. In the present context the effect of the counter-ion (sodium/potassium) will not be significant. The properties of the members of the category are consistent across all end points. The supporting substance (1-hydroxyethylidene)bisphosphonic acid, calcium salt (the calcium salt of HEDP) is used to support the chronic daphnia endpoint.

The category is expressed as Phosphonic Acid Compounds Group 2 because two other groups have been identified, with close structural analogy to the present one. Group 1 is Amino tris(methylenephosphonic acid) (6419-19-8) and

its sodium salts; Group 3 is Diethylene triamine penta(methylene phosphonic acid) (CAS 15827-60-8) and its sodium salts.

Human Health

Animal studies demonstrate that gastrointestinal absorption of 1-hydroxy-1,1-ethane-diphosphonic acid and its salts is low, with the majority of the dose excreted in the faeces. Of the material that enters the systemic circulation, a substantial amount is excreted via urine while bone is the only tissue to exhibit deposition of radioactivity (although it is noted that no adverse skeletal changes were present in sub-chronic and chronic studies suggesting this is of limited toxicological relevance). Internal body burdens are increased after injection, presumably reflecting greater systemic availability.

HEDP and its salts are of moderate acute toxicity to mammals. The rat acute oral LD_{50} of the acid is 1536-2003 mg/kg while the dermal LD_{50} is>6000 mg/kg. The mouse oral LD_{50} is 1100mg/kg. Tests on two salts indicate lower LD_{50} values. The oral LD_{50} for the disodium salt (CAS 7414-83-7) was 1340 mg/kg (rat), 3300mg/kg (mouse) and 581 mg/kg (rabbit). For the tetrasodium salt (CAS 3794-83-0) the values were 940 and 1219 mg/kg in separate studies, with dermal LD_{50} values of >2300 mg/kg. Based on these findings it could be assumed that all sodium and potassium salts will be of moderate acute toxicity, since the effect of these counter-ions will not be significant.

HEDP is considered to be a severe eye irritant/corrosive. Three salts have been tested and these have been found to be mild (CAS 3794-83-0) or moderate irritants (CAS 7414-83-7 and 29329-71-3). Since these results have been obtained on formulations, and higher doses of the pure salts could have been tested, the results obtained may underestimate the irritancy of the pure salts.

The acid and one of the salts (CAS 3794-83-0) are not skin irritants. There is evidence that CAS 29329-73-3 is an irritant when tested under occlusion for 24 hours, but is only slightly irritating when tested under semi-occlusive conditions for 4 hours. CAS 7414-83-7 has been reported to be slightly irritating, but this is a secondary reference, not available for review. HEDP is not a skin sensitiser.

Sub-chronic dietary administration of HEDP in the dog (10000 ppm, equivalent to 1746 or 1620 mg/kg bw/day for males and females respectively) resulted in minor effects associated with perturbations of iron and calcium homeostasis (possibly linked to impaired absorption of these minerals from the diet and/or complexation with the phosphonic acid). The systemic NOAEL from this study is therefore considered to be ≥1746 mg/kg bw/day. A 90 day rat study indicates an NOAEL of >1724 mg bw/kg/day since, again, the only treatment related changes appeared due to perturbations of iron and calcium uptake and homeostasis and were therefore considered to be of doubtful toxicological significance. There is a robust chronic toxicity study on a sodium salt, where indications of anaemia were induced, although these had resolved by the end of the study. A NOAEL of 24 mg bw/kg/day is assigned based on the observation of anaemia at the higher doses.

Sub-chronic toxicity studies demonstrate no adverse microscopic changes in the reproductive organs of male and female rats or dogs given HEDP and its salts at exposures equivalent to approx. 1500-1800 mg/kg bw/day. Results from a study of unknown reliability are consistent with no effect on pregnancy rate in male and female albino rats following continuous administration of up to 0.5% disodium salt in the diet, giving an approximate NOAEL of >447 mg/kg bw/day (the highest dose tested). These observations are consistent with data for phosphonic acid compounds from Group 1 and Group 3, which were not selectively toxic to the male or female reproductive system and which returned NOAELs for reproductive toxicity in the range 275-312 mg/kg bw/day. Additionally, no abnormalities in the reproductive organs were seen in a 2-year study with the sodium salt of HEDP. Using a weight of evidence approach, it is concluded that HEDP is also not likely to be selectively toxic to the reproductive system.

Similar limitations also apply to pregnancy data available for HEDP, with a developmental NOAEL of >250 mg/kg bw/day (the highest dose tested) obtained from a gavage study of unknown reliability in the rabbit. This is broadly comparable with an oral NOAEL of around >1000 mg/kg bw/day obtained in rats given structurally-related analogues from Group 1 and Group 3 during pregnancy. Since physiochemical and physiological considerations indicate that the parent acid and other Group 2 salts will exhibit broadly similar effects on fetal development, a weight of evidence approach leads to a developmental NOAEL of >250 mg/kg bw/day for HEDP and its salts.

Although the mutagenicity data available on HEDP are of limited reliability they provide some evidence for a lack of mutagenic potential. Negative responses were seen in a bacterial mutagenicity assay and a mammalian cell gene mutation assay. A salt has previously been reported to be negative in a bacterial assay and a micronucleus test, although this is secondary literature and therefore of unknown validity. Related acids (ATMP, DTPMP) have been shown to be negative in well-conducted bacterial mutagenicity assays. Conflicting results have been obtained for mammalian gene mutation assays. Positive responses in this assay in the presence of S9 are believed to be artefactual (see SIARs for ATMP and DTPMP). Therefore, despite the absence of a robust genetic toxicology test package performed to current standards, HEDP or its salts are not likely to pose a genotoxic hazard.

Overall, the subchronic toxic effects of HEDP are primarily related to its ability to chelate metal ions and affect calcium and iron homeostasis. The lowest NOAEL is >1724 mg/kg based on a 90 day rat study. There is evidence that some of the salts may have a higher toxicity, as indicated by lower oral LD_{50} values for a sodium salt and lower effect levels for haematological parameters for a sodium salt in a 2 year chronic toxicity study (NOAEL of 24 mg/kg bw/d).

Conclusion for Human Health

The chemicals in this category possess properties indicating a hazard for human health (severe eye irritant/corrosive for the pure acid and its salts, reversible anaemia caused by the substances' ability to chelate metal ions and affect calcium and iron homeostasis). Although these hazards do not warrant further work as they are related to pH effects and chelation properties, they should nevertheless be noted by chemical safety professionals and users.

Environment

HEDP is a diphosphonic acid of molecular weight 206. The phosphonic acid function is a strong acid, and it is frequently produced as a salt for reasons of ease of use. It can form stable complexes with polyvalent metal ions. As a consequence of the ionisation over typical pH ranges, it is of high water solubility (>690 g/l) and low octanol-water partition coefficient (log K_{ow} = -3.52). Its vapour pressure is very low (estimated as $1.24E^{-09}$ Pa). At pH 7, HEDP in water will be fully ionised twice and half of the molecules will be ionised three times.

There is a possibility that the emission of a phosphonic acid could locally decrease the pH in the aquatic environment. In the normal use of these substances, their pH, concentration and water quality have to be monitored very carefully. Therefore, a significant decrease of the pH of the receiving water is not expected. Furthermore, the substances are usually used as salts with near-neutral pH, and their effects on pH are further buffered by the presence of metal ions. Generally the changes in pH of the receiving water should stay within the natural range of the pH, and for this reason, adverse effects on the aquatic environment are not expected due to release of the phosphonic acids.

HEDP and its salts may enter the environment via normal use in water treatment applications. It is predicted and has been shown to be adsorbed by inorganic matrices, and therefore adsorption to sewage sludge and soil is strong. They are not readily biodegradable in laboratory studies carried out under standard conditions. Although these data suggest the potential for persistence, there is, however, evidence of partial degradation by abiotic processes in natural waters, and biodegradation following acclimation, or under conditions of low inorganic phosphate. . In the presence of commonly found metal ions possessing redox properties, such as iron and copper, metal-catalysed photodegradation can be rapid, which promotes further biodegradation. HEDP is not bioaccumulative (measured BCF in fish <2).

As complexing agents, these substances could remobilise metals in the environment; however, their high degree of adsorption to sediments suggests that this is unlikely to occur.

HEDP and its salts are of low acute toxicity to fish. Acute LC_{50}/TL_{50} values determined in short-term and prolonged-term exposure tests are equal to or greater than 180 mg/l. HEDP and its salts are of low acute toxicity to aquatic invertebrates, as supported by 9 results from 5 test species. The lowest reliable acute toxic concentration was determined for HEDP for the invertebrate *Daphnia magna*, with a 48-h EC_{50} of 167 mg/l. A sub-lethal test with the oyster, *Crassostrea virginica*, yielded a 96-hour EC_{50} for effects on shell growth of 81 mg/l and a NOEC of <52 mg/l. A NOEC of 6.75 mg/l was obtained in a reliable 28-day reproduction test on HEDP with *Daphnia magna*. A reproduction study, of unassignable reliability, was conducted with the sodium salt and with the supporting substance

(1-hydroxyethylidene)bisphosphonic acid, calcium salt (the calcium salt of HEDP), which gave NOECs of 0.1 mg/l ad 3.0 mg/l, respectively. Deficiencies with the 2Na test (non-monotonic dose-response curve) and its inconsistency with the general pattern of toxicity to aquatic invertebrates mean that the result can be discounted.

There are no data for the effects of HEDP on sediment-dwelling organisms. However, given the low order of acute toxicity of ATMP acid and DTPMP salts to the marine sediment living amphipod *Corophium volutator*, it is not expected that HEDP and its salts would show significant toxicity to sediment-dwelling organisms. HEDP is of low acute toxicity to sewage sludge micro-organisms (*Pseudomonas putida* 30-min EC_0: ≥580 mg/l).

The effects of HEDP observed in tests with algae are likely to be a consequence of nutrient limitation caused by complexation and not true toxicity. Thus, a 96-hour E_rC_{50} for HEDP to *Selenastrum capricornutum*[1] of 3 mg/l is likely to over-estimate the true toxicity. A 14-day NOEC for HEDP to *S. capricornutum* of 13 mg/l, which might also be subject to the potential effects of complexation, indicates that HEDP is likely to be of low chronic toxicity to algae, atlhough there is evidence that the cultures did not remain in exponential growth during the phase of the test extending from 96 hours to 14 days.

HEDP and/or its di-sodium salt are of low acute toxicity to earthworms (*Eisenia foetida* 14-day LC_{50}: >960 mg/kg dw) and terrestrial plants (*Avena sativa* 14-day EC_{50}: >960 mg/l). HEDP is of low acute toxicity to birds when administered via the dietary exposure route (*Anas platyrhynchos* and *Colinus virginianus* 14-day LC_{50}: >284 mg/kg bw).

[1]Now known as *Pseudokirchneriella subcapitata*

Conclusion for the Environment

HEDP and its salts possess properties indicating a hazard for the environment (EC50 in the range 1 – 10 mg/l for algae). However these hazards do not warrant further work as they are related to acute toxicity, pH effects and metal chelation, which may become evident only at very high exposure levels. The substances are not readily biodegradable but have a low potential for bioaccumulation.

Exposure

Current worldwide production of ATMP, HEDP and DTPMP (and their salts) is estimated to be in the range of 50,000 to 100,000 metric tonnes annually. The major uses of HEDP and its salts are as an additive in water treatment, where its ability to both complex with metal ions, and to prevent crystalline scale deposition in solution and onto surfaces through adsorption, are utilised. The substances are also used in detergent and cleaning applications and cosmetics (HEDP only), and in the paper, textiles and photographic industries, and also in off-shore oil well applications.

The major route of environmental exposure is expected to be release, often via wastewater treatment plants, to rivers. Agricultural land could be exposed via spreading of sewage sludge. Oil well use would lead to direct exposure of the marine environment. In rivers, they are expected to partition predominantly to sediment.

Human exposure to HEDP or its salts in manufacturing and formulating is possible, but due to the use of personal protective equipment, limited to accidental situation. Where exposure can occur, dermal exposure is the most likely route of exposure. In these cases PPE is recommended. The concentration of the substance in the product, together with PPE/engineering controls are important factors in the assessment of risk associated with the hazardous properties (mainly corrosivity/irritancy). Where concentrated solutions are handled, engineering controls and PPE are used to control exposure and reduce the risk from the corrosive/irritant properties. In downstream uses, where consumer exposure is possible, much more dilute concentrations are used, which significantly reduces or removes the likelihood of corrosivity/irritancy effects.

Consumer exposure is being assessed in more detail as part of the HERA project (HERA, in progress www.heraproject.com/).

SIDS INITIAL ASSESSMENT PROFILE

<table>
<tr><td>Category Name</td><td colspan="2">Aliphatic Secondary Amines</td></tr>
<tr><td>Category Members:

CAS Registry Numbers, Chemical Names</td><td colspan="2">124-40-3 Dimethylamine (DMA)
109-89-7 Diethylamine (DEA)
142-84-7 Dipropylamine (DPA)
108-18-9 Diisopropylamine (DIPA)
111-92-2 Dibutylamine (DBA)
110-96-3 Diisobutylamine (DIBA)
<u>DPeA - A mixture of the following 3 isomers</u>:
2050-92-2 Dipentylamine
61361-18-0 N-(2-methylbutyl)-1-pentanamine
27094-65-1 2-Methyl-N-(2-methylbutyl)-1-butanamine</td></tr>
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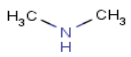
DMA</td><td>  </td></tr>
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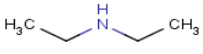
DEA</td><td>  </td></tr>
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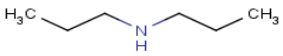
DPA</td><td>  </td></tr>
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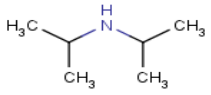
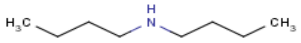
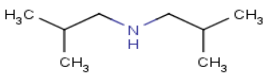
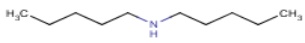
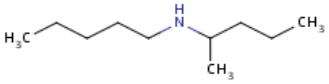
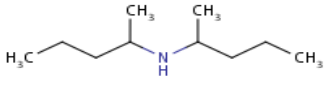
	108-18-9 **DIPA**	
	111-92-2 **DBA**	
	110-96-3 **DIBA**	
	2050-92-2 **One isomer of DPeA**	
	61361-18-0 **One isomer of DPeA**	
	27094-65-1 **One isomer of DPeA**	

SUMMARY CONCLUSIONS OF THE SIAR

Analogue/Category Rationale

The Aliphatic Secondary Amines category is limited to the nine sponsored substances as mentioned above.

Structure and physical chemical properties

The Aliphatic Secondary Amines category is represented by the structure R-NH-R', where R is an alkyl group that may be linear or branched; the alkyl group may include an atom or group that will not react with or substantially affect the properties of the amine function. The tendency to share the nonbonded electron pair on the nitrogen underlies the chemical behavior of amines as a group.

The Aliphatic Secondary Amines category members are structurally similar showing a trend in physical-chemical properties and ecotoxicity and similar toxicological properties. This category is defined as below:

- a structure which contains only aliphatic organic substituents; elemental compositions of carbon, hydrogen and nitrogen;
- a consistent incremental change across the group consisting of an increasing number of carbon atoms or branching. The change is constant in that it is restricted to adding elements that do not greatly change the physico-chemical properties of the amino moiety. This is evidenced by the consistency of pKa values of the protonated forms, which vary across the narrow range of 10.73 to 11.16; and
- molecular weights of < 500 Dalton, classifying the aliphatic secondary amines as low molecular weight aliphatic amines.

Toxicological profile

Observed corrosive properties overwhelm the systemic toxicity of the aliphatic secondary amines in most cases, including acute toxicity; the known acute oral, dermal and respiratory effects are generally related to the alkaline properties and are expected to be a general feature of the category. Structure-activity similarities for mammalian toxicity and structure-activity relationships (SAR) shown for aquatic toxicity endpoints lend support to the category.

Metabolic profile

In general, members of the Aliphatic Secondary Amines category can be considered to be comparable in metabolism. Metabolism of aliphatic secondary amines to aldehydes can be viewed as a bioactivation reaction since aldehydes are biologically reactive. However, DIPA is a known outlier for which some data are available to cover the endpoints. Due to structural differences, DIPA may be metabolized by different pathways (oxidized to acetone and either isopropylamine or N-hydroxy-isopropylamine) than the rest of the category.

Using the category approach, read across has been performed from the tested members to those without available data. Read-across approach has been used for addressing the mammalian toxicity and environmental endpoints where no data were available on individual substances (see below). Taking a precautionary approach, category members without toxicity or environmental fate data are regarded the same as the worst case read across approach. Specifically, where no toxicity data exist or are limited, category members will be considered irritating/corrosive, to be clastogenic in vitro, cause effects on male reproductive organs and parameters (except DPeA), or cause developmental toxicity (except DMA and DPeA).

Substance	Eye irritation	Skin sensitization	Repeated dose	In vitro mutagenicity[(1)]	In vivo mutagenicity	Effects on reproductive organs or fertility	Developmental toxicity

DMA	X	Read across	X	X	X	Read across	X
DEA	X	X	X	X	X	X	Read across
DPA	X	Read across	Read across	Read across (CA)	Read across	Read across	Read across
DIPA	X	X	X	X	Read across	X+Read across	Read across
DBA	X	X	X	X	X	X	X
DIBA	Read across	Read across	Read across	Read across (CA)	Read across	Read across	Read across
DPeA	Read across	X	X	X	Read across	X	X

X = data available; (1) Chromosome aberration = CA

Substance	**Acute aquatic toxicity**		
	Fish	Aquatic invertebrates	Aquatic plants
DMA	X	X	X
DEA	X	X	X
DPA	Read across	X	X
DIPA	X	X	X
DBA	X	X	X
DIBA	X	X	X
DPeA	X	X	X

Note that DPeA is a mixture of three isomers (CAS No 2050-92-2: 15-30%; CAS No 61361-18-0: 50-65%; and CAS No 27094-65-1: 10-25%). The reported physical-chemical properties tests were conducted with CAS No 2050-92-2. Human health and environmental toxicity testing was conducted with the mixed isomers, with the exception of the bacterial reverse mutation assay, for which the test substance could not be determined.

In some cases, the tested substance was the salts of amines to avoid damage to the gastrointestinal tract following gavage administration due to the caustic mode of action. Testing the salt also provides the ability to distinguish between symptoms caused by local effects such as irritation or corrosion and symptoms that are due to systemic toxicity as follows:

Substance	**Toxicokinetics**	***In vitro* chromosome aberration**	**Carcinogenicity**	**Developmental toxicity**
DMA	Tested as the hydrochloride (dimethylamine hydrochloride (CAS No. 506-59-2))	Tested as the hydrochloride (dimethylamine hydrochloride (CAS No. 506-59-2))	-	Tested as the hydrochloride (dimethylamine hydrochloride (CAS No. 506-59-2))
DEA	-	-	Tested as the hydrochloride (diethylamine hydrochloride (CAS No. 660-68-4))	-
DBA	-	-	-	Tested as the hydrochloride (dibutylamine hydrochloride, CAS No. 6287-40-7))
DPeA	-	-	-	Tested as the hydrochloride (diamylamine hydrochloride)*

*Repeated dose and reproductive endpoints also tested

Physical-chemical Properties

The substances are gases (**DMA** only) or liquids, with measured (or not specified) melting points that range from -92.2 °C (**DMA**) to -7.85°C (**DPeA**). The measured (or not specified) boiling points range from 7.0 °C (**DMA**) to 202.5 °C (DPeA). Measured (or not specified) vapor pressures range from 0.203 hPa at 25 °C (**DPeA**) to 1688 hPa at 20 °C (**DMA**). Water solubility correlates well with structure; longer chain functionalities result in lower water solubility values. Water solubility values range from miscible at 25 °C for **DMA** and **DEA** to 0.798 g/L for DPeA at 20 °C. Measured data on the log Kow are available for all members except **DPeA**; modeling was used to fill this endpoint. The log Kow values are <3 for the category members (except for **DPeA** = 3.61 - 3.76 for the three isomers; estimated; uncharged molecule). pH adjustment was not mentioned for the measured log Kow values (pH adjustment was mentioned for DMA). The pKa values are similar for the aliphatic secondary amines (protonated), with measured and estimated values between 10.73 and 11.16, but the neutral, or uncharged, aliphatic secondary amines have pKas ranging from 30 to 40.

Human Health

For those category members for which read-across is applied, the lowest effect value (for example, $LC(D)_{50}$ or N(L)OAEC/N(L)OAEL) is used, as well as overall toxicity for other endpoints. The attached Annex provides a summary of the read across values for mammalian toxicity.

Absorption and distribution of aliphatic secondary amines by the dermal, oral and inhalation routes is expected because they have low molecular weights and are both water and lipid soluble. The primary excretory pathway for the aliphatic secondary amines is expected to be urinary excretion based on data with **DMA**. Metabolism of aliphatic secondary amines to aldehydes can be viewed as a bioactivation reaction since aldehydes are biologically reactive. Due to structural differences, **DIPA** may be metabolized by different pathways (oxidized to acetone and either isopropylamine or N-hydroxy-isopropylamine).

Acute inhalation studies are available for all of the aliphatic secondary amines. Four hour vapor LC_{50} values (rat) ranged from 0.28 mg/L (**DPeA**; EPA OPP 81-3) to 17.3 mg/L (**DEA**; similar to OECD TG 403). Clinical signs and findings at gross necropsy were consistent with generally severe local effects of eye and respiratory irritation, respiratory distress and lung damage. Dermal LD_{50} values (rat or rabbit) are available for all of the aliphatic secondary amines. Dermal LD_{50} values ranged from 500 to 1000 mg/kg-bw (**DEA, DPA, DBA, DPeA**; no guideline specified or similar to OECD TG 402) to greater than 1000 (**DIBA**; no guideline specified) or 2000 mg/kg-bw (**DMA**; no guideline specified, and **DIPA**; similar to OECD TG 402). Severe skin necrosis at the site of application was noted in most studies. Similar results including severe skin necrosis would be expected for all substances based on structural similarities. Acute oral LD_{50} values (rat) ranged between 86 (**DPeA**) and 1000 mg/kg-bw (**DMA**) (both similar to OECD TG 401). Clinical signs generally included breathing abnormalities, oral-nasal wetness and/or staining, lethargy, effects on gait, poor condition, tremor/spasm, convulsions, eye closure, atonia and loss of coordination. Site of contact effects (irritation/corrosion) in the gastrointestinal tract were the most common finding noted at gross necropsy. Acute oral studies were not located for **DIPA** or **DIBA**.

All members of the aliphatic secondary amine category are corrosive to the skin (rabbits, primarily in Draize tests or similar to OECD TG 404). No eye irritation data are available for DIBA and DPeA. Based on the available data for the remaining category members (rabbit, no guideline specified or similar to OECD TG 405) and known eye irritation potential of alkyl amines in general, it is expected that all the amines in the category are corrosive to the eye. The aliphatic secondary amines are respiratory irritants in acute inhalation or respiratory irritation studies with rats.

There was no clear evidence of skin sensitization potential for four aliphatic secondary amines in a test with mice (similar to OECD TG 429) or in three guinea pig studies (similar to OECD TG 406). Data were not located for **DMA, DPA,** or **DIBA**, but these would not be expected to be skin sensitizers based on the existing data for other members of the category.

The inhalation or oral repeated dose toxicity has been studied for several of the Aliphatic Secondary Amines

category members; no reliable dermal repeated dose toxicity studies are available. Local and systemic LOAECs/NOAECs are determined for these studies, although the distinction is somewhat arbitrary given some of the severe effects observed on the respiratory tract. In 12-month inhalation toxicity studies in rats and mice using **DMA** (no guideline specified), local NOAECs were not established and the local LOAECs were 0.018 mg/L in both rats and mice, based on significant concentration-related lesions in the nasal passages progressing from inflammation to metaplasia, hyperplasia and necrosis in some cases; male and female mice also exhibited decreased body weights. The systemic NOAEC for rats in this study is 0.092 mg/L based on biologically-relevant decreases in body weight at the highest concentration (0.32 mg/L). Changes in hematology and clinical chemistry were also seen at this concentration (although it is not clear whether the effects were seen at 6 or 12 months). Significant non-treatment related mortality in mice precluded setting a systemic NOAEC and LOAEC for mice. For **DEA**, effects on the respiratory tract were observed in a 3-month inhalation study in rats and mice (similar to OECD TG 413) at concentrations of 0.096 mg/L and higher, resulting in a local NOAEC of 0.048 mg/L. In this study, **DEA** also exacerbated clonic seizures of the individually-housed rats (apparently at concentrations of 0.096 mg/L and higher, but data are limited to determine the exact concentrations). In this study, sperm motility was decreased in both rats and mice at 0.096 mg/L and higher, resulting in a systemic NOAEC of 0.048 mg/L for both species. Rats exposed to **DIPA** by inhalation for one month exhibited nasal and corneal lesions and decreased lymphocyte counts at all concentrations, resulting in local and systemic LOAECs at the lowest concentration of 0.1 mg/L. In a 3-month study designed to evaluate respiratory and reproductive effects (no guideline specified), rats exposed to **DBA** for 90 days exhibited nasal lesions and decreased body weights primarily at 0.142 mg/L and higher. A NOAEC for systemic effects could not be determined because the study focused only on the respiratory and reproductive tracts. The LOAEC for local irritation of the upper respiratory tract (nasal cavities) was 0.051 mg/L. In a combined repeated-dose reproduction/developmental toxicity study (OECD TG 422) with **DPeA**, male rats were dosed orally (by gavage) for 32 days including two weeks premating; females were dosed during premating, after the mating period, and during gestation and lactation. The oral NOAEL for **DPeA** was 4 mg/kg bw/day based on signs of aggression at 13 mg/kg bw/day and higher; tremors and piloerection were seen at 40 mg/kg bw/day.

The aliphatic secondary amines were not mutagenic *in vitro* in bacterial reverse mutation (similar to OECD TG 471) using S. *typhimurium*, and mammalian cell assays (mutation at the HGPRT locus of Chinese Hamster Ovary cells (CHO), OECD TG 476). *In vitro*, **DMA** was marginal for chromosomal aberrations with metabolic activation (no guideline), and in a second study did not induce chromosomal aberrations (as DMA-HCl; no guideline). However, the study using **DMA-HCl** did not evaluate conditions with metabolic activation and therefore it is not known whether **DMA-HCl** would induce chromosomal aberrations in the presence of activation. Thus, the positive result from the **DMA** study suggests **DMA** may induce chrosomal aberrations. DIPA did not induce chromosomal aberrations in human lymphocytes in the presence or absence of metabolic activation (guideline not specified). **DBA** was marginal for chromosomal aberrations *in vitro* (CHO, similar to OECD TG 473); this test was conducted only without metabolic activation. DPeA induced chromosomal aberrations *in vitro* (Chinese hamster lung fibroblasts (V79), OECD TG 473) in the presence of metabolic activation. In an *in vivo* chromosome aberration study in rats exposed to **DMA** by inhalation for 90 days (no guideline specified) the incidence of cells with chromosomal breakage did not exceed controls and the incidence of aneuploid cells was significantly higher compared to controls. An *in vivo* micronucleus assay in mice exposed to **DEA** via inhalation (similar to OECD TG 474) and an *in vivo* micronucleus assay in mice exposed orally to **DBA** (OECD TG 475) were both negative.

Two-year inhalation carcinogenicity studies with **DMA** or **DEA** at concentrations up to 0.32 or 0.37 mg/L, respectively, in rats (OECD TG 451 or similar), and with **DEA** at concentrations up to 0.19 mg/L in mice (OECD TG 451) were negative. A 30-month study, in which guinea pigs were exposed to 4000 mg/L **DEA HCl** in drinking water (no guideline specified), was also negative for carcinogenicity.

An increase in relative testis weight and reduced sperm motility were observed in male rats and mice exposed to **DEA** via inhalation for 90 days at 0.096 mg/L or greater in a study similar to OECD TG 413; male mice exhibited increased testes weights at 0.37 mg/L.. Rats exposed to **DIPA** via inhalation for one month exhibited atrophy and decreased secretion of seminal vesicles, and increased relative testes weights at 2.0 mg/L, a dose also associated with a variety of corrosive and other significant effects. Test substance-related microscopic changes were not observed in the reproductive organs of either males or female rats exposed by inhalation for

91 days to **DBA** concentrations up to 0.448 mg/L (highest concentration tested) in a study similar to OECD TG 413. In an OECD TG 422 study with **DPeA** administered via gavage, there was no effect on reproductive performance of male and female rats, including mating index, gestation index, mean number of implantation sites, post-implantation loss, mean number of pups, or live birth index at doses up to 40 mg/kg-bw (highest dose tested), when exposed for 32 days (males) or, during premating, after mating period, during gestation and lactation (females).

Developmental effects were not observed in an OECD TG 414 with pregnant rats exposed by oral (gavage) to **DMA HCl** at doses up to 1000 mg/kg-bw on GD 6 through GD 19; the NOAEL (developmental toxicity) was 1000 mg/kg bw/day as there was no evidence of an adverse effect on fetal morphology. In an OECD TG 414 study, pregnant Wistar rats were administered **DBA HCl** by oral (gavage) on GD 6 - 19 at doses up to 150 mg/kg bw/day. The NOAEL for maternal toxicity is 15 mg/kg bw/d based on clinical pathological effects at dose levels of 50 mg/kg bw/d and above. At 150 mg/kg bw/day, there was a statistically significant reduction in mean number and mean percent viable male foetuses ($p < 0.05$). Although not statistically significant, post-implantation loss showed a dose-response relationship in this study, with 4.9%, 7.1%, 7.8% and 9.0% in controls, 15, 50 and 150 mg/kg bw/day, respectively. The NOAEL for developmental toxicity is 50 mg/kg-bw/day based on reduced mean number and percent of viable foetuses. In a study conducted according to OECD TG 422, Wistar rats were administered **DPeA** by oral (gavage) at doses up to 40 mg/kg bw/day; substance related effects were not observed and the NOAEL for developmental/teratogenic effects was 40 mg/kg bw, the highest dose tested.

The Aliphatic Secondary Amines category members possess properties indicating a hazard for human health (acute toxicity, irritating/corrosive properties, genotoxicity (chromosomal aberrations), repeated-dose toxicity, effects related to male reproductive toxicity except for DPeA, developmental toxicity in the presence of maternal toxicity for category members except DMA and DPeA). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Environment

The aliphatic secondary amines are not expected to undergo hydrolysis under environmental conditions. The substances lack functional groups where this process would be relevant. OECD TG 111 studies have not been conducted for the aliphatic secondary amines. In water solution, all of the simple alkyl amines share the property of forming ammonium ions. This is due to the ability of the free electron pair on the amine nitrogen to pick up a proton from water and form a hydroxide ion raising the solution pH. Estimated pKa values of >10.5 indicate that the aliphatic secondary amines will exist primarily as cations in the environment (relevant pH 5.0 – 9.0). However, the EPIWIN modeling program predicts environmental fate endpoints for aliphatic secondary amines in their uncharged form.

In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of <1 day. For the aliphatic secondary amines, EPIWIN Level III fugacity modeling predicts that, when distributed equally to air, water and soil, the aliphatic secondary amines will partition to water and soil with negligible distribution to air and sediment. The substances will partition with higher relative distributions to soil compared to water and this tendency increases proportionally with molecular weight of the aliphatic secondary amine.

Biodegradation data are available for all chemicals in this category. DPeA was tested as a mixture. With the exception of DIPA, these single chemicals are readily biodegradable (OECD TG 301). In an OECD TG 301D, **DIPA** degraded 11% BOD after 28 days (not readily biodegradable).

Predicted BCF values, from BCFBAF Program v3.01 in EPIWIN v4.10, range from 3.16 to 139.7 indicating that they have low bioconcentration potential and are not expected to be bioaccumulative.

The following acute aquatic toxicity test results using buffered/unbuffered conditions have been determined for the aliphatic secondary amines (key and supporting studies are presented; the supporting studies are used to illustrate pH effects). “Estimated” values are based on modelling using the ECOSAR Program (v1.00; ECOSAR Class used was Aliphatic Amines; all predicted values fall within the applicability domain).

Fish:

Substance	Species	LC50 (96 hr; mg/L)	Remark (measured/nominal; pH adjusted)	Estimated values (ECOSAR 1.0) (96 hr, mg/L)
DMA	*Oncorhynchus mykiss*	118 17	not specified; hard water not specified; soft water	161
	Poecilia reticulate	210	not specified; pH not specified	
	Oncorhynchus mykiss	120 20	not specified; hard water not specified; soft water	
DEA	*Oryzias latipes*	27	Measured; pH not specified	66.8
	Oncorhynchus mykiss	182 25	not specified; hard water not specified; soft water	
	Pimephales promelas	855	nominal; pH adjusted	
	Poecilia reticulate	130	nominal; pH not specified	
DPA	Read across to DEA and DBA 27 – 855 (hard water or unspecified); 5.5 – 25 (soft water)			23.7
DIPA	*Leuciscus idus*	26 >100	nominal, not pH adjusted nominal, pH adjusted	29.1
	Oncorhynchus mykiss	196 37	not specified; hard water not specified; soft water	
	Salmo gairdneri	42	not specified; pH not specified	
	Lepomis macrochirus	75	not specified; pH not specified	
	Pimephales promelas	40	not specified; pH not specified	
	Gasterosteus aculeatus	798	measured; pH not specified	
DBA	*Oncorhynchus mykiss*	37 5.5	not specified; hard water not specified; soft water	7.8
DIBA	*Leuciscus idus*	26 >100	nominal, not pH adjusted nominal, pH adjusted	9.5
DPeA	*Oncorhynchus mykiss*	3.9 mg/L	measured, not pH adjusted	2.4

Aquatic invertebrates:

Substance	Species	EC50 (48 hr; mg/L)	Remark (measured/nominal; pH adjusted)	Estimated values (ECOSAR 1.0) (48 hr, mg/L)
DMA	*Daphnia magna*	88.7	nominal; not pH adjusted	10.3
	Daphnia magna	50	not specified; pH not specified	
DEA	*Ceriodaphnia dubia*	4.6	measured; pH not specified	5.3

	Daphnia magna	56	nominal; pH not specified	
	Daphnia magna	58	measured; pH not specified	
	Daphnia magna	100	not specified; pH not specified	
DPA	*Daphnia magna*	73.34	nominal; not pH adjusted	2.3
DIPA	*Daphnia magna*	110	not specified; pH not specified	2.7
	Daphnia magna	24 hour LC50 = 187	not specified; pH not specified	
DBA	*Ceriodaphnia dubia*	8.4	measured; pH not specified	0.9
	Daphnia magna	65.98	nominal; not pH adjusted	
DIBA	*Daphnia magna*	>71	measured; pH not specified	1.1
	Daphnia magna	35	not specified; pH not specified	
DPeA	*Daphnia magna*	23	measured; not pH adjusted	0.4

Algae:

Substance	Species	EC50 (72 hr; mg/L)	Remark (endpoint; measured/nominal; pH adjusted)	Estimated values (ECOSAR 1.0) (96 hr, mg/L)
DMA	*Pseudokirchneriella subcapitata*	96 hr EC_{50} = 9	growth rate; pH not specified	2.2
	Chlorella pyrenoidosa	96 hr EC_{50} = 30	biomass; not specified; pH not specified	
	Pseudokirchneriella subcapitata/	6.2	growth; not specified; pH not specified	
DEA	*Pseudokirchneriella subcapitata*	54	growth rate; measured, pH not specified	1.5
	Pseudokirchneriella subcapitata	96 hr EC_{50} = 20	growth; not specified; pH not specified	
	Chlorella pyrenoidosa	96 hr EC_{50} = 56	growth; not specified; pH not specified	
	Scenedesmus sp.	96 hr TTC = 4	not specified; pH not specified	
DPA	*Desmodesmus subspicatus*	11.8	growth rate; nominal; not pH adjusted	0.9
DIPA	*Selenastrum sp*.	96 hr EC_{50} = 20	not specified; pH not specified	1.04
DBA	*Desmodesmus subspicatus*	16.91 9.43	growth rate; nominal; not pH adjusted biomass; nominal; not pH adjusted	0.5
	Desmodesmus subspicatus	42.55 5.14	growth rate; nominal; not pH adjusted biomass; nominal; not pH adjusted	
	Desmodesmus	16.19	growth rate; nominal; not pH adjusted	

	subspicatus	7.17	biomass; nominal; not pH adjusted	
	Pseudokirchneriella subcapitata	96 hr EC_{50} = 19	not specified; pH not specified	
DIBA	*Pseudokirchneriella subcapitata*	48 hr EC_{50} = 16	growth rate; nominal; pH 7	0.58
DPeA	*Selenastrum capricornutum*	1.7	growth rate; measured; not pH adjusted	0.27

The following chronic toxicity test results have been determined:

Fish

Substance	**Species**	**Result (mg/L)**	**Remark** measured/nominal; pH adjusted
DMA	*Oncorhynchus mykiss*	30 d NOEC = 20 (juvenile) 50 d NOEC = 0.6 (egg fry)	No details specified
DIPA	*Gasterosteus aculeatus*	35 d NOEC (mortality and sublethal effects; growth excluded) = 187 35 d NOEC (embryonic stage) = 582	measured measured

Aquatic invertebrates

Substance	**Species**	**Result (mg/L)**	**Remark** measured/nominal; pH adjusted
DEA	*Daphnia magna*	21 day NOEC = 4.2	measured; pH not specified

The Aliphatic Secondary Amines possess properties indicating a hazard for the environment (acute aquatic toxicity values > 1 and ≤ 100 mg/L). With the exception of DIPA, the aliphatic secondary amines are readily biodegradable, and are not expected to be bioaccumulative. 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 production volumes for the sponsor country (US) for (2006) were obtained from Inventory Update Reporting.

Substance	**Production Volume (tonnes)**
DMA	45,359 - <226,796
DEA	4536 - < 22,680
DPA	4536 - < 22,680
DIPA	< 227
DBA	4536 - < 22,680
DIBA	No data reported
DPeA	227 – <907

DMA, DEA, DPA, DIPA, **DBA** and **DIBA** are used for the synthesis of other chemical substances; they are

consumed in reactions and no longer retain their chemical identities. **DMA, DPA, DBA, DIBA** and **DPeA** are used as solvents in industrial gas manufacturing and other chemical product and preparation manufacturing. **DEA** is used as a processing aid in rubber production; it is consumed in reactions and no longer retains its chemical identity. **DMA**, **DPA, DBA**, **DIBA** and **DPeA** are used in commercial or consumer soaps and detergents.

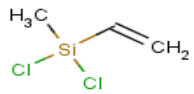
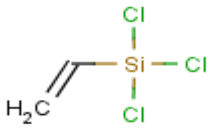
The most likely route of human occupational exposure is either via dermal contact or inhalation; most of these materials are highly irritating or corrosive to the skin and are respiratory irritants and adequate protective equipment is required if any splash hazard is present. Examples of potential occupational exposure scenarios include sampling for quality control, line breaks, pack-out after manufacturing, and charging reactor vessels for downstream users. **Consumer e**xposure is intended when the category members are used in soaps and detergents. During manufacturing, **DMA** and **DPeA** are vented to the atmosphere through a flare, and aqueous waste streams are biologically treated before being discharged to surface water. Downstream environmental releases of all category members may occur through fugitive air emissions. **DMA, DPA, DBA, DIBA and DPeA** may be released through on-site land disposal. Distribution of **DEA** and **DIPA** to wastewater is expected to be moderate. No monitoring data are available.

ANNEX
Summary of Mammalian Toxicity Data Read Across Approach
(Oral = mg/kg bw/day; Inhalation = mg/L)

Substance	Acute toxicity (inhalation and oral)	Repeated dose (oral)	Repeated dose (inhalation) *	Gene mutation in vitro	Chromosome aberration in vitro	Chromosome aberration in vivo	Effects on fertility (oral) and reproductive organs (inhalation)	Developmental toxicity (oral)
DMA	**LC50 inh = 9.9 (60 min)** **LD50 oral = 1000**	NOAEL = 4 (RA)	**LOAEC (local) = 0.018** **NOAEC (systemic) = 0.092**	**Negative**	**Positive/ Marginal (weight of evidence)**	**Positive**	NOAEL oral = 40 (RA) Dec. sperm motility (inh) >0.096 (RA)	**NOAEL = 1000**
DEA	**LC50 inh = 17.3 mg/l** **LD50 oral = 540**	NOAEL = 4 (RA)	**NOAEC (local) = 0.048** **NOAEC (systemic) = 0.048**	**Negative**	Positive (RA)	**Negative**	NOAEL oral = 40 (RA) **Dec. sperm motility (inh) >0.096**	NOAEL = 50 (RA)
DPA	**LC50 inh > 8.22 (60 min)** **LD50 oral = 495 and 933**	NOAEL = 4 (RA)	LOAEC (local) = 0.018 (RA) NOAEC (systemic) = 0.048 (RA)	**Negative**	Positive (RA)	Positive (RA)	NOAEL oral = 40 (RA) Dec. sperm motility(inh) >0.096 (RA)	NOAEL = 50 (RA)
DIPA	**LC50 inh = 5.35** LD50 oral = 86 (RA)	NOAEL = 4 (RA)	**LOAEC(local) = 0.1** **LOAEC (systemic) = 0.1**	**Negative**	**Negative**	Positive (RA)	NOAEL oral = 40 (RA) **NOAEC=0.6 (inh)** Dec. sperm motility (inh) >0.096 (RA)	NOAEL = 50 (RA)
DBA	**LC50 inh = 1.15 mg/l** **LD50 oral = 550 mg/kg bw**	NOAEL = 4 (RA)	**NOAEC (local) = 0.142** NOAEC (systemic) = 0.048 (RA)	**Negative**	**Positive/ Marginal**	**Negative**	NOAEL oral = 40 (RA) Dec. sperm motility (inh) >0.096 (RA)	NOAEL = 50 (RA)
DIBA	**LC50 inh > 2.6 mg/l** LD50 oral = 86 (RA)	NOAEL = 4 (RA)	LOAEC (local) = 0.018 (RA) NOAEC (systemic) = 0.048 (RA)	**Negative**	Positive (RA)	Positive (RA)	NOAEL oral = 40 (RA) Dec. sperm motility (inh) >0.096 (RA)	NOAEL = 50 (RA)
DPeA	**LC50 inh = 0.238** **LD50 oral = 86**	**NOAEL = 4**	LOAEC (local) = 0.018 (RA) NOAEC (systemic) = 0.048 (RA)	**Negative**	**Positive**	Positive (RA)	**NOAEL oral = 40 [maximum tolerated dose]**	**NOAEL oral = 40**

*Subchronic and chronic studies
RA=Read Across

SIDS INITIAL ASSESSMENT PROFILE

Category Name	Vinyl Chlorosilanes
CAS No(s).	124-70-9 75-94-5
Chemical Name(s)	Dichloromethyl(vinyl)silane (**VDCS**) Trichlorovinylsilane (**VTCS**)
Structural Formula(s)	 **VDCS**  **VTCS**

SUMMARY CONCLUSIONS OF THE SIAR

Analogue/Category Rationale

Chlorosilanes react rapidly when exposed to moisture or polar reagents, producing hydrogen chloride (HCl; CAS No. 7647-01-0) and the corresponding silanols (in general, siloxane oligomers and polymers). For the two vinyl chlorosilanes in the category, the half-lives are expected to be <1 minute based on data from two analogous substances, dimethyldichlorosilane (DMDCS; CAS No. 75-78-5) and methyltrichlorosilane (MTCS; CAS No. 75-79-6).

The silanols expected to be produced following vinyl chlorosilane hydrolysis are vinylmethylsilanediol, CAS No 3959-12-4 (from **VDCS**) and vinylsilanetriol, CAS No 143-48-6 (from **VTCS**). The silanols can condense spontaneously to form highly cross-linked polymeric gels in uncontrolled environments. Because of these properties, they cannot be readily isolated without spontaneously forming highly cross-linked polymeric gels in uncontrolled environments and as such cannot be tested.

VDCS hydrolyzes to form two moles of HCl and one mole of vinylmethylsilanediol, whereas **VTCS** forms three moles of HCl and one mole of vinylsilanetriol. The category is supported by (1) similar structures of category members, (2) the common hydrolysis product HCl and (3) similarities in physical-chemical properties of the silanol products (high water solubility and low log K_{ow}).

Hydrolysis Analogues. It is appropriate to use other chlorosilane data to estimate hydrolysis of the sponsored substances. As noted above, analogues used for hydrolysis are DMDCS and MTCS.

Human Health and Aquatic Toxicity Analogues. Trimethoxyvinylsilane (VTMS; CAS No. 2768-02-7) hydrolyzes at pH 4, 7 and 9 with $t_{1/2} \leq$10 minutes, < 2.4 hours and <10 minutes, respectively. The final products of hydrolysis are expected to be methanol and vinylsilanetriol; toxicity due to hydrolysis to methanol is expected to be negligible.

In aqueous environments, exposures to VTMS are likely to be transient and observed toxicity is likely due primarily to the hydrolysis products methanol, vinylsilanetriol, and condensed silanetriol materials (high molecular weight polymers). Because one of the sponsored substances (**VTCS**) has the same expected product (vinylsilanetriol) as VTMS and due to similarities between this product and vinylmethylsilanediol, the analogue VTMS can be used as a supporting substance for the vinyl chlorosilanes. Due to rapid hydrolysis of the vinyl chlorosilanes and expected corrosive effects of one of the products (HCl), the data for HCl are also presented for a complete consideration of the toxicity of hydrolysis products for both human health and aquatic toxicity endpoints. No test data are available for short-term toxicity of **VDCS** to aquatic organisms. Reliable data are available for the read-across substance, dimethylsilanediol (DMSD, CAS 1066-42-8). DMSD is a close structural analogue of vinylmethylsilanediol. Read-across from DMSD to vinylmethylsilanediol is appropriate because both are small molecule alkylsilanols whose properties are dominated by presence of the silanediol group.

HCl, VTMS, DMDCS, and MTCS have been previously presented and agreed in the OECD programme; DMSD has been previously used as an analogue, most recently for chloroalkylchlorosilanes at CoCAM 3. These data can be found at http://www.oecd.org/env/hazard/data.

Read Across Strategy

	Environmental fate		**Mammalian toxicity**			**Environmental effects**
Substance	**Hydrolysis**	**Biodegradation**	**Skin, Eye, Resp. tract (RT) irritation**	**Repeated dose toxicity, Reproductive toxicity**	**Genetic toxicity (chromosome aberration)**	**Aquatic toxicity to Fish, Daphnid and Algae**
VDCS	DMDCS	X	**VTCS** (RT)	VTMS, HCl	X, HCl, VTMS	VTMS, DMSD, HCl
VTCS	MTCS	**VDCS**; VTMS	HCl (skin, eye, RT)		X, HCl, VTMS	VTMS, HCl

X= data available

Physical-chemical Properties

The sponsored substances are liquids with a measured melting point of -95 °C, measured boiling points of 91.4 °C (**VTCS**) to 93.8 °C (**VDCS**), and vapour pressures of 58.75 hPa (**VDCS**, extrapolated) to 87.99 hPa (**VTCS**, extrapolated). The calculated octanol-water partition coefficients (log K_{ow}) are 2.4 (**VTCS**) and 2.6 (**VDCS**), and the calculated water solubilities are 802.3 (**VDCS**) and 1338 (**VTCS**) mg/L at 25 °C. The calculated water solubility and log Kow values may not be relevant because the substances are hydrolytically unstable.

Human Health

No data are available on the toxicokinetics, metabolism and distribution of the vinyl chlorosilanes. However,

these substances are expected to rapidly hydrolyze on contact with moisture. Although the silanol hydrolysis products are not expected to be absorbed across the skin or respiratory epithelium,damage to membranes caused by HCl's corrosivity might enhance the uptake of the sponsored substances or the silanol hydrolysis products. The hydrophilic nature of the silanol hydrolysis products is expected to limit diffusion across membranes and accumulation in fatty tissues. Hydrogen and chloride ions will enter the body's natural homeostatic processes. HCl will rapidly dissociate and its effects are thought to be a result of pH change (local deposition of H^+). The low molecular weight and water solubility of the silanols suggest elimination via the kidneys in urine.

The acute inhalation toxicity of the vinyl chlorosilanes is well characterized, and is expected to result from HCl exposure. The 1-hour nominal acute inhalation LC_{50} for **VDCS** in rats was > 8.61 mg/L and $\leq$ 9.61 mg/L. For **VTCS**, the 4-hour value in rats is < 0.73 mg/L, and the 1-hour values in rats were 10.63 and 13.13 mg/L (both nominal values). Clinical signs and necropsy findings for animals that died during the study reflected the corrosive nature of the test substance. Inhalation LC_{50} values for HCl were determined to be 4.2-4.7 mg/L for 1 hour for rats. The dermal LD_{50} of **VTCS** in rabbits was ca. 864 mg/kg bw; dermal toxicity data were not located for **VDCS**. The oral LD_{50}s in rats were between 200 and 2000 mg/kg (**VDCS**) and 1280 mg/kg (**VTCS**); corrosive effects were observed in the gastrointestinal tract (site of contact). The acute oral LD_{50} values of HCl were determined to be 238-277 mg/kg bw for female rats.

Based on results from HCl the sponsored substances are considered corrosive to the skin and eyes. Vinyl chlorosilanes are considered respiratory tract irritants based on data from acute inhalation toxicity studies with HCl and the sponsored substances

No data are available to evaluate the sensitisation of vinyl chlorosilanes.

Data from the supporting substance VTMS and the hydrolysis product HCl are used to fill the repeated-dose toxicity endpoint for the vinyl chlorosilanes. Systemic effects following repeated inhalation of VTMS (exposure likely as a mixture with silanol hydrolysis products) and HCl have been observed. In a repeated-dose toxicity study [TG unknown], rats (20/sex/concentration) were exposed for six hours per day, five days per week, for 14 weeks to vapor of VTMS at concentrations of 0, 0.06, 0.6 or 2.4 mg/L, respectively, resulting in effects primarily on the urinary bladder and kidney. The LOAEC was determined to be 0.6 mg/L and the NOAEC was 0.06 mg/L. During 90-day repeated dose inhalation toxicity studies, local effects of HCl irritation were observed in groups exposed to 0.015 mg/L and above. The NOAEC for systemic toxicity for HCl, excluding the local effects of irritation, has been determined to be 0.030 mg/L for rats and mice. Based on these data, the vinyl chlorosilanes may result in repeated dose inhalation toxicity, with an NOAEC of 0.60 mg/L (HCl) for both category members.

In a combined repeated-dose/reproductive/developmental toxicity screening test [OECD TG 422], male and female rats were administered VTMS via gavage at 62.5, 250 and 1000 mg/kg bw/day for up to 43 days, resulting in effects primarily on the urinary bladder, intestine, kidney, and thymus in both sexes at all doses. The NOAEL was not established in this study. The LOAEL was 62.5 mg/kg bw/day (decreased urine osmolality and sodium, potassium and chloride concentrations (males) and slight decrease in body weight and body weight gain (females)). Similar effects are expected for the vinyl chlorosilane category members. Based on these data, the vinyl chlorosilanes may result in repeated dose oral toxicity, with a LOAEL of 62.5 mg/kg bw (VTMS) for both category members.

VTCS did not induce gene mutations in two bacterial mutagenicity assays (OECD TG 471). **VDCS** is considered mutagenic in *Salmonella* strain TA 1535 in the presence of hamster microsomal enzyme with metabolic activation (reducing conditions) (OECD TG 471) and was negative in the presence and absence of rat liver S9 metabolic activation (OECD TG 471), negative in the mouse lymphoma assay (OECD TG 476) and negative for the induction of chromosome aberrations in mammalian cells (OECD 473). The hydrolysis product, HCl, did not induce gene mutations in bacteria. Positive results in the *in vitro* chromosome aberration test with HCl were considered to be the effect of low pH. **VTMS** was negative in a reliable and valid *in vivo* micronucleus assay (OECD TG 474).

The weight of evidence suggests that the Vinyl Chlorosilanes may not be genotoxic. However, the positive finding in one bacterial strain under reducing conditions leaves a residual uncertainity for gene mutation potential.

No data are available for the carcinogenicity of the vinyl chlorosilanes.

No data are available on the reproductive toxicity of the vinyl chlorosilanes; data are available for the supporting substance, VTMS and the hydrolysis product, HCl. In the combined repeated-dose/reproductive/developmental toxicity screening test [OECD TG 422], there were no effects on reproductive performance of parental rats when VTMS was administered by oral gavage. The NOAEL was 1000 mg/kg bw/day for males, and 250 mg/kg bw/day for females (based on a reduced number of estrous cases). There were no effects on developmental parameters; the NOAEL for developmental effects was 1000 mg/kg bw.

Exposure of pregnant rats to VTMS by inhalation including 14 days pre-mating through lactation day 4 resulted in a NOAEC of 0.15 mg/L for maternal toxicity. There was evidence of slightly delayed skeletal ossification in fetuses from the 1.8 mg/L group; the NOAEC for developmental effects was 0.60 mg/L. No reliable studies have been reported regarding toxicity to reproduction and development in animals after oral, dermal or inhalation exposure to hydrogen chloride/hydrochloric acid. Because the proton (H^+) and chloride (Cl^-) ions are the normal constituents in the body fluid of animal species, lower concentration of hydrogen chloride gas/mist or solution does not seem to cause adverse effects to animals. In fact, the cells of gastric glands secrete hydrochloric acid into the cavity of stomach and orally administered sulfuric acid, which result in pH change as well, did not cause developmental toxicity to laboratory animals. These facts indicate that hydrogen chloride/hydrochloric acid is not expected to have developmental toxicity. In addition, no effects on the gonads were observed in a 90-day inhalation repeated-dose study with HCl up to concentrations of 0.073 mg/L. Based on these data, the vinyl chlorosilanes may result in developmental toxicity at high concentrations in inhalation studies, with a NOAEC of 0.60 mg/L (VTMS) for both category members.

The vinyl chlorosilanes possess properties indicating a hazard for human health (lethality from acute studies (inhalation, oral, and dermal); corrosivity and severe irritation to the skin, eyes, respiratory tract, and GI tract; repeated dose toxicity, potential *in vitro* gene mutation; developmental toxicity (only at high concentrations via inhalation at maternally toxic concentrations). 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 module, found in the current version of EPI Suite (v4.10), may improve estimates for silanes and siloxanes for this endpoint. However, there is still uncertainty associated with the calculated values and they should be used with caution whenever they are reported.

The chlorine group is the most active functional group of these molecules and determines many aspects of the behaviour of the category members. The vinyl chlorosilanes are expected to undergo rapid hydrolysis in the presence of water to form two or three moles of HCl and one mole of silanediol or silanetriol, depending on the parent substance. Hydrolysis is the primary reaction in aqueous systems. Hydrolysis studies were not conducted on the vinyl chlorosilanes. The vinyl chlorosilanes hydrolyze rapidly; the half-lives are expected to be <1 minute based on data from two analogous substances, DMDCS and MTCS. Observed rates of hydrolysis were so rapid that it was not possible to distinguish among the different pH conditions.

The overall rate constants for reaction with OH radicals in the atmosphere for the vinyl chlorosilanes and resulting half-lives due to indirect photolysis are ca. 26 x 10^{12} cm^3/molecule-sec and 5 hours for the category members. Any potential for photodegradation might be superseded by hydrolysis of the parent compound depending on the concentration of water vapor in the air. The sponsored substance, **VDCS**, was not readily biodegradable in an OECD TG 301A test and the supporting substance VTMS was not readily biodegradable in an OECD TG 301F test. Based on this information, the sponsored substance, **VTCS**, is not expected to be readily biodegradable. Due to rapid hydrolysis of the sponsored and supporting substances, any potential for biodegradation is likely to be of the hydrolysis products. Consequently, the only biodegradable materials in the test system will be silanols, and condensed silanol materials (high molecular weight polymers). At high concentrations, the silanols will condense to form highly cross-linked, high molecular weight polymers that are water insoluble and effectively nonbiodegradable.

A level III fugacity model calculation with equal and continuous distributions to air, water and soil

compartments suggests that the vinyl chlorosilanes will distribute mainly to the air (ca. 48 %) and soil (ca. 47%) compartments, with minor distribution to water (ca. 5%) and negligible distribution to sediments (<0.1). Since the parent materials are not expected to be released to soil or water based on their uses and handling, a scenario of 100% emission to air is more realistic. When the vinyl chlorosilanes are released to air exclusively, the fugacity model predicts that 99.8% is reacted. The unreacted 0.2% remains in air (100%). The modeling results show that the environmental fate of the vinyl chlorosilanes is controlled by their high reactivity with water in all compartments. Level III fugacity modeling using equal loading rates of 1000 kg/h each for air, soil and water predicts that the hydrolysis products will distribute mainly to soil (c. 70-80 %), with a smaller fraction to water (ca. 20-27 %) and negligible amounts to sediment and air. Based on the more realistic scenario of 100% release to air, the model predicts that vinylmethylsilanediol and vinylsilanetriol will be distributed mainly in soil (ca. 93%) and water (ca. 7%). Fugacity modeling of HCl is not applicable. The calculated Henry's law constants for both vinyl chlorosilanes are not applicable due to their rapid hydrolysis.

The bioaccumulation potential of the vinyl chlorosilanes was not measured due to rapid hydrolysis. The estimated BCFs using the BCFBAF Program (v3.01) are 16.8 L/kg wet-wt for **VTCS** and 24.1 L/kg wet-wt for **VDCS**, indicating the vinyl chlorosilanes are not expected to bioaccumulate. For both the hydrolysis products, the estimated BCF is 3.2 L/kg wet-wt.

Acute aquatic toxicity data are not available for vinyl chlorosilanes. The vinyl chlorosilanes undergo rapid hydrolysis, which would occur during testing; therefore, exposure to parent chlorosilane is likely to be transient and observed toxicity would likely be due to its hydrolysis products, HCl and the respective silanol hydrolysis products. Data are available for the supporting substance, VTMS and the silanol, DMSD.

Fish

VTMS [*Brachydanio rerio*]	96 h LC50 >100 mg/L (nominal) [static]
DMSD [*Oncorhynchus mykiss*]	96 h LC50 >120 mg/L (measured) [static]
HCl [*Cyprinus carpio*]	96 h LC50 = 4.92 mg/L (pH 4.3) (measured; pH) [semi-static]

Invertebrate

VTMS [*Daphnia magna*]	48 h EC50 = 168.7 mg/L (nominal) [static]
DMSD [*Daphnia magna*]	48 h EC50 >117 mg/L (measured) [static]
HCl [*Daphnia magna*]	48 h EC50 = 0.492 mg/L (pH 5.3) (measured; pH) [semi-static]

Algae

VTMS [*Scenedesmus subspicatus*]	72 h ErC50; EbC50 >100 mg/L (nominal)
DMSD [*Pseudokirchneriella subcapitata*]	72 h ErC50, EbC50 > 118 mg/L (measured) [static]
HCl [Selenastrum capricornutum]	72 h ErC50 = 0.492 mg/L (pH 5.3) [static](measured; pH)

The hazard of hydrochloric acid for the environment is caused by the proton (pH) effect. For this reason the effect of hydrogen chloride on the organisms depends on the buffer capacity of the aquatic ecosystem. Also the variation in acute toxicity for aquatic organisms can be explained to a significant extent by the variation in buffer capacity of the test medium. For example, LC50 values of acute fish toxicity tests varied from 4.92 to 282 mg/L. The toxicity values to *Selenastrum capricornutum* 72h-EC50 is 0.780 mg/L at pH 5.1 for biomass, 0.492 mg/L at pH 5.3 for growth rate, and the 72h-NOEC is 0.097 mg/L at pH 6.0 for biomass and growth rate. The 48h-EC50 for *Daphnia magna* is 0.492 mg/L at pH 5.3 based on immobilization.

Based on the properties of the hydrolysis product, HCl, the vinyl chlorosilanes possess properties

indicating a hazard for the environment (acute toxicity to fish between 1 and 100 mg/L, acute toxicity to aquatic invertebrates and toxicity to algae < 1 mg/L). Toxic effects are expected primarily from the hydrolysis products (in particular hydrogen chloride, and depend on the buffering capacity of a particular aquatic environment. Therefore, the stated effect levels pertain to unbuffered systems and can be viewed as conservative). The vinyl chlorosilanes and their hydrolysis products are not expected to be readily biodegradable or 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

The estimated annual production volumes for the category members are:

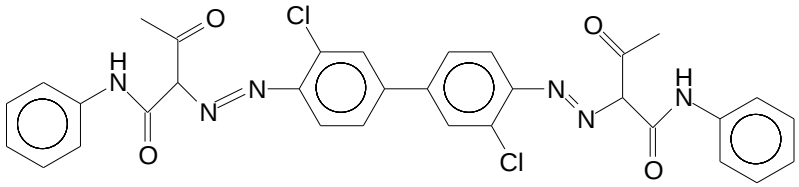
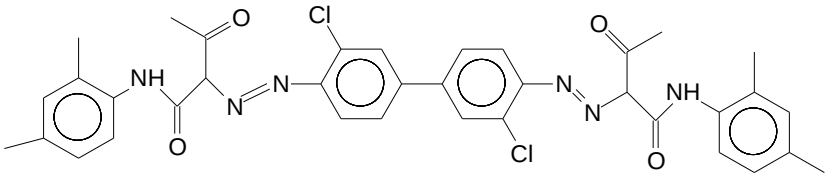
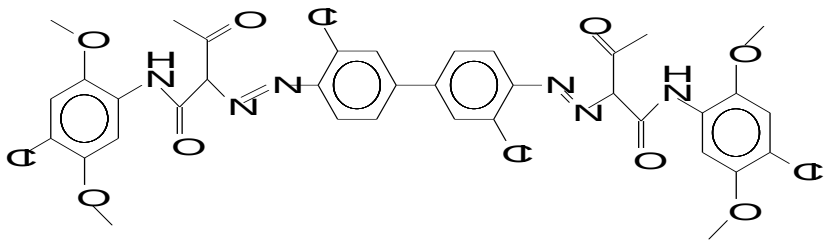
Substance	Estimated United States 2010 Production (metric tonnes)	Estimated European 2010 production (metric tonnes)	Estimated Japanese 2010 production (metric tonnes)
VDCS	454 – 4536	45 – 907	454 – 4536
VTCS	454 – 4536	0	0

100% of the vinyl chlorosilanes, by volume, are used as intermediates in the manufacture of commercial organosiloxanes. The vinyl chlorosilanes are reacted during use and lose their chemical identities.

The vinyl chlorosilanes are produced and processed in closed systems. There are no intentional releases to the environment from the manufacturing processes among the companies that are sponsoring this case. Many engineering controls are in place at all the companies sponsoring this case to prevent occupational exposure such as local and general ventilation, ventilation systems tied into scrubbers with nitrogen padding, ambient temperature, closed loop unloading and dry break connections. Employees involved in chlorosilane production and application are required to use personal protective equipment (PPE) such as a respirator with organic vapor cartridges, slicker suit, Viton (chemical resistant) gloves, and rubber boots. For any situation (e.g. equipment maintenance and repair) where potential exposure to chlorosilanes is expected, the use of acid resistant protective equipment, respiratory equipment and face shield is recommended because of their hazardous properties. Environmental exposure is not expected.

There are no consumer uses of the vinyl chlorosilanes.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	Pigment Yellow 12: 6358-85-6 Pigment Yellow 13: 5102-83-0 Pigment Yellow 83: 5567-15-7
Chemical Name	Pigment Yellow 12: Butanamide, 2,2'[(3,3'-dichloro[1,1'-biphenyl]-4,4'diyl)bis(azo)]bis[3-oxy-N-phenyl- Pigment Yellow 13: Butanamide, 2,2'[(3,3'-dichloro[1,1'-biphenyl]-4,4'diyl)bis(azo)]bis[N-(2,4-dimethylphenyl)-3-oxo- Pigment Yellow 83: Butanamide, 2,2'[(3,3'-dichloro[1,1'-biphenyl]-4,4'diyl)bis(azo)]bis[N-(4-chloro-2,5-dimethoxyphenyl)-3-oxo-
Structural Formula	Pigment Yellow 12:  Pigment Yellow 13:  Pigment Yellow 83: 

SUMMARY CONCLUSIONS OF THE SIAR

Category Rationale

The Diarylide Yellow Pigments category includes molecules with similar chemical structure; all contain the chloro-substituted biphenyl moiety, azo-moieties, keto groups and a substituted or non-substituted phenyl ring at both ends of the molecule, which is connected to the central part of the molecule via an amide bond. The only difference is in the substitution of the outer aniline rings, e.g. methyl, chloro and methoxy. They are expected to display essentially the same trend in environmental, ecotoxicological and toxicological behaviour based on the available data.

Physical-chemical properties

The substances are highly coloured solids which decompose before melting (>300 °C). Estimated vapour pressures range from 2.4^{-23} Pa to 2.9^{-19} Pa at 25 °C. Water solubilities are very low, with measured values between 0.35 µg/L (24 - 25 °C) and 8.1 µg/L (23 - 24 °C). The substances' solubility in n-octanol has been measured and ranges between 8.5 and 49.8 µg/L. Measured data on the log Kow are not available owing to testing being technically not feasible; modeling was used to fill this endpoint. The estimated log Kow values (KOWWIN v1.67) fall between 6.8 and 8.1 (although values estimated according to the ratio of the octanol solubility to the water solubility are $\leq$ 2.1). Dissociation constant, pKa, is not relevant for these very low water solubility substances.

Human Health

Standard single exposure toxicokinetics studies indicate essentially no potential for uptake via the oral and dermal routes. However, following repeated oral exposure at high dose levels, there is some evidence that a very limited uptake of the compound (or its impurities) could occur, based on observations of staining of the mucosal surfaces of internal organs (although the possibility of contamination during necropsy cannot be excluded). In an oral reproductive developmental screening study, staining of the pups could indicate a potential for limited placental transfer, again at a high dose level. Given that the pigment yellows are essentially not absorbed into the body, metabolism is not relevant. However, the presence of very low levels of 3,3'-dichlorobenzidine has been demonstrated in two studies using very sensitive techniques following oral administration of some yellow pigment compounds. It seems likely that this is due to the presence of a mono-azo impurity in some of the yellow pigment parent compounds, which is absorbed and subsequently metabolised. No 3,3'-dichlorobenzidine was found in the urine of experimental animals after exposure orally or via the lungs in long term studies. Following ingestion, the vast majority of the pigments are excreted unchanged in the faeces.

The acute oral LD50 values for rats are >3000 mg/kg bw for Pigment Yellow 13 and >1,750 mg/kg bw for Pigment Yellow 83. The acute oral LD50 values derived from studies in experimental animals are >1,750 mg/kg bw for the three Diarylide Yellow Pigments. For acute dermal toxicity a single LD50 of >3,000 mg/kg bw is available for Pigment Yellow 13. No deaths or clinical signs of toxicity were observed following oral or dermal exposure. The inhalation LC50 available is >4,448 mg/m^3 for Pigment Yellow 13. Tachypnoea, dyspnoea, exophthalmos, ruffled fur and curved or ventral body position were observed, although all animals recovered and no gross abnormalities were observed at necropsy.

All three pigments may be minimally irritating when in contact with the skin. Based on the available data the pigments have a minimal to slight potential for eye irritation. There is no indication that the three pigments are sensitisers.

No adverse effects were seen after 4-7 weeks oral administration of Pigment Yellow 12 at 1000 mg/kg/day (NOAEL), the highest dose tested in a well conducted and reported test of repeated dose toxicity (OECD TG422) study. Furthermore, in the cases of Pigment Yellow 12 and 83, no toxicologically significant effects were observed in a range of chronic toxicity studies of lesser quality (in terms of reporting) in rats and mice at doses up to 6500 mg/kg/day. Based on the kinetics of the three pigments and the chemical similarities, it can be concluded that these findings can be extrapolated to all three pigments.

For the inhalation route the effects seen are related to the deposition of dust particles in the lungs, leading to

Pigment Yellow 13 related effects even at the lowest exposure concentration of 54 mg/m^3 (local LOAEL). Systemically no effects were observed at the highest concentration tested, 410 mg/m^3 (systemic NOAEL).

All three pigments are not genotoxic in bacterial tests. Pigment Yellow 12 did not induce clastogenic effects in mammalian cells. Based on the chemical similarities between the three pigments, it is predicted that all three Yellow Pigments will not induce chromosomal changes in mammalian cells. There are no *in vitro* data to suggest that the pigments are genotoxic *in vivo*.

No increased tumour incidence after treatment with Pigment Yellow 12 and 83 were observed in several long-term studies in rats and mice (NOAEL (rat) > 630 mg/kg; NOAEL (mouse) > 1,960 mg/kg). Based on chemical similarity it can be concluded that the three pigments are not carcinogenic.

It can be concluded that Pigment Yellow 12 does not have any adverse effects on reproductive parameters. There was no evidence of teratogenicity. The NOAEL for maternal and reproductive toxicity is >1,000 mg/kg bw. Supporting evidence is also available from the fact that no changes on the reproductive organs were observed in the studies of repeat dose toxicity and carcinogenicity study with Pigment Yellow 83. In view of the structural similarities and similar kinetics no effects on reproduction or development are expected from Pigment Yellow 13 and Pigment Yellow 83.

The substances in this category do not present a hazard for human health due to their low hazard profile. Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Environment

The pigments have a calculated half-life for photo-oxidation of 1.7 – 4.5 hours (indirect reaction with OH-radical) and are expected to be hydrolytically stable. Fugacity modelling (Mackay Level III) predicts that the pigments will partition primarily to sediment (>98%) if released to the aquatic compartment only. Fugacity modelling for these substances is uncertain and the results should be treated with caution, because it is not clear that the substances fall within the applicability domain of the model. Based on the QSAR estimated log Kows the pigments have high potential for adsorption to soil (predicted Log Koc 5.61 – 5.77). The experimental data indicate that the pigments are not biodegradable (OECD 301C, Pigment Yellow 13 (36.6% dispersion in water) did not degrade during the 28-day incubation period).

The results of calculations of bioaccumulation potential are contradictory, given the high predicted log Kow values of the substances. No definitive experimental data on bioaccumulation are available. However based on the low measured solubilites in n-octanol, which may serve as an indicator for uptake into organisms and partitioning to lipids, and together with the molecular dimensions of the substances it can be concluded that these substances are unlikely to be of concern with regard to bioaccumulation. (Note: two of these substances were considered in the EU Technical Committee for New and Existing Substances PBT working group. The conclusion that they did not meet the criteria for a B (BCF ≥ 2000) or vB (BCF ≥ 5000) substance was drawn based on this information).

The acute LC50/EC50 of the pigments to fish and daphnia are above the water solubility limit. In 72h algal tests with Pigment Yellow 12 and 83, the ErC50s were also above the water solubility limit. Although some effects on biomass were reported in one algal study for Pigment Yellow 12 (below 50%), significant fluctuations were observed in the algal results. Further algal testing on Pigment Yellow 12 indicated no effects at solubility and these are considered key studies based on a weight of evidence approach. The NOEC in a daphnia chronic reproduction study was set at the water solubility limit as no effects were reported at the nominal concentration of 1 mg/L. No toxicity towards micro-organisms was observed at the solubility limit. Overall, available studies revealed no acute or chronic toxicity at concentrations orders of magnitude above the water solubility limit and at, or near, the water solubility limit. Based on the very low water and n-octanol solubility, exposure of aquatic organisms to the pigments is expected to be low. Partitioning to sediment may be possible based on the high sorptive potential (log Koc = 5.61 – 5.77). Two reliable long term studies in sediment dwelling organisms are available on pigment yellow 12 and 83 (both according to OECD 225: Sediment-Water Lumbriculus Toxicity Test Using Spiked Sediment); in both studies no effects were seen at the (limit) concentration tested, hence the 28-day NOEC was 1000 mg/kg sediment dry weight (nominal). Two reliable long term studies in earthworms are available on pigment yellow 12 and 83 (according to OECD Guideline 222:

Earthworm (*Eisenia fetida*) Reproduction Test); in both studies no statistically significant differences were observed between test group and controls at the one concentration tested (limit test), hence the 28-day (for mortality and biomass) and 56-day (for reproduction) NOECs were 1000 mg/kg soil dry weight (nominal).

The diarylide pigments do not present a hazard to the environment due to their low hazard profile. They have a low potential for bioaccumulation but are not readily biodegradable. Adequate screening-level data are available to characterize the environmental hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

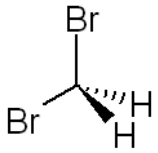
Exposure

For the year 2001 the global market for the three diarylide yellow pigments under evaluation was about 50,000 tonnes. The pigments are used as colouring agents in industrial and decorative paints, inks and plastics (polymers), cosmetics (Pigment Yellow 13 and 83) and textiles (Pigment Yellow 12).

Worker exposure to the pigments can occur during handling and cleaning operations. The principal route of exposure is by inhalation. Skin contact may be possible. Consumer exposure is expected to be negligible as consumer products only contain the pigments in a matrix. Exposure to consumers from PY13 and PY83 might be expected as the substances are approved cosmetic ingredients in Europe, however no information on the quantities used for this application are available.

There is potential environmental exposure arising from the production and processing of the substances. In addition exposure after paper recycling can not be excluded.

SIDS INITIAL ASSESSMENT PROFILE

CAS No(s).	74-95-3
Chemical Name(s)	DIBROMOMETHANE (DBM)
Structural Formula(s)	

SUMMARY CONCLUSIONS OF THE SIAR

Physical-chemical Properties

Dibromomethane is a clear, colourless liquid with a sweetish odour and a measured boiling point of 94±1°C and a measured vapour pressure of 4700 Pa at 25°C. The measured octanol-water partition coefficient (log K_{ow}) is 1.68, and the measured water solubility is 9000 mg/L at 20°C.

Human Health

Toxicokinetics

A standard toxicokinetic study is not available. Dibromomethane appears to be absorbed after oral and inhalation exposure in rats and rabbits (concluded based on repeated dose toxicity section) and after dermal exposure.

Dibromomethane was metabolized *in vitro* to carbon monoxide and inorganic bromide by microsomal enzymes of the liver, lungs, and kidney, but not of the brain or spleen. The oxidation appears to be catalysed by a cytochrome P-450 dependent system. During dermal exposure, the metabolism of dibromomethane was saturable as indicated by the nonlinear increase in plasma bromide ion concentration. Intraperitoneal administration of 522 mg/kg dibromomethane to male rats resulted in a peak of carboxyhemoglobin level of 14% of the hemoglobin concentration at 4 hours treatment. By 10 hours after treatment, the carboxyhemoglobin level was approaching the pre-treatment level. Repeated daily exposure did not result in accumulation of carboxyhemoglobin. The only information regarding the excretion of dibromomethane is that the metabolite carbon monoxide is excreted in the exhaled air.

Acute Toxicity

In a 4-hour inhalation study CD albino rats were exposed to 21.4 - 22.3 mg/L dibromomethane. Immediately after exposure excessive fluid excretion was observed, accompanied by impaired spontaneous motor activity as exhibited by slow breathing, uncoordinated and atactic walk, continuous tremor, and excessive preening. All these effects wore off within about 3 hours when most of the exposed animals were found in deep sleep**.** No mortalities occurred and no toxicologically relevant changes were noted on autopsy at 18 and 20 days post treatment. An LC_{50} was > 22.3 mg/L.

A rat oral LD_{50} > 1000 mg/kg bw was derived from a 14 day range-finding reproduction/developmental toxicity test with six animals. Clinical signs were bodyweight loss and a decline in the clinical condition.

No reliable acute dermal toxicity information is available.

Skin and Eye Irritation

Dibromomethane was moderately to severely irritating to the skin and moderately irritating to the eye in rabbits in two reliable studies.

Skin Sensitisation

Dibromomethane was not a skin sensitiser in a Local lymph node assay performed in mice.

Repeated Dose Toxicity

The repeated dose toxicity of dibromomethane has been investigated via the inhalation route. No reliable data for oral repeated dose toxicity were available. Based on substance volatility, exposure through the inhalation route can be consider as a major route of exposure.

Oral Route

No reliable repeated dose toxicity study for the oral route is available.

In a reproductive and developmental toxicity screening test, rats (10 animals/sex/dose) received 0, 50, 150, 500 mg/kg bw/day of dibromomethane via gavage for 40 days. No treatment related deaths were observed in either sex. There were no significant treatment-related clinical signs of toxicity. At 500 mg/kg bw/day, lower bodyweight gain and lower food conversion efficiency was observed in females during gestation. However, this study has the following limitations: there were only histopathological examinations and organ weight determinations for reproductive organs, and no clinical chemistry or haemathology was conducted. The NOAEL for repeated dose oral toxicity can be considered to be 150 mg/kg bw/day.

Supporting information on repeated dose oral toxicity of dibromomethane was derived from a preliminary 14-day oral repeated dose range-finding study for a reproduction/developmental toxicity screening test. There was no information on food consumption, haematology, clinical biochemistry, organ weight changes, macroscopical/histopathological findings. Treatment related effects (clinical signs and decreased body weight gain) were observed mainly in males at dose level 1000 mg/kg bw/day (highest dose tested). The NOAEL for repeated dose oral toxicity can be considered to be 500 mg/kg bw/day.

Inhalation Route

Repeated exposure of rats and rabbits to 1000 mg/L dibromomethane for 73 days caused effects on coordination, weight gain and histopathological changes in the lungs, liver and kidneys in rats. Rabbits were less affected, but their blood bromide was elevated and degeneration of liver and kidney occurred. Repeated exposure of rats and rabbits at lower dose of 200 mg/L dibromomethane resulted in much less effect, but evidence of stress was still present and histopathological changes were found in livers and kidneys of rats and rabbits. Based on these effects, the LOAEC for rats can be set to 200 mg/L (1422 mg/m^3).

Repeated inhalation exposure of rats and dogs to 25 - 150 mg/L dibromomethane for 90 days showed no significant exposure related effects on gross pathology, histopathologic examination, and urinalysis. There were slight increases in liver weight in female rats at 75 and 150 mg/L and dose–related increases in percent saturation of carboxyhemoglobin at > 25 mg/L in both sexes of rats and at 150 mg/L in dogs. The NOAEL for rats was determined to be 25 mg/L and the LOAEL was set to 75 mg/L. The NOAEL for dogs was determined to be 75 mg/L and the LOAEL was set to 150 mg/L.

Genetic Toxicity

Dibromomethane was found to be mutagenic with and without mammalian metabolic activation in three (limited) Ames tests. In an *in vitro* mammalian chromosome aberration test conducted in human lymphocytes dibromomethane was found positive. Therefore, it is concluded that dibromomethane is mutagenic *in vitro.*

Dibromomethane was reported not mutagenic in a *Drosophila melanogaster* sex-linked recessive lethal study. There are no *in vivo* mammalian genotoxic studies available. Therefore, it is concluded that the *in vivo* potential of dibromomethane has not been adequately investigated.

Carcinogenicity

No data are available for the carcinogenicity of dibromomethane from standard carcinogenicity studies. In a 90-day repeated dose inhalation toxicity study in rats with 2 years post exposure observation period, gross pathological examination revealed no indication of any increased incidence of nontumours or tumour-like lesions at any exposure level.

Fertility/developmental toxicity

The reproductive toxicity of dibromomethane was well investigated in a reproductive and developmental toxicity screening test in rats. In this study, dibromomethane was administered via gavage to 10 animals/sex/dose at 0, 50, 150, 500 mg/kg bw/day, for 40 days. No death were observed in either sex. There were no significant treatment-related clinical signs of toxicity. At 500 mg/kg bw/day, lower bodyweight gain and lower food conversion efficiency was observed in females during gestation. At 50 or 150 mg/kg bw/day, mating performance, fertility and gestation length were unaffected by treatment. However, treatment at 500 mg/kg bw/day was associated with an effect on mating performance (increased pre-coital interval) and a reduction in litter size at birth. Treatment at 500 mg/kg bw/day did not adversely affect fertility with 8/10 females achieving pregnancy.

Necropsy did not indicate any effect of the test material on adult animals. The NOAEL for reproductive and developmental toxicity was considered to be 150 mg/kg bw/day.

Dibromomethane possesses properties indicating a hazard for human health (skin and eye irritation, *in vitro* mutagenicity and reproductive toxicity (fertility and 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

Environmental fate properties

The hydrolysis half-life for this compound is 143 days.

In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of 105.9 days. No ready biodegradation guideline studies are available. BIOWIN estimation predict that the substance is not readily biodegradable. However, a non-guideline study shows a half life value of 2 days based on 14C labelled CO_2 evolution from natural salt water and fresh water sediments. This suggest that dibromomethane is degradable in the environment and will not be persistent.

A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that dibromomethane will distribute to the air (33.9 %), water (35.9%) and soil (30.1%) and negligible distribution to the sediments compartment (0.098%). If released only to the air compartment, dibromomethane stays in the air compartment (96%) with negligible amounts in other compartments. A Henry's law constant of 83.3 $Pa.m^3$/mole at 25 °C suggests that volatilization of chemical dibromomethane from the water phase is expected to be high. A log K_{oc} of 1.475 was estimated based on the log K_{ow} and indicates a low potential for accumulation in soil.

The bioaccumulation potential is predicted to be low based on a BCF value of 5.963 estimated with BCFWIN.

Aquatic Toxicity

The following acute toxicity test results have been determined for aquatic species, e.g.:

Fish [*Rainbow Trout*]	96 h LC_{50} = 45 mg/L (nominal) Semi static
Invertebrate [*Daphnia magna*]	48 h EC_{50} = 66 mg/L (nominal) Semi static
Algae [*Pseudokirchneriella subcapitata*]	96 h E_rC_{50} = 150 mg/L (growth rate method) (measured)

Algae [*Pseudokirchneriella subcapitata*] 96 h E_bC_{50} = 95 mg/L (area under growth curve method)

The fish and daphnia tests were conducted in sealed vessels to prevent volatilization, and analytically monitoring was performed in all three ecotoxicity tests.

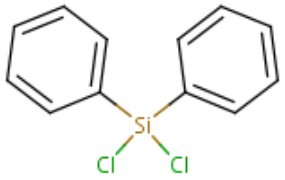
Dibromomethane possesses properties indicating a hazard for the environment (acute aquatic toxicity values between 10 and 100 mg/L). The chemical is considered biodegradable and has a low bioaccumulation potential. Adequate screening-level data are available to characterize the hazard to the environment for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Exposure

Dibromomethane is commercially produced with an annual estimated production volume of several thousands of tonnes in Israel (sponsor country), and a similar amount in USA. Some production might be available in China. Dibromomethane is mainly produced by reaction of methylene chloride with hydrogen bromide. Dibromomethane is used as an intermediate in the production of organic intermediates, fine chemicals and as an organic solvent.

No monitoring data for effluents/drinking water/surface water/in occupational settings/etc are available.

SIDS INITIAL ASSESSMENT PROFILE

CAS No(s).	80-10-4
Chemical Name(s)	Dichlorodiphenylsilane (**DClDPS**)
Structural Formula(s)	**DClDPS**: 

SUMMARY CONCLUSIONS OF THE SIAR

Analogue Rationale

Chlorosilanes, including **DClDPS**, react rapidly when exposed to moisture or polar reagents (those that are protic and as such contain a dissociable H^+), producing hydrogen chloride (HCl; CAS No. 7647-01-0) and diphenylsilanediol (CAS No 947-42-2)[1]. Each mole of **DClDPS** hydrolyses to form two moles of HCl and one mole of diphenylsilanediol. The hydrolysis half-life of **DClDPS** is < 1 minute at 1.5ºC for pH 4, 7, and 9.

Human Health, Aquatic Toxicity and Environmental Fate Analogues
(1) Hydrolysis products of **DClDPS** are used to characterize toxicity due to its very fast hydrolysis. Data for hydrolysis products HCl and diphenylsilanediol are used to represent repeated dose mammalian toxicity and acute aquatic toxicity. HCl is also used to represent acute toxicity, irritation, and genotoxicity.

(2) Structural analogues are used directly as read across substances, or through rapid hydrolysis to a structurally similar silanediol, to characterize the toxicity of **DClDPS**. A structurally analogous phenylchlorosilane, trichlorophenylsilane (TClPS, CAS No. 98-13-5), with the same expected rapid hydrolysis rate as **DClDPS,** is used to represent the biodegradation and chromosome aberration endpoints**.**

HCl was presented and agreed under the OECD Cooperative Chemicals Assessment Programme (http://www.oecd.org/env/hazard/data).

[1]When prepared under very controlled conditions, the hydrolysis product, diphenylsilanediol will crystallize from solution before it can react to form siloxanes. The crystal structure locks in the special configuration, thereby preventing the silanediols from condensing and allows separation of diphenylsilanediol for testing. In solution, diphenylsilanediol will condense to form oligomers. Under "normal" conditions, and depending on pH and concentration in water, silanediols such as diphenylsilanediol can condense to form highly cross-linked, high molecular weight polymers, further reducing the potential for exposure.

The read across strategy for **DClDPS** follows:

Env. Fate	Mammalian toxicity				Environmental effects
Bio-degradation	**Acute toxicity**	**Irritation**	**Repeated dose toxicity**	**Genetic toxicity (chromosome aberration)**	**Aquatic toxicity to Fish, Daphnid and Algae**
TClPS	HCl	HCl	Diphenylsilanediol, HCl	TClPS, HCl	Diphenylsilanediol, HCl

Physical-chemical Properties

DClDPS is a colorless liquid at 20 °C and 1013 hPa with measured melting point of -22°C, measured boiling point of 305°C and estimated vapour pressure of 0.00078 hPa at 25 °C. The calculated octanol-water partition coefficient (log K_{ow}) is 5.06 (reliability = 4), and the estimated water solubility is 2.8 mg/L at 25 °C. The calculated water solubility and log K_{ow} values may not be accurate because the substance is hydrolytically unstable.

Human Health

No data are available on the toxicokinetics, metabolism and distribution of **DClDPS**. However, **DClDPS** rapidly hydrolyses to HCl and diphenylsilanediol on contact with moisture. Damage to membranes caused by the corrosive nature of HCl might enhance the uptake of **DClDPS** or the silanol hydrolysis product. Hydrogen and chloride ions will enter the body's natural homeostatic processes. HCl will rapidly dissociate and its effects are thought to be a result of pH change (local deposition of H^+). Repeated dose exposure studies with diphenylsilanediol suggest the silanol is absorbed following oral exposure, distributed systemically and metabolized/eliminated through the liver and kidneys.

Acute inhalation studies were not located for **DClDPS**. The acute inhalation toxicity of **DClDPS** is expected to be well characterized by the effects of HCl exposure, rather than systemic effects of silanol hydrolysis products. The principal clinical signs are expected to be indicative of respiratory and ocular effects resulting from HCl exposure. Inhalation LC_{50} values (one hour exposure) for HCl were determined to be 4.2 - 4.7 mg/L for rats and 1.7 mg/L for mice. The acute oral LD_{50} values of HCl were determined to be 238 - 277 mg/kg bw for female rats. An acute toxicity study was not located for diphenylsilanediol.

Irritation data are not available for **DClDPS**. **DClDPS** rapidly hydrolyses to HCl and the associated silanol. HCl is corrosive and highly irritating to the skin, eyes and respiratory tract. As such, **DClDPS** is expected to be corrosive to the skin, cause serious damage to the eyes and be highly irritating to the respiratory tract. Sensitization data are not available for **DClDPS** or the expected hydrolysis products.

Repeated dose toxicity data are not available for **DClDPS**. Repeated oral exposure to the expected hydrolysis product, diphenylsilanediol and inhalation data for the hydrolysis product HCl are available. The NOAEL following repeated gavage exposure of rats to diphenylsilanediol for 21 days was 400 mg/kg bw (highest dose tested). In a 14-day study with beagle dogs, repeated dose administration of diphenylsilanediol at 500 mg/kg bw for 14 days produced effects that included neurological effects, marked reduction in body weight and effects on liver, kidney and adrenal gland. Exposure at 50 mg/kg bw produced some of these same effects, albeit at a lower incidence/severity. In repeated dose toxicity studies of HCl by the inhalation route, local irritant effects were observed in the groups of rats and mice exposed to 0.015 mg/L and above for 90 days. The inhalation NOAEC for systemic toxicity for HCl, excluding the local effects of irritation, has been determined to be 0.030 mg/L, with a LOAEC of 0.075 mg/L. The toxicity of **DClDPS** is expected to be well-characterized by the effects of HCl inhalation exposure, the prevalent route of the **DClDPS** exposure.

DClDPS did not induce gene mutations in bacterial cells *in vitro* [similar or equivalent to OECD TG 471]. TClPS was negative for induction of gene mutations in bacterial [similar to OECD TG 471] and mouse

lymphoma cells [OECD TG 476]. A chromosomal aberration study was not located for **DClDPS**. The hydrolysis products, diphenylsilanediol and HCl, did not induce gene mutations in bacterial cells. Positive results in the *in vitro* chromosome aberration test with HCl were considered to be the effect of low pH. Based on the available data, **DClDPS** is not expected to be genotoxic.

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

Reproductive toxicity data are not available for **DClDPS** or the hydrolysis product diphenylsilanediol**;** no additional testing is needed because **DClDPS** is a site-limited intermediate and is produced and used in closed systems. Information for the hydrolysis product HCl is used to partially fill the reproductive toxicity endpoint for **DClDPS**. No reliable studies have been reported regarding toxicity to reproduction and development in animals after oral, dermal or inhalation exposure to hydrogen chloride/hydrochloric acid. Because proton and chloride ions are the normal constituents in the body fluid of animal species, low concentrations of hydrogen chloride gas/mist or solution do not seem to cause adverse effects to mammals. In fact, the cells of gastric glands secrete hydrochloric acid into the cavity of the stomach and orally administered sulfuric acid, which results in pH change as well, did not cause developmental toxicity to laboratory animals. These facts indicate that hydrogen chloride/hydrochloric acid is not expected to have developmental toxicity. In addition, no effects on the gonads were observed in a 90-day inhalation repeated-dose study up to concentrations of 0.075 mg/L.

Diphenyldichlorosilane possesses properties indicating a hazard for human health [lethality from acute inhalation, corrosive and highly irritating to the skin, eyes and respiratory tract (based on the hydrolysis product, HCl) and repeated dose toxicity (based on the hydrolysis product, diphenylsilanediol)]. Data on reproductive toxicity are not available, however, based on use of this chemical in the sponsor country (closed system site-limited intermediate), additional testing for this endpoint is not needed. 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 module, found in the current version of EPI Suite (v4.10), may improve estimates for silanes and siloxanes for this endpoint. However, there is still uncertainty associated with the calculated values and they should be used with caution whenever they are reported.

The chlorine group is the most active functional group for **DClDPS** and determines many aspects of its behaviour. Each mole of **DClDPS** undergoes rapid hydrolysis in the presence of moisture to form two moles of HCl and one mole of diphenylsilanediol. An OECD TG 111 (Hydrolysis as a Function of pH) test was conducted at 1.5ºC for **DClDPS**; half-lives of less than one minute were reported at pH 4, 7, and 9.

In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of 2.7 days. Any potential for photodegradation might be superseded by hydrolysis of the parent compound depending on the concentration of water vapour in the air. The biodegradation of supporting substance TClPS was determined in OECD TG 310; there was essentially no (1%) biodegradation of the test substance in 28 days. HCl is an inorganic compound and biodegradation tests are not applicable. Based on this information, **DClDPS** is not expected to be readily biodegradable. Due to rapid hydrolysis of **DClDPS**, any potential for biodegradation is likely to be of the hydrolysis products. Consequently, the only biodegradable materials in the test system will be silanols, and condensed silanol materials (high molecular weight polymers). At high concentrations (>500 mg/L), the silanols will condense to form highly cross linked, high molecular weight polymers that are water insoluble and effectively nonbiodegradable.

A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that **DClDPS** will distribute mainly to the air (47.6%) and soil (47.7%) compartments with minor distribution to the water and sediment compartments. Level III fugacity modeling using equal loading rates of 1000 kg/h each for air, soil and water predicts that the hydrolysis product, diphenylsilanediol, will distribute mainly to soil (76.9 %), with a smaller fraction to water (13.9 %) and negligible amounts to sediment and air. Based on the more realistic scenario of 100% release to air, the model predicts that diphenylsilanediol will be distributed mainly in air (94.5%), with minor distribution to water (3.3%) and

sediment (2.8%).

DClDPS is not expected to bioaccumulate in the aquatic environment based on rapid hydrolysis to diphenylsilanediol, which has an estimated BCF of 9.7 L/kg. The calculated bioconcentration factor for **DClDPS** is 1009 L/kg wet-wt.

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

Test substance	Species	Result (mg/L)	Guideline; Test type
Fish, acute toxicity			
Supporting hydrolysis products			
Diphenylsilanediol	*Oncorhynchus mykiss*	96-hr LC_{50} = 39 (measured)	OECD TG 203; static
HCl	*Cyprinus carpio*	96-hr LC_{50} = 4.92 (pH = 4.3)	OECD TG 203; semi-static
Aquatic invertebrate, acute toxicity			
Supporting hydrolysis products			
Diphenylsilanediol	*Daphnia magna*	48-hr EC_{50} = 24 (measured)	OECD TG 202; static
HCl	*Daphnia magna*	48-hr EC_{50} = 0.492 (pH= 5.3)	OECD TG 202; not specified
Aquatic plants, acute toxicity			
Supporting hydrolysis products			
Diphenylsilanediol	*Pseudokirchneriella subcapitata*	72-hr E_rC_{50} = 9.0 72-hr E_bC_{50} = 2.8 96-hr E_rC_{50} = 11 96-hr E_bC_{50} = 2.7 (measured)	OECD TG 201; static
HCl	*Pseudokirchneriella subcapitata*	72-hr E_rC_{50} = 0.492 (pH= 5.3)	OECD TG 201; static

Based on the properties of the hydrolysis products, HCl and diphenylsilanediol, DClDPS possesses properties indicating a hazard for the environment (acute toxicity to fish between 1 and 100 mg/L). Based on the hydrolysis product HCl, DClDPS posseses properties indicating a hazard for the environment (acute toxicity to aquatic invertebrates and to algae < 1 mg/L). Toxic effects are expected primarily from the hydrolysis products. DClDPS has a low potential for bioaccumulation and is not expected to be readily biodegradable. 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 and import volumes (metric tonnes) for 2010 are summarized below.

United States		**Europe**		**Japan**	
Production	**Import**	**Production**	**Import**	**Production**	**Import**
454 - 2268	4.5 - 454	0	4.5 - 454	454 - 3629	0

Ranges are provided to protect confidential business information. **DClDPS** is used in formulations up to 100% as intermediates for silicone oligomers and polymers. No parent substance is expected to remain after end use.

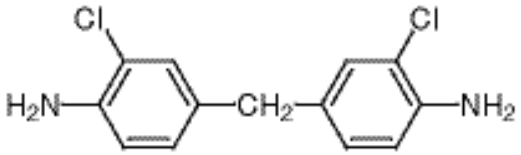
DClDPS is produced and processed in closed systems; commercial customers use **DClDPS** in closed systems. Due to the dynamic and exothermic nature of the processes incorporating chlorosilanes, many engineering controls are always in place to prevent occupational exposure such as water scrubber devices and related equipment; closed sampling loop; and local and general ventilation. Employees involved in chlorosilane production and application use personal protective equipment (PPE) such as safety glasses or goggles, steel-

tipped shoes, flame-resistant clothing, hard hats, chemical resistant gloves, and respirator masks. Potential routes of exposure include inhalation and dermal exposure.

There are no consumer uses for **DClDPS**.

Environmental exposure is not expected.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	101-14-4
Chemical Names	4,4'-Methylenebis(2-chloroaniline)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

To avoid duplication of assessment work, only summary information of genotoxicity and carcinogenicity in IARC monographs[1] and Toxicological Profiles by ATSDR[2] and State of the Science Reports by Health Canada[3] is described, as secondary information, in this SIAP. Robust study summaries for new genotoxicity studies were generated for the purpose of the OECD Cooperative Chemicals Assessment Programme.

Physical-chemical properties

Pure 4,4'-methylenebis(2-chloroaniline) is a colourless and crystalline solid, but the commonly used forms (industry grade) of this chemical are tan-coloured pellets or flakes with a faint, amine-like odour. Melting point is 110 °C. Boiling point cannot be obtained because this substance decomposes on heating above 277 °C. Density is 1.44 g/cm^3. Measured value of vapour pressure is 5.19×10^{-7} Pa at 25 °C. Measured value of water solubility is 0.509 mg/L at 20 °C. Measured value of partition coefficient between octanol and water (log K_{ow}) is 3.66 at 25 °C. 4,4'-Methylenebis(2-chloroaniline) exists in the neutral form between pH 3 and pH 9 in water.

Human Health

Toxicokinetics

Absorption: 4,4'-methylenebis(2-chloroaniline) seems to be easily absorbed via the oral route based on the similar urinary excretion profile for i.p. and oral administration in rats. It was estimated that 2.4 - 10% or 11.5 - 21.9% of the dose was absorbed through the skin in 24 h in dogs or in 72 h in rats. Less substance was absorbed from the skin if the skin was washed within 8 h after application in dogs.

Distribution: The distribution of 4,4'-methylenebis(2-chloroaniline) in rats and dogs is relatively similar after oral and dermal exposures, and 4,4'-methylenebis(2-chloroaniline) was detected in the various tissues such as the liver (mainly), kidney, fat, lung, spleen, urinary bladder, and/or testes.

Metabolism: 4,4'-methylenebis(2-chloroaniline) metabolism can proceed via several pathways: N-acetylation, N-hydroxylation, which may be followed by N-oxidation, and ring hydroxylation. Some of these processes may be followed by conjugation. In workers occupationally exposed to 4,4'-methylenebis(2-chloroaniline), N-acetyl-4,4'-methylenebis(2-chloroaniline) and N,N′-diacetyl-4,4'-methylenebis(2-chloroaniline) were observed in urine

[1] IARC (1993). *Occupational exposures of hairdressers and barbers and personal use of hair colourants; some hair dyes, cosmetic colourants, industrial dyestuffs and aromatic amines.* IARC Monogr Eval Carcinog Risks Hum, 57, 271–303. IARC (2010). *Some aromatic amines, organic dyes, and related exposures.* IARC Monogr Eval Carcinog Risks Hum, 99, 325. IARC (2012). *Chemical agents and related occupations.* IARC Monogr Eval Carcinog Risks Hum, 100F, 73–82.

[2] ATSDER (1994). *Toxicological Profile for 4,4'-Methylenebis(2-chloroaniline)*, Agency for Toxic Substances and Disease Registry, U.S. Department of Health and Human Services.

[3] Health Canada (2005). *State of the Science Report for a Screening Health Assessment: 4,4'-Methylenebis(2-chlorobenzenamine) [MBOCA]*; CAS No. 101-14-4. 14 pp.

samples.

Adducts formation: 4,4'-methylenebis(2-chloroaniline) forms N-(deoxyadenosin-8-yl)-4-amino-3-chlorobenzyl alcohol. This adduct was found in urothelial cells that were exfoliated into urine of a worker who was accidentally sprayed with 4,4'-methylenebis(2-chloroaniline) on his upper body. The same DNA adduct was found in rats. Adduct formations with DNA were found in the liver, lung and kidney of rats and in the liver and bladder of dogs. Hemoglobin adduct was also found in workers exposed to 4,4'-methylenebis(2-chloroaniline) and in rats.

Excretion: the major route of elimination was faeces and urine in rats and dogs. The rate of excretion of radiolabelled 4,4'-methylenebis(2-chloroaniline) in urine and faeces was very high in the first 24 h (68.3%) but decreased rapidly (2.07%) by the 3rd day in rats treated by 4,4'-methylenebis(2-chloroaniline) by gavage. A significant amount of the substance was recovered from faeces after dermal and intravenous administration. It is considered that most of absorbed 4,4'-methylenebis(2-chloroaniline) is excreted in bile. 4,4'-Methylenebis(2-chloroaniline) was also found in urine samples of occupationally exposed workers.

Acute toxicity

The dermal LD_{50} of 4,4'-methylenebis(2-chloroaniline) in rats was reported to be greater than 2000 mg/kg bw (OECD TG 402). Neither substance related mortality nor clinical signs of toxicity were observed. The oral LD_{50} value was greater than 2000 mg/kg bw for female rats following a study conducted according to OECD guideline 423. The substance caused unkempt fur and deep breathing and temporary dark red discoloration of the ear auricles and limbs. Necropsy of the dead animal revealed white foci in the liver, dark red adrenals, dark red foci in the forestomach and glandular stomach, and dark red contents in the intestine from the jejunum to ileum.

Irritation

4,4'-Methylenebis(2-chloroaniline) was not corrosive to isolated bovine eyes (OECD TG 437). 4,4'-Methylenebis(2-chloroaniline) was not irritating to human epidermis (OECD TG 439). According to the limited human information, signs of toxicity from exposure of workers to molten or hot 4,4'-methylenebis(2-chloroaniline) that was sprayed accidentally on the upper body or face included slight erythema in affected skin areas (from upper body exposure), burning sensation in affected skin areas (from upper body and face exposure), burning sensation and conjunctivitis in both eyes (from face exposure), and upset stomach (from face exposure), even after attempts at decontamination in the workers. However, it is difficult to say if the effects were caused by the chemical or the temperature of the chemical.

Sensitization

4,4'-Methylenebis(2-chloroaniline) was not sensitising in a local lymph node assay (OECD TG 429).

Repeated dose toxicity

In a repeated dose oral toxicity study in rats following OECD TG 422, the substance was administered via gavage to 12 animals/sex/dose at 0 (vehicle, olive oil), 0.4, 2, 10, and 50 mg/kg bw/day, for 42 days (males) or from 14 days before mating to the 4th day of lactation. As recovery groups, 5/12 males at 0 and 50 mg/kg bw/day were observed for 14 days after the administration period. An additional five females at 0 and 50 mg/kg bw/day were treated for 42 days without mating and observed for 14 days as satellite groups. No death was observed in either sex. Treatment-related effects such as salivation in both sexes and significant decrease in female's body weight in later stages of pregnancy were observed at 50 mg/kg bw/day. Significant decreases in the levels of total protein and albumin in the 50 mg/kg bw/day groups in both males and females and in the 10 mg/kg bw/day groups only in females were observed. There were increases in absolute and/or relative weights of the liver in both sexes, and absolute and relative weights of the spleen and relative weights of the thyroid in females at 50 mg/kg bw/day. Increases of relative weights of the kidney were observed in females at $\geq$ 10 mg/kg bw/day. Histopathology revealed centrilobular swelling and mid-zonal fatty degeneration of hepatocytes in both sexes at 50 mg/kg bw/day. Increase in basophilic tubules in the kidney was dose dependant in males starting at 10 mg/kg bw/day. In the spleen, hemosiderin deposits were significantly higher in males at $\geq$ 10 mg/kg bw/day and females at 50 mg/kg bw/day. Furthermore, increased extramedullary hematopoiesis was observed in females in the 50 mg/kg bw/day group. In recovery animals that had been dosed at 50 mg/kg bw/day, significantly higher relative weights

of the liver and kidneys in females, and significantly lower changes in mean corpuscular hemoglobin concentration and hematocrit in males and in methemoglobin in females were also observed. Based on the changes in clinical chemistry in females (decreased albumin and total protein) and histopathological findings in the kidney, liver and spleen, the NOAEL for systemic toxicity in this OECD TG 422 study in rats (exposure duration = 42 - 55 days) was considered to be 2 mg/kg bw/day.

There are four supporting chronic studies in rats, mice, or dogs, designed as carcinogenicity studies, and providing only limited information.

4,4'-Methylenebis(2-chloroaniline) treatment in the diet for 18 months shortened survival times and decreased body weight in rats and mice.

In a study conducted in rats (25 – 50/sex/dose), hepatomegaly, fatty change, necrosis, fibrosis, and bile duct proliferation in the liver was observed in both sexes at 50 mg/kg bw/day (only dose tested).

Similar changes were seen in 6 female dogs given 4,4'-methylenebis(2-chloroaniline) in a gelatine capsule at ca. 7.6 - 11.8 mg/kg bw/day for 9 years. Histopathology revealed nodular hepatic hyperplasia and disruption of liver architecture. A statistically significant increase in serum glutamic-pyruvic transaminase was also observed. Based on the occurrence of hepatic effects in dogs exposed to 4,4'-methylenebis(2-chloroaniline), the chronic LOAEL was determined to be 7.6 mg/kg bw/day.

Genotoxicity

In a bacterial reverse mutation assay performed according to OECD TG 471, 4,4'-methylenebis(2-chloroaniline) was positive in *Salmonella typhimurium* TA100 and TA98 with metabolic activation. An *in vitro* chromosomal aberration test (OECD TG 473) in cultured Chinese hamster lung fibroblasts (CHL/IU) cells was positive without metabolic activation.

The following is other reliable information in IARC monographs, Toxicological Profiles and Health Canada State of the Science Reports:

4,4'-Methylenebis(2-chloroaniline) was shown to cause prophage induction in *Escherichia coli* and differential toxicity in *Bacillus subtilis* rec-deficient strains. It was mutagenic to *S. typhimurium, E. coli*, and at the Tk locus in mouse lymphoma L5178Y cells, but not to *Saccharomyces cerevisiae*. 4,4'-Methylenebis(2-chloroaniline) caused aneuploidy in *S. cerevisiae* but demonstrated equivocal results with regard to gene conversion and did not induce mitotic crossing-over in the same organism. It induced unscheduled DNA synthesis in primary cultures of hepatocytes from mice, rats, and Syrian hamsters. Sister chromatid exchange, but not chromosomal aberration, was induced in Chinese hamster ovary cells. 4,4'-Methylenebis(2-chloroaniline) induced cell transformation in mammalian (hamster/rat/mouse) cells and inhibited gap-junctional intercellular communication in cultured rat liver cells. Positive results were observed in *in vitro* micronuclei assays.

An *in vivo* assay, sister chromatid exchange in lymphocytes of rats, was positive. *In vivo* studies in bone marrow and peripheral blood of rats showed no evidence of micronuclei induction, but a positive result was observed in mice at a high dose in a two-phase micronucleus assay. 4,4'-Methylenebis(2-chloroaniline) induced mutation in *Drosophila melanogaster*. DNA damage was observed in the liver, urinary bladder and brain of mice by a comet assay.

Based on these results, 4,4'-methylenebis(2-chloroaniline) is considered to be genotoxic *in vitro* and *in vivo*.

Carcinogenicity

Summary information for carcinogenicity in IARC monographs (classified in group 1) is as follows: Oral administration of 4,4'-methylenebis(2-chloroaniline) increased the incidence of liver tumours in female mice. In a series of experiments in which rats were fed either standard or low protein diets, it induced liver cell tumours and malignant lung tumours in males and females in one study, a few liver cell tumours in male rats in a second study, lung adenocarcinomas and hepatocellular tumours in males and females in a third study, and malignant lung tumours, mammary gland adenocarcinomas, Zymbal gland carcinomas, and hepatocellular carcinomas in a fourth study. Oral administration of 4,4'-methylenebis(2-chloroaniline) to female beagle dogs produced

transitional cell carcinomas of the urinary bladder and urethra. Subcutaneous administration to rats produced hepatocellular carcinomas and malignant lung tumours.

Bladder cytology surveys identified bladder cancer cases in workers exposed to 4,4'-methylenebis(2-chloroaniline) in Michigan, USA, New Jersey, USA, and Taiwan, China. A cohort of 308 male 4,4'-methylenebis(2-chloroaniline) production workers in the United Kingdom found one bladder cancer death during 1979 – 2007, with 0.18 deaths expected (SMR 5.6; 95%CI: 0.14 – 31.2), based on the United Kingdom mortality rates. However, no adequate epidemiological studies were available to evaluate an association between 4,4'-methylenebis(2-chloroaniline) and bladder cancer risk.

Other relevant data

The provable carcinogenic mechanism of 4,4'-methylenebis(2-chloroaniline) includes, metabolic activation and formation of DNA adducts. DNA adducts were considered to be produced after N-oxidation of 4,4'-methylenebis(2-chloroaniline) to N-hydroxy-4,4'-methylenebis(2-chloroaniline) (see toxicokinetics section for further information for the DNA adducts). On the other hand, a cross-sectional survey at 4,4'-methylenebis(2-chloroaniline) producing factories showed that neither the 4,4'-methylenebis(2-chloroaniline)-exposed workers nor the high urinary 4,4'-methylenebis(2-chloroaniline) workers had a significant increase in the mean plasma 8-OHdG level after adjustment for potential confounders. This result suggested that oxidative DNA damage does not play an important role in the carcinogenic processes of 4,4'-methylenebis(2-chloroaniline).

Overall, 4,4'-methylenebis(2-chloroaniline) is considered to be carcinogenic based on the tumours observed in a range of tissues in a number of animal studies.

Reproductive toxicity

The reproductive toxicity of 4,4'-methylenebis(2-chloroaniline) was investigated in a reproductive and developmental toxicity screening test in rats OECD TG 422. In this study, 4,4'-methylenebis(2-chloroaniline) was administered via gavage to 12 animals/sex/dose at 0 (vehicle, olive oil), 0.4, 2, 10, and 50 mg/kg bw/day, for 42 days (males) or from 14 days before mating to the 4th day of lactation (42 - 52 days). No death was observed in either sex. A significant decrease in body weight was observed in dams in the late pregnancy period at 50 mg/kg bw/day, but it was considered to be general toxicity rather than reproductive toxicity. No effects were observed in the reproductive organ weights and histopathological examination of the reproductive organs. During the mating period, pseudopregnancy (no copulation) was observed in 1 and 2 females at only 2 mg/kg bw/day and 10 mg/kg bw/day, respectively. However, this effect was not statistically significant and was not dose-dependent. The prolonged pairing days until copulation was significantly observed at 50 mg/kg bw/day. No other adverse effects on reproductive/developmental parameters (such as copulation index, implantation index, fertility index, gestation index, maternal behaviour; numbers of offspring, or live offspring at birth or day 4, sex ratios of offspring, live birth index, viability index, body weight at birth or on day 4) were observed. Based on increased paring days until copulation at 50 mg/kg bw/day, the NOAEL for reproductive toxicity was considered to be 10 mg/kg bw/day. The NOAEL for developmental toxicity was considered to be 50 mg/kg bw/day (highest dose tested) based on no toxicological effects.

4,4'-Methylenebis(2-chloroaniline) possesses properties indicating a hazard for human health (repeated dose toxicity (anemia, methemoglobinemia, effects on kidney, liver and spleen), genotoxicity, carcinogenicity (tumours of liver, lung, mammary gland, Zymbal gland, bladder, urethra) and 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

4,4'-Methylenebis(2-chloroaniline) in the atmosphere is expected to be degraded by hydroxyl radicals. Using AOPWIN (ver. 1.92a), a calculated half-life time of 0.14 days and a rate constant of 77.5×10^{-12} cm^3/molecule-sec are obtained for the indirect photo-oxidation of 4,4'-methylenebis(2-chloroaniline) by reaction with hydroxyl radicals in air. For the purposes of the AOPWIN, it is assumed that the concentration of hydroxyl radicals in air is 1.5×10^6 OH/cm^3 and that the hydroxyl radicals are available to react with 4,4'- methylenebis(2-chloroaniline) for 12 hours/day.

It is thought that 4,4'-methylenebis(2-chloroaniline) is not hydrolyzed due to the lack of hydrolysable functional groups in its structure. A ready biodegradation test on 4,4'-methylenebis(2-chloroaniline) based on a protocol equivalent to OECD TG 301C was conducted with activated sludge. 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 with a cultivation period of four weeks. The test result showed 0 % degradation by BOD. BIOWIN (ver. 4.10) prediction shows no biodegradability of 4,4'-methylenebis(2-chloroaniline). According to these results, 4,4'-methylenebis(2-chloroaniline) is considered to be not readily biodegradable.

A study on 4,4'-methylenebis(2-chloroaniline) according to a protocol equivalent to OECD TG 305 with carp was performed. Bioconcentration factors of 130 - 398 and 114 - 232 were obtained for the concentration of 50 µg/L and of 5 µg/L, respectively, for the 8-week exposure period. Using an octanol-water partition coefficient (log K_{ow}) of 3.66, a bioconcentration factor of 121 was calculated with BCFBAFWIN, version 3.01. This chemical has a low potential for bioaccumulation.

Fugacity level III calculations show that 4,4'-methylenebis(2-chloroaniline) is mainly distributed in soil (84.7 %) and water (12.0 %) compartments if equally and continuously released to the air, soil and water. A Henry's law constant of 2.72×10^{-4} Pa.m^3/mole at 20 - 25 °C suggests that 4,4'-methylenebis(2-chloroaniline) is non-volatile from water. A soil adsorption coefficient of log K_{oc} = 3.56 indicates that 4,4'-methylenebis(2-chloroaniline) has adsorption potential to soil and sediment.

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

Fish [*Oryzias latipes*]: 96 h LC_{50} = 0.61 - 0.66 mg/L (nominal, semistatic), OECD-TG 203

Daphnid [*Daphnia magna*]: 48 h EC_{50} = 0.25 - 0.92 mg/L (measured, static), OECD-TG 202

Algae [*Pseudokirchneriella subcapitata*]: 72 h E_rC_{50} > 0.85 mg/L (measured, growth rate, static), OECD-TG 201

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

Daphnid [*Daphnia magna*]: 21 d EC_{50} = 0.052 mg/L (nominal, semistatic) OECD-TG 211

21 d LOEC = 0.03 mg/L (nominal, semistatic), OECD-TG 211

21 d NOEC = 0.0095 mg/L (nominal, semistatic), OECD-TG 211

21 d LOEC = 0.075 mg/L (nominal, semistatic), OECD-TG 202, part 2

21 d NOEC = 0.0375 mg/L (nominal, semistatic), OECD-TG 202, part 2

Algae[*Pseudokirchneriella subcapitata*]: 72 h NOE_rC = 0.54 mg/L (measured, growth rate, static), OECD-TG 201

The following chronic sediment toxicity test result has been determined for aquatic species:

Chironomid [*Chironomus yoshimatsui*] 27 d EC_{50} = 150 mg/Kg dry sediment

27 d LOEC = 180 mg/Kg dry sediment

27 d NOEC = 84 mg/Kg dry sediment (measured, emergence rate) OECD-TG 218

4,4'-Methylenebis(2-chloroaniline) possesses properties indicating a hazard for the environment (acute aquatic toxicity values less than 1 mg/L for fish and invertebrates, chronic aquatic toxicity values less than 1 mg/L for algae and less than 0.01mg/L for invertebrates). This chemical is not 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

Total amounts of production and import of 4,4'-methylenebis(2-chloroaniline) in Japan (sponsor country) were reported to be 2,751 tonnes (fiscal year 2010) and 3,013 tonnes (fiscal year 2011). In the United States, total

amounts of production and/or import were reported to be between 500,000 - 1 million pounds (between 227 to 454 tonnes) in 2006 according to the inventory updating rule. Total volume of production and import in the European Union is in a range of 1000 - 10,000 tonnes/year. Production volume in the world is not available. 4,4'-Methylenebis(2-chloroaniline) is manufactured based on the reaction of formaldehyde with 2-chloroaniline.

4,4'-Methylenebis(2-chloroaniline) is used as a curing agent for polyurethanes and epoxy resins which are used in the manufacture of specialized products, particularly integral-skin polyurethane semi-rigid foam and solid urethane rubber moulding such as gear blanks and industrial tires. 4,4'-Methylenebis(2-chloroaniline) is added to vary the hardness, flexibility, and impact strength of these products.

4,4'-Methylenebis(2-chloroaniline) is also used as a coating in chemical reactions to set glues, plastics and adhesives. A use of 4,4'-methylenebis(2-chloroaniline) in Japan is as a curing agent in water-proofing materials, flooring materials and pavement materials.

Based on the Japanese Pollutant Release and Transfer Register system which is equivalent to the TRI system, 171 kg of 4,4'-methylenebis(2-chloroaniline) was released into the atmosphere and no releases were estimated into surface water, lands and landfills in fiscal year 2009. Based on the TRI in the United States, a total of 617 kg (1,362 pounds) of 4,4'-methylenebis(2-chloroaniline) was released into the atmosphere from manufacturing and processing facilities in 1991. No discharges into surface water and land were reported.

During the environmental survey and monitoring of chemicals conducted by the Japanese Ministry of Environment, 4,4'-methylenebis(2-chloroaniline) was not detected in surface water in any of 6 different localities (detection limit of 30 ng/L), although 4,4'-methylenebis(2-chloroaniline) was detected in sediments in three places out of 7 localities in fiscal year 2005. Concentrations detected in sediments were 19 - 32 ng/g-dry wt, 8 - 9 ng/g-dry wt and 9 ng/g-dry wt. 4,4'-Methylenebis(2-chloroaniline) was not detected in surface water nor in sediments in any of 36 different localities (detection limit of 0.17 µg/L for surface water and detection limit of 0.031 µg/g-dry wt for sediment) in fiscal year 1999.

As mentioned above, release to the atmosphere is limited and releases to surface water and soil are negligible. It is thought that environmental release of 4,4'-methylenebis(2-chloroaniline) is not high.

As the vapour pressure is low, inhalation of vapour is not expected except when 4,4'-methylenebis(2-chloroaniline) is melted for manufacture of polyurethanes. Inhalation of dust may be a main exposure route where workers handle this chemical directly during emptying bags of 4,4'-methylenebis(2-chloroaniline) pellets. It is indicated by the toxicokinetics investigations that dermal intake is possible. In order to prevent exposure to inhaled dust and dermal intakes, proper engineering control (enclosure, local exhaust ventilation) and/or personal protective equipment are necessary at manufacturing and processing sites. A time weight average threshold limit value of 4,4'-methylenebis(2-chloroaniline) is decided to be 0.01 ppm (0.11 mg/m^3) by the American Conference of Industrial Hygienists.

Although trace amounts of unreacted 4,4'-methylenebis(2-chloroaniline) may be present in consumer products manufactured from polyurethane resins, no data have been identified on potential concentrations.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	107-18-6
Chemical Name	2-Propen-1-ol
Structural Formula	CH_2=CH-CH_2-OH

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Animal studies demonstrate that 2-propen-1-ol appears to be oxidised readily in the liver, giving a variety of metabolic products, such as acrolein, acrylic acid, glycidaldehyde, and glyceraldehyde. Among these metabolites, the most reactive metabolite, acrolein may cause hepatotoxicity in the liver.

The inhalation LC50 is 0.140-0.150 mg/L for 8 hours exposure in rats under vapour conditions. In the OECD TG 403 study, the LC50 is > 0.530 mg/L under mist conditions in rats. No deaths were observed at the concentration of 0.530 mg/L after 4 hours' exposure. The dermal LD50 (rabbit) is 89 mg/kg bw. The oral LD50 values are 70 and 99-105 in rats, 96 in mice and 71 mg/kg bw in rabbits. The intraperitoneal LD50 values are 37 and 42 in rats, and 60 mg/kg bw in mice. A 55-year old man died within 100 minutes of oral ingestion of 2-propen-1-ol. The amount ingested was assumed to be 212 g of 2-propen-1-ol at the maximum. Death was attributed to acrolein-induced cardiotoxicity.

2-Propen-1-ol is considered to be slightly irritating to the skin and irritating to eyes in animals. Moreover, 2-propen-1-ol may cause irritation of the eye and nasal mucosa in humans. 2-Propen-1-ol is considered not to be a skin sensitizer in guinea pigs [OECD TG 406].

In a repeat dose inhalation toxicity study, male rats were exposed to 2-propen-1-ol at nominal concentrations of 0, 0.0024, 0.0047, 0.012, 0.047, 0.095, 0.142, 0.237 or 0.355 mg/L for 7 hours/day, 5 days/week for 12 weeks. Histopathology showed that there was slight congestion of the lungs and liver at the dose of 0.355 mg/L (150 ppm). The NOAEL for inhalation toxicity in male rats is 0.012 mg/L (5 ppm) based on a significant decrease in body weight gain in groups exposed to 0.047 mg/L (20 ppm) and higher.

In a repeated dose oral toxicity study, 2-propen-1-ol had adverse effects on kidney tissues in rats, administered in the drinking water continuously for 15 weeks at or above a level of 100 ppm (8.3 mg/kg bw/day in males and 6.9 mg/kg bw/day in females). The NOAEL was 50 ppm of 2-propen-1-ol in drinking water (equivalent to 4.8 mg/kg bw/day in male rats and 6.2 mg/kg bw/day in female rats) based on adverse effects on kidney tissues (increases in absolute kidney weight and relative kidney weight) for females and on an increase in relative stomach weight for male and females at 100 ppm.

The *in vitro* studies, including reverse mutation assays in bacteria (*S. Typhimurium*: positive in T1535 with S9, TA100 without S9; negative in TA97, TA98, TA100 and TA1535 without S9), microbial forward mutation and fungal point mutation assays (*Streptomyces coelicolor* and *Aspergillus nidulans*, respectively: negative) and gene mutation in mammalian cells (V79 cells: positive) gave conflicting results, , while the *in vivo* studies concerning micronucleus and the dominant lethal assay in rodents gave negative results. Based on these data *in vitro* and *in vivo*, there is equivocal evidence that 2-propen-1-ol may be genotoxic.

A carcinogenicity study was conducted with male and female Fischer 344 rats via drinking water (300 mg/L, total dose of 3.2 g) for 106 weeks, followed by observation until natural death (123-132 weeks). The study gave no clear evidence of carcinogenicity in male rats, but there was equivocal evidence of carcinogenicity in the liver of female rats.

Reproductive/developmental toxicity was studied in SD rats by gavage at doses of 0, 2, 8 or 40 mg/kg bw/day [OECD TG 421]. Males were dosed from 14 days before mating for total of 42 days, and females were dosed from 14 days before mating throughout the mating and pregnancy period to day 3 of lactation. The autopsy was conducted on the day after the final administration. No deaths were found in any group. Clinical findings in parental animals at 40 mg/kg bw/day were salivation, decrease in locomotor activity, irregular respiration (male and female), lacrimation and loose stool (male). Histopathological examinations at 40 mg/kg bw/day revealed atrophy of the thymus and

hyperplasia of luteal cells in the ovary in females, necrosis, fibrosis, proliferation of bile duct, hypertrophy, and brown pigment deposition in perilobular hepatocytes, and diffuse clear cell changes in males and females, and hyperplasia of squamous epithelium in the forestomach in males. In male rats, no changes in histopathological findings or weight of the testes and epididymis were found. In females, extension of mean oestrous cycle length and increase in females with irregular oestrous cycle were observed at 40 mg/kg/day group. There were no adverse effects on the other reproductive performance parameters (such as the mating index, fertility index, numbers of corpora lutea or implantations, implantation index, delivery index, gestation index, gestation length, parturition or maternal behaviour). In examination of offspring, decrease in viability index on day 4 and total litter loss (from one dam) were observed at 40 mg/kg bw/day group. There were no treatment-related findings in the external appearance, general conditions and necropsy findings in the offspring.

The NOAEL is considered to be 8 mg/kg bw/day for general toxicity and reproductive/developmental toxicity. In a prenatal developmental study conducted in SD rats, 2-propen-1-ol was administered by gavage at doses of 0, 10, 35, or 50 mg/kg bw/day to pregnant rats on gestation days 9 to19 [OECD TG 414]. At doses of 10 mg/kg bw/day and higher significant toxicity in dams was observed. Maternal toxicities at 35 and 50 mg/kg bw/day were mortalities, clinical findings, reductions in body weight gain and feed consumption, macroscopic liver findings and increased liver weights. One female at 10 mg/kg bw/day also had macroscopic liver findings. An increased frequency of total litter loss was observed at 35 and 50 mg/kg bw/day dose levels. In case of total litter loss, severe toxicities were observed in the dam (loss of body weight, severe decreases in feed consumption, and evidence of significant liver toxicity). Despite the severe maternal toxicity observed, there were no 2-propen-1-ol related increases in malformation rates or incidence of variations. 2-Propen-1-ol had no effects on intrauterine growth or survival in the fetuses from dams that survived to necropsy. Therefore, 10 mg/kg bw/day was considered to be the LOAEL for maternal toxicity, based on liver findings, and 10 mg/kg bw/day was considered to be the NOAEL for developmental toxicity, based on an increased frequency of total litter loss at 35 and 50 mg/kg bw/day, when 2-propen-1-ol was administered orally by gavage to pregnant rats.

2-Propen-1-ol possesses properties indicating a hazard for human health (acute toxicity, repeated dose toxicity, irritation, genotoxicity, carcinogenicity, reproductive/developmental toxicity). Adequate screening level data are available to characterize the human health hazard for the purposes of the Cooperative Chemicals Assessment Programme.

Environment

2-Propen-1-ol is a colourless liquid and is miscible with water. Melting point, boiling point, vapour pressure and partition coefficient are -129 °C, 96.9 °C, 25 hPa (20 °C) and log Kow = 0.17, respectively. 2-Propen-1-ol is not expected to be hydrolyzed under normal environmental conditions. Indirect photo-oxidation by hydroxy radicals in the atmosphere is predicted to occur with a half-life of 4.32 hours. 2-Propen-1-ol is readily biodegradable under aerobic conditions within 14 days (BOD = 86 %). The estimated BCF is 3.2 and there is low potential for bioaccumulation. Fugacity Model Mackay level III calculations indicate that 2-propen-1-ol will be distributed mainly to air (67.6 %) water (25.1 %) and soil (7.3 %) compartment if released to air, while 2-propen-1-ol will stay exclusively in the water compartment (99.7 %) if released to water. If released to soil, 2-propen-1-ol will be distributed mainly to the water (19.4 %) and soil (80.4 %) compartment. If released simultaneously to air, soil and water, 2-propen-1-ol will be distributed mainly to water (62.1 %) and soil (36.7 %) compartment. Henry's Law constant is 4.99×10^{-6} atm.m^3/mole.

Acute toxicities to fish (96-h LC50) are 0.59 mg/L (Medaka) [OECD TG 203] and 0.32 mg/L (Fathead minnow). Acute toxicity to *Daphnia magna* (48-h EC50) is 2.1 mg/ L [OECD TG 202]. The 48-h LC50 in Polychaete (*Ophryotrocha diadema*) is 0.33-1.0 mg/ L. Acute toxicities to green algae (*Pseudokirchneriella subcapitata*) are 5.4 mg/L (72-h ErC50) and 2.3 mg/L (72-h EbC50) [OECD TG 201]. The NOEC of 21-d chronic toxicity in *Daphnia magna* is 0.92 mg/L [OECD TG 211]. The NOEC value in green algae (*Pseudokirchneriella subcapitata*) is 0.93 mg/L (72-h for growth rate and biomass) [OECD TG 201].

2-Propen-1-ol possesses properties indicating a hazard for the environment (acute toxicity in algae, fish and daphnia and chronic toxicity in daphnia). Adequate screening level data are available to characterize the environmental hazard for the purposes of the Cooperative Chemicals Assessment Programme.

Exposure

The production volume of 2-propen-1-ol was estimated at 136,100 t/year worldwide in 2003 and 45,000 t/year in Japan in 2001. Two producers in Japan account for approx 30-40 % of global production. 2-Propen-1-ol is an

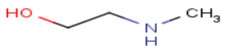
important starting material, and is used in the manufacture of 1,4-butandeiol, 2-methyl-1,3-propandiol, allyl diglycol carbonate, diallyl phthalate, diallyl isophthalate, allyl glycidyl ether, epichlorohydrin, allyl methacrylate, styrene 2-propen-1-ol and resins for coating applications, flavorings such as allyl hexanoate, contact herbicide, as an intermediate for manufacturing pharmaceuticals, fire retardants and herbicides.

2-Propen-1-ol is exclusively used as an intermediate in chemical synthesis. Occupational exposure is possible by the inhalation and dermal routes at the manufacturing and user sites. No consumer use is known for 2-propen-1-ol. However, monitoring data provided by the sponsor country indicate that potential indirect exposure via the environment is anticipated.

Consumers may be potentially exposed to 2-propen-1-ol from ingestion of foods. 2-Propen-1-ol has been detected in crab meat, mussels and garlic. 2-Propen-1-ol is rapidly formed in the body from the hydrolysis of allyl esters used as flavour agents in food. The estimated intake of 2-propen-1-ol from this route is 18µg/kg bw/day in Europe and 5.8 µg/kg bw/day in the USA.

MOE, Japan monitored 2-propen-1-ol concentrations in the environment such as air, well water, sea water and river water throughout Japan. Based on these studies the estimated human exposure (EHE) is calculated to be 0.027 ug/kg bw/day under the standardised Japanese condition. A second Japanese monitoring study performed in the Kitakyushu-city area reported that no 2-propen-1-ol was detected in sea water, river water, reservoir water and effluent of sewage treatment plant in addition to well water, tap water and rain water at the limit of detection of 0.008ug/L.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	109-83-1
Chemical Name	Ethanol, 2-(methylamino)- (MMEA)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Physical-chemical Properties

2-(Methylamino)ethanol (MMEA) is a colorless liquid with a measured melting point of -5 °C, a measured boiling point of 159.5 °C and a calculated vapour pressure of 0.98 hPa at 20 °C. The measured octanol-water partition coefficient (log K_{ow}) is -0.91 at 25 °C and pH 10.6 - 11.0, and the measured water solubility is 1000 g/L at 20 °C. The measured pKa of the protonated amine is 9.95 at 20 °C. Unprotonated amines typically have pKa values of 30 - 40.

Human Health

Absorption of MMEA by the dermal, oral and inhalation routes is expected because it has a low molecular weight and is soluble in both water and lipid. The major routes of metabolism of secondary amines such as MMEA involve various oxidative processes, including N-oxidation and dealkylation followed by deamination and conjugation, and other enzyme-catalyzed reactions leading to detoxification and excretion.

The dermal LD_{50}s in male and female rabbits were 1880 and 1006 mg/kg bw, respectively; the dermal LD_{50} in rats was > 2000 mg/kg bw. The oral LD_{50}s in rats were 1391 mg/kg bw (females), 1908 mg/kg bw (males) and 1880 mg/kg bw (combined sexes) [similar to OECD 401]. MMEA caused irritation and ulceration at the site of contact following dermal or oral exposure.

MMEA is corrosive to rabbit skin [study similar to OECD TG 404] and rabbit eyes [study similar to OECD TG 405].

MMEA was not sensitizing in a standard guinea pig sensitization study [similar to OECD TG 406].

In an OECD 422 study with rats, the LOAEL for repeated-dose systemic toxicity in males was 50 mg/kg bw/day (lowest dose tested) based on renal tubular degeneration. In female rats, the NOAEL of 50 mg/kg bw/day and the LOAEL of 150 mg/kg bw/day were identified based on changes in haematology parameters, blood in urine, increased urea, and adverse histological changes in kidneys, spleen, and liver that were accompanied by changes in the weights of these organs.

MMEA did not result in gene mutations in bacteria (guideline not indicated) or mammalian cells (OECD TG 476) *in vitro* and did not induce chromosomal aberrations in mammalian cells *in vitro* (OECD TG 473). MMEA is not considered mutagenic.

No data are available for the carcinogenicity of MMEA.

In an OECD TG 422 oral gavage study with rats, the NOAEL for reproductive toxicity (fertility and

reproductive performance) for MMEA was 50 mg/kg bw/day. The LOAEL was 150 mg/kg bw/day, as tubular degeneration of the testis, vacuolization of ovarian sex cord stroma, and reduced fertility index were observed at 150 and 450 mg/kg bw/day. At 450 mg/kg bw/day, no pups were delivered; at 150 mg/kg bw/day one stillborn pup (but no live pups) was delivered. The NOAEL for developmental toxicity (embryotoxic / teratogenic effects) was 50 mg/kg bw/day based on the calculation of post-implantation loss at 150 and 450 mg/kg bw/day. Pregnant rats exposed to MMEA vapor by inhalation at a concentration (near the saturation point) of 0.46 mg/L for gestation days 7-15 showed no maternal or fetotoxicity; the NOAEC for maternal and developmental toxicity was 0.46 mg/L (the only concentration tested).

MMEA possesses properties indicating a hazard for human health (acute toxicity; corrosive to skin, eyes, respiratory tract, and/or the site of contact; systemic toxicity (liver, kidney and spleen); reproductive and 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

An OECD TG 111 (Hydrolysis as a Function of pH) study has not been conducted for MMEA. MMEA is not expected to undergo hydrolysis under environmental conditions because the substance lacks functional groups where this process would be relevant. MMEA is likely to exist predominantly as the protonated amine (i.e. charged, cationic form) in water at environmentally relevant pH; as such, results from EPISUITE should be interpreted with caution. The EPI Suite modeling results are based on the unprotonated neutral form of MMEA.

In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of 1.6 hours (1.5×10^6 OH-radicals/cm³; 12-h day). An OECD TG 301A study (new version) resulted in 92 - 93% biodegradation after 21 days. MMEA is readily biodegradable.

A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that MMEA will distribute mainly to the soil (54.3%) and water (45.2%) compartments with minor distribution to the air compartment (0.4%) and sediment compartment (0.09%). Volatilization from water is expected to be low based on the calculated Henry's law constant of 4.6×10^{-8} Pa-m^3/mole (charged molecule at pH 7.0). A K_{oc} of 1.3 for neutral MMEA and a pH-corrected K_{oc} of 18 for the charged molecule at pH 7.0 was estimated; these Koc values suggest that MMEA will be mobile in soils. However, cationic forms of molecules generally bind more strongly to soils that contain organic carbon and clay than the neutral form of MMEA.

The bioaccumulation potential is predicted to be low based on a BCF value of 3.16 L/kg wet-wt estimated with BCFWIN.

The following acute toxicity test results have been determined for aquatic species, e.g.:

Fish [*Oncorhynchus mykiss*]	96 h LC_{50} = 100 mg/L (semi-static; no further details)
Invertebrate [*Daphnia magna*]	48 h LC_{50} = 33 mg/L (measured; static; pH not adjusted; pH 8.0 – 9.9) [EU Method C.2]
Algae [*Desmodesmus subspicatus*]	72 h ErC_{50} = 28.1 mg/L, 72 h EbC_{50} = 18.4 mg/L, 72 h LOEC = 6.25 mg/L; NOEC = 3.13 mg/L (biomass; measured; pH not adjusted; pH 7.98 – 9.65) [EU Method C.3]

In the acute *Daphnia magna* test, pH values of up to pH 9.9 were measured after 3 h, exceeding the tolerable pH-range of pH 6.0 – pH 9.0. Therefore, the observed adverse effects may be at least partly caused by a pH shift to more alkaline pH values at higher test item concentrations.

MMEA possesses properties indicating a hazard for the environment (acute aquatic toxicity values between 1 and 100 mg/L for aquatic plants and invertebrates). MMEA is readily biodegradable and not expected to bioaccumulate. Adequate screening-level data are available to characterize the hazard to the environment for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Exposure

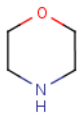
MMEA is commercially produced with an annual production volume of 4212 tonnes in the United States (sponsor country) in the year 2012. Worldwide production volume is not available. MMEA is a component of an amine gas treating solvent mixture used for removal of contaminants from natural gas and natural gas liquids. It is also used as an intermediate and an additive in coatings and paints, thinners, and paint removers.

The most likely route of human occupational exposure is either via dermal contact or inhalation; MMEA is corrosive to the skin and adequate protective equipment is required if any splash hazard is present. In addition, employee health and safety training provides employees with an understanding of the potential for skin and eye damage from direct contact.

In an occupational setting, exposure to MMEA could occur during charging of reactor vessels, and sampling for quality control. Use of MMEA in consumer products has not been reported.

Environmental releases of MMEA could occur through fugitive air emissions.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	110-91-8
Chemical Name	Morpholine
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Analogue Rationale

For human health endpoints, in some cases, the tested substance was a salt or acid of morpholine to avoid damage to the gastrointestinal tract following gavage administration due to the caustic mode of action. Testing the salt or acid also provides the ability to distinguish between symptoms caused by local effects and those that are due to systemic toxicity. Tested substances included morpholine hydrochloride (HCl), CAS No. 10024-89-2 (toxicokinetics and developmental toxicity); morpholine palmitate, CAS No. not available (toxicokinetics); morpholine oleic acid salt, CAS No. 1095-66-5 (MOAS; repeated dose toxicity), and morpholine fatty acid salt, CAS No. not available (mutagenicity). Note that the salts of morpholine used as analogues dissociate upon dissolution so that the tested chemical species *in vivo* is the same as the sponsored chemical. The counter ions are chloride and naturally occuring fatty acid substances and as such are not expected to contribute to the toxicological profile of morpholine.

Physical-chemical Properties

Morpholine is a liquid with a measured melting point of -4.9 °C, a measured boiling point of 128.3 °C at 1013 hPa and a measured vapour pressure of 9.8 hPa at 20.3 °C. The measured octanol-water partition coefficient (log K_{ow}) is -2.55 at 25 °C and pH 7, and the substance is completely miscible in water. The pKa of the protonated form is 8.49 at 25 °C (measured; expressed as the acidity of the conjugate acid).

Human Health

Absorption of morpholine by the dermal, oral and inhalation routes is expected because it has low molecular weight and is both water and lipid soluble. Based on the recovery of morpholine or morpholine salts in urine following inhalation or oral exposure, absorption is expected to be at least 55 or 90%, respectively. Morpholine (information from morpholine HCl) is well distributed following all routes of exposure, with distribution primarily to the kidney, intestine and muscle. The highest concentration is expected to be in the kidney. The major routes of metabolism of morpholine involve various oxidative processes, including N-oxidation and dealkylation followed by deamination and conjugation, and other enzyme-catalyzed reactions leading to detoxification and excretion. However, most of the administered dose is excreted in its non-metabolized form. The primary excretory pathway for morpholine (information from morpholine HCl or morpholine palmitate) is urinary excretion.

Acute inhalation studies are available for morpholine, although discrete LC_{50} values were not determined. There was no mortality in rats exposed to nominal concentrations of 24 mg/L for 4 hours (similar to OECD TG 403). There were signs of irritation, but there were no effects on body weight and no findings at gross necropsy.

There was 100% mortality in rats exposed to vapour concentrations of 21.14 mg/L (nominal) for 5.5 hours or 4.6 - 5.4 mg/L (measured) for 6 hours; 33% mortality was found in rats exposed to 28.8 mg/L (nominal) for 3 hours (similar to OECD TG 403). Clinical signs and findings at gross necropsy were consistent with generally severe local effects of eye and respiratory irritation, respiratory distress and lung damage. A dermal LD_{50} value (rabbit) of 500 mg/kg bw was determined following a 24-hour occluded exposure (similar to OECD TG 402); clinical signs were not reported in this study. Oral LD_{50} values were 1050 - 1900 mg/kg bw in rats (all studies similar to OECD TG 401). Clinical signs reported include breathing abnormalities, oral-nasal wetness and/or staining, effects on gait, postural abnormalities, and eye closure. Site of contact effects (irritation/corrosion) in the gastrointestinal tract were the only findings noted at gross necropsy. Based on the oral toxicity studies, females may be more sensitive than males.

Undiluted morpholine is corrosive to the skin (OECD TG 404) and the eyes (OECD TG 405) of rabbits. Respiratory irritation studies were not available. Signs of respiratory irritation were noted during an acute inhalation toxicity study in rats described above.

Morpholine was not sensitizing in a standard (Buehler) guinea pig sensitization study.

Systemic NOAECs following repeated whole body vapor inhalation exposure of rats to morpholine ranged from 0.543 mg/L (0, 0.036, 0.186 and 0.543 mg/L for 104 weeks; similar to OECD TG 453) to 0.89 mg/L (0, 0.089, 0.36, and 0.89 mg/L for 13 weeks; similar to OECD TG 413), which were the highest concentrations tested in each study. Local NOAECs following repeated inhalation exposure to morpholine ranged from 0.036 mg/L (104 weeks) to 0.36 mg/L (13 weeks). Focal erosion of the nasal turbinates was observed in rats following inhalation exposure to 0.89 mg/L for 13 weeks and necrosis of the nasal turbinates was observed in rats following inhalation exposure to 0.186 mg/L for 104 weeks.

In mice exposed to MOAS in drinking water (~ 0, 140, 200, 400 and 700 mg/kg bw/day) for 91 days, cloudy swelling of the proximal tubules of the kidneys was observed at 700 mg/kg bw/day in drinking water. The NOAEL for oral systemic toxicity for morpholine in mice was 400 mg/kg bw/day.

In mice exposed to MOAS in drinking water (~ 0, 0.4 and 1.5 g/kg bw/day for males; ~ 0, 0.5 and 1.5 g/kg bw/day for females) for 96 weeks, followed by 8 weeks of tap water, reduction in body weight was observed in both sexes given 1.5 g/kg bw/day and in females given 0.5 g/kg bw/day. Water consumption was also decreased in both sexes at 1.5 g/kg bw/day compared to controls consuming tap water. Significant increases in blood-urea nitrogen concentrations were only observed in the 1.5 g/kg bw/day male group. A NOAEL was not identified based on a reduction in body weights in females at 0.5 g/kg bw/day and both sexes at 1.5 g/kg bw/day.

Moderate adiposis of the liver was observed in rats administered 500 mg/kg bw/day morpholine (only dose tested) in the diet for 56 days; this was the established LOAEL.

In rats administered morpholine by gavage (0, 160, 320 and 800 mg/kg bw/day) for 30 days, swelling, congestion, necrosis and/or desquamation of the liver, kidneys, lungs and stomach were observed; the LOAEL was 160 mg/kg bw/day. In guinea pigs administered morpholine by gavage (0, 90, 180 or 450 mg/kg bw/day) for 30 days, clinical signs of toxicity included prostration, sneezing and coughing. Effects on the kidney (cloudy swelling, congestion, necrotic tubules), liver (cloudy swelling, congestion, necrosis and fatty degeneration), spleen and stomach (necrosis) were seen at all treatment levels; the LOAEL was 90 mg/kg bw/day.

Morpholine did not increase reverse mutations in *E. coli* or *S. cerevisiae* or in three studies with *S. typhimurium* (including one study conducted with morpholine fatty acid salt) *in vitro* (all similar to OECD TG 471). However, weak positive results for gene mutations were noted in another study with *S. typhimurium* (Ames test) and in an *in vitro* study of mammalian (mouse lymphoma) cells (similar to OECD TG 476) at high and/or cytotoxic doses. One negative and one positive result were observed in two *in vitro* mammalian (BALB/3T3 mouse) cell transformation assays (EU Method B.21). No increases in the frequency of sister chromatid exchanges (CHO cells; similar to OECD TG 479) or unscheduled DNA synthesis (rat hepatocytes; similar to OECD TG 482) were observed in *in vitro* studies of mammalian cells. Morpholine fatty acid salt did not induce chromosome aberrations in mammalian (CHL cells; no guideline specified) cells *in vitro*. In an *in vivo* study, morpholine did not induce chromosomal aberrations or micronuclei in hamster embryos (no guideline specified). Based on the weight of evidence, with special regard to the equivocal findings of the gene mutation studies conducted at high doses *in vitro*, and the negative results for clastogenicity *in vitro* and *in vivo*,

morpholine is not considered to be genotoxic.

Carcinogenicity studies conducted via the inhalation (similar to OECD TG 453) and oral (no guideline specified) routes of exposure indicate morpholine is not carcinogenic.

A standard toxicity to fertility study was not located. There were no effects of morpholine on the reproductive organs examined in 13-week (exposure concentrations of 0, 0.089, 0.36, and 0.89 mg/L; similar to OECD TG 413) or 104-week (exposure concentrations of 0, 0.036, 0.186 and 0.543 mg/L; similar to OECD TG 453) repeated dose vapour inhalation studies with rats; the NOAEC for effects on reproductive organs was 0.543 mg/L (NOAEC from longest duration study). In a prenatal developmental toxicity study (OECD TG 414), pregnant rats were administered morpholine HCl by oral (gavage) at doses 0, 75, 250 and 750 mg/kg bw/day for gestation day 6 - 19. The maternal NOAEL was 75 mg/kg bw/day based on hematological changes. There were no effects on gestational parameters and fetal examinations revealed no effects on sex distribution of the fetuses, fetal body weights or placenta weights. Fetal findings in this study were primarily limited to skeletal variations (slight increase in delayed ossification) in the mid- and high-dose groups, and are considered to be transient in nature, and secondary to maternal toxicity. These findings were regarded to be of no toxicological relevance and are not considered adverse. The NOAEL for prenatal development toxicity was 750 mg/kg bw/day (highest dose tested).

Morpholine possess properties indicating a hazard for human health (acute toxicity; corrosive to skin, eyes, respiratory tract, and/or the site of contact; repeated-dose toxicity [liver and kidney)]). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Environment

Morpholine is considered resistant to hydrolysis because it does not contain labile functional groups; hydrolysis is not expected under environmental conditions. Morpholine is expected to exist in its protonated form at pH 5 - 7. At pH 8 and pH 9 the degree of ionization was estimated at 65% and 15%, respectively, using SPARC v4.2.

In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of 0.9 hours ($1.5x10^6$ OH/cm³; 12-h day). Morpholine was considered readily biodegradable, fulfilling the 10-d window criteria, in a biodegradation test according to OECD TG 301E (92.6 % in 22 days) after a lag phase of 15 days. Supporting studies according to OECD TG 302B confirm that morpholine is inherently biodegradable under aerobic conditions when morpholine-degrading organisms are present and after acclimation of these organisms is achieved.

A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that morpholine will distribute mainly to the soil (57.9%) and water (41.7%) compartments with a negligible amount in the air and sediments compartment. Henry's Law constants of 1.15 x 10^{-2} Pa-m^3/mole for the neutral molecule and 3.60 x 10^{-4} Pa-m^3/mole for cationic morpholine at pH 7.0 suggest that volatilization of morpholine from the water phase is not expected to be high. A K_{oc} of 7.4 for neutral morpholine and a pH-corrected K_{oc} of 76 for the charged molecule at pH 7.0 was estimated; these Koc values suggest that morpholine will be mobile in soils. However, cationic forms of molecules generally bind more strongly to soils that contain organic carbon and clay than the neutral form of morpholine.

Morpholine is not expected to bioaccumulate in the aquatic environment based on measured bioconcentration factors of < 2.8 (0.5 mg/L) and < 0.3 - 0.65 (5 mg/L) in an OECD 305C study.

The following acute toxicity test results have been determined for aquatic species, e.g.:

Fish

Species	Results (mg/L) (nominal/measured)
Oryzias latipes	96-h LC_{50} >100 (nominal, verified by measurement)

Invertebrates

Species	Results (mg/L) (nominal/measured)
Daphnia magna	48-hr EC_{50} = 45 (nominal, verified by measurement)

Algae

Species	Results (mg/L) (nominal/measured)
Pseudokirchneriella subcapitata	72-hr E_rC_{50} = 58, 72-hr E_bC_{50} = 51, 72-hr NOE_rC = 30.9; 72-hr NOE_bC = 30.9 (nominal, verified by measurement)

The following chronic toxicity test results have been determined:

Species	Result (mg/L)
Daphnia magna	21-day NOEC (reproduction) = 5, 21-day EC_{50} (reproduction) = 12 (nominal, verified by measurement)

Morpholine possesses properties indicating a hazard for the environment (acute aquatic toxicity values between 10 and 100 mg/L for invertebrates and algae). Morpholine is readily biodegradable and is not expected to bioaccumulate. Adequate screening-level data are available to characterize the hazard to the environment for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Exposure

Morpholine is commercially produced with a 2005 production volume of 4536 – 22,680 tonnes in the sponsor country (United States). Morpholine is used in industry as a versatile intermediate for chemical synthesis, e.g. for the production of rubber chemicals, pharmaceuticals, pesticides and optical brighteners. Functionally, morpholine is used as a solvent (which becomes part of product formulation or mixture) in industrial gas manufacturing and in other chemical product and preparation manufacturing.

Furthermore, formulations containing morpholine are used by professionals in many applications e.g. coatings, adhesives, paints, cement/asphalt and lubricants.

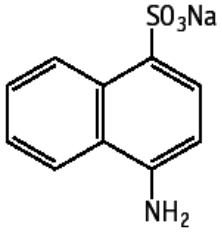
In addition, morpholine is used in commercial or consumer soaps and detergents.

The most likely route of human occupational exposure is either via dermal contact or inhalation; morpholine is corrosive and adequate protective equipment is required. In addition, employee health and safety training is recommended to provide employees with an understanding of the potential for skin and eye damage from direct contact.

Consumer exposure can occur through the use of commercial or consumer soaps and detergents.

Environmental releases of morpholine could occur through fugitive air emissions and on-site land disposal.

INITIAL TARGETED ASSESSMENT PROFILE

CAS No.	130-13-2
Chemical Name	4-Amino-1-naphthalenesulfonic 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, *in vitro* mutagenicity and developmental toxicity. 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).

4-Amino-1-naphthalenesulfonic 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

4-Amino-1-naphthalenesulfonic acid sodium salt is a brown crystalline solid at room temperature. Melting point is 280 °C, and boiling point is calculated to be 634.6 °C by MPBPWIN (version 1.43). However, this chemical may be decomposed before the temperature reaches 634.6 °C. Partition coefficient between octanol and water (log K_{ow}) is -2.34. Vapour pressure is estimated to be 2.07×10^{-12} Pa at 25 °C. Water solubility is 1×10^{6} mg/L at 25 °C.

Human Health

In a limited and old toxicokinetics study with rabbits, 4-amino-1-naphthalenesulfonic acid sodium salt (50mg/mL) or inulin were administered by rapid intravenous injection into a median ear vein. Blood samples were taken at frequent intervals. Urine was collected for 3 - 5 days. It was found that 4-amino-1-naphthalenesulfonic acid bound strongly to blood and was not fully released by the protein precipitant. 4-Amino-1-naphthalenesulfonic acid had a greater clearance value compared with inulin. It was concluded that 4-amino-1-naphthalenesulfonic acid is actively secreted into the renal tubule.

No acute toxicity study is available for 4-amino-1-naphthalenesulfonic acid sodium salt. However, in a 7-day dose range finding study for a 28-day repeated dose toxicity test, no deaths or clinical signs of toxicity were observed at a dose as high as 1000 mg/kg bw/day in rats. Therefore, the oral LD_{50} for 4-amino-1-naphthalenesulfonic acid sodium salt was considered to be greater than 1000 mg/kg bw in rats.

A 28-day repeated dose toxicity study was conducted in accordance with the Japanese guideline (similar to OECD Guideline 407). In this study, 4-amino-1-naphthalenesulfonic acid sodium salt was administered to 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 treatment-related changes in general conditions, food consumption, body weights, urinary findings, results of hematological analysis or pathological findings. Blood chemical analysis revealed increases in GPT activity in males and in the creatinine and calcium levels in females in the 1000 mg/kg bw/day group. Since these biochemical changes were slight and no related changes were found for the organ weight or histopathology, the NOAEL for 4-amino-1-naphthalenesulfonic acid sodium salt is considered to be 1000 mg/kg bw/day in male and female rats in the 28-day repeated dose oral toxicity test.

In bacterial mutation studies using *Salmonella typhimurium* and *Escherichia coli* [including OECD guideline study (TG471 and 472)], 4-amino-1-naphthalenesulfonic acid sodium salt was negative in all tested strains with and without metabolic activation. In an *in vitro* chromosome aberration test using CHL/IU cells (OECD TG 473), 4-amino-1-naphthalenesulfonic acid sodium salt was also negative for structural chromosomal aberration or polyploidy induction with and without metabolic activation. *In vivo* genotoxicity data are not available. Based on these results, 4-amino-1-naphthalenesulfonic acid sodium salt is considered to be non genotoxic *in vitro*.

As for the developmental toxicity, one prenatal toxicity study was available. 4-Amino-1-naphthalenesulfonic acid sodium salt was administered by gavage to female rats at 0 (vehicle: distilled water), 15, 30, 100 or 200 mg/kg bw/day during days 0 - 19 of pregnancy. None of the animals died during the treatment period, neither were any adverse clinical signs observed, although no information on the body weight, food and water consumption and histopathological findings in dams were available. No significant effects were found on total number of corpora lutea and implantations, number of corpora lutea per dam, and the percentage of implantation loss. In the 200 mg/kg bw/day group, the number of resorption per litter and the incidence of total litter loss were increased. There were no significant differences in the total number of fetuses per litter, the number of live fetuses per litter or the mean weight of the fetuses between the control and 4-amino-1-naphthalenesulfonic acid sodium salt-treated groups. No dose-related increase was found in the number of offspring with external, skeletal, sternebral or soft-tissue abnormalities. Based on these findings, the NOAEL for developmental toxicity of 4-amino-1-naphthalenesulfonic acid sodium salt was considered to be 100 mg/kg bw/day in rats.

Agreed Hazard Conclusions

Based on the available information, 4-amino-1-naphthalenesulfonic acid sodium salt posseses properties indicating a hazard for one human health endpoint (developmental toxicity) targeted in this assessment.

Available Exposure

Production and/or import volume of 4-amino-1-naphthalenesulfonic acid sodium salt was reported to be less than 1,000 tones/year in fiscal year 2010 in Japan. Production volumes in other countries are not available. 4-Amino-1-naphthalenesulfonic acid sodium salt is used as an intermediate for azo-dyes.

SIDS INITIAL ASSESSMENT PROFILE

Chemical Name	2-aminoethanol
CAS Number	141-43-5
Structural Formula	$HO\text{-}CH_2\text{-}CH_2\text{-}NH_2$

SUMMARY CONCLUSIONS OF THE SIAR

Analogue Justification

The hydrochloride salt (MEA-HCl; CAS 2002-24-6) was used for the two generation reproduction toxicity study in rats. Once dissolved and dissociated there is no difference expected in the toxicity of MEA and the hydrochloride salt.

Physical-chemical Properties

2-Aminoethanol (monoethanolamine; MEA) is an organic, colorless, viscous liquid with an unpleasant, fishy, ammoniac odour. The melting point was measured at 4 °C at atmospheric pressure and the measured boiling point was 167 °C at 101 kPa. The measured density of 1.02 g/cm^3 at 20 °C is slightly higher than that of water. The vapor pressure of 0.5 hPa at 20 °C can be calculated from a regression, which was derived by dynamic vapor pressure measurements. MEA is completely miscible with water at ambient temperature. The measured n-octanol/water partition coefficient (log K_{ow}) was determined to be -2.3 at 25 °C (pH 6.8 - 7.3). A measured pKa value (expected to be the value for the protonated form of MEA) in water is 9.5. The pKa of MEA itself is likely to be in the high 20s or 30s.

Human Health

MEA is present in nature as a nitrogenous base in phospholipids, which constitute the building blocks of cell membranes in animals. MEA applied to skin preparations *in vitro* showed steady state penetration rates of 123.1 (mouse) > 73.8 (rabbit) > 42.5 (rat) > 7.9 (human) µg/cm²/h. MEA is metabolized to acetaldehyde and ammonia; the reaction is catalyzed by ethanolamine deaminase and further degraded to CO_2 via the formation of ethanolamine-O-phosphate. MEA was shown to be a natural metabolite in the urine of rats, cats, dogs, rabbits and humans. MEA is also metabolized to ammonia and acetaldehyde by ethanolamine deaminase, the latter one is further metabolized to CO_2.

MEA has moderate acute oral toxicity, but has low toxicity after inhalative or dermal exposure.

The inhalation LC_{50} for 6 hours exposure was >520 ppm (1300 mg/m^3) and using modified Haber's law the calculated 4 h LC_{50} was >1487 mg/m^3. Also no mortalities were reported upon exposure of rats to saturated vapor concentrations of MEA for 8 h.

The key oral LD_{50} values were 1089 and 1515 mg/kg bw in male and female rats.

The dermal LD_{50} value was 2504 mg/kg in the male rabbit and 2881 mg/kg in the female rabbit.

The unspecific clinical effects seen in acute studies consisted of sluggishness, prostration, unkempt appearance, piloerection, lacrimation, emaciation, kyphosis and unsteady gait beside local irritant effects in the form of eyrthema, edema, ecchymosis, descquamation, necrosis, ulceration, and scabs after dermal exposure.

MEA is corrosive to the skin and corrosive or causes severe eye irritation in laboratory animals.

MEA is not a skin sensitizer in animals.

Available information in humans is ambiguous as there are negative but also several reports of dermatitis and positive epicutaneous test reactions to MEA, particularly in metalworkers exposed regularly to cooling lubricants.

The inhalation exposure of rats to MEA for 28 days caused concentration-related lesions in larynx, trachea and lung. No histopathological effects were seen in any other organ outside the respiratory tract. The NOAEC for systemic toxicity is the highest concentration tested of 150 mg/m³. The NOAEC for local portal of entry effects was the lowest tested concentration of 10 mg/m³. In a two-generation oral reproductive toxicity study with MEA-HCl, the NOAEL for general systemic toxicity was 300 mg/kg bw/day based on reduced body weight gain and/or food consumption. Repeated dose dermal toxicity studies have not been conducted.

MEA did not induce reverse mutations in *Salmonella typhimurium* or *Escherichia coli* and had no effect on gene conversion in *Saccharomyces cerevisiae*. In mammalian *in vitro* systems, MEA did not induce chromosomal aberrations in rat hepatocytes, gene mutation in mouse lymphoma cells or Chinese hamster lung fibroblasts. In the hamster embryo cells no morphological transformation were induced. *In vivo*, MEA showed no chromosome-damaging effect or any impairment of chromosome distribution in the course of mitosis in a mouse micronucleus test. Overall, information from both *in vitro* and *in vivo* tests that cover relevant endpoints indicates that MEA is not genotoxic.

No reliable data are available to assess the carcinogenicity of MEA.

A two-generation reproduction toxicity study in rats with dietary MEA-HCl administration demonstrated clear NOAELs for systemic and reproductive toxicity including effects on fertility at 300 mg/kg bw/day. Only at 1000 mg/kg bw/day, which is generally accepted as a limit dose level, minor effects were noted. Males at this dose showed a minor functional impairment of fertility in the form of decreased weights of epididymides and cauda epididymidis and reductions in the number of homogenization resistant caudal epididymal sperm. However, there was neither an effect on mating success nor histomorphological evidence of testicular toxicity. Females at this dose had decreased numbers of implants and increased resorption rates resulting in smaller litters associated with indications of systemic toxicity. There was virtually no effect on the pre- and postnatal development of the progeny in both generations up to the limit dose level of 1000 mg/kg bw/day representing a NOAEL for developmental toxicity.

MEA was investigated for prenatal developmental toxicity in several oral studies in rats. Studies conducted according to GLP and OECD guidelines indicated a NOAEL for maternal toxicity in the range of 120 – 300 mg/kg bw/day. There was no indication of prenatal developmental toxicity including teratogenicity in these studies up to the highest dose levels tested (450 – 500 mg/kg bw/day). A non-GLP and non-guideline study with low numbers of pregnant rats (10 per dose) was primarily designed to evaluate whether MEA would more affect specific fetal subtypes dependent on their *in utero* position relative to siblings of the same or opposite sex. This test used atypical interpretation criteria and was performed with Long-Evans strain rats, which is clearly susceptible to developmental toxicity, as ca. 14% of dead or malformed foetuses were seen in the control group. Embryotoxicity was seen that included increases in *in utero* deaths and numbers of pups with morphological changes (up to approximately 50% when combined) currently predominantly classified as variations. The LOAEL for developmental toxicity was 50 mg/kg bw/day.

In mice, limited developmental toxicity in the form of decreased numbers of viable litters was only noted in the Chernoff and Kavlock oral screening test at a dose level of 850 mg/kg bw/day that caused also maternal mortality.

Prenatal developmental toxicity of MEA following dermal application was investigated in rats and rabbits. In rats, maternal toxicity was indicated by reduced maternal body weight gain. In addition, moderate to severe skin irritation was recorded. The NOAEL for maternal toxicity was 75 mg/kg bw/day. Although the observed maternal skin irritation represented a certain level of stress, no indication for prenatal developmental toxicity and especially no morphological alterations were induced up to the highest dose level tested. The NOAEL for prenatal developmental toxicity including teratogenicity was 225 mg/kg bw/day. Marked skin irritation occurred in rabbits but there was no indication of any systemic effect. The NOAEL for local effects was 10 mg/kg bw/day and the NOAEL for systemic maternal toxicity, prenatal developmental toxicity including teratogenicity was 75 mg/kg bw/day (the highest dose tested).

MEA is not a developmental toxicant after dermal exposure. Oral GLP, guideline developmental toxicity studies additionally suggest that MEA is not a developmental toxicant at maternally toxic doses. An indication of developmental toxicity was observed in one oral study conducted under non-GLP and non-guideline conditions with a very sensitive strain of rat. Minor effects on reproductive performance and fertility, without histopathological correlate or influence of mating success, were only noted at the limit dose of 1000 mg/kg bw/day, a dose also associated with systemic toxicity in the parents.

MEA possesses properties indicating a hazard for human health (at low doses, corrosive or irritating to eyes, skin, respiratory tract, and/or site of contact, and reproductive/developmental toxicity (postimplantation loss) at high doses). Adequate screening level data are available to characterize the human health hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Environment

MEA is expected to be hydrolytically stable in the natural environment, since it does not contain any hydrolysable groups. The molecule will exist as a cation in water at environmentally relevant pH. It should be noted, however, that EPISuite predicts certain environmental fate endpoints in their uncharged forms. Therefore, there will be some differences between predicted and actual results.

Based on an AOP v1.92-estimate uncharged MEA is indirectly photo-degraded in the atmosphere by reaction with hydroxyl radicals with a half-life ($t_{1/2}$) of about 10.74 hours assuming a hydroxyl radical concentration of 500,000 molecule/cm³ and a 24-h day.

Level III fugacity modelling, using loading rates of 1000 kg/h each for air, soil and water, provides the percent distribution when the MEA is released simultaneously to all three compartments. Distribution to air, water, soil and sediment was calculated to be 0.46%, 40.6%, 58.9% and 0.08%, respectively. Based on model results the main target compartments of MEA are water and soil. The Henry's law constant for the uncharged molecule was calculated with HENRYWIN v3.20 (Bond estimation method) to be 0.000037 $Pa.m^3/mol$ at 25 °C. A pH corrected Henry's law constant at pH 7 of 0.00000963 $Pa.m^3/mol$ at 25 °C (estimated) suggests that volatilization of MEA from the water phase is not expected.

There are several ready biodegradation studies (OECD TG 301) available for MEA. In one of the studies, OECD 301 A study (DOC-die-away-test), MEA was inoculated in non-adapted, domestic sludge under aerobic conditions. Degradation was followed by DOC analysis at frequent intervals over a 21-day period. The initial concentration was 20 mg DOC/L. Elimination after 1, 4, 6, 11, 13 and 21 day was 9%, 97%, 95%, 95%, 95% and 94%, respectively. Thus, MEA was shown to be readily biodegradable. This was confirmed by at least 5 other reliable biodegradability tests.

Based on the measured partition coefficient (log K_{ow}) of –2.3 and an estimated bioconcentration factor (BCF) of 3.16, MEA is not expected to bioaccumulate**.**

The aquatic toxicity MEA to fish, invertebrates, algae and microorganisms was comprehensively investigated. Taking into account very high solubility of MEA in water, results based on nominal concentrations are as valid as based on measured concentration. The lowest reliable acute toxicity values for aquatic species are as follows:

Goldfish (*Carassius auratus,* fish)	96-h LC_{50} = 170 mg/L (measured; pH 10.1)
Daphnia magna (invertebrates)	48-h EC_{50} = 32.6 mg/L (measured; pH 7.3-9.1)
Pseudokirchneriella subcapitata (algae)	72-h E_rC_{50} = 2.8 mg/L (nominal; pH 8.0-9.7)
	72-h NOE_rC = 1 mg/L (nominal; pH 8.0–9.7)
Pseudomonas putida. (microorganisms)	17-h EC_{50} = 110 mg/L (nominal, pH 8.1-9.8)
Domestic activated sludge (microorganisms)	30-min EC_{10} >1000 mg/L (nominal)

In an early-life stage reproduction toxicity test in Japanese killifish (*Oryzias latipes*), the NOEC (30 days) was

1.24 mg/L and LOEC was 3.55 mg/L.

Chronic exposure to Brook trout *(Salvelinus fontinalis)* for up to 100 days resulted in NOECs (60 or 100 days (days) of >14.1 mg/L or >20 mg/L for survival, length and weight. The NOEC (100 days) for reproduction was 1.77 mg/L.

In a chronic toxicity test on reproduction of the water flea *Daphnia magna*, the NOEC (21 days) was 0.85 mg/L for reproduction and the EC_{50} (21 days) was 2.52 mg/L for reproduction as well.

MEA possess properties indicating a hazard for the environment (acute aquatic toxicity values between 1 and 100 mg/L and chronic aquatic toxicity values <1 mg/L). The chemical is readily biodegradable and is not expected to bioaccumulate. Adequate screening-level data are available to characterize the hazard to the environment for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Exposure

MEA is synthesized in a continuous, closed process by reacting one mole of ethylene oxide (EO) with one mole of ammonia.

The estimated production, imports, exports, and consumption of ethanolamines (MEA, DEA, and TEA) in 2011 by major consuming regions in thousand metric tons was as follows:

	Annual Capacity (year-end)	Production	Imports	Exports	Consumption
North America (United States, Canada, Mexico)	775	663	57	154	566
Central and South America	110	77	29	4	103
Western Europe	427	386	92	78	400
Central and Eastern Europe	57	41	12.5	16.9	36.6
Africa	0	0	7.7	0	7.7
Middle East	30	20	15.2	12.5	22.7
Asia	975	421	182	133	470
Oceania	0	0	7	0	7
Total	2,374	1,608	402	397	1,612
SOURCE: CEH estimates.					

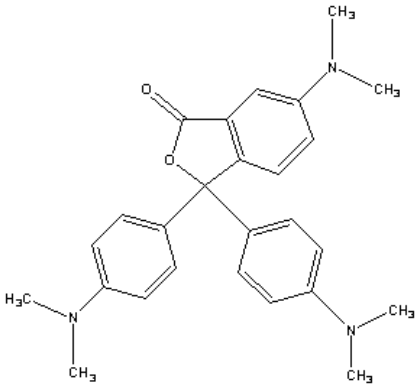
Synthesis of MEA takes place in a closed continuous process. Therefore worker exposure during manufacture is limited. Major uses of ethanolamines in 2007 were for the production of surfactants, herbicides and gas treatment applications.

MEA is present in many household products and personal care products, such as laundry detergents, fabric softeners, oven and grill cleaners, glass and surface cleaners, disinfectants, mildew and mold removers, floor strippers and cleaners, grout cleaner, kitchen cleaners, household degreasers, personal care and hand cleaners and soaps, in hair color formulations and mousses. The typical reported concentration ranges for MEA in personal care products ar e 1 – 18% outbind://28/ - _msocom_1, however, for floor strippers up to 30% and for grout and tile cleaners up to 99% are reported for single products.

The exposure of MEA to the environment from industrial settings is anticipated to be low because synthesis and production of MEA takes place in a closed continuous process. Transfer of this material 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. MEA is stored in closed tanks or pressurized cylinders and transported in tank cars and tank trucks, and smaller amounts are transported in drums, pressurized cylinders or Intermediate Bulk Containers (IBCs). Its use as a dispersing agent for agricultural chemicals will result in its direct release to the environment. In addition, emission to the environment is expected from use of consumer products (laundry detergents and cleaning agents). The possibility of a release to air or environment is low and

even if there is a release, MEA is readily photo- and biodegradable.

INITIAL TARGETED ASSESSMENT PROFILE

CAS No.	1552-42-7
Chemical Name	3,3-Bis(*p*-dimethylaminophenyl)-6-dimethylaminophthalide
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, *in vitro* mutagenicity and reproductive/developmental toxicity. 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).

3,3-Bis(*p*-dimethylaminophenyl)-6-dimethylaminophthalide 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) of Japan, and the toxicological profile was re-assessed for the OECD Cooperative Chemicals Assessment Programme.

Physical-Chemical Properties

3,3-Bis(*p*-dimethylaminophenyl)-6-dimethylaminophthalide is a pale yellow-green powder at room temperature. Melting point is 179 - 180 °C, and boiling point is calculated to be 546.2 °C by MPBPWIN (version 1.43). However, this chemical may be decomposed before the temperature reaches 546.2 °C. Measured partition

coefficient between octanol and water (log K_{ow}) is 5.27. Vapour pressure is estimated to be 5.9×10^{-9} Pa at 25 °C by MPBPWIN. Measured water solubility is < 10 mg/L at 25 °C.

Human Health

The oral LD_{50} of the substance was greater than 2000 mg/kg bw (OECD TG 401) in rats. The substance did not cause death. There were no acute data for the inhalation or dermal routes, as well as no data on acute toxicity in humans.

The only available repeated dose study in experimental animals or humans is a 28-day repeated dose toxicity study conducted in rats according to the Japanese guideline (similar to OECD Guideline 407). Rats were administered 3,3-bis(p-dimethylaminophenyl)-6-dimethylaminophthalide by gavage at 0 (vehicle control: 0.5 % sodium carboxymethylcellulose mixed with 0.1 % Tween 80), 8, 30, 120, and 500 mg/kg bw/day. No deaths or clinical signs were observed. All adverse effects were observed at only 500 mg/kg bw/day. A 10 % increased relative weight of the liver was found in females, although no histopathological changes in female liver were observed. There were diffuse hypertrophy of thyroid follicular cells in males (3/6) and females (3/6), and focal inflammatory cell infiltration of lymphocytes in females (1/6) in the thyroid. Hypertrophy of chief cells in the parathyroid was also observed in males (4/6). Centrilobular hypertrophy of hepatocytes was observed in males (1/6). At the end of the recovery period, these changes were not observed. Based on increased relative weight of the liver in females and histopathological changes in the liver and thyroid (parathyroid) at 500 mg/kg bw/day in males and females, the NOAEL of this study was considered to be 120 mg/kg bw/day in both sexes.

In a bacterial mutation study using *Salmonella typhimurium* and *Escherichia coli* (OECD TG 471), 3,3-bis(*p*-dimethylaminophenyl)-6-dimethylaminophthalide 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), 3,3-bis(*p*-dimethylaminophenyl)-6-dimethylaminophthalide did not induce structural chromosomal aberrations or polyploidy with and without metabolic activation. No *in vivo* mutagenicity data are available. Based on these results, 3,3-bis(*p*-dimethylaminophenyl)-6-dimethylaminophthalide is considered to be non genotoxic *in vitro*.

A reproduction and developmental toxicity screening test was conducted according to the OECD Guideline 421 under GLP. Rats (12 animals/sex/dose) were given 3,3-bis(*p*-dimethylaminophenyl)-6-dimethylaminophthalide by gavage at doses of 0, 100, 300 or 1000 mg/kg bw/day (solvent: 0.5 % sodium carboxymethylcellulose). Males were dosed for 42 days (including pre-mating) and females were dosed up to 45 days from 14 days before mating to day 3 of lactation (including the mating period, gestation period, and delivery). No deaths or clinical signs were observed. The histopathological observation revealed no effects on the reproductive organs (only reproductive organs were assessed). No effects were observed for reproductive and developmental parameters.

The NOAEL of reproduction and developmental toxicity was considered to be 1000 mg/kg bw/day, the highest dose tested in rats.

Agreed Hazard Conclusions

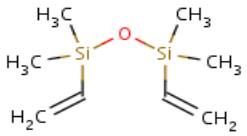
Based on available information, 3,3-bis(p-dimethylaminophenyl)-6-dimethylaminophthalide does not possess properties indicating a hazard for human health endpoints targeted in this assessment.

Available Exposure

Production and/or import volume of 3,3-bis(*p*-dimethylaminophenyl)-6-dimethylaminophthalide was reported to be less than 1,000 tones/year in fiscal year 2010 in Japan. The production and/or import volume of 3,3-bis(*p*-dimethylaminophenyl)-6-dimethylaminophthalide l in the United States was less than 500,000 pounds (227 tons) according to the 2006 Inventory Updated Reporting. Production volume in the world is not available.

3,3-Bis(*p*-dimethylaminophenyl)-6-dimethylaminophthalide is used as a raw material for dyes, such as a dye in carbonless copy paper based on the substance's property to change its own colour with temperature. It may be used in consumer products and dermal consumer exposure is possible.

SIDS INITIAL ASSESSMENT PROFILE

CAS No(s).	2627-95-4
Chemical Name(s)	1,1,3,3-tetramethyl-1,3-divinyldisiloxane
Structural Formula(s)	

SUMMARY CONCLUSIONS OF THE SIAR

Physical-chemical Properties

1,1,3,3-Tetramethyl-1,3-divinyldisiloxane is a liquid with a measured melting point of -99.7 °C, a measured boiling point of 140 °C and a vapour pressure of 1.655 x 10^3 Pa at 25 ºC (extrapolated from a curve that included temperatures from 11.1 to 18.0 ºC). The measured octanol-water partition coefficient (log K_{ow}) is 5.36, and the measured water solubility is 0.207 mg/L at 20 °C.

Human Health

In a systemic bioavailability study with mice, analysis of plasma showed that 1,1,3,3-tetramethyl-1,3-divinyldisiloxane was detected in the blood at approximately one and four hours at all concentrations (500, 1000, and 2000 mg/kg bw) following gavage administration.

The oral LD_{50} of 1,1,3,3-tetramethyl-1,3-divinyldisiloxane is greater than 5000 mg/kg bw in male and female Sprague-Dawley rats following a study conducted similar to OECD 401; there were no reported effects.

1,1,3,3-Tetramethyl-1,3-divinyldisiloxane is not irritating to the skin of rabbits. No experimental data are available for eye irritation in animals.

No experimental data are available for skin sensitisation in animals.

Repeated-dose toxicity data are available for this test substance via inhalation (14-day study) and oral gavage (OECD TG 422). In a 14-day whole body vapour inhalation study, male and female rats were exposed to the test substance by whole body vapour inhalation six hours/day, five days/week for two weeks at measured concentrations of 0, 0.038, 3.8 and 1.9 mg/L. A statistically significant increase in female spleen and liver weight was observed at 1.9 mg/L. Microscopic examination of the tissues revealed no significant histopathological changes in the respiratory tract, selected organs (including spleen and liver) or tissues.

In an OECD 422 study, male and female rats were administered the test substance by oral gavage at doses of 0, 50, 150 or 600 mg/kg bw/day. Adrenal cortical hypertrophy and vacuolation of the pituitary were observed in male rats at all doses; therefore, 50 mg/kg bw/day is the LOAEL for males. The NOAEL for systemic toxicity in female rats was 50 mg/kg bw/day based on liver effects at 150 and 600 mg/kg bw/day.

The substance did not induce gene mutations in an *in vitro* bacterial reverse mutation assay (similar to OECD TG 471) and was negative in an *in vivo* mouse micronucleus assay (OECD TG 474).

No data are available for the carcinogenicity of 1,1,3,3-tetramethyl-1,3-divinyldisiloxane.

In a combined repeated-dose/reproductive/developmental toxicity screening test (OECD TG 422), Crl:CD(SD) rats (10/sex/dose) were administered the test substance at 0 (corn oil), 50, 150, and 600 mg/kg bw/day via gavage. No treatment-related adverse effects on evaluated reproductive parameters were observed. The reproductive NOAEL was 600 mg/kg bw/day (the highest dose level evaluated). The NOAEL for developmental toxicity was 150 mg/kg bw/day based on the decreased postnatal survival and pup body weights in the 600 mg/kg bw/day group.

1,1,3,3-Tetramethyl-1,3-divinyldisiloxane possesses properties indicating a hazard for human health (repeated dose toxicity [liver, adrenal gland, pituitary gland], developmental toxicity at high doses). 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 K_{ow} module, found in the current version of EPI Suite (v4.10), may improve estimates for silanes and siloxanes for this endpoint. However, there is still uncertainty associated with the calculated values and they should be used with caution whenever they are reported.

In an OECD TG 111 study, the hydrolysis half-lives for 1,1,3,3-tetramethyl-1,3-divinyldisiloxane at pH 5, 7 and 9 and 25 °C were 3.7 hours, 5.8 days and 2.6 hours, respectively.

In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of 0.2 days based on a 12-hr day h and hydroxyl radical concentration of 1.5×10^{6} molecules/cm^3. The overall second-order ozone rate constant was 0.35×10^{-17} cm^3/molecule-sec corresponding to a half-life of 3.274 days assuming an ozone concentration of 7×10^{11} mol/cm^3. In an OECD TG 301D study, 1,1,3,3-tetramethyl-1,3-divinyldisiloxane was not readily biodegradable.

A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that 1,1,3,3-tetramethyl-1,3-divinyldisiloxane will distribute mainly to the water (84.4 %) compartment with minor distribution to the air (10.1%), soil (1.8%) and sediment (3.7%) compartments. The predicted behavior is controlled by the high volatility and the short half-life in air. A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that the expected hydrolysis product, ethenyldimethylsilanol (CAS No 5906-75-2), will distribute mainly to the soil (71.8 %) and water (27.5%) compartments with minor distribution to the air and sediment compartments (<1%). The expected hydrolysis rate of 1,1,3,3-tetramethyl-1,3-divinyldisiloxane in natural waters could be reduced due to absorption to sediments. However, without a measured value of sediment K_{oc} for the substance, the significance of this effect of absorption for 1,1,3,3-tetramethyl-1,3-divinyldisiloxane is not known. The calculated soil adsorption coefficient (log K_{oc}) is 3.12 (MCI method). A calculated Henry's law constant of 1.49×10^{6} Pa-m^3/mole at 20 ºC suggests that volatilization from the water phase is expected to be high. 1,1,3,3-Tetramethyl-1,3-divinyldisiloxane may be expected to bioaccumulate in the aquatic environment based on a calculated bioconcentration factor of 1598 L/kg wet-wt. The estimated BCF for the expected hydrolysis product, ethenyldimethylsilanol (CAS No 5906-75-2), is 4.52 L/kg wet-wt, indicating this hydrolysis product is not expected to bioaccumulate.

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

Species	Effect level	Comments	Study Design
Acute toxicity			
Fish [*Oncorhynchus mykiss*]	96 h LC_{50} >0.13 mg/L (measured)	functional limit of solubility	OECD TG 203, flow through
Aquatic Invertebrates [*Daphnia magna*]	48 h EC_{50} >0.10 mg/L (measured)	functional limit of solubility	OECD TG 202, static
Algae [*Pseudokirchnerella subcapitata*]	72 h ErC_{50} and E_bC_{50} >0.12 mg/L (measured;	growth rate method and area under growth curve method; measured; highest	OECD TG 201, static

	highest concentration tested) 72 h NOEC=0.12 mg/L (measured)	concentration tested	
Chronic toxicity			
Invertebrate [*Daphnia magna*]	21 d NOEC >0.12 mg/L (TWA measured; highest concentration tested)	immobilization, reproduction	OECD TG 211, static renewal

TWA=time-weighted average (mean measured test concentration)

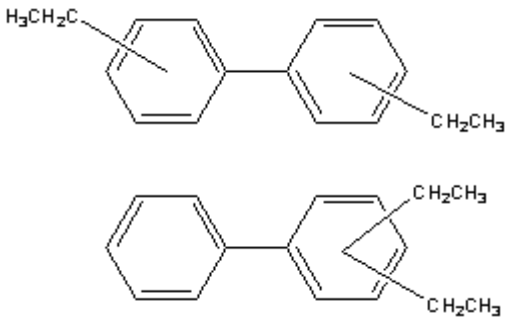
1,1,3,3-Tetramethyl-1,3-divinyldisiloxane possesses properties indicating a low hazard profile (at the limit of water solubility). It has potential to bioaccumulate and is not readily biodegradable. Adequate screening-level data are available to characterize the environmental hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Exposure

In the United States (sponsor country), production volume of 1,1,3,3-tetramethyl-1,3-divinyldisiloxane in 2012 was ca. 454 - 4540 tonnes. In the United States, production volume of 1,1,3,3-tetramethyl-1,3-divinyldisiloxane in 2005 was ca. 454 - 1814 tonnes. In 2005, 1,1,3,3-tetramethyl-1,3-divinyldisiloxane was produced in Europe (45 - 340 tonnes) and Japan (ca. 454 - 1814 tonnes). Less than 227 tonnes are imported into each of the three regions. Ranges are provided to protect confidential business information. The substance is used only as an intermediate for manufacturing polymers and basic organic compounds. No parent substance is expected to remain after end use.

1,1,3,3-Tetramethyl-1,3-divinyldisiloxane is manufactured in closed systems. Use of engineering controls at the manufacturing site includes general and local ventilation; grounding and bonding, nitrogen gas pad and purge, water scrubber devices and related equipment; and closed sampling systems is recommended. Recommended personal protective equipment includes impermeable chemical resistant gloves, goggles, fire resistant clothing, safety shoes, hard hat, and respirators. Potential routes of exposure during routine operations (such as sampling) at the manufacturing site include dermal and inhalation. There are no industrial consumer uses of the substance. There are no consumer uses of the substance.

INITIAL TARGETED ASSESSMENT PROFILE

CAS No.	28575-17-9
Chemical Name	Diethylbiphenyl
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).

Diethylbiphenyl is classified as a Monitoring 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

Diethylbiphenyl is composed of several isomers, as ethyl groups can be attached in different positions to the biphenyl structure. These isomers consist of either each phenyl ring being ethyl-substituted or only one phenyl ring being substituted with two ethyl groups. CAS registration numbers that refer to the isomers substituted on both phenyl rings with an ethyl group are as follows.

2,2'-Diethyl-1,1'-biphenyl CAS number: 13049-35-9

2,3'-Diethyl-1,1'-biphenyl	CAS number: 13049-36-0
2,4'-Diethyl-1,1'-biphenyl	CAS number: 13049-37-1
3,3'-Diethyl-1,1'-biphenyl	CAS number: 13049-38-2
3,4'-Diethyl-1,1'-biphenyl	CAS number: 13049-39-3
4,4'-Diethyl-1,1'-biphenyl	CAS number: 13049-40-6

However, this assessment report focuses on dieithylbiphenyl with CAS number 2875-17-9, which is a commercially available mixture of constituents. All QSAR calculations with EPISUITE were performed using this CAS registration number. It should be noted that MPBPWIN, KOWWIN, WATERNTWIN and WSKOWIN do not distinguish the difference of the position of ethyl groups on the phenyl rings. This means the calculated values of boiling point, vapour pressure, Log K_{ow} and water solubility are the same for all isomers.

Information on physical-chemical properties of diethylbiphenyl is limited. Diethylbiphenyl is a pale-yellow transparent liquid. Melting point of diethylbiphenyl is less than - 30 °C. Boiling point is estimated to be 330.4 °C by MPBPWIN (version 1.43). Vapour pressure for diethylbiphenyl is calculated to be 0.0163 Pa at 25 °C by MPBPWIN (version 1.43). Water solubility for diethylbiphenyl is estimated to be 0.102 mg/L at 25 °C by WATERNTWIN (version 1.01) and 0.403 mg/L at 25 °C by WSKOWIN (version 1.42). Partition coefficient between octanol and water (log K_{ow}) for diethylbiphenyl is calculated to be 5.38 by KOWWIN (version 1.68). QSAR calculations were conducted by inputting the CAS number of 28575-17-9 (CAS number for diethylbiphenyl) into the QSAR software.

Human Health

No acute toxicity study for diethylbiphenyl is available. In a dose range finding study for a 28 day repeated dose toxicity study, rats were given diethylbiphenyl at 0 (vehicle control: corn oil), 62.5, 250 or 1000 mg/kg bw/day for 7 days. No deaths were observed up to 1000 mg/kg bw/day. The LD_{50} was considered to be greater than 1000 mg/kg bw.

A 28-day repeated dose toxicity study was conducted in rats according to the Japanese guideline (similar to OECD Guideline 407). Rats were administered diethylbiphenyl by gavage at 0 (vehicle control: corn oil), 15, 60, and 240 mg/kg bw/day. No deaths or clinical signs were observed. All adverse effects were observed at only 240 mg/kg bw/day. Increases in prothrombin time, activated partial thromboplastin time, and total cholesterol level were observed in males. At the end of the administration period, relative weight of the liver was significantly increased in males and females, absolute weight of the liver was significantly increased in females, and relative weight of the kidney was significantly increased in males. The main changes of the liver and the kidney, which are considered to be due to test substance treatment, are as follows. At the end of the administration period, in the liver, hypertrophy of centrilobular hepatocytes was observed in 3 males, and in the kidney, mild hyaline droplet in the proximal tubular epithelial cell cytoplasm was observed in 2 males. This finding in male kidney is related to alpha 2u-globulin accumulation, which is a specific male rat change and not relevant for humans. Based on these findings at 240 mg/kg bw/day in males and females, the NOAEL of this study was considered to be 60 mg/kg bw/day.

In a bacterial mutation study using *Salmonella typhimurium* and *Escherichia coli* (OECD TG 471), diethylbiphenyl 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), diethylbiphenyl did not induce structural chromosomal aberrations or polyploidy with and without metabolic activation. No *in vivo* mutagenicity data are available. Based on these results, diethylbiphenyl is considered to be non genotoxic *in vitro*.

Agreed Hazard Conclusions

Based on available information, diethylbiphenyl does not possess properties indicating a hazard for human health endpoints targeted in this assessment.

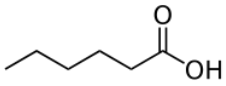
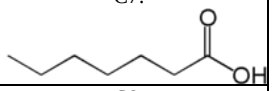
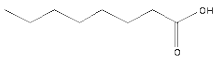
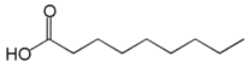
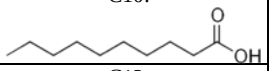
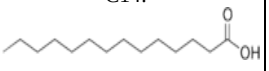
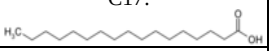
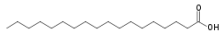
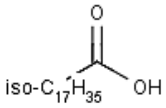
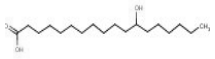
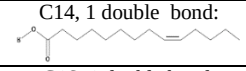
Available Exposure

Production and/or import volume of diethylbipheniyl in Japan is unknown. Production volume in other countries is also unavailable. Diethylbipheniyl is used as a solvent and as a heat medium.

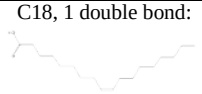
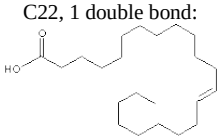
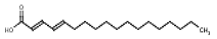
SIDS INITIAL ASSESSMENT PROFILE

Category name	Aliphatic Acids Category

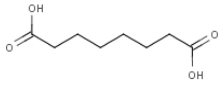
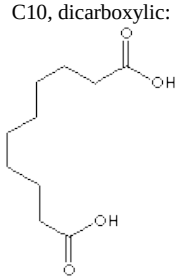
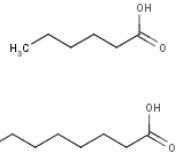
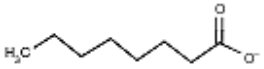
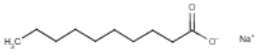
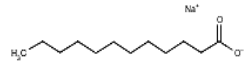
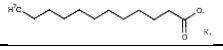
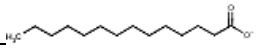
CAS No(s), Chemical name(s) and structural formula(s) [1]

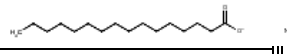
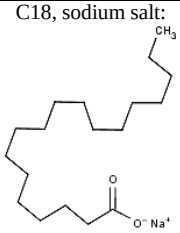
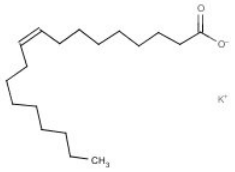
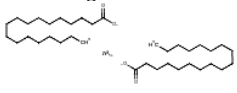
CAS No	IUPAC or CAS Name	Structural Formula
Single component – Saturated (12)		
142-62-1	Hexanoic acid	C6: 
111-14-8	Heptanoic acid	C7: 
124-07-2	Octanoic acid	C8: 
112-05-0	Nonanoic acid	C9: 
334-48-5	Decanoic acid	C10: 
143-07-7	Dodecanoic acid	C12: 
544-63-8	Tetradecanoic acid	C14: 
57-10-3	Hexadecanoic 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: 

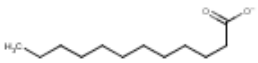
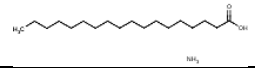
[1] The table is organized according to general aliphatic acid structure. Specifically, by increasing carbon chain length, with any structure variations (e.g., unsaturated, dicarboxylic, double bonds, hydroxyls, salts) appearing after the corresponding base structure.

112-80-1	(Z)-Octadec-9-enoic acid; 9-Octadecenoic acid, (Z)-	C18, 1 double bond: 
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

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

67701-06-8	Fatty acids, C14-18 and C16-18-unsaturated	Not Applicable
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	C14, sodium salt: 

	salt	
408-35-5	Sodium hexadecanoate; Hexadecanoic acid, sodium salt	C16, sodium 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

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

compounds. The potassium salts include saturated, single component mono-unsaturated and multi-component 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.

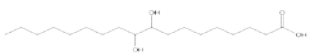
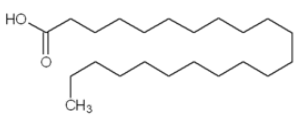
A single component saturated aliphatic acid contains a hydroxyl group (**12-hydroxy-octadecanoic acid, CAS 106-14-9**); this additional side chain is not a functional group on the molecule and is not expected to affect the properties of the substance.

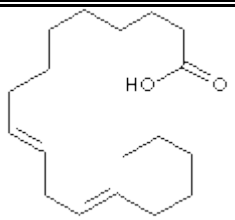
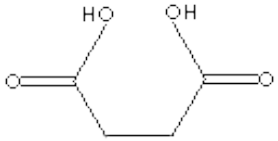
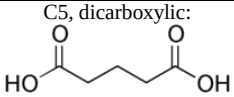
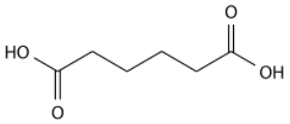
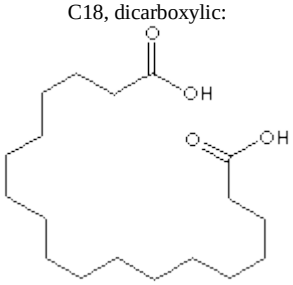
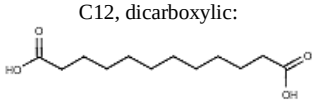
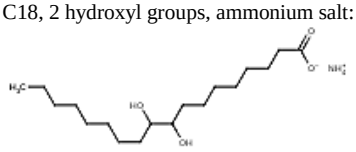
Sponsored substances also include single-chain length and multi-component chain length dicarboxylic acids; the dicarboxylic acids have no structural differences in functional groups.

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]				
91032-02-9	Fatty acids, C12-18, potassium salt	Not applicable	C12-18, potassium salts	Not applicable
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	X	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				
91032-02-9	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 were 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 10,000 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 bw/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 bw/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 bw/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 of 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 471, *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
Octanoic acid; 124-07-2	*Oryzias latipes*	57 (freshwater, nominal, 48 hr) 150 (seawater, measured, 48 hr)	No guideline specified; semi-static
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
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 201
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	OECD TG 201

		water solubility); WAF = 0.14-0.19 (measured; limit of expected water solubility)	
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 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)
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 =	RA to *61790-12-3* (negative)	WOE Single component saturated	WOE Dicarboxylic acids (negative)	RA to CAS *61790-12-3*, NOAEL = 5000	RA to CAS *61790-12-3* NOAEL = 5000

		2500 (90d)		(negative)		(F0,F1)	
67701-06-8	**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
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 =	RA to CAS *110-94-1* NOAEL = (maternal) =

						1000 (M)	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 = 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)
67701-09-1	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 112-85-6 NOAEL = 1000 (42d)	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	RA to *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)	*Not irritating*	***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 mg/L	RA to 693-23-2 EC0 > 5.8 (limit test: highest conc tested was at the WS limit for the 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 ^{o}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 ^{o}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 ^{o}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 ^{o}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 ^{o}C – C18: 0.597 (measured) C18:1 0.0115 C18:2a 0.0377 C18:2b 0.0377	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

	C18:3 0.124 (modeled)				
90990-15-1	C12: 4.81 –C18: 0.597 (measured) C18:1 0.0115 C18:2 8.17 C18:2a 0.0377 C18:2b 0.0377 C18:3 0.124 (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)
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 91032-02-9* (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.

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	Highly soluble molybdenum salts
Chemical Name(s) and CAS No(s).	Sodium molybdate: CAS 10102-40-6 for sodium molybdate dihydrate CAS 7631-95-0 for sodium molybdate (anhydrous) Ammonium dimolybdate: CAS 27546-07-2 Ammonium heptamolybdate: CAS 12054-85-2 for ammonium heptamolybdate tetrahydrate CAS 12027-67-7 for ammonium heptamolybdate (anhydrous)
Structural Formula(s)	$Na_2MoO_4 \cdot 2\ H_2O$ Na_2MoO_4 $(NH_4)_2Mo_2O_7$ $(NH_4)_6Mo_7O_{24} \cdot 4\ H_2O$ $(NH_4)_6Mo_7O_{24}$

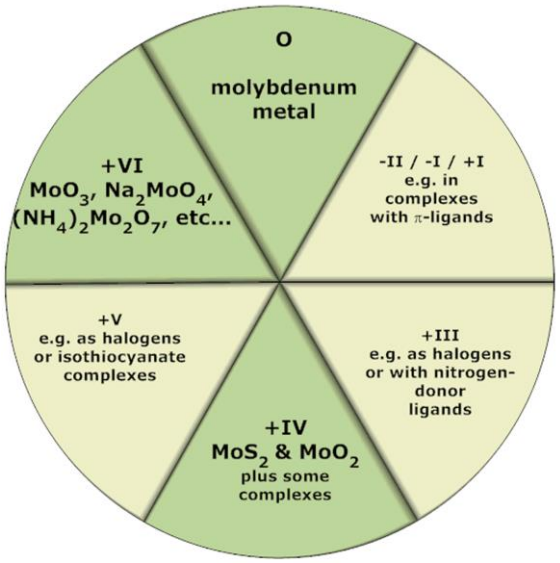
SUMMARY CONCLUSIONS OF THE SIAR

Rationale for molybdenum salts category

The substances included in this category are the higher volume molybdate salts available on the market.

The category is based on a common moiety of concern, the molybdate anion $[MoO_4]^{2-}$. All category members are potential contributors of this moiety. The counter ions of the molybdate salts (i.e. sodium and ammonium), due to their ubiquitous presence in biota and/or their essential role in human physiology, are not addressed further as they are not considered to contribute to any toxicity of the molybdate salts.

The chemistry of molybdenum is complex, allowing a wide range of valences as summarised in the graph below:



Several of these are only stable in isolated complexated form, and only three forms are industrially produced: molybdenum metal (valency 0), MoS_2 and MoO_2 (+IV) and various molybdates as well as MoO_3 (+VI). However, it has been demonstrated that upon dissolution in aquatic media, molybdenum substances of the valency states 0, +IV and +VI transform into the hexavalent molybdate anion.

Environment:

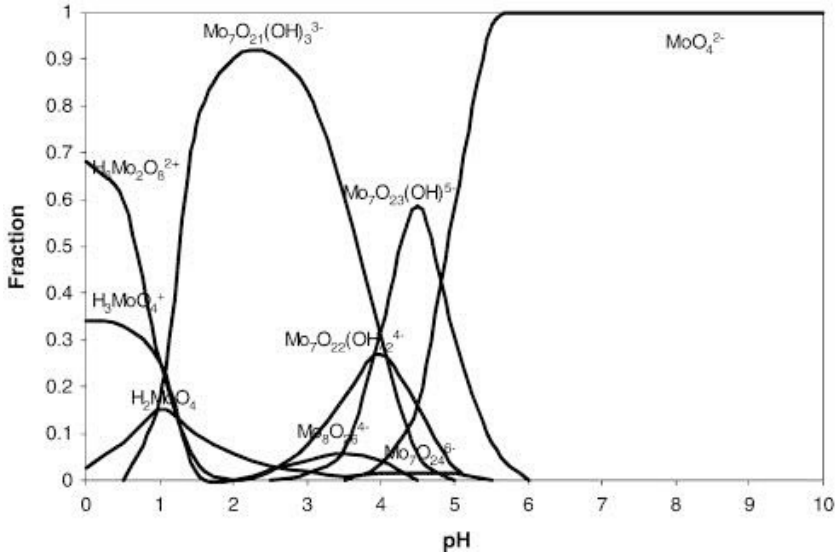
The speciation of molybdenum in aqueous media as a function of pH and molybdenum concentration has been thoroughly investigated and reported upon in open literature. Under environmentally relevant conditions, molybdenum compounds transform rapidly to the molybdate anion, $[MoO_4]^{2-}$, as underpinned by the UV-spectra of aqueous solutions of molybdenum compounds that demonstrate that molybdate is the only dissolved molybdenum species present. Also, under physiological conditions (pH > 6.5), the sole molybdenum species present is the molybdate anion. The derivation of environmental fate data such as adsorption/desorption coefficients and bioconcentration/bioaccumulation factors are based on measured concentrations of dissolved and total molybdenum in water/solids/biological tissues, and reflect the physicochemical and biological properties of the molybdate anion.

Environmental effects testing is conducted using sodium molybdate dihydrate as the model compound given that it is the most soluble, and the results, where appropriate, form the basis of read-across to the endpoints for less soluble substances.

Human Health:

The category includes the three molybdate substances sodium molybdate, ammonium dimolybdate and ammonium heptamolybdate. They are characterised by high water solubility (>> 100 mg/L) and under physiological circumstances will dissociate into the molybdate anion ($[MoO_4]^{2-}$. This is also the species by which molybdenum as an essential trace element is taken up into the body from nutritional sources.

The species in solutions of sodium molybdate at dilute concentrations (i.e. below ca. 10 mg/L) and neutral pH is the molybdate ion, $[MoO_4]^{2-}$; as the pH is lowered, the $[MoO_4]^{2-}$ ion becomes increasingly protonated, yielding $[HMoO_4]^-$ and finally $[H_2MoO_4]$ species. At higher concentrations, the protonated molybdate species are in equilibrium with the heptamolybdate anionic species. The distribution of molybdenum species in aquatic media as a function of pH is shown in the graph below at an exemplary total molybdenum concentration of 21.2 mmol/L. In conclusion, at physiologically relevant concentrations and pH, the only molybdenum species present is the molybdate $[MoO_4]^{2-}$ anion:



The human health hazard assessment addresses a large variety of effects and different exposure patterns (acute/long-term, local/systemic...). In general, for toxic effects requiring systemic uptake of the chemical, grouping is applied for all substances in the category, based on the molybdate anion $[MoO_4]^{2-}$ as the common and only physiologically relevant ion upon dissolution. Molybdate is the form in which molybdenum is taken up into organisms and is present in blood. In most cases the key toxicological studies considered in such chapters on systemic effects have been conducted with the soluble substances sodium molybdate and/or ammonium dimolybdate.

Analogous substance justification

Since the toxicological effects of substances within the category are associated with the release of molybdate anions, in some cases (*repeated dose inhalation toxicity and carcinogenicity*) data on the analogous substance molybdenum trioxide (CAS 1313-27-5) are included, but limited to the assessment of systemic toxicological effects. In this context, it is important to note that molybdenum trioxide is moderately soluble and reacts with water under acidification to molybdate anions as follows:

$$MoO_3 + H_2O \rightarrow [MoO_4]^{2-} + 2\ H^+$$

Based on the above considerations, molybdenum trioxide upon systemic uptake into the body will be present in dissolved form as molybdate anions, and therefore toxicity/toxicokinetic data can be read across from molybdenum trioxide to the category substance for systemic toxicity. Note: for local effects, the strong acidification during the dissolution/dissociation reaction with water is considered to impart the unique irritation potential of molybdenum trioxide, which is not observed with the molybdates encompassed in the category.

Annex 1 of this document is a table identifying the category members and the compounds used for read across for each endpoint.

Physical-chemical Properties

Sodium molybdate is typically marketed as the dihydrate, which is a colourless to white, odourless crystalline powder, with a relative density of 2.59 (measured at 23.3 °C). Upon heating of the hydrated form, water of crystallization is lost and the anhydrous form is formed. The melting point for anhydrous sodium molybdate is reported at 687 °C. The water solubility at 20°C is 654.2 g/L (measured) for sodium molybdate dihydrate, corresponding to 259 g Mo/L.

Ammonium dimolybdate is a white-to-greyish, and odourless powder, with a relative density of 2.97 (measured at 20 °C). Ammonium dimolybdate decomposes from ca. 150 °C (evolution of ammonia). Formation of ammonium octamolybdate takes place from ca. 225 °C, with subsequent calcination to MoO_3 at higher temperatures. Distinct melting or boiling points are not available. The water solubility of ammonium dimolybdate at 20 °C is 228.4 g/L (measured), corresponding to 129 g Mo/L.

Ammonium heptamolybdate is typically marketed as the tetrahydrate, which is a colourless or slightly greenish

or yellowish, odourless, crystalline powder with a relative density of 2.86 (measured at 20 °C). A decomposition temperature of ammonium heptamolybdate of 90 °C is reported in literature. This likely refers to the evolution of water of crystallisation when heating the tetrahydrate form. At higher temperatures, evolution of ammonia is expected. Distinct melting or boiling points are not available. The water solubility of ammonium heptamolybdate tetrahydrate at 20 °C is 206.5 g/L (measured), corresponding to 112 g Mo/L.

Remark: Vapour pressure, Kow and pKa are considered relevant parameters for the fate and effects assessment of organic chemicals only. They are not applicable to metals/inorganics and thus not mentioned above.

Essentiality

Molybdenum is an essential trace element for humans and mammals. Molybdenum-containing enzymes catalyse redox reactions and are found in many plants and animal organisms. In animals and humans, sulphite oxidase, xanthine oxidoreductase, aldehyde oxidase and mitochondrial amidoxime reducing component require molybdenum linked with a pterin (molybdopterin) as the cofactor. In plants, molybdenum is essential to growth as a component of the enzymes nitrate reductase and nitrogenase.

Human Health

Toxicokinetics

The distinction between the highly bioaccessible category substances and other poorly accessible molybdenum substances has been verified in *in vitro* bioaccessibility studies with six different molybdenum substances. Sodium molybdate (representative for the three highly water-soluble category substances) is characterised by high bioaccessibility (60 - 100%), whereas other moderately to poorly soluble molybdenum substances (such as molybdenum metal, molybdenum dioxide and molybdenum disulfide) have shown a low bioaccessibility (less than 1 - 6%). Separate investigations, however, document that upon dissolution, substances with different initial oxidation state of the molybdenum atom(s) all transform to the molybdate anions.

Dermal absorption: in vitro (human skin), the dermal absorption of sodium molybdate has been shown to be low to negligible (ca. 0.2% of the applied dose).

Absorption following ingestion or inhalation: published animal data on the toxicokinetics of molybdenum substances suffer from several shortcomings and are not considered relevant for human health hazard characterisation. However, recently conducted repeated dose animal toxicity studies included blood kinetics, from which a valuable comparison of absorption following inhalation and oral exposures to molybdate substances can be derived. When comparing blood monitoring data from 28d and 90d oral studies with those from a 2yr inhalation study, it is reasonable to assume that molybdate blood levels in rats following inhalation of 100 mg/m^3 molybdenum trioxide (ca. 67 mg Mo/m^3) are similar to those resulting from dietary exposure to 17 - 20 mg Mo/kg bw/d (in the form of sodium molybdate in the diet). These blood values show that molybdenum trioxide administered by inhalation in the NTP study (as 100 mg MoO_3/m^3) was readily absorbed, yielding a systemic molybdate dose comparable to approx. 20 mg Mo/kg bw/d.

Relevant human data on inhalation absorption are not available for any molybdenum-derived substance.

Oral absorption (human data): metabolic ward studies with male human volunteers involving a combination of dietary molybdenum levels (22, 72, 121, 467 and 1,490 µg Mo/d) and dual stable isotope tracer methodology (^{97}Mo/^{100}Mo or ^{95}Mo/^{96}Mo administered either orally or i.v.) yielded the following conclusions:

- the oral absorption of molybdates is in the range of approx. 85% - 93%;

- dietary constituents may play a role in uptake efficiency: whereas oral absorption in fasted subjects is close to 100%, the co-administration in matrices such as solid food or black tea can reduce absorption to as much as 50% and 10%, respectively.

Distribution: Upon uptake, the highly soluble molybdate anions are widely distributed in the body. The highest molybdenum concentrations are found in kidneys, liver and bone. However, there is no apparent accumulation of molybdenum in animal or human tissues.

Metabolism: The highly bioavailable molybdate substances in the category are not subject to metabolism.

Excretion: The elimination of molybdates in humans from plasma is rapid and predominantly via renal excretion (>80%) with less via faeces (<10%); increasing dietary molybdate intake results in elevated absorption but with a concomitant rise in urinary excretion, whereas the fraction of tissue deposition decreased, indicating that the uptake of molybdates is not regulated at the level of absorption, but instead renal elimination

appears to be the most relevant pathway for regulating systemic levels of molybdates.

Metal-metal interactions: using stable Mo/Cu isotopes (^{97}Mo, ^{100}Mo and ^{65}Cu), the influence of molybdate intake on the metabolism of copper was investigated in human depletion/repletion studies: neither did the variation of molybdate dietary intakes (22-1490 µg/d) nor an extended depletion/repletion period have any statistically significant effect on serum or urinary copper levels, and copper absorption and retention was also largely unaltered. Overall, very low or high dietary molybdate intakes up to 1490 µg/d did not influence copper metabolism or copper status when receiving a stable intake of 1.63 mg/ Cu/d for a period of 120 days.

Acute toxicity

Table: available key study data for acute toxicity

Route of administration / endpoint / test guideline	**Test substance**	**Endpoint value**
Inhalation (OECD TG 403)		
LC_{50}, rat(m/f)	Sodium molybdate (anhydrous) Na_2MoO_4	> 1930 mg/m³
LC_{50}, rat(m/f)	Ammonium dimolybdate $(NH_4)_2Mo_2O_7$	> 2080 mg/m³
Dermal (OECD TG 402)		
LD_{50}, dermal, rat (m/f)	Sodium molybdate (anhydrous) Na_2MoO_4	> 2000 mg/kg bw
LD_{50}, dermal, rat, (m/f)	Ammonium dimolybdate $(NH_4)_2Mo_2O_7$	> 2000 mg/kg bw
Oral (OECD TG 401)		
LD_{50}, oral, rat (m/f)	Sodium molybdate (anhydrous) Na_2MoO_4	4233 mg/kg bw
LD_{50}, oral, rat (m/f)	Ammonium dimolybdate $(NH_4)_2Mo_2O_7$	3883 mg/kg bw

In the dermal studies with sodium and ammonium molybdate, there were no signs of systemic reaction to treatment, no indication of dermal irritation and no macroscopic abnormalities upon necropsy. In the acute oral studies with sodium and ammonium dimolybdate, there were no bodyweight changes or macroscopic abnormalities; clinical observations in most animals included pilo-erection, hunched posture, abnormal gait, lethargy and decreased respiratory rate, ptosis and diarrhoea. In the acute inhalation toxicity studies with these two substances, only minor bodyweight losses were observed, but there were neither clinical observations indicative of a response specific to the test material nor any macroscopic or microscopic findings of toxicological relevance.

In conclusion, sodium molybdate and ammonium dimolybdate show low acute toxicity, when taken up via the oral, dermal or inhalation route. Based on the category justification ammonium heptamolybdate is expected to also be of low acute toxicity.

Skin, eye and respiratory irritation

Table: available key study data for skin and eye irritation

Test substance	**Study type**	**Result**
Sodium molybdate (anhydrous) Na_2MoO_4	Skin irritation, *in vivo* (OECD TG 404)	Not irritating
	Eye irritation, *in vivo* (OECD TG 405)	Not irritating
Ammonium dimolybdate $(NH_4)_2Mo_2O_7$	Skin irritation, *in vivo* (OECD TG 404)	Not irritating
	Eye irritation, *in vivo* (OECD TG 405)	Not irritating

Reliable *in vivo* skin and eye irritation studies are available for sodium molybdate and ammonium dimolybdate. These studies demonstrate that these substances are not irritating to skin or eyes. In the absence of endpoint-specific test systems for respiratory irritation, reference is made to acute inhalation toxicity studies

with the category members sodium molybdate and ammonium dimolybdate: no clinical observations were made during exposure or during the subsequent the observation period that would represent test-substance-related signs of respiratory irritation. No macroscopic or microscopic findings indicating irritation were made in the respiratory tract following terminal necropsy. The third substance in the category, ammonium heptamolybdate, is not assumed to be irritating or corrosive to skin, eyes or the respiratory tract either, based on chemical similarity and similar water solubility as ammonium dimolybdate. A saturated solution of ammonium heptamolybdate in water has a pH of 5.8, so that no irritating effects are expected due to extreme acidity or alkalinity values, either.

Skin Sensitisation

Table: available key study data for skin sensitisation

Test substance	**Study type**	**Result**
Sodium molybdate (anhydrous) Na_2MoO_4	Skin sensitisation studies in guinea pigs (maximisation test) (OECD TG 406)	Not sensitizing
Ammonium dimolybdate $(NH_4)_2Mo_2O_7$	Skin sensitisation studies in guinea pigs (maximisation test) (OECD TG 406)	Not sensitizing

Guinea pig maximisation tests with sodium molybdate and ammonium dimolybdate do not indicate a sensitising potential of these substances. It is unlikely that the very similar ammonium heptamolybdate would exhibit sensitising properties. In patch tests on humans with 1% ammonium heptamolybdate in water a very low positive response rate is reported (3 out of 787 patients in 7 years). In conclusion, the substances in the molybdenum salts category do not show a potential for skin sensitisation.

Repeated-dose Toxicity

Table: available key study data for repeated dose toxicity

Test substance	**Study type / details**	**Key results**
Sodium molybdate (dihydrate) $Na_2MoO_4 \cdot 2\ H_2O$	In a 90-day **oral** repeated dose toxicity study, OECD TG 408 with additional parameters from OECD TG 416,which also included a 60 day recovery phase, disodium molybdate was administered to male and female rats at doses of 5, 17 or 60 mg/kg bw/day of Mo (administered as sodium molybdate dihydrate via feed).	Reduced bodyweight gains were observed only in the 60 mg Mo/kg bw/day dose group. The effect was more pronounced in males, which was partly due to a slightly reduced food intake and partly due to reduced food conversion efficiency. During the recovery phase food consumption in the 60 mg/kg bw/day males and females returned to a value comparable to the control animals. Light microscopic evaluation of control and 60 mg Mo/kg bw/day animals showed test item-related findings in the kidneys (slight diffuse hyperplasia of the proximal tubules) of two 60 mg Mo/kg bw/day females. No such findings were reported for the animals after the 60-day recovery phase. Compared to controls, serum copper levels, and liver and kidney copper concentrations, were significantly increased in both males and females in the group given the highest dose of 60 mg Mo/kg bw/day. Without any toxicological or histopathological correlate, these increases are not considered adverse. The **NOAEL was 17 mg Mo/kg bw/day** based on the effects on body weights and kidneys seen at 60 mg Mo/kg bw/day.
Molybdenum trioxide MoO_3	A 13-week **inhalation** toxicity study with molybdenum trioxide in rats	Finding (rats): At all exposure concentrations, no treatment-related effects on mortality, clinical signs, final mean body weights, organ weights,

	and mice (NTP) was in compliance with FDA GLP Regulations, 21 CFR, Part 58. The results are well-documented; historical control data are also included. 10 male + 10 female rats or mice per group were exposed in chambers to 0, 1, 3, 10, 30, 100 mg MoO_3/m^3 for 6.5 hours per day, 5 days per week for 13 weeks. The test substance is characterised as follows: MoO3, purity: ca. 99%, particle size: MMAD (µm) ± GSD in the range from 1.33 ± 1.93 to 1.60 ± 1.83. The NTP also conducted 2-year inhalation studies in rats and mice at 0, 10, 30 and 100 mg MoO_3/m^3. In addition to local effects in the lung, a comprehensive set of systemic end points was studied including body weight changes, reproductive parameters, and full histological evaluation of a wide range of tissues including the reproductive organs.	haematology or clinical chemistry parameters, sperm counts or motility and liver copper concentrations were observed at all concentrations. No treatment-related gross or microscopic lesions were observed. **Thus, the concentration of 100 mg MoO_3/m^3 (corresponding to 66.7 mg Mo/m^3) represents a true NOAEC** in this 13-week inhalation study on rats, since no adverse effects were seen up to and including the highest concentration tested. Findings (mice): There were no adverse treatment-related effects on mortality, clinical signs, final mean body weights, organ weights, haematology or clinical chemistry parameters, and epididymal weights, sperm counts, or motility were observed at any concentrations. Also, no treatment-related gross or microscopic lesions were observed. However, there were significant increases in liver copper concentrations in female mice exposed to 30 mg/m^3 and 100 mg/m^3, as well as in male mice exposed to 100 mg/m^3 compared to those of the control groups; without any toxicological or histopathological correlate, these increases are not considered adverse. Thus, the 13-week inhalation study on mice yields a **NOAEC of 100 mg MoO_3/m^3 (corresponding to 66.7 mg Mo/m^3), and a NOEC of 10 mg MoO_3/m^3 (corresponding to 6.7 mg Mo/m^3).** **In the two year studies in rats and mice,** regarding systemic effects, despite the longer exposure duration, no adverse systemic effects were observed in the 2 year studies in rats and mice and both the 13-week and 2-year inhalation studies resulted in identical NOAECs for systemic toxicity of 100 mg MoO_3/m^3.

Human data has been evaluated and is considered to be of insufficient relevance and/or reliability to derive definitive conclusions on the repeated dose toxicity of molybdenum substances.

The sub-chronic inhalation toxicity study with MoO_3 is applicable to molybdates in so far as the general systemic toxicological effects and parameters can be read across to molybdate salts (see justification for category and analogous substance).

In the 90-day oral toxicity study with sodium molybdate dihydrate effects were observed at the highest dose of 60 mg Mo/kg bw/day (with the NOAEL at the next lower dose at 17 mg Mo/kg bw/day). Therefore, a health hazard for repeated dose toxicity cannot be ruled out for the three category substances. Taking the low degree of severity of the observed effects into account, it is concluded that the category substances have a low repeated dose toxicity hazard.

Genetic Toxicity

In a bacterial reverse mutation assay/Ames test with multiple strains of *Salmonella typhimurium* (OECD TG 471) sodium molybdate dihydrate was negative both with and without metabolic activation. An *in vitro* test on induction of micronuclei in cultured human peripherial blood lymphocites (OECD TG 487) sodium molybdate dihydrate was negative with and without metabolic activation. In an *in vitro* test for mutations at the thymidine kinase (tk) locus of mouse lymphoma cells (OECD TG 476), sodium molybdate dihydrate was negative with and without metabolic activation. Based on these results and further supporting data, molybdate salts are considered to be non-genotoxic *in vitro*.

Reliable *in vivo* genotoxicity studies are not available.

Carcinogenicity

Two year NTP toxicology and carcinogenicity studies describe molybdenum trioxide (analogous substance) administration to rats and mice via inhalation at doses up to 100 mg MoO_3/m^3 (ca. 67 mg Mo/m^3). It is applicable to molybdates in so far as the general systemic toxicological effects and parameters can be read across to molybdate salts (see rationale for category and use of data from analogous substance). Both in rats and mice (male and female), there was no evidence of systemic carcinogenicity in the NTP study. The local effects in the respiratory tract observed following inhalation of MoO_3 are considered to be specific to MoO_3 and are not to be read across to the category substances.

Based on these results, the molybdenum substances discussed in this SIAP are considered to have no carcinogenic potential.

Toxicity to reproductive organs and fertility and on developmental toxicity

Table: available key study data for toxicity to reproductive organs and fertility of molybdenum substances

Test substance	Study type / details	Key results
Sodium molybdate (dihydrate) $Na_2MoO_4 \cdot 2\ H_2O$	In a 90-day repeated dose toxicity study (OECD TG 408) disodium molybdate was administered to male and female rats at doses of 5, 17 or 60 mg/kg bw/day of Mo (molybdenum in disodium molybdate dihydrate) via feed. **In addition to the standard examination parameters, the following examinations were conducted to assess any adverse effects on sexual function and fertility: vaginal cytology, oestrous cycle, sperm parameters (count, motility and morphology, testicular spermatid counts), in accordance with OECD TG 416.**	**The NOAEL for effects on reproductive organs, sperm and oestrous cycle is 60 mg Mo/kg bw/day.** There were no test substance related changes in the male or female reproductive tissues (testes, epididymis, prostate, seminal vesicles, ovaries, uterus or vagina). There were no test substance-related effects on vaginal cytology and oestrous cycles during weeks 7 - 9 of the dosing phase (i.e., the period during which vaginal cytology and oestrous cycles were evaluated). No test-item related changes in organ weight of testes or secondary sex organs and no effect on spermatid or sperm counts, motility or morphology were observed. All other recorded microscopic findings were considered incidental and unrelated to administration of disodium molybdate dihydrate. They occurred at similar incidences in the control and test substance treated groups or they were sporadic with no relationship to dose.
Sodium molybdate (dihydrate) Na_2MoO_4 . 2 H2O	A guideline compliant **prenatal developmental toxicity study** (according to OECD TG 414, under GLP) in rats with the test item sodium molybdate is available. Exposure was during gestational days 6 through 20 via the diet, in four dose groups (ca. 3, 10, 20 and 40 mg Mo/kg bw/day) and a control group (plain diet).	There were no treatment or dose-related effects on maternal body weights, weight changes, feed consumption in grams/day or grams/kg, body weight/day, or on maternal clinical observations, pregnancy indices, or maternal organ weights at any dose. There were also no biological or statistical differences among groups for the numbers of ovarian corpora lutea/female, for uterine implantation sites, or for uterine implantation losses per female at any dose. Statistically significantly increased copper levels in kidneys and livers were observed at 40 mg Mo/kg bw/day, but not at 20 mg Mo/kg bw/day. **Therefore, the NOAEL for maternal toxicity is 40 mg Mo/kg bw/day, and the NOEL for maternal toxicity is 20 mg Mo/kg bw/day.** There were no biological or statistical differences among groups for the numbers of foetuses, foetal

		sex ratios, foetal body weights, foetal external, visceral or skeletal malformations or variations per female at any dose. The incidences of the few foetal malformations and the more common foetal variations observed in the study were comparable to the historical control database of the laboratory on this rat strain and supplier. The foetal effects in this study also did not exhibit any treatment- or dose- related pattern of increased incidences and/or severities. **The NOAEL for developmental toxicity is therefore 40 mg Mo/kg bw/day.**

Effects on fertility: A 90-day repeated dose toxicity study (OECD TG 408) with disodium molybdate (dihydrate) is available which was modified to additionally assess any adverse effects on sexual function and fertility. At the highest tested dose (60 mg Mo/kg bw/day, administered as ca. 151 mg $Na_2MoO_4 \cdot 2\ H_2O$ via feed) there were no test substance-related effects on vaginal cytology and oestrous cycles. No test-item related changes in organ weight of testes or secondary sex organs and no effect on spermatid or sperm counts, motility or morphology were observed.

Developmental toxicity: A guideline compliant prenatal developmental toxicity study (according to OECD TG 414, under GLP) in rats with the test item sodium molybdate (dihydrate) is available. At the highest tested dose (40 mg Mo/kgbw/day, administered as ca. 100 mg $Na_2MoO_4 \cdot 2\ H_2O$ via feed) no dose-related adverse effects on development of the offspring were observed.

Conclusion

For the *molybdenum salts category substances* adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

No health hazards have been identified for acute toxicity, irritation, sensitisation, mutagenicity, reproductive toxicity and carcinogenicity. A health hazard for repeated dose toxicity cannot be ruled out for the three category substances based on effects observed at the highest tested dose of 60 mg Mo/kg bw/day in a 90-day oral toxicity study conducted with the test substance sodium molybdate dihydrate. Taking into account the low degree of severity of the observed effects, it is concluded that the category substances have a low repeated dose toxicity hazard.

Environment

Physicochemical processes like hydrolysis, photo-oxidation and (bio-)degradation are not relevant for chemical inorganic substances such as elemental molybdenum and molybdenum salts that only occur in the environment as molybdate.

Transport and distribution of naturally-occurring elements such as molybdenum over the different environmental compartments is predominantly determined by their solubility and binding affinities to organic matter and other solid particles that occur in soil and sediment (e.g., clay particles, precipitated hydroxides). All of the molybdenum compounds of this category are highly soluble. Therefore, when entering in the aquatic environment as the soluble molybdate, precipitation as an insoluble inorganic is unlikely to occur. Typical K_d values for molybdenum to suspended solids, sediment and soil are 2793, 1778 and 871 L/kg, respectively. No McKay Level III modelling was conducted as this type of modelling is not relevant for the inorganic substances of this category.

Reported whole-body bioaccumulation factors for fish vary more than 2 orders of magnitude (i.e., 0.05 – 71.6) but, as theoretically predicted for essential elements, there is a distinct close relationship between exposure concentration and BAF, i.e., decreasing BAFs with increasing Mo-levels in the water column, showing homeostatic control of Mo by these organisms. Similar findings are observed for aquatic invertebrate species. The homeostatic control of Mo in fish (*O.mykiss*) is observed to continue to function up to and within the milligram range of exposure. Bioaccumulation factors in the terrestrial compartment are situated around 0.2 - 4 for plants and 0.4 - 3.4 for invertebrates (dry weight basis).

There are no indications or evidence that biomagnification occurs in aquatic or terrestrial food chains.

Aquatic toxicity of molybdate (expressed as mg Mo/L) (test substance: sodium molybdate dihydrate unless indicated otherwise)

The following acute toxicity test results have been determined for aquatic species. Values are based on measured levels unless specified otherwise:

Species	**Endpoint**	**Value (mg Mo/L)**	**Type[a]**	**Guideline**
Pimephales promelas	96h-LC_{50}	609.1	s-s	OECD TG 203
Oncorhynchus mykiss	96h-LC_{50}	7600[b] 800-1320[b] 781-1339[c]	s-s s s	OECD TG 203
Daphnia magna	48h-LC_{50}	130.9[b] 2729.4 2847.5 1680.4-1776.6	s s s s-s	OECD TG 202 EPA/600/4-90/027F ASTM 1980 OECD TG 202, EPA OPP 72-2
Ceriodaphnia dubia	48h-LC_{50}	1005.5-1024.6	s-s	OECD TG 202, EPA OPP 72-2
Girardia dorotocephala	96h-LC_{50}	1226	s-s	ASTM 2002
Pseudokircheriella subcapitata	72h-E_rC_{50} (growth rate)	362.9, >419.9, 1094.5, 1568.9[d] 289.2 – 390.9[e] geomean: 331.1[f]	s s	OECD TG 201

[a]: f-t: flow-through ; s-s: semi-static / static renewal ; s: static
[b]: nominal
[c]: recalculated LC_{50}, logistic fit
[d]: UGhent strain ; [e]: CIMM strain (most sensitive strain tested)
f: geometric mean of 4 values for the CIMM strain

The following aquatic chronic toxicity test results have been determined for the freshwater environment. Values are based on measured exposure levels unless mentioned otherwise.

Species	**Endpoint**	**Value (mg Mo/L)**	**Type[a]**	**Guideline**
Fish				
Oncorhynchus mykiss	78d-$EC_{10,biomass}$ 32d-$NOEC_{mortality}$ 32d-$NOEC_{mortality}$ 12m-$NOEC_{mortality,growth}$	43.2 200[b] 750[b] >17	f-t f-t s-s f-t	OECD TG 210 EPS 1/RM/28 EPS 1/RM/28 No guideline specified
Oncochynchus kisutch	20wk-$NOEC_{develop}$	≥ 19.5	f-t	No guideline specified
Pimephales promelas	34d-$EC_{10,biomass}$ 32d-$EC_{10,biomass}$	39.9 90.9	f-t n.s.	OECD TG 210 ASTM E1241-98
Invertebrates				
Daphnia magna	21d-$EC_{10,reproduction}$	62.8 105.6 108	s-s s-s s-s	OECD TG 211 OECD No 211 ASTM, 1997
Ceriodaphnia dubia	7d-$EC_{10,reproduction}$	50.8-78.2	s-s	EPA-821-R-02-013
Chironomus riparius	14d-$EC_{10,growth\ rate}$	121.4	s-s	OECD TG 218
Brachyonus calyciflorus	48h-$EC_{10,reproduction}$	193.6	s	conform to APHA 8420, 1998
Gastropods				
Lymnaea stagnalis	28d-$EC_{10,growth\ rate}$	221.8	s-s	No guideline specified
Amphibians				
Xenopus laevis	4d-$EC_{10,development}$	115.9	s-s	conform to APHA

				8420, 1998
Algae and higher plants				
Pseudokirchneriella subcapitata	72h-$E_rC_{10,growth\ rate}$	156[b] 283.8[d] 62.5–366.2[d] 61.2–88.7[e] geomean: 74.3[cf]	s s s s	OECD TG 201
Lemna minor	7d-$EC_{10,growth\ rate}$	241.5	s	OECD TG 221

[a]: f-t: flow-through ; s-s: semi-static / static renewal ; s: static ; n.s.: not specified
[b]: based on nominal value
[c]: geometric mean of 4 values that were obtained with the most sensitive strain
[d]: UGhent strain ; [e]: CIMM strain (most sensitive strain tested)
f: geometric mean of 4 values for the CIMM strain

The following aquatic chronic toxicity test results have been determined for the marine environment. Values are based on measured exposure levels:

Species	**Endpoint**	**Value (mg Mo/L)**	**Type[a]**	**Guideline**
Fish				
Cyprinodon variegatus	28d-$EC_{10,biomass}$	84.1	f-t	ASTM E1241
Invertebrates				
Acartia tonsa	20d-$EC_{10,F1\ development}$	7.96	s-s	ASTM STP667
Americamysis bahia	28d-$EC_{10,growth/development}$	>116	f-t	ASTM E1191-97, EPA OPPTS 850.1350
Molluscs				
Crassostrea gigas	48h-$EC_{10,development}$	1,174	s	ASTM 724-98
Mytilus edulis	48h-$EC_{10,development}$	4.4[b]	s	No guideline specified
Algae and higher plants				
Dunaliella tertiolecta	72h-$EC_{10,growth\ rate}$	881	s	ISO 10253
Phaeodactylum tricornutum	72h-$EC_{10,growth\ rate}$	169.9	s	ISO 10253
Ceramium tenuicorne	72h-$EC_{10,growth\ rate-length}$	274	s	ISO 10253
Echinoderms				
Strongylocentrotus purpuratus	48h-$EC_{10,development}$	325.8	s	ASTM E1563-95, EPA/600/R-95/136
Dendraster excentricus	48h-$EC_{10,development}$	233.6	s	ASTM E1563-95, EPA/600/R-95/136

[a]: f-t: flow-through ; s-s: semi-static ; s: static
[b]: effect levels based on nominal levels ; no guidance specified ; test substance was ammonium heptamolybdate

Terrestrial toxicity of molybdate (expressed as mg Mo/kg dw) (test substance: sodium molybdate dihydrate)

Terrestrial chronic toxicity test results have been conducted on 10 different soil types. Ranges of EC_{10}-values – based on measured Mo-levels - were determined for the following organisms (test name/OECD TG No.):

Species	**Endpoint**	**Value (mg Mo/kg dw)**	**Guideline**
Plants			
Brassica napus	21d-EC_{10}	5–2,847	ISO 11269-2
Trifolium pratense	21d-EC_{10}	5–1,505	ISO 11269-2
Lolium perenne	21d-EC_{10}	15–3,479	ISO 11269-2

Lycopersicon esculentum	21d-EC_{10}	9–1,578	ISO 11269-2
Hordeum vulgare	4d-EC_{10}	28–436	ISO 11269-1
Soil invertebrates			
Enchytraeus crypticus	28d-EC_{10}	67.2–>2,817	OECD TG 220
Eisenia andrei	56d-EC_{10}	8.88–455	OECD TG 222
Folsomia candida	28d-EC_{10}	39–1,865	ISO 11267
Micro-organisms			
Substrate-induced nitrification	28d-ÈC_{10}	35 – >10,001	ISO 14238
Substrate-induced respiration	24h-EC_{10}	10 – >10,003	OECD TG 217
Plant residue mineralisation	28d-EC_{10}	164 – >10,003	No guideline specified

Bioavailability models have been developed for the terrestrial environment. These models describe the relationship between specific soil parameters on one hand (soil pH, organic matter content), and the no-effect concentration for a specific organism and end parameter on the other hand. Toxicity of molybdate to soil organisms generally decreases (i.e. increasing EC_{50} values) with decreasing pH and increasing clay content, organic matter content and iron oxide content. The range of each parameter in the tested soils more or less defines the range of applicability for these relationships.

All the ecotoxicological information that is presented here has been published in peer-reviewed journals.

Conclusion

For the *highly soluble molybdenum salts category* adequate screening-level data are available to characterize the hazard to the environment for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Molybdate released from the substances in this category has a low bioaccumulation potential, and is regulated in aquatic organisms up to the mg/L range. *Highly soluble molybdenum salts category* substances do not present a hazard for the environment based on their low hazard profile.

Exposure

Production: Global production levels of category substances totalled approximately 30,000 tonnes in 2011. EU tonnage bands indicate the smallest tonnage band within the category as 100 – 1,000 tonnes for ammonium heptamolybdate, and the largest for both ammonium dimolybdate and sodium molybdate as 1,000 – 10,000 tonnes. Main production countries include: Chile, China, Germany, United States of America. Main uses for the category substances range from corrosion inhibition, to flame retardant/smoke suppressant, to micronutrient input into mineral supplements and fertilizers.

Environment: Molybdenum is a naturally occurring element that can be found at background levels in water, sediment and soil. The main input of (anthropogenic) molybdenum in the environment as a result of industrial activities will occur via the aquatic compartments (effluent, mine tailings) where it will be present in the form of molybdate. A part of this dissolved fraction will bind to the sediment layer (K_d of 1778 L/kg, see Environment section). Anthropogenic input to the terrestrial compartment will occur through the application of sewage sludge to land, or via stack emissions (local point source).

Environmental monitoring: Background levels of molybdenum in water, sediment and soil are reported in the EU FOREGS Geochemical Atlas (Forum of European Geological Surveys). Typical background concentration levels in Europe are 0.28 µg Mo/L for surface water, 0.58 mg Mo/kg dw for sediment, and 0.59 mg Mo/kg dw for topsoil. Extensive datasets with ambient Mo-levels in water were received from different EU-countries (Belgium, Finland, Germany, The Netherlands, Sweden, United Kingdom), and country-specific reasonable worst-case (RWC) ambient levels were situated between 0.62 and 5.1 µg Mo/L (typical EU-value: 2.30 µg Mo/L). The RWC ambient level represents the 90th percentiles of ambient waters that are not directly affected by point source contamination (diffuse sources only). For the terrestrial compartment there is a large (n >5000) data set on ambient Mo-levels in European arable and grassland soils, resulting in ambient reasonable worst-case values of 0.86 mg Mo/kg dw and 1.04 mg Mo/kg dw, respectively. Using the limited information on ambient molybdenum concentrations in sediment (data for Finland, Germany, Spain, Sweden, United Kingdom), a reasonable worst-case ambient concentration of 3.77 mg Mo/kg dw was determined.

Human Exposure: Trace levels of molybdenum (present as soluble molybdate) are found in a wide variety of foods, and human exposure to molybdenum may occur via the diet, drinking water and occupational exposure from mining operations and industrial uses.

Occupational Exposure: Workers can be exposed to dusts of molybdenum substances during their manufacture and use. Primary routes of exposure at the workplace are via inhalation and dermal contact. Direct oral exposure (ingestion) is considered to be negligible; however, indirect oral exposure in connection with the inhalational exposures may give a contribution to the internal systemic dose. Inhaled material that is deposited in the mouth and upper airways can be subject to mucociliary clearance and then swallowed.

The category substances are not of particular concern regarding local effects on the skin, and absorption through skin is negligible. As a matter of general industrial hygiene, to protect against general dusts and also against heat in some workplaces, protective clothing and gloves are worn where necessary.

Inhalation exposure is possible where dry powder forms of molybdenum metal or molybdate salts are handled, e.g. raw material handling, substance transfer between reaction vessels, and packaging/bagging operations. With regard to molybdenum metal, abrasive techniques such as polishing or grinding, and hot processes like forging, cutting and welding can lead to the formation of metal dusts or fumes. At such workplaces, direct exposure of the worker is reduced by risk management measures, such as automation or enclosure of the process or installation of exhaust ventilation systems. If such measures are not applicable – or where necessary, in addition to those measures - personal respiratory protective equipment is used.

Consumer Exposure: Opportunities are few for consumer exposure to category substances. Sodium molybdate and ammonium dimolybdate are added in trace amounts (as molybdate) to mineral supplements. Sodium molybdate is also used as a micronutrient in fertilizers, a water treatment chemical and in coolants/anti-freeze.

Annex I: Overview of toxicological data (reliable study results) for substances in the molybdate salts category and use of analogous substance data

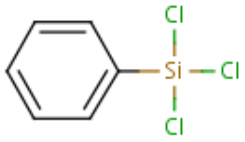
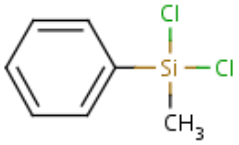
	molybdate salts category			analogous substance
	sodium molybdate	**ammonium dimolybdate**	**ammonium heptamolybdate**	**molybdenum trioxide**
Acute toxicity, oral	OECD TG 401: LD_{50} = 4233 mg/kg bw (anhydrous sodium molybdate)	OECD TG 401: LD_{50} = 3883 mg/kg bw	Estimated [(1)]: LD_{50} = ca. 3400 mg/kg bw (anhydrous ammonium heptamolybdate)	*)
Acute toxicity, dermal	OECD TG 402: LD_{50} > 2000 mg/kg bw (anhydrous sodium molybdate)	OECD TG 402: LD_{50} > 2000 mg/kg bw	LD_{50} > 2000 mg/kg bw (anhydrous ammonium heptamolybdate) (read-across within category)	*)
Acute toxicity, inhalation	OECD TG 403: LC_{50} > 1930 mg/m³ (anhydrous sodium molybdate)	OECD TG 403: LC_{50} > 2080 mg/m³	Estimated [(1)]: LC_{50} > ca. 1500 mg/m³ (anhydrous ammonium heptamolybdate)	*)
Skin irritation	OECD TG 404: not irritating	OECD TG 404: not irritating	not irritating (read-across within category)	*)
Eye irritation	OECD TG 405: not irritating	OECD TG 405: not irritating	not irritating (read-across within category)	*)
Respiratory irritation	OECD TG 403: not irritating	OECD TG 403: not irritating	not irritating (read-across within category)	*)
Skin Sensitisation	OECD TG 406: not sensitising	OECD TG 406: not sensitising	not sensitising (read-across within category)	no data
Mutagenicity/Genetic toxicity	OECD TG 471,476,487: not mutagenic / not clastogenic	not mutagenic / not clastogenic (read-across within category)	not mutagenic / not clastogenic (read-across within category)	no data
Repeated dose toxicity, oral	90-day study (OECD TG 408): NOAEL, systemic = 17 mg Mo/kg bw/day LOAEL, systemic = 60 mg Mo/kg bw/day	NOAEL, systemic = 17 mg Mo/kg bw/day LOAEL, systemic = 60 mg Mo/kg bw/day (read-across within category)	NOAEL, systemic = 17 mg Mo/kg bw/day LOAEL, systemic = 60 mg Mo/kg bw/day (read-across within category)	no data
Repeated dose toxicity, inhalation	$NOAEC_{rats/mice}$ (systemic effects) = 66.7 mg Mo/m³ $NOEC_{mice}$ = 6.7 mg Mo/m³) (read-across for systemic effects from analogous substance)	$NOAEC_{rats/mice}$ (systemic effects) = 66.7 mg Mo/m³ $NOEC_{mice}$ = 6.7 mg Mo/m³) (read-across for systemic effects from analogous substance)	$NOAEC_{rats/mice}$ (systemic effects) = 66.7 mg Mo/m³ $NOEC_{mice}$ = 6.7 mg Mo/m³) (read-across for systemic effects from analogous substance)	90-day and 2-year studies in rats and mice (similar to OECD TG 413+453): $NOAEC_{rats/mice}$ (systemic effects) = 66.7 mg Mo/m³ (highest test concentration) $NOEC_{mice}$ = 6.7 mg Mo/m³)

Reproductive toxicity: effects on fertility	90-day study (OECD TG 408) with additional parameters addressing fertility: $NOAEL_{fertility}$ = 60 mg Mo/kg bw/day (highest dose)	$NOAEL_{fertility}$ = 60 mg Mo/kg bw/day (read-across within category)	$NOAEL_{fertility}$ = 60 mg Mo/kg bw/day (read-across within category)	no data
Reproductive toxicity: developmental toxicity	Developmental toxicity study (OECD TG 414): $NOAEL_{development}$ = 40 mg Mo/kg bw/day (highest dose) $NOAEL_{maternal}$ = 40 mg Mo/kg bw/day (highest dose) $NOEL_{maternal}$ = 20 mg Mo/kg bw/day	$NOAEL_{development}$ = 40 mg Mo/kg bw/day $NOAEL_{maternal}$ = 40 mg Mo/kg bw/day $NOEL_{maternal}$ = 20 mg Mo/kg bw/day (read-across within category)	$NOAEL_{development}$ = 40 mg Mo/kg bw/day $NOAEL_{maternal}$ = 40 mg Mo/kg bw/day $NOEL_{maternal}$ = 20 mg Mo/kg bw/day (read-across within category)	no data
Carcinogenicity	NOAEL (systemic carcinogenicity) = 66.7 mg Mo/m³ (read-across for systemic effects from analogous substance)	NOAEL (systemic carcinogenicity) = 66.7 mg Mo/m³ (read-across for systemic effects from analogous substance)	NOAEL (systemic carcinogenicity) = 66.7 mg Mo/m³ (read-across for systemic effects from analogous substance)	2-year inhalation studies in rats and mice (similar to OECD TG 453): NOAEL (systemic carcinogenicity) = 66.7 mg Mo/m³ (highest test concentration)

*) Since data from the category substances are available, the existing supportive data for MoO_3 as an analogous substance is not presented. Data from the analogous substance MoO_3 is only used where no data for category substances is available: for repeated dose toxicity (absence of systemic effects following inhalation of MoO_3) and for carcinogenicity (absence systemic carcinogenicity following inhalation of MoO_3).

[1)] The LD_{50} and LC_{50} for anhydrous ammonium heptamolybdate have been estimated based on the experimentally determined LD_{50}/LC_{50} anhydrous sodium molybdate as the worst case surrogate. The re-calculation is based on the stoichiometric content of Mo in each compound.

SIDS INITIAL ASSESSMENT PROFILE

Category name	Phenylchlorosilane Category
CAS No(s).	98-13-5 149-74-6
Chemical Name(s)	Trichlorophenylsilane (**TClPS**) Dichloromethylphenylsilane (**DClMPS**)
Structural Formula(s)	**TClPS**:  **DClMPS**: 

SUMMARY CONCLUSIONS OF THE SIAR

Analogue/Category Rationale

These chemicals can be represented by a similar general molecular formula:

$(Cl)_xSiPh(Me)_{(3-x)}$

Where Cl = chlorine, x = 2 or 3;

Si = silicon [=1];

Ph = phenyl, [=1];

Me = CH_3

Chlorosilanes, including the phenyl chlorosilanes, react rapidly when exposed to moisture or polar reagents (those that are protic and as such contain a dissociable H_+), producing hydrogen chloride (HCl; CAS No. 7647-01-0) and the corresponding silanols (in general, siloxane oligomers and polymers at concentrations greater than 500 mg/L). Specifically, **TClPS** hydrolyses to form three moles of HCl and one mole of phenylsilanetriol, and **DClMPS** hydrolyses to form two moles of HCl and one mole of methylphenylsilanediol. The half-lives of the phenylchlorosilanes are expected to be < 1 minute based on data with supporting substance diphenyldichlorosilane (DClDPS, CAS No. 80-10-4); data are not available for **TClPS** or **DClMPS**. The assessment for **TClPS** focuses exclusively on the sponsored substance which contains up to 1% benzene as an impurity.

As noted, the silanols resulting from initial hydrolysis can condense spontaneously to form highly cross-linked polymeric gels in uncontrolled environments. Exposure to parent chlorosilane is likely to be transient and observed toxicity in standard test systems will therefore, depending on the conditions of the system (e.g. pH and concentration of test material), likely be to hydrolysis products and condensed silanol material (at concentrations greater than 500 mg/L).

Hydrolysis analogues. DClDPS hydrolyses rapidly in contact with water (half-life 0.2 minutes at pH 7 and 1.5 ^{o}C). Based on the rapid hydrolysis of DClDPS, similar rates of hydrolysis are expected for **TClPS** and **DClMPS**.

Human Health and Aquatic Toxicity Analogues.

(1) Due to their reactivity, the category members are expected to hydrolyse prior to exposure, or locally at the port of entry, to form HCl and a corresponding silanol hydrolysis product. The levels of chlorosilane required to generate concentrations near those tested for corresponding or analogous silanols would result in severely corrosive HCl concentrations. Therefore, data for HCl can be used to partially address the toxicity of the phenylchlorosilanes. The primary hazard for the sponsored phenylchlorosilanes is considered to be exposure to the hydrogen chloride hydrolysis product.

(2) A previously assessed alkoxysilane, trimethoxy(phenyl)silane (TMPS; CAS No 2996-92-1) hydrolyses to form three moles of methanol and one mole of phenylsilanetriol (CAS No 3047-74-3, the same expected hydrolysis product as **TClPS**). TMPS hydrolyses more slowly at pH 7 (half-life ca. 0.4 hours), but under acidic conditions such as in the stomach following ingestion, much more rapid hydrolysis can be expected. While phenylsilanetriol is not the expected hydrolysis product of **DClMPS**, both phenylsilanetriol and methylphenylsilanediol are expected to be water soluble due to the hydroxy groups on the silicon, have low log Kow values, and are expected to be readily absorbed and excreted. Hydrolysis of the sponsored substances produces HCl, while TMPS produces methanol as a hydrolysis product. The contribution of methanol from TMPS to the toxicity assessment of the sponsored substances is expected to be negligible as compared to the effects of HCl. TMPS is considered to be a suitable analogue for human toxicity endpoints for **DClMPS**.

HCl and TMPS were presented and agreed under the OECD Cooperative Chemicals Assessment Programme (http://www.oecd.org/env/hazard/data). The assessment for **TClPS** focuses exclusively on the sponsored substance which contains up to 1% benzene (CAS No. 71-43-2) as an impurity. Benzene has also previously been presented and agreed under the OECD HPV Chemicals Programme (http://www.oecd.org/env/hazard/data).

The read across strategy for the phenylchlorosilanes follows:

Endpoint	**TClPS**	**DClMPS**
Hydrolysis	DClDPS	DClDPS
Biodegradation	Data available	**TClPS**
Acute inhalation toxicity	HCl	HCl
Acute oral toxicity	**DClMPS**, TMPS, HCl	Data available
Skin, eye and respiratory tract irritation	HCl	HCl
Repeated dose toxicity: inhalation	TMPS, HCl	TMPS, HCl
Repeated dose toxicity: oral	TMPS	TMPS
Genetic toxicity *in vitro*: gene mutation	Data available	Data available

Genetic toxicity *in vitro*: chromosome aberration	TMPS, HCl	TMPS, HCl
Toxicity to fertility	TMPS, HCl	TMPS, HCl
Developmental toxicity	TMPS, HCl	TMPS, HCl

Physical-chemical Properties

The category members are liquids with measured melting points of -49.4 (**DClMPS**) and -40 °C (**TClPS**), measured boiling points of 201.8 (**TClPS**) and 206 – 207 °C (**DClMPS**) and vapour pressures of 0.44 (**TClPS**; estimated) and 0.47 (**DClMPS**; extrapolated) hPa at 20 ºC. The calculated octanol-water partition coefficients (log K_{ow}) are 3.60 (**TClPS**) and 3.8 (**DClMPS**; reliability = 4), and the estimated water solubilities are 48.7 (**DClMPS**) and 78.5 mg/L (**TClPS**) at 20 °C. The calculated water solubility and log K_{ow} values may not be accurate because the substances are hydrolytically unstable.

Human Health

No data are available on the toxicokinetics, metabolism and distribution of the phenylchlorosilanes. However, these substances rapidly hydrolyse to HCl and the corresponding silanol hydrolysis products on contact with moisture. Damage to membranes caused by the corrosive nature of HCl might enhance the uptake of the sponsored substances or the silanol hydrolysis products. Hydrogen and chloride ions will enter the body's natural homeostatic processes. HCl will rapidly dissociate and its effects are thought to be a result of pH change (local deposition of H^+). The hydrophilic nature of phenylsilanediol or –triol may limit diffusion across certain membranes. The low molecular weight and high water solubility of the silanols suggest elimination via the kidneys in urine.

Acute inhalation studies were not located for the phenylchlorosilanes. The acute inhalation toxicity of the phenylchlorosilanes is expected to be well-characterized by the effects of HCl exposure, rather than systemic effects of silanol hydrolysis products. The principal clinical signs are expected to be indicative of respiratory and ocular effects resulting from HCl exposure. Inhalation LC_{50} values for HCl were determined to be 4.2 - 4.7 mg/L for 1 hour for rats. The oral LD_{50} for one of the phenylchlorosilane category members, **DClMPS**, was >200 to <2000 mg/kg bw in rats [OECD TG 423]. For the supporting substance TMPS, in an acute toxicity study conducted according to OECD TG 425, a total of 7 female rats were administered TMPS by oral gavage including 4 animals at 2000 and 3 animals at 550 mg/kg bw in polyethylene glycol 300. When the single animal dosed at 2000 mg/kg bw in a limit test died spontaneously on study day 2, a main test with 6 animals was conducted. In the main test, all three animals dosed at 2000 mg/kg bw had to be killed in extremis on study days 4, 5 or 6 and all animals dosed at 550 mg/kg bw survived. Animals at 2000 mg/kg bw appeared unhealthy; effects on respiration, coordination and body weight loss were noted. Slight ruffled fur and slight sedation were observed in two of three animals dosed at 550 mg/kg bw; no clinical signs were observed in the third animal dosed at 550 mg/kg bw. There was no effect on body weight at 550 mg/kg bw. Three animals dosed at 2000 mg/kg bw showed a greater than 20% loss of body weight prior to being killed in extremis; no body weight was recorded at the spontaneous death of the first animal dosed at 2000 mg/kg bw that was found dead on test day 2. Macroscopic findings at 2000 mg/kg bw included light red congested lungs, black brown stomach distended with gas, tan discoloration of kidneys, and spleen reduced in size; there were no macroscopic findings at 550 mg/kg bw. The estimated LD_{50} was 1049 mg/kg bw. The acute oral LD_{50} values of HCl were determined to be 238 - 277 mg/kg bw for female rats.

Irritation data are not available for the sponsored substances. The phenylchlorosilanes rapidly hydrolyse to HCl and the associated silanol. HCl is corrosive and highly irritating to the skin, eyes and respiratory tract. As such, the sponsored substances are expected to be corrosive to the skin, cause serious damage to the eyes and be highly irritating to the respiratory tract. Sensitization data are not available for the phenylchlorosilanes or the expected hydrolysis products.

Repeated dose toxicity data are not available for the sponsored substances. Data from supporting substance TMPS and hydrolysis product HCl are used to fill the repeated-dose toxicity endpoint for the phenylchlorosilanes. TMPS was administered to four groups of 10 rats/sex/dose level by gavage daily at 0 (dried and deacidified corn oil), 100, 250 and 500 mg/kg bw/day. Males were exposed for 28 days (including 14 days

prior to pairing) and females were exposed for 14 days prior to pairing, through the pairing and gestation periods until the F1 generation reached day 4 postpartum. Administration of TMPS at 500 mg/kg bw/day caused a reduction of food consumption in males during the first week of treatment and in females during the pre-pairing period up to day 14 of the gestation period. Reduced body weight was noted in males throughout the study and in females throughout the gestation period. Kidney weight was increased in males and thickened urinary bladder in males and females was seen at this dose. An increase of concentration of urea, bile acids and cholesterol was also noted in males at 500 mg/kg bw/day. Multifocal tubular degeneration/regeneration and transitional cell hyperplasia of kidney were noted in males and females. At 250 mg/kg bw/day, an increase in the urea and bile acid concentrations was observed. Multifocal tubular degeneration/regeneration and transitional cell hyperplasia of kidney were noted in males and females at this dose. The urinary bladder was observed to be thickened in males and females at all dose levels. This finding correlated with the histopathology examination showing perivascular lymphoid cell infiltration and transitional cell hyperplasia of the urinary bladder. Based on the findings in urinary bladder, a NOAEL (No Observed Adverse Effect Level) for systemic toxicity of TMPS could not be established. The LOAEL was 100 mg/kg bw/day. For the analogue substance TMPS, in a 4-week whole-body vapour inhalation (7 hr/day, 5 days/week) study conducted similar to OECD TG 412, there were no adverse treatment-related effects noted at any of the vapour concentrations administered. The NOAEC was determined to be 649 mg/m^3 (highest concentration tested). In repeated dose toxicity studies of HCl by the inhalation route, local irritant effects were observed in the groups of rats and mice exposed to 0.015 mg/L and above for 90 days. The inhalation NOAEC for systemic toxicity for HCl, excluding the local effects of irritation, has been determined to be 0.030 mg/L, with a LOAEC of 0.075 mg/L. The toxicity of the phenylchlorosilanes is expected to be well characterized by the effects of HCl inhalation exposure, the prevalent route of the phenylchlorosilanes exposure.

The sponsored substances did not induce gene mutations in bacterial cells *in vitro* [similar or equivalent to OECD TG 471], and the sponsored substance **TClPS** was negative for induction of gene mutations in mouse lymphoma cells [OECD TG 476]. Chromosomal aberration studies were not located for the sponsored substances. The supporting substance TMPS did not induce gene mutations in bacterial cells [similar to OECD TG 471], but did induce chromosomal aberrations in Chinese hamster V79 cells *in vitro* in the presence of metabolic activation [OECD TG 473]. Based on these results, TMPS is considered to be genotoxic *in vitro*. The hydrolysis product HCl did not induce gene mutations in bacterial cells. Positive results in the *in vitro* chromosome aberration test with HCl were considered to be the effect of low pH. Based on the available data, the phenylchlorosilanes are not expected to cause gene mutations *in vitro*; it may be clastogenic *in vitro*.

No data are available for the carcinogenicity of the phenylchlorosilanes.

Toxicity for reproduction data are not available for the sponsored substances. Data for supporting substance TMPS and hydrolysis product HCl are used to fill the reproductive toxicity endpoint for the phenylchlorosilanes. In the combined repeated-dose/reproductive/developmental toxicity screening test [OECD TG 422] with TMPS, the NOAEL for reproductive/developmental toxicity was 500 mg/kg bw/day (highest dose tested). The LOAEL for maternal toxicity was 100 mg/kg bw/day. Overall, TMPS did not show evidence of reproductive/developmental toxicity. No reliable studies have been reported regarding toxicity to reproduction and development in animals after oral, dermal or inhalation exposure to hydrogen chloride/hydrochloric acid. Because proton and chloride ion are the normal constituents in the body fluid of animal species, low concentrations of hydrogen chloride gas/mist or solution do not seem to cause adverse effects to animals. In fact, the cells of gastric glands secrete hydrochloric acid into the cavity of stomach and orally administered sulfuric acid, which results in pH change as well, did not cause developmental toxicity to laboratory animals. These facts indicate that hydrogen chloride/hydrochloric acid is not expected to have developmental toxicity. In addition, no effects on the gonads were observed in a 90-day inhalation repeated-dose study up to concentrations of 0.075 mg/L HCl. The toxicity of the phenylchlorosilanes is expected to be well-characterized by the effects of HCl inhalation exposure, the prevalent route of the phenylchlorosilanes exposure, and the phenylchlorosilanes are not expected to be reproductive toxicants.

The sponsored phenylchlorosilanes possess properties indicating a hazard for human health [lethality from acute studies (oral and inhalation), corrosive and highly irritating to the skin, eyes and respiratory tract (based on hydrolysis product, HCl), repeated dose toxicity (based on analogue substance, TMPS), and genotoxic (clastogenic *in vitro* based on analogue substance, TMPS)]. 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 module, found in the current version of EPI Suite (v4.10), may improve estimates for silanes and siloxanes for this endpoint. However, there is still uncertainty associated with the calculated values and they should be used with caution whenever they are reported.

The chlorine group is the most active functional group on these molecules and determines many aspects of the behaviour of the category members. The phenylchlorosilanes undergo rapid hydrolysis in the presence of moisture to form two or three moles of HCl and one mole of di- or tri- silanol, depending on the parent substance. An OECD TG 111 (Hydrolysis as a Function of pH) test was conducted at 1.5 ºC for supporting substance DClDPS; half-lives of less than one minute were reported at pH 4, 7, and 9. Likewise, **TClPS** and **DClMPS** are expected to hydrolyse rapidly under environmentally relevant conditions.

In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with half-lives of 2.7 to 5.5 days. Any potential for photodegradation might be superseded by hydrolysis of the parent compound depending on the concentration of water vapour in the air. The biodegradation of **TClPS** was determined in OECD TG 310; there was essentially no (1%) biodegradation of the test substance in 28 days. HCl is an inorganic compound and biodegradation tests are not applicable. Based on this information, the sponsored substances are not expected to be readily biodegradable. Due to rapid hydrolysis of the sponsored substances, any potential for biodegradation is likely to be of the hydrolysis products. Consequently, the only biodegradable materials in the test system will be silanols, and condensed silanol materials (high molecular weight polymers). At high concentrations (>500mg/L), the silanols will condense to form highly cross linked, high molecular weight polymers that are water insoluble and effectively nonbiodegradable.

A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that the sponsored substances will distribute mainly to the air (47.6%) and soil (47.7%) compartments with minor distribution to the water and sediment compartments. Level III fugacity modeling using equal loading rates of 1000 kg/h each for air, soil and water predicts that the silanol hydrolysis products will distribute mainly to soil (ca. 83%), with a smaller fraction to water (ca. 16%) and negligible amounts to sediment and air. Based on the more realistic scenario of 100% release to air, the model predicts that the silanol hydrolysis products will be distributed mainly in air (96%) and water (ca. 4%).

The sponsored substances are not expected to bioaccumulate in the aquatic environment based on rapid hydrolysis to silanols, with estimated BCFs of 3.2 L/kg wet-wt. The calculated bioconcentration factors for the sponsored substances were 110 (**TClPS**) - 1009 (**DClMPS**) L/kg wet-wt

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

Test substance	Species	Result (mg/L)	Guideline; Test type
Fish, acute toxicity			
Sponsored substances			
TClPS	*Oncorhynchus mykiss*	96-hr LC_{50} >100 (nominal; pH adjusted to 7.0)	OECD TG 203; static
DClMPS			
Supporting hydrolysis products DClDPS			
HCl	*Cyprinus carpio*	96-hr LC_{50} = 4.92 (pH = 4.3)	OECD TG 203; semi-static
Aquatic invertebrate, acute toxicity			
Sponsored substances			
TClPS	*Daphnia magna*	48-hr EC_{50} > 100 (nominal; pH adjusted to 7.0)	OECD TG 202; static
DClMPS	*Daphnia magna*	48-hr EC_{50} = 38	OECD TG 202; static

		(without pH adjustment; nominal); >100 (with pH adjustment to 7.9; nominal)	
Supporting hydrolysis products DClDPS			
HCl	*Daphnia magna*	48-hr EC_{50} = 0.492 (pH= 5.3)	OECD TG 202; not specified
Aquatic plants, acute toxicity			
Sponsored substances			
TClPS	*Pseudokirchneriella subcapitata*	72-hr E_rC_{50} and E_bC_{50} > 100 (nominal; pH adjusted to 7.0)	OECD TG 201; static
Supporting hydrolysis products DClDPS			
HCl	*Pseudokirchneriella subcapitata*	72-hr E_rC_{50} = 0.492 (pH= 5.3)	OECD TG 201; static

The sponsored phenylchlorosilanes possess properties indicating a hazard for the environment (acute aquatic toxicity values between < 1 and 100 mg/L). The hydrolysis product, HCl, has properties that can result in toxicity of < 1 mg/L to aquatic organisms in poorly buffered systems, mainly due to acidification of the test medium. The sponsored phenylchlorosilanes and their hydrolysis products have low potential for bioaccumulation and are not readily biodegradable. 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 and import volumes (metric tonnes) for 2010 are summarized below.

Substance	**United States**		**Europe**		**Japan**	
	Production	**Import**	**Production**	**Import**	**Production**	**Import**
TClPS	2268 - 9072	<454	0	0	227 – 2268	0
DClMPS	454 - 3629	0	0	0	0	0

Ranges are provided to protect confidential business information. **TClPS** is used in formulations up to 100% as intermediates for silicone oligomers and polymers. **DClMPS** is used in formulations at 100% as an intermediate (details not provided). No parent substance is expected to remain after end use.

The phenylchlorosilanes are produced and processed in closed systems; commercial customers use the phenylchlorosilanes in closed systems. Due to the dynamic and exothermic nature of the processes incorporating chlorosilanes, many engineering controls are always in place to prevent occupational exposure such as water scrubber devices and related equipment; closed sampling loop; and local and general ventilation. Employees involved in chlorosilane production and application use personal protective equipment (PPE) such as safety glasses or goggles, steel-tipped shoes, flame-resistant clothing, hard hats, chemical resistant gloves, and respirator masks. Potential routes of exposure include inhalation and dermal exposure.

There are no consumer uses of the phenylchlorosilanes.

Environmental exposure is not expected.

WEIGHT OF EVIDENCE ASSESSMENT FOR THE SKIN SENSITISATION POTENTIAL OF 4-ISOPROPYLANILINE (CUMIDINE, CAS 99-88-7)

This report documents a case study in which a "weight of evidence" (WoE) approach is used that would allow a conclusion to be drawn on a specific hazard endpoint for which data are not available (skin sensitisation) for a discrete chemical, 4-isopropylaniline (cumidine). The purpose of the report is to demonstrate how such a WoE argument can be built using all available evidence (existing data, read across and alternative methods including (quantitative) structure-activity relationship (QSAR) predictions), with the expectation that it could serve as an example of "best practice" for member countries interested in applying similar approaches for other chemicals and related endpoints. The report been prepared by experts from the Netherlands and Denmark with support from the OECD Secretariat.

An assessment of the industrial chemical 4-isopropylaniline, sponsored by Japan, was agreed at CoCAM 3 in October 2012. Experimental data on skin sensitisation were not available for the chemical. As its chemical structure is similar to substances known to be potent skin sensitizers, some member countries expressed an interest in exploring this endpoint further (although it is not a SIDS endpoint). The current case study was produced to this end, and has been agreed by CoCAM and by the Task Force on Hazard Assessment. The report is now being forwarded to the Joint Meeting for endorsement by written procedure so that it can be declassified and published in the OECD Series on Testing and Assessment. The aim of making this report publicly available is so that it can act as an example on which member countries can base their own weight of evidence approaches.

ACTION REQUIRED: The Joint Meeting is requested to endorse the draft report for declassification by the 22nd April 2014.

Executive Summary

This Weight of Evidence case study has been prepared by experts from the Netherlands and Denmark, with support from the OECD Secretariat.

A hazard assessment of the industrial chemical 4-isopropylaniline (CAS 99-88-7) prepared by the Japanese authorities was discussed by OECD member countries at an OECD Cooperative Chemicals Assessment Meeting (CoCAM) on October 16 – 18th 2012.

Skin sensitisation is not a mandatory OECD SIDS endpoint, which means that there are no formal requirements for evaluation or generation of test data to conclude on this endpoint in a chemical hazard assessment of the OECD. However, if any data are available for this endpoint, they should be included in the assessment.

No experimental test data on skin sensitisation were available for 4-isopropylaniline. However, the chemical structure of this substance is similar to substances known to be potent skin sensitizers, including some well-known hair colouring agents such as *p*-phenylenediamine, *p*-toluenediamine and *p*-aminophenol. Therefore, it was decided that a case study with non-test information on skin sensitisation of 4-isopropylaniline would be prepared.

This case study aims to provide all available and relevant (non-testing) evidence on skin sensitization potential for 4-isopropylaniline, and subsequently uses a Weight of Evidence (WoE) approach to arrive at a conclusion. Although some evidence on its own may be considered insufficient (e.g. a QSAR prediction that has an out-of-applicability domain warning) to reach a conclusion, this information can still be taken into account in a WoE approach, especially if the information confirms other (equally or more reliable) sources of information. The WoE assessment presents a hypothesis on skin metabolism and mechanism through which the substance of interest can cause skin sensitization. Five structural analogues for which experimental skin sensitization data are available were selected based on this mechanism and the other selection criteria that are detailed in the document. Furthermore, positive predictions for the substance of interest from five independent QSAR models are presented, and the QSAR predictions for the selected structural analogues by these same QSAR models show the ability of the QSARs to (correctly) predict skin sensitization potential for this type of substance.

All this information points to the same conclusion: 4-isopropylaniline would very likely be a skin sensitizer.

[TO BE ADDED IF DECLASSIFIED: The Joint Meeting agreed to the declassification of this report on XX MONTH 2014. This document is published under the responsibility of the Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology.]

Contents

Substance Identity

4-Isopropylaniline is a *para*-substituted aromatic amine. The identity and structure of 4-isopropylaniline are given below in figure 1. Its hazard profile was assessed within the OECD Cooperative Chemicals Assessment Programme in October 2012; the SIDS assessment was agreed and is publicly available (OECD 2013). The physico-chemical properties of 4-isopropylaniline are available as Annex 1 to this report.

CAS Number: 99-88-7

IUPAC Name: 4-Isopropylaniline

Molecular Formula: $C_9H_{13}N$

Structural Formula: 

Molecular Weight: 135.21

Synonyms: Aniline, 4-(1-methylethyl)-
p-Isopropylaniline
4-Aminocumene
4-(1-Methylethyl)benzenamine
4-Cumidine

Figure 1. Structure and identity of 4-isopropylaniline (see Annex 1 for physico-chemical properties).

Substance Profile and Proposed Mechanism

4-Isopropylaniline does not contain any substructures that alert for potential protein binding according to the OECD QSAR Toolbox (v 3.0). However, it is believed that the sensitizing potential of *aromatic amines* depends on their biotransformation into reactive species. These metabolites can be formed via enzymatic transformations in the skin. One of these possible routes is the oxidation of amines to *N*-hydroxylamines which are then oxidized to *nitroso compounds* that can react with proteins through nucleophilic addition reactions (Estrada *et al*, 2004).

The nitroso group is strongly electron withdrawing and similar to the carbonyl group (C=O). There is polarisation of the N=O bond and it behaves as a weak C=O. It undergoes addition of nucleophiles and condensation with primary amines. Oxygen is more electronegative than nitrogen, and the polarized N=O bond gives the nitrogen atom some degree of positive charge that attracts negatively charged nucleophiles and makes reaction with body proteins (Pr-SH, protein thiols) possible (Estrada *et al*, 2004; Eyer *et al*, 1994; Hopkins *et al*, 2005 cited from the OECD QSAR Toolbox (v3.0)). The structural alert acting through the mechanism of nucleophilic addition is illustrated below (figure 2).

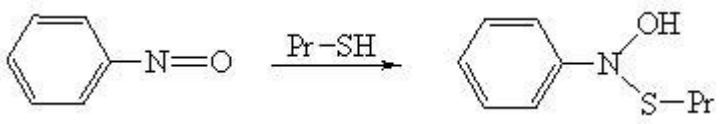


Figure 2. Structural alert acting through nucleophilic addition at the nitroso group.

The skin metabolism simulator of the OECD QSAR Toolbox (v3.0) indeed generates a metabolite of 4-isopropylaniline with a nitroso group (see figure 3 and table 1) which, according to the Oasis profiler for protein binding, binds to protein via nucleophilic addition at the polarized N-functional double bond (likelihood of generation and amount not stated; also see table 1).

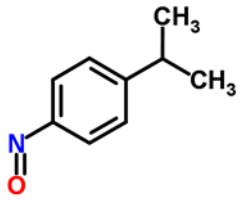


Figure 3. 4-isopropyl nitrosobenzene, skin metabolite of 4-isopropylaniline predicted by the skin metabolism simulator of the OECD QSAR Toolbox (SMILES: c1(C(C)C)ccc(N=O)cc1)

The mechanism proposed by the DEREK knowledge database also proposes that nitroso-formation of anilines by skin cytochrome p-450 enzymes leads to skin sensitization potential of (parent) substances that have a primary or secondary substituted aromatic amino-group (alert nr. 427 in the skin sensitization module of DEREK).
Experimental evidence, although limited to one substance, that aromatic nitroso-compounds are indeed skin sensitizers comes from reports on the contact allergenic effect in humans for *N*,*N*-dimethyl-p-nitroso-aniline (CAS-RN 138-89-6) (Kayser & Schlede, 2001).

Analogue Approach

When the focus of the assessment is on filling data gaps for one specific chemical, empirical data from one or more similar chemical(s) ("the analogue(s)") or "source" chemical can be used to predict the same endpoint for the "target" chemical, which is considered to be "similar." This analogue approach is useful when the target and source chemicals share a known common mode (and/or mechanism) of action, and the adverse effect(s) driven by this mode (and/or mechanism) of action is evaluated.

Read-across hypothesis

The read-across hypothesis that supports the analogue approach for anilines is based on two primary considerations (mechanistic and metabolic):

1. The skin sensitization potential of the aniline derivatives can be based on the reactivity of the amino group which depends on the mesomeric interaction with the aromatic system. Factors that may influence this mesomeric interaction include steric factors and further substituents on the aromatic group (IARC 2010). Thus, reactivity of the amino group of the analogues needs to be comparable to the reactivity of the amino group of 4-isopropylaniline.

2. The aniline derivatives are metabolically activated by *N*-oxidation in the skin in order to exert skin sensitization properties (Payne & Walsh 1994). Only analogues that follow this metabolic pathway are suitable to use for read-across to 4-isopropylaniline.

Identification and selection of analogues

A relatively large range of aromatic amines have been tested for skin sensitization. The following selection criteria that reflect the read-across hypothesis were applied in order to identify the most suitable analogues:

Selection criteria for analogues	Reasoning
1. Must be an aniline	The target chemical is an aniline.
2. Must not be substituted in the *ortho* position	Due to potential steric interactions that may result in chemical reactivity that differs from the target chemical.
3. If present, substituents on the aromatic ring must have weak electron donating properties	The isopropyl substituent on the target chemical has weak electron donating properties. This property is known to affect the chemical reactivity of the amino group (Gross & Seybold 2000; Argese *et al*. 2002). Substituents on suitable analogues should therefore have similar electron donating properties.
4. Must be able to form a protein reactive functional group by N-oxidation in the skin.	The amino group in itself has no structural alerts for skin sensitization. It is well known from other aromatic amines that this group needs to undergo N-oxidation before exerting sensitizing properties.
5. Must have *in vivo* test data for skin sensitization	This data is needed for read across

Analogues that fulfill the selection criteria were identified in the following way:

- Analogue identification in the OECD QSAR Toolbox
- Search on the ECHA disseminated website for REACH registered substances containing “aniline” in their names
- Identification of analogues used in the training set of QSAR models (Danish QSAR Database and VEGA)

Five analogues were selected (see table 1). None of the methods mentioned above proved alone to be sufficient to identify all five analogues. However, all methods gave varying degrees of overlap, meaning that the same analogues were detected with at least two of the three methods.

Selection criterion 3 was applied by deselecting anilines containing substituents that are known to have different electron withdrawing/donating properties compared to the alkyl substituent in 4-isopropylaniline. Therefore, only chemicals containing alkyl or alkyl-like substituents were selected. This also means that extreme sensitizers like *p*-phenylenediamine (PPD) and *p*-toluene diamine (PTD) were excluded from the group. In addition, the E_{LUMO} (lowest unoccupied molecular orbital) was calculated in the OECD QSAR Toolbox for 4-isopropylaniline and its analogues. E_{LUMO} is a descriptor for hydrogen bonding capacity and has a good correlation with reactivity of aniline-derivatives (R = 0.86) (Argese *et al*, 2002).

Selection criterion 4 was first applied by use of the skin metabolism simulator in the OECD QSAR Toolbox (v3.0). However, the 5 selected analogues were checked for additional information on metabolism in the following sources: REACH registrations on the ECHA disseminated website, the EU RAR for aniline and the OECD SIDS for *p*-Toluidine, *m*-Toluidine and 4-isopropylaniline. In addition, mutagenicity of anilines is also believed to be dependent on N-oxidation of the amino group. Therefore, it was checked whether or not positive responses were recorded in *in vitro* assays with S9. A positive result in such an assay would be an indication of N-oxidation. Finally, a mutagenic response *in vitro* can also be used in its own right as an indicator for skin sensitization potential since there is a positive correlation between these two effect types (e.g. Hilton *et al*, 1993; Mekenyan *et al*, 2010; Patlewicz *et al*, 2010; Rosenkranz *et al*, 1999).

Results for the analogues

The five structural analogues are presented in table 1 (split between 1a, suitable analogues, and 1b, more distant analogues) below. A more detailed description of test results for the analogues and an assessment of their suitability for read-across is presented in Annex 2.

Table 1a: Target Chemical and Structural Analogues that are Suitable for Read Across

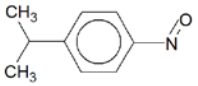
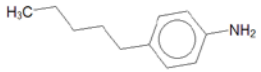
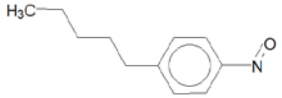
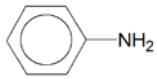
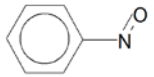
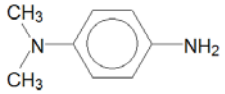
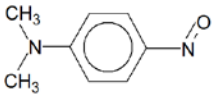
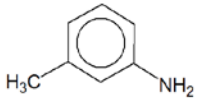
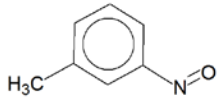
Chemical	Predicted metabolite using skin metabolism simulator (OECD QSAR Toolbox, v. 3.1)	Protein binding profile for skin metabolite (OASIS, v.1.1)	$E_{LUMO\ (eV}$ for parent compound / skin metabolite)	Selection criteria assessment	*In vitro* genotoxicity	Experimental data on *in vivo* skin sensitization[1]
4-Isopropylaniline (CAS 99-88-7) 	 SMILES: c1(C(C)C)ccc(N=O)cc1	Nucleophilic addition reaction at polarized N-functional double bond	0.636 / -0.563	Target chemical	Gene mutation with S9	Target chemical No test data available
p-Toluidine (CAS 106-49-0) 	 SMILES: c1(N=O)ccc(C)cc1	Nucleophilic addition reaction at polarized N-functional double bond	0.617 / -0.552	Very close structural analogue	Clastogenicity with S9	Positive in GPMT (Klimisch code 2) Kleniewska and Maibach, 1980; OECD, 2005
4-Pentylaniline (CAS 33228-44-3) 	 SMILES: c1(N=O)ccc(CCCCC)cc1	Nucleophilic addition reaction at polarized N-functional double bond	0.622 / -0.767	Very close structural analogue	No information available	Positive in LLNA Roberts et al, 2007
Aniline (CAS 62-53-3) 	 SMILES: c1(N=O)ccccc1	Nucleophilic addition reaction at polarized N-functional double bond	0.640 / -0.408	Close structural analogue	Clastogenicity and possible gene mutation with S9	Positive in 2 of 3 GPMTs (Studies judged reliable for use in EU Existing Substances regulation) EU, 2004.

Table 1b: More Distant Structural Analogues

Chemical	Predicted metabolite using skin metabolism simulator (OECD QSAR Toolbox, v. 3.1)	Protein binding profile for skin metabolite (OASIS, v.1.1)	$E_{LUMO\ (eV}$ for parent compound / skin metabolite)	Selection criteria assessment	*In vitro* genotoxicity	Experimental data on *in vivo* skin sensitization[1]
N,*N*-Dimethyl-*p*-benzenediamine (CAS 99-98-9) 	 SMILES: c1(N=O)ccc(N(C)C)cc1	Nucleophilic addition reaction at polarized N-functional double bond	0.600 / -0.691	Outlier in the category; read across should be performed with caution	Gene mutation with S9	Positive in GPMT NICEATM/ICCVAM, 1999 Skin sensitiser US National Library of Medicine, 2012 [2]
m-Toluidine (CAS 108-44-1) 	 SMILES: c1(N=O)cc(C)ccc1	Nucleophilic addition reaction at polarized N-functional double bond	0.605 / -0.759	Outlier in the category; read across should be performed with caution	Not genotoxic	Negative in LLNA (Klimisch code 1) ECHA, 2013

[1] More details on experimental results can be found in Annex 2. No assessment of data quality has been performed. Reliabilities, when available, have been taken from relevant assessment frameworks.

[2] Information from Haz-Map, which comes from textbooks, journal articles, the Documentation of the Threshold Limit Values (published by ACGIH), and electronic databases such as NLM's Hazardous Substances Data Bank (HSDB®).

Interpretation of experimental results for the analogues

The two closest analogues to 4-isopropylaniline (*p*-toluidine and 4-pentylaniline) both tested positive for skin sensitization. The two analogues differ from the target chemical only by the number of carbon atoms and the degree of branching in the *p*-alkyl chain. Based on the descriptors that have been included in this assessment (structural features, electron withdrawing/donating properties of substituents, E_{LUMO}, *in vitro* genotoxicity, and metabolism), the two closest analogues are suitable to use for read-across for skin sensitization. A conclusion on potency for the target chemical is not possible, but it could be envisaged that the sensitization potency of 4-isopropylaniline (substituent with 3 carbon atoms) is in between that of *p*-toluidine (substituent with 1 carbon atom) and 4-pentylaniline (substituent with 5 carbon atoms).

Two of the five identified analogues were rated as outliers in the group after closer examination of the available information. *N*,*N*-Dimethyl-*p*-benzenediamine differs from 4-isopropylaniline in structural features; the substituent containing a tertiary amine, which are known to increase the electron withdrawing properties compared to an alkyl group. In addition, a second predicted skin metabolite for this chemical has different alerts for protein binding according to TIMES-SS and the OECD QSAR Toolbox (v3.0) (OASIS protein binding). This does not disqualify *N*,*N*-Dimethyl-*p*-benzenediamine as an analogue, but means that there is a higher degree of uncertainty involved in the read across to this substance.

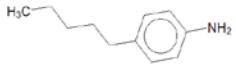
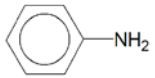
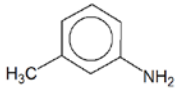
The second outlier, *m*-toluidine, differs from the rest of the group in its structural features (substituted in the *meta* position) and in the available test data (negative results for skin sensitization and *in vitro* genotoxicity). It is not possible to explain the differences from the applied chemical reactivity descriptors since E_{LUMO} is in the same range as for *para*-substituted anilines and since the electron donating tendency is very similar for methyl groups placed in the *para* and *meta* position (Gross & Seybold, 2000). It is therefore speculated that the differences are caused by differences in the metabolic pathway.

The effects of *para*-substituted anilines compared to *meta*- or *ortho*-substituted ones have also been reported in human case studies. Positive reactions in patch tests have been reported in monitoring surveys and in studies with patients suffering from eczematous dermatitis. Here, the positive reactions are often associated with a group allergy to other aromatic amines which are substituted at the *para* position (*para*-group compound cross reactivity) (EU, 2004).

QSAR Estimates for Skin Sensitization

All QSAR predictions are summarized in Table 2, both for 4-isopropylaniline and the five structural analogues for which experimental data on skin sensitization are present.

Table 2: Skin Sensitization Potential Predictions from Five Independent QSAR Models for 4-Isopropylaniline and its Analogues

Chemical	Danish QSAR Database (MC4PC)[1]	VEGA/ CAESAR, v.2.1.5[2]	DEREK Nexus v.1.5[3]	TOPKAT[4] Sensitizer vs. non-sensitizer	TOPKAT[5] Severe vs. moderate	TIMES-SS[6]
4-Isopropylaniline (CAS 99-88-7) 	**Sensitizer** Inside AD P=90% Reliability: 2	**Sensitizer** AD warning P=88% Reliability: 2	**Sensitizer** Plausible Reliability: 2	**Sensitizer** outside OPS but inside OPS limits, P=100% Reliability: 2	**Severe** inside OPS P=100% Reliability: 2	**Weak Sensitizer** Out of AD Active is: Metabolite Reliability: 2
p-Toluidine (CAS 106-49-0) 	Sensitizer Inside AD P=90%	Sensitizer Inside AD 88%	Sensitizer Plausible	Sensitizer Inside OPS P=100%	Moderate Inside OPS P=0%	Strong Sensitizer Out of AD Active is: Metabolite
4-Pentylaniline (CAS 33228-44-3) 	Sensitizer Inside AD P= 90%	Sensitizer Inside AD 88%	Sensitizer Plausible	Sensitizer Inside OPS P=100%	Moderate Inside OPS P=0%	Strong Sensitizer Out of AD Active is: Metabolite
Aniline (CAS 62-53-3) 	Sensitizer Inside AD P = 90%	Sensitizer Inside AD P=88%	Sensitizer Plausible	Sensitizer Inside OPS P=100%	Moderate Inside OPS P=0%	Weak Sensitizer Inside AD Active is: Metabolite
N,*N*-Dimethyl-*p*-benzenediamine (CAS 99-98-9) 	Sensitizer Inside AD P=90%	Sensitizer Inside AD P=90%	Sensitizer Plausible	Sensitizer Inside OPS P=97.5%	Severe Inside OPS P=100%	Strong Sensitizer Inside AD Active is: Metabolite
m-Toluidine (CAS 108-44-1) 	Sensitizer Inside AD P = 90%	Sensitizer Inside AD P=88%	Sensitizer Plausible	Sensitizer Inside OPS P=100%	Moderate Inside OPS P=0%	Weak Sensitizer out of AD Active is: Metabolite

Note on highlighting: predictions highlighted in green affirm experimental findings (see tables 1a and 1b); predictions highlighted in red contradict experimental findings. Further discussion is included below.

[1] Danish QSAR Database (internal version): MC Score = internal score, the breakpoint between Neg (negative) and Pos (positive) is 25. P = probability that positive prediction is correct. See appendices for detailed prediction and Applicability Domain information

[2] VEGA/CAESAR Skin Sensitization model v.2.1.5. See appendices for detailed prediction and Applicability Domain information

[3] DEREK Knowledge Base 2012 1.0 (Lhasa Ltd, Leeds, UK). See appendices for detailed prediction information

[4] TOPKAT v6.2, as implemented in the Accelrys Discovery Suite software. This first classifier model distinguishes between Sensitizers and non-sensitizers. The manual states that a score of >70% should be interpreted as a positive prediction of skin sensitization potential The OPS (= Optimal Prediction Space) is a multivariate statistical TOPKAT indication of model applicability domain. See appendices for detailed information.

[5] TOPKAT v6.2 as implemented in the Accelrys Discovery Suite software. This second skin sensitization classifier model distinguishes between severe and mild/moderate skin sensitizers. It can be used to get an indication of the skin sensitization potential for those substances which are predicted to be a sensitizer by the previous TOPKAT module. The manual states that a score of P>70% should be interpreted as a prediction of SEVERE skin sensitization. The OPS (= Optimal Prediction Space) is a multivariate statistical TOPKAT indication of model applicability domain.

[6] Predictions from the TIMES-Skin Sensitization model v16.18 . For the interpretation of the predictions (red/green highlight) the prediction of non- or weak-sensitizer was interpreted (in accordance with the interpretation of LLNA potency classes for classification and labelling purposes) as Non-sensitizer and mild/moderate-, strong- and extreme-sensitizer were considered Sensitizers. If the TIMES prediction of weak sensitizer is interpreted as Sensitizer (for classification and labelling) all predictions, with the exception of *m*-toluidine would be correct.

MULTICASE MC4PC (version 2.4.1.4)

The substance is predicted to be very active in the commercial model A33 "Allergic contact dermatitis". The identified alert is the aromatic amine in the para position to the substitution. The alert is based on 20 molecules of which 18 are active. The Danish QSAR Model predicts all analogues substituted in the *para* position to be "very active" (internal score 59-67, the breakpoint between positive and negative is 25) whereas those that are not substituted in the *para* position (*m*-toluidine and aniline) are still predicted to be "moderately active" (internal score 39; hence the model is able to discriminate between substitution in the *para* and *meta* positions). The two metabolites proposed by the OECD QSAR Toolbox (see table 1a) were also predicted to be "very active". The prediction was inside the applicability domain of the model and considering the predictive performance for the structural analogues, is judged to be of good quality (Reliability 2: reliable with restrictions).

VEGA / CAESAR (version 2.1.5, program downloaded from the Vega site (Vega, 2013))

The compound is predicted to be a sensitizer (Active: 0.88, Inactive: 0.12), however with an applicability domain warning (some atom-centered fragments of the compound have not been found in the compounds of the training set, or are rare fragments). The applicability domain indicator is borderline (0.79 where 0.80 is considered inside the domain). Nevertheless, the predictions from the VEGA / CAESAR model for the structural analogues are all inside the applicability domain (as defined by the VEGA / CAESAR model), and the predictions for the *para*- and non-substituted anilines are all correct. These results indicate that the QSAR model is capable of predicting this type of substance (*para*-substitituted anilines) with high reliability (Reliability 2: reliable with restrictions).

DEREK for Windows prediction

4-Isopropylaniline was predicted to be a PLAUSIBLE skin sensitizer based on the structural alert "Aromatic primary or secondary amine" (alert number 427). The DEREKfW prediction "PLAUSIBLE" means that there is a structural alert in the assessed compound for skin sensitization and all other requirements described in the alert description are fulfilled. Based on this positive DEREKfW prediction and the correct predictions of the structural analogues (except for the *meta*-substituted analogue), *para*-isopropylaniline (CAS 99-88-7) is predicted to be a skin sensitizer (Reliability 2: reliable with restrictions).

TOPKAT 6.2

The TopKat model predicts both the substance of interest, as well as the aniline analogues to be skin sensitizers. Again, the predictions are correct for the *para*- and un-substituted anilines, whereas the *meta*-substituted aniline is a False Positive. All predictions for the analogues were well within the TopKat defined Optimal Prediction Space (OPS). The prediction from the TOPKAT 6.2 model for *para*-isopropylaniline was not within the OPS, but still considered within the OPS limits, i.e. still within the applicability domain. The prediction from the TOPKAT Sensitizer vs. non-sensitizer model is therefore considered reliable (Reliability 2: reliable with restrictions). The TOPKAT Severe vs Mild/moderate sensitizers model prediction that 4-isopropylaniline will be a Severe sensitizer is slightly less reliable, as the prediction for the analogue 4-pentylaniline has to be considered wrong.

TIMES Skin Sensitization model (version 16.18 with autoxidation)

The target substance is predicted to be a weak skin sensitizer, where the activity is due to autooxidation to a hydroperoxide and metabolism to an aromatic nitroso compound (see section "Substance profile"). However, the structure was out of the model structure domain. If a prediction is out of the applicability domain this does not necessarily mean that the prediction is therefore not valid, or is incorrect. It indicates that the uncertainty about the reliability of the model is increased, as the performance statistics from the training and/or validation datasets might not be applicable to this specific substance. All models set the applicability domain thresholds differently and some are stricter than others. For example, the TIMES SS requires 100% of the fragments to be covered correctly as well as key physical-chemical parameters and this check is done for the generated metabolites as well followed by an alert performance (response space) check. Other models set cut-offs for fragments space lower (at ~80% for example). Therefore variation in the parameters employed in a model's internal determination of whether a substance falls within its applicability domain requires consideration in examining relative reliability across models. Given the conservative applicability domain categorization that is applied in the TIMES SS model (see also Teubner *et al*, 2013) and the fact that the model correctly predicts the skin sensitizing property of the analogous substances a reliability score of 2 is assigned (reliable with restrictions).
As TIMES SS gives a prediction on a scale of skin sensitization potency (non- weak-, mild/moderate-, strong- and extreme- sensitizer) an interpretation in binary terms (sensitizer / non-sensitizer) is needed. If the interpretation of LLNA potency for classification and labelling purposes is applied, a TIMES prediction of non- or weak-sensitization would be interpreted as Non-sensitizer. The prediction for 4-isopropylaniline is then that it is not a skin sensitizer (for classification and labelling purposes). The prediction for the analogue aniline is then consequently incorrect, but the predictions for *N*,*N*-dimethyl-*p*-aniline and *m*-toluidine would be correct. If a TIMES prediction of weak-sensitizer is interpreted meaning that the substance is a sensitizer for classification and labelling purposes, all *para*-substituted aniline analogues are predicted correct, but *m*-toluidine is a false positive prediction, similar to the predictions of (all) the other QSAR models[1].

Quantitative Predictivity of Combination of Multiple QSAR Models

As no single QSAR model is considered valid as a stand-alone replacement of an animal test, there is the need to assess the (QSAR) evidence in combination. The question is whether two or more positive predictions from QSAR models actually give a higher probability that the conclusion will be correct. This has been analysed in a recent publication by Rorije et al (2013) using Bayesian statistics. The procedure uses the individual predictive performance (sensitivity, specificity) of models, tests and assays to predict the outcome of an LLNA. Bayesian statistics are applied to calculate the probability that a prediction from a battery of tests and/or models will correctly predict the outcome of an LLNA. This probability is a quantitative measure of the reliability of a prediction when (QSAR) models are combined. What is additionally needed is an indication of what is considered sufficient reliability to allow replacement of the animal test. This can be deduced from the reliability/reproducibility of the *in vivo* GPMT test correctly predicting the outcome of an LLNA (and vice versa). Both *in vivo* test results are accepted as stand-alone results under REACH, and also in the OECD CoCAM process. Therefore the probability with which the GPMT can predict the outcome in the LLNA can be considered sufficient. The probability that a substance is tested positive in the GPMT, and will also be tested positive in an LLNA was calculated in a rigorous official validation study of the LLNA to be **83%** (NICEATM-ICCVAM, 1999). A battery of alternative tests and/or models can therefore be considered sufficiently reliable to replace an in vivo test result if it reaches at least this threshold probability of 83%.

[1] Note that these QSAR predictions are not aligned with GHS criteria, as discussed in detail in Teubner et al. (2013).

In the analysis the individual predictive performance (sensitivity, specificity) of DEREKfW, TIMES-SS and the OECD QSAR Toolbox alerts is evaluated, *without taking into account any applicability domain information.* This means that TIMES-SS predictions which were considered to be out of the applicability domain were *included* in the calculation of the predictive statistics in this analysis. The calculated Bayesian probability that a substance will test positive in the LLNA test, given that these three models agree with each other (table 6 in Rorije et al, 2013), is **85.9%.** This is already above the probability of 83% with which a positive GPMT can predict a positive LLNA outcome. The actual observed percentage of correct predictions of the battery of these three models, without taking into account applicability domain information, when all three models predict positive, was **89.5%,** using a set of 522 substances for which LLNA results are available.

The additional evidence from positive CAESAR, MultiCASE and TOPKAT model predictions are likely to increase this probability even further however, statistics were not calculated for these specific models (Rorije, 2013).

Conclusion

A weight of evidence analysis of the experimental data on structural analogues, and QSAR model predictions, gives a strong indication that 4-isopropylaniline is a skin sensitizer.

4-isopropylaniline is structurally related to *p*-toluidine (CAS 106-49-0), aniline (CAS 62-53-3), and 4-pentylaniline (CAS 33228-44-3), which are known skin sensitisers. All of these substances, except aniline, are *para*-substituted and are predicted to form reactive nitrosamines. The analogous substance *N*,*N*-dimethyl-*p*-benzenediamine (CAS 99-98-9) also tests positive for skin sensitization but is judged to be an outlier in the category. The analogous substance *m*-toluidine (CAS 108-44-1) (which is substituted at the *meta* position and therefore less suitable for read-across purposes), is not thought to form reactive nitrosamine and tests negative for skin sensitisation. Further, there are positive QSAR predictions from five different models which are deemed reliable (reliability 2: reliable with restrictions). In addition, there are profiler alerts in the OECD QSAR Toolbox consistent with the current knowledge as e.g. presented in the DEREK knowledge database on metabolic activation in the skin for aromatic amines.

Statistically, the probability that a substance for which a battery of QSAR models is in agreement in their positive predictions will be around 90% correct in predicting a positive outcome in the LLNA. This is well above the (statistical) reliability of experimental tests that is implicitly accepted in regulatory frameworks.

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Appendices (SEPARATE DOCUMENTS)

I. QSAR predictions from the Danish EPA QSAR database (MultiCASE MC4PC)

II. QSAR predictions from the DEREK nexus v.1.5

III. QSAR predictions from VEGA/CAESAR v2.1.5

IV. QSAR predictions from TOPKAT v6.2 Skin Sensitization models

V. QSAR predictions from TIMES Skin Sensitization (OASIS) v.16.18

VI. QMRF for the Multicase skin sensitization model in the Danish QSAR database

VII. QMRF and QPRF for the DEREK skin sensitization model

Annex 1: Physico-chemical Properties of 4-Isopropylaniline[1]

Property	Value	Reliability
Physical state/appearance	Pale yellow clear liquid	2
Melting point	<-100 °C	2
Boiling point	226-227 °C at 745 mmHg	2
Density	0.953 g/cm^3 at 20 °C	2
Vapour pressure	5.62 Pa at 25 °C[1)]	1
Water solubility	2390 mg/L at 20 °C[2)]	1
Partition coefficient between octanol and water	log K_{ow} = 2.3 at 25 °C[3)]	1
Dissociation constant	pKa=5.00 at 25 °C	1
Soil adsorption coefficient	log K_{oc} =2.53 [4)] KOCWIN	2
Henry's Law constant	0.318 Pa.m^3/mol at 20 – 25 °C [5)] 0.375 Pa.m^3/mole at 25 °C [6)] HENRYWIN	2 2

Table Notes:
Vapour pressure at 25 °C was extrapolated by the following regression expression, which was obtained from the results of a test according to OECD test-guieline104: "Vapour pressure: Gas saturation method" in compliance with GLP.
log P (Pa) = -3062.69/T + 11.0224
Test was conducted according to OECD test-guideline 105: "Water solubility: flask method" in compliance with GLP.
Test was conducted according to OECD test-guideline 107: "Partition coefficient (n-octanol /water): Shake flask method" in compliance with GLP.
The value is estimated by MCI method.
Henry's law constant is calculated by vapour pressure of 5.62 Pa at 25 °C divided by water solubility of 2390 mg/L at 20 °C.
The value is estimated by bond method.

[1] Taken from OECD, 2013; for references, refer to OECD, 2013.

Annex 2: Analogue Results

The five selected analogues are presented individually below with information on skin metabolism, skin sensitization, mutagenicity, mechanistic considerations and a qualitative judgment on their suitability for read-across to 4-isopropylaniline for skin sensitization.

_p_-Toluidine (CAS 106-49-0)

Skin metabolism: No information on skin metabolism is available in the OECD SIDS (OECD 2005). The REACH registration on the ECHA dissemination website contains references to *in vitro* assays which confirm that N-oxidation is a possible metabolic pathway for *p*-toluidine (e.g. Doerge & Corbett, 1991). The skin metabolism simulator in the OECD QSAR Toolbox (v3.0) predicts four potential skin metabolites with the active C-nitroso metabolite as one of them. The positive result in the sensitization test and some mutagenic response in the presence of S9 also indicates N-oxidation. In conclusion, there are strong indications that N-oxidation is a relevant metabolic pathway in the skin.

Skin sensitization: *p*-Toluidine was concluded to be a skin sensitizer at OECD SIAM 21 (OECD 2005). Patch test was performed with 10 guinea pigs using a 2 % *p*-toluidine petrolatum solution and occlusive dressing for induction. 14 days later, 4 concentrations for the challenge procedure were used: 2 %, 1 %, 0.5 %, 0.25 %. *p*-Toluidine was evaluated as sensitizing because 8/10 guinea pigs showed a positive reaction in the highest concentration (2 %). 6/10, 4/10 and 0/10 animals showed a positive reaction after challenge with 1, 0.5 or 0.25% *p*-toluidine. The positive control was served by *p*-phenylene diamine (Kleniewska and Maibach, 1980). This study was rated a Klimisch score of 2.

In addition the following study with humans is reported in the SIAR (OECD 2005): 58 dermatitis patients, known to be hypersensitive to *p*-phenylene diamine, were patch tested with 2 % *p*-toluidine in yellow paraffin. 63.8 % (37) of the patients showed positive reactions (Kleniewska, 1975). The study is not assignable because only patients with dermatitis and already sensitized to *p*-phenylene diamine were included in the test.

Mutagenicity: *p*-Toluidine does not induce point mutations in the vast majority of *in vitro* Ames tests (a positive result is reported for the strain TA100 with hamster S9). In Chinese hamster lung cells *p*-toluidine is clastogenic in the presence but not in the absence of S9-mix (OECD 2005).

Structural and mechanistic considerations: *p*-Toluidine is substituted in the *para* position and the methyl substituent has a weak electron donating property which is comparable to 4-isopropylaniline. $E_{LUMO,}$ which is used as a descriptor for hydrogen bonding capacity, is very similar to that of 4-isopropylaniline.

Conclusion: *p*-Toluidine is judged to be a very close analogue to 4-isopropylaniline and suitable to use for read-across for skin sensitization.

4-Pentylaniline (CAS 33228-44-3)

Skin metabolism: No test data for skin metabolism (or any other type of metabolism) have been identified. The skin metabolism simulator in the OECD QSAR Toolbox (v3.0) predicts seven potential skin metabolites with the active C-nitroso metabolite as one of them. The positive result in the LLNA test also indicates a potential for N-oxidation in the skin. In conclusion, there are indications that N-oxidation is a relevant metabolic pathway in the skin.

Skin sensitization: 4-pentylaniline was found to be a strong sensitizer in the LLNA test (Roberts *et al*, 2007).

Mutagenicity: No information is available.

Structural and mechanistic considerations: 4-Pentylaniline is substituted in the *para* position and the pentyl substituent has a weak electron donating property which is comparable to 4-isopropylaniline. $E_{LUMO,}$ which is used as a descriptor for hydrogen bonding capacity, is very similar to that of 4-isopropylaniline.

Conclusion: 4-Pentylaniline is judged to be a close analogue to 4-isopropylaniline and suitable to use for read-across for skin sensitization.

<u>*m*-Toluidine (CAS 108-44-1)</u>

Skin metabolism: According to a BUA report cited in OECD (2005), *m*-toluidine is rapidly absorbed via the gastrointestinal tract, via skin and is metabolized by ring hydroxylation. However, other evidence suggests that N-oxidation is also a relevant metabolic pathway. The OECD SIDS for *m*-toluidine (OECD 2003) cites an older study in which the protein reactive metabolite, *m*-nitrosotoluene is measured in blood after a single injection of 111.1 mg *m*-toluidine-HCl/kg b.w. to dogs. The skin metabolism simulator in the OECD QSAR Toolbox (v3.0) predicts four potential skin metabolites with the active C-nitroso metabolite as one of them. However, negative results in the LLNA test and in 14 genotoxicity *in vitro* assays suggest that N-oxidation may play a smaller role compared to ring hydroxylation metabolism for *m*-toluidine.

Skin sensitization: A GLP compliant LLNA test (OECD 429) is reported in the REACH registration dossier on the ECHA webpage. Dermal application of 2, 10 and 50% of *m*-toluidine on both ears of female NMR mice for three consecutive days did not show an increase in the stimulation indices for cell counts or for weights of the draining lymph nodes. Hence, according to this assay the substance has no sensitization potential.

Mutagenicity: 14 *in vitro* studies are presented in the REACH registration dossier on the ECHA webpage. No mutagenic potential has been identified in these studies. The conclusion in the OECD SIDS is that *m*-toluidine is considered not to be genotoxic (OECD 2003).

Structural and mechanistic considerations: *m*-Toluidine is substituted in the *meta* position and thereby differs from 4-isopropylaniline, which is substituted in *para* position. However, the methyl substituent has a weak electron donating property which is comparable to 4-isopropylaniline. $E_{LUMO,}$ which is used as a descriptor for hydrogen bonding capacity, is also very similar to that of 4-isopropylaniline.

Conclusion: There are some indications that (at least quantitatively) differences exist in metabolism between *m*-toluidine and 4-isopropylaniline. Hence, read-across from *m*-toluidine to 4-isopropylaniline should be performed with caution.

<u>Aniline (CAS 62-53-3)</u>

Skin metabolism: According to the EU Risk assessment report for aniline (EU 2004) no information is available on skin metabolism from animal studies. However, non-dermal toxicokinetic studies demonstrate that the protein reactive metabolite nitrozobenzene is generated, although the quantity seems to be route and species specific (EU 2004). The skin metabolism simulator in the OECD QSAR Toolbox (v3.0) predicts two potential skin metabolites with the active C-nitroso metabolite as one of them. In addition, positive findings in two of three sensitization studies, and the induced potential for *in vitro* mutagenicity by addition of S9, support the generation of a protein reactive metabolite.

Skin sensitization: According to the EU risk assessment report (EU 2004), animal data revealed a mild to moderate sensitisation rate. In 2/3 guinea pig tests a positive rate of 10% and 50% are documented. In the test revealing a 50% positive result 20% aniline was used for challenge, while the tests demonstrating weak or negative results used very low challenge concentrations (challenge with 10% aniline resulted in 1/10 sensitised animals, challenge with 1% aniline in no sensitisation at all). In humans positive reactions have also been reported, mainly in patients suffering from eczematous dermatitis. The positive reactions are often associated with *para*-group compound cross reactivity. In addition, in humans aniline shows cross-reactivity to substances of the *para*-substituted compound group, which has to be considered as a hazard by itself. Based on animal and human data, aniline has a harmonised classification for skin sensitisation in the EU and as such is labelled with the R-phrase R 43 "May cause sensitisation by skin contact".

Mutagenicity: According to EU (2004) aniline is negative in routine bacterial mutation tests. In mammalian cell cultures positive effects were obtained with respect to chromosomal effects, SCE and possibly for gene mutations. In general, stronger effects are induced in the presence of an exogenous metabolic activation system than in its absence.

Structural and mechanistic considerations: Aniline is unsubstituted and thereby differs from 4-isopropylaniline, which is substituted in the *para* position. $E_{LUMO,}$ which is used as a descriptor for hydrogen bonding capacity, is also very similar to that of 4-isopropylaniline.

Conclusion: Aniline is judged to be an acceptable analogue to 4-isopropylaniline.

***N,N*-Dimethyl-*p*-benzenediamine (CAS 99-98-9)**

Skin metabolism: No relevant test data have been identified. The skin metabolism simulator in the OECD QSAR Toolbox (v3.0) predicts two potential skin metabolites with the active C-nitroso metabolite as one of them. However, the other potential skin metabolite has a different alert for protein binding.

Skin sensitization: The substance was found to be a strong sensitizer in a GPMT (Dossou *et al*. 1985). In addition three cases of allergic contact dermatitis due to N,N-dimethyl-*p*-benzenediamine exposure to humans are reported in the literature (Price & Shupack 1978).

Mutagenicity: A positive response is recorded in some bacterial strains in AMES but only with metabolic activation (OECD QSAR Toolbox – the original reference could not be located).

Structural and mechanistic considerations: *N,N*-Dimethyl-*p*-benzenediamine is substituted in the *para* position. The substituent contains a tertiary amine which has electron withdrawing properties. However, the electron donating property of the two attached methyl groups may counteract this to some degree. $E_{LUMO,}$ which is used as a descriptor for hydrogen bonding capacity, is very similar to that of 4-isopropylaniline.

Conclusion: There are potentially differences in the mesomeric interaction from the substituent compared to 4-isopropylaniline. In addition, the metabolites for this chemical have different alerts for protein binding according to TIMES-SS and the OECD QSAR Toolbox (v3.0) (OASIS protein binding). Hence, read-across from *N,N*-dimethyl-*p*-benzenediamine to 4-isopropylaniline should be performed with caution.

REFERENCES: see main report reference list