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ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY**

**SIDS INITIAL ASSESSMENT PROFILES AGREED IN THE COURSE OF THE
OECD COOPERATIVE CHEMICALS ASSESSMENT PROGRAMME IN 2012**

**Series on Testing & Assessment
No. 243**

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IOMC

INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS

A cooperative agreement among **FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD**

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

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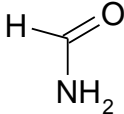
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SIDS INITIAL ASSESSMENT PROFILE

CAS No.	75-12-7
Chemical Name	Formamide
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

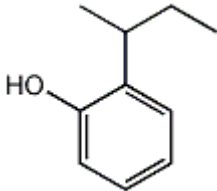
Toxicokinetic and other toxicity studies show that formamide is readily absorbed after inhalation, oral and dermal application. Maximum plasma levels are reached within 1 – 2 hours in rats and mice. Elimination half-life from plasma is approx. 15 hours in rats and only 4 - 6 hours in mice. Approx. 30% of the dose is excreted unchanged in urine within 72 hours, a high fraction is excreted as CO₂ (rats about 30%, mice about 50%), and only minor quantities are excreted with the feces (1 – 3%). Protein binding increased with time in both species. The metabolism depended on the activity of microsomal enzymes, specifically CYP2E1, and in analogy to methylformamide it was proposed that formamide is oxidized to isocyanic acid, which reacts with nucleophils and decomposes in the presence of water to ammonia and CO₂. The formation of carbon monoxide during metabolism is unlikely. Toxicokinetic studies indicate presence of a first pass effect.

No signs of toxicity and mortality were noted in a rat Inhalation Hazard Test (8 hours, saturated atmosphere, 20°C). Clinical signs of toxicity (escape reaction, irritation of mucous membranes, dyspnea, apathy, and loss of weight) and mortality (one of 12 exposed rats) were seen after an 8-hour exposure when the saturated formamide atmosphere was generated at 150°C. Clinical signs were also seen in all rat groups when very high test substance concentrations were generated either at elevated temperature (100 to 210°C) or using a nebulizer (body weight losses, lethargy, hunched posture, clear or red ocular discharges, red nasal discharge, partially closed eyes, diarrhea, and brown-stained perineum). The inhalation LC₅₀ is > 21 mg/L (4 hr, in the atmosphere generated using an evaporator heated to 100-210°C). The acute dermal LD₅₀ in rats is estimated to be > 3000 mg/kg bw, based on two independent OECD TG 411 90-day repeated dose rat studies. Mortalities were 1/20 and 3/20, respectively, in the groups receiving 3000 mg/kg bw/day. The oral rat LD₅₀ was approx. 5325 mg/kg bw in a pre-guideline study that was conducted similar to the method described in OECD TG 401; a LD₅₀ of 3200 mg/kg bw was calculated in a less robust acute oral rat study.

There is no valid skin irritation study. Formamide was slightly irritating to the rabbit's eye in a test performed corresponding to OECD TG 405. The effects were described as reversible. No valid sensitization study is known to exist.

In a 4-week oral gavage rat study similar to OECD TG 407 male and female rats received 34, 113, 340, and 1130 mg/kg bw/day. No effects were noted at the lowest dose level, whereas 340 and 1130 mg/kg bw/day caused 50% and 100% mortality, respectively. Animals at 113 mg/kg bw/day and higher showed loss of appetite, extreme body weight loss (7 – 11% at 113 mg/kg bw/day and 44 - 51% at 340 mg/kg bw/day), and failure of reflexes. Along with prostration, general organ atrophy and tissue damage (especially of the gastrointestinal tract, testes, adrenal gland and kidney) was noted. Changes in hematological parameters were also observed at 113 mg/kg bw/d. Most of these effects were reversible as the effects were less

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	89-72-5
Chemical Name	2-sec-Butylphenol
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Physical-chemical properties**

2-sec-Butylphenol is a pale yellow clear liquid. Melting point and boiling point are 16 °C and 228 °C respectively. Density is 0.9804 g/m³ at 25 °C. Vapour pressure at 25 °C extrapolated from the experimental value is 109 Pa. Partition coefficient between octanol and water (log K_{ow}) is 3.49 and water solubility is 1520 mg/L at 20 °C. Dissociation constant (pKa) is 10.48 at 25 °C shows that 2-sec-butylphenol exists primarily as its neutral species in the environment at pH values between 6 and 9. Soil adsorption coefficient (log K_{oc}) is 3.242.

Human Health

No specific studies were conducted on absorption, distribution, metabolism, or excretion in mammals. Death was observed in acute oral and dermal toxicity tests, and 2-sec-butylphenol was considered to be absorbed via the gastrointestinal tract or skin.

Oral LD₅₀ values were >500 and <1000 mg/kg bw (in corn oil) in male and female Crj:CD(SD) rats (OECD TG 401), > 200 and < 2000 mg/kg bw (in arachis oil) in SD rats (OECD TG 401), 340 mg/kg (undiluted) in CD male and female rats, and > 600 and < 2400 mg/kg bw in guinea pigs. Effects were observed on body posture, behavior, and respiration, and pathological lesions in the digestive and respiratory organs in rats. Dermal LD₅₀ values were 5560 mg/kg bw in rabbits and >1500 and < 3000 mg/kg bw in guinea pigs. The inhalation LC₅₀ value for 4-h exposure was >1.78 mg/L (vapor) in rats.

In rabbits, 2-sec-butylphenol caused corrosion in four reliable skin irritation assays (one study was conducted following OECD TG 404, the other three studies did not follow OECD Guidelines) and irreversible eye irritation by the Draize method.

Neither experimental data in animals nor human case reports were available for skin sensitization. The OECD QSAR application tool box showed a negative result on skin sensitization by three kinds of profiling analysis (protein binding by OASIS, protein binding by OECD, Protein Binding Potency) which predict the potential of a chemical to bind to protein.

In a repeated-dose oral toxicity study in rats, following OECD TG 422, 2-sec-butylphenol was administered by gavage to 13 animals/sex/dose at 0 (vehicle, corn oil), 12, 60, and 300 mg/kg bw/day for 42 days (males) or from 14 days before mating until the third day of lactation (females; total, 49 days). No death was observed in either sex. Treatment-related effects such as transient salivation after dosing, decreased activity, prone lateral position, ataxic gait, and incomplete eyelid opening were observed at dose levels of 300 mg/kg bw/day. Some of these clinical signs such as salivation and decreased locomotor activity were also observed in males administered 60 mg/kg bw/day. Increase in relative liver weight was observed in males and females at a dose level of 300 mg/kg bw/day. Histopathological examination of the liver revealed hypertrophy of the centrilobular hepatocytes in males administered 300 mg/kg bw/day but not in females treated with the same dose. No treatment-related effects on body weight, food consumption, hematological findings, biochemical findings, or macroscopic findings were observed at any dose. Based on the clinical signs in males at 60 mg/kg bw/day and the clinical signs and the

effects on the liver in females at 300 mg/kg bw/day, the no-observed-adverse-effect levels (NOAELs) for repeated-dose oral toxicity were considered to be 12 and 60 mg/kg bw/day for male and female rats, respectively.

In a bacterial reverse mutation assay performed according to OECD TG 471 and 472 and two other studies, 2-sec-butylphenol was negative in *Salmonella typhimurium* and *Escherichia coli* WP2uvrA with and without metabolic activation. In an *in vitro* chromosomal aberration test (OECD TG 473 and Japanese guidelines for screening mutagenicity of chemicals) in Chinese hamster lung fibroblast (CHL/IU) cells, it was positive with and without metabolic activation. In an *in vivo* micronucleus assay performed in rats according to OECD TG 474 in rats, 2-sec-butylphenol was negative. Based on these results, 2-sec-butylphenol was considered to be non genotoxic *in vivo*.

No data was available on the carcinogenicity of 2-sec-butylphenol.

2-sec-Butylphenol was investigated in a reproductive and developmental toxicity screening test conducted in rats according to OECD TG 422. 2-sec-Butylphenol was administered by gavage to 13 animals/sex/dose at 0, 12, 60, and 300 mg/kg bw/day for 42 days (males) and from 14 days before mating until the third day of lactation (females; total, 49 days). No adverse effects on reproductive/developmental parameters were observed at any dose level tested. Based on these results, the NOAEL for reproductive and developmental toxicity was considered to be 300 mg/kg bw/day.

2-sec-Butylphenol may have properties that are hazardous for human health (skin/eye irritation and repeated-dose toxicity). Adequate screening data are available to characterize the human health hazard for the purposes of the Cooperative Chemicals Assessment Programme.

Environment

2-sec-Butylphenol entering in the atmosphere is expected to be degraded by hydroxyl radicals. Using AOPWIN (version 1.92a), a calculated half-life time of 0.242 days and a rate constant of 44.1×10^{-12} cm³/molecule-sec are obtained for the indirect photo-oxidation of 2-sec-butylphenol by reaction with hydroxyl radicals in air. Concentration of hydroxyl radicals was assumed to be 1.5×10^6 OH/cm³ and time frame of hydroxyl radicals is 12 hours/day.

2-sec-Butylphenol is not hydrolyzed due to the lack of hydrolysable functional groups. A study according to OECD test-guideline 111 showed no hydrolysis of 2-sec-butylphenol in water at pH 4, 7 and 9 in 50 °C after five days.

An OECD test guideline 301C test was conducted in compliance with GLP on 2-sec-butylphenol with activated sludge at a test concentration of 100 mg/L. The test result showed 0 % biodegradation by BOD after four weeks. The low degradation observed might be caused by toxicity to micro-organisms at the concentration tested. EC₅₀ value of 2-sec-butylphenol to the micro-organisms is < 100 mg/L according to a study following OECD test guideline 209 without GLP compliance. Another study according to OECD test guideline 301D in compliance with GLP at both test concentrations of 1.5 mg/L and 3.0 mg/L showed 63 % biodegradation by BOD within a 10-day window after four weeks with an inoculum obtained from a municipal sewage treatment plant. An inherent biodegradation study with OECD test guideline 302C without GLP compliance indicated 90-91 % biodegradation by BOD after four weeks. Overall, 2-sec-butylphenol is considered to be readily biodegradable.

In a study performed according to OECD test-guideline 305 with carp exposed to 2-sec-butylphenol, bio-concentration factors of 27 and 16 were obtained for concentrations of 1 µg/L and of 10 µg/L respectively for a 28-day exposure period. Using an octanol-water partition coefficient (log Kow) of 3.49, a bio-concentration factor of 101.5 was calculated with BCFBAF, version 3.00. This chemical is not expected to bioaccumulate.

Fugacity modelling (level III) for 2-sec-butylphenol was conducted using EPISUITE, version 4.0. When equal and continuous release to air, water and soil is assumed, 2-sec-butylphenol is mainly distributed in water and soil compartments. If released to the water compartment only, 2-sec-butylphenol stays in the water compartment. A Henry's law constant of 10.8 Pa.m³/mole at 20/25 °C suggests that volatilization of 2-sec-butylphenol from water is expected to be moderate.

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

Fish [<i>Oryzias latipes</i>]:	96 h LC ₅₀ = 6.0 mg/L (nominal, semistatic), OECD-TG 203
Daphnid [<i>Daphnia magna</i>]:	48 h EC ₅₀ = 4.0 mg/L (nominal, semistatic), OECD-TG 202
	48 h EC ₅₀ = 3.7 mg/L (measured, static), OECD-TG 202

Shrimp [<i>Crangon septemspinosa</i>]:	96 h LC ₅₀ = 1.3 mg/L (measured, semistatic)
Algae [<i>Pseudokirchneriella subcapitata</i>]:	72 h ErC ₅₀ = 6.9 mg/L (nominal, growth rate, static), OECD-TG 201
	72 h ErC ₅₀ = 10 mg/L (measured, growth rate, static), OECD-TG 201
	72 h EbC ₅₀ = 3.6 mg/L (nominal, area under growth curve, static), OECD-TG 201
Micro-organisms:	3 h EC ₅₀ < 100 mg/L, OECD-TG 209
The following chronic toxicity test results have been determined for aquatic species:	
Daphnid [<i>Daphnia magna</i>]:	21 d LOEC = 1.0 mg/L (nominal, semistatic), OECD-TG 211
	21 d NOEC = 0.32 mg/L (nominal, semistatic), OECD-TG 211
Algae [<i>Pseudokirchneriella subcapitata</i>]:	72 h NOErC = 1.8 mg/L (nominal, growth rate, static), OECD-TG 201
	72 h NOErC = 0.82 mg/L (measured, growth rate, static), OECD-TG 201
	72 h NOEbC = 1.8 mg/L (nominal, area under growth curve, static), OECD-TG 201

2-sec-Butylphenol possesses properties indicating a hazard for the environment (acute aquatic toxicity values between 1 and 10 mg/L for fish, invertebrate and algae and chronic toxicity below 1 mg/L for invertebrate). This chemical is considered to be readily biodegradable and has a low potential for bioaccumulation. 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 2-sec-butylphenol in 2007 and 2008 reported in Japan (sponsor country) were 421 and 265 tonnes/year, respectively. Worldwide production volumes are not available.

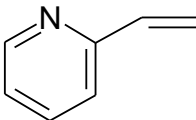
2-sec-Butylphenol is obtained with high selectivity by reaction of phenol with n-butenes at 250-300 °C using gamma- aluminum trioxide as catalyst and at a pressure of 3.5×10^6 - 8.0×10^6 Pa which keeps both reactants in the liquid phase. 2-sec-Butylphenol is used as a chemical intermediate in preparation of resins, plasticizers, surface-active agents. In Japan (sponsor country), 2-sec-butylphenol is used as a raw material in agrochemicals and liquid-crystal materials.

No detailed information concerning the release during manufacturing and processing was obtained. 2-sec-Butylphenol may result in a limited release to the environment as this chemical is used as an intermediate or raw material.

Although this chemical is to be produced in a closed system, occupational exposure through inhalation of vapour and dermal route is anticipated when a worker handles this chemical directly.

As 2-sec-butylphenol is used as an intermediate or a raw material, no consumer exposure is expected.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	100-69-6
Chemical Name	2-Vinylpyridine
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Physical-chemical properties**

2-Vinylpyridine is colourless liquid with unpleasant, nauseating odour at standard temperature. Measured melting point and boiling point are below - 100 °C and 161.7 °C respectively. Vapour pressure at 25 °C extrapolated from the experimental value is 4.56×10^{-1} kPa. Measured partition coefficient between octanol and water ($\log K_{ow}$) is 1.54 and measured water solubility is 26.7 g/L at 20 °C. Measured dissociation constant of $pK_a = 5.06$ shows that 2-vinylpyridine exists primarily as its neutral species in the environment at pH values between 6 and 9.

Human Health

No specific studies were found on the absorption, distribution, metabolism, or excretion of 2-vinylpyridine in mammals. However, deaths occurred in acute oral and dermal toxicity tests. Therefore, 2-vinylpyridine is considered to be absorbed readily from the gastrointestinal tract and through the skin.

Dermal LD_{50} of 2-vinylpyridine was 640 mg/kg bw in rabbits and 0.16 mL/kg (160 mg/kg bw) in guinea pigs. Oral LD_{50} in rats ranged between >50 and <300 mg/kg bw (OECD TG423), and clinical signs of toxicity included excessive salivation, soft feces, reddening of legs and auricles, soiling of perioral and perianal regions, tachypnea, prostration, weakness, tremors, vasodilatation, and anorexia. According to secondary information, inhalation exposure of 2-vinylpyridine in humans caused systemic signs including headache, nausea, nervousness, and anorexia.

In rabbits, undiluted 2-vinylpyridine caused severe eye irritation and skin corrosion. In guinea pigs, it caused severe skin irritation. According to secondary information, 2-vinylpyridine caused skin, eye and respiratory tract irritation in humans.

In a mouse local lymph node assay similar to OECD TG 429, 2-vinylpyridine was sensitizing. In a study providing only limited information, moderate sensitization was found in guinea pigs. Two case reports indicated that 2-vinylpyridine may induce skin sensitization in humans.

The repeated dose oral toxicity of 2-vinylpyridine has been investigated in four reliable studies in rats and is particularly well demonstrated in 28- and 92-day studies. Due to the corrosive nature of the substance, the NOAEL and/or LOAEL of each repeated dose study were separately assessed for local and systemic effects.

A 28-day study was conducted in accordance with Japanese guidelines for repeated dose toxicity tests in mammalian species under GLP compliance. The substance was administered by gavage to 5 or 10 animals/sex/dose at 0 (vehicle, corn oil), 12.5, 50, and 200 mg/kg bw/day 7 days/week for 4 weeks with a 14-day recovery period in rats. Five animals/sex from the 0 and 200 mg/kg dose groups were categorized as recovery groups. No deaths were observed in either sex. Salivation in both sexes and decreases in body weight and food consumption in males were observed at 200 mg/kg bw/day. Relative testis weights increased in males receiving 200 mg/kg bw/day. Absolute and relative spleen weights decreased and relative liver weights increased in females receiving 200 mg/kg bw/day. Squamous hyperplasia and submucosal edema in the forestomach were observed in both sexes receiving 50 and 200 mg/kg bw/day, along with thickening of the mucosa at the higher dose. Submucosal edema and/or erosion in the glandular stomach were also observed in females receiving 50 or

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200 mg/kg bw/day. On the basis of the toxicological effects on the stomach, the NOAEL of local and systemic effects for this 28-day repeated dose oral toxicity study was estimated to be 12.5 mg/kg bw/day for both sexes in rats.

A 92-day study was conducted in accordance with the EPA OPPS 870.31000 (90-day oral toxicity in rodents) guideline under GLP compliance. 2-Vinylpyridine in corn oil suspension was administered to rats (30 animals/sex/group) by gavage at doses of 0, 20, 60, or 180 mg/kg bw/day (5 days/week for 92 days). Convulsions and sialorrhea were observed in the 180 mg/kg bw/day dose group. Clinical chemistry showed dose-dependent decreases in mean AST values (60 and 180 mg/kg bw/day) that were accompanied by an increase in relative liver weights. Relative kidney weights increased in males at ≥ 20 mg/kg bw/day and in females at 180 mg/kg bw/day. Hyperkeratosis and acanthosis of the gastric epithelium increased in a dose-dependent manner from 20 mg/kg bw/day. On the basis of increased relative kidney weights in males and histopathological changes in the gastric epithelium at 20 mg/kg bw/day, the LOAELs of both local and systemic effects for this 92-day study were estimated to be 20 mg/kg bw/day.

On the basis of these results from all available studies, the overall NOAEL for local and systemic effects for repeated oral dose toxicity was estimated to be 12.5 mg/kg bw/day.

In a bacterial reverse mutation assay (Ames test) with multiple strains of *Salmonella typhimurium* and *Escherichia coli* (OECD TG 471 and 472 and Japanese guidelines for screening mutagenicity testing of chemicals), 2-vinylpyridine showed clear mutagenic responses in *Escherichia coli* with exogenous metabolic activation, although no mutagenicity to *Salmonella typhimurium* was observed with or without exogenous metabolic activation. In three other studies with *Salmonella typhimurium* strains, mutagenicity was only observed in the presence of exogenous reductive metabolic activation. In addition, an *in vitro* chromosomal aberration test (OECD TG 473) showed positive results both with and without metabolic activation. No *in vivo* data were identified. On the basis of these results, 2-vinylpyridine is considered to be genotoxic *in vitro*.

No adequate carcinogenicity studies were identified.

In a reproduction/developmental toxicity screening test, rats (12 animals/sex/dose) were orally administered 2-vinylpyridine by gavage at a dose of 0, 20, 50, or 125 mg/kg bw/day (OECD TG 421; GLP). The compound was administered to males for 42 days from day 14 before mating to the day before sacrifice and to females from day 14 before mating and throughout mating and pregnancy to day 3 of lactation (maximum 47 days in total). Parental general toxicities (hyperplasia and hyperkeratosis of the squamous epithelium in the forestomach) were observed at 20 mg/kg bw/day and more. In the 125 mg/kg bw/day group, nine females died or were euthanized between days 22 of gestation and day 1 of lactation due to prolonged parturition. The remaining three females at the high dose were euthanized between day 1 and day 4 of lactation, following total litter loss. Significant decreased bodyweight gain was observed during gestation and on day 0 of lactation and persistent diestrus was observed in 2 females, and an irregular estradiol cycle was observed in 1 female in the 125 mg/kg bw/day dose group. Abnormal lactation and cannibalism was observed at 125 mg/kg bw/day. Although changes in spermatogenesis in male were observed at 125 mg/kg bw/day, fertility index was not significantly affected. In the 50 mg/kg bw/day, one female was euthanized due to dystocia and one female was euthanized following total litter loss on day 0 of lactation. In the dam with dystocia all pups were still-born. The pup deaths observed between day 0 and day 4 of lactation in the 2 top doses suggest a developmental effect. Body weights in pups were lower than the control animals at days 1 and 4 of lactation at 20 and 50 mg/kg bw/day, respectively. No morphological abnormalities associated with 2-vinylpyridine administration were found in any pup. On the basis of the dystocia at 50 mg/kg bw/day, the NOAEL for reproductive toxicity was estimated to be 20 mg/kg bw/day. On the basis of decreased body weights in pups in all treatment groups, the LOAEL for developmental toxicity was estimated to be 20 mg/kg bw/day in rats, the lowest dose tested.

2-Vinylpyridine possesses properties indicating a hazard for human health (acute oral and dermal toxicity, skin/eye/respiratory tract irritation, skin sensitization, repeated dose toxicity, *in vitro* genotoxicity, and reproductive/developmental toxicity). Adequate screening level data are available to characterize human health hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Environment

In the atmosphere, 2-vinylpyridine is expected to be degraded by hydroxyl radicals. A calculated half-life time of 0.40 days is obtained by AOPWIN (version 1.92a) for the indirect photo-oxidation by reaction with hydroxyl radicals in air.

2-Vinylpyridine is not hydrolysed due to the lack of hydrolysable functional groups. A hydrolysis test according to OECD test guideline 111 showed no hydrolysis of 2-vinylpyridine in water at pH 4, 7 and 9 in 50 °C after five

days.

An OECD test guideline 301C study was conducted with 2-vinylpyridine 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 0 % degradation by BOD. According to the result, 2-vinylpyridine is considered to be not-readily biodegradable.

No experimental information was available on the bio-concentration on 2-vinylpyridine. Using an octanol-water partition coefficient (log Kow) of 1.54, a bio-concentration factor of 4.82 was calculated with BCFBAF (version 3.01). This chemical is not expected to bioaccumulate.

Fugacity level III calculations show that 2-vinylpyridine is mainly distributed to the soil compartment (73.7 %) and water compartment (25.6 %) if equally and continuously released to the air, soil and water. A Henry's law constant of 1.80 Pa.m³/mole at 25 °C suggests that 2-vinylpyridine is moderately volatile from water. A soil adsorption coefficient of Log K_{oc} = 2.34 indicates 2-vinylpyridine has low adsorption to soil and sediment.

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

Fish [<i>Oryzias latipes</i>]:	96 h LC ₅₀ = 6.5 mg/L (nominal; all measured concentrations were within 20% of the nominal, semistatic), OECD TG 203
Daphnid [<i>Daphnia magna</i>]:	48 h EC ₅₀ = 9.5 mg/L (measured, static), OECD TG 202
Algae [<i>Pseudokirchneriella subcapitata</i>]:	72 h ErC ₅₀ = 62 mg/L (measured, growth rate, static), OECD TG 201

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

Daphnid [<i>Daphnia magna</i>]:	21 d LOEC = 1.8 mg/L (measured, semistatic), OECD TG 211
	21 d LOEC(reproduction) < or = 0.22 mg/L (measured, semistatic, based on the total number of juveniles per parent animal at the start of the test), OECD TG 211
	21 d NOEC(reproduction) = 0.90 mg/L (measured, semistatic, based on the total number of juveniles per parent animal alive at the end of the test), OECD TG 211
	21 d NOEC(reproduction) < 0.22 mg/L (measured, semistatic, based on the total number of juveniles per parent animal at the start of the test), OECD TG 211
Algae [<i>Pseudokirchneriella subcapitata</i>]:	72 h NOErC = 27 mg/L (measured; growth rate, static), OECD TG 201

2-Vinylpyridine possesses properties indicating a hazard for the environment (acute aquatic toxicity values between 1 and 100 mg/L for fish, invertebrate and algae and chronic toxicity below 1 mg/L for invertebrate). This chemical is considered not readily biodegradable and has a low potential for bioaccumulation. Adequate screening-level data are available to characterize the hazard to the environment for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Exposure

Production and/or import volume of 2-vinylpyridine in Japan (sponsor country) was reported to be 958, 673 and 871 tonnes/year in fiscal years 2005, 2006 and 2007, respectively. Production and/or import volume of 2-vinylpyridine in the United States was between 1 million and 10 million pounds (454 - 4,540 tonnes) during 2006 according to Inventory Updated Reporting. Production volume in the world is not available.

2-Vinylpyridine is produced by treatment of 2-methylpyridine with aqueous formaldehyde, followed by dehydration of the resulting intermediate alcohol.

2-Vinylpyridine is used as a raw material for resins used in adhesive for car tire cords, pharmaceuticals and surfactant in Japan. 2-Vinylpyridine is also used as a monomer for producing polyvinylpyridine polymers and used in synthetic rubbers, photographic film, and ion-exchange resins, as well as pharmaceuticals.

In a nation-wide environmental survey of chemicals conducted by Japanese Ministry of Environment in fiscal year 2004, 2-vinylpyridine was detected in environmental air in one place with the level of 6.2 – 18 ng/m³.

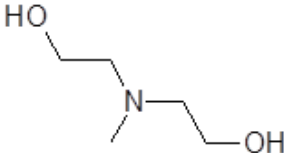
According to the Japanese PRTR (Pollution Release and Transfer Register) system, reported amounts of 2-vinylpyridine released into air and public water are 0.25 tonnes and 0.94 tonnes respectively in fiscal year 2009. Reported amounts of 2-vinylpyridine transferred to off-site was 2.7 tonnes and no transfer to the sewage treatment plant was reported.

Taking into account the situation mentioned above, environmental exposure of 2-vinylpyridine is expected to be low.

2-Vinylpyridine is processed to synthetic rubber in closed system in Japan and no significant release during processing is expected. Although this chemical is produced in a closed system, occupational exposure through inhalation of vapour and the dermal route is anticipated when a worker handles this chemical directly.

As 2-vinylpyridine is used as a raw material or an intermediate, no significant consumer exposure to this chemical is anticipated. A study reported that trace amounts of 2-vinylpyridine was detected from cigarette smoke.

SIDS INITIAL ASSESSMENT PROFILE

CAS No(s).	105-59-9
Chemical Name(s)	Ethanol, 2,2'-(methylimino)bis- (MDEA)
Structural Formula(s)	

SUMMARY CONCLUSIONS OF THE SIAR

Physical-chemical Properties

2,2'-(Methylimino)bisethanol (MDEA) is a liquid with a melting point of -21.3 °C at 1013 hPa (measured), a boiling point of 243.3 °C at 1013.3 hPa (measured) and an extrapolated vapour pressure of 0.0031 hPa at 20 °C. The measured octanol-water partition coefficient ($\log K_{ow}$) is -1.08 at 25 °C and pH 10.1 and the water solubility is > 1000 g/L at 20 °C (measured). The measured pKa value of the protonated form of MDEA in water was 8.52 (25 °C).

Human Health

MDEA is readily absorbed from the skin and distributed to internal organs. Metabolic processes play an important role in the elimination of this compound. The main route of excretion after dermal exposure is through the urine. Absorption from the gastrointestinal tract is also expected based on the low molecular weight of the substance.

Single exposures of rats to saturated vapour atmospheres of MDEA did not result in mortality or other signs of local or systemic toxicity in tests similar to OECD TG 403; LC₅₀ values were not determined. Dermal LD₅₀ values for rabbits of > 2000 mg/kg bw have been calculated from studies similar to OECD TG 402; sluggishness, unsteady gait, emaciation and prostration were noted after application of undiluted MDEA but surviving animals recovered during the observation period. Oral (gavage) LD₅₀'s for rats were \geq 1945 mg/kg bw in studies similar to OECD TG 401; staining, lacrimation (some bloody), diarrhea, postural changes, sluggishness, and prostration were observed, but surviving animals recovered post dosing. After oral gavage, bronchitis and bronchiectasis was noted in surviving animals.

MDEA was not irritating to the skin in a study similar to OECD TG 404, but skin irritation (with some necrosis in females) was seen in the 90-day dermal repeated-dose study. MDEA is a moderate eye irritant based on results of a study similar to OECD TG 405. Signs of respiratory irritation have not been reported in acute vapour inhalation studies.

In a study similar to OECD TG 406 (skin sensitisation; guinea pig maximization procedure), MDEA produced sporadic irritation but did not produce dermal sensitization in guinea pigs.

In a study similar to OECD TG 411, 10 rats/sex/dose were administered MDEA at 0, 100, 250 and 750 mg/kg bw/day under occlusive cover for 6 hours/day, 5 days/week for 90 days. MDEA produced moderate to severe irritation at the site of treatment at the highest two doses, characterized by desquamation, excoriation, ulceration, necrosis, eschar, acanthosis, hyper- and parakeratosis, fibrosis, and dermatitis. No systemic effects were observed. The NOAEL was 100 mg/kg bw/day for local effects and 750 mg/kg bw/day (the highest dose tested) for systemic toxicity.

MDEA did not induce gene mutations in bacteria or mammalian cells *in vitro* in studies similar to OECD TG 471 or 476, respectively, or induce micronuclei *in vivo* in a study similar to OECD TG 474. Based on these

results, MDEA is not considered to be genotoxic. No data are available for the carcinogenicity of MDEA.

In an OECD TG 421 oral gavage study, male and female rats were administered MDEA at 0, 100, 300 and 1000 mg/kg bw before and during mating (both sexes) and during gestation and for 4 days of lactation (females). The NOAEL for general, systemic toxicity was 100 mg/kg bw/day for the F₀ parental male and female rats based on decreased body weights at the higher doses. The NOAEL for reproductive toxicity was 300 mg/kg bw/day based on increased duration of gestation. The NOAEL for developmental toxicity was 300 mg/kg bw/day, based on litter loss, insufficient lactation behaviour (less or no milk in the stomach) and reduced viability index and reduced postnatal offspring weight gain. In a prenatal developmental OECD 414 dermal study, pregnant rats were administered 0, 250, 500 or 1000 mg/kg bw under occluded patches for 6 hours/day on gestation days 6 to 15. No increase in the total number of malformations or variations (external, visceral, or skeletal) was observed. The NOAEL for maternal toxicity in rats was 250 mg/kg bw/day based on severe dermal irritation. The NOAEL for developmental toxicity was 1000 mg/kg bw/day (the highest dose tested).

MDEA possesses properties indicating a hazard for human health (eye irritation, some severe skin irritation and systemic toxicity following repeated exposure, reproductive 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

MDEA is expected to be hydrolytically stable in the natural environment. The majority of MDEA will exist as a cation in water at environmentally relevant pH (pH 5-8). It should be noted, however, that EPISuite predicts environmental fate endpoints for MDEA in its uncharged form. Therefore, there will be some differences between predicted and actual results.

In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of 1.3 hours. In an OECD TG 301A ready biodegradability test, 96 % biodegradation was observed after 18 days. Similar results were obtained in an inherent biodegradability test (OECD TG 302B) and a Kombi test although in an OECD TG 301C ready biodegradability test, 7% biodegradation was observed after 28 days. In a ready test with natural seawater according to OECD TG 306 the substance was not readily biodegradable (15% in 63 days). MDEA is considered readily biodegradable under aerobic conditions in freshwater compartments and not readily biodegradable in marine environment..

A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that MDEA will distribute mainly to the soil (62%) and water (37.9%) compartments with minor distribution to the air and sediment compartment (<0.1%). A pH corrected Henry's law constant at pH 7 of 2.56×10^{-7} Pa m³/mol at 25 °C (estimated) suggests that volatilization of MDEA from the water phase is not expected to be high.

MDEA is not expected to bioaccumulate in the aquatic environment based on an estimated BCF value of 3.16.

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

Fish

[<i>Leuciscus idus</i>]	96 h LC ₅₀ = 1466 mg/L (nominal; static)
[<i>Leuciscus idus</i>]	96 h LC ₅₀ > 1000 — 2200 mg/L (nominal; static)
[<i>Cyprinodon variegatus</i>]	96 h LC ₅₀ > 1000 mg/L (nominal; semi-static)
[<i>Pimephales promelas</i> fry]	96 h LC ₅₀ = 1170 mg/L (nominal; static)

Invertebrates

[<i>Daphnia magna</i>]	48 h LC ₅₀ = 233 mg/L (nominal; static)
[<i>Daphnia magna</i>]	48 h LC ₅₀ = 230 mg/L (nominal; static)

Algae

[<i>Desmodesmus subspicatus</i>]	72 h ErC ₅₀ = 175.7 mg/L (growth rate; nominal)
	72 h EbC ₅₀ = 55.0 mg/L (area under growth curve; nominal)
[<i>Skeletonema costatum</i>]	72 h ErC ₅₀ = 410 mg/L (growth rate method; nominal)
	72 h EbC ₅₀ = 110 mg/L (area under growth curve; nominal)

MDEA has a low hazard profile for the environment. The chemical is readily biodegradable in fresh

water 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

In the Sponsor Country (USA), production volume was 22,680 to < 45,360 tonnes in 2005. MDEA can be used as an intermediate. MDEA is used mainly in the construction industry. Other applications of MDEA include use as an additive in lubricants and coatings. Potential exposure routes for workers include dermal and inhalation. In its use as lubricants/coatings, there may be consumer uses. Exposure would be by the dermal and/or inhalation routes.

INITIAL TARGETED ASSESSMENT PROFILE

CAS No.	106-93-4
Chemical Name	Ethane, 1,2-dibromo- (1,2-Dibromoethane)
Structural Formula	$ \begin{array}{c} \text{H} \quad \text{H} \\ \quad \\ \text{Br}-\text{C}-\text{C}-\text{Br} \\ \quad \\ \text{H} \quad \text{H} \end{array} $
SUMMARY CONCLUSIONS OF THE TARGETED ASSESSMENT	
<p>NOTE: The present assessment is targeted to address the following human health endpoints: carcinogenicity and genotoxicity; and the following environment endpoints: photodegradation, stability 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.</p> <p>The final screening assessment has been published under the responsibility of the Government of Canada. [http://www.ec.gc.ca/ese-ees/default.asp?lang=En&n=C1B0BBD3-1].</p> <p>Rationale for Targeting the Assessment</p> <p>The Government of Canada "categorized" or prioritized all 23,000 chemical substances on its Domestic Substances List (DSL) from 1999 to September 2006, as required by its <i>Canadian Environmental Protection Act, 1999</i> (CEPA 1999). Using information from Canadian industry, academic research and other countries, Government of Canada scientists applied a set of rigorous tools to the 23,000 chemical substances on the DSL. They were categorized to identify those that were: inherently toxic to humans or to the environment and that might be persistent and/or bioaccumulative; and substances to which people might have greatest potential for exposure. During this priority-setting exercise, distinct approaches were taken for identifying substances of likely concern for human health and the environment, and subsequent assessment activities may have focused on either human health or ecological endpoints. Through categorization, the Government of Canada has identified approximately 4,000 of the 23,000 chemical substances on the DSL as priorities for further assessment, research and/or measures to control their use or release.</p> <p>The substance 1,2-dibromoethane was identified as a priority for assessment because it was considered to meet the criteria for persistence and inherent toxicity to aquatic organisms, as well as for greatest potential for human exposure.</p> <p>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.</p> <p>Physical-chemical properties</p> <p>The substance, 1,2-dibromoethane, is a liquid at ambient temperature, and has a melting point of 9.9°C, boiling</p>	

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point of 131.6°C and vapour pressure of 1493 Pa at 25°C (all measured values). The measured octanol-water partition coefficient ($\log K_{ow}$) is 1.96, and the measured water solubility is 3910 mg/L at 25°C. The organic carbon-water partition coefficient ($\log K_{oc}$) was estimated to be 1.70 (PCKOCWIN 2008).

Human Health Targeted Endpoints

The majority of the studies described here have been reviewed by the International Agency for Research on Cancer (IARC 1999). Additional data [designated in square brackets] relevant to the screening assessment were also included.

Genotoxicity: A sufficient genotoxicity database was available.

- The chemical induced gene mutations in the majority of many bacterial [including data reviewed by IARC and additional data] and ascomycetes fungi mutation assays conducted with and without metabolic activation.
- It induced gene mutations in mouse L5178Y and Chinese hamster cells with and without metabolic activation, human cell lines without activation, and the lacZ reversion assay in *E. coli* [additional data].
- Chromosomal aberration and induction of sister chromatid exchanges (SCEs) were positive in Chinese hamster cells with and without metabolic activation, while SCE was positive in human lymphocytes without metabolic activation.
- 1,2-Dibromoethane induced unscheduled DNA synthesis in human and opossum lymphocytes, rat hepatocytes and spermatocytes, and mouse germ cells.
- It also induced micronuclei in human lymphocytes.
- DNA damage, strand break and binding studies were mostly positive in various bacterial and mammalian cells, including human hepatocytes and testicular and nasal mucosa cells, although negative results were observed for *B. subtilis* in a DNA damage study and for *E. coli* and mouse Ehrlich ascities in a DNA binding study.
- Indicator tests such as mitotic gene conversion was positive in yeast cells, somatic segregation was positive in ascomycetes fungi, cell proliferation was positive in human lymphocytes, SOS induction was mostly positive in bacterial cells, and cell transformation assays showed mixed results in mouse Balb/c 3T3 mouse cells.

Overall, *in vitro* mutagenicity, clastogenicity and DNA damage assays showed positive results.

The genotoxic effects of 1,2-dibromoethane were corroborated in a series of *in vivo* studies.

- *D. melanogaster* showed positive results for somatic gene mutation and recombination and sex-linked recessive lethal mutations.
- DNA damage, strand break, and binding [including DNA damage and binding data reviewed by IARC and additional studies] studies were all positive in rats and/or mice (many different organ cells tested).
- Mixed results were observed in micronuclei assays in mice (positive in peripheral blood [additional data] but negative in bone marrow and reticulocytes) and unscheduled DNA synthesis in rats (hepatocytes and spermatocytes analyzed).
- 1,2-Dibromoethane did not induce chromosomal aberrations or SCEs in the bone marrow of mice treated via intraperitoneal injection.
- DNA repair exclusive of unscheduled DNA synthesis was negative in the mouse (hepatocytes) and the dominant lethal test was negative in both rats and mice, and the specific locus test was negative in the mouse.

Based on the weight of evidence, 1,2-dibromoethane was genotoxic *in vivo*.

Carcinogenicity potential was determined on the basis of long-term oral, inhalation and dermal studies. In each

of these bioassays, significant increases in incidence of tumours were observed at the lowest exposure level tested and higher.

Oral

In an oral carcinogenicity bioassay in rats, males were exposed by gavage to a time-weighted average of 0, 38 or 41 mg/kg-bw per day (5 days/week for up to 49 weeks), and females were exposed to 0, 37 or 39 mg/kg-bw per day (5 days/week for up to 61 weeks). Both sexes initially received 0, 40 or 80 mg/kg-bw per day of 1,2-dibromoethane, but, due to excessive mortality, the exposure levels and the overall duration of the study were reduced. In both sexes, there were significant increases in the incidence of squamous cell carcinomas of the forestomach in exposed groups (0/20 for both male and female controls, 45/50 for low-dose males, 33/50 for high-dose males, 40/50 for low-dose females, 29/50 for high-dose females). In males in the low-dose group, there was a significant increase in the incidence of hemangiosarcomas of the circulatory system (0/20 controls, 11/50 low dose); after time-adjusted analysis in high-dose females, there was a significant increase in the incidence of hepatocellular carcinomas (0/20 controls, 5/25 high dose).

In an oral carcinogenicity bioassay in mice, animals were exposed by gavage to time-weighted average doses of 0, 62 or 107 mg/kg-bw per day (5 days/week for 53 weeks) of 1,2-dibromoethane. Mortality was high in all treated groups and due to this, all males and high-dose females were sacrificed at wk 78 (25 wks after dosing ceased). Low-dose females were sacrificed at wk 90. There were significant increases in the incidence of squamous cell carcinomas of the forestomach (males: vehicle control, 0/20; low dose, 45/50; high dose, 29/49; females: vehicle control, 0/20; low dose, 46/49; high dose, 28/50) and in alveolar/bronchiolar adenomas (males: control, 0/20; high dose, 10/47; females: control, 0/20; low dose, 11/43). The lowest non-neoplastic LOAEL for the oral carcinogenicity studies was found in the rat study: 38 (male) and 37 (female) mg/kg-bw per day based on hyperkeratosis and acanthosis of the forestomach in females, and degenerative changes in the liver, cortical cell degeneration of the adrenal gland and testicular atrophy in males (lowest dose tested, carcinogenic dose). The non-neoplastic effects in the forestomach and liver are considered as separate or precursor effects to the tumours observed in these organs.

In another oral study, mice were administered 0 or 4 mmol/L 1,2-dibromoethane (equivalent to 0 or 103-116 mg/kg bw/day) in distilled drinking-water for 450 days. Squamous-cell carcinomas of the forestomach (26/28 males and 27/29 females) and squamous-cell papilloma of the oesophagus (3/30 females) were observed compared to none in 45 male and 50 female controls.

Inhalation

In a carcinogenicity bioassay, rats were exposed by inhalation to 0, 10 or 40 ppm 1,2-dibromoethane (equivalent to 0, 77 or 308 mg/m³) 6 h/day, 5 days/week, for 88–103 weeks. High mortality at the high concentration (90% in males, 84% in females) resulted in sacrifice of the remaining high-dose animals at wks 88 (males) or 91 (females). There were significant increases in the incidence of nasal cavity carcinomas at high doses (males: controls, 0/50; high dose, 21/50; females: controls, 0/50; high dose, 25/50) and adenocarcinomas at both doses (males: controls, 0/50; low dose, 20/50; high dose, 28/50; females: controls, 0/50; low dose, 20/50; high dose, 29/50) and adenomas at low doses (males: control, 0/50; low dose, 11/50; females: controls, 0/50; low dose, 11/50). There was a significant increase in the incidence of hemangiosarcomas of the circulatory system in the high-dose groups of both sexes (males: controls, 0/50; high dose, 15/50; females: controls, 0/50; high dose, 5/50). Female rats had a significantly increased incidence of mammary gland fibroadenomas (controls, 4/50; low dose, 29/50; high dose, 24/50), and the highest-dose females exhibited significant levels of alveolar/bronchiolar adenomas combined with carcinomas (controls, 0/50; high dose, 5/47). Male rats had a significant increase in the incidence of tunica vaginalis mesotheliomas at both doses (controls, 0/50; low dose, 7/50; high dose, 25/50) and nasal cavity adenomatous polyps at the low dose (controls, 0/50; low dose, 18/50).

In a carcinogenicity bioassay in mice, animals were exposed by inhalation to 0, 10, or 40 ppm 1,2-dibromoethane (equivalent to 0, 77 or 308 mg/m³) 6 h/day, 5 days/week, for 78–103 weeks). High mortality in both treated and control males resulted in sacrifice of all remaining males at wk 78. In females, high mortality was observed only at the high concentration (86%), and all remaining females at this concentration were sacrificed at wk 90. There were significantly increased incidences of alveolar/bronchiolar carcinomas (males: control, 0/41; high dose, 19/46; females: control, 1/49; high dose, 37/50) and adenomas (males: controls, 0/41; high dose, 11/46; females: controls, 3/49; high dose, 13/50) in the highest-dose groups of both sexes. In dosed females, there was also a significantly increased incidence of hemangiosarcomas of the circulatory system

(controls, 0/50; low dose, 11/50; high dose, 23/50), subcutaneous fibrosarcomas (controls, 0/50; low dose, 5/50; high dose, 11/50), nasal cavity carcinomas (controls, 0/50; high dose, 6/50) and mammary gland adenocarcinomas (controls, 2/50; low dose, 14/50; high dose, 8/50). The lowest non-neoplastic LOAEL for the inhalation carcinogenicity studies was found in the rat study: 77 mg/m³, based on toxic nephropathy and testicular degeneration in males, retinal atrophy and adrenal cortex degeneration in females and increases in hepatic necrosis in both sexes (lowest dose tested, carcinogenic dose). The non-neoplastic effects in the testes are considered as separate to the tunica vaginalis tumours observed in this organ.

Additional inhalation carcinogenicity studies in rats exposed to 1,2-dibromoethane for 18 months to 0 or 20 ppm (equivalent to 0 or 154 mg/m³) resulted in haemangiosarcomas of the spleen and subcutaneous mesenchymal tumours in both sexes and mammary tumours in females, and in mice exposed to 1,2-dibromoethane for up to 2 years to 10 or 40 ppm (equivalent to 77 or 308 mg/m³) resulted in a dose-related increase in hyperplastic lesions of the nasal cavity squamous epithelium of both sexes.

Dermal

In a dermal carcinogenicity bioassay, female mice were given 0, 25 or 50 mg/mouse in acetone, dermally, 3 times a week for 440–594 days. There was a significant increase in the incidence of benign lung papillomas at both dose levels (low dose, 24/30; high dose, 26/30) and a significant increase in the incidence of skin combined squamous cell papillomas and carcinomas (3/30), as well as skin papillomas (5/30) at the high dose

Carcinogenicity Potential in Humans

There was very limited information on carcinogenicity in humans. Mortality was assessed in employees occupationally exposed to 1,2-dibromoethane in two production units while working as still and reactor operators (level of exposure was not provided in secondary accounts). In the first production unit, there were 2 deaths from malignant neoplasms (3.6 expected), and in the second production unit, there were 5 deaths from malignant neoplasms (2.2 expected). However, employees of the second production unit were also exposed to other chemicals, and overall there was no increase in total deaths or malignant neoplasms with increased exposure.

Based on the available human and animal/in vitro data, the International Agency for Research on Cancer (IARC) concluded that there is inadequate evidence in humans and sufficient evidence in experimental animals for the carcinogenicity of 1,2-dibromoethane; 1,2-dibromoethane was classified as probably carcinogenic to humans (Group 2A).

1,2-Dibromoethane possesses properties indicating a hazard for the human health endpoints, carcinogenicity and genotoxicity (increases in tumour incidences in rats and mice exposed via multiple routes, clear evidence of genotoxicity).

Environment

According to the results of Level III fugacity modelling (EQC 2003), 1,2-dibromoethane is expected to distribute mainly into air (93.7%) if only released into the atmospheric compartment. If only released into water, the substance is expected to mainly reside in water (85.6%), to some extent partition to air (13.7%) and to weakly adsorb to suspended solids and sediment (<1%). If only released to soil, the substance will mostly reside in this environmental compartment (79%), and also partition to water (6.54%) and air (14.4%). When released equally to all three compartments, 1,2-dibromoethane is expected to distribute in air at 28.9%, water at 58.8%, soil at 12.1% and sediment <1%. A Henry's Law Constant of 65.9 Pa·m³/mole at 25 °C also suggests that the substance volatilizes and may evaporate from surface of water or soil into air. The log K_{oc}, based on the log K_{ow}, was estimated as 1.70 (PCKOCWIN 2008), which indicates a low potential of the substance to accumulate in soil and sediment.

Based on its physical-chemical properties, a characteristic travel distance (CTD) has been used as an indicator for long range transport potential. The CTD has been calculated as 51 022 km for 1,2-dibromoethane (TaPL3 2000), hence the substance is considered to have a high potential for long-range transport in air (CTD > 2000 km).

1,2-Dibromoethane degrades very slowly in the atmosphere, with a measured half-life of 64 to 69 days, by reaction with photochemically-produced hydroxyl radicals. The photooxidation half-life in air has been reported between 10.7 to 107 days. From surface water, the substance volatilizes rapidly into the air (volatilization half-

lives ranging from 1 to 16 days). Otherwise, hydrolysis is the primary mode of degradation for 1,2-dibromoethane in water, occurring at a very slow rate (hydrolysis half-lives ranging from 354 days to 13.2 years). In soil, most of the substance is expected to be lost by volatilization to the atmosphere and by leaching to surface waters and groundwater. Otherwise, the substance is almost completely degraded within 1 week by soil microorganisms.

1,2-dibromoethane is not expected to bioaccumulate in organisms based on experimental bioconcentration factors (BCF) ranging from <1 to 20. An experimental log K_{ow} value of 1.96 for 1,2-dibromoethane also suggests that this chemical has low potential to bioaccumulate in biota.

Experimental data have been identified for 1,2-dibromoethane relating to acute and chronic toxicity of the substance to fish and aquatic invertebrates, as summarized below. The reported values were measured concentrations, unless otherwise indicated.

Acute

- Fish, Japanese medaka (*Oryzias latipes*), LC_{50} (96hr) = 32.1 mg/L
- Fish, fathead minnow (*Pimephales promelas*), LC_{50} (96hr) = 4.30 mg/L
- *Daphnia magna*, LC_{50} (48hr) = 6.5 mg/L
- *Ceriodaphnia dubia*, LC_{50} (48hr) = 3.61 mg/L

Chronic

- Fish, Japanese medaka (*Oryzias latipes*)
 - NOEC (12d reproduction) = 0.034 mg/L – The NOEC is based on the concentration used in the study's flow-through control group, where no toxic effect was observed.
 - LOEC (12d reproduction) = 0.133 mg/L. The LOEC is based on the lowest of three exposure concentrations found to cause a toxic effect in the study.
 - The maximum acceptable toxicant concentration (MATC) = 0.067 mg/L, The MATC was calculated as the geometric mean between the NOEC and LOEC values in the study.
- Fish, Japanese medaka (*Oryzias latipes*), carcinogenicity at 6.20 mg/L with exposure of 73 to 97 days

1,2-Dibromoethane possesses properties indicating hazard to the environment (chronic aquatic toxicity below 1 mg/L). Additionally, the substance has potential for long range transport in air and it is not expected to degrade rapidly in water. It is not expected to bioaccumulate.

Exposure Summary Information

1,2 dibromoethane is solely used in Canada (Sponsor country) as a scavenger of lead to prevent build-up of lead oxide in engines running on leaded gasoline. Presently, 99.8% of gasoline used in Canada is unleaded. Use of leaded gasoline in aircraft represented 98% of total leaded fuel in Canada in 2009, while high-performance competition vehicles represented 2%. However, leaded aviation gasoline may represent a small percentage (approximately 1.5%) of total aircraft fuel.

Globally, 1,2-dibromoethane is used principally as a chemical intermediate and industrial solvent. Uses include activation of magnesium in the preparation of Grignard reagents; use as a chemical intermediate in the production of plastic, latex, and vinyl bromide; a flame retardant used in modacrylic fibres; and use in the formulation of polyester dyes, resins and waxes. Some 1,2-dibromoethane may remain as an unintended manufacturing residue in articles. Use of 1,2-dibromoethane in consumer products has not been identified.

1,2-Dibromoethane was introduced worldwide as a soil and grain fumigant in 1946. Canada and the United States discontinued its use in pesticide products in 1984, and it was subsequently banned as an agricultural pesticide in member states of the European Union and many other countries. Today, 1,2-dibromoethane is listed under the Prior Informed Consent (PIC) procedure of the Rotterdam Convention, 1998, under the sponsorship of the United Nations Food and Agriculture Organization and the United Nations Environment Programme.

Based on the most recent survey for this compound, between 10 000 and 100 000 kg of 1,2-dibromoethane were reported to be imported into Canada in the 2000 calendar year. 1,2-Dibromoethane was also reported to be manufactured in or imported into Canada in the 2000 calendar year, in a mixture of a product at a low concentration (< 1% w/w); however the total quantity of 1,2-dibromoethane in the product at a low concentration

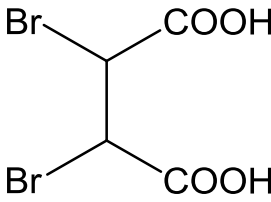
(<1% w/w) in 2000 was unknown.

1,2-Dibromoethane is not reportable to Canada's National Pollutant Release Inventory. According to the United States Toxics Release Inventory Program, total on-site and off-site disposal or other releases of 1,2-dibromoethane in the 2007 calendar year amounted to 1921 kg, where 1686 kg were released as fugitive air emissions, 96 kg as point source air emissions, 0.45 kg as surface water discharges and 0 kg as land treatment. This indicates that air may be the primary receiving compartment of 1,2-dibromoethane releases.

In addition, 1,2-dibromoethane appears to be formed naturally by microalgae growth and has been detected in ocean waters and air. Arctic brown, red and green macroalgae release volatile halogenated organic compounds including 1,2-dibromoethane. The extent of the contribution of these natural sources to global emissions is unknown. Baseline concentrations of 1,2-dibromoethane were found in air (20 ng/m³) and in marine waters (0.02 ng/L) collected from open areas of the North and South Atlantic Ocean. The source of the compound could be the natural production by algae and/or the anthropogenic emissions.

General population exposure to 1,2-dibromoethane is expected mainly through indoor air. Drinking water and food and beverages are considered to be more minor sources of overall general population exposure. As no consumer products containing 1,2-dibromoethane were identified in Canada, exposure from use of consumer products is not expected.

INITIAL TARGETED ASSESSMENT PROFILE

CAS No.	526-78-3
Chemical Name	2,3-Dibromosuccinic acid
Structural Formula	

SUMMARY CONCLUSIONS OF THE TARGETED ASSESSMENT

NOTE: The present assessment is 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.

2,3-Dibromosuccinic acid was evaluated as “not biodegradable (persistent)” and “moderately 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 the ITAP. In order to determine whether this chemical is classified as a Type II monitoring chemical substance, the initial hazard assessment of 2,3-dibromosuccinic acid was conducted for the acute toxicity, repeated dose toxicity and mutagenicity by MHLW (Ministry of Health, Labour and Welfare, Japan) in October 2006.

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

Physical-chemical properties

2,3-Dibromosuccinic acid has *D*-form, *L*-form *DL*-form and *meso*-form because of its stereo structure. 2,3-Dibromosuccinic acid is a crystalline solid at standard temperature and pressure. Melting points are 167 °C (*DL*-form), 157–158 °C (*D*-form) and 270–273 °C (*meso*-form). The *L*-form is decomposed at 157–158 °C; the *meso*-form is also reported to be decomposed at 255–256 °C. The partition coefficient between octanol and water ($\log K_{ow}$) is -0.21. The vapour pressure is calculated to be 5.52×10^{-4} Pa at 25 °C. The water solubility is 20 g/L at 17 °C (*meso*-form or *DL*-form). The dissociation constant of pKa1 = 1.4 and pKa2 = 3.4 shows that 2,3-dibromosuccinic mainly exists under its anionic form at environmental pH values. Compositions of isomeric forms in the tested substance were not specified in the following studies.

Human Health

An acute oral toxicity study was conducted under OECD TG 401 in compliance with GLP. The oral LD₅₀ value

was more than 2000 mg/kg bw for both sexes in rats. No deaths or clinical signs of toxicity were observed.

A repeated dose oral toxicity study in rats was conducted following a Guideline for 28-Day Repeated Dose Toxicity Test in Mammalian Species (Chemical Substances Control Law of Japan). In this study, 2,3-dibromosuccinic acid was administered via gavage at 0 (vehicle control: 0.5% sodium carboxymethyl cellulose solution), 20, 140 or 1000 mg/kg bw/day for 28 days. There were no treatment-related deaths and no toxicological effects in either sex. Based on the findings, the NOAEL for this 28-day repeated dose toxicity study is considered to be 1000 mg/kg bw/day (the highest dose tested) for both sexes.

In a bacterial mutation study using *Salmonella typhimurium* and *Escherichia coli* (Japanese Guideline, in compliance with GLP using a buffered solution), 2,3-dibromosuccinic acid was negative with or without metabolic activation when tested up to a cytotoxic concentration. In an *in vitro* chromosome aberration test using CHL/IU cells (Japanese Guideline, in compliance with GLP), 2,3-dibromosuccinic acid was also negative with or without metabolic activation. Based on these results, 2,3-dibromosuccinic acid is not considered to be genotoxic *in vitro*.

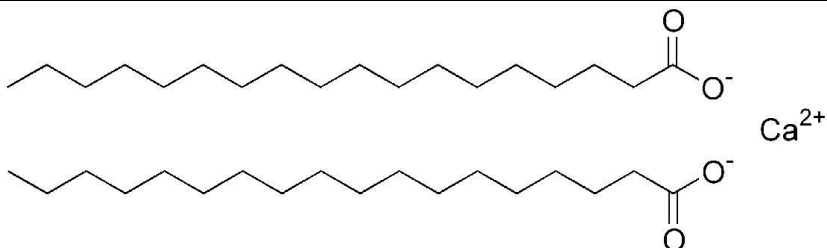
Agreed hazard conclusions

This chemical has a low hazard profile for the human health endpoints (acute toxicity, repeated dose toxicity, gene mutations and chromosomal aberrations) targeted in this assessment.

Available Exposure information

The production volume of 2,3-dibromosuccinic acid in Japan (sponsor country) is not known. 2,3-Dibromosuccinic acid is used as a raw material in the production of pharmaceutical products, antiseptic agents and fungicides in the sponsor country.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	1592-23-0
Chemical Name	Calcium distearate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Physical and chemical properties**

Calcium distearate is a white powder with a melting point of 179-180°C and a calculated boiling point of 661.06°C. It has a bulk density of $\leq 0.32 \text{ g/cm}^3$ and a calculated vapour pressure of $6 \times 10^{-12} \text{ Pa}$ at 25°C. The octanol-water partition coefficient ($\log K_{ow}$) is not applicable for calcium distearate as it has surfactant properties, and it is slightly soluble ($\leq 2 \text{ mg/L}$ at 35°C).

Human Health

Stearic acid is a fatty acid that occurs naturally in some animal and vegetable fats and oils and is a normal product of the metabolism of fats. The distribution, metabolism, excretion and storage of radiolabeled ^{14}C -sodium stearate were investigated. Radiolabeled ^{14}C -sodium stearate was administered by stomach tube to rats at a dose of 10Ci 100g of body weight. Negligible amounts (0.1% of the 0.18 mg doses) of the ^{14}C appeared in the urine or feces. Calcium is required for the proper functioning of numerous intracellular and extracellular processes, including muscle contraction, nerve conduction, hormone release and blood coagulation. The calcium ion plays a unique role in intracellular signalling and is involved in the regulation of enzymes and the maintenance of calcium homeostasis is critical.

The oral LD_{50} value of calcium distearate was higher than 2,000 mg/kg bw for female rats [OECD TG 423, Acute Toxic Class Method]. Three animals were dosed with 2,000 mg/kg bw (1st step, no mortality found), following by 2nd step with three additional animals and also 2,000 mg/kg bw dosing. No toxicologically relevant effects were found during necropsy. Loss of body weight, diarrhea and stains around mouth were observed in 1st step. Soiled perineal region, prone position and inanimation were noted in 1st and 2nd step. Those clinical effects were fully recovered at the end of the observation period.

Less reliable studies are available for the skin and eye irritation in animals of calcium distearate. No skin irritation was apparently seen in animal studies in which undisclosed concentrations [probably neat in one case] of calcium stearate were applied to the skin of rats, rabbits and guinea pigs. Also stearic acid showed no evidence of irritation after 24 hours covered application to the intact or abraded skin of rabbits and only mild and temporary effects on the eyes of rabbits. Calcium stearate has a long history of use in cosmetic and skin pharmaceutical preparations, suggesting that such use is unlikely to cause significant irritation. According to one standard test, the material has been used neat in patch test to identify sensitized individuals. This may suggest that the neat calcium stearate is unlikely to cause irritation in humans.

No data are available for skin sensitization in animals.

In a 28-day repeated dose oral toxicity study in rats following OECD TG 407, the substance was administered

via gavage to 5 animals/sex/dose at 0, 500, 1000 and 2000 mg/kg bw/day for 4 weeks. No death was observed in either sex. There were no treatment-related effects observed for clinical signs, body weight, food consumption, urinalysis, hematology, serum biochemistry, necropsy findings and organ weights at any dose. Based on the results, the NOAEL for repeated dose oral toxicity was considered to be 2000 mg/kg bw/day in both sexes (the highest dose tested).

In a bacterial reverse mutation assay [OECD TG 471] with multiple strains of *Salmonella typhimurium* TA98, TA100, TA1535, TA1537 and *Escherichia coli* WP2uvrA, calcium distearate was negative both with and without metabolic activation, when tested up to the limit of solubility. In an *in vitro* chromosomal aberration test [OECD TG 473], it was also negative with and without metabolic activation. Based on these results, calcium distearate is considered to be non genotoxic *in vitro*.

No data are available for the carcinogenicity of calcium distearate.

The reproductive toxicity of calcium distearate has been investigated in a reproductive and developmental toxicity screening test in rats [OECD TG 421]. In this study, calcium distearate was administered via gavage to 10 animals/sex/dose at 0, 250, 500 and 1000 mg/kg bw/day, 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. There were no deaths among the treated males and females. There were no treatment related effects on parental animals nor in F1 neonates observed at any dose. Therefore, the NOAEL for reproductive and developmental toxicity was considered to be 1000 mg/kg bw/day in males and females. Based on these results, calcium distearate is considered not to be a reproductive and developmental toxicant.

Calcium distearate has a low hazard profile for human health. Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Environment

Hydrolysis is not expected to occur, as metal salts of fatty acids do not contain functional groups that undergo hydrolysis. In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of 2.99 hours. Several biodegradation tests (OECD TG301B and 301C) showed biodegradation of 55-99%. The weight of evidence indicates that calcium distearate is readily biodegradable under aerobic conditions.

A level III fugacity model calculation for neutral form is considered of no relevance, as at environmentally relevant pH, calcium distearate has surfactant properties. A Henry's law constant of 4.37×10^{-4} atm.m³/mole suggests that volatilization of calcium distearate from the water phase is expected to be low.

The BCF value based on log K_{ow} is not applicable to calcium distearate as it has surfactant properties.

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

Fish [*Oryzias latipes*, OECD TG 203] 96 h LC₅₀ > 2.7 mg/L (highest concentration measured in solution, >100 mg/L nominal)

Invertebrate [*Daphnia magna*, OECD TG 202] 48 h EC₅₀ >100 mg/L (nominal)

Algae [*P. subcapitata*, OECD TG 201]

72 h E_rC₅₀ > 3.5 mg/L (growth rate, highest concentration measured in solution, >100 mg/L, nominal)

72 h E_yC₅₀ > 3.5 mg/L (yield, highest concentration measured in solution, >100 mg/L, nominal)

Calcium distearate has a low hazard profile for the environment. Adequate screening-level data are available to characterize the environmental hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Exposure

In the Republic of Korea (sponsor country), the production, use and import volumes of calcium distearate were 9,237, 12,456 and 2,751 tonnes in 2006, respectively. In Sweden, Denmark, Norway and Finland, estimated use volumes of calcium distearate were approx. 2,967, 3,051, 2,795, 2,830 and 2,033 tonnes in 2005, 2006,

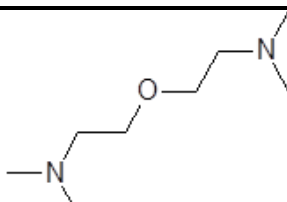
2007, 2008 and 2009, respectively.

Calcium distearate is mainly used as stabilizers in plastics additive, lubricants for paper manufacture, paint and ink additives, oxidising agents and synthetic resin in the sponsor country. There is no evidence that calcium distearate is hazardous to the public when it is used as a direct food additive. Food grade calcium distearate is used as flavouring agent and as thickening agent in pharmaceutical products. It is also used as an opacifying agent in shampoos and as a water-in-oil emulsifier in hair grooming products and as an anti-caking agent in dehydrated vegetable products, salt, onion and garlic powder.

The Joint FAO/WHO Expert Committee on Food Additives, reviewing stearic acid and certain of its salts, including calcium stearate, concluded that provided the cation (calcium in this case) 'does not add excessively to the normal body load', these materials need not be considered differently from dietary fatty acids. The committee therefore considered it unnecessary to ascribe a specific acceptable daily intake (ADI) to calcium stearate.

In use facilities of the sponsor country, calcium distearate is handled in closed systems. No monitoring data are available from workplace. Occupational exposure is managed with personal protective equipment such as dust mask, cleanroom garments and gloves.

SIDS INITIAL ASSESSMENT PROFILE

CAS No(s).	3033-62-3
Chemical Name(s)	Ethanamine, 2-oxybis[N, N-dimethyl]- (DMAEE)
Structural Formula(s)	

SUMMARY CONCLUSIONS OF THE SIAR

Physical-chemical Properties

2-Oxibis[N,N-dimethyl]ethanamine (DMAEE) is a liquid with a melting point of $-80\text{ }^{\circ}\text{C}$ (measured), a boiling point of $189.9\text{ }^{\circ}\text{C}$ at 1013 hPa (interpolated from vapor pressure curve) and a vapor pressure of 0.49 hPa at $20\text{ }^{\circ}\text{C}$ (extrapolated from vapor pressure curve). The calculated water solubility (from K_{ow}) is 1000 g/L at $25\text{ }^{\circ}\text{C}$ and the calculated octanol-water partition coefficient ($\log K_{ow}$) is -0.54 (uncharged molecule). The estimated pKa values for the protonated form of DMAEE in water are 9.77 and 8.19 at $20\text{ }^{\circ}\text{C}$.

Human Health

Studies with rats and rabbits indicate DMAEE is rapidly absorbed following dermal or inhalation exposure. It is eliminated, largely unchanged, primarily in the urine. In rats, 53-58% or 24% is eliminated in urine as a percent of inhalation concentration or dermal dose, respectively. Some distribution to organs and tissues (ca. 6.4-8% in the liver, kidney, bone marrow, brain, fat (perirenal), heart, lung, muscle, spleen and testes/ovaries) was also seen after dermal exposure; up to 1% was distributed to tissues after inhalation. Based on the intravenous studies, the elimination half-life for DMAEE is ~13-14 hours in the rats, and 24-40 hours in the rabbit.

The 4-hour aerosol inhalation LC_{50} for DMAEE with male and female rats is 4 mg/L [BASF standard method]; the 6 hour vapor inhalation LC_{50} for DMAEE with male and female rats is 1.088 mg/L [similar to OECD TG 403]. Signs of toxicity were predominantly associated with site of contact effects (including respiratory changes, eye and nose irritation or corrosion), and hypoactivity. In one inhalation study, piloerection and effects on posture and gait were also seen. There were no findings at gross necropsy for surviving animals in either acute inhalation study. Site of contact effects (irritation/inflammation of the respiratory tract) was observed in animals that died (both studies). The dermal LD_{50} for rabbits was ca. 315 mg/kg bw (24 hours, undiluted test substance); severe skin necrosis was noted at the site of application [similar to OECD TG 402]. Other effects following dermal contact included hypoactivity and altered gait/posture. Also, in males in one study, dyspnea and mottled, red lungs in both sexes were the most common observations at necropsy. Oral (gavage) LD_{50} values for DMAEE range from 609 - 677 mg/kg bw (male and female rats) [OECD TG 401] up to 1045 mg/kg bw (male rats) [no guideline specified]. Clinical findings included hypoactivity, gasping/shortness of breath, ataxia, prostration, emaciation and unkempt fur. In one oral study, necropsy findings included pulmonary congestion and petechiae, gastric hemorrhages and liver congestion.

Neat DMAEE is corrosive when applied to the skin of rabbits [e.g., OECD TG 404]. It is injurious to eyes after direct instillation of undiluted and 10-15% aqueous solutions or irritating to the eye following whole body inhalation [no guideline specified]. Slight (marginal) increases in corneal thickness continued throughout the post-exposure period. It is also irritating to the respiratory tract in acute inhalation studies [similar to OECD TG 403].

DMAEE was not sensitizing in a standard guinea pig sensitization study [EU Method B.6]. In patch tests in humans who had symptoms of contact dermatitis, DMAEE has been associated with some allergic responses.

Rats (15/sex/group) were exposed to DMAEE by inhalation at 0, 0.22, 1.25 or 5.8 ppm (ca. 0, 0.0014, 0.008 or 0.036 mg/L, respectively) 6 hrs/day, 5 days/wk for 14 weeks. A 6-week recovery period was also included. Signs of ocular and respiratory irritation included swollen periocular tissue at all exposures and periocular and perinasal encrustation, cloudy eyes, and keratitis at 5.8 ppm. Color changes or opacity of the eyes were observed in one male and six females from the 5.8 ppm group, but were not present after 6 weeks of recovery. Microscopic lesions involving the eyes, nostrils, skin of the ears and eyelids, larynx, trachea, and lungs (bronchi and bronchioles) were seen at the highest exposure. The size and number of vacuoles in the mucosal epithelium increased with the duration of exposure. Decreased body weight was observed at the highest exposure. Urinalysis showed slight decreases in creatinine, sodium, potassium, and chloride at 5.8 ppm for both sexes. Changes in hematology and clinical chemistry were also noted at the highest concentration. Significant increases in male adrenal and testes weights relative to both body and brain weights were observed at 5.8 ppm, but no accompanying changes in histopathology were seen. Effects observed at the end of the recovery period included swollen periocular tissue (1.25 and 5.8 ppm) and microscopic lesions of the nasal cavity (all exposure groups). The LOAEC (for local effects) was determined to be 0.0014 mg/L due to various signs of irritation of the eye and respiratory tract at all concentrations. The NOAEC for systemic effects for males was 0.008 mg/L based on decreased body weights and changes in urinalysis at 0.036 mg/L. The NOAEC for systemic effects for females was 0.036 mg/L, the highest concentration tested.

Rabbits (10/sex/dose) were administered DMAEE in water dermally (under occlusive cover) at 0, 0.69, 2.0 or 5.3 mg/kg bw/day for 6 hrs/day, 5 days/wk for 13 weeks [no guideline was specified]. There were no signs of systemic toxicity. Skin irritation in both sexes included erythema, desquamation, edema and fissuring in a dose-response manner. Epidermal vacuolization occurred at 2 and 5.3 mg/kg bw/day and acanthosis occurred at all doses in both sexes with increasing severity. In most cases, the skin irritation effects were reversible during the recovery period. The NOAEL (systemic) was 5.3 mg/kg bw/day (highest dose tested). For local effects (based on dermatitis/skin irritation) the LOAEL was 0.69 mg/kg bw/day. In a nine-day dermal study in rats, skin irritation and necrosis was seen at all doses (7.1-9.2 mg/kg bw/day and higher); degeneration of the tubular epithelium and dilation of tubules was seen in the kidney at 5 and 10% dose (14-18 mg/kg bw/day and 28-37 mg/kg bw/day, respectively).

DMAEE has shown no evidence of mutagenicity *in vitro*, in the Ames bacterial test (similar to OECD TG 471) and the mammalian cell HGPRT assay (guideline not specified). A sister chromatid exchange assay with CHO cells gave equivocal results, while there was no evidence of genotoxicity in an *in vivo* mammalian erythrocyte micronucleus test (similar to OECD TG 474). The weight of evidence suggests that DMAEE is not genotoxic.

No data were available for the carcinogenicity of DMAEE.

Repeated inhalation exposure (14 weeks) of DMAEE by rats at concentrations of 0, 0.0014, 0.008 or 0.036 mg/L (measured) resulted in increased relative testes weights but no histopathological changes. There were no reproductive organ effects in female animals. Effects on reproductive organs were not observed in a 90-d repeated dose dermal study with rabbits. In a prenatal developmental toxicity study [no guideline specified], pregnant rabbits were exposed to DMAEE at ca. 0, 2.4, 12 or 24 mg/kg bw/day in water via the dermal route for 6 hrs/day from gestation days 6 through 18. The NOAEL for maternal systemic and local toxicity was ca. 2.4 mg/kg bw/day based on renal lesions and severe skin effects, respectively, at higher doses. The NOAEL for developmental toxicity was ca. 12 mg/kg bw/day based on decreased mean litter weight at 24 mg/kg bw/day.

DMAEE possesses properties indicating a hazard for human health (acute inhalation, oral and dermal toxicity; corrosive or irritating to the skin, eye and respiratory tract; repeated dose toxicity (site of contact and systemic effects); developmental effects 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

DMAEE is expected to be hydrolytically stable in the natural environment since it doesn't contain any functional group susceptible to hydrolysis. In the atmosphere, indirect photooxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of 0.61 hours. In an OECD TG 302B inherent biodegradability study using activated sludge from an industrial wastewater treatment plant, DMAEE degraded <10% after 28 days. In a ready biodegradability study similar to OECD TG 301 F, DMAEE degraded 2% in 28 days. DMAEE is not readily biodegradable under aerobic conditions.

A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that DMAEE will distribute mainly to the soil (67.1%) and water (32.8%) compartments with minor distribution to the air and sediment compartments (<0.1%). It should be noted, however, that EPISuite predicts most environmental fate endpoints for DMAEE in its uncharged form. Therefore, there will be some differences between predicted and actual results. A Henry's law constant of 3.79×10^{-10} Pa-m³/mol (Bond Estimate) and 1.21×10^{-5} Pa-m³/mol (Group Estimate) at 25 °C suggests that volatilization of DMAEE from the water phase is not expected to be high. The model estimate is for the uncharged molecule. DMAEE is not expected to bioaccumulate in the aquatic environment based on an estimated BCF value of 3.16 L/kg wet-wt.

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

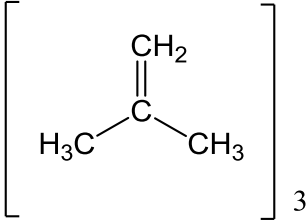
Fish [<i>Brachydanio rerio</i>]	96 h LC ₅₀ = 131 mg/L (nominal concentrations confirmed by measured values; semi-static; unbuffered, pH 8.4 to 9.8)
Invertebrate [<i>Daphnia magna</i>]	48 h EC ₅₀ = 102 mg/L (measured; static; buffered, pH 7.7-7.9)
Algae [<i>Pseudokirchnerella subcapitata</i>]	72 h ErC ₅₀ = 24 mg/; 72 h EyC ₅₀ = 4.7 (measured; static; buffered, pH 8.2 to 9.2)
[<i>Pseudokirchnerella subcapitata</i>]	72 h ErC ₅₀ = 23 mg/L (nominal; static; unbuffered, pH 7.7 to 9.9)

DMAEE possesses properties indicating a hazard for the environment (acute aquatic toxicity values for algae between 1 and 100 mg/L). The chemical is not 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

DMAEE is commercially produced with an annual production volume in the United States (sponsor country) of 450 to < 4500 metric tons in 2005. DMAEE is produced in closed systems. DMAEE is used as a polyurethane catalyst for flexible foam, semi-rigid foam and rigid foam. It is a powerful blowing catalyst in polyurethane foam. The amine in the foam is released during and right after foaming in the plant, where air handling removes the material. What is left of the amine after the initial foaming will slowly be released over time. Possible exposures for workers might be via inhalation or dermal routes. There are no known consumer uses of DMAEE.

INITIAL TARGETED ASSESSMENT PROFILE

CAS No.	7756-94-7
Chemical Name	Triisobutylene
Structural Formula	

SUMMARY CONCLUSIONS OF THE TARGETED ASSESSMENT

NOTE: The present assessment 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 for long-term toxicity to 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.

Triisobutylene was evaluated as “not biodegradable (persistent)” and “moderately 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 the ITAP. In order to determine whether this chemical is classified as a Type II monitoring chemical substance, the initial hazard assessment of triisobutylene was conducted for acute toxicity, repeated dose toxicity and mutagenicity by MHLW (Ministry of Health, Labour and Welfare, Japan) in October 2006.

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

Physical-chemical properties

Triisobutylene is a mixture of branched chain isomers. Triisobutylene is colourless liquid at standard temperature and pressure. Melting point is below - 76 °C (measured) and boiling point is 180 °C (measured) respectively. Calculated value of the octanol-water partition coefficient (log K_{ow}) is 5.85. Vapour pressure is calculated to be 142 Pa at 31 °C. Water solubility is calculated to be 0.19 mg/L at 20 °C by WATERNT.

Human Health

An acute oral toxicity study was conducted in rats following OECD TG 401 in compliance with GLP. The oral LD_{50} value was higher than 2000 mg/kg bw for both sexes. No deaths were observed. A decrease in spontaneous motor activity and diarrhoea were observed in both sexes.

A repeated dose oral toxicity study in rats was conducted following a Guideline for 28-Day Repeated Dose Toxicity Test in Mammalian Species (Chemical Substances Control Law of Japan). In this study, triisobutylene was administered via gavage at 0 (vehicle control: corn oil), 30, 150 and 750 mg/kg bw/day. Triisobutylene did not induce any toxic effects in terms of clinical signs, body weight changes or food consumption. Red blood cell counts decreased slightly in females at 150 mg/kg bw/day and above. An increase in albumin was observed in males and females at 750 mg/kg bw/day, an increase in creatinine was observed in males at 750 mg/kg bw/day. Urine volume increased in males and females at 750 mg/kg bw/day and the specific gravity of the urine decreased in males and females at 750 mg/kg bw/day. Relative liver weights increased in males at 150 mg/kg bw/day or more, and in females at 750 mg/kg bw/day. Relative kidney weights increased in males at 150 mg/kg bw/day or more. Histopathological examination revealed swelling of liver cells in both sexes at 150 mg/kg bw/day or more and eosinophilic bodies in renal tubules (which was possibly alpha-2u globulin nephropathy; however, it was not proven by histochemical staining) in males at 150 mg/kg bw/day or more. Based on these findings, the NOAEL for repeat dose toxicity was considered to be 30 mg/kg bw/day for both sexes.

In a bacterial mutation study using *Salmonella typhimurium* and *Escherichia coli* (Japanese Guideline, in compliance with GLP), triisobutylene was negative with or without metabolic activation when tested up to a cytotoxic concentration. In an *in vitro* chromosome aberration test using CHL/IU cells (Japanese Guideline, in compliance with GLP), triisobutylene was also negative with or without metabolic activation when tested up to a cytotoxic concentration. Based on these results, triisobutylene was not considered to be genotoxic *in vitro*.

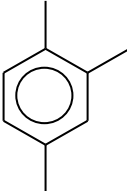
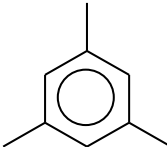
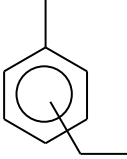
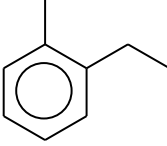
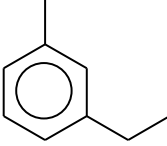
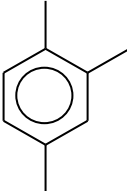
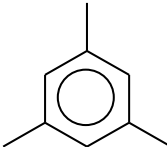
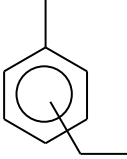
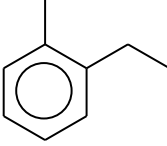
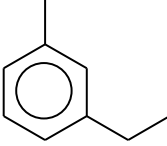
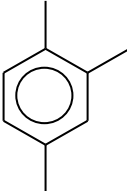
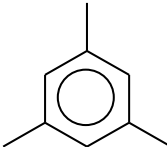
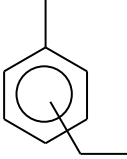
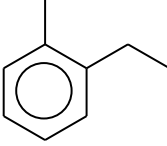
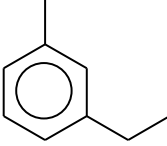
Agreed hazard conclusions

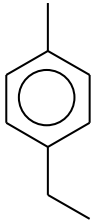
Triisobutylene possesses properties indicating a hazard to human health (repeated dose toxicity) in this targeted assessment.

Available Exposure

The volume of production and import of “Alkene (C = 10 – 50)” in which triisobutylene is included in Japan (sponsor country) was 10,000 -100,000 tonnes in fiscal year of 2007. However, the production volume of triisobutylene in the sponsor country is not known. Triisobutylene is used as a lubricant additive and a raw material in the production of surface active agents in the sponsor country. It is also known that triisobutylene is used to make rubber products, oil additives and motor fuels.

SIDS INITIAL ASSESSMENT PROFILE

Chemical Category	C ₉ Aromatic Hydrocarbon Solvents Category																	
CAS Numbers and Chemical Names	95-63-6 108-67-8 25550-14-5 64742-95-6	Benzene, 1,2,4-trimethyl Benzene, 1,3,5-trimethyl Benzene, ethylmethyl (ethyltoluene mixed isomers) Solvent naphtha, (petroleum), light aromatic																
CAS Numbers with Structural Formula	<table border="0" style="width: 100%;"> <thead> <tr> <th style="text-align: left;">Structural Formula</th> <th style="text-align: right;">CAS RN</th> </tr> </thead> <tbody> <tr> <td> C_9H_{12}  </td> <td style="text-align: right; vertical-align: bottom;">95-63-6</td> </tr> <tr> <td> C_9H_{12}  </td> <td style="text-align: right; vertical-align: bottom;">108-67-8</td> </tr> <tr> <td colspan="2"> Generalized structure; non-isomer specific: C_9H_{12} (average) </td> </tr> <tr> <td>  </td> <td style="text-align: right; vertical-align: bottom;">25550-14-5</td> </tr> <tr> <td colspan="2"> Specific isomeric structures shown below: </td> </tr> <tr> <td>  </td> <td style="text-align: right; vertical-align: bottom;">1,2-Ethyltoluene</td> </tr> <tr> <td>  </td> <td style="text-align: right; vertical-align: bottom;">1,3-Ethyltoluene</td> </tr> </tbody> </table>		Structural Formula	CAS RN	C_9H_{12} 	95-63-6	C_9H_{12} 	108-67-8	Generalized structure; non-isomer specific: C_9H_{12} (average)			25550-14-5	Specific isomeric structures shown below:			1,2-Ethyltoluene		1,3-Ethyltoluene
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Specific isomeric structures shown below:																		
	1,2-Ethyltoluene																	
	1,3-Ethyltoluene																	

		<p>1,4-Ethyltoluene</p> <p>C_9H_{12} (average)</p> <p>Solvent naphtha, (petroleum), light aromatic 64742-95-6</p> <p>[Can contain all structures pictured above; a UVCB substance containing aromatic molecules (one-ring) composed of carbon and hydrogen and consisting of C_9 aromatic hydrocarbons (approximately 90%). The category only includes substances with boiling ranges between $\sim 160^\circ C$ to $\sim 175^\circ C$. The chemical substance definition is a CAS RN definition and reflects a broader boiling range ($135^\circ C$ to $210^\circ C$) than the hydrocarbon solvent category member with CAS RN 64742-95-6, which ranges from $\sim 160^\circ C$ to $\sim 175^\circ C$.]</p>
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SUMMARY CONCLUSIONS OF THE SIAR

Category Justification

The C_9 Aromatic Hydrocarbons Solvents Category is comprised of a petroleum naphtha refinery stream, "Solvent naphtha, (petroleum), light aromatic," (CAS RN 64742-95-6; hereafter referred to as C_9 aromatic naphtha), from which the other, more chemically pure members of this category are isolated. These other members include several C_9 aromatic isomers (1,2,4-trimethylbenzene, 1,3,5-trimethylbenzene, and mixed ethyltoluenes) that have relatively limited production and are used primarily as chemical intermediates. The justification for including these isolated C_9 aromatic isomers in the category includes:

- 1) Trimethylbenzene (TMB) and ethyltoluene (ET) isomers are major constituents in the C_9 aromatic naphtha. The C_9 aromatic naphtha, which was tested under a 1985 U.S. TSCA Section 4 test rule, was required to have a minimum total ET-TMB content of 75%. Commercial C_9 aromatic naphtha typically contains 1,2,4-trimethylbenzene at 20-45%, 1,3,5-trimethylbenzene at 8-15%, and mixed ethyltoluenes at 25-35%.
- 2) For category members that have data, physicochemical properties are very similar. In addition, existing data indicate that the mammalian and acute aquatic toxicity of the isolated C_9 aromatic isomer substances are similar to the C_9 aromatic mixture.

The four substances in this category contain >99% hydrocarbons. The composition of the C_9 aromatic naphtha substance (CAS RN 64742-95-6) will vary somewhat, but generally contains <1% aliphatics and >90% C_9 aromatic hydrocarbons. This substance may contain C_8 and C_{10} aromatic hydrocarbons, typically in the range 5-10%, though these are not considered impurities, they are constituents of the substance. This substance may contain traces of benzene (<10 ppmv), sulfur (<10 ppmv), and nitrogen (<10 ppmv); however, these chemicals are considered impurities that are intentionally removed during production. The three remaining category members typically have purities of >98%.

Analogue Justification

Human health data for 1,2,3-trimethylbenzene (1,2,3-TMB; CAS RN 526-73-8) are used to support this category. 1,2,3-TMB data can be used because the chemical is present in solvent naphtha (CAS RN 64742-95-6) at approximately 6% by weight and because 1,2,3-TMB is an isomer of two other category members (1,2,4-TMB and 1,3,5-TMB).

Physical-chemical properties

The physical properties of the C_9 Aromatic Hydrocarbon Solvents Category members are given in ranges as the substances do not differ significantly in these properties: Melting point ($^\circ C$) ranges from -95.5 to -43.8; boiling

point (°C) ranges from 161.2 to 173.2; relative density (g/cm³ at 25°C) ranges from 0.861 to 0.881; vapour pressure (hPa at 25°C) ranges from 2.80 to 4.05; water solubility (mg/L at 25°C) ranges from 40 to 75; and the log Kow (at 25°C) ranges from 3.42 to 3.90. These substances are colorless liquids at 25°C.

Human Health

Acute Toxicity

Acute toxicity studies (oral, dermal and inhalation routes of exposure) have been conducted in rats using various solvent products containing predominantly mixed C₉ aromatic hydrocarbons (CAS RN 64742-95-6). Inhalation LC50's range from 6,000 to 10,000 mg/m³ for C₉ aromatic naphtha and 18,000 to 24,000 mg/m³ for 1,2,4 and 1,3,5-TMB, respectively. A rat oral LD50 reported for 1,2,4-TMB is 5 grams/kg bw and a rat dermal LD50 for the C₉ aromatic naphtha is >4 ml/kg bw. These data indicate that C₉ aromatic solvents show that LD50/LC50 values are greater than limit doses for acute toxicity studies established under OECD test guidelines.

Irritation and Sensitization

Several irritation studies, including skin, eye, and lung/respiratory system, have been conducted on members of the category. The results indicate that C₉ aromatic hydrocarbon solvents are mildly to moderately irritating to the skin, minimally irritating to the eye, and have the potential to irritate the respiratory tract and cause depression of respiratory rates in mice. Respiratory irritation is a key endpoint in the current occupational exposure limits established for C₉ aromatic hydrocarbon solvents and trimethylbenzenes. No evidence of skin sensitization was identified.

Repeated Dose Toxicity

Inhalation: The results from a subchronic (3 month) neurotoxicity study and a one-year chronic study (6 hr/day, 5 days/week) indicate that effects from inhalation exposure to C₉ Aromatic Hydrocarbon Solvents on systemic toxicity are slight. A battery of neurotoxicity and neurobehavioral endpoints were evaluated in the 3-month inhalation study on C₉ aromatic naphtha tested at concentrations of 0, 101, 452, or 1320 ppm (0, 500, 2,220, or 6,500 mg/m³). In this study, other than a transient weight reduction in the high exposure group (not statistically significant at termination of exposures), no effects were reported on neuropathology or neuro/behavioral parameters. The NOAEL for systemic and/or neurotoxicity was 6,500 mg/m³, the highest concentration tested.

In an inhalation study of a commercial blend, rats were exposed to C₉ aromatic naphtha concentrations of 0, 96, 198, or 373 ppm (0, 470, 970, 1830 mg/m³) for 6 hr/day, 5 days/week, for 12 months. Liver and kidney weights were increased in the high exposure group but no accompanying histopathology was observed in these organs. The NOAEL was considered to be the high exposure level of 373 ppm, or 1830 mg/m³. In two subchronic rat inhalation studies, both of three months duration, rats were exposed to the individual TMB isomers (1,2,4- and 1,3,5-) to nominal concentrations of 0, 25, 100, or 250 ppm (0, 123, 492, or 1230 mg/m³). Respiratory irritation was observed at 492 (100 ppm) and 1230 mg/m³ (250 ppm) and no systemic toxicity was observed in either study. For both pure isomers, the NOELs are 25 ppm or 123 mg/m³ for respiratory irritation and 250 ppm or 1230 mg/m³ for systemic effects.

Oral: The C₉ aromatic naphtha has not been tested via the oral route of exposure. Individual TMB isomers have been evaluated in a series of repeated-dose oral studies ranging from 14 days to 3 months over a wide range of doses. The effects observed in these studies included increased liver and kidney weights, changes in blood chemistry, increased salivation, and decreased weight gain at higher doses. Organ weight changes appeared to be adaptive as they were not accompanied by histopathological effects. Blood changes appeared sporadic and without pattern. One study reported hyaline droplet nephropathy in male rats at the highest dose (1000 mg/kg bw-day), an effect that is often associated with alpha-2μ-globulin-induced nephropathy and not considered relevant to humans. The doses at which effects were detected were 100 mg/kg-bw day or above (an exception was the pilot 14 day oral study – LOAEL 150 mg/kg bw-day - but the follow-up three month study that had a LOAEL of 600 mg/kg bw-day with a NOAEL of 200 mg/kg bw-day). Since effects generally were not severe and could be considered adaptive or spurious, oral exposure does not appear to pose a high toxicity hazard for pure trimethylbenzene isomers.

Mutagenicity

In vitro genotoxicity testing of a variety of C₉ aromatics has been conducted in both bacterial and mammalian cells. *In vitro* point mutation tests were conducted with *Salmonella typhimurium* and *Escherichia coli* bacterial strains, as well as with cultured mammalian cells such as the Chinese hamster cell ovary cells (HGPRT assay) with and without metabolic activation. In addition, several types of *in vitro* chromosomal aberration tests have

been performed (chromosome aberration frequency in Chinese hamster ovary and lung cells, sister chromatid exchange in CHO cells). Results were negative both with and without metabolic activation for all category members. For the supporting chemical 1,2,3-TMB, a single *in vitro* chromosome aberration test was weakly positive. In an *in vivo* bone marrow cytogenetics test, rats were exposed to C₉ aromatic naphtha at concentrations of 0, 153, 471, or 1540 ppm (0, 750, 2,310, or 7,560 mg/m³) 6 hr/day, for 5 days. No evidence of *in vivo* somatic cell genotoxicity was detected. Based on the cumulative results of these assays, genetic toxicity is unlikely for substances in the C₉ Aromatic Hydrocarbon Solvents Category.

Reproductive and Developmental Toxicity

Results from the three-generation reproduction inhalation study in rats indicate limited effects from C₉ aromatic naphtha. In each of three generations (F0, F1 and F2), rats were exposed to High Flash Aromatic Naphtha (CAS RN 64742-95-6) via whole body inhalation at target concentrations of 0, 100, 500, or 1500 ppm (actual mean concentrations throughout the full study period were 0, 103, 495, or 1480 ppm, equivalent to 0, 505, 2430, or 7265 mg/m³, respectively). In each generation, both sexes were exposed for 10 weeks prior to and two weeks during mating for 6 hrs/day, 5 days/wks. Female rats in the F0, F1, and F2 generation were then exposed during gestation days 0-20 and lactation days 5-21 for 6 hrs/day, 7 days/wk. The age at exposure initiation differed among generations; F0 rats were exposed starting at 9 weeks of age, F1 exposure began at 5-7 weeks, and F2 exposure began at postnatal day (PND) 22. In the F0 and F1 parental generations, 30 rats/sex/group were exposed and mated. However, in the F2 generation, 40/sex/group were initially exposed due to concerns for toxicity, and 30/sex/group were randomly selected for mating, except that all survivors were used at 1480 ppm. F3 litters were not exposed directly and were sacrificed on lactation day 21.

Systemic Effects on Parental Generations: The F0 males showed statistically and biologically significantly decreased mean body weight by ~15% at 1480 ppm when compared with controls. Seven females died or were sacrificed *in extremis* at 1480 ppm. The F0 female rats in the 495 ppm exposed group had a 13% decrease in body weight gain when adjusted for initial body weight when compared to controls. The F1 parents at 1480 ppm had statistically significantly decreased mean body weights (by ~13% (females) and 22% (males)), and locomotor activity. F1 parents at 1480 ppm had increased ataxia and mortality (six females). Most F2 parents (70/80) exposed to 1480 ppm died within the first week. The remaining animals survived throughout the rest of the exposure period. At week 4 and continuing through the study, F2 parents at 1480 ppm had statistically significant mean body weights much lower than controls (~33% for males; ~28% for females); body weights at 495 ppm were also reduced significantly (by 13% in males and 15% in females). The male rats in the 495 ppm exposed group had a 12% decrease in body weight gain when adjusted for initial body weight when compared to controls. Based on reduced body weight observed, the overall systemic toxicity LOAEC is 495 ppm (2430 mg/m³).

Reproductive Toxicity - Effects on Parental Generations: There were no pathological changes noted in the reproductive organs of any animal of the F0, F1, or F2 generation. No effects were reported on sperm morphology, gestational period, number of implantation sites, or post-implantation loss in any generation. Also, there were no statistically or biologically significant differences in any of the reproductive parameters, including: number of mated females, copulatory index, copulatory interval, number of females delivering a litter, number of females delivering a live litter, or male fertility in the F0 or in the F2 generation. Male fertility was statistically significantly reduced at 1480 ppm in the F1 rats. However, male fertility was not affected in the F0 or in the F2 generations; therefore, the biological significance of this change is unknown and may or may not be attributed to the test substance. No reproductive effects were observed in the F0 or F1 dams exposed to 1480 ppm (7265 mg/m³). Due to excessive mortality at the highest concentration (1480 ppm, only six dams available) in the F2 generation, a complete evaluation is precluded. However, no clear signs of reproductive toxicity were observed in the F2 generation. Therefore, the reproductive NOAEC is considered 495 ppm (2430 mg/m³), which excludes analysis of the highest concentration due to excessive mortality.

Developmental Toxicity - Effects on Pups: Because of significant maternal toxicity (including mortality) in dams in all generations at the highest concentration (1480 ppm), effects in offspring at 1480 ppm are not reported here. No significant effects were observed in the F1 and F2 generation offspring at 103 or 495 ppm. However, in F3 offspring, body weights and body weight gain were reduced by ~ 10-11% compared with controls at 495 ppm for approximately a week (PND 14 through 21). Maternal body weight was also depressed by ~ 12% throughout the gestational period compared with controls. The overall developmental LOAEC from this study is 495 ppm (2430 mg/m³) based on the body weights reductions observed in the F3 offspring.

Conclusion: No effects on reproductive parameters were observed at any exposure concentration, although a confident assessment of the group exposed at the highest concentration was not possible. A potential developmental effect (reduction in mean pup weight and weight gain) was observed at a concentration that was

also associated with maternal toxicity.

Chemicals in this category possess properties indicating a hazard for human health (respiratory, eye, and skin irritation). 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 air, category member constituents have the potential to rapidly degrade through indirect photolytic processes mediated primarily by hydroxyl radicals with calculated degradation half-lives ranging from 0.54 to 2.81 days (based on a 12-hour day and a hydroxyl radical concentration of 5×10^5). Aqueous photolysis and hydrolysis will not contribute to the transformation of category chemical constituents in aquatic environments because they are either poorly reactive or not susceptible to these reactions.

Results of the Mackay Level I environmental distribution model show that chemical constituents of C₉ Aromatic Hydrocarbon Solvents Category members have the potential to partition to air (96.8 to 98.9 %), with a negligible amount partitioning to water (0.2 to 0.6%) and soil (0.9 to 2.7%). In comparison, Level III modeling indicates that category members partition primarily to soil (66.3 to 79.6%) and water (17.8 to 25.0%) compartments rather than air (2.4 to 8.4%) when an equal emission rate (1000 kg/hr) is assumed to each of the air, water, and soil compartments. When release (1000 kg/hr) is modeled only to either the air, water, or soil compartment, constituents are indicated in the modeling to partition primarily (>94%) to the compartment to which they are emitted as advection and degradation influence constituent concentration in compartments to which constituents are not released.

Solvent naphtha, (pet.), light aromatic (CAS RN 64742-95-6), 1,2,4-trimethylbenzene (CAS RN 95-63-6), and 1-ethyl-3-methylbenzene (CAS RN 620-14-4) were determined to be readily biodegradable based on the studies that used the TG OECD 301F (the latter substance is used to characterize the potential biodegradability of the category member, ethylmethylbenzene (CAS RN 25550-14-5)). These three substances exceed 60% biodegradation in 28 days and met the 10-day window criterion for ready biodegradation. In comparison 1,3,5-trimethylbenzene (CAS RN 108-67-8) was not readily biodegradable. It achieved 42% biodegradation after 28 days and 60% biodegradation after 39 days. The result for the multi-constituent substance (CAS RN 64742-95-6), a UVCB, characterizes the biodegradability of that substance as a whole, but it does not suggest that each constituent is equally biodegradable. As with all ready biodegradation test guidelines, the test system and study design used with these substances (OECD TG 301F) is not capable of distinguishing the relative contribution of the substances' constituents to the total biodegradation measured.

Based on Henry's Law constants (HLCs) representing a potential to volatilize from water that range from 590 to 1000 Pa-m³/mole, the potential to volatilize from surface waters for chemicals in the C₉ Aromatic Hydrocarbon Solvents Category is expected to be high.

Based on the measured bioconcentration factors that range from 23 to 342 for 1,2,4-trimethylbenzene and 1,3,5-trimethylbenzene, the category members are not expected to be bioaccumulative.

Acute toxicity values used to characterize this category for fish (LL₅₀; LC₅₀) and invertebrates (EL₅₀; EC₅₀) range from 3.5 to 9.2 mg/L, based on measured data. For algae, one study for a category member (CAS RN 64742-95-6) resulted in a 72-hr EC₅₀ of 2.4 mg/L (biomass) and 2.7 mg/L (growth rate) based on measured concentrations. The algal 72-hour NOEC (no observed effect concentration) for biomass and growth rate is 1.3 mg/L, based on mean measured concentrations. A 21-day *Daphnia magna* reproduction study with 1,3,5-trimethylbenzene (CAS RN 108-67-8) resulted in a NOEC value of 0.4 mg/L, based on a minimum measured value.

Chemicals in this category possess properties indicating a hazard for the environment (acute toxicity for fish, invertebrates, and algae from 1 to 10 mg/L). Category members are readily biodegradable, except 1,3,5-trimethylbenzene (CAS RN 108-67-8). Category members are not expected to be bioaccumulative. Adequate screening-level data are available to characterize the environmental hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Use/Exposure

Annual worldwide production of C₉ aromatic naphtha (CAS RN 64742-95-6) for solvent use is estimated at 500,00-250,000 metric tonnes. U.S. solvent applications are primarily industrial coatings/sealants, marine paint, wood deck sealer, and automotive applications such as fuel injection cleaner and fuel additive diluent. Production of the individual trimethylbenzene isomers in the U.S. is estimated at 50,000-100,000 tonnes for 1,2,4-trimethylbenzene and 500-5,000 tonnes for 1,3,5-trimethylbenzene. Ethyltoluene (mixed isomers)

production in the U.S. is estimated at 5,000-25,000 tonnes. The trimethylbenzene isomers and ethyltoluenes are used largely as chemical intermediates. Exposure to C₉ aromatic hydrocarbons has been reported in a number of environmental and indoor air exposure assessments. There are anthropogenic and biogenic environmental sources of C₉ aromatics, such as automobile emissions, tobacco smoke, forest fires and other combustion products, in addition to industrial and consumer exposure sources. Occupational exposures were reported in the range of <1 to 3 ppm (<1 to 15 mg/m³) for solvent-use industries and 0 to 1.3 ppm (0 to 6 mg/m³) for chemical manufacturing industries. The reported non-occupational exposures are generally in the range of <1 to 5 ppb (<1 to 25 µg/m³), though these levels are often somewhat elevated in homes or offices that have recently been renovated or in homes of heavy smokers.

SIDS INITIAL ASSESSMENT PROFILE

Chemical Category	C ₉ -C ₁₄ Aliphatic [2-25% aromatic] Hydrocarbon Solvents Category											
Chemical Names and CAS Registry Numbers	Substance Name Stoddard solvent Kerosine, petroleum, hydrodesulfurized Naphtha, petroleum, hydrodesulfurized heavy Solvent naphtha, petroleum, medium aliphatic	CAS Number 8052-41-3 64742-81-0 64742-82-1 64742-88-7 Note: Substances in this category are also commonly known as mineral spirits, white spirits, or Stoddard solvent.										
Structural Formula and CAS Registry Numbers	<table border="0"> <thead> <tr> <th data-bbox="341 779 501 808">CAS Number</th> <th data-bbox="533 779 782 808">Chemical Description</th> </tr> </thead> <tbody> <tr> <td data-bbox="341 824 469 853">8052-41-3[†]</td> <td data-bbox="533 824 1347 887">Includes C₈ to C₁₄ branched, linear, and cyclic paraffins and aromatics (6 to 18%), <50ppmV benzene</td> </tr> <tr> <td data-bbox="341 902 469 931">64742-81-0[†]</td> <td data-bbox="533 902 1347 965">Includes C₉ to C₁₄ branched, linear, and cyclic paraffins and aromatics (10 to 25%), <100 ppmV benzene</td> </tr> <tr> <td data-bbox="341 981 469 1010">64742-82-1[†]</td> <td data-bbox="533 981 1347 1043">Includes C₈ to C₁₃ branched, linear, and cyclic paraffins and aromatics (15 to 25%), <100 ppmV benzene</td> </tr> <tr> <td data-bbox="341 1059 469 1088">64742-88-7[†]</td> <td data-bbox="533 1059 1347 1122">Includes C₈ to C₁₃ branched, linear, and cyclic paraffins and aromatics (14 to 20%), <50 ppmV benzene</td> </tr> </tbody> </table>	CAS Number	Chemical Description	8052-41-3 [†]	Includes C ₈ to C ₁₄ branched, linear, and cyclic paraffins and aromatics (6 to 18%), <50ppmV benzene	64742-81-0 [†]	Includes C ₉ to C ₁₄ branched, linear, and cyclic paraffins and aromatics (10 to 25%), <100 ppmV benzene	64742-82-1 [†]	Includes C ₈ to C ₁₃ branched, linear, and cyclic paraffins and aromatics (15 to 25%), <100 ppmV benzene	64742-88-7 [†]	Includes C ₈ to C ₁₃ branched, linear, and cyclic paraffins and aromatics (14 to 20%), <50 ppmV benzene	<p>Individual category member substances are comprised of aliphatic hydrocarbon molecules whose carbon numbers range between C₉ and C₁₄; approximately 80% of the aliphatic constituents for a given substance fall within the C₉-C₁₄ carbon range and <100 ppmV benzene.</p> <p>In some instances, the carbon range of a test substance is more precisely defined in the test protocol. In these instances, the specific carbon range (e.g. C₈-C₁₀, C₉-C₁₀, etc.) will be specified in the SIAP.</p> <p>* It should be noted that other substances defined by the same CAS RNs may have boiling ranges outside the range of 143-254° C and that these substances are not covered by the category.</p> <p>[†]Denotes a UVCB substance. UVCBs are defined as chemical substances of unknown or variable composition, complex reaction products or biological materials.</p>
CAS Number	Chemical Description											
8052-41-3 [†]	Includes C ₈ to C ₁₄ branched, linear, and cyclic paraffins and aromatics (6 to 18%), <50ppmV benzene											
64742-81-0 [†]	Includes C ₉ to C ₁₄ branched, linear, and cyclic paraffins and aromatics (10 to 25%), <100 ppmV benzene											
64742-82-1 [†]	Includes C ₈ to C ₁₃ branched, linear, and cyclic paraffins and aromatics (15 to 25%), <100 ppmV benzene											
64742-88-7 [†]	Includes C ₈ to C ₁₃ branched, linear, and cyclic paraffins and aromatics (14 to 20%), <50 ppmV benzene											

The category has been defined for members with specific constituents/component profiles or composition as outlined in the full SIDS Initial Assessment Report and the SIDS Dossiers.

The substances in the C₉-C₁₄ Aliphatic [2-25% aromatic] Hydrocarbon Solvents Category contain >99% hydrocarbons. Category members are described as UVCBs (Unknown or Variable Composition, Complex Reaction Products and Biological Materials) because they are composed of a defined, progressive carbon number range that includes various types of hydrocarbons: aliphatic molecules (linear, branched, and cyclic) and aromatic molecules (generally one-ring alkylbenzenes), predominantly in the C₉ to C₁₄ range. Benzene and sulfur content of category members is extremely low, typically <10 ppm with some substances identified as having <100 ppm, because these compounds are intentionally removed.

As complex hydrocarbon substances, some of the category members share CAS RNs with some petroleum process streams.

This assessment only applies to CAS RNs with the constituent profiles and compositions described within this assessment. Consequently, the conclusions of this assessment do not specifically apply to all petroleum process streams with the same CAS number as those belonging to the C₉-C₁₄ Aliphatic [2-25% aromatic] Hydrocarbon Solvents Category or to substances with constituents (i.e. benzene) outside the category ranges. Production of hydrocarbon solvents is differentiated from other refinery substances such as gasoline and diesel fuel by additional processing steps leading to finished substances with a narrow distillation range, a defined aromatic content, removal of benzene, polyaromatic hydrocarbons (PAHs), sulfur- and nitrogen-containing compounds, and low color.

Table 1 - Typical compositional data for representative commercial C₉₋₁₄ aliphatic [2-25% aromatic] hydrocarbon solvents

CAS No.	Carbon * Number (range)	Aliphatics*			Aromatics *	Ethyl- benzene*	Naphthalene *	Benzene *
		% total	% iso- n-, cyclo	% n-, cyclo	% total	%	%	ppmv
8052-41-3	8-14	82-94	38-84	8-50	8-17	<0.2	< 0.5	< 50
64742-82-1	8-13	77-85	40-65	15-40	15-25	<0.3	< 0.1	<100
64742-81-0	9-13	73-88	40-55	25-35	10-22	<0.1	<0.3	< 100
	9-16**	77.3	~42.0	>28.0	22.2	na	~0.6	na
64742-88-7	8-13	80-86	35-50	10-46	14-20	~0.3	<0.1	<50

* The values in this table are approximate values reported from manufacture analyses and are not specifications.

** Analogue substance, with same CAS RN (64742-81-0) as contained by the category; see above.

< Less than detection limit (detection limit reported)

nd not detected

na not available

Table 2 - Typical Carbon Number Range for the Aliphatic Molecules in the C₉₋₁₄ aliphatic [2-25% aromatic] hydrocarbon solvents category

Identification of chemicals defined by processing procedures	Typical Carbon Number Range for the Aliphatic Molecules (%)									
	< C8	C8	C9	C10	C11	C12	C13	C14	C15 to C16	Total Aromatics
Stoddard solvent 8052-41-3	~0.5	~2	~11	~25	~30	~13	~3	~0.5		~15
Naphtha, petroleum, hydrodesulfurized heavy 64742-82-1	~0.5	~1	~9	~27	~35	~7	~0.5			~20
Kerosine, petroleum, hydrodesulfurized 64742-81-0			~0.5	~3	~8	~24	~30	~10	~3.5	~21
Kerosine, petroleum, hydrodesulfurized 64742-81-0*			~1	~5	~8	~10	~20	~12	~20	~22
Solvent naphtha, petroleum, aliphatic medium 64742-88-7		~2	~10	~17	~40	~13	~1			~17

* Analogue substance, with same CAS RN (64742-81-0) as contained by the category.

SUMMARY CONCLUSIONS OF THE SIAR

Category Definition/Justification

The C₉-C₁₄ Aliphatic [2-25% Aromatic] Hydrocarbon Solvents Category is comprised of four CAS numbers that are associated with complex aliphatic hydrocarbon solvent commercial products that can contain up to 25% aromatic content. These hydrocarbon solvent products are generally defined by boiling range and/or flash point and the predominant carbon number range of these products is primarily within the range from C₉ to C₁₄ (approximately 80%). The chemical constituents in these complex UVCB substances may include straight chain (n-), branched (iso-) and cyclic aliphatic hydrocarbons and aromatic hydrocarbons (generally one-ring aromatics). These products may be sold under a variety of brand, commercial and trade names, such as mineral spirits, Stoddard solvent and white spirits, and they may be associated with one or more of the four Chemical Abstract Services (CAS) Registry Numbers (RN) for this category.

Assignment of CAS RNs for complex hydrocarbon products is generally based on a hierarchy of considerations including hydrocarbon type(s), carbon number range, distillation range, and last processing step. One documented source of criteria for assignment of CAS RNs for complex hydrocarbons is provided by the U.S. EPA on proceedings for development of the TSCA inventory for U.S. chemicals. These criteria, however, may allow the same CAS RN to be applied to various hydrocarbons and petroleum-derived substances with somewhat different composition and applications (e.g., solvents, fuels, lubricants, etc.). Similarly, different CAS RN can be applied to substances of similar composition and application. In the case of this C₉-C₁₄ Aliphatic [2-25% Aromatics] Hydrocarbon Solvents Category, the four CAS RNs described here are all applied to compositionally similar and generally commercial interchangeable hydrocarbon solvents. This similarity of composition and commercial applications is the primary justification for evaluating these substances in a category. Further, the existing toxicology data shows that substances in this category have a similar order of toxicity and support the grouping of these substances as a category.

Category Member Conventional Naming

The naming convention used to identify category members is based on their general compositions (predominant carbon number range and hydrocarbon type, specifically aromatics) and is intended to identify hydrocarbon

solvent substances manufactured by various companies that are sufficiently similar with regard to composition such that their physical and biological properties would exhibit similar if not identical values. The naming convention as applied to hydrocarbon solvents was seen as a means to provide an immediate understanding of the type of solvent and its composition to allow for an accurate grouping of hydrocarbon substances within categories. As UVCBs, some of the hydrocarbon solvent category members share CAS RNs with some petroleum process streams, which have broader boiling ranges and consequently are compositionally more complex.

Category members (CAS RN 8052-41-3, 64742-81-0, 64742-82-1, and 64742-88-7) meet the criteria for UVCB substances because they contain a relatively large number of discrete chemical constituents and the exact composition of some of the constituent chemicals may be unknown. The general naming convention guidance was developed and used for category members as follows:

"Hydrocarbons", the first part of the name, recognizes the specific chemical class.

The carbon number range typically identifies at least 80% of the chemical constituents in the substance.

The structures are identified by the types of hydrocarbons present: n-paraffins (n-alkanes), iso-paraffins (isoalkanes), cyclic-paraffins or naphthenic (cyclics), and aromatics. The first three are mentioned when present in the substance at a level between 10 and 80%. Aromatics will be indicated when present at levels greater than 2% or less than or equal to 25%.

Components with specific toxicology or classification will be mentioned, using the classification cut-off as an indication level (according to EU DSD [Dangerous Substances Directive] and GHS [Global Harmonized System of Classification and Labeling of Chemicals] guidance).

Read-Across Substance Identification

In addition to the available physical and biological data for substances in this category, data for the following analogues are also presented, as necessary, to support the characterization of selected endpoints:

CAS RN 64771-72-8; Hydrocarbons, C₁₂-C₁₄, n-alkanes, <2% aromatics

CAS RN 90622-57-4; Hydrocarbons, C₁₀-C₁₂, isoalkanes, <2% aromatics

CAS RN 90622-58-5; Hydrocarbons, C₁₁-C₁₃, isoalkanes, <2% aromatics

CAS RN 8008-20-6 ; JP-8 (having a carbon range of 8-16 and ~25% aromatics)

CAS RN 64742-81-0 ; Kerosine, petroleum, hydrodesulfurized (C₉-C₁₆, wide cut UVCB)

CAS RN 64742-48-9 ; dearomatised white spirit, consisting of carbon molecules primarily in the C₈-C₁₁ range and containing approximately 30% n-alkanes, 20% isoalkanes, 50% cycloalkanes, and less than 0.5% aromatics.

CAS RN 108-67-8 ; 1,3,5-trimethylbenzene

The two read-across substances, Hydrocarbons, C₁₂-C₁₄, n-alkanes, <2% aromatics and Hydrocarbons, C₁₀-C₁₂, isoalkanes, <2% aromatics form a physical-chemical continuum with the C₉-C₁₄ Aliphatic [2-25% aromatic] Hydrocarbon Solvents Category and contain a range of carbons and physical-chemical properties that are either immediately above or below the range specified for the C₉-C₁₄ Aliphatic [2-25% aromatic] Hydrocarbon Solvents Category.

Jet fuel (JP-8), a U.S. military fuel, is a wide cut hydrocarbon stream and is less refined than the hydrocarbon solvents. JP-8 is a complex hydrocarbon substance (UVCB) that has a carbon number range of C₈-C₁₆, a boiling range of approximately 150 – 290°C, and an aromatic content of approximately 25% and approximates the physical/chemical properties of the C₉-C₁₄ Aliphatic [2-25% aromatic] Hydrocarbon Solvents. Since JP-8 is not as severely refined as the C₉-C₁₄ Aliphatic [2-25% aromatic] Hydrocarbon Solvents, test results from JP-8 could be considered a "worst-case" scenario when used as read-across to the C₉-C₁₄ Aliphatic [2-25% aromatic] Hydrocarbon Solvents.

Another analogue substance has a CAS RN contained by this category 64742-81-0 (hydrodesulfurized kerosene) and is defined as *C₉₋₁₆ mixed aliphatics/aromatics with 22% aromatic content*. Although the carbon number range extends beyond the category definition, the similarity in constituent content over the carbon range shared by the analogue and category members is sufficiently similar to justify the use of the analogue data (see Table 1 for composition).

Table 4 – Data for the following analogues are also presented to support the characterization of selected endpoints.

Analogue (CAS RN)	Composition	Endpoint(s) Characterized
64771-72-8	Hydrocarbons, C ₁₂ -C ₁₄ , n-alkanes, <2% aromatics	Biodegradation
90622-57-4	Hydrocarbons, C ₁₀ -C ₁₂ , isoalkanes, <2% aromatics	Biodegradation Chronic Aquatic Toxicity
90622-58-5	Hydrocarbons, C ₁₁ -C ₁₃ , isoalkanes, <2% aromatics	Chronic Aquatic Toxicity
64742-81-0	Kerosine, petroleum, hydrodesulfurized (C ₉ -C ₁₆ , wide cut UVCB)	Acute Toxicity Irritation Sensitization In vitro genotoxicity
8008-20-6	JP-8	Reproductive Toxicity Chronic Fish Toxicity
64742-48-9	Dearomatised white spirit, consisting of carbon molecules primarily in the C ₈ -C ₁₁ range and containing approximately 30% n-alkanes, 20% isoalkanes, 50% cycloalkanes, and less than 0.5% aromatics	toxicokinetics
108-67-8	1,3,5-trimethylbenzene	toxicokinetics

Substances in the C₉₋₁₄ Aliphatic [2-25% Aromatic] Hydrocarbon Solvents Category are composed of a range of paraffinic and aromatic hydrocarbons that fall within a carbon number (C) range of 9 to 14. As a result, many of the category member physicochemical properties are characterized by a range of values as a function of composition because a single value is not possible. For example, a complex hydrocarbon will not exhibit a single P_{ow} value, but rather a range based on constituent composition. This would be the case regardless of whether the data were measured using a standard testing procedure or calculated based on the individual constituent chemicals.

For several of the physical-chemical properties, the value range is based on a series of representative hydrocarbons that were selected by industry, based on hydrocarbon process (distillation) knowledge, to accurately characterize category members. The hydrocarbons selected include paraffins and aromatics from C₉ to C₁₄:

<u>Chemical Name</u>	<u>CAS RN</u>
n-nonane	111-84-2
2-methyloctane	n/a
1,2,4-trimethylcyclohexane	2234-75-5
1,2,4-trimethylbenzene	95-63-6
1,2,3,4-tetrahydronaphthalene	119-64-2
1,3-dimethyl-2-ethylbenzene	2870-04-4
2,4-dimethyl-nonane	n/a
n-tridecane	629-50-5
2,5-dimethyl-undecane	n/a
2,3,6-trimethyldecalin	n/a
n-tetradecane	629-59-4
2,5,6,9-tetramethyldecane	n/a
2,3,6,7-tetramethyldecalin	n/a

n/a = not available

Physicochemical Properties

The members of the C₉-C₁₄ Aliphatic [2-25% Aromatic] Hydrocarbon Solvents Category are liquids at room temperature. The measured melting point values for constituents range from -83.5 to 18.1°C. The initial boiling points range from approximately 143 to 160°C and the final boiling points from 205 to 254°C. The measured

Vapour pressure for constituents range from 0.02 to 8.3 hPa at 20° to 25°C. The calculated Water solubility values range from 0.01 to 94.3 mg/L (at 25°C) for constituents, with a relative density range of 0.77 to 0.81 g/cm³ (at 20°/4° C). The measured log Pow values for category member constituents range from 3.5 – 7.2 (at 25°C). Viscosity values range from 0.98 mm²/sec to 1.6 mm²/sec at 20°C.

Human Health

Toxicokinetics, Metabolism, and Distribution

The study of the toxicokinetics of the C₉₋₁₄ Aliphatic [2-25% Aromatic] Hydrocarbon Solvents Category is complex as this category comprises a mixture of hydrocarbons. However, these hydrocarbons display similar chemical properties. The relative percentage of the single compounds and their different physical and chemical properties greatly affects the toxicokinetics of this class of hydrocarbons. The inhalation absorption of materials in this category depends on several factors including concentration in the inspired air, blood partition coefficient, pulmonary ventilation, and pulmonary flow. However, studies have generally shown that materials in this category are readily absorbed through the lungs.

It is estimated that 61% - 81% of a C₉-C₁₄ hydrocarbon solvent would be absorbed when ingested. C₉-C₁₄ aliphatic, 2-25% aromatic hydrocarbon fluids are typically metabolized by side chain oxidation to alcohol and carboxylic acid derivatives. These metabolites can be glucuronidated and excreted in the urine or further metabolized before being excreted. The majority of the metabolites are expected to be excreted in the urine and to a lower extent, in the feces. Excretion is expected to be rapid with the majority of the elimination occurring within the first 24 hours of exposure.

Absorption

When inhaled, white spirit constituents were readily absorbed. After a 30-minute exposure at rest to approximately 1040 mg/m³ of the aliphatic components, the concentration in alveolar air was 255 mg/m³ (25 % of the concentration in the inspiratory air). The corresponding arterial blood concentration was 1.7 mg/kg. When alveolar ventilation tripled (50 W exercise), the alveolar concentration increased to 515 mg/m³ (50 % of the concentration in inspiratory air), whereas the arterial concentration rose to 3.5 mg/kg. When alveolar ventilation was raised to 60 L/min (150 W exercise), the alveolar concentration rose to about 60 % of the concentration in inspiratory air. Thirty minutes following exposure, alveolar concentration was ~180 mg/m³ and arterial concentration was near 0 mg/kg.

After a 30-minute exposure at rest to approximately 210 mg/m³ of the aromatic components, the concentration in alveolar air after 30 minutes was about 30 mg/m³ (15% of the concentration in the inspiratory air). The corresponding arterial blood concentration was approximately 0.2 mg/kg. When alveolar ventilation tripled (50 W exercise), the alveolar concentration increased to about 20% of the concentration in inspiratory air. However, the arterial blood concentration increased from 0.2 to 0.7 mg/kg. When alveolar ventilation was raised to 60 L/min (150 W exercise), the alveolar concentration rose to about 150 mg/m³ and the arterial blood concentration was 0.9 mg/kg. Thirty minutes following exposure, alveolar concentration was ~20 mg/m³ and arterial concentration was near 0 mg/kg. Pulmonary ventilation appeared to be more important to uptake in arterial blood than to circulation. The results are believed to be due to the differing solubilities of aliphatic and aromatic components in blood, (i.e., aromatic components are generally more soluble in blood than aliphatic and alicyclic hydrocarbon components).

Distribution

Studies have shown that following absorption, members of the C₉₋₁₄ Aliphatic [2-25% Aromatic] Hydrocarbon Solvents Category are widely distributed throughout the body of both humans and animals and preferentially accumulate in the adipose tissues due to the lipophilic nature of the solvents.

A toxicokinetic study on the distributions of C₉ to C₁₀ alkanes, aromatics and cycloalkanes in blood, brain, liver, kidney and perirenal fat demonstrated that aromatics generally showed higher blood concentrations than alkanes and cycloalkanes. C₉ cycloalkanes showed higher brain concentrations than the corresponding aromatics and alkanes, while brain concentrations of C₁₀ alkanes were slightly greater than C₁₀ cycloalkane concentrations, which in turn were greater than C₁₀ aromatic concentrations. Fat contained the highest concentrations of each of the hydrocarbons examined; concentrations of aromatics and cycloalkanes in fat were higher than concentrations of alkanes. The concentrations of aromatics in fat decreased on each successive day of exposure, which could be an indication of a higher rate of metabolic elimination. Brain/blood ratios of 11.4, 2.0 and 11.4, and fat/blood ratios of 113, 63 and 135 were found for n-nonane, trimethylbenzene and trimethylcyclohexane, respectively. A marked decrease in biological concentrations of trimethylbenzene and trimethylcyclohexane during the initial phase of exposure indicates that these hydrocarbons are capable of inducing their own metabolic conversion resulting in lower steady state levels.

Metabolism

Very little is known about the metabolic fate of the C₉₋₁₄ Aliphatic [2-25% Aromatic] Hydrocarbon Solvents

Category since metabolic studies have most frequently been conducted with single hydrocarbons and not with hydrocarbon mixtures. Consequently, it is difficult to predict the extent of the metabolic conversion of single components in a mixture because several factors may influence the metabolism, e.g., substrate saturation of the metabolizing enzymes, competition phenomena and enhancement or inhibition of enzyme systems.

Aliphatic hydrocarbons are known to undergo oxidative conversion, catalyzed by monooxygenases, to alcohols. The cytochrome P-450 dependent monooxygenases, located mainly in the endoplasmic reticulum of liver cells, are responsible for this first metabolic transition. Polycyclic aromatic hydrocarbons are oxidized by P450 enzymes in an initial step in the activation process. The resultant epoxide intermediates are usually more reactive than the parent compounds and have been shown to require further metabolism to evoke their critical carcinogenic potentials. These epoxide metabolites have been shown to be readily hydrolyzed to dihydrodiol metabolites by microsomal epoxide hydrolases and finally oxidized again by P450 enzymes to form highly reactive diol-epoxides that can interact with DNA to initiate cell transformation.

Excretion

Most of the information concerning the elimination and excretion of aliphatic and aromatic hydrocarbons has been derived from studies involving exposure to single substances. Few studies have systematically evaluated the elimination and excretion of complex hydrocarbons mixtures such as those found in the C₉₋₁₄ Aliphatic [2-25% Aromatic] Hydrocarbon Solvents Category. Generally speaking, it is expected that components or metabolites of materials such as Stoddard solvent/white spirit that are volatile but have low solubility in the blood, would be rapidly exhaled from the lungs. Like for absorption, this process is governed by blood/gas solubility ratios. Components with low blood/gas ratios would be most rapidly excreted from the lungs because of their low blood solubility, while those with high blood/gas solubility ratios would be eliminated less efficiently by the lungs due to their high blood solubility; this situation is exactly the reverse of that for inhalation absorption. The aromatic hydrocarbons are expected to be excreted primarily in the urine.

One study conducted reported that ten minutes after exposure had ceased, the expiratory concentration levels of aliphatics and aromatics were found to be about 12% of the initial exposure level for both fractions. Sixteen hours later, the levels in expiratory air had fallen to 2% (aliphatics) and 4% (aromatics) of the initial exposure level. The overall half-life of white spirit in adipose tissue was determined to be 46-48 hours in one study. These results indicate that steady state in adipose tissue will be reached after approximately 3 weeks following continuous exposure.

A 3-week inhalation study conducted in rats exposed for 6 hours/day, 5 days/week at levels of 2290 and 4580 mg/m³ found white spirit (20% aromatics) concentration in the brain of 3.4 and 10.2 mg/kg wet weight, respectively immediately preceding exposure cessation. In a follow up study that only examined the aliphatic components of white spirits, male rats were exposed by inhalation to 0, 400 (2290 mg/m³) or 800 ppm (4580 mg/m³) of dearomatised white spirit (CAS 64742-48-9) for 6 hr/day, 5 day/week for 3 weeks. Five rats from each group were sacrificed immediately after the exposure duration of 1, 2, or 3 weeks and 2, 4, 6, or 24 hr after the end of 3 weeks' exposure. Immediately follow the end of the 3 weeks of exposure, the concentration of total white spirit was 1.5 and 5.6 mg/kg in blood; 7.1 and 17.1 mg/kg in brain; 432 and 1452 mg/kg in fat tissue at the exposure levels of 400 and 800 ppm respectively. Two hours after the end of exposure the white spirit concentration decreased to about 25% in blood and 50% in brain. The authors calculated that the post-exposure half-life in blood could be separated into two phases with half-lives of approximately 1 and 8 hr; in brain tissue two slopes with half-lives of 2 and 15 hr were identified. In adipose tissue, only one slope with half-life of about 30 hr was identified.

A study using 1,3,5-trimethylbenzene (TMB; CAS RN 108-67-8) as a surrogate for the aromatic fraction of white spirit was observed to have a biphasic elimination with half-lives of 13h and 60 h with peak elimination occurring 4-8 hours after the end of the exposure. It is expected that metabolites are rapidly eliminated in the urine following the cessation of exposure, although a slower elimination from the adipose tissue is expected.

Acute Toxicity Summary

The available acute toxicity data demonstrate that hydrocarbon solvent substances tested in the C₉₋₁₄ Aliphatic [2-25% Aromatic] Hydrocarbon Solvents Category did not demonstrate acute toxicity at the limit dose by the oral, dermal, and inhalation routes of exposure.

Acute Inhalation Toxicity

Six acute inhalation toxicity test (similar or equivalent to OECD TG 403) were conducted on C₉₋₁₄ Aliphatic [2-25% Aromatic] Hydrocarbon Solvents. Four studies were conducted on male and female rats using substances with the CAS RN 8052-41-3 vapours; the LC₅₀ were between >5500 mg/m³ to >12190 mg/m³. No deaths were reported in these four studies. One study was conducted in rats using C₉₋₁₃ Aliphatic [2-25% Aromatic] Hydrocarbon Solvents (CAS RN 64742-88-7); the LC₅₀ was > 710 ppm, which was the highest attainable concentration (54% of saturation). Finally, one study using hydrodesulfurized kerosene (CAS RN 64742-81-0)

was conducted on rats, no deaths were reported at the highest dose tested (5.2 mg/L).

Acute Dermal Toxicity

Five dermal toxicity studies (similar or equivalent to OECD TG 402) were conducted on commercial C₉₋₁₄ Aliphatic [2-25% Aromatic] Hydrocarbon Solvents (CAS RNs 8052-41-3, 64742-82-1, 64742-88-7). The dermal LD₅₀ in rabbits was greater than 3.0 g/kg in all five studies. One acute dermal study was conducted in rats using C_{9-C13} Mixed aliphatics and aromatics (CAS RN 64742-82-1); the LD₅₀ > 4 mL/kg bw.

Acute Oral Toxicity (gavage administration)

The acute oral toxicity studies (equivalent or similar to OECD TG 401) were conducted in male and female rats on commercial C₉₋₁₄ Aliphatic [2-25% Aromatic] Hydrocarbon Solvents (CAS RNs 8052-41-3, 64742-82-1, 64742-88-7). The LD₅₀ was >5.0 g/ kg bw for test materials with the CAS RN 8052-41-3. One study conducted in rats with C_{9-C13} Aliphatics and 2-25% aromatics (CAS RN 64742-82-1) had a LD₅₀ > 8.0 mL/kg. The last study was conducted in rats with C_{9-C13} Aliphatics and 2-25% aromatics (CAS RN 64742-88-7); the LD₅₀ was > 25.0 mL/kg. This assessment does not include less refined substances that share the same CAS number or substances with a higher benzene content. The C₉₋₁₄ Aliphatic [2-25% Aromatic] Hydrocarbon Solvents products may be an aspiration hazard based on their viscosities. Chemicals with a viscosity of <20.5 mm²/sec at 40°C should also be considered an aspiration hazard (the accidental inhalation of fluids into the lungs).

Irritation and Sensitisation

Irritation studies (equivalent or similar to OECD TG 404) were conducted in rabbits on commercial C₉₋₁₄ Aliphatic [2-25% Aromatic] Hydrocarbon Solvents (CAS RN 8052-41-3 and 64742-88-7). In dermal irritation tests, the erythema score (24, 48, 72 hour) results were 1.04 to 2.1. The edema score (24, 48, 72 hour) results were 0.0 to 0.67. One study (CAS RN 8052-41-3) used an occlusive dressing and a 24 hour continuous exposure; under these conditions the test material was irritating. Due to the occlusive nature of the dressing, these conditions are not anticipated to be encountered outside of experimental settings. The results of these studies indicate that C₉₋₁₄ Aliphatic [2-25% Aromatic] Hydrocarbon Solvents are minimal to mild irritants to rabbits.

Several eye irritation studies (equivalent or similar to OECD TG 405) were conducted in rabbits on commercial C₉₋₁₄ Aliphatic [2-25% Aromatic] Hydrocarbon Solvents (CAS RN 8052-41-3, 64742-82-1, and 64742-88-7). The average conjunctivae score (24, 48, 72 hours) results were 0.0 to 0.22. The average chemosis score (24, 48, 72 hour) results were 0.0 to 0.05; all iritis and cornea opacity scores were 0 for all studies. These results suggest that these solvents produce no to minimal irritation to the eyes of rabbits.

Two respiratory irritation studies were conducted in mice on commercial C₉₋₁₄ Aliphatic [2-25% Aromatic] Hydrocarbon Solvents (CAS RN 8052-41-3 and 64742-82-1). The RD₅₀ = 10 mg/L and no effects observed at 4.4 mg/L (CAS RN 8052-41-3) Exposure to 6, 87, or 172 ppm produced 7, 16, and 15% decreases in breathing rate, respectively (CAS RN 64742-82-1). Sensory irritation was evident in the breathing patterns of the test animals; the test substances produced only slight irritation in the respiratory tract.

Two studies (equivalent or similar to OECD TG 406) were available on the sensitisation potential of C₉₋₁₄ Aliphatic [2-25% Aromatic] Hydrocarbon Solvents (CAS RN 8052-41-3 and 64742-82-1). Tests were conducted using guinea pigs; both test yielded negative results. Based on these data, the C₉₋₁₄ Aliphatic [2-25% Aromatic] Hydrocarbon Solvents are not expected to be sensitizers.

Based on the data presented above, the category members are not expected to be eye irritants; the category members are expected to be minimal skin irritants under semi-occlusive conditions. No toxicological studies have demonstrated skin defatting (which may result in cracking of the skin) but it is a well-known property of organic solvents. Category members are not expected to have the potential to cause skin sensitization. This assessment does not include less refined substances that share the same CAS number or substances with a higher benzene content.

Repeated Dose Toxicity (Inhalation)

Three inhalation repeated dose studies were located for the C₉₋₁₄ Aliphatic [2-25% Aromatic] Hydrocarbon Solvents Category.

A repeated dose inhalation study was conducted in C_{5-C12} (but primarily C_{8-C12}) Mixed paraffin and aromatics (CAS RN 64742-82-1). Hydrocarbons, C₉ - C₁₂, n-alkanes, isoalkanes, cyclics, 2-25% aromatics (CAS RN 64742-82-1) was administered via inhalation to rats at concentrations of 0.049 (7.8 ppm), 0.10 (16 ppm), or 0.23 mg/L (37 ppm) of 140° flash aliphatic solvent for 6 hours a day, 5 days per week for 14 weeks (similar to OECD TG 413). No adverse effects were observed at the highest dose tested. The only significant finding was slight to moderate tubular regeneration in male rats which is consistent with alpha-2u-globulin induced nephropathy. Alpha-2u-globulin is not relevant to human health. Based on these observations, the repeat inhalation concentration NOAEC is 0.23 mg/L (37 ppm) for C₉ - C₁₂, n-alkanes, isoalkanes, cyclics, 2-25% aromatics.

In a second study, C₉-C₁₂ Mixed paraffin and aromatics (CAS RN 64742-82-1). Hydrocarbons, C₉ - C₁₂, n-alkanes, isoalkanes, cyclics, 2-25% aromatics (CAS RN 64742-82-1; aromatic content ~19%) was administered via inhalation to rats at concentrations of 0, 100, or 300 ppm for 6 hours a day, 5 days a week for 12 weeks. No mortality occurred during the study. The only adverse effects observed in this study were significant elevations in absolute and relative kidney weights in male rats. These observed effects were consistent with alpha-2u-globulin induced nephropathy in male rats, an effect that is not relevant to human health. The NOAEC for this study was 294 ppm.

In a third repeated-dose inhalation study, rats were exposed to 2000, 4000, or 8000 mg/m³ (345, 690, or 1293 ppm, respectively) of a C₉-13 hydrocarbon solvent containing 19% aromatics (CAS RN 64742-82-1) for 6 hours per day, 5 days week for 13 weeks. No deaths were observed. Clinical signs of toxicity were absent in the 2000 and 4000 mg/m³ dose groups, with some lethargy noted in the 8000 mg/m³ dose group. Body weight gain was slightly reduced in the 4000 mg/m³ males (-4.1%) and in the 8000 mg/m³ males and females (-6.6% and -4.5%, respectively). These body weight reductions were not biologically significant.

There were several haematological parameters that were statistically, but not biologically, significant in the exposed male rats. Total red blood cell count was reduced in the 2000, 4000, or 8000 mg/m³ males (-4.1%, -6.2%, -7.0%, respectively). Packed cell volume was slightly reduced in the 2000, 4000, or 8000 mg/m³ males (-2.9%, -4.2%, -5.0%, respectively). Red blood cell volume was slightly increased at all dose level (< +3%) and mean cell haemoglobin was elevated to +5.5% in all dose groups. There were no changes to haematological parameters in female rats. There were no changes in reticulocytes count or in bilirubin and haemoglobin levels. Given the minimal changes within biologically normal values, these haematological changes were not considered biologically significant.

Splenic weight was slightly statistically increased in the 4000 mg/m³ males; the absolute splenic weight was +23.6% of control. However, at the low dose and at the high dose, there was no corresponding increase in spleen weight. Given the lack of a dose response and lack of pathological findings, this effect is not considered to be biologically relevant.

Kidney weights were marginally increased in the 4000 and 8000 mg/m³ female exposure groups (≤5%) but no exposure-related renal lesions were identified in the female rats and these effects were not considered biologically relevant. Male kidney weights were increased at all exposure levels. Hyaline intracytoplasmic inclusions and an increased incidence of tubular degeneration change were recorded in cortical tubules in all exposed male groups. These effects are consistent with α₂u-globulin effects in male rats. Exposure of male rats to hydrocarbon solvents results in the formation of α₂u-globulin protein complexes in the kidney. These complexes accumulate in rat kidney cells and produce sex and species-specific histopathological changes. Since α₂u-globulin protein is not present in humans, the changes in the male rat kidney as a consequence of an α₂u-globulin mediated process are not useful or relevant for assessing human risk.

An increase in female liver weights was observed at all dose levels but no lesions were histologically identified in the liver. In the absence of histological hepatic changes, this increase in liver weight was regarded as an hyperfunctional adaptation rather than a toxic effect. The NOAEC for this study was 4000 mg/m³.

Repeated Dose Toxicity (Oral)

A 28 -day subchronic oral repeated dose toxicity study (OECD TG 407) was conducted on Hydrocarbons, C₁₁-C₁₄, n-alkanes, isoalkanes, cyclics, aromatics (2-25%) (CAS RN 64742-81-0) using male and female Crj: CD (SD) rats. Groups of 5 rats of each sex were given doses of 0.14 (116 mg/kg), 0.42 (347 mg/kg), or 1.28 (1056 mg/kg) mL/kg of test substance in corn oil for 30 days. Animals were examined for clinical signs, mortality, body weight, food consumption, water consumption, and food conversion. After sacrifice clinical chemistry, hematology, clinical chemistry, urinalysis, organ weights, histopathology, and gross pathology were examined. There was no mortality during the experiment. Renal damage was observed in male rats at all dose levels. This type of renal pathology is specific to male rats due to an alpha₂u-globulin-mediated process that is not relevant to humans. Female rats exhibited adaptive liver changes at the highest dosage and was not considered an adverse effect. The LOAEL for male rats was 0.14 ml/kg/day based on renal damage, which is not relevant to human health. The female NOAEL was 1.28 (1056 mg/kg) mL/kg.

In repeated-dose toxicity studies, exposure of male rats to hydrocarbon solvents results in the formation of α₂u-globulin protein complexes in the kidney. These complexes accumulate in rat kidney cells and produce sex and species-specific histopathological changes. Since α₂u-globulin protein is not present in humans, the changes in the male rat kidney as a consequence of an α₂u-globulin mediated process are not useful or relevant for assessing human risk. Some studies have reported liver effects and some hematological changes, but these effects have generally not been dose-related or consistent between studies. Based on the data above, the C₉₋₁₄ Aliphatic [2-25% Aromatic] Hydrocarbon Solvents Category members are expected to present low toxicity after repeated dose exposure.

Repeated Dose Toxicity (Dermal)

A 13 week subchronic dermal repeated dose toxicity study was conducted on the read-across substance hydrodesulfurized kerosene (CAS RN 64742-81-0) using groups of 12 male and 12 female rats. Test material was applied at concentrations of 0, 20, 40 or 60% (v/v) (0 (mineral oil), 165, 330 or 495 mg/kg/day, respectively) five consecutive days each week for 13 weeks under a semi-occlusive dressing. An additional group in the vehicle controls and high dose group were maintained for a 4-week recovery period following dosing for 13 weeks. During the week prior to the first dose, each rat was subjected to a functional observation battery (FOB) and was conducted again 1, 6 and 24 hours after the first dose and at 7 and 14 days. All animals survived until scheduled termination. Treatment related dermal irritation was noted in the animals. There were no test substance-related effects on survival, clinical observations (apart from skin irritation), neurobehavioral signs or ophthalmological findings. The only clinical observations during the study were related to skin irritation at the application site. There was a generally dose-related increase in the incidence and severity of erythema, edema, epidermal scaling, scab formation, thickening of the skin and ulceration at the treated site. The FOB screen did not demonstrate any substance-related effects. Growth rates were unaffected by treatment. Hematological and serum clinical parameters were unaffected by treatment. There were no treatment-related microscopic changes in the tissues examined with the exception of the findings in the skin. The skin observations were minimal in nature with a severity score less than 1 on a 1 [low] to 4 [severe] scale. The findings included acanthosis, ulceration, parakeratosis, chronic active inflammation and hyperkeratosis. Recovery group animals revealed complete recovery in the females and minimal hyperkeratosis in the high dose group males. No effects were found in the animals subjected to a detailed neuropathological examination. The systemic NOAEL is 495 mg/kg. It should also be noted that the more highly refined hydrocarbon solvents are not dermal irritants.

Mutagenicity*In vitro* Studies

Several *in vitro* genotoxicity assays have been conducted on substances in the C₉₋₁₄ Aliphatic [2-25% Aromatics] Hydrocarbon Solvents Category. Stoddard solvent (CAS RN 8052-41-3) was tested in a standard Ames Salmonella typhimurium assay, a mouse lymphoma assay, and a mutation assay in *S. cerevisiae* both in the presence and absence of metabolic activation. There was no evidence of mutagenic activity in any of these *in vitro* studies. In addition, hydrodesulfurized kerosene (CAS RN 64742-81-0), an analogue, containing C₉-C₁₆ mixed aliphatics and 18% aromatics, did not induce sister chromatid exchanges in Chinese hamster ovary cells with and without metabolic activation. This substance was also negative in a standard Ames assay and mouse lymphoma assay.

In vivo Studies

The *in vivo* germ cell mutation was assessed in a dominant lethal inhalation study on a C₈-C₁₃ mixed aliphatic hydrocarbon solvent containing 21% aromatics (CAS RN 64742-82-1). There were no treatment-related effects under the conditions of this test. Rats were exposed via inhalation to 100 or 300 ppm. Exposure did not produce genotoxicity in the germ cells of treated male rats.

In vivo assays were conducted on members of the C₉-C₁₄ Aliphatic [2-25% Aromatics] Category. Stoddard solvent (CAS RN 8052-41-3) showed no evidence of chromosome aberrations in a rat bone marrow cytogenetic assay. In addition, Stoddard Solvent was evaluated in a mouse bone marrow micronucleus assay. There was no evidence of mutagenic activity in this test. Although the substance tested was referred to as a Stoddard Solvent and identified as having physical characteristics consistent with the category, because there was no specific information on the CAS RN for this material or carbon number range, the results are used only as additional supportive evidence.

Members of the C₉-C₁₄ Aliphatic [2-25% Aromatic] Hydrocarbon Solvents Category have shown no mutagenic activity in a number of *in vitro* bacterial and mammalian cell mutagenicity tests. In addition, they have been negative in *in vivo* mouse and rat bone marrow mutagenicity assays. This assessment does not include less refined substances that share the same CAS number or substances with a higher benzene content.

Reproductive and Developmental Toxicity

There are no studies for reproductive or developmental effects conducted with C₉-C₁₄ Aliphatic [2-25% Aromatics] Hydrocarbon Solvents Category products, however there is data available in the read-across substance hydrodesulfurized kerosene (CAS RN 64742-81-0, analogue) and JP-8 (CAS RN 8008-20-6, analogue), which is a less refined C₉-C₁₆ mixed aliphatic hydrocarbon with up to 25% aromatic content.

In the first study, male rats were given 0, 750, 1500 or 3000 mg/kg neat JP-8 (CAS RN: 8008-20-6; an aliphatic carbon range of C₈-C₁₆, aromatics <25%) daily by gavage for 70 days prior to mating with naive females to assess fertility and sperm parameters (similar to OECD TG 415). Males were allowed to mate while continuing to receive treatment. Aside from a decrement in male body weight in the 3000 mg/kg bw/day dose group, no clinical signs were observed. There were no statistical differences noted in any reproductive parameter measured. The

reproductive NOAEL = 3000 mg/kg bw/day for male rats.

In the second study, female rats were dosed (0, 325, 750, 1500 mg/kg) with neat JP-8 (CAS RN: 8008-20-6; an aliphatic carbon range of C₈-C₁₆, aromatics <25%) daily by gavage for a total of 21 weeks (90-day plus mating with naive males, gestation and lactation) in an effort to assess general toxicity, fertility and reproductive endpoints (similar to OECD TG 415). The NOAEL was 1500 mg/kg bw/day for female fertility, the highest dose tested. The NOAEL for the pup was 750 mg/kg bw/day based on a decrease in body weight which correlated with a decrease in maternal body weight at 1500 mg/kg bw/day.

A reproductive/developmental toxicity screening study was conducted in rats with an analogue substance, hydrodesulfurized kerosine (C₉-C₁₆ mixed aliphatics/aromatics with 18% aromatic content), by the dermal route of exposure. 0, 165, 330, and 494 mg/kg test material was administered daily for approximately seven weeks (pre-mating, mating and through Day 19 of gestation) to groups of 10 female rats via dermal application, at a dose volume of 1 ml/kg. Male rats also received daily administration of the same concentrations and dose volume. In addition, one "sham" treated control group (10 males and 10 females) received no test material. Exposure began two weeks prior to mating for 7 days/week. F0 males continued to be exposed daily throughout mating, female gestation and postpartum period and throughout the female necropsy period. F0 females continued to be exposed throughout the mating period and gestation days 0-19. Slight to moderate skin irritation was produced at 494 mg/kg dose group in both sexes, but no apparent maternal, reproductive or developmental toxicity was observed. No clinical signs of toxicity and no effects on body weights, food consumption, fertility or absolute organ weights were observed. Relative kidney weights were higher in male rats at the high dose. No microscopic changes in testes, epididymides or ovaries of parental animals were observed. However, skin changes associated with irritation were observed in male rats in all groups and in female rats in the high dose group. There were no differences in mean number of corpora lutea, implantation sites and live pups per litter. Pups born from treated dams showed comparable body weights and weight gain. Viability index on postpartum day 4 was >97%. No gross anomalies were observed in the pups. In summary, the NOAEL for reproductive and developmental toxicity in this study was 494 mg/kg.

A developmental inhalation toxicity study was conducted in rats with an analogue substance, hydrodesulfurized kerosine (C₉-C₁₆ mixed aliphatics/aromatics with 18% aromatics). In this study, pregnant female rats (20/dose group) were exposed to 0, 100 and 400 ppm kerosine for 6 hours per day on days 6 through 15 of gestation. Actual doses received were 106.4 ppm and 364 ppm kerosine. There were no treatment-related deaths in the study. Lung mottling was observed at necropsy in two females exposed to 100 ppm, but this was not considered to be treatment-related. No other maternal abnormalities were noted. There were no statistically significant differences between the control and treated animals with respect to clinical observations, body weights, food consumption or uterine measurements. No visible differences were observed in the pups treated with 106.4 ppm and 364 ppm kerosine compared to controls. No statistically significant differences were observed in sex ratios, number of litters, litter size, live fetuses, or fetal weights between treated and control groups. Some skeletal changes, mainly related to retarded bone ossification, were noted in both the control and treated fetuses. However, these changes have routinely been observed by this laboratory in this particular strain of rat. Neither the frequency nor character of these changes indicated an adverse effect on fetal growth and development. The NOAEL for both maternal and developmental effects was 364 ppm.

A segment II inhalation teratology study was conducted in rats with a C₈-C₁₃ mixed aliphatic/aromatic solvent containing 19% aromatics (CAS RN 8052-41-3). In this study, pregnant female rats (20/dose group) were exposed to 0, 100, and 300 ppm of test material for 6 hours per day on days 6 through 15 of gestation. This study included a chamber-exposed negative control and an acetylsalicylic acid positive control (400 mg/kg/day by gastric intubation from days 6 to 15). No mortality occurred during the study. No treatment-related physical observations were observed. Treated females gained more weight than chamber-exposed controls during the post-dosing interval. Pregnancy rates were comparable to chamber-exposed controls. The mean number of corpora lutea was significantly decreased in the 300 ppm dose group but was not considered to be a treatment-related effect since ovulation occurred prior to initiation of treatment. An increase in implantation efficiency was observed in treated groups but is not considered indicative of an adverse effect. The number of live fetuses, resorption sites and the incidence of dams with one or more resorption sites were comparable with controls. Few gross lesions were observed at necropsy but no treatment-related effect was indicated. Mean crown-rump distances (both sexes) were considered comparable between the chamber-exposed and treated groups. Although some statistically significant differences were observed in crown-rump distances between these same groups, the differences were slight with no apparent dose-response pattern and were not considered to be treatment-related. Sex ratio was unremarkable. The incidence of fetuses with ossification variations was comparable to chamber-exposed controls. No treatment-related effects were observed for external, soft tissue and skeletal evaluations of fetuses recovered from treated females. The NOAEL for maternal and developmental toxicity was 300 ppm.

A prenatal development toxicity study equivalent or similar to OECD TG 414 was conducted using groups of 26 or 27 female rats. Female rats were exposed by inhalation to white spirit (CAS RN not specified but reported in CAS RN 8052-41-3 dossier) at concentrations of 0, 600, or 2400 mg/m³ (0, 100, and 400 ppm, respectively) for 6

hours per day on days 6 to 15 of gestation. No maternal toxicity or differences in litter size or average fetal weight were seen between the groups. There were no statistical differences for skeletal variations between the control group and the 100 ppm or the 400 ppm exposed group. Based on this information, the developmental NOAEC = 400 ppm, the highest concentration tested.

The available data on potential reproductive and developmental effects of members of the C₉-C₁₄ Aliphatic [2-25% Aromatic] Hydrocarbon Solvents Category are limited to animal studies. These studies suggest that these solvents are not expected to be reproductive or developmental toxicants. This assessment does not include less refined substances that share the same CAS number or substances with a higher benzene content.

Carcinogenicity

No carcinogenicity studies for C₉₋₁₄ Aliphatic [2-25% Aromatic] Hydrocarbon Solvents Category members were located in the scientific literature.

Neurotoxicity/Neurobehavioral

Animal Models

A number of acute and subchronic inhalation neurotoxicity studies were conducted in rats exposed to white spirits and examined numerous endpoints including, but not limited to, visual discrimination performance, coordinated movement, spontaneous activity, grip strength, and peripheral nerve conduction time. In some subchronic studies, food and water intake, neuropathology evaluations, and/or reversibility of effects were also evaluated. There is no consistent evidence that chronic, low-level solvent exposure in animal models produce irreversible CNS effects.

In a short-term study with white spirit vapors containing 20 volume % aromatics, male rats were exposed to 0, 200, 400, or 800 ppm white spirit vapors for 8 hrs/day for 3 consecutive days with behavioral tests conducted immediately after exposures. This study confirmed that acute (from the first day) white spirit exposure at 200 to 800 ppm could produce transient behavioral effects. In a subchronic study, male rats were exposed to 0, 200, 400, or 800 ppm white spirit vapors for 8 hrs/day, 5 days/week for 26 weeks with behavioral tests generally conducted weekly at least 10 hours after the last daily exposure. No persistent changes in neurobehavioral functioning were observed. In addition, no exposure-related changes in brain, spinal cord, or sciatic nerve were seen in light microscopy studies.

Another study examined the behavioral effects of exposure to white spirits containing 20 volume % aromatics in adult (3-month) and aged (15-month) rats. In these experiments, rats were exposed to white spirits (0, 400, or 800 ppm) for 6 hrs/day, 5 days/week for 6 months. After an exposure-free period of two months, neurobehavioral, pathological, and neurochemical examinations were performed. There was no neurobehavioral white spirit-induced neurotoxicity. As expected, age-related differences in motor activity were detected, however, no dose-related macroscopic or histopathological changes were found. The concentration of neurotransmitters noradrenaline (NA), dopamine (DA), and 5-hydroxytryptamine (5-HT) in various brain regions and in whole brain was changed in the 400 and 800 ppm groups. The significance of changes in neurotransmitter levels is difficult to evaluate and in the absence of any pathological or functional changes, it is difficult to determine if this is toxicological, phenomenological, compensatory, or merely a random variation.

An evaluation on the effects of white spirits (20 volume % aromatics) on synaptosomal neurochemistry in rats was conducted. Rats were exposed to white spirits by inhalation (0, 400, or 800 ppm) for 6 hrs/day, 5 days/week for either 3 weeks or 6 months. Synaptosomal neurochemistry was investigated as an index of the in situ conditions in the presynaptic nerve terminal. In both dosing regimens, the relative and absolute yields of synaptosomal protein were significantly reduced in the two exposed groups. An increase in synaptosomal NA, DA, and 5-HT concentrations, high-affinity 5-HT uptake rate and uptake capacity after 3 weeks and 6 months of exposure.

In a more recent study, the effects of high aromatic versus low aromatic white spirit on rat brain 5-hydroxytryptamine (5-HT) receptor functions and synaptic remodeling were examined. In this study, male rats were exposed to 0, 400, or 800 ppm of aromatic (20 vol. % aromatics) or dearomatized white spirit (catalytically hydrogenated white spirit) in the inhaled air for 6 hours/day, 7 days/week for 3 weeks. Both types of white spirit at 800 ppm decreased the binding capacity for the 5-HT_{2A} receptor. The aromatic type decreased the equilibrium dissociation constant of the 5-HT_{2A} and 5-HT₄ receptors and the NCAM increased in the hippocampus and the NCAM/SNAP-25 ratio decreased in the entorhinal cortex at 800 ppm. There were no effects reported for the dearomatized white spirit in any brain region. Again, in the absence of any pathological or functional changes, it is difficult to determine the significance of these acute effects.

Levels of glutathione and the activity of glutamine synthetase were assayed in the brain in male rats. Rats were exposed at 5 months of age (young) or 14 months of age (aged) were exposed to 0, 400 (2290 mg/m³), or 800 ppm (4580 mg/m³) aromatic white spirit (14-21% aromatics) in air for 6 hours/day, 7 days/week for 3 weeks. Solvent inhalation significantly increased the level of glutamine synthetase within the P2 fraction of hippocampus from both young and aged rats, but cortical levels of glutamine synthetase were unaffected by treatment. The changes found in brain tissue did not reveal evidence of oxidative stress. However, the changes suggested that glial

activation was taking place.

Male rats to 575 (100 ppm), 2875 (500 ppm), or 5750 mg/m³ (1000 ppm) white spirit vapor (11.7% aromatics) for 4 to 17 weeks, 5 days a week for 6 hours/day. The neurochemical effects included a dose-dependent decrease in the cerebellar succinate dehydrogenase activity for 8 weeks while creatine kinase activity increased after 12 weeks. The dose-dependent increase in creatine kinase its activity may therefore indicate an early astroglial proliferation as the specific activity in the glial cell fraction was below or within the control range. The absence of significant demyelination is indicated by unaltered 2',3'-cyclic nucleotide 3'-phosphohydrolase, a notion also sustained by grossly unaltered acid proteinase activity involved in the degradation of myelin protein. The lowest exposure concentration in this study, 575 mg/m³ (100 ppm) represents a virtual "no effect" level for rats in the 17-week study.

Neurotoxicity endpoints following dermal exposure to white spirits containing up to 17 volume % aromatics were examined in rats. White spirits (210-260 mg) were applied to the tail 3 hr/day, 5 days/week, for 6 weeks. No change in motor conduction velocity was observed, although some electrophysiological changes occurred. Morphological analysis of the tail nerve revealed axon swelling, widening of the nodes of Ranvier, and/or demyelinated foci in the axons.

A physiologically-based pharmacokinetic (PBPK) model was developed in rats using white spirit (WS) and two marker compounds, 1,2,4-trimethyl benzene (TMB) and n-decane (NDEC). The rat models were then allometrically scaled to obtain models for inhalatory exposure for humans. The human models were validated with blood and alveolar air kinetics of TMB and NDEC, measured in human volunteers. In general, the curves predicting the blood and brain levels in rats and the blood levels in humans fit well with the measured data. A WS exposure concentration of 344 mg/m³ was predicted to result in a human brain concentration of TMB equivalent to that in the brains of rats exposed to 600 mg/m³ WS (the no effect level for acute CNS effects in rats). A similar calculation for NDEC in human brains equated to an external exposure of 721 mg/m³ WS. From these results the no effect level for acute CNS effects in humans was predicted to be in the range of 344 to 721 mg/m³. To test this PBPK model, volunteers were exposed to WS for four hours at approximately 570 mg/m³, and a number of neurobehavioral parameters were monitored. Of these, the only statistically significant finding was a small change in reaction time. Thus, it was determined that 570 mg/m³ represented either a no effect or a minimal effect level for acute CNS effects in humans. Of note, TMB was found to be the compound with the lower estimated NOEL and LOEL. This indicates that aromatic compounds might be more important than aliphatic compounds, for the acute CNS effect of WS.

Human Experience/Epidemiology - Neurological Effects

Several studies conducted were conducted to evaluate white spirit's acute (<1 hour) effects in humans, including:

- 3 to 5 minutes of exposure to 400 ppm Stoddard solvent "produced no marked effects, and subsequent evaluations it was concluded that the irritating concentration of Stoddard solvent was 370 ppm and that the low and high odor thresholds were 1.00 ppm and 120 ppm
- 15-minute inhalation produced eye irritation in one of six volunteers (ages 22 to 61 years) at 150 ppm and was reported at 470 ppm Stoddard solvent by all six volunteers
- 30 min exposure to white spirits in 15 young adult males exposed at 440-875 ppm solvent produced nausea and vertigo.

30 minute exposures to white spirits at 175 to 440 ppm at rest or during exercise demonstrated a linear relationship between alveolar and arterial concentrations of the individual solvent components; pulmonary absorption of the aliphatics ranged from 46% to 59% and that of the aromatics, 58% to 70%. Total systemic absorption was somewhat greater during exercise, but the proportion of circulating aliphatic to aromatic components decreased with increasing physical activity.

Chronic Exposure to White Spirit

The chronic toxicity of white spirits in humans focuses exclusively on retrospective epidemiology studies whose subjects were primarily workers in the paint industry in the 1960's and 80's. Many of these studies estimate inhalation exposure rather than use measured data. While it is true that white spirit was the predominant organic solvent used during this time period, other aromatic solvents (e.g. xylene and toluene) were also used. Several of the epidemiological studies acknowledge this co-exposure issue. Finally, many of these studies fail to adequately characterize the type of white spirit used. The white spirit (or Stoddard Solvent) used at the time was typically comprised of 80-85% aliphatic molecules with carbon chain lengths in the C8 to C11 range and an aromatic content of 15- 20%. While no CAS numbers are given in these reports, the following CAS numbers correspond to the type of white spirit used at the time:

Stoddard solvent - CAS number: 8052-41-3

Naphtha (petroleum), hydrodesulphurized heavy - CAS number: 64742-82-1

Solvent naphtha (petroleum), medium aliphatic - CAS number: 64742-88-7

The following reports have been determined by peer reviewed literature to be the dispositive studies on the potential for white spirits to cause chronic CNS effects in occupational workers (located in the Dossier with the CAS Number: 8052-41-3 as no CAS number was identified in the following studies).

In a cross-sectional study, 219 housepainters and 229 reinforcement workers were assessed using 8 neuropsychological tests to determine intelligence and psychomotor performance. The mean exposure period was 22 years with an estimated average level of white spirit of 40 ppm (232 mg/m³) during working hours; exposure indices made for total lifetime exposure and average exposure levels. Among painters, there were significantly increased prevalence of acute symptoms such as nausea, runny noses and malaise. Short-term visual memory and simple reaction time were affected, however, when pre-exposure intellectual level was taken into account, the painters performed more poorly only in the visual memory test. The authors conclude that the result imply that adverse psychological effects exist.

In a cross-sectional study, 101 construction painters and 31 dry wall tapers. It should be noted that due to language barriers and other factors, the control group was not used in the evaluation. All analyses were reported as internal comparisons between painter groups. The researchers grouped the painters based on their level of exposure and compared these groups to each other, however, the exposure levels used were not reported. The painters had worked as both construction and maintenance painters, jobs which use different solvent systems. The painters were assessed using 8 neuropsychological tests to determine intelligence and psychomotor performance. The subjects were interviewed to assess subjective complaints and then given a neurobehavioral examination a computer evaluated neurobehavioral evaluation system (NES). The mean exposure period was 18 years. The results of the 21 NES tests were compared by regression analysis to 4 measures of exposure, EI lifetime, EI past year, weeks of exposure in past year, and days of exposure in past year. There were only two correlations which were significant at the 0.05 level, symbol digit latency ($p = 0.04$) and digit span forward ($p = 0.03$) and both of these were for weeks of exposure in the previous year rather than for years or lifetime exposure. Among painters, dose-related increase in symptoms such as dizziness, nausea, fatigue, feeling of drunkenness and mood tensions were observed. The authors conclude that the described pattern of the occurrence of symptoms without clear evidence of function deficit is consistent with central nervous system disorder as classified by the World Health Organisation.

In a cross-sectional study, 186 construction painters were compared to each other (there was no reference group) and assessed using 9 neuropsychological tests to determine intelligence and psychomotor performance. Since solvent identity and exposure concentrations were not explicitly identified, painters were grouped based on the paint application method (e.g. spray, roll, brush, or mixed). This information on intensity and duration were combined and to create exposure indices. Stratification to 6 subgroups, according to the index of lifetime exposure intensity (LEI), was done. The mean exposure period was 12 years. Unadjusted as well as adjusted (adjustments were made by regression analysis to account for the factors age, race, education, social status and alcohol habits) was used. Significant effects were associated with lifetime exposure, but not years worked as a painter, for five mood parameters. A significant latency ($p=0.006$) in the symbol-digit test was associated with the lifetime exposure indices, but was not significant when compared to years worked as a painter.

In a cross-sectional study, 85 painters (consisting of house painters, ship painters, industrial painters, and silk screen painters) and 85 bricklayers were assessed using a neuropsychological I test battery (13 tests intellectual functions and psychomotor performance), neurological tests (motor performance, coordination, reflexes, sensitivity), and by neurophysiological examination (CT). White spirit was estimated to account for about 75% of the total solvent exposure. The mean exposure period was 32.5 years with an average daily solvent consumption (estimated as paint consumed) of 1.3 l/d = 41.4 (l/d) years. Solvent exposure was graded according to the cumulative solvent consumption. Low exp.: < 15 (l/d) years (n=22); medium exp.: 15-30 (l/d) years (n=29); high exp.: > 30 (l/d) years (n=33). Twenty-one painters had been exposed during the latest week before examination. The following odds ratios (OR) for painters compared to bricklayers were found for the development of fatigue, poor memory, difficulty in concentration, emotional lability and depression: high exp.: OR= 5.0 ($p < 0.05$) and medium exp.: OR= 3.6 ($p < 0.05$). In 9 of the 14 "don't-hold" tests, the low exposed painters performed better than the bricklayers; highly exposed painters performed worse than the brick layers in 13 out of 14 tests. Only when the medium and high exposure painters are grouped together is there a statistically significant effect in the following "don't hold" tests: symbol digit ($p = 0.0016$), and block design time ($p = 0.033$). In CT scanning, the cerebral atrophy index significantly ($p < 0.0014$) correlated with exposure. However, the CT scanner was an early model and produced poor quality images and the authors did not state whether the measurements were outside the normal range. As the exposure assessment did not consider dermal exposure or fully consider the work patterns of the

painters, for example the use of thinners was not considered. The authors conclude that the risk of developing neurological conditions seems to be increased for accumulated exposure levels above ~15 (l/d) years, corresponding to ~6 years with a daily time weighted average exposure to 100 ppm of organic solvent.

In a cross-sectional study, 135 house painters and 71 house carpenters, affiliated with their respective trade unions for at least 10 years before 1970, were assessed using a neuropsychological test battery (12 psychometric tests). Solvent identity was not determined, though the author states that in the latter part of the 1950s and in the 1960s, white spirit was the dominating solvent in alkyd-based paints; though the authors acknowledge that co-exposure to xylene and toluene also occurred. Their lifetime organic solvent exposure was evaluated through the aid of an interview. Painters were divided into three categories: low (130 exposure-limit months), intermediate (130 – 250 exposure-limit months), and high (>250 exposure-limit months). The exposure-limit was estimated to be 540 mg/m³. Twelve psychometric tests were used to evaluate the group. Only in the block design test did the painters perform worse than the carpenters; the painters' performance decreased with increasing cumulative exposure and was likely confounded by recent solvent exposure. In the majority of the psychometric tests, the carpenters (no exposure) performed worse than painters with low exposure. Painters with the largest cumulative dose tended to perform worse than the painters. The 52 painters with the heaviest cumulative exposures and 45 carpenters were examined for psychiatric diagnosis, with electroencephalography and auditory evoked potential. These three investigations showed no difference between the painters and the carpenters. The "profile of mood state" was not different between any of the groups. Magnetic resonance tomography of the brain for 15 painters and 15 age-matched carpenters was conducted; there were no statistical differences in the T1 relaxation in white matter or in ventricle width. The authors considered that the symptoms were causally related to the solvent exposures and that the cumulative exposure to solvents below 130 exposure-limit months does not lead to functionally lasting disturbance of the nervous system. The authors concluded that exposure > 250 exposure-limit months could be associated with a higher risk of symptoms as evident by decreased performance on a few psychometric tests. However, aside from the block design test, painters in the high dose only had a statistically significant decrease in the Corsi block (backward; p = 0.05) and the finger tap (maximum frequency; p = 0.04) tests.

Human Experience/Epidemiology - Other Effects

Chronic exposure to high concentrations of white spirit can produce health effects. Follicular dermatitis can develop rapidly on repeated immersion of the hands and forearms in Stoddard solvent and combined percutaneous and inhalation exposure of Stoddard solvent (at concentrations associated with nausea) has been held responsible for production of frank hepatic toxicity and jaundice. A number of fatalities due to aplastic anemia have been ascribed to occupational and consumer use of Stoddard-type solvents. Unquantified occupational exposure to white spirits (83% paraffins, 17% aromatics) for 4-months produced nausea and vomiting in workers. One individual developed aplastic anemia; bone marrow depression was confirmed on sternal biopsy. This employee died several months later of septicemia. Although approximate boiling point ranges are variably reported, none of these isolated cases of anemia reported included chemical characterization of the particular solvents.

A review of the epidemiological literature regarding exposure to white spirit with the CAS RN of 8052-41-3, 64742-82-1, and 64742-88-7 has been conducted. Similar reviews have been conducted by the International Programme on Chemical Safety (IPCS) and Scientific Committee on Occupational Exposure Limit (SCOEL). The IPCS and SCOEL evaluations were also re-evaluated by the ECHA Committee for Risk Assessment (RAC). These evaluations include retrospective epidemiological studies involving painters with long-term exposure to white spirit. Confounding factors in these studies include co-exposure to other solvents and a lack of measured exposure data. Epidemiological studies reported an increased incidence of complaints of memory impairment, fatigue, impaired concentration, irritability, dizziness, headache, anxiety and apathy. Several studies that included neuropsychological tests demonstrated impairment in some of these tests; primarily in the short-term visual memory test and in the symbol-digit test. In some studies, life-time exposure to high concentrations of white spirit was correlated with an increase incidence of effect. Using a weight of evidence approach, the RAC concluded that chronic exposure to these white spirits cause adverse central nervous system (CNS) effects that can progress in severity. These CNS effects can include deficits in psychomotor, perception, memory parameters, and disturbances in mood.

Initial Assessment for Human Health

Based on a review of the available toxicology data, members of the C9-C14 Aliphatic [2-25% Aromatic] Hydrocarbon Solvents Category have a low potential for acute toxicity by the oral, dermal, and inhalation routes of exposure. However, if aspirated into the lungs, they may cause bronchopneumonia that may be fatal within 24 hours. Solvents in this category are slight to mild skin irritants in animals, depending on the duration and conditions of exposure. However, they produce only minimal eye irritation. Prolonged or repeated exposure can lead to severe irritant dermatitis due to defatting of the skin. The available data suggest that solvents in this category are not skin sensitizers, mutagens, or carcinogenic.

A review of the epidemiological literature regarding exposure to white spirit with the CAS RN of 8052-41-3, 64742-82-1, and 64742-88-7 has been conducted by the International Programme on Chemical Safety (IPCS) and Scientific Committee on Occupational Exposure Limit (SCOEL). The IPCS and SCOEL evaluations were also re-evaluated by the ECHA Committee for Risk Assessment (RAC). These evaluations include retrospective epidemiological studies involving painters with long-term exposure to white spirit. Confounding factors in these studies include co-exposure to other solvents and a lack of measured exposure data. Epidemiological studies reported an increased incidence of complaints of memory impairment, fatigue, impaired concentration, irritability, dizziness, headache, anxiety and apathy. Several studies that included neuropsychological tests demonstrated impairment in some of these tests; primarily in the short-term visual memory test and in the symbol-digit test. In some studies, life-time exposure to high concentrations of white spirit was correlated with an increase incidence of effect. Using a weight of evidence approach, the RAC concluded that chronic exposure to these white spirits cause adverse central nervous system (CNS) effects that can progress in severity. These CNS effects can include deficits in psychomotor, perception, memory parameters, and disturbances in mood.

The C₉₋₁₄ Aliphatic [2-25% Aromatic] Hydrocarbon Solvents Category substances may possess properties indicating hazard for human health (aspiration and possible skin defatting with repeated exposure). A review of the epidemiological literature indicates prolonged and repeated exposure to high concentrations of white spirits with the CAS RN 8052-41-3, 64742-82-1, and 64742-88-7 are considered to have chronic adverse effects on the central nervous system. Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Environment

Members of the C₉-C₁₄ Aliphatic [2-25% aromatics] Hydrocarbon Solvents Category have the potential to volatilize from surface waters, based on Henry's Law constants (HLC) representing volatility for category members that range from 46 to 9.7×10^5 Pa-m³/mole (at 25°C). In the air, category members have the potential to rapidly degrade through indirect photolytic processes mediated primarily by hydroxyl radicals ([•]OH) with calculated degradation half-lives ranging from 0.42 to 1.10 days or 10.8 to 26.4 hours based on a 12-hr day and an [•]OH concentration of 1.5×10^6 [•]OH/cm³. Aqueous photolysis and hydrolysis will not contribute to the transformation of category chemical constituents in aquatic environments because they are either poorly or not susceptible to these reactions. These chemicals are unlikely to degrade by hydrolysis as they lack a functional group that is hydrolytically reactive.

Mackay Level III modeling indicates that category member constituents partition mostly to the soil and water compartments rather than air compartment when an equal emission rate (1000 kg/hr) to the air, water, and soil compartment is assumed. When release occurs only to either the air, water, or soil compartment, constituents are indicated in the modeling to partition largely to the compartment to which they are released.

When released primarily to the air compartment, the primary mode of removal would be via indirect photodegradation. Although the substances and their chemical constituents demonstrate a range of water solubility with most constituents having relatively low solubility, wet deposition of category chemical constituents is not likely to play a significant role in their atmospheric fate because of their rapid photodegradation. Volatilization to the air can contribute to the loss of category chemical constituents from aqueous and terrestrial habitats.

Determining the biodegradation potential of UVCBs can be challenging. The result for each multi-constituent substance (UVCB) characterizes the biodegradability of that substance as a whole, but it does not suggest that each constituent of the UVCB is equally biodegradable. As with all ready biodegradation test guidelines, the test system and study design used with these substances (OECD TG 301F) is not capable of distinguishing the relative contribution of the substances' constituents to the total biodegradation measured (constituents with higher branching/cyclic structures may degrade to a lesser extent than linear and less branched structures). The n-paraffin constituents have the potential to biodegrade rapidly based on results that support their characterization as readily biodegradable (80 to 83% in 28 days). In comparison, iso-paraffinic constituents are expected to demonstrate a slower rate of biodegradation based on results for an analogue isoparaffinic substance, which was shown not to be readily biodegradable, but did demonstrate a moderate extent of biodegradation (41%) over an extended period of time (41 days). A multi-constituent member of the category, a C₉₋₁₃ mixed aliphatics and aromatics (19% aromatic) substance (CAS RN. 64742-82-1), biodegraded to an extent of 75% after 28 days and was readily biodegradable based on a study that used the OECD 301F test guideline. The overall conclusion for C₉-C₁₄ Aliphatic [2-25% aromatics] Hydrocarbon Solvents Category members: some components of the category members (e.g. n-paraffins) are readily biodegradable, but some (tertiary and quaternary branched components) components may be less biodegradable, not meeting the readily biodegradable criteria.

Category members have a potential to bioaccumulate, based on calculated log BCF values for constituents that range from 2.15 to 4.06, and calculated BCF values of 142 to 11,430 L/kg wet-weight that take into account

biotransformation of the chemicals in fish tissue. Results of BCF studies for several constituent chemicals of category members are also available. Reported BCF ranges for n-dodecane of 240 to 2870 l/kg wet weight, using carp and rainbow trout. Also reported are a BCF value for iso-nonanes of 1468 l/kg wet weight with carp. Additional studies for other constituent chemicals were reported for trimethylbenzene and 1,2,3,4-tetrahydronaphthalene, with values of 154 to 783 (carp and trout), and 147 to 536 l/kg (carp), respectively. Determining the bioaccumulation potential of UVCBs can be challenging. BCF values for n-paraffins, iso-paraffins, and cycloparaffins can be different due to differences in metabolism. Constituents with higher branching/cyclic structures may therefore bioaccumulate to a greater extent than linear and less branched structures. It should be noted that for highly lipophilic constituents uptake through the diet may exceed the direct uptake through water.

Although limited data are available, it may be shown that category members are expected to exhibit acute toxic effects to aquatic organisms in the range of 1 to 100 mg/L, based on nominal loading levels, with three studies with category members and three studies with an analogue substance. A chronic study with *Daphnia magna* and a substance in the C₉-C₁₃ range (C₉₋₁₃ mixed aliphatics and aromatics (19% aromatic)) indicated a 21-day NOEL of 0.28 mg/L, based on nominal loading levels. Additional chronic work using fish with the analogue JP-8 (C₈-C₁₆ range) indicate a NOEC = 1 mg/l based on measured concentration for a warm water fish, and a NOEC <1.4 mg/l (LOEC = 1.4 mg/l) for a cold water fish. Chronic studies using *Daphnia magna* with analogue substances in the C10-C12 isoparaffinic range (CAS RN 90622-57-4) indicated an effect (NOEC = 0.025mg/l, based on measured concentration), but isoparaffins in the C11-C13 range showed no observed effects up to 1 mg/L (highest nominal loading tested) for CAS RN: 90622-58-5. QSAR values for the representative constituents (listed on page 4) were generated using EPISuite version 4.10. Acute 96-hour fish toxicity ranged from <0.01 to 3.4 mg/l. Acute 48-hour daphnid toxicity ranged from <0.01 to 2.4 mg/l. And acute 96-hour algae toxicity ranged from <0.01 to 2.3 mg/l. The model indicated that water solubility of the alkanes and isoalkanes may be too low to give rise to acute aquatic toxicity, but the aromatics are expected to have sufficient water solubility to contribute to the acute aquatic toxicity. Calculated values for the three representative aromatic constituents, which are believed to drive the acute aquatic toxicity, ranged from 1.4 to 3.4 mg/l for fish, 1.1 to 2.4 mg/l for daphnids, and 1.3 to 2.3 mg/l for algae.

Table 5 - Selected data that characterize the acute aquatic toxicity of members of the C₉-C₁₄ Aliphatic Hydrocarbon Solvents [2-25% aromatics] Category

Substance (CAS RN)	Freshwater Fish 96-hr (mg/l)	Freshwater Invertebrate (<i>Daphnia magna</i>) 48-hr (mg/l)	Freshwater Alga (<i>Pseudokirchneriella subcapitata</i>) 72-hr (mg/l)
Stoddard solvent (8052-41-3) Hydrocarbons, C9-C13 (aromatics 19%)		96-hr LL ₅₀ = 3.5 (<i>Chaetogammarus. marinus</i>)	EbL ₅₀ = 2.5 EbC ₅₀ = 0.58 ErL ₅₀ = 5.5 ErC ₅₀ = 1.2 NOELR(b,r) = 0.76 NOEC(b,r) = 0.16
Hydrocarbons, C8-C12, n-alkanes, isoalkanes, cyclics, aromatics (2- 25%) CAS RN 64742-82-1	LL ₅₀ = 41.4 LC ₅₀ = 2.5	3 - 10 (EL ₅₀)	1 - 3 (EL ₅₀) (growth rate) 1 - 3 (EL ₅₀) (biomass) NOEL = 1.0 (growth rate and biomass)
Kerosine, hydrodesulphurized, C8- C15, aromatics (2-25%) CAS RN 64742-81-0 (read-across)	LL ₅₀ = 25 NOEL = 6.8	EL ₅₀ = 1.4 NOEL = 0.3	IrL ₅₀ = 8.3 IbL ₅₀ = 15 NOEL(b,r) = 4.0 (growth rate and biomass)

Table 6. Chronic aquatic toxicity data for C₉₋₁₄ Aliphatic [2-25% Aromatic] Hydrocarbons Solvents Category members

Test Material (CAS #)	Freshwater Fish (mg/L)	Freshwater Invertebrate (<i>Daphnia magna</i>) 21-day (mg/L)	Freshwater alga (<i>Pseudokirchneriella subcapitata</i>) 96-hr (mg/L)
Stoddard solvent (8052-41-3) Hydrocarbons, C ₉ -C ₁₃ (aromatics 19%)		EiL ₅₀ = 1.62 EiC ₅₀ = 0.43 ErepL ₅₀ = 1.19 ErepC ₅₀ = 0.33 NOELRig = 1.4 NOECig = 0.37 NOELRrep = 0.28 NOECrep = 0.10	NOELR(b,r) = 0.76 NOEC(b,r) = 0.16
JP-8 C ₈ -C ₁₆ , aromatics (25%) CAS RN 8008-20-6	NOEC = 1.0 (<i>J. floridae</i>) NOEC < 1.4 LOEC = 1.4 (<i>O. mykiss</i>)		
Hydrocarbons, C ₁₀ -C ₁₂ , isoalkanes, <2% aromatics CAS RN 90622-57-4		NOECrep = 0.025	
Hydrocarbons, C ₁₁ -C ₁₃ , isoalkanes, <2% aromatics CAS RN 90622-58-5		NOELrep = 1	

i Immobilization
rep Reproduction
ig Immobilization and growth
b Biomass
r Growth rate

Environment Conclusion

Chemicals in this category possess properties indicating a potential hazard for the environment (acute toxicity for fish, invertebrates, and algae (in the range of 1 to 100 mg/l) based on nominal loadings; available chronic toxicity data for invertebrates, fish, and algae are in the range of 0.1 – 1.0 mg/l, based on nominal loadings, not excluding that some members of the category might have a toxicity below 0.1mg/l. Category members have a potential to bioaccumulate. Some components of the category members (e.g. n-paraffins) are readily biodegradable, but some components (tertiary and quaternary branched components) may be less biodegradable, not meeting the readily biodegradable criteria. Adequate screening-level data are available to characterize the environmental hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Production/Use/Exposure

Production

As reported to the U.S. Environmental Protection Agency for the year 2006, companies produced or imported the following volumes of C₉-C₁₄ Aliphatic [2-25% aromatic] hydrocarbon solvents. Note that the Volume Survey is overall volume for the entire individual CAS RN and includes fuels, solvents and all other uses. It is expected that the solvent portion of the volume for the C₉-C₁₄ Aliphatic [2-25% aromatic] Hydrocarbon Solvents Category would be significantly lower than the aggregate production volume:

- Stoddard solvent, CAS RN 8052-41-3: 100 to <500 million pounds (<227000 tonnes)
- Kerosine, petroleum, hydrodesulfurized , CAS RN 64742-81-0: 1 billion lbs and greater (454000 tonnes)
- Naphtha, petroleum, hydrodesulfurized heavy, CAS RN 64742-82-1: 1 billion lbs and greater (454000 tonnes)
- Solvent naphtha, petroleum, medium aliphatic, CAS RN 64742-88-7: 1 billion lbs and greater (454000 tonnes)

Production of these C₉-C₁₄ aliphatic [2-25% aromatics] hydrocarbon solvents is differentiated from other refinery substances such as gasoline and diesel fuel by including additional processing steps leading to finished substances with narrow distillation ranges, removal of sulfur- and nitrogen-containing compounds, and low color. The aromatic content in these substances is controlled to meet specific performance characteristics. These additional refining steps provide these hydrocarbon solvents with qualities suitable for applications in consumer goods.

Use

Hydrocarbon solvents in the C₉-C₁₄ range with aromatic content between 2 and 25% are considered to have a medium rate of evaporation and have a number of applications, including auto motive products, paints and coatings, degreasers, wood/floor wax, diluent in asphalt applications, and as a pesticide carrier base. The predominant commercial uses of C₉-C₁₄ Aliphatic [2-25% aromatic] hydrocarbon solvent substances are in paints and coatings, industrial solvents.

Exposure

The sources for potential environmental exposure to C₉-C₁₄ Aliphatic [2-25% aromatic] Hydrocarbon Solvents Category substances could include releases from chemical and petroleum manufacturing/processing facilities, releases from facilities that use C₉-C₁₄ Aliphatic [2-25% aromatic] Category substances, and releases from industrial products that include C₉-C₁₄ Aliphatic [2-25% aromatic] Category substances.

The occupational exposure in a manufacturing facility would be expected to be relatively low because the process, storage and handling operations are confined by system containment.

Consumers in the general population are expected to be limited due to its infrequent and short-term exposures.

SIDS INITIAL ASSESSMENT PROFILE

Chemical Category	C₁₀-C₁₃ Aromatic Hydrocarbon Solvents Category								
CAS Numbers and Chemical Names	<table border="0"> <thead> <tr> <th data-bbox="512 439 1082 472">Substance Name (Synonyms, Common Names)</th> <th data-bbox="1150 439 1321 472">CAS Number</th> </tr> </thead> <tbody> <tr> <td data-bbox="512 477 1082 689">Solvent naphtha, (petroleum), heavy aromatic Hydrocarbons, C₁₀, aromatics, >1% naphthalene Hydrocarbons, C₁₀, aromatics, <1% naphthalene Hydrocarbons, C₁₀-C₁₃, aromatics, >1% naphthalene Hydrocarbons, C₁₀-C₁₃, aromatics, <1% naphthalene C₉₋₁₀ Aromatics, Predominantly C₉-C₁₀ Alkylbenzenes and Naphthalene</td> <td data-bbox="1193 477 1321 510">64742-94-5</td> </tr> <tr> <td data-bbox="512 723 1082 757">Aromatics Hydrocarbons, C₉ – 11</td> <td data-bbox="1193 723 1321 757">70693-06-0</td> </tr> <tr> <td data-bbox="512 790 1082 869">Naphthalene, methyl- (Mixed) Hydrocarbons, C₁₁, aromatics</td> <td data-bbox="1201 790 1321 824">1321-94-4</td> </tr> </tbody> </table>	Substance Name (Synonyms, Common Names)	CAS Number	Solvent naphtha, (petroleum), heavy aromatic Hydrocarbons, C ₁₀ , aromatics, >1% naphthalene Hydrocarbons, C ₁₀ , aromatics, <1% naphthalene Hydrocarbons, C ₁₀ -C ₁₃ , aromatics, >1% naphthalene Hydrocarbons, C ₁₀ -C ₁₃ , aromatics, <1% naphthalene C ₉₋₁₀ Aromatics, Predominantly C ₉ -C ₁₀ Alkylbenzenes and Naphthalene	64742-94-5	Aromatics Hydrocarbons, C ₉ – 11	70693-06-0	Naphthalene, methyl- (Mixed) Hydrocarbons, C ₁₁ , aromatics	1321-94-4
Substance Name (Synonyms, Common Names)	CAS Number								
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Aromatics Hydrocarbons, C ₉ – 11	70693-06-0								
Naphthalene, methyl- (Mixed) Hydrocarbons, C ₁₁ , aromatics	1321-94-4								
CAS Numbers with Structural Formula	<table border="0"> <thead> <tr> <th data-bbox="512 891 767 925">Structural Formula</th> <th data-bbox="1150 891 1321 925">CAS Number</th> </tr> </thead> <tbody> <tr> <td data-bbox="512 958 1082 1171">UVCB substances containing aromatic (one-ring or two-ring) molecules of carbon and hydrogen. They consist of C₉-C₁₆ aromatic hydrocarbons having carbon numbers predominantly (approximately 80%) in the C₁₀ to C₁₃ range. The category only includes substances that have boiling ranges falling within approximately ~182 °C to ~288°C.</td> <td data-bbox="1193 1144 1321 1205">64742-94-5 70693-06-0</td> </tr> </tbody> </table>	Structural Formula	CAS Number	UVCB substances containing aromatic (one-ring or two-ring) molecules of carbon and hydrogen. They consist of C ₉ -C ₁₆ aromatic hydrocarbons having carbon numbers predominantly (approximately 80%) in the C ₁₀ to C ₁₃ range. The category only includes substances that have boiling ranges falling within approximately ~182 °C to ~288°C.	64742-94-5 70693-06-0				
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	<p>The category has been defined for members with specific constituents/component profiles or composition as outlined in the full SIDS Initial Assessment Report and the SIDS Dossiers. The carbon number range of category members identifies at minimum approximately 80% of the chemical constituents in the substance. There may be instances where a category member could fall slightly below the 80% carbon number range. In these situations the justification for keeping those members in the C₁₀-13 aromatics category is because their composition allows their evaluation within this category.</p> <p>The substances in this category contain >98% aromatic hydrocarbons. The composition of the C₁₀-C₁₃ Aromatic Hydrocarbon Solvents Category (CAS Registry Number (RN) 64742-94-5, 70693-06-0 and 1321-94-4) will vary somewhat, but generally contains aromatic (one- or 2-ring) molecules composed of carbon and hydrogen, predominantly in the C₁₀-C₁₃ range. No molecules with three or more rings are present. These substances may contain traces of benzene (<1 ppmv; <0.0001%), sulphur (<10 ppmv; <0.001%), and nitrogen (<10 ppmv; <0.001%).</p> <p>As complex hydrocarbon substances, some of the category members share CAS RNs with some petroleum process streams.</p> <p>This assessment only applies to CAS RNs with the constituent profiles and compositions described within this assessment. Consequently, the conclusions of this assessment do not apply to petroleum process streams with the same CAS number as those belonging to the C₁₀-C₁₃ Aromatic Hydrocarbon Solvents Category.</p>								

Identification of chemicals defined by processing procedures	Typical Carbon Number Range (%)					
	C9	C10	C11	C12	C13	C14-C16
Hydrocarbons C10, aromatics, >1% naphthalene (CAS RN 64742-94-5) Boiling Range ~ 185-205°C	~9	~77	~14	-	-	-
Hydrocarbons, C10, aromatics, <1% naphthalene (CAS RN 64742-94-5) Boiling Range ~185-200°C	~10	~81	~9	-	-	-
C ₉₋₁₀ Aromatics, Predominantly C ₉ -C ₁₀ Alkylbenzenes and Naphthalene (CAS RN 64742-94-5) Boiling Range ~179-214°C	~ 22	~78	-	-	-	-
Aromatics Hydrocarbons, C ₉ – C ₁₁ (CAS RN 70693-06-0) Boiling Range~182-188°C	≤10	≤90	<2			
Hydrocarbons, C ₁₀ -C ₁₃ , aromatics, >1% naphthalene (CAS RN 64742-94-5) Boiling Range ~ 230-285°C	-	~10	~36	~26	~17	~11
Hydrocarbons, C ₁₀ -C ₁₃ , aromatics, <1% naphthalene (CAS RN 64742-94-5) Boiling Range ~ 235-275°C	-	< 1	~39	~22	~15	~23
Hydrocarbons, C11, aromatics (CAS RN1321-94-4) Boiling Range ~238-242°C	-	-	~100	-	-	-

SUMMARY CONCLUSIONS OF THE SIAR

Category Justification

The C₁₀ to C₁₃ Aromatic Hydrocarbon Solvents Category is comprised of aromatic hydrocarbons composed of alkylated benzenes and alkylated naphthalenes, with a predominant (approximately 80%) carbon number in the range of C₁₀ to C₁₃. A few products in this category may contain approximately 10% naphthalene. The multi-constituent category members are also referred to as chemical substances of unknown or variable composition, complex reaction products or biological materials (UVCBs), a term that is used to characterize these members in the European Union REACH (Registration, Evaluation, and Authorization of Chemicals) legislation and the USEPA Toxic Substances Control Act (TSCA) Inventory Representation Guidance.

Assignment of CAS RNs to hydrocarbon substances is generally based on a hierarchy of considerations including hydrocarbon type(s), carbon number and/or range, distillation temperature and/or range, and last processing step in the production process. One documented source of criteria for assignment of CAS RNs for multi-constituent hydrocarbon substances is provided by the U.S. EPA on proceedings for development of the TSCA inventory for U.S. chemicals. These criteria, however, may allow the same CAS RN to be applied to differing hydrocarbon and petroleum-derived substances (hydrocarbon streams) with somewhat different compositions and applications (e.g., solvents, fuels, lubricants, etc.). Similarly, different CAS RNs can be applied to substances of similar composition and application.

In the case of the C₁₀-C₁₃ Aromatic Hydrocarbon Solvents Category, the three CAS RNs are assigned to commercial hydrocarbon solvents, whose composition and commercial applications provide the primary justification for evaluating these substances as a category. Further, the existing toxicology data show that substances in this category follow a similar mode of action (non-polar narcosis) and have similar orders of aquatic and mammalian toxicity, which further supports the grouping of these substances into a category. The toxicity studies representing the C₁₀-C₁₃ Aromatic Hydrocarbon Solvents Category were conducted on products in commerce that are multi-constituent substances. Most of the studies used to characterize the toxicity of this category are taken from the Dossier for CAS RN 64742-94-5. Although the substance studied, (hydrocarbons, C₁₀-C₁₃, aromatics, >1% naphthalene) contains a lower percentage of C₁₄ to C₁₆ constituents than the low naphthalene substance (hydrocarbons, C₁₀-C₁₃, aromatics, <1% naphthalene), water solubility limitations of these constituents will minimize their bioavailability and ability to cause additional adverse effects. Therefore, the results of the studies reported should adequately characterize the potential acute aquatic toxicity of this carbon number range.

Additionally, data from the C₉ Aromatic Hydrocarbon Solvents Category for a C₉ aromatic UVCB has been included, where appropriate, to further support the conclusions of this submission for select human health and physical-chemical endpoints. The use of C₉ Hydrocarbon Solvent category data is justified since some of the UVCB substances in the C₁₀-C₁₃ Hydrocarbon Solvents Category may contain as much as 22% C₉ aromatic hydrocarbons.

Data has also been used from the 2-Methylnaphthalene (CAS RN 91-57-6) submission, where appropriate, to further support the conclusions with regard to methylnaphthalene (CAS RN 1321-94-4).

Category Member Conventional Naming

The naming convention used to identify category members is based on their general compositions (predominant carbon number range and hydrocarbon type, specifically aromatics) and is intended to identify hydrocarbon solvent substances manufactured by various companies that are sufficiently similar with regard to composition such that their physical and biological properties would exhibit similar if not identical values. The naming convention as applied to hydrocarbon solvents was seen as a means to provide an immediate understanding of the type of solvent and its composition to allow for an accurate grouping of hydrocarbon substances within categories. As UVCBs, some of the hydrocarbon solvent category members share CAS RNs with some petroleum process streams, which have broader boiling ranges and consequently are compositionally more complex.

Production of C₁₀-C₁₃ aromatics hydrocarbon solvents is differentiated from other refinery streams such as gasoline and diesel fuel by additional processing steps leading to finished substances with narrower distillation ranges, removal of sulfur- and nitrogen-containing compounds, and low color. Category members (CAS RN 64742-94-5 and CAS RN 70693-06-0) meet the criteria for UVCB substances because they contain a relatively large number of discrete chemical constituents and the exact composition of some of the constituent chemicals may be unknown. However, Methyl Naphthalene(s) (CAS Registry Number (RN) 1321-94-4) is recognized by TSCA as a Class 1 substance with a specific molecular formula and so it is not a UVCB. It should also be noted that CAS RN 1321-94-4 is no longer offered commercially as a hydrocarbon solvent by those manufacturers

represented in the group sponsoring this category. The general naming convention guidance was developed and used for category members as follows:

"Hydrocarbons", the first part of the name, recognizes the specific chemical class.

The carbon number range typically identifies at least 80% of the chemical constituents in the substance.

The structures are identified by the types of hydrocarbons present: n-paraffins (n-alkanes), iso-paraffins (isoalkanes), cyclic-paraffins or naphthenics (cyclics), and aromatics. The first three are mentioned when present in the substance at a level between 10 and 80%. Aromatics will be indicated as per HPV category and when present as a smaller fraction, identified at levels less than or greater than 2%.

Components with specific toxicology or classification will be mentioned, using the classification cut-off as an indication level (according to EU DSD (Dangerous Substances Directive) and GHS (Global Harmonized System of Classification and Labeling of Chemicals) guidance).

Applying this guidance results in the following names for UVCB members that could be considered as members of the C₁₀-C₁₃ Aromatic Hydrocarbon Solvents Category (not all of these substances may have data available but are otherwise characterized with data for at least one category member or analog):

Hydrocarbons, C₁₀, aromatics, >1% naphthalene
Hydrocarbons, C₁₀, aromatics, <1% naphthalene
Aromatic Hydrocarbons, C₉-C₁₁
Hydrocarbons, C₁₀-C₁₃, aromatics, >1% naphthalene
Hydrocarbons, C₁₀-C₁₃, aromatics, <1% naphthalene
Hydrocarbons, C₁₁, aromatics

Analog Identification

In addition to the available physical and biological data for substances in this category, data for the following analogs are also presented, as necessary, to support the characterization of selected endpoints:

CAS RN 90-12-0; 1-methylnaphthalene
CAS RN 91-57-6; 2-methylnaphthalene
CAS RN 95-63-6; 1,2,4-trimethylbenzene
CAS RN 25550-14-5; 1-ethyl-3-methylbenzene
CAS RN 64742-95-6; Hydrocarbons, C₉, aromatics

The five analog substances represent specific isomers of the more complex stream. The analog substances are hydrocarbon constituents that fall within the carbon range of the category members. By a similar mode of toxic action, non-polar narcosis, data from these substances can be considered as read across when assessing the potential toxicity of the category members. Indeed, when the acute aquatic toxicity data for the read-across candidates are compared to toxicities of all category members, they fall within a similar range of toxicity, which supports their use in the overall assessment of category members.

Substances in the C₁₀-C₁₃ Aromatic Hydrocarbon Solvents Category can be composed of a single chemical or a range of hydrocarbons that can include aromatic structures that fall predominantly within a C number range of 10 to 13. As a result, some category member's physicochemical properties can be characterized by a range of values as a function of composition because a single value is not possible. For example, a multi-constituent hydrocarbon substance will not exhibit a single P_{ow} value, but rather a range based on its composition. This would be the case regardless of whether the data were measured using a standard testing procedure or calculated based on the individual constituent chemicals.

For some properties, the value range is based on a series of representative hydrocarbons that were selected by industry, based on hydrocarbon process (distillation) knowledge, to accurately characterize category members. The hydrocarbons selected (see the following list) include alkylated benzenes and alkylated naphthalenes from C₁₀-C₁₆. Alkylated benzenes and alkylated naphthalenes were selected as representative chemicals since this is the compositional make-up of the UVCB substances in this category. Chemicals with single multi-carbon chains and/or multiple methyl groups were chosen to provide the most comprehensive range of expected values.

<u>Chemical Name</u>	<u>CAS RN</u>
1,2,3,5-tetra-methylbenzene	527-53-7
1-methyl-2-n-propylbenzene	1074-17-5
1,2-dimethyl-4-ethylbenzene	934-80-5
naphthalene	91-20-3
2-ethyl-naphthalene	939-27-5
1,3-dimethyl-naphthalene	575-41-7
2,6-dimethyl-naphthalene	581-42-0
4-methyl biphenyl	644-08-6
2-butyl-naphthalene	1134-62-9
1,2,3,4-tetramethyl-naphthalene	n/a
1-pentyl-naphthalene	n/a
1,2,3,4,5-pentamethyl-naphthalene	n/a
1-hexyl-naphthalene	2876-53-1
1,2,3,4,5,7-hexamethyl-naphthalene	n/a

n/a = not available

Physico-chemical Properties

The members of the C₁₀-C₁₃ Aromatic Hydrocarbon Solvents Category are liquids at room temperature. Value ranges are based on a series of 14 representative hydrocarbons that were selected by industry, based on hydrocarbon process (distillation) knowledge, to accurately characterize category members. The melting point values range from -66.9 to 112 °C (measured; this applies to constituents in the C₁₀-C₁₃ range; as well as category members with constituents ranging up to C₁₆). The boiling points range from ~182°C to ~288°C (359°F to 554°F) (measured; for category members with constituents in the C₁₆ range the boiling point range could extend to 326°C). The vapor pressure values range from 0.003 to 1.33 hPa at 25 °C (calculated; this applies to constituents in the C₁₀-C₁₃ range; for category members with constituents ranging up to C₁₆ the vapor pressure range could extend down to 0.0003 hPa). Water solubility values range from 1.7 to 31.9 mg/L (calculated; this applies to constituents in the C₁₀-C₁₃ range; for category members with constituents ranging up to C₁₆ the water solubility range could extend down to 0.12 mg/L) with a relative density range of 0.68 to 0.78 g/cm³ (measured; this applies to constituents in the C₉-C₁₆ range). The log P_{ow} values for the category members range from 3.2 to 4.5 (calculated; this applies to constituents in the C₁₀-C₁₃ range; for category members with constituents ranging up to C₁₆ the log P_{ow} values range could extend to 6.45).

Human Health

Toxicokinetics, Metabolism, and Distribution

There are no metabolism studies specifically for the C₁₀-C₁₃ Aromatic Hydrocarbon Solvents Category. However, several short chain alkyl naphthalene analog hydrocarbon constituents (1-methylnaphthalene, 2-methylnaphthalene) and naphthalene fall within the carbon number range of this category. Due to the structural similarity of these molecules to other constituents of the C₁₀-C₁₃ Aromatics Hydrocarbon Solvents, it seems reasonable to assume that the solvents would have toxicokinetic properties similar to those of these constituents. Absorption rates were studied for naphthalene and the methyl naphthalenes components (1-methyl naphthalene and 2-methylnaphthalene) in a study using human volunteers and were reported to be approximately 300-500 ng/cm²/hr. The potential for systemic doses from inhalation exposures is unknown.

C₁₀-C₁₃ Aromatic Hydrocarbon Solvents Category products are typically metabolized by side chain oxidation to alcohol and carboxylic acid derivatives. In guinea pigs dosed orally, the methylnaphthalenes are preferentially metabolized by side chain oxidation to form naphthoic acids, although ring oxidation can also occur. These metabolites can be glucuronidated and excreted in the urine or further metabolized before being excreted. The majority of the metabolites are excreted in the urine and to a lower extent, in the feces. Excretion is rapid with the majority of the elimination occurring within the first 24 hours of exposure. Even though the material has the potential to be rapidly excreted, it may not be excluded that the substance may have a slight potential to bioaccumulate in the tissues (e.g., brain, liver, kidney and fat tissues).

Acute Toxicity

The available acute toxicity data demonstrate that hydrocarbon solvent substances tested in the C₁₀-C₁₃ Aromatics Hydrocarbon Solvents Category, containing alkylbenzenes and alkylnaphthalenes, show toxicity by the single dose oral route in rats ranged from 2.7 (CAS RN 1321-94-4; mixed methyl naphthalenes) to 7.0 g/kg bwt (CAS RN 64742-94-5; C₁₀-13 aromatics, >1% naphthalene). For the CAS RN 1321-94-4; mixed methyl naphthalenes

product, a single oral dose of undiluted test material at 3162 mg/kg bw resulted in death for 5 of 5 male rats and death for 4 of 5 females; at 5000 mg/kg bw, death for 4 of 5 male rats (3 on day 1 and 1 on day 3) and death for 4 of 5 females (4 on day 1). At the 2000 mg/kg bw, 0 of 5 males and 1 of 5 females died (2 days after dosing). The surviving animals were observed for 14 days after the day of dosing. Common signs of systemic toxicity noted in all dose groups were hunched posture, lethargy, pilo-erection and decreased respiratory rate with additional signs of ataxia and labored respiration. Isolated incidents of red/brown stains around the eyes and/or snout, increased salivation, and loss of righting reflex were noted. Common abnormalities noted at necropsy of animals that died during the study were hemorrhagic lungs, dark liver, dark kidneys, sloughing of the non-glandular epithelium of the stomach and hemorrhage or severe hemorrhage of the gastric mucosa. No organ abnormalities were noted at necropsy of animals that were killed at the end of the study,

For the CAS RN 64742-94-5; C₁₀-C₁₃ aromatics, >1% naphthalene study, five rats per sex per dose were given a single dose of 0.5, 1.5, 5.0 g/kg bwt. All animals in the 0.5 g/kg and 1.5 g/kg bwt dose groups survived to study termination and displayed an increase in body weight over their Day 0 values. No observable abnormalities were noted for the majority of the animals. Single incidences of dry red material around the penis, urine and ano-genital staining, and oral and ocular discharge were noted. Soft stool was noted in 1 female in the 0.5 g/kg dose group at 6 hours and in 1 male animal in the 1.5 g/kg dose group from 1 hour to day 1. There were no observable abnormalities for all animals at postmortem examination. For the 5.0 g/kg bwt dose group, 5 animals died prior to scheduled termination (2 males on Day 2, 2 females on Day 3 and 1 female on Day 4). Surviving animals displayed an increase in body weight over their Day 0 values. The most frequently noted clinical observation included ano-genital and urine staining, oral and nasal discharges, small amount of stool, soft stool, hypoactivity and decrease in food consumption. Postmortem examination of animals which succumbed revealed a high incidence of distension and abnormal contents of the stomach and small intestines, staining of the fur and lung discoloration. Also noted at a lower incidence were liver discoloration, distension and abnormal contents of the cecum and urinary bladder. Four of the 5 survivors in this group displayed no observable abnormalities, while the remaining animal exhibited alopecia.

A single dose acute dermal toxicity study resulted in an LD₅₀ of 2.0 g/kg for CAS RN 1321-94-4 mixed methyl naphthalenes (14 day observation duration). The study consisted of a group of ten fasted rats (five males and five females) given a single 24-hour, semi-occluded dermal application of undiluted material to intact skin at a dose level of 2000 mg/kg bw. No deaths occurred in this study. No signs of systemic toxicity or skin irritation were noted. Body weight changes were not impacted significantly. No abnormalities were noted at necropsy. A single dose acute dermal toxicity study resulted in an LD₅₀ of 2.0 g/kg for the CAS RN 64742-94-5; C₁₀-C₁₃ aromatics, >1% naphthalene product. A group of rabbits (5 animals per sex) were given a single dermal application of test material. The exposure site was occluded for 24 hours. All animals survived to study termination. There were no treatment-related clinical signs. All animals gained weight over their initial Day 0 values. Topical application of test material elicited dermal irritation in all animals. Erythema, ranging from well-defined to moderate/severe were noted in all animals on Day 1. Edema ranging from very slight to moderate was observed on all animals on Day 1. Edema was not observed in any animal on Day 7. At postmortem examination, there was no evidence of macroscopic abnormalities. Four males and 2 females were noted with desquamation and/or eschar on the dose site which was consistent with their inlife dermal observations.

The available acute toxicity data demonstrate that hydrocarbon solvent substances tested in the C₁₀-C₁₃ Aromatics Hydrocarbon Solvents Category, containing alkylbenzenes and alkylnaphthalenes, show toxicity by the oral route of in rats ranged from 2.7 (CAS RN 1321-94-4; mixed methyl naphthalenes) to 7.0 g/kg (CAS RN 64742-94-5; C₁₀-C₁₃ aromatics, >1% naphthalene). Single dose 14 day duration acute dermal toxicity results were LD₅₀s of 2.0 g/kg for CAS RN 1321-94-4 mixed methyl naphthalenes and CAS RN 64742-94-5; C₁₀-C₁₃ aromatics, >1% naphthalene.

Acute single 4- hour exposure, inhalation LC₅₀ values ranged from >169 to >4688 mg/m³. In most cases the values were dependent on the inherent physicochemical properties of the test material, e.g., volatility, thus limiting the study design to the maximum achievable saturated vapor concentration. In rats, exposed to CAS RN 64742-94-5; C₁₀-C₁₃ aromatics, >1% naphthalene, the value was > 169 and 4778 mg/m³. Even under conditions that resulted in exposure of aerosols and vapor, e.g., exceeding the saturated vapor concentration of C₁₀-C₁₃ aromatics, >1% naphthalene, the LC₅₀ was >1073 mg/m³ in mice.

Irritation

Irritation studies were conducted in rabbits with commercial C₁₀ – C₁₃ Aromatic Hydrocarbon Solvents Category products (CAS RN 64742-94-5; C₁₀ aromatics >1% naphthalene and CAS RN 64742-94-5; C₁₀-C₁₃ aromatics, >1% naphthalene) and the Primary Irritation Index results ranged from 1.08 to 1.83 out of a possible score of 8, respectively. However, if the irritation scores are interpreted according to newer OECD testing guidelines (24, 48, 72 hour averages for erythema and for edema), the values are 0.94 (erythema) and 0.06 (edema), and 1.5

(erythema) and 0.33 (edema), respectively for the same tests.

Eye irritation studies were conducted in rabbits on a commercial C₁₀ – C₁₃ Aromatic Hydrocarbon Solvents Category product with CAS RN 64742-94-5; C₁₀ aromatics, >1% naphthalene and results indicated a maximum Draize score of 12 on a scale of 0 - 110, indicating the test material was minimally irritating to the eyes of rabbits.

A single respiratory irritation study conducted in mice with a representative C₁₀ – C₁₃ Aromatic Hydrocarbon Solvents Category product showed an RD₅₀ of 20.3 mg/m³ indicating that CAS RN 64742-94-5; C₁₀-C₁₃ aromatics, >1% naphthalene has the potential to moderately irritate the respiratory tract and cause depression in respiratory rates in mice.

Sensitization

No experimental animal studies were made available by members of the C₁₀-C₁₃ aromatic hydrocarbon solvents consortium for sensitization.

Human Dermal Irritation and Sensitization

Two studies evaluated the skin irritating and sensitizing capabilities of two commercial C₁₀ – C₁₃ Aromatic Hydrocarbon Solvents Category products on humans. These studies were conducted with and without UV irradiation of the contact sites with 26 volunteer subjects examined and screened by the physician-author of the report(s). The studies were conducted according to the same protocol, briefly described here. The first study was conducted with commercial product CAS RN 64742-94-5; C₁₀-C₁₃ aromatics, >1% naphthalene (Boiling Point Range 185-205°C and ~ 91% within C10-C13 carbon range); the second was conducted with commercial product CAS RN 64742-94-5; C₁₀-C₁₃ aromatics, >1% naphthalene (Boiling Point Range 230-285°C and ~ 89% within C10-C13 carbon range). Each study had 3 phases.

In Phase I, the MED (Minimum Erythemogenic Dose - UVB light produced Erythemogenic Effects) was determined to set the exposure for combined UVB exposure and dermal application of the test material. Five sites on the back and 5 sites on the arm were exposed to UVB light for 10, 20, 30, 40 or 50 seconds at 10 cm from the exposure site. Sites were examined at 18 and 24 hours. In Phase II, determination of phototoxicity and primary irritancy was measured. On each arm, 4 test sites were used with a 5th site serving as a control (no test material applied). On Day 1, each testing site had 0.3 g of a 50% w/w test material in U.S.P. Petrolatum applied to it and held in contact with the skin for 24 hours under a semi-occlusive dressing. On day 2, after 24 hours, participants returned and had 0.3 ml of a neat solution of test material (or water if control) applied to the same sites. The right arm was exposed to UVA (phototoxicity) and the left arm was not (primary irritant study); both arms were examined for irritation. Participants returned at 24, 48, and 72 hours for an examination for dermal irritation. In Phase III, determination of photocontact and contact allergenic capabilities were assessed. On each side of the back, 9 test sites were used for experimental purposes with a 10th site serving as a control (no test material applied). The left side of the back was used to evaluate the irritant and contact allergenic propensities with the evaluation of photocontact allergenic propensities were performed on the right side. 0.3 g of a 30% w/w test material:vehicle solution was used at each experimental site for the evaluation of the propensities. Dermal irritation and damage was assessed and scored according to a modified Draize scale.

The assessments of the two studies showed the following results: Phase II test materials did not elicit any effects which could be construed as a characteristic of a phototoxic propensity or of a primary irritant. Skin patches exposed to test material displayed no signs of skin irritation. The dermal irritation scores were 0 (Draize Score) for all subjects (26 people), on all days (5 days) of exposure to test material. A faint erythema (score of 1) was observed in skin patches exposed to test material and UV light for most subjects; however, subjects exposed to only UV light displayed a similar erythema (score of 1). In Phase III, the test materials showed no evidence of being a photocontact allergen and no evidence of being either a primary irritant or a contact allergen. No erythema was observed during the rechallenge phase of exposure (score of 0 for all subjects).

The data above should be analyzed using a weight of evidence approach. The human data should be given more weight since human exposure data is more relevant to the general populace. Since no irritation was noted in the human volunteer studies, and only minimal irritation was noted in the rabbit studies, the conclusion is that the C₁₀ – C₁₃ Aromatic Hydrocarbon Solvents Category pose a minimal skin irritation risk to humans. Based on eye irritation data, the C₁₀ – C₁₃ Aromatic Hydrocarbon Solvents Category pose a minimal eye irritation risk. These chemicals may possess properties indicating hazard for human health for irritation of the respiratory tract.

Repeated Dose Toxicity

A 90-day subchronic, repeated-dose, oral gavage study conducted on a C₁₀-C₁₃ Aromatic Hydrocarbon Solvents Category substance (CAS RN. 64742-94-5) showed a low order of systemic toxicity.

Rats (10/sex/dose group) were dosed with 0, 300, 600, or 1200 mg/kg bw/day (including a 28-day satellite recovery high-dose group) for three days. The high dose for the satellite and main study animals was adjusted to 1000 mg/kg bw/day from the 4th day on (in this 90-day study) due to the clinical response displayed in the first 3 days (ano-genital staining, emaciation and hypoactivity) in several animals. During the first week of the study, food consumption in male rats was significantly decreased compared to controls and the male body weights in the high dose group were significantly reduced compared to controls at all intervals throughout the study. However, all male groups gained weight at a rate similar to the control group. This effect was not seen in females. There were ten early deaths, 1 female low-dose group, 1 female mid-dose group, 3 male and 4 female high-dose group (includes 1 female moribund euthanasia), and 1 female satellite group. Based on gross postmortem results and/or pathology findings, 1 female mid-dose group, 2 male high-dose group, and 1 female satellite group deaths were the result of dosing trauma or aspiration of test material.

The majority of animals in the 300 and 600 mg/kg bw/day groups displayed no observable abnormalities during the test period. The high dose group and satellite animals were dosed initially at 1200 mg/kg bw/day for 3 days and then doses were adjusted to 1000 mg/kg bw/day due to the response displayed by the animals. In the 1000 mg/kg bw/day group and satellite recovery groups, clinical signs included ano-genital staining, alopecia and emaciation in both sexes. There were no signs of toxicity with the exception of emaciation and related observations. Hypothermia and hypoactivity were noted in several animals primarily just prior to their deaths. Male body weights in the high dose group were significantly reduced compared to controls at all intervals throughout the study beginning in the first week of the study. After this interval, the groups gained weight at a rate similar to the control group. This effect was not seen in females. During the first week of the study, food consumption in male rats was significantly decreased compared to controls.

Changes in the liver were noted and include hypertrophy – predominantly centrilobular seen in the females at all dose levels and sporadically in the males along with a low incidence of periportal hepatocellular hypertrophy was seen in the high dose males and/or female rats. The changes corresponded to the significant increase in the mean liver weights (absolute and relative) and an increase in the gamma-glutamyl transferase and cholesterol values seen at termination in the females. An increased incidence and/or severity of thyroid follicular epithelium hypertrophy and/or hyperplasia (not distinguished in the report), was observed in the male rats at all dose levels and in the mid and high dose group females. A low, sporadic incidence of submucosal edema and inflammation, focal mucosal necrosis and hemorrhage was noted involving the glandular and/or non-glandular areas of the stomach. Inflammation and necrosis in the stomach of some treated animals were attributed to the effects of intubation of a locally irritating substance on the gastrointestinal tract. A significant increase in the mean kidney weights (absolute and relative) was noted at termination but no corresponding changes in the kidneys were observed by the pathologist. Although the absolute testes weights at the highest dose level were not statistically different from control weights, the relative testes weights (relative to final body weight) were significantly increased only in the highest dose level due to the significantly decreased final body weights. These effects are considered to be an adaptive response. There were no treatment-related histopathological changes in any testes examined.

Increased hemosiderosis in the splenic red pulp was seen in the male and female rats of the 600 and 1000 mg/kg bw/day dose levels. While several hematological parameters were statistically significantly altered, the effects were not considered to be biologically relevant and were not considered to be the cause of the noted hemosiderosis. The following results were noted:

Bone Marrow – There were no adverse pathology findings of the bone marrow in any animal at any dose.

Hematocrit - There was no dose response for male rats. The hematocrit count was statistically affected at all dose levels; however, all treated male rats had hematocrit counts that were 95% of control. Hematocrit counts were only statistically affected for the female rats at 600 mg/kg bw/day (96% of control). Hematocrit counts were not different from controls in the recovery group that was initially dosed with 1000 mg/kg bw/day. Hematocrit levels returned to normal in the recovery group (initially dosed with 1000 mg/kg bw/day). Since only the male rats were statistically affected, no dose response was observed, and experimental values were within 10% of controls (normal physiological range), these changes are not considered to be an adverse effect.

MCHC – Only male rats in the 1000 mg/kg bw/day group were statistically affected; however, the MCHC level was 97.5% of control. Female rats were statistically affected at all doses, however, no dose response was observed. The values (% of control) for MCHC were 96.7%, 96.9%, 96% for the 300, 600, and 1000 mg/kg bw/day treated female rats respectively. MCHC levels returned to normal in the recovery group (initially dosed

with 1000 mg/kg bw/day). Since only the female rats were statistically affected, no dose response was observed, and experimental values were within 10% of controls (normal physiological range), these changes are not considered to be an adverse effect.

RBC– Only male rats in the 600 and 1000 mg/kg bw/day groups were statistically affected. The values for RBC levels (% of control) were 95% and 91.5% for the 600 and 1000 mg/kg bw/day groups, respectively. Female rat RBC levels were not significantly decreased at any test dose. RBC levels returned to normal in the recovery group (initially dosed with 1000 mg/kg bw/day). Since only the male rats showed a significant decrease in RBC counts, it is unlikely that this change is an adverse effect or is related to the splenic hemosiderosis observed in both sexes of rats. The decrease observed in the male rats was less than 10% of control (normal physiological range) and these changes are not considered to be an adverse effect.

Hemoglobin – Male rats exposed to 300, 600, and 1000 mg/kg bw/day had decreased hemoglobin counts of 95%, 95%, and 92.5% of control, respectively. Female rat hemoglobin count was 93% of control at the 600 and 1000 mg/kg bw/day doses. Hemoglobin concentrations returned to normal in the recovery group (initially dosed with 1000 mg/kg bw/day). Since no dose response was observed in either the male or female rats, and experimental values were within 10% of controls (normal physiological range), these changes are not considered to be an adverse effect.

In conclusion, there were some differences which were statistically different but the differences were not large, and accordingly, were not considered to be biologically relevant and were not related to the observed hemosiderosis in the spleen. It should also be noted that while the test material contains methyl naphthalene, the minor changes to hematological parameters noted in studies with methyl naphthalene were not biologically relevant and were different than the minor changes noted in this study.

Hyperplasia of the urinary bladder mucosa was most prevalent in the male rats and was noted in all dosage groups as well as urinary bladder concretions. The concretions and bladder epithelium hyperplasia are not relevant to human health. IARC published a scientific report on rat bladder tumour formation and its relevance to human health outcomes. IARC states that “large quantitative differences in susceptibility exist among species and between the sexes... [which] must be considered...”. In the absence of bladder neoplasms, as is the case in this study, the IARC Advisory Group concluded that the production of bladder cancer in rats is not predictive of carcinogenic hazard to humans provided that certain criteria are met. The C10-C13 Aromatics satisfy the critical criteria including:

- The lack of genotoxic activity
- C10-C13 Aromatics are not known to produce tumours at any other site in the experimental animals
- Human occupational experience indicates that cancer is not a significant risk in the exposed population.

The incidence and severity of the urinary bladder correlates with increasing dose and with the noted concretions in the male rats. No concretions are noted in the male rat recovery group and the incidence and severity of the mucosa hyperplasia were trending towards reversibility; no male rats were observed with moderate hyperplasia, two male rats were observed with slight hyperplasia, and three male rats were observed with only minimal hyperplasia, indicating recovery. The slight mucosa hyperplasia observed in the female rats at the highest dose tested (two), returned to background levels in the recovery group. Second, except for two female rats at the highest dose test, the hyperplasia is only noted in male rats. $\alpha_2\mu$ -globulin nephropathy is a syndrome of renal damage that occurs only in male rats when repeatedly exposed to hydrocarbons. There are several hallmark criteria that characterize $\alpha_2\mu$ -globulin nephropathy, including the accumulation of $\alpha_2\mu$ -globulin, urothelial hyperplasia, lesions are only present in the male rat, and a lack of genotoxicity. Further $\alpha_2\mu$ -globulin concentrations in the male rat urine have been implicated in bladder hyperplasia and the tumorigenesis associated with some chemicals (e.g. saccharin). Interspecies and sex differences have been noted in rats and in strains with lower $\alpha_2\mu$ -globulin concentration, urothelial effects were not observed. These effects to the bladder were determined by IARC to be not relevant to human health. The test data and pathology report for C10-C13 Aromatics is consistent with an $\alpha_2\mu$ -globulin nephropathy.

The results indicate that the formation of urinary bladder concretions in male rats likely caused mechanical irritation of the transitional epithelium that lead to the noted non-proliferative hyperplasia in the mucosa. Based on the recommendation from IARC, the hyperplasia is not considered to be relevant to human health.

The relative organ weights, clinical chemistry and hematology data indicated recovery during the 28 day recovery period. The liver, thyroid, and stomach, changes seen at the 90-day termination, appeared to be reversible findings as they were not observed or returned to background levels in the satellite recovery group after the 28-day recovery period.

The changes seen in the spleen at the main study termination were at lower incidence and/or severity in the

satellite recovery group, which indicates a trend towards reversibility. Based on the results of this study, the LOAEL for this test material is 600 mg/kg bw/day and the NOAEL for this test material is 300 mg/kg bw/day.

Sub-Chronic Studies with Methyl Naphthalene

Several studies in mice were conducted with either the test material 2-methyl naphthalene [CAS RN 91-57-6] or with a methyl naphthalene mixture [CAS RN 1321-94-4]. These study results should only be applied to the category member, mixed methyl naphthalenes [CAS RN 1321-94-4] as the toxicological findings were not observed in the other category members (see study above).

A chronic oral dietary study was conducted with 2-methyl naphthalene [CAS RN 91-57-6] in mice; average intakes were 0, 54.3 or 113.8 mg/kg bw/day for males and 0, 50.3, or 107.6 mg/kg bw/day for females. A low incidence of mortality from various causes was observed in males and females at all dose groups (including control group). A 7.5% decrease in body weight gains in males of 113.8 mg/kg bw/day group was noted. Hematology endpoints including a decrease in immature and mature neutrophils and an increase in lymphocytes counts were noted in the treated females compared with the controls, however no significant effects were observed in the treated males. It should be noted that numerical values and statistics were not reported for the hematological parameters. The most sensitive effects were a significant increase in neutral fat levels and pulmonary alveolar proteinosis observed in both treated groups. A LOAEL of 54.3 and 50.3 mg/kg bw/day 2-methylnaphthalene (0.075% in diet) was determined for male and female mice, respectively.

Three sub-chronic dermal studies were conducted with mixed methylnaphthalenes [1-methyl and 2-methylnaphthalene; CAS RN 1321-94-4] were conducted in mice.

Mixed methylnaphthalene (119 mg/kg bw/day) was applied to backs of female mice twice a week for 30 weeks. Pulmonary alveolar proteinosis was noted in all exposed mice; the implication is that mixed methyl naphthalene can be absorbed through the dermis and elicit pulmonary toxicity via blood flow. Pulmonary alveoli which had proteinosis were filled with cholesterol crystals, an amorphous eosinophilic material, and myelinoid structures of various dimensions and mononucleated giant cells with foamy cytoplasm. The LOAEL for repeated dose dermal toxicity of mixed methyl naphthalene was considered to be 119 mg/kg bw/application.

In a second dermal sub-chronic study, mixed methylnaphthalene was dissolved in acetone and applied to the shaved backs of mice at 0, 118.8 or 237.6 mg/kg bw/twice a week for 50 weeks. Mixed methylnaphthalene exposure induced cholesterol ester and increased levels of lung triglyceride, phospholipid, cholesterol, and dipalmitoyl-glycerophosphocholine in the lungs of treated mice. The LOAEL for repeated dose dermal toxicity was 118.8 mg/kg bw/application in mice based on changes observed in the lungs.

Mixed methylnaphthalene (0, 29.7 or 118.8 mg/kg bw) was applied on the shaved skin of mice backs twice weekly for 30 weeks in another dermal study. The dermal exposure to methylnaphthalene resulted in a 97 % increase in lipid pneumonia. The LOAEL for repeated dose dermal toxicity of methylnaphthalene was 29.7 mg/kg bw/application in female mice.

Conclusion for Mixed Methyl Naphthalenes [CAS RN CAS RN 1321-94-4]

Repeated dose studies with mixed methylnaphthalene indicate a moderate degree of toxicity for mice exposed via oral or dermal routes. An oral LOAEL of 0.075% (equivalent to 54.3 mg/kg bw/day in males and 50.3 mg/kg bw/day in females) was determined in a dietary study of 2-methylnaphthalene. A dermal LOAEL for mixed methylnaphthalene was considered to be 29.7 mg/kg bw/application in mice. The pulmonary toxicity observed in mice for the mixed naphthalenes was not been observed in a sub-chronic oral study using rats (see above).

Mutagenicity

C₁₀-C₁₃ Aromatic Hydrocarbon Solvents Category substances (Hydrocarbons, C₁₀-C₁₃, aromatics, >1% naphthalene [CAS RN 64742-94-5] and Hydrocarbons, C₁₁, aromatics [CAS RN 1321-94-4]) tested *in vitro* (Reverse Microbial Mutagenesis [Ames] Assay, Salmonella typhimurium / TA98, TA100 or TA102, TA1535, and TA1537 or TA1538, with and without activation), and Hydrocarbons, C₁₀-C₁₃, aromatics, >1% naphthalene [CAS RN 64742-94-5] *in vivo* (mouse micronucleus test) showed no indication of genetic toxicity via increased mutation frequencies in any of the tester strains or evidence of induced cytogenetic damage in mouse bone marrow cells of mice at doses up to and including 1.0 g/kg bw. Results of these studies indicate that members of the C₁₀-C₁₃ Aromatic Hydrocarbon Solvents Category are unlikely to cause genetic damage in laboratory animals.

Reproductive and Developmental Toxicity

Results from the three-generation reproduction inhalation study in rats indicate limited effects from C₉ aromatic naphtha. In each of three generations (F0, F1 and F2), rats were exposed to High Flash Aromatic Naphtha

(CASRN 64742-95-6) via whole body inhalation at target concentrations of 0, 100, 500, or 1500 ppm (actual mean concentrations throughout the full study period were 0, 103, 495, or 1480 ppm, equivalent to 0, 505, 2430, or 7265 mg/m³, respectively). In each generation, both sexes were exposed for 10 weeks prior to and two weeks during mating for 6 hrs/day, 5 days/wks. Female rats in the F0, F1, and F2 generation were then exposed during gestation days 0-20 and lactation days 5-21 for 6 hrs/day, 7 days/wk. The age at exposure initiation differed among generations; F0 rats were exposed starting at 9 weeks of age, F1 exposure began at 5-7 weeks, and F2 exposure began at postnatal day (PND) 22. In the F0 and F1 parental generations, 30 rats/sex/group were exposed and mated. However, in the F2 generation, 40/sex/group were initially exposed due to concerns for toxicity, and 30/sex/group were randomly selected for mating, except that all survivors were used at 1480 ppm. F3 litters were not exposed directly and were sacrificed on lactation day 21.

Systemic Effects on Parental Generations: The F0 males showed statistically and biologically significantly decreased mean body weight by ~15% at 1480 ppm when compared with controls. Seven females died or were sacrificed *in extremis* at 1480 ppm. The F0 female rats in the 495 ppm exposed group had a 13% decrease in body weight gain when adjusted for initial body weight when compared to controls. The F1 parents at 1480 ppm had statistically significantly decreased mean body weights (by ~13% (females) and 22% (males)), and locomotor activity. F1 parents at 1480 ppm had increased ataxia and mortality (six females). Most F2 parents (70/80) exposed to 1480 ppm died within the first week. The remaining animals survived throughout the rest of the exposure period. At week 4 and continuing through the study, F2 parents at 1480 ppm had statistically significant mean body weights much lower than controls (~33% for males; ~28% for females); body weights at 495 ppm were also reduced significantly (by 13% in males and 15% in females). The male rats in the 495 ppm exposed group had a 12% decrease in body weight gain when adjusted for initial body weight when compared to controls. Based on reduced body weight observed, the overall systemic toxicity LOAEC is 495 ppm (2430 mg/m³).

Reproductive Toxicity - Effects on Parental Generations: There were no pathological changes noted in the reproductive organs of any animal of the F0, F1, or F2 generation. No effects were reported on sperm morphology, gestational period, number of implantation sites, or post-implantation loss in any generation. Also, there were no statistically or biologically significant differences in any of the reproductive parameters, including: number of mated females, copulatory index, copulatory interval, number of females delivering a litter, number of females delivering a live litter, or male fertility in the F0 or in the F2 generation. Male fertility was statistically significantly reduced at 1480 ppm in the F1 rats. However, male fertility was not affected in the F0 or in the F2 generations; therefore, the biological significance of this change is unknown and may or may not be attributed to the test substance. No reproductive effects were observed in the F0 or F1 dams exposed to 1480 ppm (7265 mg/m³). Due to excessive mortality at the highest concentration (1480 ppm, only six dams available) in the F2 generation, a complete evaluation is precluded. However, no clear signs of reproductive toxicity were observed in the F2 generation. Therefore, the reproductive NOAEC is considered 495 ppm (2430 mg/m³), which excludes analysis of the highest concentration due to excessive mortality.

Developmental Toxicity - Effects on Pups: Because of significant maternal toxicity (including mortality) in dams in all generations at the highest concentration (1480 ppm), effects in offspring at 1480 ppm are not reported here. No significant effects were observed in the F1 and F2 generation offspring at 103 or 495 ppm. However, in F3 offspring, body weights and body weight gain were reduced by ~ 10-11% compared with controls at 495 ppm for approximately a week (PND 14 through 21). Maternal body weight was also depressed by ~ 12% throughout the gestational period compared with controls. The overall developmental LOAEC from this study is 495 ppm (2430 mg/m³) based on the body weights reductions observed in the F3 offspring.

Conclusion: No effects on reproductive parameters were observed at any exposure concentration, although a confident assessment of the group exposed at the highest concentration was not possible. A potential developmental effect (reduction in mean pup weight and weight gain) was observed at a concentration that was also associated with maternal toxicity.

Neurotoxicity

Neurotoxicity and neurobehavioral endpoints were not specifically evaluated in the 90-day subchronic oral toxicity study using CAS RN. 64742-94-5, mentioned above; however, there was no evidence of pathologic changes to nervous tissue or neurobehavioral changes based on the clinical observations. No overt clinical signs of neurotoxicity were induced by the tested C₁₀-C₁₃ Aromatic Hydrocarbon Solvent Category materials in the acute or repeated dose toxicity studies. In an inhalation neurobehavioral study in rats using C₁₀-C₁₁ aromatic hydrocarbons [CAS RN 64742-94-5] as the test substance, there was evidence of mild, reversible effects on gait, motor activity, and visual discrimination. Functional observation and motor activity tests as well as each of the visual discrimination performance tests, were conducted on 8 control animals and 8 animals in each of the test exposure levels. The hydrocarbon fluid tested was: C₁₀ - C₁₁ mixed isomer aromatic solvent at dose levels of 200, 600, and 2000 mg/m³. The highest concentration was approximately the maximally attainable vapor concentration

at 20°C. The rats were exposed for periods of 8 hours per day for 3 consecutive days. Baseline data were collected before the first exposure and the test data were collected immediately after the first and third exposure period. Separate animals for the visual discrimination testing were trained for 4 weeks, 5 days per week, prior to their exposure periods. Statistically significant effects in these domains were apparent in the high exposure group (2000 mg/m³). Post exposure studies demonstrated the reversibility of all effects. These data, as well as evidence from previous studies, suggested that short-term exposures to levels below approximately 1000 mg/m³ are unlikely to produce profound CNS effects.

These chemicals may possess properties indicating hazard for human health (irritation of the respiratory tract, eye, and skin, and transient acute CNS effects at high exposure concentrations). These hazards do not warrant further work as they are related to reversible acute toxicity which may become evident only at high exposure levels. They should nevertheless be noted by chemical safety professionals and users. Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Environment

Fate

Members of the C₁₀-C₁₃ Aromatic Hydrocarbon Solvents Category have the potential to volatilize from surface waters at significant rates from water (at 25°C) that range from 10 to 1403 Pa·m³/mole, based on Henry's Law constants (HLCs). In the air, category members have the potential to degrade through indirect photolytic processes mediated primarily by hydroxyl radicals (•OH) with calculated degradation half-lives ranging from 1.9 to 14.6 hours or 0.05 to 1.4 days, based on a 12-hr day and an •OH concentration of 1.5 x 10⁶ •OH/cm³. Aqueous photolysis will not contribute to the transformation of category chemical constituents in aquatic environments because they are either poorly or not susceptible to this reaction.

Results of Mackay Level I distribution modeling, at steady state, show that category chemical constituents will partition primarily to the air (0.4 to 90.5%) and soil (9.0 to 97.3%) compartments, with a small amount partitioning to water (0.1 to 20.6%), and sediment (0.2-2.2%). Mackay Level III modeling indicates that category member constituents partition mostly to the soil (71.9 to 85.0%) and water (9.7 to 15.8%) compartments rather than air (0.1 to 2.3%) or sediment (0.8-11.2%) compartments when an equal emission rate (1000 kg/hr) to the air, water, and soil compartment is assumed. When release occurs only to either the air, water, or soil compartment, constituents are indicated in the modeling to partition primarily to the compartment to which they are released.

When released primarily to the air compartment, the primary mode of removal would be via indirect photodegradation mediated by •OH radicals. In spite of their water solubility, wet deposition of category chemical constituents is not likely to play a significant role in their atmospheric fate because of rapid photodegradation. Volatilization to the air will contribute to the loss of category chemical constituents from aqueous and terrestrial habitats.

Chemical constituents of C₁₀-C₁₃ Aromatic Hydrocarbon Solvents Category members have the potential to partition to water at significant concentrations only when emitted to this compartment. However, the levels of these constituents that may occur in aquatic environments are unlikely to degrade by hydrolysis because they lack a functional group that is hydrolytically reactive. Therefore, this degradative process will not contribute to the removal of category member constituents from the environment.

Determining the biodegradation potential of UVCBs can be challenging. The result for each multi-constituent substance (UVCB) characterizes the biodegradability of that substance as a whole, but it does not suggest that each constituent of the UVCB is equally biodegradable. As with all ready biodegradation test guidelines, the test system and study design used with these substances (OECD TG 301F) is not capable of distinguishing the relative contribution of the substances' constituents to the total biodegradation measured (constituents with higher branching/cyclic structures may degrade to a lesser extent than linear and less branched structures). Hydrocarbons, C₁₀-C₁₃, aromatics, >1% naphthalene (CAS RN 64742-94-5), which contains chemical constituents from all category members (a UVCB), was shown to be biodegradable based on two 28-day biodegradation studies with test substance concentrations of approximately 35 to 45 mg/l that resulted in 61% biodegradation. In another study following OECD 301F test guidelines, the analogue substance, 2-methylnaphthalene (CAS RN 91-57-6) biodegraded to an extent of 50% after 28 days. The study was extended to 67 days, at which point the percent biodegradation of 2-methylnaphthalene was 67%. C₉ components of this category were evaluated as part of the C₉ Aromatic Hydrocarbon Solvents Category (reviewed at SIAM 21). Hydrocarbons, C₉, aromatics (CAS RN 64742-95-6), 1,2,4-trimethylbenzene (CAS RN. 95-63-6), and 1-ethyl-3-methylbenzene (CAS RN 64742-95-6) were determined to be readily biodegradable (the latter substance is used as an analog to characterize the

potential biodegradability of the category member, ethylmethylbenzene (CAS RN 25550-14-5). These three substances exceed 60% biodegradation in 28 days and met the 10-day window criteria for ready biodegradation.

Standardized tests to assess bioaccumulation potential are intended for single substances and are not appropriate for more complex substances (UVCB). Representative substances, or constituent chemicals, can be used to make conservative predictions of bioaccumulation potential. Results of bioconcentration factor (BCF) studies for several constituent chemicals of category members are available. BCF data range from 2 to 1416 l/kg wet weight for several constituent chemicals in the C₁₀ to C₁₂ range. QSARs values for BCF were estimated to range from 177 to 3932 L/kg wet for representative constituents (as listed above) in the C₁₀ to C₁₆ range. Values for methylnaphthalenes (CAS RN 1321-94-4) and 2-methylnaphthalene were estimated at 498 and 646 L/kg wet, respectively as well. Based on this data, category members have a potential to bioaccumulate.

Aquatic Toxicity

Sufficient data (see table below), based on both nominal and measured concentrations, are available for category substances to characterize the fish and invertebrate acute toxicity and alga toxicity of the C₁₀-C₁₃ Aromatic Hydrocarbon Solvents Category. These studies were conducted on the Water Accommodated Fractions (WAF) of the test substances. Acute aquatic toxicity of category members for freshwater fish and invertebrates ranged from 2 to 13.6 (96hr-LL₅₀) and 1.0 to 10 (48hr-EL₅₀) mg/l, respectively, based on nominal loadings. Results, based on measured concentrations, reportedly ranged from 0.8 to 2.3 mg/l for fish, and 0.5 to 0.95mg/l for invertebrates. Acute aquatic toxicity to freshwater algae (72-hr-EL₅₀) for category members ranged from 1 to 10.9 mg/l based on both biomass and growth rate and nominal loadings of the test substances. Measured results for toxicity to algae ranged from 0.29 to 0.43 mg/l.

Results of computer modeling, using EPISuite v.4.0, further support the experimental results with acute aquatic toxicity (LC/EC₅₀) in the range of 0.1 to 3 mg/l for all three trophic levels. Values are based on a series of 14 representative hydrocarbons (see page 4 of this document) that were selected by industry, based on hydrocarbon process (distillation) knowledge, to accurately characterize category members.

Acute toxicity values used to characterize the C₉ components of this category come from the C₉ Aromatic Hydrocarbon Solvents Category (reviewed at SIAM 21). For fish (LL₅₀; LC₅₀) and invertebrates (EL₅₀; EC₅₀) range from 3.5 to 7.7 mg/L, based on measured data. For algae, one study for a category member (CAS No. 64742-95-6); resulted in a 72-hr EC₅₀ of 2.4 (biomass) and 2.7 (growth rate) mg/L, based on the measured concentrations.

Acute toxicity values used to characterize the methylnaphthalenes of this category come from the 2-methylnaphthalene submission (CAS RN 91-57-6; reviewed at SIAM 25). For fish (LC₅₀) and invertebrates (EC₅₀) range from 1.5 to 3.0 mg/L, based on measured data. For algae, one study resulted in a 72-hr EC₅₀ of 0.7 (biomass) and 2.3 (growth rate) mg/L, based on the measured concentrations.

Selected data that characterize the acute aquatic toxicity of members of the C₁₀-C₁₃ Aromatic Hydrocarbon Solvents Category

Substance (CAS RN)	Freshwater Fish 96-hr (mg/l)	Freshwater Invertebrate (<i>Daphnia magna</i>) 48-hr (mg/l)	Freshwater Alga (<i>Pseudokirchneriella subcapitata</i>) 72-hr (mg/l)
Hydrocarbons, C ₁₀ -C ₁₃ , aromatics, >1% naphthalene (64742-94-5)	3.0 (LL ₅₀) 2.3 (LC ₅₀) <i>(Oncorhynchus mykiss)</i>	1.1 (EL ₅₀) 0.95 (EC ₅₀)	7.9 (EL ₅₀) (growth rate) 0.42 (EC ₅₀) 3.8 (EL ₅₀) (biomass) 0.29 (EC ₅₀) NOELR = 0.22 NOEC = 0.07 (growth rate and biomass)
C _{9,10} Aromatics, Predominantly C ₉ -C ₁₀ Alkylbenzenes and Naphthalene	2 - 5 (LL ₅₀) <i>(Oncorhynchus mykiss)</i>	3 - 10 (EL ₅₀)	1 - 3 (EL ₅₀) (growth rate) 1 - 3 (EL ₅₀) (biomass) NOEL = 1.0 (growth rate and biomass)

(64742-94-5)			
Hydrocarbons, C ₁₀ , aromatics, >1% naphthalene	13.6 (LL ₅₀) 0.84 (LC ₅₀) (<i>Oncorhynchus mykiss</i>)	10.1 (EL ₅₀) 0.55 (EC ₅₀)	10.9 (EL ₅₀) (growth rate) 0.43 (EC ₅₀) 8.5 (EL ₅₀) (biomass) 0.34 (EC ₅₀) NOELR = 2.5 NOEC = 0.09 (growth rate and biomass)
(64742-94-5)			

Terrestrial Toxicity

The avian acute oral LD₅₀ value for one of the more chemically complex category members (Hydrocarbons, C₁₀, aromatics, >1% naphthalene; CAS RN 64742-94-5) was determined to be greater than 2,250 mg/kg body weight, the highest dose tested, based on the lack of mortality observed in all dosage groups. The avian oral LC₅₀ value for the same substance was determined to be greater than 6,500 ppm (mg/kg feed), also based on the lack of mortality observed in all dosage groups. Since only one species was tested, these data represent a low potential for members of the C₁₀ to C₁₃ Aromatic Hydrocarbon Solvents Category to cause toxicity to terrestrial organisms.

Chemicals in this C₁₀ to C₁₃ Aromatic Hydrocarbon Solvents Category possess properties indicating a potential hazard for the environment (acute toxicity for fish, invertebrates, and algae (<1 mg/l)). Category members have a potential to bioaccumulate. Category members/substances are not readily biodegradable, but have shown the potential to biodegrade from 50% to greater than 60% in standardized tests. Adequate screening-level data are available to characterize the environmental hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Use/Exposure

Production

United States aggregate production capacities for the products in the C₁₀-C₁₃ Aromatic Hydrocarbon Solvents Category, as indicated by their CAS RN, in the 2006 EPA IUR database, were: >10 million to 50 million pounds (CAS RN 1321-94-4); 1 billion pounds and greater pounds (CAS RN 70993-06-0); and >1 billion pounds (CAS RN 64742-94-5) per annum. Volume Survey is overall volume for the entire individual CAS RN and includes fuels, solvents and all other uses. It is expected that the solvent portion of the volume for the C₁₀-C₁₃ Aromatic Hydrocarbon Solvents Category would be significantly lower than the aggregate production volume. It should also be noted that CAS RN 1321-94-4 is no longer offered commercially by those manufacturers represented in the group sponsoring this category. This assessment only applies to CAS RNs with the constituent profiles and compositions described within this assessment. Consequently, the conclusions of this assessment do not apply to petroleum process streams with the same CAS number as those belonging to the C₁₀-C₁₃ Aromatic Hydrocarbon Solvents Category.

Use

Hydrocarbon solvents in the C₁₀-C₁₃ Aromatic Hydrocarbon Solvents Category are generally used in coatings, cleaning agents, agricultural chemicals, fuel additives, functional fluids, and laboratory agents.

Exposure

The sources for potential environmental exposure to C₁₀ to C₁₃ Aromatic Hydrocarbon Solvents Category substances could include releases from chemical and petroleum manufacturing/processing facilities, releases from facilities that use C₁₀ to C₁₃ Aromatic Hydrocarbon Solvents Category substances, releases from industrial products that include C₁₀ to C₁₃ aromatics, automotive sources (fuel evaporate emissions and exhaust), and possibly biogenic and combustion sources.


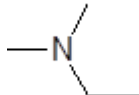
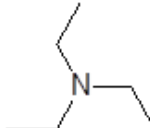
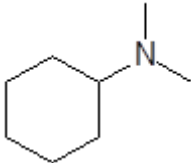
C₁₀ to C₁₃ Aromatic Hydrocarbon Solvents Category members are used in uses in coatings, cleaning agents, agricultural chemicals, fuel additives, functional fluids, and laboratory agents. Occupational exposure includes workers exposed during the manufacture of the product stream and includes office workers. In general,

occupational (manufacturing) exposure to category members is well within applicable exposure limits, and office air data are comparable to ambient residential levels.

The occupational exposure in a manufacturing facility would be expected to be relatively low because the process, storage and handling operations are confined by system containment. A comprehensive review and assessment was conducted of published occupational exposure literature published between 1960 and 1997 for industries that use hydrocarbon solvents, including painting, industrial manufacturing, printing, and construction. Approximately 350 publications were determined to have adequate information for quantitative hydrocarbon solvent exposure assessment and the data from these publications were included in a computer database. Occupational exposure data on C₁₀ to C₁₃ aromatic hydrocarbons were identified in this review. The review publication referenced four publications that provided data on C₁₀ to C₁₃ aromatic hydrocarbons. The arithmetic mean of the 96 samples was 1.8 mg/m³ and ranged from 0 to 10 mg/m³.

The characteristic odor of the solvents in the C₁₀ to C₁₃ Aromatic Hydrocarbon Solvents Category limits their use in consumer products and therefore they are not typically found in indoor air.

SIDS INITIAL ASSESSMENT PROFILE

[Category Name]	Tertiary Amines	
CAS No(s).	75-50-3 598-56-1 121-44-8 98-94-2	
Chemical Name(s)	Trimethylamine (TMA) Ethanamine, N, N-dimethyl- (DMEA) Triethylamine (TEA) Cyclohexylamine, N, N-dimethyl- (DMCHA)	
Structure(s)	75-50-3	
	598-56-1	
	121-44-8	
	98-94-2	

SUMMARY CONCLUSIONS OF THE SIAR

Category Rationale

The tertiary amines category is currently limited to the four sponsored substances mentioned above. The tertiary amines category is represented by R-N(R'')-R'; with elemental compositions of only carbon, hydrogen and nitrogen. The structure has a single and tertiary amino-group, where R is an aliphatic hydrocarbon constituent that has no more than two linear carbon atoms or one cyclic group.

The nitrogen in an amine bears an unshared pair of electrons. The tendency to share these electrons underlies the chemical behavior of amines as a group. Furthermore, all category members have molecular weights of < 200 Daltons.

The category members demonstrate a consistent incremental change (trend) in number of carbon atoms, physical-chemical properties, and ecotoxicity and similar mammalian toxicity that correlate well with the structures of category members.

Specifically, the physical-chemical properties correlate well with structure, as an increase in side groups leads to an increase in melting point, boiling point and partition coefficient, and a decrease in vapor pressure and water solubility.

The aquatic toxicity of aliphatic amines is generally related to the length of the hydrophobic carbon chains (which mirrors octanol-water partition coefficient); the longer the chain the more toxic to aquatic organisms.

Observed corrosive properties, related to the alkaline properties of the compounds, are a general feature of the category and are the dominant effects for human health endpoints.

A read-across approach has been used for addressing the mammalian and ecotoxicity endpoints where no data were available on individual substances (as indicated in the table below).

Substance	Mammalian toxicity endpoints			Ecotoxicity
	Repeated dose toxicity	Effects on Fertility	Developmental toxicity	Algae
TMA	X	X	X	X
DMEA	READ ACROSS	READ ACROSS	READ ACROSS	X
TEA	X	READ ACROSS	READ ACROSS	READ ACROSS
DMCHA	X	X	X	X

Physical-chemical Properties

The physical-chemical properties correlate well with structure, as an increase in side groups leads to an increase in melting point, boiling point and partition coefficient, and a decrease in vapor pressure and water solubility. The substances are liquids except **TMA**, which is a gas, with melting points that range from -117 (**TMA**, measured) to <-77 °C (**DMCHA**, measured). The measured boiling points range from 2.9 °C at 1013 hPa (**TMA**) to 162.3 °C at 1013 hPa (**DMCHA**). Measured vapor pressures range from 3.17 hPa at 21.5 °C (**DMCHA**) to 1909 hPa at 20 °C (**TMA**). Water solubility correlates well with structure; longer chain or cyclic functionalities result in lower water solubility values. Water solubility values range from 13.4 g/L at 20 °C (**DMCHA**) to 409.6 g/L at 19 °C (**TMA**). Measured data on the log Kow are available for all members except **TEA**; modeling was used to fill this endpoint. The log Kow range from 0.245 at 25 °C (**TMA**) to 2.01 at 20 °C (**DMCHA**). The pKa values of the protonated forms of the tertiary amines in water (both measured and estimated values) range between 9.91 and 10.75. In addition, due to the ionizing properties, water solutions of

the category members are stable (substances remain in water) despite high vapor pressures. This is confirmed by pH-corrected Henry's Law constant values, which are below 1 Pa m³/mol at pH 7. Hence, the transport of the substances from the water phase into the atmosphere is expected to be low.

Human Health

There is sufficient evidence from human and rat studies to conclude that these amines are extensively absorbed following ingestion or inhalation, and rapidly excreted, mainly in the urine, as either the parent compound and/or its N-oxide (**TMA**, **DMEA** and **TEA**). Some dealkylation may also occur. Metabolic routes for **DMCHA** were not located.

The acute 4-hour vapor inhalation LC₅₀s in rats was > 5.9 mg/L (**TMA**) and 10.9 mg/L (**TEA**) [most are equivalent or similar to OECD TG 403]. The acute 1-hour vapor inhalation LC₅₀s in rats ranged from >2.3 - <15.4 (**DMEA**) to 19.1 mg/L (**TMA**). The acute inhalation toxicity of the tertiary amines is generally characterized by local respiratory and ocular effects. **TEA** has an acute dermal LD₅₀ of 580 mg/kg bw in rabbits. For rats, acute dermal toxicity ranged from 380 mg/kg bw (**DMCHA**) to > 5000 mg/kg bw (**TMA** as a 45% solution) [most are equivalent or similar to OECD TG 402]. The acute dermal toxicity of the tertiary amines is generally characterized by signs of acute systemic toxicity (such as effects on respiration, gait and posture, convulsions and ataxia, and lethargy) in moribund animals and localized signs of skin irritation or necrosis. The acute oral LD₅₀s for these substances in rats ranged from 272 – 289 mg/kg bw (**DMCHA**) to 1200 mg/kg bw (**TMA**) [most are equivalent or similar to OECD TG 401]. The acute oral toxicity of the tertiary amines is generally characterized by signs of acute systemic toxicity (such as effects on respiration, gait and posture, convulsions, tremors and ataxia, eye and nasal discharge, salivation and lethargy) in moribund animals and localized signs of gastrointestinal irritation.

The tertiary amines are generally corrosive to the skin [in studies with rabbits similar to OECD TG 404; patch tests] and eyes [in studies with rabbits similar to OECD TG 405 as well as in acute inhalation studies with rats] and are respiratory tract irritants in acute inhalation studies [in rats or mice in studies similar to OECD TG 403]. Workers who have been exposed to certain amine vapors have been known to experience a phenomenon known as "blue haze." Prominent effects on vision include dilated pupils, loss of accommodation, and corneal edema, which may result in hazy (looking through smoke) or blurry (out of focus) vision and halo perception. The exact mechanism is unknown. The visual symptoms are usually transient and rapidly decrease when removed from exposure to tertiary amine vapors.

DMEA and **DMCHA** were tested for skin sensitization in a guinea pig maximization test [similar to OECD TG 406], and **DMCHA** was tested in a mouse local lymph node assay [OECD TG 429]. These substances were negative in all of the tests. It is anticipated that the remaining tertiary amines also would not be sensitizing to the skin.

Repeated inhalation by rats (sex not specified) for 5 hrs/day for 7 months to **TMA** at 0, 0.025 or 0.075 mg/L resulted in severe lung effects and multiple effects in the liver, kidney and spleen at both doses, resulting in a systemic and local LOAEC of 0.025 mg/L. Male and female rats exposed to **TEA** via inhalation for 6 hrs/day, 5 days/week for 28 weeks did not exhibit significant effects at concentrations up to 1.02 mg/L (NOAEC); necrosis of nasal passages and squamous metaplasia in the trachea and mortality was observed in rats exposed to **TEA** for 10 days via inhalation to 4.3 mg/L (LOAEC). Male and female rats exposed to 0, 0.026, 0.10 or 0.39 mg/L **DMCHA** via whole-body inhalation for 9 exposures exhibited slight hyperplasia and hypertrophy of nasal mucosa at 0.39 mg/L and decreased body weights at all concentrations; the NOAEC was 0.104 mg/L.

Repeated oral (gavage) exposure of male and female rats to **TMA** resulted primarily in local (site of contact) effects in the gastrointestinal tract (and decreased body weight/protein levels in males) at 200 mg/kg bw/day with a NOAEL 40 mg/kg bw/day [OECD TG 422]. When **TMA** was administered in the diet as the hydrochloride salt to male rats for 90 days, the NOAEL was 79 mg/kg bw/day for **TMA** [administered as ca. 130 mg/kg bw/day as **TMA-HCl**]; site of contact effects were not observed [guideline not specified], which is expected from administration of the salt and from the fact that the substance was administered via diet and not via gavage. At the highest dose of **TMA-HCl** (500 mg/kg bw/day), reduced size of the seminal vesicles and effects on the prostate were seen. Repeated dietary administration of **DMCHA** to male and female rats for \geq 28

days did not produce systemic or local toxicity up to the highest dose tested [OECD TG 422]. The NOAEL was 1500 ppm (equivalent to 91-104 and 85-147 mg/kg bw/day for males and females, respectively).

Repeated dose toxicity data were not located for **DMEA**. Read across from category members **TMA** and **TEA** suggests both systemic toxicity as well as effects at the site of contact (respiratory tract or gastrointestinal tract) are expected.

Negative results are available for bacteria [similar to OECD TG 471; all category members], *in vitro* mammalian gene mutation assays (OECD 476; **TEA** and **DMEA**), *in vitro* mammalian chromosomal aberration assays [similar to OECD TG 473; **TMA**, **DMEA** and **DMCHA**], *in vitro* sister chromatid exchange [no guideline specified; **TEA**], *in vitro* DNA Damage and Repair - Unscheduled DNA Synthesis [similar to EU Method B.18; **DMCHA**] and *in vivo* micronucleus tests [OECD TG 474] (**TEA**). Based on these studies, the tertiary amines are not considered genotoxic.

No data are available for the carcinogenicity of the tertiary amines category members.

TMA [OECD TG 422], **TEA** [similar to OECD TG 413], and **DMCHA** [OECD TG 422] have been tested for effects on fertility and/or developmental toxicity. When administered orally by gavage, **TMA** had no effects on fertility or developmental parameters, and the NOAEL was 200 mg/kg bw/day (the highest dose tested) for F1 offspring. The parental NOAEL for **TMA** was 40 mg/kg bw/day, based on systemic toxicity at 200 mg/kg bw/day. At the highest dose of **TMA-HCl** (administered at 500 mg/kg-bw/day) in the 90 day dietary study in male rats, reduced size of the seminal vesicles and effects on the prostate were seen. Groups of male and female rats were exposed to **TEA** by whole body vapor inhalation at concentrations of 0, 0.10 or 1.02 mg/L (nominal) for 6 hours/day, 5 days/week for 28 weeks; there were no gross or microscopic findings in reproductive organs up to the highest concentration tested. Following dietary administration of **DMCHA**, the NOAEL for reproductive toxicity and parental systemic toxicity was 1500 ppm (highest dose tested, equivalent to 91-104 and 85-147 mg/kg bw/day for males and females, respectively; nominal). The NOAEL for developmental toxicity from the study was 150 ppm (8.5-15 mg/kg bw/day) based on decreased pup weights at 500 and 1500 ppm (28-49 and 85-147 mg/kg bw/day).

The tertiary amines category members possess properties indicating a hazard for human health (acute toxicity for some of the tertiary amines; corrosive to skin, eyes, respiratory tract, and/or the site of contact; some systemic toxicity at higher doses following repeated exposure of TMA and by read-across to DMEA; developmental toxicity of DMCHA limited to decreased pup weights); based on read-across, TEA and DMEA may also cause similar developmental effects by the oral route.). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Environment

These substances are expected to be hydrolytically stable in the natural environment. The majority of the tertiary amines will likely exist as cations 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.

In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is estimated (one measurement for **TEA**) to occur with a half-life of <1 day. Based on absorbance properties, photodegradation is expected to be negligible. Biodegradation data for all the tertiary amines category members indicate that they are readily biodegradable in standard ready biodegradation tests [OECD TGs 301A, 301C and 301D].

For the tertiary amines, EPIWIN Level III fugacity modeling predicts that, when distributed equally to air, water and soil, for most of the amines (except **TMA**), the substances will partition more towards the soil compartment relative to the water compartment; the favored distribution towards soil increases proportionally with molecular weight of the primary amine. **TMA** will partition more towards the water compartment relative to the soil compartment. Minimal to negligible tertiary amines are predicted to partition to the air and sediment

compartments. Measured BCF values for **TEA** were <0.5-5 (0.5 mg/L) and <4.9 (0.05 mg/L) [OECD TG 305C]. Estimated BCF values were <1 (**TMA**), 3.16 (**DMEA**) and 19.84-35.66 (**DMCHA**). The tertiary amine category members are not expected to bioaccumulate.

The following acute toxicity test results have been determined for aquatic species; most tests were conducted in un-neutralized conditions although a few results are available for neutralized conditions. The un-neutralized tests conditions can be considered as worst case. In those tests where the OECD guideline recommended pH limits for fish [6.0 – 8.5] and *Daphnia* [6.0 – 9.0] were exceeded at the higher test concentrations, it is possible that the observed adverse effects may have been caused by a pH shift of the test medium.

Fish

Substance	Species	96 hr LC ₅₀ (mg/L)	Remark
TMA	<i>Leuciscus idus</i>	48 h LC ₅₀ = 610	nominal; not specified; neutralized pH 7.0
	<i>Leuciscus idus</i>	48 h LC ₅₀ = 25	nominal; not specified; not neutralized pH 10.2
	<i>Oryzias latipes</i>	48 h LC ₅₀ = 1000	nominal; static; pH not specified
DMEA	<i>Leuciscus idus</i>	>100	nominal; static; neutralized pH 8
	<i>Leuciscus idus</i>	38.3	nominal; static; not neutralized; pH at test start: 7.9-9.5; pH at test end: 7.7-7.8
TEA	<i>Oncorhynchus mykiss</i>	36	measured; flow-through; not neutralized pH 7.2-7.3
	<i>Danio rerio</i>	7 d, LC ₅₀ = 180; EC ₅₀ (total embryotoxicity) = 53; LOEC _(mortality) = 320; LOEC _(total embryotoxicity) = 100 [note: total embryotoxicity = lethality and malformations]	nominal; flow-through; not specified
DMCHA	<i>Leuciscus idus</i>	>100	nominal; static; neutralized pH 7.8-7.9
	<i>Leuciscus idus</i>	31.6	nominal; static; not neutralized; pH at test start: 8.3-10.0; pH at test end: 7.9-8.0, with pH not measured at two highest concentrations due to 100% mortality
	<i>Oncorhynchus mykiss</i>	28	measured; static; not neutralized pH 7.2-10

Invertebrates

Substance	Species	48 hr EC ₅₀ (mg/L)	Remark
TMA	<i>Daphnia magna</i>	139.95	nominal; static; not neutralized; pH at test start: 8.75-10.49; pH at test end: 8.11-9.33
DMEA	<i>Daphnia magna</i>	39.23	nominal; static; not neutralized; pH at test start: 8.89-10.57; pH at test end: 8.23-9.45
TEA	<i>Ceriodaphnia dubia</i>	17	measured; semi-static; not neutralized: pH at test start 8; pH at test end > 8.5 at 3 highest concentrations (out of 5)
	<i>Daphnia magna</i>	200	nominal; static; not neutralized; pH not specified
	<i>Ceriodaphnia dubia</i>	7 d, NOEC = 7.1 mg/L	measured, semi-static; not neutralized pH 8
DMCHA	<i>Daphnia magna</i>	75	measured; static; not neutralized pH 7.6-9.4

Algae

Substance	Species	72 hr EC ₅₀ (mg/L)	Remark
TMA	<i>Desmodesmus subspicatus</i>	ErC ₅₀ = 150; EbC ₅₀ = 90.6	nominal; not neutralized; pH at test start: 8.1-9.7; pH at test end (uninoculated) 8.2-8.5; pH at test (inoculated) 8.5-9.9

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DMEA	<i>Desmodemus subspicatus</i>	ErC ₅₀ = 24.2; EbC ₅₀ = 17	nominal; not neutralized; pH at test start: 8.6-9.4; pH at test end (uninoculated) 8.1-8.2; pH at test (inoculated) 8.3-9.0
TEA	No data located		read-across
DMCHA	<i>Desmodemus subspicatus</i>	ErC ₅₀ >2; EbC ₅₀ = 0.79	nominal; not specified

The following chronic toxicity test results have been determined:

Fish

Substance	Species	Result (mg/L)	Remark
TEA	<i>Oncorhynchus mykiss</i>	60d, LOEC _(body weight) = 3.2 m, LOEC _(body length) = 100, LOEC _(mortality) >100, LOEC _(total embryotoxicity) >100	nominal; semi-static; not specified

The tertiary amines category members possess properties indicating a hazard for the environment (acute aquatic toxicity values between 1 and 100 mg/L). The category members are readily biodegradable and are 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

In the sponsor country (United States), several companies reported manufacturing or importing the tertiary amines:

Substance	Production Volume (metric tons)
TMA	45,400 < 227,000
DMEA	454 < 4,540
TEA	4,540 < 22,700
DMCHA	454 < 4,540

Tertiary amines can be synthesized in various ways but the reaction between ammonia and alcohols forms the basis for most of the present commercial processes for making tertiary amines.

Major uses for the category members are as follows:

TMA. as a proton scavenger, an intermediate in the synthesis of a variety of organic chemicals, surfactant, as a solvent, as a warning agent in natural gas (due to its odor), and other applications include bacteriocides, disinfectants, insect attractant. The hydrochloride salt of **TMA** is used to make specialty chemicals in the electronics industry.

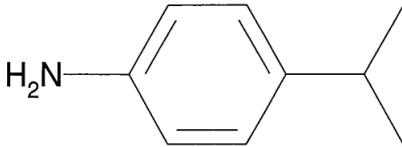
DMEA. mainly in the foundry industry, as a catalyst for the production of sand cores (cold box process). It is also used in the manufacturing of pharmaceutical active ingredients, intermediates in making other compounds, casting resins, and laboratory uses.

TEA. in the production of chemicals (principally as an organic base in the preparation of quaternary ammonium products but also in the synthesis of pesticides, pharmaceuticals, paints and coatings, and corrosion inhibitors, catalyst in polymerization reactions), in gas treatment, use in foundry and mining chemicals. an extraction solvent in pharmaceutical applications.

DMCHA. as a catalyst used primarily to promote the urethane (polyol - isocyanate) reaction in a wide range of rigid foam (insulation) applications. Other potential uses are in flexible foams, coatings, adhesives, sealants and elastomers, and a gel catalyst.

According to a survey of the American Chemistry Council Amines Panel producers, all of the members of the Tertiary Amines category are produced in closed systems. Inhalation and dermal exposure may be possible during occupational use. Primary uses of the tertiary amines are within industrial settings. However, some category members may be present in some consumer products. Some environmental releases are possible.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	99-88-7
Chemical Name	4-Isopropylaniline
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Physical-chemical properties**

4-Isopropylaniline is a liquid. The melting point and the boiling point are <-100 °C (measured) and 226-227 °C at 745 mmHg (measured), respectively. The density is 0.953 g/m³ at 20 °C (measured). The vapour pressure at 25 °C extrapolated from the experimental value is 5.62 Pa (measured). The partition coefficient between octanol and water (log K_{ow}) is 2.3 at 25 °C (measured) and the water solubility is 2390 mg/L at 20 °C (measured). The dissociation constant (pK_a) is 5.00 and shows that 4-isopropylaniline exists primarily as its neutral species in the environment at pH values between 6 and 9 (measured). Soil adsorption coefficient (log K_{oc}) is 2.53 by KOCWIN ver. 2.00. The Henry's law constant of 0.318 Pa.m³/mol at 20/25 °C is calculated by vapour pressure of 5.62 Pa at 25 °C divided by water solubility of 2390 mg/L at 20 °C.

Human Health

No specific studies were conducted on absorption, distribution, metabolism, or excretion in mammals. The following experimental data on the acute oral toxicity and repeated oral toxicity indicate that 4-isopropylaniline was absorbed via the gastrointestinal tract in rats and distributed via the circulatory system.

The oral LD₅₀ value was 985 mg/kg bw (95 % CL: 846–1146 mg/kg bw) in rats (OECD TG 401). 4-Isopropylaniline caused various changes in movement (abnormal gait and hypoactivity), posture (prone, lateral and hunchback position) and general condition (abnormal distention, lacrimation, salivation and dirty hair). Although there were no reliable data for acute inhalation and dermal toxicity, the dermal LD₅₀ value was reported to be 1000-1030 mg/kg bw in rats in the secondary literature.

In a primary dermal irritation study in rabbits (OECD TG 404), 4-isopropylaniline caused irreversible skin reaction (erythema, edema, scar formation, etc.) after 4-hour exposure. It was concluded that this chemical was corrosive to the skin. No data are available for eye irritation, but eye corrosivity is expected due to the physicochemical properties.

No data are available for skin sensitization.

The combined investigation of repeated dose toxicity and reproduction/developmental toxicity screening of 4-isopropylaniline with the application of OECD TG 422 is reported. 4-Isopropylaniline was administered by gavage to 12 animals/sex/dose at 0 (vehicle, corn oil), 6, 20, and 60 mg/kg bw/day for 48 days in males or from 14 days before mating to the third day of lactation in females (total, 41–45 days). One female of the 60 mg/kg bw/day group was found dead at day 25 of gestation (43rd administration day). No death was observed in male animals. Test substance-related effects such as anemic eyeballs and transient salivation were observed in both sexes (≥ 20 mg/kg bw/day) and pallor was noted in females during gestation (60 mg/kg bw/day). Hematology and clinical chemistry parameters showed anemia, and methemoglobin levels were significantly increased (≥ 20 mg/kg bw/day). The absolute and/or relative weights of the liver and spleen increased significantly in both sexes (60 mg/kg bw/day or ≥ 20 mg/kg bw/day). Abnormal histopathological findings were observed in the bone marrow (increase of hematopoiesis), spleen (congestion, deposits of pigment, and extramedullary

hematopoiesis), and liver (extramedullary hematopoiesis, deposits of pigment, and hypertrophy of hepatocytes) in both sexes (60 mg/kg bw/day or ≥ 20 mg/kg bw/day). Based on these findings, methemoglobinemia and/or anemia data, and related abnormal clinical signs and pathological findings, the no-observed-adverse-effect level (NOAEL) for repeated-dose oral toxicity was determined to be 6 mg/kg bw/day for both sexes.

In a bacterial reverse mutation assay performed according to OECD TG 471, 4-isopropylaniline was mutagenic to *Salmonella typhimurium* TA100 and TA1535 with exogenous metabolic activation. This chemical was negative in *Salmonella* strains TA98 and TA1537 and *Escherichia coli* WP2 *uvrA* with or without metabolic activation. In the HPRT-test with V79 Chinese hamster cells, 4-isopropylaniline did not induce gene mutations either with or without metabolic activation (OECD TG 476). In *in vitro* chromosomal aberration tests (OECD TG 473) in Chinese hamster lung fibroblast (CHL/IU) cells and V79 Chinese hamster cells, 4-isopropylaniline did not induce chromosomal aberrations with and without metabolic activation. In an *in vivo* micronucleus assay performed in mice according to OECD TG 474, 4-isopropylaniline did not induce chromosomal aberrations. Based on these results, 4-isopropylaniline was not considered to be clastogenic *in vitro* and *in vivo*, but it is not possible to exclude the genotoxicity of this chemical because the potential to cause gene mutations has not been investigated *in vivo*.

No data were available on the carcinogenicity of 4-isopropylaniline.

4-Isopropylaniline was investigated in a reproductive and developmental toxicity screening test conducted in rats according to OECD TG 422. One female parent of the 60 mg/kg bw/day group died during delivery at day 25 of gestation (43rd administration day). No abnormalities were observed on the reproductive organs and other reproductive parameters of parental animals. Effects on the offspring included a significant reduction of the viability index of male pups on day 4 after birth and body weight of male and female pups on the day of birth in the 60 mg/kg bw/day group. Based on these results, the NOAEL for reproductive toxicity in parental animals was determined to be 60 mg/kg bw/day, and the NOAEL for developmental toxicity in offspring was determined to be 20 mg/kg bw/day. However, developmental effects were observed only at a dose which induced significant systemic/maternal toxicity, and there were no other significant effects on developmental parameters of offspring.

4-Isopropylaniline possesses properties indicating a hazard for human health (corrosivity, repeated-dose toxicity and gene mutation *in vitro*). Adequate screening data are available to characterize the human health hazard for the purpose of the OECD Cooperative Chemicals Assessment Programme.

Environment

In the atmosphere, 4-isopropylaniline is expected to be degraded by hydroxyl radicals. A calculated half-life time of 0.081 days (sunlight is irradiated as 12 hours a day) is obtained by AOPWIN (version 1.92a) for the indirect photo-oxidation by reaction with hydroxyl radicals in air. This chemical is expected to photodegrade rapidly in the atmosphere.

A study according to OECD test-guideline 111 showed no hydrolysis of 4-isopropylaniline in water at pH 4, 7 and 9 in 50 °C after five days.

An OECD test guideline 301C test was conducted with 4-isopropylaniline 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 1 % degradation by BOD. According to the result, 4-isopropylaniline is considered to be not-readily biodegradable.

In a study performed according to OECD test-guideline 305 with carp exposed to 4-isopropylaniline, steady-state bio-concentration factors of 8.0 and 6.4 were obtained for the concentration of 10 µg/L and of 100 µg/L respectively for 28-day exposure period. Using an octanol-water partition coefficient (log K_{ow}) of 2.3, a bio-concentration factor of 21.7 was calculated with BCFBAF, version 3.01. This chemical is not expected to bioaccumulate.

Fugacity level III calculations show that 4-isopropylaniline is mainly distributed to the water compartment (19.9 %) and soil compartment (79.6 %) if equally and continuously released to the air, soil and water. A Henry's law constant of 0.318 Pa.m³/mole at 25 °C suggests that slight volatilization of 4-isopropylaniline from water is expected. A soil adsorption coefficient of log K_{oc} = 2.53 indicates 4-Isopropylaniline has moderate adsorption to soil and sediment.

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

Fish [*Oryzias latipes*]: 96 h LC₅₀ = 46 mg/L (nominal; all measured concentrations were

within 20% of the nominal, semistatic), OECD TG 203

Daphnid [*Daphnia magna*]: 48 h EC₅₀ = 1.5 mg/L (nominal, static), OECD TG 202

Algae [*Pseudokirchneriellasubcapitata*]: 72 h ErC₅₀ = 18 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 LOEC = 0.0093 mg/L (nominal, semistatic) , OECD TG 211

21 d NOEC = 0.0051 mg/L (nominal, semistatic) , OECD TG 211

Algae [*Pseudokirchneriellasubcapitata*]:

72 h LOErC = 1.73 mg/L (measured; growth rate, static) , OECD TG 201

72 h NOErC = 0.68 mg/L (measured; growth rate, static) , OECD TG 201

4-Isopropylaniline possesses properties indicating a hazard for the environment (acute aquatic toxicity values between 1 and 100 mg/L for fish, invertebrate and algae and chronic toxicity less than 1 mg/L for invertebrate and algae). This chemical is considered not readily biodegradable and has a low bioaccumulation potential. Adequate screening-level data are available to characterize the hazard to the environment for the purpose of the OECD Cooperative Chemicals Assessment Programme.

Exposure

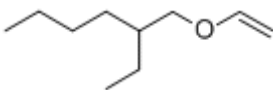
Production and/or import volume of 4-isopropylaniline in Japan (sponsor country) was reported to be <100 tonnes/year in fiscal year 2009. Production volume in the world is not available.

4-Isopropylaniline is manufactured with aniline and isopropyl alcohol or manufactured by nitration and subsequent reduction of cumene. 4-Isopropylaniline is used as a raw material for herbicide, dye and pigment. 4-Isopropylaniline results in the limited release to the environment as a chemical of raw materials for herbicide, dye and pigment in Japan.

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

As 4-isopropylaniline is used as an intermediate in herbicides, dyes and pigments, consumer exposure is considered to be negligible.

INITIAL TARGETED ASSESSMENT PROFILE

CAS No.	103-44-6
Chemical Name	2-Ethylhexyl vinyl ether
Structural Formula	

SUMMARY CONCLUSIONS OF THE TARGETED ASSESSMENT

NOTE: The present assessment is 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.

2-Ethylhexyl vinyl ether was evaluated as “not biodegradable (persistent)” and “moderately 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-ethylhexyl vinyl ether was conducted for the repeated dose toxicity and mutagenicity by MHLW (Ministry of Health, Labour and Welfare, Japan) in 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-Ethylhexyl vinyl ether is a clear colorless liquid at standard temperature and pressure. The melting point and boiling point are -100 °C and 177.7 °C, respectively. The measured value of partition coefficient between octanol and water (log K_{ow}) is 5.5. Vapour pressure is estimated to be 229 Pa at 25 °C. The measured value of water solubility is 1.8 mg/L at 25 °C.

Human Health

The oral LD₅₀ in rats was 1350 mg/kg bw, and the dermal LD₅₀ in rabbits was 3.56 mL/kg bw (equivalent to 2.9 mg/kg bw).

A 28-day repeated dose toxicity study in rats was conducted according to the Guideline under the Chemical Substances Control Law of Japan in compliance with GLP. In this study, 2-ethylhexyl vinyl ether was administered via gavage at 0 (vehicle control: olive oil), 8, 30 and 125 mg/kg bw/day for 28 days. No treatment-related death were observed in treated animals. No adverse effects were observed on clinical signs, results of manipulative test, grip strength, motor activity, or body weight. Urinary occult blood was observed in

males at 125 mg/kg bw/day. On blood chemistry examination, an increase in the ALP in males at 30 mg/kg bw/day and in females at 125 mg/kg bw/day was observed, and increases in the total cholesterol and the phospholipid were observed in males and females at 125 mg/kg bw/day. An increase in relative liver weight was observed in males at ≥ 30 mg/kg bw/day and in females at 125 mg/kg bw/day. An increase in relative kidney weight and relative testis weight were observed in males at 125 mg/kg bw/day. Histopathologically, the hypertrophy of centrilobular hepatocytes was observed in males at ≥ 30 mg/kg bw/day and in females at 125 mg/kg bw/day, single cell hepatocyte necrosis was also observed in male and female at 125 mg/kg bw/day. Eosinophilic body in the tubular cell in the kidney was observed in males at 125 mg/kg bw/day. Based on increases in the ALP and relative liver weight, and the hypertrophy of centrilobular hepatocytes observed in males at 30 mg/kg bw/day and in females at 125 mg/kg bw/day, the NOAELs of repeated dose oral toxicity are considered to be 8 mg/kg bw/day in males and 30 mg/kg bw/day in females.

In a bacterial mutation study (OECD TG 471) using *Salmonella typhimurium* and *Escherichia coli*, 2-ethylhexyl vinyl ether was negative with or without metabolic activation. In an *in vitro* chromosome aberration test (OECD TG 473) using CHL/IU cells, 2-ethylhexyl vinyl ether was also negative with or without metabolic activation. Based on these results, 2-ethylhexyl vinyl ether is not considered to be genotoxic *in vitro*.

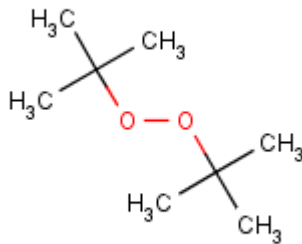
This chemical possesses properties indicating a hazard for one human health endpoint (repeated dose toxicity: liver toxicity) targeted in this assessment.

Exposure

Production and/or import volume of alkyl vinyl ether in Japan (sponsor country) was reported to be less than 1,000 tonnes in fiscal year 2010 according to the notification of annual manufactured and/or imported quantities under Chemical Substances Control Law. Production and/or import volume of 2-ethylhexyl vinyl ether is not available. Production volume in the world is not available.

2-Ethylhexyl vinyl ether is used as a raw material for resins or as an intermediate for pharmaceutical products and fragrances. 2-Ethylhexyl vinyl ether is also used in insecticides, adhesives and viscosity index improver.

SIDS INITIAL ASSESSMENT PROFILE

CAS No(s).	110-05-4
Chemical Name(s)	Di-tert-butyl peroxide (DTBP)
Structural Formula(s)	

SUMMARY CONCLUSIONS OF THE SIAR**Physical-chemical Properties**

DTBP is a liquid with a melting point of <-29 °C (measured), a boiling point of >80 °C (decomposes) and a measured vapour pressure of 32.97 hPa at 20 °C. The measured octanol-water partition coefficient ($\log K_{ow}$) is 3.2 at 22 °C, and the measured water solubility is 171 mg/L at 20 °C.

Human Health

No toxicokinetic data are available. Based on physical-chemical properties (e.g. water solubility and octanol-water partition coefficient), some degree of absorption would be expected by the dermal and oral route. Clinical signs suggested that absorption of DTBP occurred in an acute inhalation study. Similarly, systemic effects in a repeated dose study also supports absorption following oral exposure. *In vivo*, glutathione peroxidases are expected to catalyze the reduction of organic peroxides to the corresponding stable alcohols and water using cellular glutathione as the reducing agent.

Acute toxicity data with rats are available for the inhalation, oral and dermal route for DTBP. The acute inhalation 4-h LC_{50} of DTBP, is > 22.6 mg/L air (limit concentration; analytical vapour concentration; OECD TG 436). Shivering and tachypnea were observed during exposure, and shortly following exposure; ruffled fur was observed in all animals from 1 hour after exposure until day 2. The acute dermal LD_{50} was >2000 mg/kg bw [OECD TG 402]. The acute oral toxicity LD_{50} was >2000 mg/kg bw [OECD TG 423]. Clinical signs of toxicity were limited to slight shivering seen in one female 3 hours following oral exposure to DTBP. DTBP is not irritating to the skin [OECD TG 404] or eyes [OECD TG 405] of rabbits. In a standard skin sensitization study in guinea pigs [OECD TG 406], DTBP was not considered a skin sensitizer.

Repeated-dose toxicity data are available for DTBP by the oral route of exposure. In a combined repeated-dose/reproductive/developmental toxicity screening test [OECD TG 422], rats (10/sex/dose) were exposed to DTBP by gavage at 0, 100, 300 or 1000 mg/kg-bw/day for 42 days (males) and ≥ 42 days (females). Increased relative weights; minimal centrilobular and diffuse hepatocellular hypertrophy in liver; moderate diffuse tubular degeneration/regeneration with slight multifocal single cell necrosis and hyaline casts as well as hyaline droplets in kidneys of males was observed at 1000 mg/kg bw/day; at 300 mg/kg bw/day increased relative liver and

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kidney weights were observed (males and females). The No Observed Adverse Effect Level (NOAEL) was 100 mg/kg bw/day.

Negative *in vitro* bacterial [OECD TG 471; bacterial reverse mutation assay] and mammalian mutagenicity assays [OECD TG 476; *In vitro* mammalian cell gene mutation test] are available for DTBP. Mixed results for the induction of chromosomal aberrations *in vivo* were reported for DTBP; the substance was negative in OECD TG 483 (mammalian spermatogonial chromosome aberration test; intraperitoneal (i.p.) injection in mice) and positive/weakly positive in OECD TG 474 (mammalian erythrocyte micronucleus test; in mice exposed by i.p. injection or oral gavage). The weight of evidence suggests DTBP is mutagenic *in vivo*.

No data are available for the carcinogenicity of DTBP.

Reproductive and developmental toxicity data are available for DTBP by the oral route of exposure. In a combined repeated-dose/reproductive/developmental toxicity screening test [OECD TG 422] (see description of repeated-dose toxicity above for study details), no reproductive and/or developmental effects were observed in rats administered DTBP up to 1000 mg/kg bw/day (limit dose). The systemic NOAEL is 100 mg/kg bw/day; the NOAEL for reproductive toxicity was 1000 mg/kg bw/day (highest dose tested).

DTBP possesses properties indicating a hazard for human health [repeated-dose toxicity (liver and kidney effects) following oral exposure and mutagenic *in vivo*]. Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Environment

In an OECD TG 111 study, DTBP was reported as stable to hydrolysis; the results of the tests at pH 4.0, pH 7.0 and pH 9.0 showed no significant degradation at 50 °C (less than 10% after 5 days).

In the atmosphere, indirect photooxidation by reaction with hydroxyl radicals for DTBP is predicted to occur with a half-life of 2 days. An OECD TG 301D with DTBP resulted in 6% biodegradation after 28 days; DTBP is not readily biodegradable under aerobic conditions.

A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that DTBP will distribute mainly to the water (45.1%) and air (38.5%) compartments with some distribution to the soil compartment (14.8%) and minor amount in the sediments compartment (1.6%). A Henry's law constant has been estimated for DTBP of 1210 Pa·m³/mole at 25 °C.

DTBP is not expected to bioaccumulate in the aquatic environment based on an estimated BCF = 60.03 L/kg wet-wt (BCFBFAF v3.00).

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

Fish, acute toxicity		
DTBP	[<i>Poecilia reticulata</i>] 96 h LC ₅₀ >water solubility ¹	nominal; semi-static
Invertebrate, acute toxicity		
DTBP	[<i>Daphnia magna</i>] 48 h EC ₅₀ >73.1 mg/L ²	measured; static; nominal limit concentration of 150 mg/L
Algae, acute toxicity		
DTBP	[<i>Pseudokirchneriella subcapitata</i>] 72 h ErC ₅₀ = 36 mg/L 72 h EyC ₅₀ = 15 mg/L NOECr = 3.9 NOECb = 1.2	measured

¹Level of water solubility= 171mg/L at 20C (measured)

²Toxicity was not observed.

DTBP possesses properties indicating a hazard for the environment (acute toxicity to algae between 1-100 mg/L). DTBP is not 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.

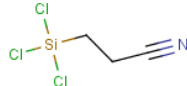
Exposure

In the sponsor country (United States), the production of DTBP in 2005 was 1-10 million pounds (450 - 4500 tonnes). Worldwide production of DTBP was estimated to be approximately 10-50 kilo tonnes in year 2010. DTBP has industrial uses. It is used in the production of polyolefins, for crosslinking/grafting polyethylene, for crosslinking rubber (ethylene propylene diene monomer (EPDM), ethylene-vinyl acetate (EVA)), for polypropylene degradation, and for emulsion polymerization. It may also be used in acrylic resin manufacturing.

Potential releases to the environment (expected to be limited) and industrial worker exposure may occur during manufacture (open and closed systems), use and spills. During manufacturing processes in which dialkylperoxides are used, the process materials are typically held at a thermal decomposition temperature for many half-lives. These products are typically incorporated at a use rate of 0.1-3% before heat exposure. However, after processing with heat exposure (e.g., extrusion or vulcanization), negligible quantities of the dialkylperoxides remain.

DTBP is most typically used as an intermediate. DTBP may be used in food contact products. DTBP is regulated for use as an accelerator for rubber articles intended for repeated use (total not to exceed 1.5% process input by weight of the rubber product). Thus, exposure to the consumer is also expected to be negligible.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	1071-22-3
Chemical Name	3-(Trichlorosilyl)propionitrile (CNT)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Analogue Justification**

3-(Trichlorosilyl)propionitrile (CNT), like all chlorosilanes, reacts rapidly when exposed to moisture or polar reagents, producing hydrogen chloride (HCl; CAS No. 7647-01-0) and the corresponding silanol: specifically, 3-(trihydroxysilyl)propanenitrile (CAS No. 182156-21-4). The hydrolysis half-life of CNT is predicted using an analogous substance, trichloro(methyl)silane (C3MS, CAS No. 75-79-6). C3MS has previously been assessed in the OECD HPV Programme as a member of the alkyl chlorosilanes category.

For mammalian toxicity and acute aquatic toxicity endpoints, data are provided for two structurally similar analogues and one hydrolysis product as follows: the sponsored substance, CNT, is structurally analogous to 3-(triethoxysilyl)propanenitrile (CNE, CAS No. 919-31-3). Both CNT and CNE hydrolyze to form 1 mole of 3-(trihydroxysilyl)propanenitrile (CAS No. 182156-21-4). CNT forms 3 moles of HCl per mole of silanetriol; CNE forms 3 moles of ethanol per mole of silanetriol. CNE and HCl have previously been assessed in the OECD HPV Programme (<http://www.oecd.org/env/hazard/data> and <http://www.chem.unep.ch/irptc/sids/OECDSIDS/7647010.pdf>, respectively). Although ethanol is a hydrolysis product associated with the analogue substance, CNE, the primary human health hazard for CNT is considered to be exposure to the hydrolysis product, HCl. Similar structures and rapid hydrolysis to the same silanol hydrolysis product support the use of CNE data for the mammalian and aquatic toxicity endpoints. The levels of CNT required to generate significantly toxic concentrations of silanols would result in toxic HCl concentrations. 3-(Trihydroxysilyl)propanenitrile cannot be isolated for testing as it is not stable. Trimethoxysilane (TMS; CAS No. 2487-90-3) is used as an analogue for acute aquatic toxicity endpoints since it hydrolyzes rapidly to form 1 mole of the silanetriol, trihydroxysilyl-silane. This analogue informs the potential toxicity associated with the silanetriol functionality in the absence of HCl. TMS has previously been assessed in the OECD HPV Programme (<http://www.oecd.org/env/hazard/data>).

Physical-chemical properties

CNT is a solid at 20°C with a measured melting point of 32 - <33°C and a measured boiling point of 95°C at 2.27 kPa (17 Torr). The extrapolated vapor pressure value from measured data is 93 Pa at 25 °C. The calculated water solubility is 1366 mg/L. The estimated log Kow of CNT is 1.52. The water solubility, log Kow and Henry's law constant values may not be relevant because the chemical is hydrolytically unstable.

Human Health

No data are available on the toxicokinetics of CNT. However, CNT rapidly hydrolyzes on contact with moisture generating 3 moles of HCl per mole of silanetriol. Hydrogen chloride dissociates; its effects are thought to be a result of pH change.

No experimental data are available for the human health endpoints for CNT.

Acute toxicity data are available for the structural analogue, CNE and the hydrolysis product, HCl. The acute inhalation hazard posed by a chlorosilane, as defined by an LC₅₀ value, is directly proportional to its chlorine content and subsequently to the HCl that is liberated during hydrolysis. The principal clinical signs were indicative of respiratory and ocular effects. Based on the testing of a range of analogous chlorosilanes, the range of 1 hour acute inhalation LC₅₀ for CNT is 8.41-10.64 mg/L (calculated). Inhalation LC₅₀ values for HCl were determined to be 4.2-4.7 mg/L for 1 hour for rats. The dermal LD₅₀ of the analogous substance, CNE, in male rabbits is 5,753 mg/kg bw; erythema with slight necrosis was observed at the application site. At the high dose, slightly congested lungs, pale and pitted kidneys and mottled livers were seen at necropsy. The oral LD₅₀ of CNE in male rats is 5,600 mg/kg bw; clinical signs included violent convulsions prior to death. Hemorrhagic lungs, mottled livers and kidneys and slightly congested adrenals were seen at necropsy. The acute oral LD₅₀ values of HCl were determined to be 238-277 mg/kg bw for female rats. Based on HCl formation, CNT possesses properties indicating possible hazards for acute inhalation toxicity, skin, eye, and respiratory tract irritation. There were no data located for skin sensitization of CNT or analogous substance CNE.

Repeated-exposure data are available for the analogous substance, CNE, and the hydrolysis product, HCl, to address the repeated-dose toxicity endpoint via inhalation and oral exposure. 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. In a combined oral repeated-dose/reproductive/developmental toxicity screening study conducted under OECD TG 422, the analogous substance, CNE was administered via oral gavage to 10 male and 20 female (10 toxicity group and 10 reproductive group females) rats at doses of 100, 500, and 1000 mg/kg-bw/day. A concurrent vehicle control group (corn oil) was also included. Males and toxicity group females were sacrificed after they had been treated for 28 days; reproductive group females were dosed 14 days before mating to day 3 of lactation up to a maximum of 44 days; reproductive group females and pups were sacrificed on day 4 postpartum. Increased organ weights (kidneys, spleen, heart and liver in males; kidneys and spleen in toxicity group females), slight reduction in red cell count (not statistically significant), hemoglobin concentration and hematocrit in males and toxicity group females and histopathological changes in kidneys (chronic tubular lesions of minimal to moderate severity with hyperplasia of the renal pelvis epithelium and renal pyelonephritis) were noted in males and toxicity group females dosed at 1000 mg/kg-bw/day. Administration of 500 mg/kg-bw/day resulted in increased organ weights (kidneys, heart and liver in males only) and histopathological changes in kidneys including chronic tubular lesions, hyperplasia of the renal pelvis epithelium and renal pyelonephritis (males and toxicity group females) and spleen including extramedullary hematopoiesis (males only). Based on these data, the NOAEL for systemic toxicity of CNE was considered to be 100 mg/kg-bw/day, with LOAEL of 500 mg/kg-bw/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 and LOAEC for systemic toxicity of HCl, excluding the local effects of irritation, have been determined to be 0.030 mg/L and 0.075 mg/L, respectively, for rats and mice. For repeated dose toxicity, local irritation effects were observed in the groups of 10 ppm and above in a 90-day inhalation study in compliance with FDA-GLP.

Genetic toxicity data are available for the analogous substance, CNE, and the hydrolysis product, HCl. CNE and HCl did not induce gene mutations [OECD TG 471] in bacteria *in vitro*. CNE did not induce chromosomal aberrations [OECD TG 473] in mammalian cells *in vitro*. 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, CNT is not expected to be genotoxic.

Carcinogenicity data are available for HCl. No pre-neoplastic or neoplastic nasal lesions were observed in a 128-week inhalation study with male rats at 10 ppm hydrogen chloride gas. No evidence of treatment related carcinogenicity was observed either in other animal studies performed by inhalation, oral or dermal administration. In humans, no association between hydrogen chloride exposure and tumor incidence was observed.

Reproductive/developmental toxicity data are available for the analogous substance, CNE. In the repeated-dose/reproductive/developmental toxicity screening test described above (OECD TG 422), systemic (parental) toxicity was seen at 500 mg/kg-bw/day and higher. Clinical signs of discomfort after test substance administration were seen such as pushing head through bedding material, stretched forelimbs and saltatory spasms. No effects were seen on reproductive organs of either sex in the toxicity groups and the reproductive group females. No effects were seen in the reproductive indices or development of fetuses. Therefore, the NOAEL for reproductive and developmental toxicity of CNE in the above combined repeated-dose/reproductive/developmental toxicity screening test is 1000 mg/kg-bw/day, the highest dose tested. The NOAEL for maternal toxicity is 100 mg/kg-bw/day. Based on these results, CNE has not shown any potential for reproductive or 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 protons and chloride ions are 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 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 good quality 90-day inhalation study up to 50 ppm.

CNT possesses properties indicating a hazard for human health (acute inhalation, severe skin, eye and respiratory tract irritation, 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.

A hydrolysis study was not conducted on CNT. Using an analogous substance, trichloro(methyl)silane (CAS No 75-79-6), CNT is expected to hydrolyze to HCl and the corresponding silanol in less than 1 minute at pH 4, 7 and 9 at 1.5°C. This is further supported by the results for two additional chlorosilane materials (Alkyl Chlorosilanes Category: SIAM 31: (<http://www.oecd.org/env/hazard/data>)), which are less similar to CNT than trichloro(methyl)silane, but that all had half-lives of less than 1 min at 1.5 °C. Observed rates of hydrolysis were so rapid in all cases that it was not possible to distinguish among the different pH conditions. CNT in air is not expected to undergo direct photolysis, but may undergo indirect photolysis through hydroxyl radical oxidation. The hydroxyl radical reaction was calculated using a 12-hr day and a hydroxyl radical concentration of 1.5E6 OH/cm³ in AOPWIN® ver. 1.92. The overall OH rate constant and estimated half-life are 0.3416 E-12 cm³/molecule-sec and 31.3 days, respectively. Any potential for photodegradation might be superseded by hydrolysis of the parent compound depending on the concentration of water vapor in the air. A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that the unreacted portion of CNT will distribute mainly to air and soil (47.5 and 47.7 %), with minor distributions to water (4.77 %) and negligible distribution to sediment (< 0.1 %) (EPI Suite (v4.10)). If released only to the air compartment (the most likely release scenario), any unreacted CNT stays in the air compartment (100%). Level III fugacity modeling, using equal loading rates of 1000 kg/h each for air, soil and water predicts that the hydrolysis product, 3-(trihydroxysilyl)propanenitrile will degrade extensively (84.7%). The remaining fraction distributes mainly to soil (78.9 %), with a small fraction going to water (21.0 %) and negligible distributions to air and sediment (< 0.1 %). Based on the more realistic scenario of 100% release to air, the fugacity modeling predicts that 3-(trihydroxysilyl)propanenitrile will degrade extensively (92.7%) in soil and water. The remaining fraction will distribute mainly to soil (91.7%), with a smaller fraction going to water (8.3%) and negligible fractions in air and sediment (<0.1%) (EPI Suite (v4.10)). Fugacity modeling of HCl is not applicable. The biodegradation of CNT was not determined due to rapid hydrolysis; 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). No measured data are available for the hydrolysis product 3-(trihydroxysilyl)propanenitrile exclusively, as it cannot be isolated for testing. The polymers are water insoluble and effectively nonbiodegradable. HCl is an inorganic compound and biodegradation tests are not applicable.

The bioaccumulation potential of CNT was not determined due to rapid hydrolysis. The estimated BCF for CNT using BCFBAF v3.01, is 4.679 L/kg wet-wt, indicating CNT is not expected to bioaccumulate.

Aquatic toxicity data are not available for CNT; the substance undergoes rapid hydrolysis, which occurs during testing; exposure to parent chlorosilane is likely to be transient and observed toxicity is likely due its hydrolysis products, HCl and 3-(trihydroxysilyl)propanenitrile. Aquatic toxicity data are available for analogous substance CNE; based on the hydrolysis half-life of 6.5 hours, the organisms were likely exposed to CNE and the hydrolysis products, ethanol and 3-(trihydroxysilyl)propanenitrile. The fish and daphnia studies on CNE were conducted as flow-through studies. The parent (unhydrolyzed) material was measured at ~ 85-90% of nominal, so most of the exposure was likely to be the parent triethoxy material. In the algae test, the material was >95% hydrolyzed after 72-h, and likely represents exposure to the silanol. The degree of toxicity caused by HCl is highly dependent on the buffer capacity of the receiving water. Aquatic toxicity endpoints for CNT are also fulfilled through the use of data from the hydrolysis product, HCl and analogous substance, TMS. TMS is used as an analogue for acute aquatic toxicity endpoints since it hydrolyzes to form 1 mole of the silanetriol, trihydroxysilyl-silane. This analogue informs the potential toxicity associated with the silanetriol functionality in the absence of HCl. Based on the rapid hydrolysis of TMS (0.2 minutes at pH 7 and 2 °C), and the static exposures; the

organisms were likely exposed to the hydrolysis products, methanol and silanetriol.

Fish

CNE [<i>Oncorhynchus mykiss</i>]	96 h LC ₅₀ >110 mg/L (OECD TG 203; flow-through, measured)
TMS [<i>Oncorhynchus mykiss</i>]	96 h LC ₅₀ >=100 mg/L (OECD TG 203; static, nominal)
HCl [<i>Oncorhynchus mykiss</i>]	96 h LC ₅₀ = 4.92 mg/L (pH = 4.3; semi-static,)

Aquatic Invertebrate

CNE [<i>Daphnia magna</i>]	48 h EC ₅₀ > 100 mg/L (OECD TG 202; flow-through, measured)
TMS [<i>Daphnia magna</i>]	48 h EC ₅₀ > 100 mg/L (OECD TG 202; static, nominal)
HCl [<i>Daphnia magna</i>]	48 h LC ₅₀ = 0.492 mg/L as 12 M HCl (pH = 5.3; nominal)

Algae

CNE [<i>Pseudokirchneriella subcapitata</i>]	72 h ErC ₅₀ and EbC ₅₀ > 3.6 mg/L (OECD TG 201; measured)
TMS [<i>Pseudokirchneriella subcapitata</i>]	72 h ErC ₅₀ and EbC ₅₀ > 100 mg/L (OECD TG 201; nominal)
HCl [<i>Selenastrum capricornutum</i>]	72 hr EC ₅₀ = 0.492 mg/L (pH = 5.3) (OECD TG 201; nominal)

Hydrogen Chloride (HCl)

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 for 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.

CNT possesses 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). CNT is not expected to be readily biodegradable and expected to have a low potential for bioaccumulation. Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Exposure

The 2010 production volumes in the United States (sponsor country) and Europe are between 500 – 5,000 tonnes and 454 - 2722 tonnes, respectively. Production was not reported in Japan. 100% of CNT is used as an intermediate for silicone oligomers, polymers, organosilane production. These uses are the same in North America, Europe and Japan.

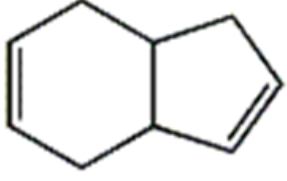
There is no intentional release of CNT to the environment.

CNT is produced and processed in closed systems; it is not shipped. Due to the dynamic and exothermic nature of the processes incorporating chlorosilanes, many engineering controls are in place at companies sponsoring this product to prevent occupational exposure including water scrubber devices and related equipment including ventilation; closed sampling loop; nitrogen pad on system; Distributed Control System (DCS) control of process with instrumentation. Employees involved in chlorosilane production and application are required to use personal protective equipment (PPE) such as safety glasses or goggles, steel-tipped shoes, flame-resistant clothing, hard hat, chemical resistant gloves; respirator with organic vapor cartridges; slicker suit. 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 the irritating or corrosive properties of chlorosilanes.

Potential routes of occupational exposure during routine operations (such as sampling operations, waste disposal and equipment maintenance) at the manufacturing site include inhalation and dermal exposure.

There are no consumer uses of CNT.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	3048-65-5
Chemical Name	3a,4,7,7a-Tetrahydroindene
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Physical-chemical properties**

3a,4,7,7a-Tetrahydroindene is a pale yellow clear liquid. The melting point and boiling point are <-100 °C (measured) and 158.9 °C (measured), respectively. The density is 0.9255 g/m³ at 20 °C (measured). The vapour pressure extrapolated from the experimental value is 694 Pa (measured) at 25 °C. The water solubility is 37.4 mg/L at 20 °C (measured). The partition coefficient between octanol and water (log K_{ow}) is 3.83 (measured) and water solubility is 37.4 mg/L at 25 °C (measured). The soil adsorption coefficient (log K_{oc}) is 2.93 by KOCWIN ver. 2.00. The Henry's law constant of 2230 Pa.m³/mole at 20/25°C is calculated by vapour pressure of 694 Pa at 25 °C divided by water solubility of 37.4 mg/L at 20 °C.

Human Health

No specific studies were conducted on absorption, distribution, metabolism, or excretion in mammals. In a combined repeated dose and reproduction/developmental toxicity screening study described below, the data indicated that 3a,4,7,7a-tetrahydroindene was absorbed via gastrointestinal tract, and distributed to the liver and kidneys.

The oral LD₅₀ value in female rats was >2000 mg/kg bw (OECD TG 423). 3a,4,7,7a-Tetrahydroindene caused temporary effects such as decreased locomotor activity, ptosis of eyelid, salivation, and slightly inhibited body weight gain. There is no information on acute dermal and acute inhalation studies.

No data are available for skin and eye irritation.

No data are available for skin sensitization.

A combined investigation of repeated dose toxicity and reproduction/developmental toxicity screening of 3a,4,7,7a-tetrahydroindene according to the OECD TG 422 has been reported. 3a,4,7,7a-Tetrahydroindene was administered by gavage to 12 animals/sex/dose at doses of 0 (vehicle, olive oil), 67, 200, and 600 mg/kg bw/day for 46 days (males) or from 14 days before mating to the third day of lactation (females: up to 46 days in total). Body weight gain was significantly suppressed in both sexes (≥ 200 mg/kg bw/day). Hematology of male animals (600 mg/kg bw/day) revealed significant but slight (only 5-6 %) decreased red blood cell (RBC) counts, hematocrit values (Ht), and hemoglobin concentrations (Hb). Absolute and/or relative liver weights were significantly increased in both sexes (male: 600 mg/kg bw/day; female: ≥ 200 mg/kg bw/day). Absolute and relative weights of both kidneys were significantly increased (male: ≥ 67 mg/kg bw/day; female: 600 mg/kg bw/day). Histopathological examination in male revealed slight hypertrophy of centrilobular hepatocytes (600 mg/kg bw/day), increase of hyaline droplets (≥ 67 mg/kg bw/day) and eosinophilic bodies of the proximal tubular epithelium in the kidney (600 mg/kg bw/day). However, these histopathological changes in the kidney are associated with accumulation of $\alpha 2u$ -globulin, a male rat-specific toxicity, and these effects are not likely related to human health. No histopathological changes were observed in female kidney. The NOAELs were considered to

be 67 mg/kg bw/day based on the effects on the liver and the decrease in body weight.

In a bacterial reverse mutation assay performed according to the OECD TG 471, 472 and the guidelines for screening mutagenicity testing of chemicals (Japan), 3a,4,7,7a-tetrahydroindene was negative in all strains tested, *Salmonella typhimurium* and *Escherichia coli*, with or without metabolic activation. In an *in vitro* chromosomal aberration test (OECD TG 473 and guidelines for screening the mutagenicity testing of chemicals, Japan) in Chinese hamster lung fibroblast (CHL/IU) cells, 3a,4,7,7a-tetrahydroindene induced structural chromosomal aberrations with metabolic activation. However, the result of this study was equivocal, because the induced chromosomal aberrations were only observed at the concentration with significant cytotoxicity (>50% decrease of mitotoxic index). In an *in vivo* micronucleus assay performed in mice according to the OECD TG 474, 3a,4,7,7a-tetrahydroindene was negative. Based on these results, this test substance was considered to be nongenotoxic *in vivo*.

No data were available on the carcinogenicity of 3a,4,7,7a-tetrahydroindene.

The reproduction/developmental toxicity of 3a,4,7,7a-tetrahydroindene was also investigated in the test described above (OECD TG 422). No abnormality was observed in any male reproductive organs. In females of the 600 mg/kg bw/day group, significant decreases were observed in the numbers of corpora lutea and implantations along with elongation of gestation. 3a,4,7,7a-Tetrahydroindene had no effect on the reproductive organs and other reproductive parameters, such as estrus cycle, or maternal behavior. The numbers of offspring or live offspring at birth were significantly decreased in the 600 mg/kg bw/day group, and these effects were considered to be caused by the decreased number of corpora lutea in the dams. Maternal toxicity was observed in dams at the top dose level (decreased body weight gain); however, the extent of this toxicity is not considered sufficient to dismiss all the effects observed (e.g. no of corpora lutea and gestation length) as a secondary, non-specific consequence of maternal toxicity. No abnormal findings were found on external or internal examinations or clinical signs of the offspring. Based on these results, the NOAELs of reproductive and developmental toxicity were determined to be 200 mg/kg bw/day for females and offspring, and 600 mg/kg bw/day for males, respectively.

3a,4,7,7a-Tetrahydroindene possesses properties indicating a hard for human health (repeated-dose toxicity and reproductive toxicity). Adequate screening data is available to characterize the human health hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Environment

3a,4,7,7a-Tetrahydroindene entering in the atmosphere is expected to be degraded by hydroxyl radicals. Using AOPWIN (version 1.92a), a calculated half-life time of 0.089 days and a rate constant of $120.0 \times 10^{-12} \text{ cm}^3/\text{molecule-sec}$ are obtained for the indirect photo-oxidation of 3a,4,7,7a-Tetrahydroindene by reaction with hydroxyl radicals in air.

3a,4,7,7a-Tetrahydroindene is not hydrolyzed due to the lack of hydrolysable functional groups. A study according to OECD test-guideline 111 showed no hydrolysis of 3a,4,7,7a-tetrahydroindene in water at pH 4, 7 and 9 in 50 °C after five days.

An OECD test guideline 301C study was conducted in compliance with GLP on 3a,4,7,7a-tetrahydroindene with activated sludge at a test concentration of 100 mg/L. The test result showed 0 % biodegradation by BOD after four weeks. Overall, 3a,4,7,7a-tetrahydroindene is considered to be not readily biodegradable.

In a study performed according to OECD test-guideline 305 with carp exposed to 3a,4,7,7a-tetrahydroindene, bio-concentration factors of 160-335 and 102-285 were obtained for concentrations of 10 µg/L and of 100 µg/L of the chemical respectively for 28-day exposure period. This chemical has low bioaccumulation potential.

Fugacity modeling (level III) for 3a,4,7,7a-tetrahydroindene was conducted using EPISUITE, version 4.0. When equal and continuous release to air, water and soil is assumed, 3a,4,7,7a-tetrahydroindene is mainly distributed in water and soil compartments. A Henry's law constant of 2230 Pa.m³/mole at 20/25 °C suggests that 3a,4,7,7a-tetrahydroindene is expected to be volatile from water. A soil adsorption coefficient of $\log K_{oc} = 2.93$ indicates 3a,4,7,7a-tetrahydroindene has moderate adsorption to soil and sediment.

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

Fish [*Oryzias latipes*]: 96 h LC₅₀ = 4.4 mg/L (measured, semistatic), OECD TG 203

Daphnid [*Daphnia magna*]: 48 h EC₅₀ = 0.73 mg/L (measured, semistatic), OECD TG 202

Algae [*Pseudokirchneriella subcapitata*]: 72 h ErC₅₀ = 7.0 mg/L (measured, growth rate, static, closed), OECD TG 201

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

Daphnid [*Daphnia magna*]: 21 d LOEC = 0.35 mg/L (measured, semistatic) , OECD TG 202 part II
21 d NOEC = 0.12 mg/L (measured, semistatic) , OECD TG 202 part II

Algae [*Pseudokirchneriella subcapitata*]:
72 h NOErC = 0.66 mg/L (measured; growth rate, static, closed) ,
OECD TG 201

3a, 4, 7, 7a-Tetrahydroindene possesses properties indicating a hazard for the environment (acute aquatic toxicity values between 1 and 10 for fish and algae and less than 1 mg/L for invertebrate and chronic toxicity less than 1 mg/L for invertebrate and algae). This chemical is considered 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

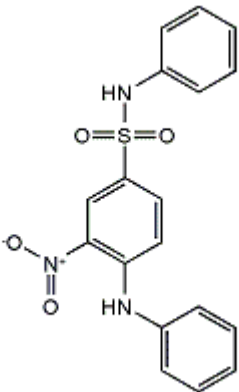
According to the information by a supplier in Japan, production volume of 3a,4,7,7a-tetrahydroindene was 1,800 tonnes in fiscal year 2011. In USA, total amounts of production and/or import was reported to be 1 to 10 million pounds (454 to 4540 tonnes) in 2006. Production volume in the world is not available.

According to the information by a supplier, 3a,4,7,7a-tetrahydroindene is obtained as a by-product oil during synthesis of vinylbornene from butadiene and cyclopentadiene. 3a,4,7,7a-Tetrahydroindene is manufactured in continuous process, and only used as a fuel. In all lifecycle-stages from the production to the consumption, 3a,4,7,7a-tetrahydroindene is treated in complete closed system. Therefore, environmental exposure of 3a,4,7,7a-tetrahydroindene is expected to be low.

Occupational exposure through inhalation of vapour and dermal route is anticipated when a worker handles this chemical directly. However, in the sponsor country, worker exposure may not be a concern because this chemical is produced in a closed system as a by-product without commercial use, and used as a fuel at production site.

As 3a,4,7,7a-tetrahydroindene is not used for consumer products, no consumer exposure is expected.

INITIAL TARGETED ASSESSMENT PROFILE

CAS No.	5124-25-4
Chemical Name	Disperse Yellow-42
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.

Disperse Yellow-42 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 Disperse Yellow-42 was conducted for the acute toxicity, repeated dose toxicity and mutagenicity by MHLW (Ministry of Health, Labour and Welfare, Japan) in June 2002 and December 2004.

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

Disperse Yellow-42 is a yellow solid at standard temperature and pressure. The measured value of melting point is 159.85 °C and the boiling point is calculated to be 536.07 °C by MPBPWIN. The measured partition coefficient between octanol and water (log Kow) is 4.60. The density is estimated to be 1.3786 g/cm³ at 25 °C. The vapour pressure is calculated to be 2.02 × 10⁻⁸ Pa at 25 °C by MPBPWIN. The measured water solubility is 0.2 mg/L at 25 °C.

Human Health

An acute oral toxicity study in rats was conducted according to OECD TG 401 under the principles of GLP. No death or toxicologically significant clinical signs were observed at 2000 mg/kg bw. Therefore, the oral LD₅₀ value was estimated to be greater than 2000 mg/kg bw for both sexes in rats.

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, Disperse Yellow-42 was administered to rats via gavage at 0 (vehicle control: 0.5% sodium carboxymethylcellulose solution), 100, 300 and 1000 mg/kg bw/day for 28 days. No death or clinical signs of toxicity were observed, and no adverse effects were found in terms of body weight, urinalysis, hematology or blood biochemistry in any group. In urinalysis, the yellowish color of urine was observed at 100 and 1000 mg/kg bw/day, but this was considered to be attributed to the color of the test substance. The relative liver and spleen weights were increased at 1000 mg/kg bw/day in females. Histopathological examination revealed centrilobular hypertrophy of hepatocytes in 3/5 males given 1000 mg/kg bw/day, but no histopathological changes were observed in the spleen. After the 14-day recovery period, centrilobular hypertrophy of hepatocytes was observed in 1/5 male in the 1000 mg/kg bw/day group, but no significant changes were found in the liver and spleen weight. Based on the hepatocyte hypertrophy in males and increased relative liver and spleen weights in females at 1000 mg/kg bw/day, the NOAEL of Disperse Yellow-42 in this 28-day study was concluded to be 300 mg/kg bw/day in both sexes.

In a bacterial mutation study using *Salmonella typhimurium* and *Escherichia coli* [OECD TG 471], Disperse Yellow-42 was negative with or without metabolic activation. In an *in vitro* chromosome aberration test using CHL/IU cells [OECD TG 473], Disperse Yellow-42 induced structural chromosomal aberrations after 6 hr short-term treatment with metabolic activation. Polyploidy was not induced in any treatment group. Based on these results, Disperse Yellow-42 is considered to be genotoxic *in vitro*.

Agreed hazard conclusions

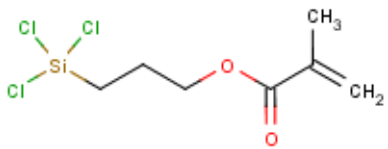
This chemical possesses properties indicating a hazard for one human health endpoint (chromosomal aberrations *in vitro*) targeted in this assessment.

Available Exposure

Production and/or import volume of Disperse Yellow-42 in Japan (sponsor country) was reported to be less than 1,000 tonnes in the fiscal year 2010 according to the notification of annual manufactured and/or imported quantities under Chemical Substances Control Law. Production and/or import volume of Disperse Yellow-42 in the United States was less than 500,000 pounds (227 tonnes) according to 2006 Inventory Updated Reporting. Production volume in the world is not available.

Disperse Yellow-42 is mainly used for dyeing and printing of polyester and its fabrics. Disperse Yellow-42 is used as a disperse dye in the sponsor country.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	7351-61-3
Chemical Name	2-Propenoic acid, 2-methyl-, 3-(trichlorosilyl)propyl ester (MPTCIS)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Analogue Justification**

Like all chlorosilanes, 2-Propenoic acid, 2-methyl-, 3-(trichlorosilyl)propyl ester (MPTCIS), reacts rapidly when exposed to moisture or polar reagents, producing hydrogen chloride (HCl; CAS No. 7647-01-0) and the corresponding silanol: (γ -methacryloxypropyl)silanetriol (CAS No. 18834-30-5). The hydrolysis half-life of MPTCIS is characterized using data for a structurally analogous chlorosilane, trichloro(methyl)silane (C3MS; CAS No 75-79-6). C3MS has previously been assessed in the OECD HPV Programme as a member of the alkyl chlorosilanes category (<http://www.oecd/env/hazard/data>). For mammalian toxicity and acute aquatic toxicity endpoints, data are provided for a structurally similar analogue, 3-trimethoxysilylpropyl methacrylate (MPTMS, CAS No. 2530-85-0) and for the hydrolysis product HCl, both of which have been previously assessed in the OECD Cooperative Chemicals Assessment Program (<http://www.oecd/env/hazard/data>). Both MPTCIS and MPTMS rapidly hydrolyze to form 1 mole of (γ -methacryloxypropyl)silanetriol (CAS No. 18834-30-5). MPTCIS also forms 3 moles of HCl per mole of silanetriol, while MPTMS forms 3 moles of methanol per mole of silanetriol. Although methanol is a hydrolysis product associated with the analogue substance, MPTMS, the primary human health hazard for MPTCIS is considered to be exposure to the hydrolysis product, HCl. Similar structures and rapid hydrolysis to the same silanol hydrolysis product support the use of MPTMS data for the mammalian and aquatic toxicity endpoints. The levels of MPTCIS required to generate significantly toxic concentrations of silanols would result in severely corrosive HCl concentrations. (γ -Methacryloxypropyl)silanetriol cannot be isolated for testing as it is not stable; in higher concentrations, it will condense to form highly cross-linked, high molecular weight polymers.

Physical-chemical properties

MPTCIS is a liquid with an estimated melting point of $-53.15\text{ }^{\circ}\text{C}$ at 1013 hPa and an estimated boiling point of $250.6\text{ }^{\circ}\text{C}$ at 1013 hPa. The extrapolated vapor pressure value from measured data is 0.017 hPa at $25\text{ }^{\circ}\text{C}$. The calculated water solubility is 98.72 mg/L. The estimated $\log K_{ow}$ of MPTCIS is 3.43. The water solubility and $\log K_{ow}$ values may not be applicable because the chemical is hydrolytically unstable.

Human Health

No data are available on the toxicokinetics of MPTCIS. However, MPTCIS rapidly hydrolyzes on contact with moisture generating 3 moles of HCl for every mole of (γ -methacryloxypropyl)silanetriol. The hydrophilic nature of (γ -methacryloxypropyl)silanetriol will limit its diffusion across membranes and its accumulation in fatty tissues and may lead to some retention in the mucous of the lungs. HCl dissociates; its effects are thought to be a result of pH change.

Experimental data regarding MPTCIS for human health toxicological endpoints are not available. Acute toxicity data are available for MPTMS and HCl. The range of 1 hour acute inhalation LC₅₀ for MPTCIS is 8.41-10.64 mg/L (predicted based on chlorine content). The principal clinical signs are expected to be indicative of respiratory and ocular effects resulting from HCl exposure. Inhalation LC₅₀ values for HCl were determined to be 4.2-4.7 mg/L for 1 hour for rats. A 4-hour LC₅₀ value for MPTMS (hydrolyzed) was >2.28 mg/L (highest attainable aerosol concentration) for rats [OECD TG 403]. The dermal LD₅₀s [OECD TG 402] of MPTMS in rats and male rabbits were 2000 mg/kg bw and greater than 2090 mg/kg bw, respectively. Clinical signs of exposure included slight erythema and edema in rats; no findings were noted for rabbits. The oral (gavage) LD₅₀ [OECD TG 401] of MPTMS in rats has been shown in several studies to be greater than 2000 mg/kg bw. Clinical signs of exposure included wet and/or dried yellow and/or clear material around the mouth, forelimb(s), anogenital area and/or base of tail. There were no findings at necropsy. The acute oral LD₅₀ values of HCl were determined to be 238-277 mg/kg bw for female rats. Acute toxicity of MPTCIS is expected to be similar to that of HCl.

MPTMS is slightly irritating to the skin and eye of rabbits. HCl is corrosive and highly irritating to the skin, eyes and respiratory tract with no data located for skin sensitization. In a guinea pig maximization test, MPTMS was a weak skin sensitizer. MPTCIS is expected to be a skin, eye, and respiratory tract irritant and a skin sensitizer.

Data from an analogous substance, MPTMS, and the hydrolysis product HCl are available to address the repeated-dose toxicity endpoint via inhalation exposure. In three 14-week repeated exposures in rats to an aerosol of MPTMS and its hydrolysis products at nominal concentrations up to 0.1 mg/L, a NOAEC was not established. MPTMS produced histopathological changes in the upper respiratory tract at nominal concentrations greater than or equal to 0.005 mg/L, the major findings being cytoplasmic hyalinization and the formation of laryngeal granulomas. In three 4-week repeated aerosol exposures in rats, there were similar findings; the measured LOAEC was 0.0135 mg/L. 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 body weight gain and liver weight changes. As a result of hydrolysis, repeated dose toxicity of MPTCIS is expected to be characterized by HCl formation.

Data for genetic toxicity are available for MPTMS and HCl. The analogous substance, MPTMS, did not induce gene mutations in bacterial or mammalian cells *in vitro*, but did induce chromosomal aberrations in mammalian cells *in vitro*. All *in vitro* studies were conducted with and without metabolic activation. MPTMS was negative for sister chromatid exchange *in vitro* and in a mouse micronucleus assay *in vivo*. MPTMS is not considered to be genotoxic *in vivo*. 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, MPTCIS is not expected to be genotoxic.

No data were available for the carcinogenicity of MPTMS. Carcinogenicity data are available for HCl. No pre-neoplastic or neoplastic nasal lesions were observed in a 128-week inhalation study with male rats at 10 ppm hydrogen chloride gas. No evidence of treatment related carcinogenicity was observed either in other animal studies performed by inhalation, oral or dermal administration. In humans, no association between hydrogen chloride exposure and tumor incidence was observed.

Data for the reproductive/developmental toxicity endpoints for the analogous substance, MPTMS are available. Repeated inhalation of aerosolized and hydrolyzed MPTMS at concentrations up to 0.1 mg/L for 14 weeks showed no adverse histopathological effects on the reproductive organs of rats; the NOAEC was established at 0.1 mg/L. In an oral gavage OECD TG 414 developmental toxicity study in rats at concentrations of 522.5, 2090 and 5225 mg/kg bw/day, maternal and developmental effects were noted at 2090 mg/kg bw/day and higher. Maternal toxicity included staining of fur, uncoordination, reductions in body weight and food consumption, increases in the absolute and relative liver and kidney weights and mortality at 2090 and/or 5225 mg/kg bw/day. Developmental effects were decreased fetal weights, increases in the incidence of soft tissue malformations and delayed ossification at 2090 and/or 5225 mg/kg bw/day. Based on these results, the NOAEL for maternal and developmental toxicity was 522.5 mg/kg bw/day. Developmental effects, consistent with a general profile of developmental delay, were observed only at the mid- and high-dose levels. These doses are quite high – 2-fold and 5-fold higher than the “limit dose” of 1000 mg/kg bw/day as specified in OECD TG 414. 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 protons and chloride ions are 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 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 repeated-dose inhalation study up to 50 ppm. Based on these data,

MPTCIS is not expected to show reproductive/developmental toxicity up to the limit dose.

MPTCIS possesses properties indicating a hazard for human health (severe skin, eye and respiratory tract irritation, 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.

A hydrolysis study was not conducted on MPTCIS. Using an analogous substance, trichloro(methyl)silane (CAS No. 75-79-6), MPTCIS is expected to hydrolyze to HCl and the corresponding silanol in less than 1 minute at pH 4, 7, and 9 at 1.5°C. MPTCIS in air is not expected to undergo direct photolysis, but may undergo indirect photolysis through hydroxyl radical oxidation. The hydroxyl radical reaction was calculated using a 12-hr day and a hydroxyl radical concentration of 1.5×10^6 OH molecules/cm³ in AOPWIN® ver. 1.92. The overall OH rate constant and estimated half-life is 2.26×10^{-11} cm³/molecule-sec and 5.7 hours, respectively. Any potential for photodegradation might be superseded by hydrolysis of the parent compound depending on the concentration of water vapor in the air. The results of Level III fugacity modeling, using equal loading rates of 1000 kg/h each for air, soil and water show that when MPTCIS is released simultaneously to all three compartments it will distribute mainly to air (47.6 %) and soil (47.7 %), with a minor fraction to water (4.77 %) and negligible distribution to sediment (< 0.1 %). Since the parent material is not expected to be released to soil or water based on its uses and handling, a scenario of 100% emission to air is more realistic. When MPTCIS is released to air exclusively, 0.2% remains in air (100%). The modeling results show that the environmental fate of MPTCIS is controlled by its 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 product, (γ -methacryloxypropyl)silanetriol, will distribute mainly to soil (82.2%), with a smaller fraction to water (17.6%) and negligible amounts to sediment and air (0.18 and < 0.1%). Based on the more realistic scenario of 100% release to air, the fugacity modeling predicts that (γ -methacryloxypropyl)silanetriol will distribute mainly to soil (94.9%), with a smaller fraction going to water (5.1%) and negligible fractions in air and sediment (<0.1%)[EPI Suite (v4.10)]. Fugacity modeling of HCl is not applicable. The biodegradation of MPTCIS was not determined due to rapid hydrolysis; any potential for biodegradation is likely to be of the hydrolysis products. Consequently, the only potentially biodegradable materials in the test system will be silanols, and condensed silanol materials (high molecular weight polymers). No measured data are available for the hydrolysis product (γ -methacryloxypropyl)silanetriol exclusively, as it cannot be isolated. Although extensive biodegradation was observed for MPTMS, this substance hydrolyzes to form methanol as a co-product, which complicates interpretation of the biodegradation studies. HCl is an inorganic compound and biodegradation tests are not applicable.

The bioaccumulation potential of MPTCIS was not determined due to rapid hydrolysis. An estimated BCF for MPTCIS is 85.41 L/kg wet-wt, indicating MPTCIS is not expected to bioaccumulate.

Aquatic toxicity data are not available for MPTCIS; the substance undergoes rapid hydrolysis, which occurs during testing; exposure to the parent chlorosilane is likely to be transient and observed toxicity is likely due its hydrolysis products, HCl and the corresponding silanol hydrolysis product. Aquatic toxicity data are available for MPTMS; based on the hydrolysis half-life of 4 hours of MPTMS, for the duration of aquatic toxicity tests, the organisms were likely exposed to both MPTMS and the hydrolysis products, methanol and (γ -methacryloxypropyl)silanetriol. MPTMS hydrolyzes to form the same silanol as the sponsored substance, MPTCIS. The fish studies on MPTMS were conducted as semi-static studies, the *Daphnia* studies were conducted under static conditions. The degree of toxicity caused by HCl is also highly dependent on the buffer capacity of the receiving water. Aquatic toxicity endpoints for MPTCIS are also fulfilled through the use of data from the hydrolysis product, HCl.

Fish

MPTMS [<i>Brachydanio rerio</i>]	96 h LC ₅₀ >100 mg/L (OECD TG 203; semi-static, measured as total Si)
HCl [<i>Oncorhynchus mykiss</i>]	96 h LC ₅₀ = 4.92 mg/L (pH 4.3; OECD TG 203; semi-static, nominal)

Aquatic Invertebrate

MPTMS [<i>Daphnia magna</i>]	48 h EC ₅₀ > 100 mg/L (OECD TG 202; static, measured as total Si)
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HCl [*Daphnia magna*] 48 h EC₅₀ > 876 mg/L (Directive 92/69/EEC, C.3; static, measured as TOC)
48 h LC₅₀ = 0.492 mg/L (pH 5.3 ; OECD TG 202, nominal)

Algae

MPTMS [*Scenedesmus subspicatus*] 72 hr ErC₅₀ , E_bC₅₀ > 100 mg/L (OECD TG 201; measured as total Si)
[*Scenedesmus subspicatus*] 72 hr ErC₅₀ , E_bC₅₀ > 536 (Directive 92/69/EEC, C.3, measured as DOC)
HCl [*Selenastrum capricornutum*] 72 hr EC₅₀ = 0.492 mg/L (pH 5.3) (OECD TG 201; nominal)

Hydrogen Chloride (HCl)

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 for 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.

MPTCIS possesses 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). MPTCIS 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

The 2010 production volume in the United States (sponsor country) ranged from 45 to 2628 tonnes. Production was not reported in Europe or Japan. 100% of MPTCIS is used as an intermediate for silicone oligomers and polymers. MPTCIS is reacted during use and loses its chemical identity.

There is no intentional release of MPTCIS to the environment.

MPTCIS is produced and processed in closed systems. Due to the dynamic and exothermic nature of the processes incorporating chlorosilanes, many engineering controls are in place to prevent occupational exposure such as water scrubber devices and related equipment including ventilation; and closed sampling loops. Employees involved in chlorosilane production and application are required to use personal protective equipment (PPE) such as safety glasses or goggles, steel-tipped shoes, flame-resistant clothing, hard hat, chemical resistant gloves; respirator mask. Potential routes of occupational exposure during routine operations (such as sampling operations, equipment maintenance and waste disposal) at the manufacturing site include inhalation and dermal exposure.

There are no consumer uses of MPTCIS.

SIDS INITIAL ASSESSMENT PROFILE

Chemical Category	C₉-C₁₄ Aliphatic [\leq2% aromatic] Hydrocarbon Solvents Category	
Chemical Names and CAS Registry Numbers	Substance Name	CAS Number
	Nonane	111-84-2
	n-Decane	124-18-5
	n-Undecane	1120-21-4
	Dodecane	112-40-3
	Tridecane	629-50-5
	Alkanes, C10-14	93924-07-3
	Alkanes, C9-11-iso-	68551-16-6
	Alkanes, C9-12-iso-	90622-57-4
	Alkanes, C10-13-iso-	68551-17-7
	Alkanes, C12-14	129813-67-8
	Alkanes C12-14 -iso	68551-19-9
	Alkanes, C11-15-iso-	90622-58-5
	Paraffins, petroleum, normal C5-20	64771-72-8
	Naphtha (petroleum), hydrotreated heavy	64742-48-9
	Solvent naphtha, petroleum, medium aliph.	64742-88-7
	Naphtha, petroleum, heavy alkylate	64741-65-7
Distillates, petroleum, hydrotreated light	64742-47-8	
Structural Formula and CAS Registry Numbers	Structural Formula	CAS Number
	<i>n-Paraffins Subcategory</i>	
	CH ₃ -(CH ₂) ₇ -CH ₃ (linear molecule)	111-84-2
	CH ₃ -(CH ₂) ₈ -CH ₃ (linear molecule)	124-18-5
	CH ₃ -(CH ₂) ₉ -CH ₃ (linear molecule)	1120-21-4
	CH ₃ -(CH ₂) ₁₀ -CH ₃ (linear molecule)	112-40-3
	CH ₃ - (CH ₂) ₈ -CH ₃ to CH ₃ - (CH ₂) ₁₂ -CH ₃	64771-72-8
	CH ₃ -(CH ₂) ₁₁ -CH ₃ (linear molecule)	629-50-5
	Various isomers of primarily C ₁₂ , C ₁₃ , and C ₁₄ alkyl-normal hydrocarbons	129813-67-8 [†]
	Various isomers of primarily C ₁₀ , C ₁₁ , C ₁₂ , C ₁₃ , and C ₁₄ alkyl-normal hydrocarbons	93924-07-3 [†]

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	<p><u>Iso-Paraffins Subcategory</u></p> $\begin{array}{c} \text{CH}_3 \quad \text{CH}_3 \\ \quad \\ \text{CH}_3-\dot{\text{C}}-\text{CH}_2-\dot{\text{C}}\text{H}_2-(\text{CH}_3)_2 \\ \\ \text{CH}_3 \end{array}$ <p>Various isomers of primarily C₁₀, C₁₁, C₁₂, and C₁₃ alkyl-branched hydrocarbons 68551-16-6[†]</p> <p>Various isomers of primarily C₉, C₁₀, C₁₁, and C₁₂ alkyl-branched hydrocarbons 90622-57-4[†]</p> <p>Various isomers of primarily C₁₀, C₁₁, C₁₂, and C₁₃ alkyl-branched hydrocarbons 68551-17-7[†]</p> <p>Various isomers of primarily C₁₂, C₁₃, and C₁₄ alkyl-branched hydrocarbons 68551-19-9[†]</p> <p>Various isomers of primarily C₁₂, C₁₃, C₁₄, and C₁₅ alkyl-branched hydrocarbons 90622-58-5[†]</p> <p><u>Multi-constituent Subcategory</u></p> <p>UVCB substances containing aliphatic (linear, branched, and/or cyclic paraffins) molecules of carbon and hydrogen, predominantly in the C₉ to C₁₄ range 64742-48-9[†] 64742-88-7[†] 64741-65-7[†] 64742-47-8[†]</p> <p><u>Description of Substances in Category</u></p> <p>Individual category member substances are comprised of aliphatic hydrocarbon molecules with carbon numbers between C₉ and C₁₄; approximately 80% of the aliphatic constituents for a given substance fall within the C₉-C₁₄ carbon range and <100 ppmV benzene. The distinguishing characteristics of this category are the limitation on carbon range (C₉-C₁₄) and the limitation of aromatic constituents to < 2% (although as shown in table 1, in most cases the levels of aromatics are well below 2%) of the total hydrocarbons present.</p> <p>In some instances, the carbon range of a test substance is provided in the test protocol or report. In these instances, the specific carbon range (e.g. C₈-C₁₀, C₉-C₁₀, etc.) will be given in the SIAP.</p> <p>* It should be noted that other substances defined by the same CAS RNs may have boiling ranges outside the range of 142.9 – 253.5 ° C and that these substances are not covered by the category.</p> <p>†Denotes a UVCB substance. UVCBs are defined as chemical substances of unknown or variable composition, complex reaction products or biological materials.</p>
	<p>The category has been defined for members with specific constituents/component profiles or composition as outlined in the full SIDS Initial Assessment Report and the SIDS Dossiers.</p>

The substances in the C₉-C₁₄ Aliphatic [\leq 2% aromatic] Hydrocarbon Solvents Category contain >98% hydrocarbons. Several category members are described as UVCBs (Unknown or Variable Composition, Complex Reaction Products and Biological Materials) because they are composed of a defined, progressive carbon number range that includes various types of hydrocarbons: aliphatic molecules (linear, branched, and cyclic) and less than 2% aromatic molecules (generally one-ring alkylbenzenes), predominantly in the C₉ to C₁₄ range. The benzene and sulphur contents of substances in this category are low; benzene levels for example are typically <3 ppm.

Some of the category members are complex hydrocarbon substances described by CAS RNs which can also be used to describe petroleum process streams and other complex substances. Thus, there are substances which are described by the same CAS numbers used by category members which are not included in the category because they do not meet the category definition (C₉-C₁₄ aliphatic hydrocarbons, \leq 2% aromatics).

The present assessment only applies to substances with the constituent profiles and compositions described within this assessment, i.e., C₉-C₁₄ aliphatic hydrocarbons < 2% aromatics. As noted above, the conclusions of this assessment do not necessarily apply to petroleum process streams with the same CAS number as those belonging to the C₉-C₁₄ Aliphatic [\leq 2% aromatic] Hydrocarbon Solvents Category or to other substances that do not meet the category definition because they have different carbon number ranges and/or higher levels of aromatics. In particular it should be noted that production of hydrocarbon solvents is differentiated from other refinery substances with similar boiling ranges such as gasoline and diesel fuel by additional processing steps leading to finished hydrocarbon solvents with relatively narrow distillation ranges, defined aromatic content, and low color (indicative of relatively low levels of benzene, other aromatics and sulfur-containing compounds).

Table 1 - Typical compositional data for representative commercial C₉-C₁₄ aliphatic [\leq 2% aromatic] hydrocarbon solvents

CAS No.	Carbon Number*	Aliphatics*			Aromatics*	Ethylbenzene*	Naphthalene*	Benzene*	
		(range)	% total	% n-, iso-					% cyclo
111-84-2	9		100	100	-	<0.01	0	0	0
124-18-5	10		100	100	-	<0.01	nd	nd	0
1120-21-4	11		100	100	-	<0.01	0	0	0
112-40-3	12		100	100	-	<0.01	0	0	0
629-50-5	13		100	100	-	<0.01	0	0	0
68551-16-6	9-11		100	100	-	0.007	0	0	0
90622-57-4	9-12		100	96-100	0-4	<0.01	na	na	<1

68551-17-7	10-13	100	100	-	0.007	0	0	0
93924-07-3	10-14	>99.98	>99.98	-	<0.02	na	na	-
129813-67-8	12-14	99.4	97.8	1.6	0.6	na	na	-
68551-19-9	12-14	99.9	99.9	-	<0.1	na	na	na
90622-58-5	11-15	100	88-100	0-12	<1	na	na	<1
64742-48-9	9-13	>99	43-97	3-57	<1	<1ppm	<1ppm	<1
64742-88-7	9-13	>98	46-52	47-54	<1.5	na	na	na
64741-65-7	9-14	99.9	37-62.9	37-62.9	<0.1	na	na	<1
64742-47-8	8-15	>99	30-60	40-70	<1	na	na	na
64771-72-8	10-14	100	100	-	<0.1	<10ppm	<10ppm	<1

* The values in this table were provided by manufacturers from analyses of commercial products and are examples, not specifications.

< Less than detection limit (detection limit reported)

nd not detected

na not available

Table 2 - Typical Carbon Number Range for the Aliphatic Molecules in the C₉-C₁₄ aliphatic [≤2% aromatic] hydrocarbon solvents category

Identification of chemicals defined by processing procedures	Typical Carbon Number Range for the Aliphatic Molecules (%) of substances in the C ₉ -C ₁₄ aliphatic (≤2% aromatic) category									
	< C8	C8	C9	C10	C11	C12	C13	C14	C15 to C16	Total Aromatics
Nonane 111-84-2			100							
Decane 124-18-5				>99.9						<0.01

Undecane 1120-21-4					>99. 9					<0.01
Dodecane 112-40-3						>99. 9				<0.01
Tridecane 629-50-5							>99. 9			<0.01
Alkanes, C10- 14 93924-07-3			~3	~16	~20	~23	~18	~12	~6	<2.0
Alkanes, C9- 11-iso- 68551-16-6		~1	~31	~35	~31	~3	~1			<0.05
Alkanes, C9- 12-iso- 90622-57-4			~2.5	~23	~36	~20	~18	~0.5		<0.05
Alkanes, C10- 13-iso- 68551-17-7			~2	~11	~34	~37	~10	~5	~1	<0.05
Alkanes, C12- 14 129813-67-8				~3	~23	~34	~24	~11	~3	<2.0
Alkanes C12- 14 –iso 68551-19-9					~14	~38	~31	~17		<0.05
Alkanes, C11- 15-iso- 90622-58-5					~21. 5	~27. 5	~20. 5	~17. 5	~13	<0.05
Paraffins, petroleum, normal C5-20 64771-72-8	~2	~5	~11	~15	~18	~19	~13	~9	~6	<2.0
Naphtha (petroleum), hydrotreated heavy 64742-48-9		~1. 1	~5	~13	~32	~33	~13	~2.2		<0.7
Solvent naphtha, petroleum, medium aliphatic 64742-88-7		~1. 5	~18	~27	~35	~10	~6.5			<2.0
Naphtha, petroleum, heavy alkylate 64741-65-7				~0.5	~13	~23	~30	~19	~14	<0.5
Distillates, petroleum, hydrotreated light 64742-47-8		~3	~26	~36	~31	~2				<2.0

SUMMARY CONCLUSIONS OF THE SIAR

Category Definition

The C₉-C₁₄ Aliphatic [\leq 2% Aromatic] Hydrocarbon Solvents Category is comprised of complex aliphatic hydrocarbon solvents that contain >98% aliphatic constituents with carbon numbers in the range of C₉-C₁₄ and less than 2% aromatic constituents. These hydrocarbon solvents which are defined by boiling range and/or flash point have carbon numbers within the range of C₉ to C₁₄ (approximately 80%). The chemical constituents in these complex UVCB substances may include straight chain (n-), branched (iso-) and cyclic aliphatic hydrocarbons but must have less than 2% aromatic hydrocarbons (generally one-ring aromatics). These products may be sold under a variety of brand, commercial and trade names and they may be associated with one or more of the Chemical Abstract Services (CAS) Registry Numbers (RN) for this category. It should be noted that the CAS registry numbers assigned to these substances are generic and can also be used to describe substances that do not meet the category description and are not included in this assessment.

Assignment of CAS RNs for complex hydrocarbon products is generally based on a hierarchy of considerations including hydrocarbon type(s), carbon number range, distillation range, and last processing step. One documented source of criteria for assignment of CAS RNs for complex hydrocarbons is provided by the U.S. EPA on proceedings for development of the TSCA inventory for U.S. chemicals. Because these CAS RN are broadly defined to encompass UVCBs, they can be applied to both hydrocarbon solvents and other petroleum-derived substances with somewhat different composition and applications (e.g., solvents, fuels, lubricants, etc.). However, because hydrocarbon solvents are manufactured to meet specific industrial needs, they tend to be more compositionally defined than other petroleum-derived materials with more narrow boiling ranges and, often, lower levels of benzene as well as sulfur- and nitrogen-containing constituents.

Category Justification

For substances in the C₉-C₁₄ Aliphatic [\leq 2% Aromatics] Hydrocarbon Solvents Category, the CAS RNs listed here are all applied to compositionally similar and generally commercially interchangeable hydrocarbon solvents. This similarity of composition is the primary justification for evaluating these substances in a category. Further, the existing toxicology and environmental effects data shows that substances in this category have a similar order of toxicity which further supports the grouping of these substances as a category.

The underlying hypothesis that justifies this category is that aliphatic hydrocarbons of similar carbon number range have similar properties. As above, the substances in this category are comprised of aliphatic constituents (normal paraffins, iso-paraffins and cycloparaffins) with carbon numbers ranging from C₉-C₁₄. One distinguishing characteristic of this category is that the substances have very low levels of aromatic constituents.

There are a number of unifying considerations which together justify the inclusion of substances within the C₉-C₁₄ Aliphatic [\leq 2% aromatics] Hydrocarbon Solvents Category. These include:

1. Similarity of Composition – Constituents of solvents in this category can include n-alkanes, iso-alkanes, or cycloalkanes or combinations thereof with carbon numbers ranging from approximately C₉-C₁₄. However, the aromatic content of these solvents does not exceed 2%.
2. Similarity of Functional Groups – The substances in this class are comprised almost entirely of aliphatic constituents. The only functional groups are alkyl side chains, which are found on most if not all constituents other than the n-alkanes.
3. Similarity of Physical / Chemical Properties – All category members have a boiling point range from 142.9 to 253.5°C, vapour pressure values in a range from 0.007 to 8.28 hPa, water solubility values range from 0.009 to 6.45 mg/L, measured log Pow values for category member constituents range from 5.0 – 7.2 (at 25°C).
4. Similarity of Metabolism – Hydrocarbon molecules in this range are absorbed from the intestinal tract but very poorly absorbed through the skin. However, once absorbed, these molecules are relatively rapidly metabolized and excreted.
5. Similarity of Mammalian Toxicity – The constituents of this class have similar toxicological properties. They are not acutely toxic, not irritating to the eyes and not sensitizing. They have differing skin irritant properties but all can produce severe irritant dermatitis due to defatting. They do not produce systemic effects (other than male rat-specific kidney changes) in repeated dose studies. They are not mutagenic. They do not produce developmental toxicity, and there is no evidence that they are toxic to the reproductive system.

6. Similarity of Environmental Toxicity – The substances in this category have similar environmental effects properties. The environmental effects data are similar for most category members in that most members do not exhibit acute aquatic toxicity due to their low water solubility. However some members do exhibit acute and chronic aquatic toxicity. Category members and their constituents are neutral organic hydrocarbons whose toxic mode of action is nonpolar narcosis. The mechanism of short-term toxicity for these chemicals is disruption of biological membrane function, and the differences between their toxicities can be explained by the differences in target tissue-partitioning behaviors of the individual hydrocarbons.
7. Similarity in Health Effects and Mechanism of Toxic Action – There are two general potential health effects associated with substances in this category, acute central nervous system (CNS) depression and, if taken into the lung in a liquid state (i.e. aspiration), chemical pneumonitis. Both of these are common effects shared by all hydrocarbon solvents. It should be noted, however, that the vapor pressures of hydrocarbons with more than 9 carbons are so low that acute effects on the central nervous system are not produced even at saturated vapor concentrations.
8. Similarity of Production Methods – Hydrocarbon solvents in this category can be produced in several ways, but in each case the manufacturing process leads to aliphatic solvents within a relatively narrow range of carbon numbers and with an overall low (<2%) aromatic hydrocarbon content.
9. Similarity of Use – Substances in this category are liquids at room temperature and are produced for use as solvents. The technical properties for which these solvents are intended require that the constituents have well defined rates of evaporation which is related to the carbon number distribution, to limit the aromatic content, and to also have very low levels of sulphur- and nitrogen-containing constituents.

Category Member Conventional Naming

The naming convention used to identify category members is based on their general compositions (predominant carbon number range and hydrocarbon type, specifically aromatics) and is intended to identify hydrocarbon solvent substances manufactured by various companies that are sufficiently similar with regard to composition such that their physical and biological properties would exhibit similar properties. The naming convention as applied to hydrocarbon solvents was seen as a means to provide more precise information on the type of solvent and its composition than is obtained from the CAS description and allows for an accurate grouping of hydrocarbon substances within categories. As UVCBs, some of the hydrocarbon solvent category members share CAS RNs with some petroleum process streams which have broader boiling ranges and consequently are compositionally more complex.

Category members (CAS RN 64771-72-8, 129813-67-8, 68551-16-6, 90622-57-4, 68551-17-7, 93924-07-3, 68551-19-9, 90622-58-5, 64742-48-9, 64742-88-7, 64741-65-7, and 64742-47-8) meet the criteria for UVCB substances because they contain a relatively large number of discrete chemical constituents and the identities of all of the constituent chemicals may be unknown. The general naming convention guidance was developed and used for category members as follows:

"Hydrocarbons", the first part of the name, recognizes the specific chemical class.

The carbon number range typically identifies at least 80% of the chemical constituents in the substance.

The structures are identified by the types of hydrocarbons present: n-paraffins (n-alkanes), iso-paraffins (isoalkanes), cyclic-paraffins or naphthenic (cyclics), and aromatics. The first three structural types of hydrocarbons are mentioned when present in the substance at a level between approximately 10 and 80%. Levels of total Aromatics are below 2% for all category members.

Read-Across Substance Identification

In addition to the available physical and biological data for substances in the C₉-C₁₄ Aliphatic [\leq 2% aromatic] Hydrocarbon Solvents category, data for the following analogues are also presented, as necessary, to support the characterization of selected endpoints:

JP-8, a commercial jet fuel (having a carbon number range of 8-16 and ~25% aromatics, but not described by CAS RN)

Hydrodesulfurized kerosene (CAS RN 64742-81-0, having a carbon number range of C₉-C₁₆ and ~ 20% aromatics)

CAS RN 8052-41-3; Stoddard Solvent; White Spirit (C₉-C₁₄, ~25% aromatics)

CAS RN 90622-58-5; Hydrocarbons, C₁₁-C₁₃, isoalkanes, <2% aromatics

CAS RN 64742-47-8; Hydrocarbons, C₁₃-C₁₆, n-alkanes, isoalkanes, cyclics, <2% aromatics

CAS RN 109-66-0; n-Pentane

CAS RN 629-59-4; n-Tetradecane

Tetramethylcyclohexane, mixed isomers (no CAS number available)

Jet fuel (JP-8), a U.S. military fuel, is a complex hydrocarbon substance (UVCB) with a carbon number range of C₈-C₁₆, a boiling range of approximately 150 – 290°C, an aromatic content of approximately 25% and approximates the physical/chemical properties of the C₉-C₁₄ Aliphatic [\leq 2% aromatic] Hydrocarbon Solvents. Since JP-8 contains substantially higher levels of aromatic constituents than the C₉-C₁₄ Aliphatic [\leq 2% aromatic] Hydrocarbon Solvents, test results from JP-8 could be considered as “worst-case” when used as read-across to the C₉-C₁₄ Aliphatic [\leq 2% aromatic] Hydrocarbon Solvents. The same logic applies to hydrodesulfurized kerosene (CAS RN 64742-81-0) and Stoddard solvent (CAS RN 8052-41-3) which contain approximately 80% aliphatic constituents with carbon numbers that overlap those found in the C₉-C₁₄ aliphatic, \leq 2% aromatics category but differ in that these other analogue substances contain aromatic (primarily alkylated single ring aromatics) at levels ranging from approximately 15-25%.

Table 3 (SIAR Table 4) – Data for the following analogues for the C₉-C₁₄ aliphatic (\leq 2% aromatics) category are provided to support the characterization of relevant endpoints.

Analogue (CAS RN)	Composition	Endpoint(s) Characterized
Commercial product not described by a CAS RN	JP-8 (a commercial fuel containing approximately 80% C ₈ -C ₁₆ aliphatic constituents and 20% aromatics, most of which are alkylated benzenes).	Dermal Absorption Reproductive Toxicity
8052-41-3	Stoddard Solvent; White Spirit – A commercial hydrocarbon solvent which contains 15-20% aromatic constituents, primarily alkylated benzene, with the remainder being aliphatic constituents with carbon numbers predominantly in the range of C ₉ -C ₁₁ .	Toxicokinetics
64742-81-0	Hydrodesulfurised kerosene, a hydrocarbon fuel consisting of hydrocarbons in the range of C ₉ -C ₁₆ and a boiling range of approximately 150-290°C. Hydrodesulfurised kerosene contains approximately 80% aliphatic constituents (C ₁₀ -C ₁₆) and 20% aromatics (mostly alkylated single ring compounds). The manufacturing process includes a hydrogenation step with removes sulfur and nitrogen.	Developmental Toxicity Reproductive Toxicity
A CAS RN for the mixed isomers is not available	Mixed Tetramethylcyclohexane (C ₁₀ cycloparaffins) isomers	Acute Toxicity Repeated Dose Toxicity
90622-58-5	Hydrocarbons, C ₁₁ -C ₁₃ , isoalkanes, <2% aromatics	Biodegradation Chronic Aquatic Toxicity
64742-47-8	Hydrocarbons, C ₁₃ -C ₁₆ , n-alkanes, isoalkanes, cyclics, <2% aromatics	Biodegradation Chronic Aquatic Toxicity
109-66-0	n-Pentane	Biodegradation
629-59-4	n-Tetradecane	Biodegradation Acute Aquatic Toxicity

Substances in the C₉-C₁₄ Aliphatic [\leq 2% Aromatic] Hydrocarbon Solvents Category are composed of paraffinic hydrocarbons that fall within a carbon number (C) range of 9 to 14 but with the levels of aromatic constituents limited to 2%. As a result, many of the category member physicochemical properties are characterized by a range of values as a function of composition because a single value is not possible. For example, complex hydrocarbon solvents do not have single P_{ow} values, but rather a range of values based on the properties of the constituents. This would be the case regardless of whether the data were measured using a standard testing procedure or calculated based on the individual constituent chemicals.

For several of the physical-chemical properties, the value range is based on a series of representative hydrocarbons that were selected by industry, based on hydrocarbon process (distillation) knowledge, to accurately characterize category members. The hydrocarbons selected to characterize the C₉-C₁₄ aliphatic ($\leq 2\%$ aromatic) category include paraffins (normal, iso-, cyclic) from C₉ to C₁₄.

Table 4: List of Representative Hydrocarbon Constituents used to characterize the physical/chemical and environmental properties of C₉-C₁₉ aliphatic [$\leq 2\%$ aromatics] category

<u>Chemical Name</u>	<u>CAS RN</u>
n-nonane	111-84-2
2-methyloctane	3221-61-2
1,2,4-trimethylcyclohexane	2234-75-5
n-decane	124-18-5
1,2,4,5-tetramethylcyclohexane	2090-38-2
decahydronaphthalene	91-17-8
n-undecane	1120-21-4
2,5-dimethyl-nonane	17302-27-1
n-dodecane	112-40-3
n-tridecane	629-50-5
2,3-dimethyl-undecane	17312-77-5
1,3,4,5-tetramethylnonane	n/a
n-tetradecane	629-59-4
2,6,10-trimethylundecane	6864-53-5
2,3,6,7-tetramethyldecalin	n/a
n/a = not available	

Physicochemical Properties

The members of the C₉-C₁₄ Aliphatic [$\leq 2\%$ Aromatic] Hydrocarbon Solvents Category are liquids at room temperature. The measured melting point values for constituents range from <-83.5 to 5.8°C . The boiling points range from approximately 142.9 to 253.5°C . The measured vapour pressure values for constituents range from 0.007 to 8.28 hPa at 20° to 25°C and cover the full carbon range (C₉ to C₁₄). The calculated water solubility values range from 0.009 to 6.45 mg/L (at 25°C) for constituents, with a relative density range of 0.718 to 0.815 g/cm³ (at 20°C). The measured log Pow values for category member constituents range from $5.0 - 7.2$ (at 25°C). Based on estimated values, the log Pow may range from 4.0 to >7.0 .

Human Health

Category members represent a wide variety of structures. Unless otherwise indicated all structural constituents (linear, branched and cyclic) of the category members have been tested for all of the individual endpoints.

Toxicokinetics, Metabolism, and Distribution

Much of the toxicokinetics data comes from studies of substances in another category, C₉-C₁₄ Aliphatic [2-25% Aromatic] Hydrocarbon Solvents and from studies of jet fuel (JP-8) constituents. However, for purposes of this document, the data on the aliphatic constituents of these other substances is directly relevant as there are similarities between the aliphatic constituents in the C₉-C₁₄ Aliphatic [$\leq 2\%$ Aromatic] Hydrocarbon Solvents Category and the C₉-C₁₄ Aliphatic [2-25% Aromatic] Hydrocarbon Solvents Category. Because these solvents are complex, the toxicokinetic studies are usually based on marker compounds such as decane. The toxicokinetic behavior of aromatic constituents can be ignored for purposes of this evaluation because (as shown in table 1), aromatic constituents are only present at low levels. Nevertheless, information on the aromatic constituents can be found in the summarized information for the C₉-C₁₄ aliphatic [2-25%] category document if it is of interest. It should also be noted that the aromatic constituents induce their own metabolism, so the rate of metabolism and excretion of both aliphatic and aromatic constituents can be enhanced in studies involving extended periods of high exposure to solvents containing aromatics; however, as the levels of aromatics are limited to a maximum of 2% for substances in this category, the contributions of aromatics to metabolic rates would probably be negligible.

Absorption

Inhalation - When inhaled, white spirit constituents were readily absorbed. The absorption of inhaled substances in this category depends on several factors including concentration in the inspired air, blood partition coefficient, pulmonary ventilation, and pulmonary flow. Generally speaking, however, studies have shown by the inhalation route that materials in this category are readily absorbed through the lungs. After a 30-minute exposure at rest to approximately

1040 mg/m³ of the aliphatic components, the concentration in alveolar air was 255 mg/m³ (25 % of the concentration in the inspiratory air). The corresponding arterial blood concentration was 1.7 mg/kg. When alveolar ventilation tripled (50 W exercise), the alveolar concentration increased to 515 mg/m³ (50 % of the concentration in inspiratory air), whereas the arterial concentration rose to 3.5 mg/kg. When alveolar ventilation was raised to 60 L/min (150 W exercise), the alveolar concentration rose to about 60 % of the concentration in inspiratory air. Thirty minutes following exposure, alveolar concentration was ~180 mg/m³ and arterial concentration was near 0 mg/kg.

Oral - It is estimated that 61% - 81% of a C₉-C₁₄ hydrocarbon solvent would be absorbed when ingested. C₉-C₁₄ aliphatic, ≤ 2% aromatic hydrocarbon solvents are metabolized by side chain oxidation to alcohol and carboxylic acid derivatives. These metabolites can be glucuronidated and excreted in the urine or further metabolized before being excreted. The majority of the metabolites are expected to be excreted in the urine and to a lower extent, in the feces. Any unabsorbed material would be excreted in the feces. Most of the excretion is expected to occur within the first 24 hours of exposure.

Dermal Absorption

There have not been any *in vivo* dermal absorption studies of C₉-C₁₄ aliphatic, < 2% aromatic hydrocarbon solvents, but there have been *in vivo* and *in vitro* percutaneous absorption studies of jet fuel, a C₉-C₁₆ aliphatic hydrocarbon substance with approximately 20% aromatics. Both *in vivo* and *in vitro* studies to assess the percutaneous absorption of aliphatic and aromatic jet fuel constituents have been conducted. Dermal flux values (ug/cm²/hr) for C₉-C₁₄ aliphatic constituents ranged from less than 1.0 to 2.5 ug/cm²/hr. Based on the data from a human volunteer study, percutaneous absorption of C₉-C₁₄ aliphatic constituents would be in the range of 0.01%/hr to 0.1%/hr and that of aromatic constituents (which constitute <2% of the total hydrocarbon constituents) would be approximately 0.2%/hr.

Distribution

Studies in rats have shown that following absorption, members of the C₉-C₁₄ Aliphatic [2-25% Aromatic] Hydrocarbon Solvents Category are widely distributed throughout the body of both humans and animals and preferentially accumulate in the adipose tissues due to the lipophilic nature of the solvents.

A toxicokinetic study on the distributions of C₉ to C₁₀ alkanes, aromatics and cycloalkanes in blood, brain, liver, kidney and perirenal fat demonstrated that aromatics generally showed higher blood concentrations than alkanes and cycloalkanes. C₉ cycloalkanes showed higher brain concentrations than the corresponding aromatics and alkanes, while brain concentrations of C₁₀ alkanes were slightly greater than C₁₀ cycloalkane concentrations, which in turn were greater than C₁₀ aromatic concentrations. Fat contained the highest concentrations of each of the hydrocarbons examined; concentrations of aromatics and cycloalkanes in fat were higher than concentrations of alkanes. Brain/blood ratios of 11.4, 2.0 and 11.4, and fat/blood ratios of 113, 63 and 135 were found for n-nonane, trimethylbenzene and trimethylcyclohexane, respectively. A marked decrease in biological concentrations of trimethylbenzene and trimethylcyclohexane during the initial phase of exposure indicates that when exposure levels are sufficiently high, these hydrocarbons are capable of inducing their own metabolic conversion resulting in lower steady state levels.

Metabolism

Information on the metabolic fate of the C₉-C₁₄ Aliphatic [2-25% Aromatic] Hydrocarbon Solvents Category constituents comes mostly from studies of hydrocarbon solvent constituents and not with complex hydrocarbon substances themselves. Aliphatic hydrocarbons undergo oxidative conversion, catalyzed by monooxygenases, to alcohols. The cytochrome P-450 dependent monooxygenases, located mainly in the endoplasmic reticulum of liver cells, are responsible for this first metabolic transition.

Excretion

Most of the information concerning the elimination and excretion of aliphatic and aromatic hydrocarbons has been derived from studies in rats involving exposure to single substances including constituents of the C₉-C₁₄ Aliphatic [2-25% Aromatic] Hydrocarbon Solvents. Generally speaking, it is expected that components or metabolites of complex hydrocarbon solvents such as Stoddard solvent/white spirit that have low solubility in the blood, would be rapidly exhaled from the lungs. As for pulmonary absorption, this process is governed by blood/gas solubility ratios. Components with low blood/gas ratios would be most rapidly excreted from the lungs because of their low blood solubility, while those with high blood/gas solubility ratios would be eliminated less efficiently by the lungs due to their high blood solubility; this situation is exactly the reverse of that for inhalation absorption. One study conducted reported that ten minutes after exposure had ceased, the expiratory concentration levels of aliphatics and aromatics were found to be about 12% of the initial exposure level for both fractions. Sixteen hours later, the levels in expiratory air had fallen to 2% (aliphatics) and 4% (aromatics) of the initial exposure level.

A 3-week inhalation study conducted in rats exposed for 6 hours/day, 5 days/week at levels of 2290 and 4580 mg/m³ found white spirit (20% aromatics) concentration in the brain of 3.4 and 10.2 mg/kg wet weight, respectively immediately preceding exposure cessation. These concentrations represented the steady state concentration during continuous exposure of these components rather than accumulation. In a follow up study to assess whether the measured concentrations did, in fact, reflect a steady state condition, male rats were exposed by inhalation to 0, 400 (2290 mg/m³) or 800 ppm (4580 mg/m³) of dearomatised white spirit (CAS 64742-48-9) for 6 hr/day, 5 day/week for 3 weeks. Five rats from each group were sacrificed immediately after the exposure duration of 1, 2, or 3 weeks and 2, 4, 6, or 24 hr after the end of 3 weeks' exposure. Immediately following the end of the 3 weeks of exposure, the concentration of total white spirit was 1.5 and 5.6 mg/kg in blood; 7.1 and 17.1 mg/kg in brain; 432 and 1452 mg/kg in fat tissue at the exposure levels of 400 and 800 ppm, respectively. Two hours after the end of exposure the white spirit concentration decreased to about 25% in blood and 50% in brain. The authors calculated that the post-exposure half-life in blood could be separated into two phases with half-lives of approximately 1 and 8 hr; in brain tissue two slopes with half-lives of 2 and 15 hr were identified. In adipose tissue, only one slope with half-life of about 30 hr was identified.

Acute Toxicity Summary

The acute toxicity data demonstrate that hydrocarbon solvent substances tested in the C₉-C₁₄ Aliphatic [\leq 2% Aromatic] Hydrocarbon Solvents Category not acutely toxic when tested at limit doses by the oral, dermal, and inhalation routes of exposure. It should be noted that the summary information (summarized in the SIAR) includes examples of acute oral and dermal toxicity studies of normal paraffins, isoparaffins, and cycloparaffins as well as solvents of mixed aliphatic constituents to show that none of these types of molecules is acutely toxic under these test conditions. The full range of constituents was covered by samples tested but as none of the studies indicated acute toxicity, the remaining studies were not considered to provide additional useful information and not included in the data compilation. The summarized information on the acute inhalation toxicity studies did include results of all tests conducted. This set of information did not cover C₁₄ constituents, but as constituents with lower carbon numbers (C₁₀-C₁₃) were tested and found to be not toxic by inhalation, it was judged that the C₁₄ constituents which are less volatile would similarly not be toxic at the maximally achievable vapor concentrations.

It should be noted, however, that these C₉-C₁₄ Aliphatic Hydrocarbon Solvents [\leq 2% Aromatics] substances present aspiration hazards if taken into the lung in the liquid state due to their physical and chemical properties, particularly viscosity.

Acute Inhalation Toxicity

Acute inhalation studies conducted according to, or similar to OECD TG 403 on commercial C₉-C₁₄ Aliphatic Hydrocarbon Solvents (\leq 2% Aromatics) (CAS RN 111-84-2, 124-18-5, 1120-21-4, 112-40-3, 629-50-5, 68551-16-6, 90622-57-4, 90622-58-5 and 64742-48-9) as well as a number of hydrocarbon solvent constituents demonstrated that the LC₅₀ value for nonane was 23775 mg/m³ but for the constituents with higher carbon numbers as well as for the mixed aliphatic solvents the LC₅₀ values were greater than the maximally attainable vapour concentrations. Solvents containing C₁₄ constituents were not tested for acute inhalation toxicity; however, based on the low vapor pressures of C₁₄ aliphatics (the maximally attainable vapor concentration for normal tetradecane is 202 mg/m³), acutely toxic effects would not be expected. The inhalation LC₅₀ data indicated that the C₉-C₁₄ Aliphatic Hydrocarbon Solvents (\leq 2% Aromatics) were not acutely toxic by inhalation.

Acute Dermal Toxicity

Acute, single application, 14-day dermal toxicity studies were conducted according to, or similar to OECD TG 402 in rabbits or rats on commercial C₉-C₁₄ Aliphatic Hydrocarbon Solvents (\leq 2% Aromatics) (CAS RN 64771-72-8, 90622-57-4, 64742-48-9, and 64742-47-8). All hydrocarbon solvent constituents were subsumed within substances shown as examples. The dermal LD₅₀ results, greater than the limit doses of 2.0 g/kg, indicate that C₉-C₁₄ Aliphatic Hydrocarbon Solvents (\leq 2% Aromatics) were not acutely toxic by dermal administration.

Acute Oral Toxicity (gavage administration)

Acute 14-day, single dose, oral gavage, toxicity studies were conducted according to, or similar to OECD TG 401 in rats on commercial C₉-C₁₄ Aliphatic Hydrocarbon Solvents [\leq 2% Aromatics] (CAS RN 64771-72-8, 90622-57-4, 64742-48-9, and 64742-47-8) and constituents (4306-65-4). All hydrocarbon solvent constituents were subsumed within substances shown as examples. The examples shown did not encompass C₉ aliphatic constituents; however, as the higher molecular weight aliphatic constituents are not acutely toxic by oral administration, it is expected that the C₉ aliphatic constituents would be similarly non-toxic. The LD₅₀ results of the oral studies in rats ranged from >5.0 to >15.8 g/kg, providing evidence that C₉-C₁₄ Aliphatic Hydrocarbon Solvents [\leq 2% Aromatics] are not acutely toxic by oral administration.

Irritation and Sensitisation Summary

The members of the C9-C14 aliphatic (<2% aromatics) category produced minimal to slight eye irritation when tested in rabbits. Similarly, the isoparaffinic, normal paraffinic, and mixed aliphatic category members produced minimal to slight skin irritation when tested in rabbits and are also not normally irritating to human skin but can produce irritant responses if evaporation is inhibited or prevented. However, cycloparaffinic hydrocarbon fluids are considered to be dermal irritants to rabbits and to humans. It should also be noted that prolonged or repeated exposure to hydrocarbon solvents can lead to severe irritant dermatitis due to defatting of the skin. The C₉-C₁₄ aliphatic (≤2% aromatics) Category members do not cause skin sensitization.

Repeated Dose Toxicity (Inhalation)

There were six repeated inhalation toxicity studies in rats, 2 with mixed aliphatic solvents, and 4 with isoparaffinic solvents. These six studies subsumed all of the constituents (C9-C14 n-paraffins, isoparaffins, cycloparaffins) in this category of solvents. There were no treatment-related mortalities, and, with one exception, no significant reductions in body weight gain. There were some reports of small but statistically significant reductions in hematological parameters but these were within the normal range and not considered toxicologically important. There were some significant changes in clinical chemistry parameters but these were small and not consistent across the studies. Of particular importance was that liver enzyme markers were not significantly elevated in any study. There were observations of liver weight increases in either male or female rats in most of the studies as well as increased kidney weights in male rats. There were no pathological changes in the liver or evidence of elevated liver enzyme markers in any of the studies. Many of the study reports drew attention to kidney effects in male rats. The pathological observations and male-rat specificity were consistent with an alpha 2u-globulin-mediated response, although the studies were conducted before the alpha 2u-globulin-mediated process was understood. However, later studies with solvents of this type have documented an increase in alpha 2u-globulin in response to exposure, providing more direct evidence that this was in fact an alpha 2u-globulin-mediated process and not relevant to humans. For comparative purposes there was also a 28 day inhalation toxicity in primates in which no significant effects were reported following exposure to 4200 mg/m³. In summary, excluding the liver weight changes as being adaptive responses and the kidney changes in male rats as being alpha 2u-globulin mediated and not relevant to humans, the overall NOAECs were the highest concentrations tested in most of the studies although there were significant reductions in body weight gain in female rats in the highest exposure group (1800 ppm) of the inhalation study using C12 isoparaffins (<2% aromatics).

The specific solvents tested by inhalation and the results of these studies (assuming liver weight increases to be adaptive rather than adverse and kidney changes in male rats to be not relevant to humans) include:

- (1) C10-C12 isoparaffins (< 2% aromatics) (CAS RN 64741-65-7). Tested in a 90 day inhalation toxicity study (OECD TG 413) in albino rats. The NOAEC was 10,400 mg/m³ (1444 ppm), the highest concentration tested.
- (2) C9-C11 n-paraffins, isoparaffins, cyclics (<2% aromatics) (CAS RN 64742-48-9). Tested in a 90 day inhalation toxicity study (OECD TG 413) in Sprague-Dawley rats. The NOAEC was 5220 mg/m³ (900 ppm), the highest concentration tested.
- (3) C10-C12 isoalkanes (<2% aromatics) (CAS RN 60742-48-9). Tested in a 90 day inhalation toxicity study (OECD TG 413) in Sprague-Dawley rats. The NOAEC was 5220 mg/m³ (900 ppm), the highest concentration tested.
- (4) C11-C14 n-paraffins, isoparaffins, cyclics (CAS RN 64742-47-8). Tested in a 90 day inhalation toxicity study (OECD TG 413) in albino rats. The NOAEC was 6000 mg/m³, the highest concentration tested.
- (5) C12 isoparaffins (<2% aromatics) (CAS RN 93685-81-5). Tested in a 90 day inhalation toxicity study (OECD TG 413) in Wistar rats. The NOAEC was 1390 mg/m³ (200 ppm) (based on reduced body weights in female rats).
- (6) C12 isoparaffins (<2% aromatics) (CAS RN 93685-81-5). Tested in a 90 day inhalation toxicity study (OECD TG 413) in Wistar rats. The NOAEC was 6257 mg/m³ (900 ppm), the highest concentration tested.
- (7) C10-C13 n-alkanes, isoalkanes, cyclics (<2% aromatics) (CAS RN 64742-48-9). Tested in a 28 day inhalation toxicity study (OECD TG 412) in Rhesus monkeys. The NOAEC was 4200 mg/m³ (615 ppm), the highest concentration tested.

Repeated Dose Toxicity (Oral)

Seven repeated oral toxicity studies in rats have been conducted, one C₁₀-C₁₃ aliphatic solvent, one C₁₁-C₁₄ aliphatic solvent, two isoparaffinic solvents (C₁₀-C₁₂, C₁₂), two normal paraffinic solvents (C₁₀, C₁₁) and a study of the analogue substance tetramethylcyclohexane. In aggregate these 7 studies covered all constituents of the C9-C14 hydrocarbon (<2% aromatics). Five of these studies were essentially in accordance with OECD TG 408 but 3 of them

included “satellite” groups of animals treated for 13 weeks with the high dose of test material and then held for an additional 28 days to assess recovery. The other two studies were repeated dose/reproductive toxicity screening studies following OECD TG 422. One of these studies included an investigation in beagle dogs and reported no significant findings. In the other studies, conducted in rats, the principal finding was a treatment-related increase in liver weights. The pathology reports described the liver changes as indicative of liver cell enlargement (hypertrophy). Liver enzyme markers were not elevated, and the liver weight changes (and histologic changes) were not observed in the animals held for 28 days without treatment. There were also kidney changes in the male rats in the studies of the lower molecular weight isoparaffinic and mixed aliphatic solvents. The kidney effects were only in male rats and the histologic findings were consistent with an alpha 2u-globulin mediated response. There were also some reports of reduced weight gain. This was most likely due to the use of corn oil as a diluent in some studies. In effect the control animals were being force fed relatively high levels of corn oil and as a consequence got a higher caloric input than the treated animals in which the corn oil was replaced by increasingly higher levels of test material.

The specific solvents tested by repeated oral administration and the results of these studies (assuming liver weight increases to be adaptive rather than adverse and kidney changes in male rats to be not relevant to humans) include:

- (1) Hydrocarbons C10-C11, n-alkanes, isoalkanes, cyclics ($\leq 2\%$ aromatics) (CAS RN 64742-48-9). Tested in a 90 day repeated oral toxicity test (OECD TG 408) in Sprague-Dawley rats. The study design included a 28 day recovery period for rats exposed to the highest dose (5000 mg/kg/day). The NOAEL was 5000 mg/kg/day, the highest concentration tested.
- (2) Hydrocarbons C11-C14, n-alkanes, isoalkanes, cyclics ($<2\%$ aromatics) (CAS RN 64742-47-8). Tested in a 90 day repeated oral toxicity test (OECD TG 408) in Sprague-Dawley rats. The study design included a 28 day recovery period for rats exposed to the highest dose (1000 mg/kg/day). The NOAEL was 1000 mg/kg/day.
- (3) Hydrocarbons C10-C12 isoalkanes ($<2\%$ aromatics) (CAS RN 64742-47-8). Tested in a 90 day repeated oral toxicity test (OECD TG 408) in Sprague-Dawley rats. The study design included a 28 day recovery period for rats exposed to the highest dose (1000 mg/kg/day). The NOAEL was 1000 mg/kg/day.
- (4) Hydrocarbons C12 isoalkanes ($\leq 25\%$ aromatics) (CAS RN 93685-81-5). Tested in a 90 day repeated oral toxicity test (OECD TG 408) in Wistar rats. The NOAEL was 1000 mg/kg/day.
- (5) Hydrocarbons C10 normal paraffins ($<2\%$ aromatics) (CAS RN 124-18-5). Tested in a repeated dose/reproductive toxicity screening test (OECD TG 422) in Wistar rats. The NOAEL was 1000 mg/kg/day.
- (6) Hydrocarbons C11 normal paraffins ($<2\%$ aromatics) (CAS RN 1120-21-4). Tested in a repeated dose/reproductive toxicity screening test (OECD TG 422) in SD rats. The NOAEL was 1000 mg/kg/day.
- (7) Tetramethylcyclohexane (C10 analogue cycloparaffinic substance, no CAS RN number provided). Tested in a 90 day dietary administration study (OECD TG 408) in rats and beagle dogs. There were no effects in either species at the highest dietary levels administered (30,000 ppm, approximately 3000 mg/kg bw/day).

Repeated Dose Toxicity (Dermal)

A 28 day dermal administration study in New Zealand white rabbits was conducted with C12-C14 normal paraffins ($< 2\%$ aromatics) (CAS RN 64771-72-8). The test material was applied daily (7 days/week) for 4 weeks to the backs of the rabbits and maintained in contact with the skin for 6 hours. Treatment levels were 0, 100, 500, or 2000 mg/kg/day. The protocol was equivalent to OECD TG 410. At the end of the treatment period the animals were examined and then sacrificed to assess the potential for target organ effects. The repeated dermal treatment under the occlusive patch conditions utilized caused severe dermal irritation in the highest treatment group (2000 mg/kg/day), leading to early termination. There was no evidence of systemic effects in animals from the highest dose group, but, because of the early terminations of some animals, conclusions based on this experimental group were considered unreliable. Accordingly, the overall NOAEL for hydrocarbons C12-C14 n-paraffins ($<2\%$ aromatics) was judged to be 500 mg/kg/day.

Repeat Dose Toxicity, overall conclusion

In summary, the members of the C₉-C₁₄ Aliphatic [$< 2\%$ aromatics] Hydrocarbon Solvents Category did not appear to produce significant systemic toxicity. Repeated dose studies have been conducted on a number of category members using inhalation as well as oral and dermal administration as routes of exposure. The studies were conducted following standard guidelines and the data were judged adequate for assessing the health hazard from exposure. The principal findings in these studies were increased liver weights in males and females and kidney changes in male rats. There were no pathologic changes, levels of liver enzyme markers were not elevated, and the weight differences were reversed when the rats were held without treatment for 28 days. The kidney changes were found only in male rats and were

consistent with effects mediated by alpha 2u-globulin, an effect that has been determined to be not relevant to humans. In addition to the studies in rats there was one inhalation toxicity study in Rhesus monkeys and a dietary study in beagle dogs. There were no reported findings in these studies.

Mutagenicity

In vitro Studies

C₉-C₁₄ aliphatic, < 2% aromatic hydrocarbons fluids are not mutagenic using *in vitro* genotoxicity assays. In bacterial tests, C₉-C₁₄ aliphatic, < 2% aromatic hydrocarbons fluids were not mutagenic in Salmonella strains tested in the presence or absence of metabolic activation. C₉-C₁₄ aliphatic, <2% aromatic hydrocarbon fluids did not induce mutations in an *in vitro* mammalian cell gene mutation assay. In sister chromatid exchange and in chromosomal aberration studies conducted under *in vitro* conditions, C₉-C₁₄ aliphatic, < 2% aromatic hydrocarbons fluids did not produce effects.

All *in vitro* genetic toxicity tests listed below had negative results for C₉-C₁₄ aliphatic, < 2% aromatic hydrocarbons solvents.

Genetic Toxicity *in vitro* – Bacterial reverse mutation assay (OECD TG 471) (CAS RN 64771-72-8, 90622-57-4, 64742-48-9; 64742-88-7). Samples tested included C10-C13 n-alkanes, C10-C13 n-alkanes, C11 n-alkanes, C10-C12 isoalkanes, C10-C13 n-alkanes, isoalkanes, cyclics.

Genetic Toxicity *in vitro* – *In vitro* Mammalian Chromosome Aberration Test (OECD TG 473) (CAS RN 64742-47-8, C11n-paraffins)

Genetic Toxicity *in vitro* - *In vitro* Mammalian Cell Gene Mutation Test (OECD TG 476) (CAS RN 64771-72-8, 31807-55-3). Samples tested were C12 isoparaffins, C11-C14 n-alkanes, isoalkanes, cyclics.

Genetic Toxicity *in vitro* – In Vitro Sister Chromatid Exchange Assay in Mammalian Cells (OECD TG 479) (CAS RN 90622-57-4). The sample tested was C10-C12 isoalkanes.

In vivo Studies

C₉-C₁₄ aliphatic, < 2% aromatic hydrocarbons fluids were not genotoxic when tested by gavage in an *in vivo* mouse bone marrow micronucleus assay, when tested by inhalation in a mouse micronucleus test, and when tested in dominant lethal studies utilizing an inhalation route of exposure.

All genetic toxicity tests listed below had negative results for C₉-C₁₄ aliphatic, < 2% aromatic hydrocarbons solvents.

Genetic Toxicity *in vivo* – Micronucleus Assay in Mouse Bone Marrow, oral (OECD TG 474) (CAS RN 64771-72-8). The sample tested was C10-C13 n-alkanes, isoalkanes, cyclics.

Genetic Toxicity *in vivo* – Micronucleus Assay in Mouse Bone Marrow, inhalation (OECD TG 474) (CAS number 64742-88-7). The sample tested was C10-C13 n-alkanes, isoalkanes, cyclics.

Genetic Toxicity *in vivo* – Genetic Toxicology: Rodent Dominant Lethal Test (OECD TG 478) (CAS RN 64771-72-8 and 90622-57-4). Samples tested were C10-C12 isoalkanes, C9-C11 n-alkanes, isoalkanes, cyclics.

Mutagenicity Overall Conclusions

Members of the C₉-C₁₄ Aliphatic [≤ 2% Aromatic] Hydrocarbon Solvents Category have shown no mutagenic activity in a number of *in vitro* bacterial, mammalian cell mutagenicity tests and were not active when tested in *in vitro* tests for chromosome aberration and sister chromatic exchange. These substances were not genotoxic when tested under *in vivo* conditions in bone marrow assays for chromosome damage and in dominant lethal tests.

Carcinogenicity

Carcinogenicity Summary

Male and Female F-344 rats and B6C3F1 mice were exposed for two years to vapors of Stoddard solvent IIC (CAS RN 64742-88-7). Exposure levels were 0, 138 (male rats only), 550, 1100 mg/m³, or 2200 mg/m³ (mice and female rats). The NTP concluded that there was some evidence of carcinogenic activity in male rats due to an increase in adrenal gland tumors and equivocal evidence of carcinogenic activity in female mice due to an increase in liver tumors. The judgment that the liver tumor incidence was equivocal was related to a determination by the NTP that these tumors were secondary to an increase in body weight in female mice. There was no evidence of carcinogenicity in female rats

or male mice.

Groups of 50 male and 50 female Wistar rats and B6C3F mice were exposed to Stoddard solvent IIC (CAS RN 64742-88-7) in two year studies. The test material was described as being composed primarily of C10-C13 aliphatic constituent with <1% aromatics. Male rats were exposed at concentrations of 0, 138, 550, or 1100 mg/m³; the female rats and mice were exposed at levels of 550, 110 or 2200 mg/m³ [the maximally attainable vapor concentration]. The exposure levels were based on 2 week and 3 month preliminary studies. Exposures were, 6 hours plus T90 (12 minutes) per day, 5 days per week for 105 weeks. Groups of 10 rats/sex/exposure level were exposed at the same levels in 14 week satellite studies to assess kidney effects. Clinical findings were recorded twice daily. The animals were weighed initially, weekly, and at the end of the studies. Necropsies were performed on all rats. The heart, right kidney, liver, lung, right testis, and thymus were weighed. Histopathologic examinations were performed on all rats and mice.

Results of the rat study

Neoplastic Effects

Kidney: In the standard evaluation of a single hematoxylin and eosin stained section of the left and right kidney, the incidences of mild to moderate renal tubule and transitional epithelial hyperplasia in 550 and 1,100 mg/m³ males were significantly increased. The incidences of renal tubule adenoma and renal tubule carcinoma in exposed groups of male rats were similar to those in the chamber controls at the standard evaluation. Renal tubule hyperplasia, adenoma, and carcinoma are thought to represent a continuum in the progression of proliferative lesions of the renal tubule epithelium. Because there were increased incidences of renal tubule hyperplasia (a preneoplastic lesion) in male rats, additional kidney sections were evaluated, and additional renal tubule hyperplasias and adenomas were identified. In the extended evaluation, the significantly increased incidences of renal tubule hyperplasia in 550 and 1,100 mg/m³ males were confirmed. In the extended evaluation, the incidence of renal tubule adenoma was greater in 1,100 mg/m³ males than in the chamber controls; however, the increase was not significant; the incidences of renal tubule carcinoma in exposed groups of males were similar to that in the chamber control group.

Adrenal Medulla: The incidences of benign and, benign or malignant pheochromocytoma (combined) occurred with positive trends in males, and the incidences in the 550 and 1,100 mg/m³ groups were significantly increased. The incidences of benign pheochromocytoma in 550 and 1,100 mg/m³ males and benign or malignant pheochromocytoma in 1,100 mg/m³ males exceeded the historical ranges in chamber controls. Benign pheochromocytomas were characterized by a proliferating mass of adrenal medullary cells that compressed adjacent tissue. Malignant pheochromocytomas were generally larger with invasion of or beyond the adrenal capsule. The incidence of hyperplasia of the adrenal medulla in 550 mg/m³ males was significantly increased. Medullary hyperplasia was characterized by an increase in basophilia of medullary cells that sometimes accompanied increased size and minimal compression of the adjacent tissue.

	Male F344/N Rats	Female F344/N Rats
Concentrations in air	Chamber control, 138, 550, or 1100 mg/m ³	Chamber control, 550, 1100, or 2200 mg/m ³
Survival rates	29/50, 19/50, 21/50, 16/50	36/50, 30/50, 32/50, 25/50
Body weights	Exposed groups similar to the chamber control group	Exposed groups similar to the chamber control group
Notable Nonneoplastic effects	In the 3 month studies there were significant increases in granular casts and cortical tubule regeneration at 550 and 1100 mg/m ³ . In 2 year studies there were significant increases in renal tubular hyperplasia at 550 and 1100 mg/m ³ and mineralization at all exposure levels.	Non-neoplastic renal effects were observed in in 3 month and two year studies..
Neoplastic effects	Adrenal medulla:benign and malignant pheochromocytoma Control = 6/50, 138 mg/m ³ = 9/50, 550 mg/m ³ = 13/50 (p < 0.05), 1100 mg/m ³ = 19/50 (p < 0.01) Kidney Renal Tubule Adenomas	The adrenal and kidney tumors in male rats were considered to have been treatment related

Control = 3/50 138 mg/m ³ = 2/50 550 mg/m ³ = 3/50 1100 mg/m ³ = 7/50

Results of the mice study

Neoplastic Findings

Liver: The incidences of hepatocellular adenoma occurred with a positive trend in female mice, and the incidences of multiple hepatocellular adenoma in male and female mice from the 2200 mg/m³ exposure group were significantly increased; however, the incidences of adenoma or carcinoma (combined) and carcinoma alone in exposed males and females were not significantly increased. The increased incidence of multiple hepatocellular adenoma in 2,200 mg/m³ males was not considered related to Stoddard solvent IIC exposure because the incidences of all adenomas (including multiple) were not significantly increased in the exposed groups. The incidences of hepatocellular adenoma in 550 and 2,200 mg/m³ males and 1,100 and 2,200 mg/m³ females and of hepatocellular adenoma or carcinoma (combined) in 550 mg/m³ males and 2,200 mg/m³ females exceeded the historical ranges in chamber controls; the incidences in chamber control males and 1,100 mg/m³ females were at the upper end of the historical ranges.

Lung: The incidences of alveolar/bronchiolar adenoma or carcinoma (combined) were decreased in exposed males, and the decrease in the 550 mg/m³ group was significant (chamber control, 13/50; 550 mg/m³, 4/49; 1,100 mg/m³, 6/50; 2,200 mg/m³, 6/50). The incidence in the chamber controls was at the lower end of the historical range in chamber controls, and the incidences in the exposed groups were less than the historical range [85/250 (34% ± 7%), range 26% - 44%].

	Male B6C3F1 Mice	Female B6C3F1 Mice
Concentrations in air	Chamber control, 550, 1100, or 2200 mg/m ³	Chamber control, 550, 1100, or 2200 mg/m ³
Survival rates	34/50, 32/50, 27/50, 32/50	36/50, 34/50, 27/50, 34/50
Body weights	Exposed groups similar to the chamber control group	Exposed groups greater than the chamber control group
Nonneoplastic effects	none	none
Neoplastic effects	None considered treatment related	Hepatocellular adenoma Control = 9/50 550 mg/m ³ = 12/50 1100 mg/m ³ = 12/50 2200 mg/m ³ = 18/50 (p = 0.032)

Conclusions

The NTP concluded that under the conditions of these 2-year inhalation studies, there was some evidence of carcinogenic activity of Stoddard solvent IIC in male F344/N rats based on increased incidences of adrenal medulla neoplasms (pheochromocytoma). There was no evidence of carcinogenic activity of Stoddard solvent IIC in female F344/N rats exposed to 550, 1100, or 2200 mg/m³.

The NTP further concluded there was no evidence of carcinogenic activity of Stoddard solvent IIC in male B6C3F1 mice exposed to 550, 1100, or 2200 mg/m³. There was equivocal evidence of carcinogenic activity of Stoddard solvent IIC in female B6C3F1 mice based on increased incidences of hepatocellular adenoma. Equivocal evidence of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related. The NTP pointed out that liver tumors in B6C3F1 mice are sensitive to body weight changes and noted that statistical analysis was consistent with the view that the increased liver tumors in female mice in this study were the consequence of increased body weight. That was the basis for the overall determination by the NTP that the evidence of carcinogenic effects in mice was equivocal.

The NTP also pointed out that the exposure of male rats to Stoddard solvent IIC resulted in non-neoplastic lesions of the kidney characteristic of alpha 2u-globulin. [The pathology data are summarized in the table above. The NTP also documented an increase in alpha 2u globulin using immuno-staining techniques.

Toxicological Relevance of Carcinogenesis Findings

As summarized above, the NTP considered that the increased liver tumor incidence in female mice was equivocal based on a statistical analysis which indicated that this increase could be explained by the increased body weights of the mice in that group. The NTP also appeared to put little weight on the renal tumors in male rats as other data were obtained during this study to show that levels of α 2u-globulin were increased providing support for the view that these tumors, although treatment-related, are not relevant to humans.

The toxicological significance of the pheochromocytomas is less clear. The appearance of elevated levels of pheochromocytomas seems to have first drawn attention in the context of an NTP carcinogenicity study of talc in which it was noted that this particular type of tumor appears spontaneously at relatively high incidence in the F344 rats. After further review of the historical information on tumors of this type, NTP scientists pointed out that hyperplasia and neoplasia of the adrenal medulla is relatively common in rats but rare in humans and other species. They suggested that there might be a link between the induction of chronic progressive nephropathy (CPN), an aging lesion particular prevalent in F344 rats which is exacerbated by certain chemical agents, and adrenal changes.

In a review on pheochromocytomas in rats, it was noted that the pheochromocytomas are a common spontaneous tumor in male Fischer 344 rats with average frequencies in control groups nearing 40% in the 1990s but between 12% and 16% since the rat diets were changed in 2000. In contrast, pheochromocytomas are rare in humans, occurring with an incidence of 1/100,000. A number of mechanisms have been proposed to account for the high incidence in humans; the authors of the review included Stoddard solvent IIC as among those for which the tumors may have been secondary to nephrotoxic effects. They also noted that “[T]here is to date no indication that the substances inducing pheochromocytomas also induce corresponding tumors in humans; however, the database for a final conclusion is inadequate. Ultimately as the underlying mechanism for pheochromocytoma development in rats is not known, they could not exclude the possibility that chemical exposure could be a risk factor in humans. But the authors did conclude that the pheochromocytomas in rats were a secondary effect, making it unlikely that it would be relevant to humans exposed at lower levels than those used in the experimental studies.

Reproductive and Developmental Toxicity

There were two developmental toxicity studies on category members (C₉-C₁₁ mixed aliphatic solvent, C₁₀-C₁₂ isoalkanes) in which exposure was by inhalation; two repeated dose/reproductive toxicity screening tests on category members (C₁₀, C₁₁ normal paraffinic solvents) in which exposure was oral; a repeated dose/reproductive toxicity screening test on a C₉-C₁₆ analogue substance in which exposure was dermal; a reproductive toxicity test on a C₉-C₁₆ analogue substance in which the exposure was oral, and a classical developmental toxicity study on a C₉-C₁₆ analogue substance. There were no effects on either fertility or development in any of these studies. Additionally, there have been 7 repeated exposure studies in which the reproductive organs were examined and found to have not been affected by test material administration.

These studies provide evidence that members of the C₉-C₁₄ Aliphatic [\leq 2% Aromatic] Hydrocarbon Solvents Category would not be expected to be reproductive or developmental toxicants.

There are several studies for reproductive and/or developmental effects that have been conducted with members of the C₉-C₁₄ Aliphatic [\leq 2% Aromatics] Hydrocarbon Solvents Category products. There is also data available for two analogue substances hydrodesulfurized kerosene (CAS RN 64742-81-0, analogue) and jet fuel (JP-8, analogue). Hydrodesulfurized kerosene was tested in a reproductive toxicity/repeated dose toxicity screening test in which test material was applied dermally. JP-8 was tested in separate studies of fertility and developmental effects. These two analogue substances are petroleum fuels, described as containing primarily C₉-C₁₆ aliphatic constituents with aromatic contents limited to a maximum of 25% (although the samples used in these tests contained about 20% aromatics. The data provided by tests of category and analogue substances subsumed the carbon numbers and molecular types found in the C₉-C₁₄ aliphatic (<25 aromatic) category.

Reproductive toxicity

The study of hydrodesulfurized kerosene (CAS RN 64742-82-1), followed the guidelines of OECD TG 421. The test material, described as a C₉-C₁₆ petroleum fuel containing approximately 80% aliphatic and 20% aromatic (primarily alkylated single ring compounds) constituents. The hydrodesulfurized kerosene was administered dermally at doses equivalent to 0, 165, 330, or 494 mg/kg/day to male and female Sprague-Dawley rats in groups of 10/sex. Dosing was initiated 14 days prior to mating and continued through 2 weeks of mating and 20 days of gestation. Females and their litters were sacrificed on post-natal day 4; all males were sacrificed 7 days after termination of the last female. The doses were chosen based on a preliminary study in which it was shown that approximately 500 mg/kg/day was the highest dose that could be repeatedly applied without producing unacceptable levels of skin irritation. Among the males there were no effects on survival or weight gain during the study, and at terminal sacrifice the only statistically

significant effect was an increase in kidney weight in animals from the high dose group. Among the females there were no effects on mating, litter size, offspring body weights or offspring survival. An overall conclusion from the study was that the No Observed Adverse Effect Level for all reproductive and developmental parameters assessed was 494 mg/kg/day, the highest dose tested.

The jet fuel reproductive toxicity studies were by oral gavage. To assess the potential for reproductive effects in males, male Sprague-Dawley rats were given 0, 750, 1500 or 3000 mg/kg JP-8 ; an aliphatic carbon range of C₉-C₁₆, aromatics <25%) daily by gavage for 70 days prior to mating with naive females to assess fertility and sperm parameters (similar to OECD TG 415). Males continued to be treated during the mating period to termination after a total of 90 days of treatment. There was a statistically significant reduction in body weight gain in male rats from the 3000 mg/kg bw/day group. But there were no effects on fertility, no changes in sperm parameters, and no gross or histological effects on reproductive organs. The reproductive NOAEL = 3000 mg/kg bw/day for male rats.

To assess the potential for reproductive effects in females, female Sprague-Dawley rats were dosed (0, 325, 750, 1500 mg/kg) with JP-8 an aliphatic carbon range of C₉-C₁₆, aromatics <25%) daily by gavage for a total of 21 weeks (90s-day plus mating with naive males, gestation and lactation) in an effort to assess general toxicity, fertility and reproductive endpoints (similar to OECD TG 415). All surviving dams were sacrificed on post-natal day 21. Body weight gain was significantly reduced in females in the 1500 mg/kg/day group. But there were no significant differences in rates of fertility, length of gestation, litter size or live birth index. There was an effect of treatment on body weight gain of offspring, but the differences between groups were reduced with increasing time without treatment. The NOAEL was 1500 mg/kg bw/day for female fertility, the highest dose tested. The NOAEL for the pups was 750 mg/kg bw/day based on a decrease in body weight which correlated with a decrease in maternal body weight at 1500 mg/kg bw/day.

A reproduction/developmental Toxicity Screening Test in Sprague-Dawley rats, similar to OECD TG 422, was conducted using Undecane (CAS RN: 1120-21-4). The administration of the test substance was carried out by oral gavage. The volume administered was 5 mL per kg of body weight in doses of 0, 100, 300 or 1000 mg/kg/day. The test material was suspended in olive oil. The dose administration period was 46 days, which including 14 days before mating and during the mating period for males. The dose administration period for the female rats began 14 days before mating and continued until after the first 3 days of nursing. The administration was started when the animals were 10 weeks old. The results of the repeated dose part of this study are summarized in the repeated dose toxicity section. In the reproductive and developmental toxicity portion of this study, There were no significant differences in body weight gain. Liver and adrenal weights were elevated in the high dose group, but there were no unusual histological findings. There were also no differences in mating frequency. No effects of undecane administration were observed on the sex cycle of females and copulation and conception of males and females. In addition, no effects of undecane administration were observed on the weights of reproductive organs (testis, epididymis and ovary) and there were no abnormalities noted in the dissection and histopathological examination. There were no histopathological findings in cases where animals failed to successfully mate; abnormal deliveries (2 in the 300 mg/kg/day group and 1 in the 1000 mg/kg/day group) were confirmed to be spontaneous and at frequencies similar to historical controls. Those cases observed in the present study were considered to be unrelated to undecane. There were no differences in the number of live pups born in the control, 100 mg/kg, or the 1000 mg/kg treated animals; there was a decrease in the 300 mg/kg group, but as no difference was noted in the 1000 mg/kg treated animals, this finding was determined by the authors to not be test material related. There was no difference in the number of pups alive on post-natal day 4. The body weights at post-natal day 4 of both males and females in the 1000 mg/kg group were slightly reduced (-5.6% and -4.1%), but were not significantly different from the weights of offspring in the control group, and there were no notable clinical or pathological effects. The NOAEL for reproductive performance and developmental effects is considered to be 1000 mg/kg/day.

A Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test similar to OECD TG 422 was conducted using decane, CAS RN: 124-18-5. Animals were dosed with 0, 25, 150, or 1000 mg/kg/day (10 ml/kg dosing volume), once a day, 7 days a week via oral gavage. No deaths or clinical signs of toxicity or behavioral changes were noted. The results of the repeated dose assessment are reported in the section on repeated dose toxicity. In the assessment of developmental and reproductive effects there were no treatment-related effects at any dose level on any of the reproductive parameters evaluated in this study. These included measures of reproductive performance (mating, conception, gestation length, and litter size), offspring survival (gestation and postnatal survival indices, percent pre- and post-implantation loss). There were no treatment-related effects at any dose level on any of the developmental parameters evaluated in this study including external abnormalities of pups, number of live and still births, mortality, sex determination, and weights of pups. Based on these data, the no-observable-adverse-effect level (NOAEL) for developmental toxicity was 1000 mg/kg/day and the NOAEL for reproductive dose and reproductive toxicity was 1000 mg/kg/day.

Developmental toxicity studies

A Prenatal Developmental Toxicity Study equivalent or similar to OECD TG 414 with Hydrocarbons, C₉-C₁₁, isoalkanes, cyclics, < 2% aromatics (CAS RN 64742-48-9). The test material was administered to pregnant female Sprague-Dawley rats by inhalation exposure to vapor concentrations of 0, 300 or 900 ppm (5220 mg/m³), 6 hours/day during gestation days 6 to 15 to assess developmental toxicity. Included in this study was a negative control (chamber exposed) group and a positive control group that was treated via gastric intubation on gestational days 6-15 with 400mg/kg/day of acetylsalicylic acid. All surviving females were sacrificed on Day 21 of gestation and fetuses were examined for external, soft tissue and skeletal malformations.

Maternal Effects. Animals treated with 900 ppm exhibited a slight increase in excessive lacrimation during the treatment and post-treatment periods. This same group also exhibited an increased incidence of brown flakes in the fur covering the head area during the treatment period. Premature delivery of the litter on Day 21 of gestation prior to maternal sacrifice was observed in one negative control female, and two test material treated females. There were no remarkable gross postmortem changes in the treated adult females. All other physical observations occurred with similar frequencies in all groups and were considered to represent common observations noted in rats in the laboratory environment. Positive control animals demonstrated maternal toxicity.

Embryotoxic / Teratogenic effects. All fetal survival, size and sex data for groups treated with test material were comparable to negative control data. Slight delays or variation in the normal ossification process were observed in treated animals. However, such variations are common as the time of normal ossification can vary and were comparable to the variation observed in the control animals. The incidence of fetuses with external malformations and incidences of litters containing malformed fetuses in the groups treated with test material were considered comparable to the control data. No significant differences in the incidence of visceral malformations was observed in the treated groups. The incidence of fetuses with soft tissue malformation in groups treated with test material was comparable to the negative control. Positive control animals demonstrated developmental toxicity.

Pregnancy rate, mortality, body weight gain and gross postmortem observations were unaffected by treatment. Hydrocarbons, C₉-C₁₁, normal paraffins, isoalkanes, cyclics, < 2% aromatics treatment at either dose level had no effect on reproductive endpoints, fetal size, sex distribution, ossification variation, or fetal examination endpoints. Thus, there was no evidence of maternal or fetal toxicity at either exposure level of Hydrocarbons, C₉-C₁₁, normal, isoalkanes, cyclics, < 2% aromatics tested. Based on these results, both the maternal and developmental NOAELs were greater than or equal to 900 ppm (5220 mg/m³).

Hydrocarbons, C₁₀-C₁₂, isoalkanes, < 2% aromatics (CAS RN 90622-57-4) was administered to pregnant female Sprague-Dawley rats by inhalation exposure to vapor concentrations of 0, 300 or 900 ppm, 6 hours/day during gestation days 6 to 15 to assess developmental toxicity. Included in this study was a negative control (chamber exposed) group and a positive control group that was treated via gastric intubation on gestational days 6-15 with 400mg/kg/day of acetylsalicylic acid.

Maternal toxic effects. Animals treated with 900 ppm exhibited a slight increase in excessive lacrimation during the treatment and post-treatment periods. This same group also exhibited an increased incidence of brown flakes in the fur covering the head area during the treatment period. Premature delivery of the litter on Day 21 of gestation prior to maternal sacrifice was observed in one negative control female, and two test material treated females. There were no remarkable gross postmortem changes in the treated adult females. All other physical observations occurred with similar frequencies in all groups and were considered to represent common observations noted in rats in the laboratory environment. Positive control animals demonstrated maternal toxicity.

Embryotoxic / teratogenic effects. All fetal survival, size and sex data for groups treated with test material were comparable to negative control data. Slight delays or variation in the normal ossification process were observed in a few treated animals. However such variations are common as the time of normal ossification can vary and were comparable to the variation observed in the control animals. The incidence of fetuses with external malformations and incidences of litters containing malformed fetuses in the groups treated with test material were considered comparable to the control data (<5% and no dose response). No significant difference in the incidence of visceral malformations was observed in the treated groups. The incidence of fetuses with soft tissue malformation in groups treated with test material was comparable to the negative control. Positive control animals demonstrated developmental toxicity.

Hydrocarbons, C₁₀-C₁₂, isoalkanes, < 2% aromatics treatment at either dose level had no effect on reproductive endpoints, fetal size, sex distribution, ossification variation, or fetal examination endpoints. Pregnancy rate, mortality, body weight gain and gross postmortem observations were unaffected by treatment. Thus, there was no evidence of maternal or fetal toxicity at either exposure level of the chemical tested. Based on these results, both the maternal and developmental NOAELs were greater than or equal to 900 ppm (5220 mg/m³).

In addition to the above, there were no apparent effects on in utero development or post-natal survival of offspring in the reproductive toxicity/developmental toxicity screening tests of the category substances decane or undecane or the analogue substances JP-8 or hydrodesulfurized kerosene. There was also a more classical developmental toxicity study of JP-8 in which test material was given by gavage to time-pregnant Sprague-Dawley rats on days 6-15 of gestation in doses of 0, 500, 1000, 1500 or 2000 mg/kg/day. There was significant maternal mortality (9/30) in the 2000 mg/kg/day group, but among the survivors, there were no significant differences in pregnancy rates, litter sizes or frequency of live fetuses/litter. The uterine examinations did not identify any malformations. There were effects on maternal weight in all of the dose groups, and significantly reduced fetal weights were noted in the 1500 and 2000 mg/kg/day groups. The authors considered that 500 mg/kg/day was a NOAEL for maternal effects and 1000 mg/kg/day was a NOAEL for fetal effects.

Neurobehavioral toxicity

Members of the C9-C14 aliphatics (<2% aromatics) category as well as a number of constituents of these solvents have been tested for acute central nervous system effects. As summarized below, aliphatic hydrocarbons with carbon numbers up to approximately C10 can produce acute, reversible effects on the central nervous system. Hydrocarbon solvents with carbon numbers greater than C10 do not produce acute CNS effects at the maximally attainable vapor concentrations. In one repeated dose study, rats were exposed to isoparaffinic hydrocarbons for 13 weeks at levels of 668, 2220, or 6646 ppm (24,300 mg/m³). There were no persistent effects in assessments of motor activity or functional observations and no pathologic changes in the central or peripheral nervous systems. A summary article reported that a low (<0.4%) aromatic aliphatic solvent (CAS RN 64742-48-9) did not cause gross or pathological changes to the central or peripheral nervous system or produce neurochemical changes. In neurobehavioral assessments no effects were found in the majority of the assessed parameters but there was a decrease in dark field motor activity. One study reported effects in an electrophysiological study.

Animal Studies

An article reports the results of neurobehavioral tests of n-octane (CAS RN 111-65-9) and n-decane (CAS RN 124-18-5) normal paraffinic constituents (n-paraffins). Clinical effects, motor activity, functional observations, and visual discrimination performance were evaluated shortly after exposure.

n-Octane. Rats were exposed for 8-hours for 3 consecutive days to 0, 1405, 4248, or 14002 mg/m³ of n-octane. There were no treatment related effects in the FOB measurements. Foot-splay was significantly increased in the 1405 mg/m³ exposure group, and hind-limb grip strength was significantly increased in the 4248 mg/m³ exposure group. As an exposure-response relationship was not demonstrated, these effects were judged to be unrelated to treatment. There were no statistically significant effects on motor activity. Visual discrimination performance testing did not reveal any treatment-related effects. There were no group differences in number of trials completed or discrimination accuracy. There were no differences in frequency of repetitive errors or in lever response latency. There was a statistically non-significant reduction in frequency of very short latency responses (<1 second), but this difference was also observed in the pretest examination, and the frequency did not change during the study. Thus, it seems unlikely that it was a treatment-related effect. Similarly, there were no treatment-related differences in short (<2 seconds) or long (>6 seconds) latency responses. The overall assessment was that n-octane did not affect visual discrimination performance at exposure levels up to 14000 mg/m³.

n-Decane. Rats were exposed for 8-hours for 3 consecutive days to 501, 1510, and 5005 mg/m³ of n-decane. The only significant difference in any of the FOB measurements was a statistically significant reduction in grip strength in the 5005 mg/m³ exposure group after the third 8-hour exposure. There were no effects on motor activity. Visual discrimination performance testing did not reveal any treatment-related differences in number of trials completed or discrimination ratios. Frequency of response during the ITI was not significantly different between groups during the 3-day exposure period. There were differences in frequency of repetitive errors and responses during the ITIs, but as the most highly exposed animals performed better than the controls, this was judged to have not been a toxicologically relevant finding. There were differences in lever response latency, but these were not statistically significant. There was a statistically significant increase in the frequency of long (i.e., >6 seconds) latency responses. The overall assessment was that n-decane had some minimal, reversible effects on visual discrimination performance at an exposure level of 5000 mg/m³. The NOAEL = 1500 mg/m³.

Rats were exposed to n-alkanes ranging from C₉-C₁₃ for 8 hour periods. In the study of nonane, Sprague-Dawley rats were exposed to concentrations ranging from 2414 to 5280 ppm. The authors reported mortality among the rats and calculated that the LC₅₀ value for nonane was 4467 ppm (23,775 mg/m³). The authors also reported that there was evidence of acute CNS effects and that both the time to onset and severity of effects was related to the vapor concentrations to which the rats were exposed. In studies of n-decane, n-undecane, n-dodecane and n-tridecane the rats were exposed for 8 hours to the maximally attainable vapor concentrations. There were no deaths and no evidence of

CNS effects. The authors also measured blood/air and brain/air ratios for these substances and reported that these ratios declined with increasing carbon number above C₁₀.

Rats were exposed to Hydrocarbons, C₉-C₁₁, cyclics, <2% aromatics (CAS RN 64742-48-9) test atmosphere for 8 hours/day for 3 consecutive days at 0 (air), 1000 mg/m³ (170ppm), 2500 mg/m³ (430ppm), 5000 mg/m³ (860ppm). All rats were checked for health and viability at least once daily. Body weight was recorded during randomization on days of testing. Results of the behavioral tests indicated only minimal effects of exposure to a C₁₀ cycloparaffinic solvent on neurobehavioral measures at the highest dose tested (5000 mg/m³) including gait abnormalities and psychomotor slowing. Short-term high level exposure to Hydrocarbons, C₉-C₁₁, cyclics, <2% aromatics induced mild and non-persistent neurobehavioral effects on functional observations and measures of learned performance. Minimal effects were observed during or after 3 consecutive 8 hour exposures to Hydrocarbons, C₉-C₁₁, cyclics, <2% aromatics at an exposure level of 5000 mg/m³. Exposure to 1000 or 2500 mg/m³ on a group basis did not induce exposure-related neurobehavioral effects. The effects are consistent with narcosis and the NOAEC = 2500 mg/m³.

Rats were exposed to Hydrocarbons, C₁₀-C₁₂, isoalkanes, <2% aromatics (CAS RN 90622-57-4) test atmosphere for 8 hours/day for 3 consecutive days at 0 (air), 500 mg/m³ (85ppm), 1500 mg/m³ (260ppm), 5000 mg/m³ (860ppm). All rats were checked for health and viability at least once daily. Body weight was recorded during randomization on days of testing. Results of the behavioral tests showed some mild effects of exposure to Hydrocarbons, C₁₀-C₁₂, isoalkanes, <2% aromatics on learned performance measurements in the highest exposed test group (5000 mg/m³). Measures of performance speed were sensitive to the effects of Hydrocarbons, C₁₀-C₁₂, isoalkanes, <2% aromatics, while measures of discrimination accuracy and stimulus control were not affected. Correct choice latencies were slightly increased and only significant in the 5000 mg/m³ exposure group. Drink response latency was not significantly changed. No significant effects were observed in functional observational measurements and in measurements of motor activity. Short-term, high-level exposure to Hydrocarbons, C₁₀-C₁₂, isoalkanes, <2% aromatics induced mild, non-persistent neurobehavioral effects on measures of learned performance. Effects were observed during or after 3 consecutive 8 hour exposures at the highest tested concentration of 5000 mg/m³. Exposure to 500 mg/m³ or 1500 mg/m³ of Hydrocarbons, C₁₀-C₁₂, isoalkanes, <2% aromatics did not induce exposure-related neurobehavioral effects. The effects are consistent with narcosis and the NOAEC = 1500 mg/m³.

The potential for isoparaffinic hydrocarbons to produce acute central nervous system effects in CFW mice was evaluated. The animals were exposed for approximately 30 minutes in operant conditioning chambers modified for vapor exposure. The parameters measured were locomotor activity and ability to respond in tests of schedule-controlled operant behavior. There were two solvents with relevance to this category, once containing C₉-C₁₁ constituents and the other C₁₀-C₁₂. The mice exposed to the C₉-C₁₁ isoparaffinic solvent exhibited increased locomotor activity at levels that were significantly elevated above control values at 4000 and 6000 ppm (34,846 mg/m³), but no significant differences were found in the test for schedule-controlled operant behavior. Exposure to the C₁₀-C₁₂ isoparaffinic solvent did not result in significant effects in either study. The authors of this study noted that because of its low vapor pressure, it was difficult to produce high vapor concentrations of the C₁₀-C₁₂ isoparaffinic solvent.

Rats were exposed to wholly vaporized light alkylate naphtha distillate (LAND-2) (CAS RN 64741-66-8) generated in nitrogen, by inhalation in whole-body exposure cages 6 h/d, 5 d/wk for 13 wk at analytical concentrations of 668, 2220, and 6646 ppm (2.4, 8.1, and 24.3 g/m³). Neurobehavioral evaluations of motor activity (MA) and functional operational battery (FOB) were performed pretest and during wk 5, 9, 14, and 18 (recovery groups). Animals were not exposed to LAND-2 on the days of neurobehavioral testing. Exposure days were added to ensure that each animal received at least 65 exposures. Following 13 wk of exposure, 12 animals/sex/group were necropsied and microscopic examination was performed on selected tissues. Nervous tissue from 6 rats/sex/group was also examined microscopically. At the end of the 4-wk recovery period, 12 animals/sex from the high and control groups were necropsied and selected tissues examined microscopically. All animals survived the treatment period and were sacrificed according to study design at the end of 13 wk or at 18 wk (recovery groups). No test-related observations were noted in the exposure chambers during any exposure period for any treatment groups or during non-exposure periods. There were small but statistically significant changes in hematological and clinical chemistry parameters, but the authors judged these effects to not be toxicologically relevant. These results are not considered LAND-2 related.

In the assessment of motor activity, the authors concluded that the effects observed are not neurotoxic effects but are indicative of acute central nervous system depression. In the functional observational battery, there was no test-material-related effect on any endpoint evaluated within the functional observational battery of tests. Pathology - At the wk 13 terminal sacrifice there were no microscopic findings in the brain, spinal cord, or peripheral nerves that could be attributable to exposure to LAND-2. The NOAEC of LAND-2 for subchronic toxicity is 6646 ppm and 6646 ppm (24300 mg/m³) for neurotoxicity.

In an article summarizing neurotoxicity studies of C₉-C₁₄ aliphatic solvents, it was reported that these substances do not produce gross or pathological changes in the central or peripheral nervous system. In neurobehavioral studies there

were no effects in most of the parameters assessed, but the authors did report decreased motor activity in the dark period. There were no effects on neurochemical parameters. In neurophysiological tests, it was reported that there were statistically significant effects in flash-evoked potential, somatosensory; evoked potential and auditory brain stem responses at exposure levels of 400 (2339 mg/m³) and 800 (4679 mg/m³) ppm. The authors of the review suggested that the neurophysiological methods may be more sensitive than histopathological, neurobehavioral and neurochemical methods.

Human effects

There are a number of reports dealing with the potential for hydrocarbon solvent exposure to cause chronic neurological effects in humans. A review of the epidemiological literature regarding exposure to hydrocarbon solvents, focusing on white spirit, a C₉-C₁₁ aliphatic hydrocarbon solvent containing approximately 15-20% aromatics and described by the CAS RN of 8052-41-3, 64742-82-1, and 64742-88-7 has been conducted. Similar reviews have been conducted by the International Programme on Chemical Safety (IPCS) and Scientific Committee on Occupational Exposure Limit (SCOEL). The IPCS and SCOEL evaluations were also re-evaluated by the ECHA Committee for Risk Assessment (RAC). These evaluations include retrospective epidemiological studies involving painters with long-term exposure to white spirit. Confounding factors in these studies include co-exposure to other solvents and a lack of measured exposure data. Epidemiological studies reported an increased incidence of complaints of memory impairment, fatigue, impaired concentration, irritability, dizziness, headache, anxiety and apathy. Several studies that included neuropsychological tests demonstrated impairment in some of these tests; primarily in the short-term visual memory test and in the symbol-digit test. In some studies, life-time exposure to high concentrations of white spirit was correlated with an increase incidence of effect. Using a weight of evidence approach, the RAC concluded that chronic exposure to these white spirits cause adverse central nervous system (CNS) effects that can progress in severity. These CNS effects can include deficits in psychomotor, perception, memory parameters, and disturbances in mood. With respect to the C₉-C₁₄ aliphatic hydrocarbon (<2% aromatics) category, it is not known whether the effects attributed to white spirit were due to the aliphatic or aromatic constituents or a combination thereof.

Chemicals in the category C₉-C₁₄ aliphatic (≤ 2%) hydrocarbon solvents possess properties indicating a hazard for human health (chemical pneumonitis if taken in to the lungs as liquids, severe irritant dermatitis due to defatting with prolonged or repeated exposure, liver enlargement and kidney changes in male rats in repeated dose toxicity studies [oral and inhalation; these changes may be secondary findings], increase in the frequency of kidney and adrenal gland tumors in male rats and liver tumors in female mice, potential for central nervous system effects). Adequate screening-level data are available to characterize the human health hazards of substances in the C₉-C₁₄ aliphatic (≤ 2%) hydrocarbon solvent category for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Environment

Members of the C₉-C₁₄ Aliphatic [≤2% aromatics] Hydrocarbon Solvents Category have the potential to volatilize from surface waters, based on Henry's Law constants (HLC) representing volatility for category members that range from 4.76 x 10⁴ to 1.67 x 10⁶ Pa·m³/mole (at 25°C). In the air, category members have the potential to rapidly degrade through indirect photolytic processes mediated primarily by hydroxyl radicals (•OH) with calculated degradation half-lives ranging from 0.42 to 1.10 days or 10.8 to 26.4 hours based on a 12-hr day and an •OH concentration of 1.5 x 10⁶ •OH/cm³. Aqueous photolysis and hydrolysis will not contribute to the transformation of category chemical constituents in aquatic environments because they are either poorly or not susceptible to these reactions. These chemicals are unlikely to degrade by hydrolysis as they lack a functional group that is hydrolytically reactive.

Mackay Level III modeling indicates that category member constituents partition mostly to the sediment and soil compartments rather than air compartment when an equal emission rate (1000 kg/hr) to the air, water, and soil compartment is assumed. When release occurs only to either the air, or soil compartment, constituents are indicated in the modeling to partition largely to the compartment to which they are released. When released to the water compartment, constituents are indicated by the model to partition to either water or sediment.

When released primarily to the air compartment, the primary mode of removal would be via indirect photodegradation. Although the substances and their chemical constituents demonstrate a range of water solubility with most constituents having relatively low solubility, wet deposition of category chemical constituents is not likely to play a significant role in their atmospheric fate because of their rapid photodegradation. Volatilization to the air can contribute to the loss of category chemical constituents from aqueous and terrestrial habitats.

Determining the biodegradation potential of UVCBs can be challenging. The result for each multi-constituent substance (UVCB) characterizes the biodegradability of that substance as a whole, but it does not suggest that each constituent of the UVCB is equally biodegradable. As with all ready biodegradation test guidelines, the test system and study design used with these substances (OECD TG 301F) is not capable of distinguishing the relative contribution of the

substances' constituents to the total biodegradation measured (constituents with higher branching/cyclic structures may degrade to a lesser extent than linear and less branched structures). The n-paraffin constituents have the potential to biodegrade rapidly based on results that support their characterization as readily biodegradable (80 to 100% in 28 days). In comparison, iso-paraffinic and cyclo-paraffinic constituents are expected to demonstrate a slower rate of biodegradation based on results for several isoparaffinic substances and one cyclo-paraffinic substance. Data for the cyclic substance covers the lower carbon range (C₉ to C₁₁) and does not meet the readily biodegradable criteria. Therefore, constituents in the higher carbon range (C₁₂ to C₁₄) are also not expected to meet this criteria. Multi-constituent members of the category biodegraded to a varied extent, based on studies that followed the OECD TG 301F. Biodegradation was dependent on their composition. The overall conclusion for C₉-C₁₄ Aliphatic [\leq 2% aromatics] Hydrocarbon Solvents Category members: some components of the category members (i.e. n-paraffins) are readily biodegradable, but some (i.e. cyclic, tertiary and quaternary branched components) may be less biodegradable, and not meet the readily biodegradable criteria.

Category members have a potential to bioaccumulate, based on calculated log BCF values for constituents that range from 2.78 to 4.06, and calculated BCF values of 598 to 11,430 L/kg wet-weight, based on the Arnot and Gobas model, that take into account biotransformation of the chemicals in fish tissue. Results of BCF studies for several constituent chemicals of category members are also available. Reported BCF ranges for n-dodecane range from 400 (aqueous) to tentative 4408 (dietary) l/kg wet weight, using fathead minnow and rainbow trout (although there are no internationally agreed methods for calculating BCF values from dietary studies). Also reported are a BCF value for iso-nonanes of 1468 l/kg wet weight with carp. Additional studies for other constituent chemicals were reported, on a wet-weight basis, for decahydronaphthalene, with values of 1290 to 2500 l/kg (carp) and 3313 l/kg (trout); and trimethyl-cyclohexane and tetramethyl-cyclohexane of 2168 l/kg and 4734 l/kg for trout, respectively. Determining the bioaccumulation potential of UVCBs can be challenging. BCF values for n-paraffins, iso-paraffins, and cycloparaffins can be different due to differences in metabolism. Constituents with higher branching/cyclic structures may therefore bioaccumulate to a greater extent than linear and less branched structures. It should be noted that for highly lipophilic constituents uptake through the diet may exceed the direct uptake through water. Estimated BAF values of 723 to 390,400 l/kg wet as derived by the BCFBAF model (Arnot and Gobas, upper trophic level including biotransformation rate estimates) of EPISuite were disregarded in this analysis because metabolism in the gut (which effectively reduces the dietary assimilation efficiency assumed in the food chain model calculation) is not specifically considered in isolation in the current model and may over-estimate bioaccumulation potential.

Acute aquatic toxicity data are available for fish, invertebrates, and freshwater algae. It may be shown that paraffinic hydrocarbons with a carbon number of 11 or greater (log Pow $>$ 5.5) do not exhibit acute aquatic toxicity due to water solubility limitations and slow uptake kinetics. Paraffinic hydrocarbons with a carbon number of 10 and below, are expected to exhibit acute aquatic toxicity in the range of 1 to 10 mg/L (based on nominal loadings), although measured LC₅₀ and EC₅₀ values of 0.01 to 0.2 mg/L have been reported. Cyclic paraffins in the C₉ to C₁₀ range have also been shown to exhibit acute aquatic toxicity in the range of 1 to 10 mg/L (based on nominal loadings). Chronic *Daphnia magna* reproduction studies with n-nonane (CAS RN 11-84-2), n-undecane (CAS RN 1120-21-4), and n-dodecane (CAS RN 112-40-3), reported NOEC values of 0.005 and 0.0057 to 0.010 mg/L for nonane and undecane, respectively, and greater than water solubility (0.004 mg/L) for dodecane. Chronic studies using *Daphnia magna* with a substance in the C₁₀-C₁₂ isoparaffinic range (CAS RN 90622-57-4) indicated an effect (NOEC = 0.025mg/L, based on measured concentration), but isoparaffins in the C₁₁-C₁₃ range showed no observed effects up to 1 mg/L (highest nominal loading tested) for CAS RN: 90622-58-5.

Chemicals in this category with a carbon length of C₁₀ and below possess properties indicating a hazard for the environment (acute toxicity for fish, invertebrates, and algae) in the range of 0.1 to 10 mg/L based on measured concentrations. Those category members with a carbon length of C₁₁ and above are not expected to exhibit acute aquatic toxicity due to water solubility limitations and slow uptake kinetics; available chronic toxicity data for invertebrates, fish, and algae are in the range of 0.005 – 1.0 mg/L, based on measured concentrations. Category members have a potential to bioaccumulate. Some components of the category members (e.g. n-paraffins) are readily biodegradable, but some components (cyclic, tertiary and quaternary branched components) may be less biodegradable, and not meet the readily biodegradable criteria. Adequate screening-level data are available to characterize the environmental hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Production/Use/Exposure

Production

As reported to the U.S. Environmental Protection Agency for the year 2006, companies produced or imported the following volumes of C₉-C₁₄ Aliphatic [\leq 2% aromatic] hydrocarbon solvents. Note that the Volume Survey is overall volume for the entire individual CAS RN and includes fuels, solvents and all other uses. It is expected that the solvent

portion of the volume for the C₉-C₁₄ Aliphatic [$<2\%$ aromatic] Hydrocarbon Solvents Category would be significantly lower than the aggregate production volume:

C₉-C₁₄ Aliphatic Hydrocarbon Solvents ($\leq 2\%$ aromatic) Production Volumes

Normal Paraffins	111-84-2	Nonane	227-454 metric tons (500 000 to < 1 million lbs)
	124-18-5	n-Decane	4,500-22,500 metric tons (10 to < 50 million lbs)
	1120-21-4	n-Undecane	22,680- 45,359 metric tons (50 to < 100 million lbs)
	112-40-3	Dodecane	22,680- 45,359 metric tons (50 to < 100 million lbs)
	629-50-5	Tridecane	22,680- 45,359 metric tons (50 to < 100 million lbs)
	64771-72-8	Paraffins, (petroleum), normal C5-20	45,359- 226,796 metric tons (100 to < 500 million lbs)
	129813-67-8	Alkanes, C12-14	No data
	93924-07-3	Alkanes, C10-14	No data
Isoparaffins	68551-16-6	Alkanes, C9-11-iso-	4,500-22,500 metric tons (10 to < 50 million lbs)
	68551-17-7	Alkanes, C10-13-iso-	4,500-22,500 metric tons (10 to < 50 million lbs)
	90622-57-4	Alkanes, C9-13	No data
	68551-19-9	Alkanes, C12-14-iso-	450-4500 metric tons (1 million to < 10 million pounds)
	90622-58-5	Alkanes, C11-15, iso-	No data
Multi-constituent Solvents	64741-65-7	Naphtha, (petroleum), heavy alkylate	226,796-450,000 metric tons (500 million to < 1 billion lbs)
	64742-47-8	Distillates, (petroleum), hydrotreated light	450,000 or greater metric tons (1 billion pounds or greater)
	64742-48-9	Naphtha, (petroleum), hydrotreated heavy	450,000 or greater metric tons (1 billion pounds or greater)
	64742-88-7	Solvent naphtha, (petroleum), medium aliph.	450,000 or greater metric tons (1 billion pounds or greater)

Production of these C₉-C₁₄ aliphatic [$\leq 2\%$ aromatics] hydrocarbon solvents is differentiated from other refinery substances such as gasoline and diesel fuel by including additional processing steps leading to finished substances with narrow distillation ranges, removal of sulfur- and nitrogen-containing compounds, and low color. The aromatic content in these substances is controlled to meet specific performance characteristics. These additional refining steps provide these hydrocarbon solvents with qualities suitable for applications in consumer goods.

Use

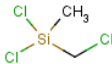
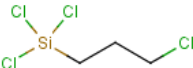
Hydrocarbon solvents in the C₉-C₁₄ range with aromatic content less than 2% are considered to have a medium rate of evaporation and have a number of applications, including automotive products, paints and coatings, degreasers, wood/floor wax, diluent in asphalt applications, and as a pesticide carrier base. The predominant commercial uses of C₉-C₁₄ Aliphatic [$\leq 2\%$ aromatics] hydrocarbon solvent substances are in paints and coatings, industrial solvents.

Exposure

Occupational workers are predominately exposed to C₉-C₁₄ aliphatic hydrocarbons, ≤ 2% aromatics, through the inhalation of vapour due to the volatility of the constituents but exposure via dermal contact can also occur.

The general population is exposed to C₉-C₁₄ aliphatic hydrocarbons, ≤ 2% aromatics, primarily through vapour inhalation or through dermal contact during the domestic use of paints and lacquers containing these substances. Due to the use pattern of all members in the category consumer exposure is expected.

SIDS INITIAL ASSESSMENT PROFILE

Category Name	Chloroalkyl chlorosilanes Category
CAS No(s). and Chemical Name(s)	1558-33-4 Silane, dichloro (chloromethyl) methyl 2550-06-3 Silane, trichloro (3-chloropropyl)-
Structural Formula(s)	 <p>CAS No. 1558-33-4</p>  <p>CAS No. 2550-06-3</p>

SUMMARY CONCLUSIONS OF THE SIAR

Analogue/Category Rationale

Chloroalkyl chlorosilanes are Si containing materials containing a single chloride terminated alkyl side chain of various length. Chlorosilanes, including the chloroalkyl 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). The half-lives of the chloroalkyl chlorosilanes are expected to be <1 minute based on data from an analogous substance, trichloro(methyl)silane (CAS No. 75-79-6). Specifically, the silanol produced following chloroalkyl chlorosilane hydrolysis is silanediol, (chloromethyl)methyl (CAS No. 3959-16-8) for silane, dichloro (chloromethyl) methyl and silanetriol, (3-chloropropyl)- (CAS No. 64426-41-1) for silane, trichloro (3-chloropropyl). Data are available for HCl (previously assessed in the OECD HPV Chemicals Programme: <http://www.chem.unep.ch/irptc/sids/OECDSIDS/7647010.pdf>).

For mammalian toxicity and acute aquatic toxicity endpoints, data are provided for a structurally similar analogue and two hydrolysis products as follows:

- The sponsored substances are structurally analogous to 3-chloropropyl trimethoxysilane (CPTMO, CAS No. 2530-87-2). Silane, dichloro (chloromethyl) methyl rapidly hydrolyzes to form 1 mole of silanediol, (chloromethyl)methyl (CAS No. 3959-16-8) and two moles of HCl. Silane, trichloro (3-chloropropyl) and CPTMO hydrolyze to form 1 mole of silanetriol, (3-chloropropyl)- (CAS No. 64426-41-1). Silane, trichloro (3-chloropropyl) forms 3 moles of HCl per mole of silanetriol; CPTMO forms 3 moles of methanol per mole of silanetriol. CPTMO has previously been assessed in the OECD HPV Chemicals Programme (<http://www.chem.unep.ch/irptc/sids/OECDSIDS/2530872.pdf>). Though not as highly unstable as the chlorosilane, CPTMO has a short hydrolysis half-life of 1 hour or less at 25 °C. Endpoints are filled in part through the use of analogues (CPTMO, DMSD) and hydrolysis products (HCl) which have similar structures or rapid hydrolysis to the same or structurally analogous silanols. The hydrolysis product, HCl, but not analogues CPTMO or DMSD, provides information on acute toxicity (e.g. site of contact and pH changes). The levels of the chloroalkyl chlorosilanes required to generate significantly toxic concentrations of silanols would result in severely corrosive HCl concentrations. It is not expected that silanetriol, (3-chloropropyl)- and silanediol, (chloromethyl)methyl can be isolated for testing as they are not stable; these silanols will condense to form highly cross-linked, high molecular weight polymers as concentration increases.
- Data for a well-studied, isolatable (stable) silanol hydrolysis product, dimethylsilanediol (DMSD; CAS No. 1066-42-8) is included to further characterize the toxicity of the sponsored substance silanol hydrolysis product.
- Although methanol is a hydrolysis product associated with the analogue substance, CPTMO, the primary human health hazard for the chloroalkyl chlorosilanes is considered to be exposure to the hydrolysis product, HCl. Human health and aquatic toxicity data for HCl are provided.

Physical-chemical Properties

Silane, dichloro (chloromethyl) methyl is a liquid with a melting point of -63.3 °C (calculated using MPBPVP v1.43 in EPI Suite v4.10), a boiling point of 121.5 °C (measured) and a vapour pressure of 54.4 hPa at 25°C (measured). The calculated octanol-water partition coefficient ($\log K_{ow}$) is 2.5, and the calculated water solubility is 484.8 mg/L, both at 25 °C. Silane, trichloro (3-chloropropyl)- is a liquid with a melting point of -48.85 °C (calculated), a boiling point of 182.3°C (measured) and a vapour pressure of 1.54 hPa at 25°C (extrapolated). The calculated octanol-water partition coefficient ($\log K_{ow}$) is 3.24, and the calculated water solubility is 64.44 mg/L, both at 25°C. The calculated water solubility and $\log K_{ow}$ 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 chloroalkyl chlorosilanes.

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However, these substances rapidly hydrolyze to their corresponding silanol, and HCl on contact with moisture. Data from the silanol, DMSD, shows penetration through human skin *in vitro*. HCl will rapidly dissociate and its effects are thought to be a result of pH change.

The acute inhalation toxicity of the chloroalkyl chlorosilanes is well characterized by the effects of HCl exposure, rather than systemic effects of silanol hydrolysis products. The 4-hour acute inhalation LC₅₀ for silane, dichloro (chloromethyl) methyl is 6.8 mg/L (OECD TG 403); the estimated LC₅₀ for a 1-hour exposure is 8.39-11.04 mg/L (calculated; similar to OECD TG 403). The estimated 1-hour LC₅₀ for silane, trichloro (3-chloropropyl-) is 8.41-10.64 mg/L. The acute inhalation hazard posed by a chlorosilane, as defined by an LC₅₀ 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. Inhalation 1-hour LC₅₀ values for HCl were determined to be 4.2-4.7 mg/L in rats. The approximate lethal dose (oral) for silane, dichloro (chloromethyl) methyl in corn oil was 2200 mg/kg bw (method not specified); the LD₅₀ for silane, trichloro (3-chloropropyl-) in corn oil was 200-2000 mg/kg bw (OECD TG 423). The oral LD₅₀ of CPTMO in rats was > 2000 mg/kg bw (OECD TG 401). The oral LD₅₀ of DMSD, was > 2000 mg/kg bw in rats; there was a general effect on condition, but no remarkable findings at necropsy (OECD TG 425). The acute oral LD₅₀ values of HCl were determined to be 238-277 mg/kg bw for female rats.

The chloroalkyl chlorosilanes rapidly hydrolyze to HCl and either silanetriol, (3-chloropropyl)- or silanediol, (chloromethyl)methyl. Silane, dichloro (chloromethyl) methyl was corrosive to the skin (Department of Transportation Skin Corrosion Test in Rabbits Regulation 49 CFR 173.240(9)(1)) and respiratory tract (OECD TG 403). Irritation data were not located for silane, trichloro (3-chloropropyl). 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, chloroalkyl chlorosilanes possesses properties indicating possible hazards for acute inhalation toxicity, skin, eye, and respiratory tract irritation.

No skin sensitization data were available for the chloroalkyl chlorosilanes or the appropriate analogue substance.

Repeated dose toxicity data for the chloroalkyl chlorosilanes were not available. Data from an analogous substance, CPTMO, a silanol, DMSD, and hydrolysis product, HCl, were used to fill the repeated-dose toxicity endpoint for the chloroalkyl chlorosilanes. The toxicity of the chloroalkyl chlorosilanes is well characterized by the effects of HCl inhalation exposure, the prevalent route of the chloroalkyl chlorosilanes exposure. Systemic effects following inhalation of an analogous substance (likely as a mixture with silanol hydrolysis products) are also well characterized. Although the effect of CPTMO on the urinary bladder and kidney was not observed in all repeated inhalation exposure studies, the NOAEC for this effect across all studies was considered to be 0.041 mg/L. The NOAEL for DMSD following repeated oral exposure was 250 mg/kg bw/day based on liver porphyria in male rats and liver vacuolation in female rats (OECD TG 422). 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. Similar effects are expected following the hydrolysis of the chloroalkyl chlorosilanes to HCl.

The sponsored substances did not induce gene mutations in bacterial cells *in vitro* (OECD TG 471). The analogous substance, CPTMO, did induce gene mutations in bacterial or mammalian cells *in vitro* but did not induce micronuclei *in vivo*. DMSD (OECD TG 471), and the hydrolysis product, HCl, did not induce gene mutations in bacterial cells. DMSD did not induce chromosomal aberrations *in vitro* in mammalian cells (OECD TG 473); 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 chloroalkyl chlorosilanes are not expected to be genotoxic.

No data were available for the carcinogenicity of the chloroalkyl chlorosilanes.

Toxicity for reproduction data for the chloroalkyl chlorosilanes were not available. However; data were available for the analogous substance, CPTMO, the silanol, DMSD and the hydrolysis product, HCl.

In an OECD TG 422 repeated dose inhalation study in rats, exposure to CPTMO up to and including the high concentration of 0.814 mg/L did not result in any signs of developmental toxicity. Based on these results the NOEL for general or reproductive toxicity was established at 0.814 mg/L. No test substance-related effects were

observed in any of the developmental parameters evaluated following repeated oral exposure to DMSD (OECD TG 422). The NOAEL for maternal and developmental toxicity of DMSD in rats was 500 mg/kg bw/day (highest dose tested). No reliable studies have been reported regarding toxicity to reproduction and development in animals after oral, dermal or inhalation exposure to HCl. 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 protons and chloride ions are 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 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 repeated-dose inhalation study up to 50 ppm. Based on data for the analogous substance and the hydrolysis product, the chloroalkyl chlorosilanes are not expected to be a reproductive or developmental toxicant.

The chloroalkyl chlorosilanes possess properties indicating a hazard for human health (lethality from acute inhalation, corrosive and highly irritating to the skin, eyes and respiratory tract, 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 on these molecules and determines many aspects of the behaviour of the category members. The chloroalkyl chlorosilanes are expected undergo rapid hydrolysis in the presence of water to form one to three moles of HCl and one mole of di- or tri- silanol, depending on the parent substance. Hydrolysis is the primary reaction in aqueous systems. Hydrolysis studies were not conducted on the chloroalkyl chlorosilanes. Using an analogous substance, trichloro(methyl)silane (CAS No. 75-79-6), the chloroalkyl chlorosilanes are expected to hydrolyze to HCl and the corresponding silanols in less than 1 minute at pH 4, 7, and 9 and 1.5 °C. This is further supported by the data for two additional chlorosilane materials (Alkyl Chlorosilanes Category: SIAM 31: <http://www.oecd.org/env/hazard/data>), which were less similar structurally, but that all had half-lives of less than 1 min at 1.5 °C. 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 for the chloroalkyl chlorosilanes and resulting half-lives due to indirect photolysis are $0.54 \text{ E-}12 \text{ cm}^3/\text{molecule-sec}$ and 19.8 days for silane, dichloro (chloromethyl) methyl and $2.11 \text{ E-}12 \text{ cm}^3/\text{molecule-sec}$ and 5.1 days for silane, trichloro (3-chloropropyl) (12-h day; $1.5 \text{ E+}6 \text{ OH/cm}^3$). 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 the chloroalkyl chlorosilanes was not determined due to rapid hydrolysis; 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). No measured data are available for the hydrolysis products. At high concentrations, the silanols will condense to form highly cross linked, high molecular weight polymers that are water insoluble and effectively non biodegradable. Based on studies of DMSD in soil at 25 °C, the substance was not readily biodegradable. HCl is an inorganic compound and biodegradation tests are not applicable.

A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that the chloroalkyl chlorosilanes will distribute mainly to the air (ca. 48 % for both substances) and soil (ca. 48% for both substances) 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 its uses and handling, a scenario of 100% emission to air is more realistic. When the chloroalkyl 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 showed that the environmental fate of the chloroalkyl chlorosilanes is controlled by

its 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 product silanediol, (chloromethyl)methyl-, will distribute mainly to soil (81.6%), with a smaller fraction to water (18.2%) and negligible amounts to sediment and air (0.11 and < 0.1%). Based on the more realistic scenario of 100% release to air, the model predicts that silanediol, (chloromethyl)methyl- will be distributed mainly in soil (91.6%) and water (8.3%). In the case of the other hydrolysis product, silanetriol, (3-chloropropyl)-, the results are similar; Level III fugacity modeling using equal loading rates of 1000 kg/h each for air, soil and water predicts that the hydrolysis product distributes mainly to soil (86.2%), with a smaller fraction to water (13.5%) and negligible amounts to sediment and air (0.22 and < 0.1%). Based on the more realistic scenario of 100% release to air, the model predicts that silanetriol, (3-chloropropyl)- will be distributed mainly in soil (95.5%) and water (4.4%). Fugacity modelling of HCl is not applicable.

The bioaccumulation potential of the chloroalkyl chlorosilanes was not measured due to rapid hydrolysis. An estimated BCF using the BCFBAF Program (v3.01) is 20.7 L/kg wet-wt for silane, dichloro (chloromethyl) methyl and 64.1 L/kg wet-wt for silane, trichloro (3-chloropropyl), indicating the chloroalkyl chlorosilanes are not expected to bioaccumulate. For the hydrolysis products, silanediol, (chloromethyl) methyl, and silanetriol, (3-chloropropyl)-, the estimated BCFs are 3.162 L/kg wet-wt.

Acute aquatic toxicity data are not available for the chloroalkyl chlorosilanes with the exception of an acute toxicity to daphnia study for silane, dichloro (chloromethyl) methyl. The chloroalkyl chlorosilanes 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. Acute toxicity test results for analogous substance CPTMO and hydrolysis products DMSD and HCl have been determined for aquatic species:

Fish

CPTMO [*Brachydanio rerio*] 96 h LC₅₀ >100 mg/L (nominal; TOC) [semi-static]
 DMSD [*Oncorhynchus mykiss*] 96 h LC₅₀ >126 mg/L (measured) [static]
 HCl [*Cyprinus carpio*] 96 h LC₅₀ = pH 4.3 (= 4.92 mg/L) (measured; pH) [semi-static]

Invertebrate

CPTMO [*Daphnia magna*] 48 h EC₅₀ = 869 mg/L (nominal) [static]
 DMSD [*Daphnia magna*] 48 h EC₅₀ >117 mg/L (measured) [static]
 HCl [*Daphnia magna*] 48 h EC₅₀ = pH 5.3 (=0.492 mg/L) (measured; pH) [semi-static]

Algae

CPTMO [*Scenedesmus subspicatus*] 72 h ErC₅₀, EbC₅₀ > 883 mg/L (nominal)
 DMSD [*Pseudokirchneriella subcapitata*] 72 h ErC₅₀, EbC₅₀ > 118 mg/L (measured) [static]-
 HCl [*Selenastrum capricornutum*] 72 h ErC₅₀ = pH 5.3 (=0.492 mg/L) [static](measured; pH)

Hydrogen Chloride (HCl)

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 for 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 products, the chloroalkyl 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 chloroalkyl 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

Dichloro (chloromethyl) methylsilane is not produced in the United States (the sponsor country). Trichloro (3-chloropropyl)silane is commercially produced with an annual production volume (year 2010) of 4536-11340 tonnes in the United States. The European production volume (year 2010) for silane, dichloro (chloromethyl) methyl was 454-2268 tonnes; trichloro (3-chloropropyl)silane is not produced in Europe. All (100%) of dichloro(chloromethyl)methylsilane and trichloro(3-chloropropyl)silane by volume are used as intermediates in the manufacture of organosilanes. The chloroalkyl chlorosilanes are reacted during use and lose their chemical identities.

The chloroalkyl 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 and include air monitoring, process control systems, collection of off-gasses through a vent system and central incineration, on-site incineration of waste, local and general ventilation, ventilation system tied into scrubbers, nitrogen pad on system, and DCS control of process with instrumentation. Employees involved in chlorosilane production and application are required to use personal protective equipment such as chemical resistant suits, gas masks or respirators, rubber boots, protective gloves and goggles/face shields. 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 irritating or corrosive properties. Environmental exposure is not expected.

There are no consumer uses of the chloroalkyl chlorosilanes.

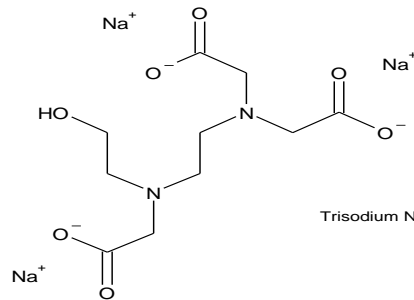
SIDS INITIAL ASSESSMENT PROFILE

Category Name	Amino Carboxylic Acid-Based Chelants Category		
CAS No(s). and Chemical Name(s)	139-33-3	Disodium EDTA; Na ₂ EDTA	Glycine, N,N'-1,2-ethanediylbis[N-(carboxymethyl)-, sodium salt (1:2)
	139-89-9	Trisodium HEDTA; Na ₃ HEDTA	Glycine,N-[2-(bis(carboxymethyl)amino)ethyl]-N-(2-hydroxyethyl)-, trisodium salt
	140-01-2	Pentasodium DTPA; Na ₅ DTPA	Glycine,N,N-bis[2-(bis(carboxymethyl)amino)ethyl]-, pentasodium salt
	1939-36-2	PDTAH ₄	Glycine,N,N'-1,3-propanediylbis[N-(carboxymethyl)-
	15708-41-5	Ferric monosodium EDTA; Fe(III)NaEDT A	Ferrate (1-), [[N,N'-1,2-ethanediylbis[N-(carboxymethyl)glycinato]](4)-N,N',O,O',ON,ON']-, sodium, (OC-6-21)
	16485-47-5	Ferrous HEDTA; Fe(II)HEDTA	<u>Ferrate(1-),[N-[2-[bis[(carboxy-.kappa.O)methyl]amino-.kappa.N]ethyl]-N-[2-(hydroxy-.kappa.O)ethyl]glycinato(3)-.kappa.N,.kappa.O]-, sodium (1:1)</u>
	17084-02-5	Ferric HEDTA; Fe(III)HEDTA	<u>Iron, [N-[2-[bis[(carboxy-.kappa.O)methyl]amino-.kappa.N]ethyl]-N-[2-(hydroxy-.kappa.O)ethyl]glycinato(3)-.kappa.N,.kappa.O]-</u>
	18719-03-4	Tetrasodium PDTA; Na ₄ PDTA	<u>Glycine,N,N'-1,3-propanediylbis[N-(carboxymethyl)-, tetrasodium salt</u>
	20824-56-0	Diammonium EDTA; (NH ₄) ₂ EDTA	Glycine,N,N'-1,2-ethanediylbis[N-(carboxymethyl)-, diammonium salt
	21265-50-9	Ferric ammonium EDTA; Fe(III)(NH ₄)E DTA	<u>Ferrate(1-), [[N,N'-1,2-ethanediylbis[N-[(carboxy-.kappa.O)methyl]glycinato-.kappa.N,.kappa.O]](4)-]-, ammonium (1:1), (OC-6-21)-</u>
	22473-78-5	Tetraammoniu m EDTA; (NH ₄) ₄ EDTA	Glycine,N,N'-1,2-ethanediylbis[N-(carboxymethyl)-, tetraammonium salt
	67859-51-2	Zinc Diammonium EDTA; Zn(NH₄)₂EDT A	Zincate (2-), [N,N'-ethylenebis(N-(carboxymethyl)glycinato)](4)-N,N',O,O',ON,ON'), diammonium (OC-6-21)-

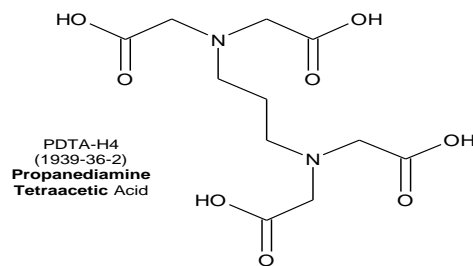
(HOOCCH₂)₂NCH₂CH₂N(CH₂COOH)₂,
 (HOOCCH₂)₂NCH₂CH₂CH₂N(CH₂COOH)₂,
 (HOOCCH₂)₂NCH₂CH₂N(CH₂CH₂OH)(CH₂COOH),
 and (HOOCCH₂)₂NCH₂CH₂N(CH₂COOH)CH₂CH₂N(CH₂COOH)₂

Note: The above structural formulas may be either uncomplexed, or complexed with metal ions Na⁺, K⁺, NH₄⁺, Zn²⁺, Ca²⁺, Fe²⁺, and/or Fe³⁺.

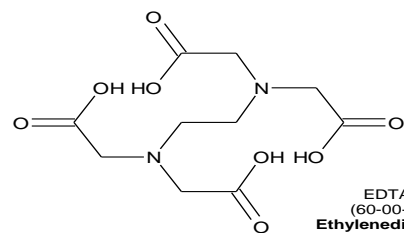
Structural Formula(s)



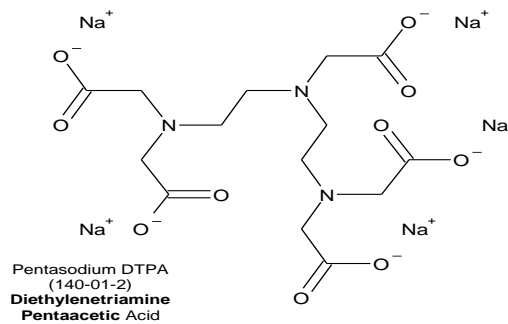
Trisodium HEDTA
 (139-89-9)
 Trisodium N-(2-Hydroxyethyl)ethylene diamine
 Triacetate



PDTA-H4
 (1939-36-2)
 Propanediamine
 Tetraacetic Acid



EDTA
 (60-00-4)
 Ethylenediamine
 Tetraacetic Acid



Pentasodium DTPA
 (140-01-2)
 Diethylenetriamine
 Pentaacetic Acid

Representative Structures of Ethylenediamine-, Propanediamine- and Diethylenetriamine-Based Chelants

SUMMARY CONCLUSIONS OF THE SIAR

Category Analogue/Justification

Members of the aminocarboxylic acid-based chelant category possess similar molecular structures that contain common functional groups. All members have a molecular structure with an ethylenediamine, propanediamine or diethylenetriamine backbone, which has 3-5 acetic acid groups attached to the nitrogens. Therefore all category members in common possess amino acid groups. In addition for one member of the ethylenediamine backbone series (hydroxyethylethylenediamine or HEDTA), a 2-hydroxyethyl group appears in place of an acetic acid group, so there are only three acetic acid groups instead of four.

The ethylenediamine structure has either four acetic acid groups (EDTA), or three acetic acid groups and one hydroxyethyl group (HEDTA). The propanediamine structures contain four acetic acid groups. Finally, the diethylenetriamine structures contain five acetic acid groups. The carboxylic acid groups may be in the form of either the free carboxylic acid or the carboxylate anion, in which one or more hydrogens have been neutralized to an ammonium or a metal salt. When no hydrogens have been substituted (EDTA, **PDTAH₄**), the chelant exists as an inner salt or zwitterion. More commonly, the substance exists as an ammonium or metallic salt.

Therefore all category members have identical functional groups (except for HEDTA, where a hydroxyethyl group is also present). It is the presence of multiple carboxylic acid groups on the amine that provides chelants with their unique metal ion chelating or sequestering properties. This common property is the important feature to consider in assessing the aquatic and mammalian toxicity of chelants and in justifying their consideration as a category.

A common mechanism of action for the chelant category, based on structural and chemical similarity, is the fundamental basis for a category approach for these closely related chemicals. The ability of chelants to remove and add ions to solution is the mechanism whereby these chemicals produce toxicity. Environmental fate and ecological and mammalian toxicity profiles are consistent within the category. Category members have demonstrated high stability to hydrolysis, and most category members are commercially available primarily or solely in aqueous solution. Category members emitted to waterways will remain dissolved in this environmental compartment. If emitted to soil or sediment, category members will exhibit high water solubility and soil mobility. This behavior is based on the presence of multiple carboxylate anion groups in the molecular structure, and is supported by the demonstrated high water solubility and negligible vapor pressure of category members. With regard to environmental biodegradation, the majority of the members of the category have been tested in actual laboratory studies with similar and predictable results from standard laboratory tests, in general being found not to be readily biodegradable. However, results of recent studies indicate that EDTA, calcium EDTA and **Na₂EDTA** can biodegrade under certain conditions.

The substantial body of evidence that chelants are not directly toxic to aquatic and mammalian organisms but exert their influence by affecting mineral balance, together with the fact that the backbone structures of the chelants in the category have similar affinities for metals supports the inclusion of these chelants in a category. Subtle differences in toxicity due to the presence of ammonium, sodium, calcium, ferric or ferrous iron or potassium can be explained by their affinity towards these metals and their ability to supply metals to organisms. According to the chemical equilibrium and kinetic properties of metal-ligand complexes, a certain portion of a free metal ion is always present in solution. This is particularly important for aquatic systems. Uncomplexed chelants like EDTA and **PDTAH₄** would be expected to add H⁺ ions to media (which would lead to decreased pH), and would chelate metals present in their milieu. The ferric iron-containing chelants would not be expected to significantly affect mineral balance at low concentrations because the affinity for ferric ion is stronger than most other ions. The **Zn(NH₄)₂EDTA** would be expected to have less of an effect than **(NH₄)₂EDTA** on zinc balance. The sodium, potassium and calcium-containing chelants would be expected to be of intermediate toxicity (between EDTA and Fe or Zn-containing chelants), since they would not affect pH as much as the acids and would provide essential ions that are not toxic in amounts that would be supplied by the chelants, but also would chelate essential ions such as Zn²⁺ and Fe²⁺ or Fe³⁺. Data show that the toxic profile of chelants in this category generally follows this pattern, and can be predicted by the type of ion that the chelant is complexed with and its affinity for the particular ion.

Log K values of metal chelates of DTPA, PDTA and HEDTA compared to EDTA ($\mu=0.1M$, $T=20^{\circ}C$)

Metal	EDTA	DTPA	PDTA	HEDTA
Fe ³⁺	25.1	28.6	21.6	19.8
Zn ²⁺	16.5	18.3	15.3	14.5
Fe ₂₊	14.3	16.5	13.4	11.6
Ca ²⁺	10.7	10.7	7.3	8.0
Na ⁺	1.66			

Using the category approach, read across has been performed (see below) from the appropriate tested members to those without available data. The toxicity of the counter-ion is considered for read-across but may not be the deciding factor in read-across. A conservative approach is used whereby read-across will always be from the most toxic substance to that without data.

Two analogue substances have previously been assessed in the OECD HPV Chemicals programme (SIAM 18): EDTA (CAS No. 60-00-4) and Na₄EDTA (CAS No. 64-02-8). The data can be viewed at <http://www.oecd.org/env/hazard/data/>. Data for counter ions can be viewed in the OECD HPV assessments for several calcium salts, ammonia category, zinc salts category and iron salts category found at: <http://www.oecd.org/env/hazard/data/>

Read-Across used for ecotoxicity endpoints for the Aminocarboxylic Acid-Based Chelants Category

Substance	CAS No.	Acute Toxicity to Fish	Acute Toxicity to Aquatic Invertebrates	Toxicity to Aquatic Plants
<i>SPONSORED SUBSTANCES</i>				
(NH ₄) ₂ EDTA	20824-56-0	X	O	O
(NH ₄) ₄ EDTA	22473-78-5	X	O	O
Zn(NH ₄) ₂ EDTA	67859-51-2	X	O	O
Fe(III)NaEDTA	15708-41-5	X	X	X
Na ₂ EDTA	139-33-3	O	X	X
Na ₃ HEDTA	139-89-9	X	X	X
Fe(III)NH ₄ EDTA	21265-50-9	X	X	X
Fe(II) HEDTA	16485-47-5	O	O	O
Fe(III) HEDTA	17084-02-5	X	O	O
PDTAH ₄	1939-36-2	X	X	O
Na ₄ PDTA	18719-03-4	O	O	O
Na ₅ DTPA	140-01-2	X	X	X
<i>ANALOGUE SUBSTANCES</i>				
EDTA	60-00-4	X	X	-
CaNa ₂ EDTA	62-33-9	X	O	-
Na ₃ EDTA	150-38-9	X	X	X
Na ₄ EDTA	64-02-8	X	X	X
K ₅ DTPA	7216-95-7	X	-	-

X = data available; O = read across; -Endpoint not addressed for this chemical

Read-Across used for human health endpoints for the Aminocarboxylic Acid-Based Chelants Category

Substance	CAS No.	S ¹	R ²	Effects on Fertility	Developmental Toxicity	Genetic Toxicity		
						Gene Mutations (<i>in vitro</i>)	Chromosomal Aberrations (<i>in vitro</i>)	<i>In vivo</i>
SPONSORED SUBSTANCES								
(NH ₄) ₂ EDTA	20824-56-0	WoE	Na ₃ EDT A	CaNa ₂ EDTA/ Na ₂ EDTA	EDTA/ Na ₃ EDTA	WoE	WoE	–
(NH ₄) ₄ EDTA	22473-78-5	WoE	Na ₃ EDT A	CaNa ₂ EDTA /Na ₂ EDTA	EDTA/ Na ₃ EDTA	WoE	WoE	–
Zn(NH ₄) ₂ EDTA	67859-51-2	WoE	Na ₃ EDT A	CaNa ₂ EDTA /Na ₂ EDTA	EDTA/ Na ₃ EDTA	WoE	X	–
Fe(III)Na EDTA	15708-41-5	WoE	X	CaNa ₂ EDTA /Na ₂ EDTA	X	X	–	X
Na ₂ EDTA	139-33-3	X	X	X	X	X	–	X
Na ₃ HEDTA	139-89-9	WoE	Na ₃ EDT A	CaNa ₂ EDTA /Na ₂ EDTA	EDTA/ Na ₃ EDTA	X	WoE	–
Fe(III)NH ₄ EDTA	21265-50-9	X	Fe(III)N a EDTA	CaNa ₂ EDTA /Na ₂ EDTA	EDTA/ Na ₃ EDTA	WoE	WoE	–
Fe(II) HEDTA	16485-47-5	WoE	Fe(III)N a EDTA	CaNa ₂ EDTA /Na ₂ EDTA	EDTA/ Na ₃ EDTA	WoE	WoE	–
Fe(III) HEDTA	17084-02-5	WoE	Fe(III)N a EDTA	CaNa ₂ EDTA /Na ₂ EDTA	EDTA/ Na ₃ EDTA	WoE	WoE	–
PDTAH ₄	1939-36-2	X	X	X	X	X	WoE	–
Na ₄ PDTA	18719-03-4	WoE	PDTAH ₄	PDTAH ₄	PDTAH ₄	WoE	WoE	–
Na ₃ DTPA	140-01-2	X	X	PDTAH ₄	X	X	WoE	–
ANALOGUE SUBSTANCES								
Substance	CAS No.	Repeated-dose toxicity	Effects on Fertility	Developmental Toxicity	Genetic Toxicity			
					Gene Mutations (<i>in vitro</i>)	Chromosomal Aberrations (<i>in vitro</i>)	<i>In vivo</i>	
EDTA	60-00-4	–	–	X	X	X	–	
CaNa ₂ EDTA	62-33-9	X	X	X	X	–	–	
Na ₃ EDTA	150-38-9	X	X	X	X	X	–	
Na ₄ EDTA	64-02-8	–	–	X	–	–	–	
K ₃ DTPA	7216-95-7	X	–	–	X	X	–	

X = data available; O = read across; –Endpoint not addressed for this chemical; WoE = weight of evidence

1 = Sensitisation

2 = Repeated-dose toxicity

Physical-Chemical Properties

The members of this category are all solid granular materials in the pure or neat state with molecular weights that range from 292 to 503 and possess similar physical/chemical properties. As metal-organic salts, or inner salts, all category members decompose before melting upon sufficient heating (generally at temperatures > 200 °C). Therefore true melting points are not applicable. Chelants that are metal salts do not exist as discrete neutral molecules, and therefore cannot volatilize, exert appreciable vapour pressure, or boil. Therefore, vapour pressure and boiling point data are not applicable for such chelants and are not determined. Henry's law constants are also expected to be negligible. Chelants that exist as neutral molecules (not metal salts) can exert vapour pressure, but in this case the vapour pressure is exceedingly low. All category members are highly soluble to miscible in water (generally > 10,000 mg/L) and insoluble in organic solvents, therefore also possessing negative partition coefficients (log K_{ows}).

Human Health

Toxicokinetics, Metabolism and Distribution

Toxicokinetic data with category members and analogues are available. By the inhalation route, aerosolized DTPA and its salts are absorbed from the respiratory tract into systemic circulation but the degree of absorption is dependent on the site of deposition. Absorption via the oral and dermal routes is expected to be low. Dermal application of radiolabeled CaNa₂EDTA to human skin showed that 0.001% was found in the urine and none was found in the blood. Studies with CaEDTA, CaNa₂EDTA, Na₂EDTA and DTPA and its salts indicate that these complexes are poorly absorbed in mammals after oral administration. EDTA and its salts are eliminated from the body, 95% via the kidneys and 5% by the bile, along with the metals and free

ionic calcium which was bound in transit through the circulatory system. In whatever salt EDTA is administered, it is likely to chelate metal ions *in vivo*.

Acute Toxicity

Data are available on the sponsored and/or analogue substances for acute toxicity via the inhalation, oral and dermal routes of exposure. Limited acute inhalation toxicity data with atmospheres enriched in the dusts of certain of the chelants were generally without effect in rats. However, inhalation of respirable dust aerosols of **Na₂EDTA** in male rats exposed to 30, 300 or 1103 mg/m³ 6 hours/day for up to 5 days produced adverse effects at all concentration levels. Mortality was observed at 1103 mg/m³ following a single 6-h exposure. These effects were fully reversed in surviving animals after a 14-day recovery. Acute dermal toxicity studies in rats with **Fe(III)NH₄EDTA**, **PDTAH₄**, **Na₄PDTA** and **K₅DTPA** showed LD₅₀ values ranging from >1800 to >2000 mg/kg bw. In rats, excepting **(NH₄)₄EDTA** (oral LD₅₀ > 1870 mg/kg bw), **Fe(III)(NH₄)EDTA** (oral LD₅₀ > 920 mg/kg bw) and **Na₄EDTA** (oral LD₅₀ equal to 1658 mg/kg bw), oral LD₅₀ values [EDTA, **(NH₄)₂EDTA**, **Zn(NH₄)₂EDTA**, **CaNa₂EDTA**, **Na₂EDTA**, **Na₃EDTA**, **Fe(III)NaEDTA**, **Na₃HEDTA**, **Fe(III)HEDTA**, **PDTAH₄**, **Na₄PDTA**, **Na₅PDTA** and **K₅DTPA**] were > 2000 mg/kg bw. At higher doses approaching the LD₅₀ values, clinical signs consisting of dyspnea, diarrhea and spastic gait were observed.

Irritation and Sensitisation

The aminocarboxylic acid-based chelants are not irritating to moderately irritating to the intact skin, and slightly to moderately irritating to the eyes in rabbits. The irritancy potential is related to the pH of the individual salt. Thus, more acidic members of the category such as **diammonium** and **disodium EDTA**, and the more basic members such as **tetrasodium PDTA** and **pentasodium salt of PDTA**, have inherently greater irritancy potential. The aminocarboxylic acid-based chelants are not skin sensitisers based on studies in mice and guinea pigs.

Repeated-dose Toxicity. Reliable data are available for oral repeated-dose studies with **Na₂EDTA**, **PDTAH₄**, **Fe(III)NaEDTA**, **Na₃EDTA**, **CaNa₂EDTA**, **K₅DTPA** and **Na₅DTPA**. The toxicity observed has been attributed to nutrient metal deficiencies, resulting from chelation of critical metal species, most notably calcium and zinc. Under physiologically relevant conditions, the salts of various category members will ionize based on the dissociation constants of the parent chelate and thus all salts of a particular parent, such as EDTA or PDTA, are assumed to chelate metal ions *in vivo* based on the inherent chelating strength of the parent chelate molecule. As in the case of zinc, deficiency is presumed to exhibit a threshold effect, and both dose and duration of exposure become important factors in the overall toxicity observed with longer-term administration.

In a 13-week repeated-dose toxicity study, rats (both sexes) fed **Na₂EDTA** (0, 1, 5, 10%) showed mortality at the highest dose. In addition, there was decreased food consumption (emaciation at 10%) and diarrhea at doses of 5% (approximately 4206 mg/kg bw/day) and above. The NOAEL was 1% (approximately 692 mg/kg bw/day). Range finding studies with higher dose levels revealed diarrhea, emaciation, loss of body weight and sometimes parakeratosis in esophagus and forestomach as well as decreased hemoglobin and hematocrit levels. In a 2-year bioassay in rats and mice (both sexes) with **Na₃EDTA** (0, 3750 or 7500 ppm) a NOAEL of 7500 ppm (approximately 500 mg/kg bw/day in rats and 938 mg/kg bw/day in mice; highest dose tested) was determined. In a 2-year dietary study, rats fed **CaNa₂EDTA** at 0, 50, 125 or 250 mg/kg bw/day showed no effect on behaviour, appearance, growth, longevity or hematology up to one year. After 1 year, there was a downward trend in hematology parameters. There were no gross pathologic findings, changes in organ weights or treatment-related lesions any organ that was examined. The NOAEL was 250 mg/kg-bw/day (highest dose tested). In a 31-day dietary study, female rats fed **CaNa₂EDTA** (0, 0.3, 1.0, 3.0 or 5.0%) showed decreased body weight gain at 5.0% (approximately 3636 mg/kg bw/day). No effects on organ weight were observed. The NOAEL was 3.0 % (approximately 2216 mg/kg bw/day). In a 14-week repeated-dose toxicity oral gavage study in rats (both sexes) with **PDTAH₄** (0, 30, 100 or 300 mg/kg bw/day), urinary zinc concentrations increased with duration of treatment in males but not females. Increased urinary zinc concentrations did not appear to be associated with systemic toxicity as no other treatment-related findings were observed. The NOAEL was determined to be 300 mg/kg bw/day. In a 28-day study [OECD TG 407], rats treated by gavage with **PDTAH₄** (0, 100, 500 or 1000 mg/kg bw/day) showed mortality at 1000 mg/kg bw/day. In male rats, hyaline droplet formation resembling alpha 2μ globulin nephropathy was observed at 500 and 1000 mg/kg bw/day. No other effects were observed. The NOAEL was determined to be 500 mg/kg-bw/day. In another 28-day study, **PDTAH₄** (0, 100, 300 or 1000 mg/kg bw/day) showed mortality at 1000 mg/kg bw/day. At 300 mg/kg bw/day, histopathological findings were thymic atrophy and bone marrow atrophy and congestion in two females and serum zinc levels were significantly

decreased (50% of controls). At 100 and 1000 mg/kg bw/day, urinary zinc levels were higher than controls. No other adverse findings were observed. The NOAEL was determined to be 100 mg/kg bw/day. In 31-day and 61-day studies, male rats fed **Fe(III)NaEDTA** up to 86.15 mg/kg bw/day had decreased plasma sodium and calcium concentrations but did not exhibit any organ toxicity. The NOAEL was considered to be 86.15 mg/kg bw/day (highest concentration tested). Iron accumulated in the liver, spleen and kidneys in a dose-related manner but this did not result in excess iron in other tissue or in iron toxicity. In a 28-day repeated-dose oral gavage study with **K₅DTPA**, rats administered 0, 83, 333 or 1330 mg/kg bw/day, showed mortality at 1330 mg/kg bw/day. Other effects reported included increased serum potassium levels, decreased body weights, clinical signs and diarrhea. Less severe effects were observed at 333 mg/kg bw/day. The NOAEL was 83 mg/kg bw/day. In a 28-day drinking water study, rats received 0, 600, 3000 or 12,000 ppm **Na₅DTPA**. Body weight reductions and histopathological changes of the urinary tract were observed at 12,000 ppm and 3000 ppm. The NOAEL was 600 ppm (approximately 75 mg/kg bw/day).

Genetic Toxicity

Available data from *in vitro* [**Na₂EDTA**, **Na₃HEDTA**, **PDTAH₄**, **Na₃EDTA**, **Fe(III)NaEDTA** and **Na₅DTPA**] and *in vivo* [**Na₂EDTA**, **Na₃EDTA** and **Fe(III)NaEDTA**] testing of representative chelant category members indicate that these materials generally do not induce gene mutations or chromosomal aberrations *in vitro* or *in vivo*. Although there have been some positive findings reported *in vitro* and *in vivo* for some category members, these positive effects have been generally attributed to the threshold mechanisms of pH changes and the chelation of critical nutrient metals such as zinc. The weight of evidence leads to a conclusion that the members of the aminocarboxylic acid-based chelants category do not present a genotoxic hazard.

Carcinogenicity

An oral two-year study with **Na₃EDTA** trihydrate in mice and rats indicated no evidence of carcinogenicity. The amino carboxylic acid-based chelants category members are not expected to be carcinogens.

Toxicity to Reproduction (Fertility and Developmental Toxicity)

Reproductive toxicity data are available that evaluate the potential for reproductive effects from exposure to **CaNa₂EDTA**, **Na₂EDTA** and **PDTAH₄**. Chronic studies with **Na₃EDTA** that included histological examination of gonadal tissues for evidence of adverse effects also showed no adverse effects on reproductive organs. In a non-guideline chronic study, no adverse clinical, histological, hematological or reproductive effects were found over 4 generations in rats fed a diet of 0, 50, 125 or 250 mg/kg bw/day of **CaNa₂EDTA**. The NOAEL for reproductive toxicity was 250 mg/kg bw/day (highest dose tested). The weight of evidence from a two-generation reproductive toxicity study in rats shows that dietary ingestion of 1% **Na₂EDTA** (approx. 920 mg/kg bw/day) had no effect on reproduction; however, no litters were produced at 5% (approx. 4600 mg/kg bw/day); the NOAEL for reproductive toxicity was 920 mg/kg bw/day. In a one-generation reproductive toxicity study [OECD TG 415] in rats fed 0, 10, 60 or 300 mg/kg bw/day **PDTAH₄** decreased male and female fertility indices, and gestational and pup survival indices were noted at 300 mg/kg bw/day. In addition, testicular toxicity changes (degeneration and/or atrophy of seminiferous tubules, decreased or absent spermatids) and increased urinary zinc and decreased serum zinc levels were observed in this group. The NOAEL for reproductive toxicity was 60 mg/kg bw/day at which dose there was no severe zinc deficiency. Observed reproductive toxicity with **PDTAH₄** is indirect, and occurring subsequent to a severe zinc deficiency. Based on available data EDTA and HEDTA based category members do not show similar reproductive effects / and similar potency. In the absence of a deficiency of essential metals which is expected under normal nutrition, none of the category members would be considered reproductive toxicants.

Developmental toxicity data are available for EDTA, **CaNa₂EDTA**, **Na₂EDTA**, **Na₃EDTA**, and **Na₅DTPA**. Data from multigenerational and prenatal developmental toxicity studies suggest that developmental effects are observed in the presence of maternal toxicity and are related to plasma zinc concentrations. Studies on developmental toxicity showed a specific fetotoxic and teratogenic potential of EDTA, **Na₂EDTA** and **CaNa₂EDTA**; a LOAEL of 1000 mg/kg bw/day was determined. Increased proportions/litter and significantly lower fetal body weights are indicative for an impaired fetal development. The pattern of malformations comprised cleft palate, severe brain deformities, eye defects, micro- or agnathia, syndactyly, clubbed legs and tail anomalies. These effects were exhibited in studies using maternally toxic dose levels. The mechanism resulting in developmental effects is found to occur via zinc depletion resulting in zinc deficit. These effects are independent of whether the acid or sodium or calcium salts are applied. In a non-guideline prenatal developmental toxicity study, rats were administered a single dose of 1245 mg/kg bw/day

Na₃EDTA on gestation days 7-14. Clinical effects included diarrhea (35% of animals) and a reduction of body weight gain during the treatment period in dams; the NOAEL for maternal toxicity was not established. There was no effect of treatment on litter size, post-implantation loss, sex ratio, fetal body weight, or mortality. There was no effect of treatment on the incidence of fetal abnormalities; the NOAEL for developmental toxicity was 1245 mg/kg bw/day. In a prenatal developmental toxicity study [OECD TG 414], rats were administered (via gavage) 0, 100, 400 or 1000 mg/kg bw/day Na₃DTPA. At 400 mg/kg bw/day there was a statistically significant increase in the total number of fetuses with skeletal variations and retardations in fetuses (shortened or absent 13th rib, rudimentary cervical ribs, delays in ossification). At 1000 mg/kg bw/day, in addition to effects observed in the mid dose, there was a reduction in litter size and an increase in number of skeletal malformations (missing thoracic and lumbar vertebrae and bipartite sternbrae) but no visceral or external malformations were present. This dose also produced a reduction in maternal body weight gain (adjusted). The NOAEL for maternal toxicity was 400 mg/kg bw/day and for developmental toxicity, 100 mg/kg bw/day. Members of the aminocarboxylic acid-based chelants category would not be expected to exhibit reproductive and developmental effects in the absence of a metal deficiency which is not expected under normal nutrition.

The members of the amino carboxylic acid-based chelants category possess properties indicating a hazard for human health (skin and eye irritation, repeated-dose toxicity and reproductive/developmental toxicity). However, these effects are associated with the chelation of metals and the subsequent toxicological effects related to metal deficiency and therefore would only be considered relevant human hazards where there is significant exposure. Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Environment:

Photodegradation experimental data (EDTA, Na₄EDTA, and Fe(III)NaEDTA) indicate that these chelants are rapidly degraded by light when they are in the hydrosphere. CO₂, formaldehyde, N-carboxymethyl-N,N'-ethylenediglycine (ED3A), N,N'-ethylenediglycine (N,N'-EDDA), N-carboxymethyl-N-aminoethyleneglycine (N,N'-EDDA), iminodiacetic acid (IDA), N-aminoethyleneglycine (EDMA), and glycine were identified as major photodegradation products of Ferric monosodium EDTA. Splitting off of acetic acid residues appears to be an important conversion step. Formation of iron complexes by chelants is believed to be a major route of photodegradation in the aqueous environment. Because ferric salts are present in the environment, and the chelants in this category will readily displace their ions for ferric iron, it is suspected that these agents will photodegrade in the aqueous environment. Photodegradation rates of 1:1 ferric complexes of both EDTA and DTPA were calculated after irradiating aqueous solutions of these complexes with light which corresponded to the spectrum of the sun at 60° N. These rates corresponded to half-lives of 11.3 and 8.04 minutes respectively for the EDTA and DTPA complexes. Since the experimental conditions were ideal, actual conditions in natural waterways that take into consideration varying sunlight and cloudiness, varying opacity and depth of water would be expected to be associated with longer half-lives. The fate of EDTA and DTPA in aquatic environments receiving waste waters from Swedish pulp and paper mills was studied with results that indicated that the rate of disappearance of these chelants was dependent on sunlight intensity, and that light has a stronger influence on DTPA than on EDTA. All members of the amino carboxylic acid-based chelants category are stable in water, and most commercial chelants are sold as aqueous solutions. These substances are highly water-soluble salts, and possess no functional groups in their molecular structures subject to hydrolysis.

Hydroxyl radical induced atmospheric degradation cannot be estimated for members of the Chelants Category. Since the chelants are salts and therefore exert no significant vapor pressure, this endpoint is not applicable for category members.

Category members emitted to waterways are likely to remain dissolved in this environmental compartment. If emitted to soil or sediment, category members are likely to exhibit appreciable to high water solubility and soil mobility. This behavior is based on the presence of multiple carboxylate anion groups in the molecular structure, and is supported by the demonstrated high water solubility and negligible vapour pressure of most category members. The EPA EPIWIN Fugacity Level III modeling has been run for category members (see SIAR), with results consistent with negligible partitioning to the atmosphere, and predominant partitioning to the hydrosphere. These results must be viewed with caution, because the Level III fugacity model has not been well validated for ionised organic salts.

Available biodegradation experimental data indicate that category members are not readily biodegradable in

soil or water in standard laboratory tests. Studies with adapted microorganisms have indicated that EDTA, calcium disodium EDTA, disodium EDTA, DTPA, **Fe(III)NH₄EDTA**, and **Fe(III)NaEDTA** can be biodegraded under certain conditions (e.g. slightly alkaline pH and long retention times). One study showed that >99% of EDTA is biodegraded in an industrial wastewater treatment plant, suggesting that laboratory methods may underestimate the potential for biodegradation in the environment. It is evident that these conditions are **not** present in municipal wastewater treatment plants (WWTP). Therefore, it is assumed that no biodegradation occurs in municipal waste water treatment plants. This is supported by monitoring studies, where no degradation was observed. As neither adsorption onto sludge nor volatilisation is expected, 100% of the widely dispersed EDTA is expected to be released into the hydrosphere.” However, EDTA used for instance by the food or pulp & paper industry is, or can be, treated biologically. Industrial WWTPs are often operated at slightly alkaline conditions and high sludge retention times. Counter-ions exert effects on the biodegradation of chelating agents. A particular strain has been identified that degrades metal-EDTA complexes with a thermodynamic stability constant below 10¹², like Ca, Mg and Mn complexes, but not those with constants > 10¹², such as Cu and Fe. Another has been shown to degrade EDTA when it was complexed with Mg, Zn, Mn, Co or Cu, but not when uncomplexed or complexed to Ca, Ni or Fe(III) ions. Conditions that favour EDTA biodegradation are also expected to lead to biodegradation of the other members of the category. The ferric-iron-containing chelants are expected to be the most resistant to biodegradation, but the most susceptible to photodegradation.

The pH of the test medium may affect aquatic toxicity of certain of the chelate salts, in particular the ammonium salts, which are generally of less toxicity in typical waters of pH range 5 to 8, but which increase in toxicity at higher pH values due to free ammonia. Aquatic toxicity testing with salts of EDTA has shown a relationship between water hardness and toxicity, with toxicities generally higher in soft water and decreasing in harder waters, due to chelation of calcium.

It could be shown in short-term tests on fish, that EDTA and Na-EDTA are more toxic in an uncomplexed form. This can only occur if they are available in over-stoichiometric amounts to the chelants. Under these conditions the complexing agents can cause nutrient deficiency by reducing the essential concentration of different ions. The higher the water hardness the higher is the concentration of EDTA necessary to cause a toxic effect expressed as mortality.

According to the results from different ecotoxicological studies, EDTA mainly influences the pathway of metal ions. For EDTA long-term studies with fish, daphnids and algae are available. The following results were found: *Danio rerio*: 35 d-NOEC > 26.8 mg/L (CaNa₂EDTA); *Daphnia magna*: 21d-NOEC = 22 mg/L; *Scenedesmus subspicatus*: 72h-EC10 = > 100 mg/L. For **Na₂EDTA**, *Daphnia magna*: 21d-NOEC = 25 mg/L. For aquatic plants, the low EC₅₀ values are related to interference of some category members with essential metal nutrients in the test medium of the standard algae test resulting in nutrient deficiency in the laboratory test. These effects can be overcome by supplementing the algae medium with growth limiting metal nutrients as seen in studies where iron complexes of EDTA are tested. In the environment, there is always a vast molar surplus of the essential nutrients in comparison with actual chelant concentrations. In general, chelants are not considered to be hazardous to plants.

Test Chemical	CAS No.	Acute Toxicity to Fish			
		Species	Time (h)	LC ₅₀ (mg/L)	NOEC (mg/L)
EDTA	60-00-4	bluegill	96	159	100
		channel catfish	96	129	
(NH₄)₂EDTA	20824-56-0	bluegill	96	936	540
(NH₄)₄EDTA	22473-78-5	bluegill	96	275	94
Zn(NH₄)₂EDTA	67859-51-2	bluegill	96	363	170
CaNa ₂ EDTA	62-33-9	bluegill	96	2340	1000
Na₂EDTA	139-33-3	guppy	96	320	
		<i>Oncorhynchus mykiss</i>	24	860 LC ₁₀₀	
Na ₃ EDTA	150-38-9	fathead minnow	96	> 300 (trihydrate)	
Na ₄ EDTA	64-02-8	bluegill	96	486	456
		<i>Leuciscus idus</i>	48	1590	
Fe(III)NH₄ EDTA	21265-50-9	fathead minnow	96	190	
Fe(III)NaEDTA	15708-41-5	bluegill	96	2592	1792
		rainbow trout (ferric potassium EDTA)	96	> 116	116
Na₃HEDTA	139-89-9	bluegill	96	331	230
		golden orfe	96	1856 (LC ₁₀₀)	860
Fe(III)HEDTA	17084-02-5	bluegill	96	2155	1490
Na₅DTPA	140-01-2	bluegill	96	424	285
K ₅ DTPA	7216-95-7	rainbow trout	96	>1000	1000

Test Chemical	CAS No.	Acute Toxicity to Aquatic Invertebrates			
		Species	Time (hr)	LC ₅₀ (mg/L)	EC ₅₀ (mg/L)
EDTA	60-00-4	<i>Daphnia magna</i>	48		113
		<i>D. magna</i>	48	~230	
		<i>Artemia salina</i>	24	280 (LC ₁₀₀)	
Na₂EDTA	139-33-3	<i>Artemia salina</i>	24		660 (EC100)
Na ₃ EDTA	150-38-9	Daphnid (trihydrate)	96		> 100
Na ₄ EDTA	64-02-8	<i>D. magna</i>	24		610
		<i>D. magna</i>	24	625	
		<i>D. magna</i>	24		1033
Fe(III)NaEDTA	15708-41-5	Daphnid	24		110
		<i>D. magna</i>	96	13-32	
		Daphnid (ferric potassium EDTA)	48		> 114
Na₃HEDTA	139-89-9	<i>D. magna</i>	48	> 500	
PDTAH₄	1939-36-2	<i>D. magna</i>		>88	
Na₅DTPA	140-01-2	<i>D. magna</i>	48		>500
K ₅ DTPA	7216-95-7	<i>D. magna</i>	48		890

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Test Chemical	CAS No.	Toxicity to Algae		
		Species	Time (h)	EC ₅₀ (mg/L)
Na ₂ EDTA	139-33-3	<i>S. quadricauda</i>	24 day	200 (NOEC)
Na ₃ EDTA	150-38-9	<i>S. capricornutum</i>	7 day	> 1 <10
Na ₄ EDTA	64-02-8	<i>S. subspicatus</i>	72	1.01
Fe(III)NH ₄ EDTA	21265-50-9	<i>S. capricornutum</i>	168	>100
Fe(III)NaEDTA	15708-41-5	<i>S. capricornutum</i> (Na ₂ -EDTA + Fe ³⁺)	72	>72.7
Na ₃ HEDTA	139-89-9	<i>S. subspicatus</i>	96	10.4
Na ₅ DTPA	140-01-2	<i>S. subspicatus</i>	72	2.62

The amino carboxylic acid-based chelants category members possess properties indicating a hazard to the environment (acute toxicity to aquatic organisms between 1-100 mg/L). However, the toxicity is associated with the chelation of essential nutrients by the category members which may not be seen in nutrient rich environments. The category members are not readily biodegradable and have low potential for bioaccumulation. Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD Cooperative Chemicals Programme.

Exposure

Environmental release of chelants during manufacture is incidental. Manufacture takes place in closed systems with incidental release to waste streams. The same incidental release is associated with the formulation of chelants into aqueous commercial mixtures or preparations. Chelants enter the environment primarily as a result of their multiple uses, which can be characterized as dispersive. The actual amount released depends on the type of use, however, most uses result in eventual environmental release to waterways, via aqueous wastes. Some aqueous waste streams undergo waste treatments, but most chelants have limited biodegradability; therefore the chelant may pass through a waste treatment system to a waterway. The predominant environmental compartmental destination is the hydrosphere. Chelants as salts have negligible volatility, and therefore cannot enter the atmosphere in significant amounts. Chelants released to soil or biota will have substantial soil mobility based on their high water solubilities, and therefore will tend to partition to water.

Aggregate Production and/or Import Volume in the United States in 2005

Substance	CAS No.	Production Volume (metric tons)
(NH ₄) ₂ EDTA	20824-56-0	454 - < 4540
(NH ₄) ₄ EDTA	22473-78-5	454 - < 4540
Zn(NH ₄) ₂ EDTA	67859-51-2	454 - < 4540
Fe(III)NaEDTA	15708-41-5	454 - < 4540
NaEDTA	139-33-3	454 - < 4540
Na ₃ HEDTA	139-89-9	4540 - < 22,680
Fe(III)NH ₄ EDTA	21265-50-9	NA
Fe(II) HEDTA	16485-47-5	NA
Fe(III) HEDTA	17084-02-5	4540 - < 22,680
PDTAH ₄	1939-36-2	227 - < 454
Na ₄ PDTA	18719-03-4	NA
Na ₅ DTPA	140-01-2	45,400 - < 226,800

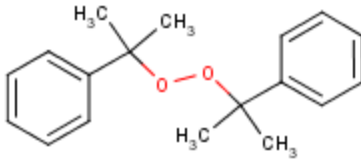
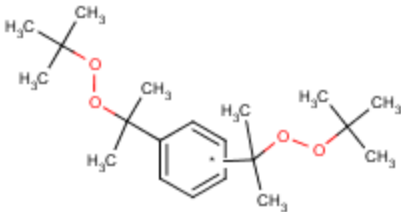
NA = Not available

Based on the expected widespread application of engineering controls (closed systems) and the lack of volatility of chelants, occupational exposure during manufacture or processing into formulations or preparations is expected to be low via the inhalation route. The most likely route of occupational exposure is through the dermal route. Dermal exposure is minimized by closed systems and personal protective equipment (e.g. gloves) when used. Industries with a higher exposure potential include the use of chelants in

the pulp and paper industry, and the textile industry where the predominant route of potential exposure will still be dermal.

Chelants are present in preparations used by consumers. A typical concentration of chelants in various consumer products is 10%. Based on negligible volatility of chelant salts and very low volatility of neutral chelants, the potential for inhalation exposure is expected to be low. However, inhalation exposure can occur when using chelant containing surface cleaners which are aerosolised. Most consumer exposure will occur by dermal contact with chelant formulations, or by the oral route. Chelants are used as approved direct and indirect food additives. In these applications the chelants function as food preservatives, or as fortifications (e.g., to improve iron status in populations). Chelant formulations are also administered clinically in treating heavy metal poisoning (e.g. lead).

SIDS INITIAL ASSESSMENT PROFILE

Category Name	Aryl Substituted Dialkyl Peroxides
CAS No(s).	80-43-3 25155-25-3
Chemical Name(s)	1,1'-(Dioxydipropane-2,2-diyl)dibenzene (DCUP) [1,3(or 1,4)-Phenylenebis(1-methylethylidene)]bis[tert-butyl] peroxide (DIPP)
Structural Formula(s)	<div style="text-align: center;">  <p>80-43-3</p> </div> <div style="text-align: center;">  <p>25155-25-3</p> </div>

SUMMARY CONCLUSIONS OF THE SIAR

Analogue/Category Rationale

The Aryl Substituted Dialkyl Peroxide category members are structurally similar showing trends in physical-chemical properties, ecotoxicity and similar toxicological properties. This category is defined as below:

- Physical / chemical similarity: The two materials in this category are not considered highly reactive, on a thermal or chemical basis. They are stable at neutral pH and ambient temperature. They each contain aryl and branched short chain alkyl groups with molecular weights, of 270 (DCUP) and 339 (DIPP) Daltons. They have log octanol water partition coefficients ($\log K_{ow}$) > 5.
- Similar structure: DCUP is composed of two isopropylbenzoyl groups and DIPP has both a substituted isopropyl benzoyl group and the *t*-butyl functional groups.
- Similar toxicological properties: Both the acute and repeated dose toxicity profiles for these materials are similar. The members of the class demonstrate low acute toxicity, little irritation, no sensitization, and are not genotoxic in *in vitro* studies. The category is adequate for the endpoints covered by this assessment however potential differences in the metabolic/degradation profiles between the two category members should be considered before extending the category rationale to other endpoints.
- Similar behaviour in the environment: The members of the class demonstrate low reactivity at neutral pH and ambient temperatures and are not expected to be highly reactive in the environment. DCUP and DIPP favour distribution to soil and sediment. DCUP and DIPP have low water solubility (<0.5 mg/L). Based on the available test data, the members of the category are not acutely toxic to aquatic organisms at the limit of water solubility, but are toxic to aquatic invertebrates on a chronic level.

Based on the chemical structures, similar physico-chemical properties and the existing toxicity information for the members of the category, read-across from DIPP to DCUP is appropriate for the human health and ecotoxicity endpoints. For DCUP, DIPP data are used as read-across for the fertility, developmental and acute fish toxicity endpoints. Hydrolysis data are not available for either category member; read across to a structurally similar alkyl substituted dialkyl peroxide is used to fill the endpoint.

Physical-chemical Properties

DCUP is a solid with a melting point of 39.8 °C (measured), a boiling point has not been determined as the substance decomposes without boiling upon heating, and a measured vapour pressure of <0.1 hPa at 60 °C. The measured octanol-water partition coefficient ($\log K_{ow}$) is 5.6 at 25 °C, and the measured water solubility is 0.43 mg/L at 20 °C. DIPP is a solid with a melting point of 37-54 °C (measured), a boiling point has not been determined as the substance decomposes without boiling upon heating, and a measured vapour pressure (valid only for the liquid peroxides) of 0.6 hPa at 100 °C. Note that the vapour pressure of solid peroxide will be lower than the extrapolated value of the liquid. The measured octanol-water partition coefficient ($\log K_{ow}$) is >5.5 and the measured water solubility is 0.04 mg/L, both at 20 °C.

Human Health

No toxicokinetic studies were available on the category members. Based on physical-chemical properties (e.g. water solubility and solid state), absorption would be expected to be low for DCUP and DIPP by the dermal route. Systemic effects in repeated dose studies with both substances supports absorption following oral exposure. *In vivo*, glutathione peroxidases are expected to catalyze the reduction of organic peroxides to the corresponding stable alcohols and water using cellular glutathione as the reducing agent.

Acute toxicity data with rats were available for the oral and dermal routes for DCUP and DIPP. The acute dermal LD₅₀s of the category members in rats was >2000 mg/kg bw [OECD TG 402]. The acute oral toxicity LD₅₀s of the category members in rats was >2000 mg/kg bw [OECD TG 401 or OECD TG 423]. Clinical signs of toxicity were not observed. The category members were not irritating to the skin of rabbits [OECD TG 404]; DCUP was not irritating to rabbit eyes, but DIPP was slightly irritating to rabbit eyes [both OECD TG 405]. In standard skin

sensitization studies in mice [OECD TG 429], the substances were not considered skin sensitizers.

Repeated-dose toxicity data were available for DCUP and DIPP by the oral route of exposure in rats. In a 28-day study [OECD TG 407], 5 rats/sex were exposed to DCUP by gavage at 0, 60, 200 or 600 mg/kg bw/day for 28 days; an additional 5 rats/sex (satellite groups) in the 0 and 600 mg/kg bw/day groups were subjected to a 14 day recovery period. There was an increase in relative liver weights in both sexes, hypertrophy and degeneration of hepatocytes in both sexes, and mobilization of Kupffer cells in males observed at 600 mg/kg bw/day; there was an increase in relative liver weights in females and hypertrophy of hepatocytes in both sexes observed at 200 mg/kg bw/day. These changes were reversible during the recovery period. The NOAEL was 60 mg/kg bw/day. In a combined repeated-dose/reproductive/developmental toxicity screening test [OECD TG 422], rats (10/sex/dose) were exposed to DIPP by gavage at 0, 100, 300 or 1000 mg/kg-bw/day for 44 days (males) and ≥ 44 days (females). At 300 and 1000 mg/kg bw/day, increased relative kidney weights in both sexes, and an increased incidence and severity of hyaline droplets in proximal convoluted tubules in males was observed. The NOAEL was 100 mg/kg bw/day. In summary, the NOAELs following repeated oral exposure of the two category members are within a narrow range of 60 to 100 mg/kg bw/day.

Negative *in vitro* bacterial [OECD TG 471] and mammalian mutagenicity assays [OECD TG 476] were available for both members of the category. Both substances tested were negative for induction of bacterial and mammalian cell gene mutations. DIPP and DCUP were negative for the induction of mammalian chromosomal aberrations *in vitro* (OECD TG 473). DIPP and DCUP were not mutagenic *in vitro*.

No data are available for the carcinogenicity of the category members.

No reproductive and developmental toxicity studies were available for DCUP. Data by the oral route of exposure were available for DIPP. In a OECD TG 422 combined repeated-dose/reproductive/developmental toxicity screening test (see description of repeated-dose toxicity above for study details), effects in rats administered DIPP at 1000 mg/kg bw/day included a reduced number of pregnant dams, fewer corpora lutea, fewer implantation sites, fewer live offspring at first litter check, and a higher postnatal loss. In addition, the surviving pups at 300 and 1000 mg/kg bw/day had reduced body weight gain until day 4 post-partum. The NOAEL for maternal systemic (maternal)/reproductive/developmental toxicity is 100 mg/kg bw/day. Reproductive effects were not considered secondary to maternal toxicity. Based on these data, DCUP is expected to exhibit effects on reproductive/developmental toxicity.

The Aryl Substituted Dialkyl Peroxides possess properties indicating a hazard for human health [repeated-dose toxicity (liver or kidney effects following oral exposure) and reproductive/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

Hydrolysis studies were not available for the category members. However, in an OECD TG 111 study an analogous substance (an alkyl substituted dialkyl peroxide; Di-tert-butyl peroxide; CAS No 110-05-4) was stable to hydrolysis; the results of the tests at pH 4.0, pH 7.0 and pH 9.0 showed no significant degradation at 50 °C (less than 10% after 5 days). The Aryl Substituted Dialkyl Peroxides are considered stable to hydrolysis; the molecules do not contain any functional groups sensitive to hydrolysis.

In the atmosphere, indirect photooxidation by reaction with hydroxyl radicals for DCUP and DIPP is predicted to occur with a half-life of 1.2 and 1.6 days, respectively. An OECD TG 301C study and OECD TG 301D study with DCUP resulted in 0 % and 18 % biodegradation after 28 days, respectively. An OECD TG 301D study with DIPP resulted in 0 % biodegradation after 28 days. The Aryl Substituted Dialkyl Peroxides were not readily biodegradable under aerobic conditions.

A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that DCUP will distribute mainly to the sediment (56.6 %) and soil (39.8%) compartments with minor distribution to the water compartment (3.29%) and negligible amount in the air compartment (0.2%). Similarly a level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that DIPP will distribute mainly to the sediment (53.2 %) and soil (45.4%) compartments with minor

distribution to the water compartment (1.2%) and negligible amount in the air compartment (0.1%). Henry's law constants have been estimated for DCUP and DIPP of 4.48 and 9.93 Pa·m³/mole at 25 °C.

In an OECD TG 305 with DCUP, the measured BCF = 137 - 1470 (0.01 mg/L) and 181 - 667 (0.001 mg/L) suggested DCUP has a low to moderate potential to bioaccumulate in the environment. Using the Gobas model, and assuming no metabolism, the BCF for DIPP was estimated to be 45,294. With metabolism taken into account, the BCF was = 536 (hepatic blood flow only) and =209 (hepatic and arterial flow). DIPP may have the potential to bioaccumulate in the environment.

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

<u>Fish, acute toxicity</u>		
DCUP	Read Across from DIPP	
DIPP	[<i>Poecilia reticulata</i>] 96 h LC ₅₀ > water solubility*	nominal; semi-static
<u>Invertebrate, acute toxicity</u>		
DCUP	[<i>Daphnia magna</i>] 48 h EC ₅₀ > 0.0.397*	measured; semi-static WAF
	[<i>Daphnia magna</i>] 48 h EC ₅₀ > water solubility*	measured; static
DIPP	[<i>Daphnia magna</i>] 48 h NOELR = ≥ 0.0219 mg/L	measured; static, highest concentration tested
<u>Algae, acute toxicity</u>		
DCUP	[<i>Pseudokirchneriella subcapitata</i>] 72 h ErC ₅₀ > water solubility* 72 h EbC ₅₀ > water solubility* NOECr > water solubility*	nominal
	[<i>Pseudokirchneriella subcapitata</i>] 72 h ErC ₅₀ > water solubility* 72 h EbC ₅₀ > water solubility* NOECr, NOECb > water solubility*	nominal
DIPP	[<i>Pseudokirchneriella subcapitata</i>] 72 h ErC ₅₀ > water solubility* 72 h EbC ₅₀ > water solubility*	measured
<u>Chronic toxicity</u>		
DCUP	[<i>Daphnia magna</i>] 21d EC ₅₀ reproduction = 0.231 mg/L 21d NOEC = 0.117 mg/L	measured; static renewal; based on average cumulative number of brood

*No effects at or below water solubility 0.43 mg/L at 20°C for DCUP and 0.04 mg/L at 20°C for DIPP

The Aryl Substituted Dialkyl Peroxides possess properties indicating a hazard for the environment (acute aquatic toxicity is not likely to occur at or below the water solubility of the substance, and chronic aquatic toxicity less than 1.0 mg/L for aquatic invertebrates). The substances are not readily biodegradable and have the potential 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

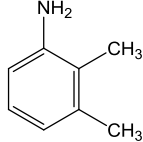
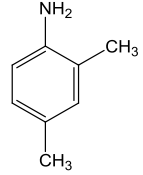
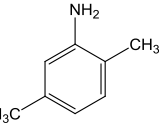
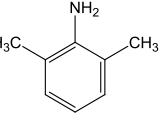
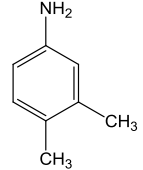
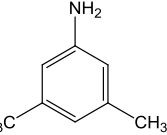
Worldwide production of DCUP was estimated to be approximately 10-50 kilo tonnes in year 2010. In the sponsor country (United States), the production of DIPP in 2005 was 1-10 million pounds (450 - 4500 tonnes). Worldwide production of DIPP was estimated to be approximately 1-10 kilo tonnes in year 2010. The dialkyl peroxides are most typically used as intermediates. The dialkyl peroxides have industrial uses. DCUP is used for the (co)polymerization of styrene and is used in the production of polyolefins and acrylics. It may also be used as a co-agent in the production of flame retardant, expandable polystyrene, and in the crosslinking of silicone materials. DIPP peroxide is used as an initiator (radical source) for the crosslinking of polymers above 170°C,

including the crosslinking of polyethylene or rubber (ethylene propylene diene monomer, ethylene-vinyl acetate).

Potential releases to the environment (expected to be limited) and industrial worker exposure may occur during manufacture (open and closed systems), use and spills. The Aryl Substituted Dialkyl Peroxides may be used in products used for food contact. The US Code of Federal Regulations (Title 21) specifies that the use of these compounds in food contact products is not to exceed 1.5%.

During manufacturing processes in which Aryl Substituted Dialkyl Peroxides are used, the process materials are typically held at a thermal decomposition temperature for many half-lives. These products are typically incorporated at a use rate of 0.1-3% before heat exposure. However, after processing with heat exposure (e.g., extrusion or vulcanization), negligible quantities of the Aryl Substituted Dialkyl Peroxides remain. Thus, exposure to the consumer is also expected to be negligible.

SIDS INITIAL ASSESSMENT PROFILE

Category Name	Dimethylaniline Category
CAS No.	87-59-2 95-68-1 95-78-3 87-62-7 95-64-7 108-69-0
Chemical Name	2,3-Dimethylaniline 2,4-Dimethylaniline 2,5-Dimethylaniline 2,6-Dimethylaniline 3,4-Dimethylaniline 3,5-Dimethylaniline
Structural Formula	<div style="display: flex; flex-direction: column; align-items: center;"> <div style="display: flex; align-items: center; margin-bottom: 20px;"> <div style="text-align: center; margin-right: 20px;"> <p>87-59-2 2,3-Dimethylaniline</p> </div> <div style="text-align: center;">  </div> </div> <div style="display: flex; align-items: center; margin-bottom: 20px;"> <div style="text-align: center; margin-right: 20px;"> <p>95-68-1 2,4-Dimethylaniline</p> </div> <div style="text-align: center;">  </div> </div> <div style="display: flex; align-items: center; margin-bottom: 20px;"> <div style="text-align: center; margin-right: 20px;"> <p>95-78-3 2,5-Dimethylaniline</p> </div> <div style="text-align: center;">  </div> </div> <div style="display: flex; align-items: center; margin-bottom: 20px;"> <div style="text-align: center; margin-right: 20px;"> <p>87-62-7 2,6-Dimethylaniline</p> </div> <div style="text-align: center;">  </div> </div> <div style="display: flex; align-items: center; margin-bottom: 20px;"> <div style="text-align: center; margin-right: 20px;"> <p>95-64-7 3,4-Dimethylaniline</p> </div> <div style="text-align: center;">  </div> </div> <div style="display: flex; align-items: center;"> <div style="text-align: center; margin-right: 20px;"> <p>108-69-0 3,5-Dimethylaniline</p> </div> <div style="text-align: center;">  </div> </div> </div>

SUMMARY CONCLUSIONS OF THE SIAR

Category Justification

The dimethylaniline category consists of six chemicals: 2,3-dimethylaniline (87-59-2), 2,4-dimethylaniline (95-68-1), 2,5-dimethylaniline (95-78-3), 2,6-dimethylaniline (87-62-7), 3,4-dimethylaniline (95-64-7) and 3,5-dimethylaniline (108-69-0).

There are a number of unifying considerations, which together justify the inclusion of members within the Dimethylaniline Category. These include:

1. Similarity of chemical structure and Functional Groups.
Direct connection of two methyl groups and one amino group to a benzene ring
2. Similarity of Physical / Chemical Properties
Melting points, boiling points, water solubility, log Kow, dissociation constants in the water.
3. Similarity of Mammalian Toxicity
Acute toxicity, repeated dose toxicity (anemia, liver and kidney damages), genotoxicity
4. Similarity in Health Effects and Mechanism of Toxic Action
Methemoglobinemia, mutagenic and clastogenic
5. Similarity of Environmental Toxicity and Fate Properties
Acute toxicity, chronic toxicity, toxicity to Microorganisms

The read across approach is used for genotoxicity, carcinogenicity and reproductive/developmental toxicity for the human health section. The similar toxicological effects identified in the repeated dose studies support the applicability of the read across approach.

CAS	87592	95681	95783	87627	95647	108690
Substance name	2,3-DMA	2,4-DMA	2,5-DMA	2,6-DMA	3,4-DMA	3,5-DMA
Mammalian toxicity endpoints						
Acute toxicity	x	x	x	x	x	x
Repeated dose toxicity	x	x	x	x	x	x
Gene mutation <i>in vitro</i>	x	x	x	x	x	x
Chromosomal aberration <i>in vitro</i>	x	x	RA	x	x	x
Gene mutation <i>in vivo</i>	RA	RA	x	x	RA	x
Micronucleus assay <i>in vivo</i>	x	x	x	x	x	x
Carcinogenicity	RA	x	x	x	RA	RA
Reproductive/Developmental toxicity	RA	RA	RA	x	RA	RA
Environmental toxicity endpoints						
Acute toxicity						
Fish	x	RA	x	x	x	x
Aquatic Invertebrates	x	x	x	x	x	x
Aquatic Plants	x	RA	x	x	x	x
Chronic toxicity						
Fish	ND	ND	ND	ND	ND	ND

Aquatic Invertebrates	x	RA	x	x	x	x
Aquatic Plants	x	RA	x	x	x	x
Toxicity to Microorganisms	x	x	x	x	x	x

x: Reliable data available

RA: Read across

ND: No data available

Physico-chemical properties

All category member substances are liquids at standard temperature and pressure except for 3,4-dimethylaniline. The melting points are in the range of $<-15\text{ }^{\circ}\text{C} - 15.5\text{ }^{\circ}\text{C}$ for 2,3-, 2,4-, 2,5-, 2,6- and 3,5-dimethylaniline, although that of 3,4-dimethylaniline is $51\text{ }^{\circ}\text{C}$. The boiling points are in the range of $214\text{-}228\text{ }^{\circ}\text{C}$, and the vapour pressures are in the range of $3.72 - 63.2\text{ Pa}$ at $20/25\text{ }^{\circ}\text{C}$. The water solubility values are in the range of $3.8\text{-}6.98\text{ g/L}$ at $22/25\text{ }^{\circ}\text{C}$, and the partition coefficients between octanol and water ($\log K_{ow}$) are in the range of $1.68\text{-}1.91$. Dissociation constants in the water are in the range of $4.02\text{-}5.17$ at $20/25\text{ }^{\circ}\text{C}$, which means the member substances exist predominantly in un-ionized form in environmental water.

Human Health

2,6-Dimethylaniline is readily absorbed through the oral route and subsequently is distributed through the body in rats. After a single oral dose of [^{14}C]-2,6-dimethylaniline, most of the radiolabel was eliminated in the urine and small amounts of the radiolabel were recovered in tissues. Rats receiving 10 daily doses had higher levels of radioactivity in the blood and other tissues, and the greatest concentrations of radioactivity were found in the red blood cells and liver. More rapid excretion of radioactivity was observed after 10 daily doses compared to a single dose. The slower clearance at later time points (biphasic elimination) were observed after i.p. administration of 2,6- and 3,5-dimethylaniline indicating metabolites bound to tissue components. 2,6-Dimethylaniline was excreted in the urine of rats as parent compound and metabolites (4-hydroxy-2,6-dimethylaniline (4-HDMA), and a trace level of N-2,6-trimethylaniline). 2,4-Dimethylaniline was excreted in the urine of rats mainly as parent compound, N-acetyl-4-amino-3-methylbenzoic acid, and a trace level of N-2,4-trimethylaniline. 2,6-Dimethylaniline was excreted in the urine of dogs as parent compound and metabolites, (4-HDMA and 2-amino-3-methylbenzoic acid). N-2,3-trimethylaniline, 2,6-dimethylnitrosobenzene and the glycine conjugate of 2-amino-3-methylbenzoic acid were also detected after 2,6-dimethylaniline treatment. 2,4-Dimethylaniline was excreted in the urine of dogs as parent compound, 6-hydroxy-2,4-dimethylaniline, 4-amino-3-methylbenzoic acid, and trace level of N-2,4-trimethylaniline. Compared to 2,6-dimethylaniline the species difference in metabolism is greater between rats and dogs for 2,4-dimethylaniline. 2,5-Dimethylaniline was excreted in the urine of rats mainly as parent compound and 4-hydroxy-2,5-dimethylaniline, and trace level of 2-amino-4-methylbenzoic acid and 3-amino-4-methylbenzoic acid. The metabolism of N-(2,6-dimethylphenyl)hydroxylamine and 4-HDMA were found as metabolites by using human liver microsomes and recombinant human P450 enzymes (CYP2A6 and CYP2E1). In addition the nonenzymatic oxidation of 4-HDMA to 3,5-dimethyl-4-iminoquinone was reported.

Based on an acute toxicity study conducted according to OECD TG 423 under GLP using female rats where all animals survived at 300 mg/kg bw while all animals died at 2000 mg/kg bw , the oral LD_{50} for 2,6-dimethylaniline was between 300 and 2000 mg/kg bw . At 300 mg/kg bw clinical signs included a slight decrease in motor activity and ptosis. At 2000 mg/kg bw , clinical signs included a severe decrease in locomotor activity, adoption of a prone position, abnormal gait, hypotonia and deep respiration. In other oral studies by NTP, the LD_{50} s for 2,6-dimethylaniline were 1160 or 1270 mg/kg bw for females and between 620 and 1250 mg/kg bw or 1310 mg/kg bw/day for male rats. In another experiment for the single oral dose toxicity of dimethylanilines in rats and mice, the following LD_{50} values (in mg/kg bw) were determined: 2,3-dimethylaniline: rats 930 , mice 1070 ; 2,4-dimethylaniline: rats 470 , mice 250 ; 2,5-dimethylaniline, rats 1300 , mice 840 ; 2,6-dimethylaniline, rats 1230 , mice 710 ; 3,4-dimethylaniline, rats 810 , mice 710 ; 3,5-dimethylaniline, rats 710 , mice 420 . No reliable information is available for the dermal route, and no information is available for the inhalation route regarding acute toxicity. For the category, LD_{50} s between $450\text{-}1310\text{ mg/kg bw}$ were observed in rats and $250\text{-}1070\text{ mg/kg bw}$ in mice suggesting all substance cause acute toxicity via the oral route.

2,4-Dimethylaniline has a weak irritant effect on the skin and irritant effects on the eyes of rabbits. 2,6-Dimethylaniline has an irritant effect on the skin and a weak irritant effect on the eyes of rabbits. 3,5-Dimethylaniline has no irritant effect on the skin and is a weak irritant in contact with the eyes of rabbits. Category members were considered to be weekly irritant to the skin and eyes of rabbits.

No information was available concerning skin sensitisation in animals for any of the dimethylaniline isomers.

Information on the sub-acute repeated dose toxicity in rats was available from 28-d studies following OECD TG 407 for 2,3-, 2,4-, 2,5-, 3,4- and 3,5- dimethylanilines and a screening study following OECD TG 422 for 2,6-dimethylaniline. Other reliable studies included a NTP study (2-week, 13-week and 2-year) for 2,6-dimethylaniline, a non-GLP 28-day study for 2,4-, 2,5-, and 2,6-dimethylanilines, a 6-month feeding study for 2,4- and 2,6-dimethylanilins, and a 5 to 20-day study for 2,4- and 2,6-dimethylanilines in rats. The toxic effects of dimethylanilines in these studies were closely comparable.

The most general target for dimethylanilines was the blood. Increased methemoglobin resulted in hemolysis, reduction of hemoglobin and erythrocyte concentration and cyanosis at sufficiently high doses of ≥ 50 mg/kg bw/day for 2,6-, 2,3-, 2,5-, 3,4- and 3,5-dimethylanilines while hematological changes were observed at 10 mg/kg bw/day for 2,4-dimethylaniline (OECD TG 422 and 407). Hemosiderin deposition in the liver, kidney and spleen were similarly observed as a secondary effect to the loss of functional erythrocytes. Especially, hemosiderin deposition in the spleen was observed for 2,3-dimethylanin at 12 mg/kg bw/day (lowest dose) in females (OECD TG 422). Extramedullary haematopoiesis, increased size of erythrocytes and swelling of the spleen occurred as compensatory actions. Additionally, the hemolysis led to changes in other blood parameters like WBC count, or increase of reticulocytes (OECD TG 422 and 407). In the NTP study for 2,6-dimethylaniline, toxic effects occurred in the hematopoietic systems at ≥ 40 mg/kg bw/day (13-week) and ≥ 310 mg/kg (2-week); however, male rats are more sensitive than female rats for effects on the hematopoietic systems. In the NTP study (2-year), body weight gains and survival were decreased at the high dose, but no indicative anemia was observed in rats fed 2,6-dimethylaniline.

Also, high urine volumes along with a decrease of the specific density, reduced pH and reduction of urinary levels of protein and ketone bodies generally occurred in treated with any category substances, generally at high doses (TG 422 and 407).

Effects on the kidney such as papillary necrosis, dilatation of renal tubules, and/or hyaline droplets were observed at 10 mg/kg bw/day in animals treated with 2,4-dimethylaniline, at 50 or 60 mg/kg bw/day in animals treated with 2,3-, 2,5- or 3,4-dimethylanilines, and at 250 or 360 mg/kg bw/day (highest dose) in animals treated with 2,6- or 3,5-dimethylanilines (OECD TG 422 and 407). 2,4-Dimethylaniline also showed stronger renal effects comparing to 2,6-dimethylaniline dosing (6-month feeding study).

There were increased relative and/or absolute weights of the liver (enlarged liver) or hypertrophy at 10 mg/kg bw/day in animal treated with 2,4- dimethylaniline, at 50 or 60 mg/kg bw/day in animals treated with 2,3-, 2,6-, 3,4- and 3,5-dimethylanilines, and at 300 mg/kg bw/day (highest dose) in animals treated with 2,5-dimethylaniline (OECD TG 422 and 407). In the NTP study for 2,6-dimethylaniline, toxic effects occurred in the hepatic systems (13-week). 2,4-Dimethylaniline showed stronger hepatic effects comparing to 2,5- and 2,6-dimethylanilines dosing (non-GLP 28-day study). This finding was also comparable with the 6-month feeding study, and more severe liver enlargement was observed in 2,4-dimethylaniline treatment (6-month feeding study). Similarly, 2,4-dimethylaniline showed hepatotoxicity after 5-20 days dosing at 117 mg/kg bw/day (25% of the estimated oral LD₅₀) while no hepatotoxicity was observed at 157.5 mg/kg bw/day (25% of the estimated oral LD₅₀) after 20 days dosing of 2,6-dimethylaniline (5 to 20-day study).

Increased absolute or relative weights of the thyroid were observed at 250 or 360 mg/kg bw/day (highest dose) in animals treated with 2,6- or 3,5-dimethylanilines (OECD TG 422 and 407).

Hyperkeratosis of the forestomach was observed in rats treated with 2,4-, 2,5- or 2,6-dimethylanilines (non GLP 28-day study) and 2,4-dimethylanilines (6-month feeding study). 2,5-Dimethylaniline was the only isomer for which hyperkeratosis of the forestomach were reported in the 28-day studies (OECD TG 407). However, these effects may be due to local irritating effects of the chemicals.

The lowest NOAEL of 2 mg/kg bw/day was derived in 2,4-dimethylaniline due to effects on the blood, liver and kidneys at 10 mg/kg bw/day. The changes were usually fully recovered within a 2 week period except for the hemosiderin deposition and in some cases, the kidney necrosis. Nevertheless both of these effects are reduced in their severity during recovery (OECD TG 422 and 407).

The LOAEL of 2 mg/kg bw/day for 2,6-dimethylaniline in dogs was derived from a non-GLP 28-day study, in which dogs were dosed 2,4-, 2,5- or 2,6-dimethylanilines at 0, 2, 10 or 50 mg/kg bw/day, and fatty degeneration of the liver was observed at 2 mg/kg bw/day in the 2,6-dimethylaniline treatment. In contrast to rats, 2,6-dimethylaniline showed stronger toxicity comparing to 2,4- and 2,5-dimethylaniline in dogs.

Based on these effects, the NOAEL of repeated oral dose ranged between 2-12 mg/kg bw/day and the LOAEL of dimethylaniline category for repeated oral dose ranged between 10-60 mg/kg bw/day in rats. Target organ systems were the blood, spleen, liver and kidneys.

In bacterial reverse mutation assays with multiple strain of *S. typhimurium* and *E. coli* (OECD TG 471), 2,3-dimethylaniline and 2,4-dimethylaniline were found to be mutagenic in TA100 and 2,6-dimethylaniline in TA100 and TA1535, both only with activation by S9 mix. On the other hand, one study by NTP showed negative results on 2,6-dimethylaniline with or without S9 mix. One bacterial reverse mutation study conducted for all six isomers showed positive results on 2,3-, 2,4-, 2,5-, and 3,4-dimethylanilines with rat or hamster S9 mix while 2,6- and 3,5-dimethylanilines were judged weakly mutagenic with rat or hamster S9 mix. In *in vitro* chromosome aberration studies (TG 473), 2,3-dimethylaniline, 2,4-dimethylaniline and 3,5-dimethylaniline showed chromosomal aberrations while 3,4-dimethylaniline did not with or without S9 mix. 2,6-Dimethylaniline induced chromosomal aberrations (TG 473) and sister chromatid exchanges in mammalian cells *in vitro* with and without S9 mix. In addition, a BALB/c-3T3 cell transformation assay showed a positive response by 2,6-dimethylaniline.

In *in vivo* gene mutation assays with MutaTM mice (nasal tissue, bone marrow and liver), 2,5- and 2,6-dimethylanilines increased mutation frequency of lacZ and cII genes in the nasal tissue, and 2,5-dimethylaniline also increased mutation frequency of lacZ gene in the bone marrow. On the other hand, 3,5-dimethylaniline showed a negative result in the *in vivo* gene mutation assay. In *in vivo* micronucleus assays, all six isomers of dimethylanilines was non-clastogenic in the bone marrow and 2,5-, 2,6- or 3,5-dimethylaniline in the peripheral blood in mice. 2,6-Dimethylaniline did not affect DNA repair in a DNA repair host-mediated assay or an unscheduled DNA synthesis assay *in vivo*. In SCG (Comet) assays *in vivo*, all six isomers of dimethylanilines induced DNA damage in the bone marrow (only for 3,4- and 3,5-dimethylanilines), lung, kidney or liver in mice.

In summary, the results from the available studies suggested that members of dimethylaniline category are mutagenic *in vitro* and *in vivo*.

In a 2-year carcinogenicity study, male and female rats were fed diets containing 0, 300, 1000 or 3000 ppm 2,6-dimethylaniline from 5 weeks of age and mated at 16 weeks of age. Females continued to receive dosed or control diets during pregnancy and lactation. The offspring were weaned at 21 days of age and groups of males and females (56/sex/group) were fed the same study diets as their parents. There were significant increases in the incidences of adenocarcinomas or carcinomas of the nasal cavity (28/56 high dose males, 24/56 high dose females and 1/56 mid dose females) and of the papillary adenomas (10/56 high dose males, 2/56 mid dose males, and 6/56 high dose females). A rhabdomyosarcoma, a rare tumour of the nasal cavity, was observed in dosed rats of each sex. In addition, the increased incidences of subcutaneous fibromas and fibrosarcomas in male and female rats and the increased incidence of neoplastic nodules of the liver in female rats may have been related to the administration of 2,6-dimethylaniline. In a two-stage nasal carcinogenesis model using male rats, the tumour-promoting activity of 2,6-dimethylaniline was evidenced. Another carcinogenicity study demonstrated that 2,4-dimethylaniline induced pulmonary tumours in female mice, and 2,5-dimethylaniline led to an increase in subcutaneous fibromas and fibrosarcoma in male rats, and in vascular tumours in male mice. It can be predicted that all members of the category may be carcinogenic due to their *in vivo* genotoxic activity.

Information on reproductive toxicity in animals is only available for 2,6-dimethylaniline. In the combined repeated dose toxicity study with reproduction/developmental toxicity screening test [OECD TG 422] described above, rats were administered 2,6-dimethylaniline by gavage at 0 (vehicle), 2, 10, 50 or 250 mg/kg bw/day. The males exhibited no alterations in reproductive parameters. At 250 mg/kg bw/day, the number of implantation sites in females was significantly lower than controls. The numbers of corpora lutea decreased with increasing dose, but the changes were not significant. There was a decrease in the numbers of pups born as the dose increased, however the decrease was not significant at any dose. There was a significant decrease in the total number of live pups on day 0 of lactation at 250 mg/kg bw/day. The NOAEL for reproductive performance of parental animals in this study was 250 mg/kg bw/day for males and 50 mg/kg bw/day for females based on a decrease in the number of implantation. The NOAEL for offspring was 50 mg/kg bw/day. However the effects were only observed in the presence of severe maternal toxicity (e.g. mortality). In the above described repeated dose toxicity studies, reproductive organ were not affected (organ weight and histopathological examinations) in males and females up to highest dose tested. A read-across approach on reproductive/developmental toxicity can be used for the other dimethylanilines.

Category dimethylaniline may have properties that are hazardous for human health (acute toxicity, skin and eye irritation, repeated-dose toxicity, genotoxicity and carcinogenicity). Adequate screening data are available to characterize the human health hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Environment

All category members are not expected to undergo hydrolysis in the environment due to the lack of hydrolysable functional groups. A hydrolysis test [OECD TG 111] for 2,6-dimethylaniline showed no hydrolysis at pH4, pH7

and pH9 at 50 °C for 5 days.

In the atmosphere, indirect photo-oxidation for 2,3-dimethylaniline, 2,4-dimethylaniline, 2,5-dimethylaniline, 2,6-dimethylaniline, 3,4-dimethylaniline and 3,5-dimethylaniline by reaction with hydroxyl radicals are predicted to occur with a half-life of 0.053, 0.066, 0.053, 0.066, 0.053 and 0.053 days, respectively.

Ready biodegradation tests [OECD TG 301C] for 2,3-dimethylaniline, 2,5-dimethylaniline, 2,6-dimethylaniline and 3,5-dimethylaniline resulted in 3, 1, 0 and 3 % biodegradation after 28 days, respectively. Inherent biodegradation test [OECD TG 302C] for 2,4-dimethylaniline and 3,4-dimethylaniline resulted in 0 and 7 % biodegradation after two weeks, respectively. All category member substances are not readily biodegradable under aerobic conditions.

A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that 2,3-dimethylaniline will distribute mainly to the soil (77.9 %) and water (21.7%) compartments with minor distribution to the sediments compartment (0.24%) and negligible amount in the air compartment (0.07%). If released only to the water compartment, 2,3-dimethylaniline stays in the water compartment (98.9%) with negligible amounts in other compartments. A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments for other category member substances showed the same distribution as 2,3-dimethylaniline.

Henry's law constant values calculated with vapour pressure divided by water solubility are 0.18-1.1 Pa.m³/mole at 20-25°C, which suggests that volatilization of category member substances from water phase is not expected to be high. A log K_{oc} of 1.8-2.0 was estimated for category member substances based on the log K_{ow} and this figure indicates a low sorption to soil and sediment. However, aromatic amines have high affinity for soil organic matter due to the high reactivity of the aromatic amine group. Therefore, dimethylamines have a low mobility in soils.

Bioaccumulation potential for 2,3-dimethylaniline and 3,5-dimethylaniline are predicted to be low based on a BCF value of 7.6 and 7.5 estimated with BCFWIN (version 3.01), respectively. 2,4-Dimethylaniline, 2,5-dimethylaniline, 2,6-dimethylaniline and 3,4-dimethylaniline are not expected to bioaccumulate in the aquatic environment based on a measured bioconcentration factor of <10, <3.8, 2.4 and <10, respectively. These results show a low potential for bioaccumulation of dimethylanilines for aquatic organisms.

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

2,3-Dimethylaniline

Fish [<i>Oryzias latipes</i>]:	96 h LC ₅₀ > 94 mg/L (measured) [OECD TG 203, semi-static]
Invertebrate [<i>Daphnia magna</i>]:	48 h EC ₅₀ = 8.9 mg/L (measured) [OECD TG 202, static]
Algae [<i>Pseudokirchneriella subcapitata</i>]:	72 h ErC ₅₀ = 41.4 mg/L (growth rate method) (measured) [OECD TG 201, static]

2,4-Dimethylaniline

Fish:	No reliable studies were identified. The predicted 96-hour LC ₅₀ , based on read across from 3,5-dimethylaniline = 33.9 mg/L; The predicted 96-hour LC ₅₀ , based on ECOSAR (v 1.11) = 37.2 mg/L
Invertebrate [<i>Daphnia magna</i>]:	48 h EC ₅₀ = 9.9 mg/L [DIN38412, static]
Algae:	No reliable studies were identified. The predicted 72-hour EC ₅₀ , based on read across from 3,4-dimethylaniline = 8.59 mg/L; The predicted 96-hour EC ₅₀ , based on ECOSAR (v 1.11) = 37.0mg/L

2,5-Dimethylaniline

Fish [<i>Oryzias latipes</i>]:	96 h LC ₅₀ > 110 mg/L (measured) [Other Guideline; Chemical Substances Control Law, Japan, semi-static]
Invertebrate [<i>Daphnia magna</i>]:	48 h EC ₅₀ = 18 mg/L (measured) [Other Guideline; Chemical Substances Control Law, Japan, static]
Algae [<i>Pseudokirchneriella subcapitata</i>]:	72 h ErC ₅₀ = 30 mg/L (growth rate method) (measured) [Other Guideline; Chemical Substances Control Law, static]

2,6-Dimethylaniline

Fish [<i>Oryzias latipes</i>]:	96 h LC ₅₀ > 97.9 mg/L (measured) [OECD TG 203, semi-static, limit test]
Invertebrate [<i>Daphnia magna</i>]:	48 h EC ₅₀ = 20 mg/L (measured) [OECD TG 202, static]
Algae [<i>Pseudokirchneriella subcapitata</i>]:	72 h ErC ₅₀ > 100 mg/L (growth rate method) (nominal) [OECD TG 201, static]

3,4-Dimethylaniline

Fish [<i>Oryzias latipes</i>]:	96 h LC ₅₀ > 97.9 mg/L (measured) [Other Guideline; Chemical Substances Control Law, Japan, semi-static]
Invertebrate [<i>Daphnia magna</i>]:	48 h EC ₅₀ = 1.09 mg/L (measured) [Other Guideline; Chemical Substances Control Law, Japan, static]
Algae [<i>Pseudokirchneriella subcapitata</i>]:	72 h ErC ₅₀ = 8.59 mg/L (growth rate method) (measured) [Other Guideline; Chemical Substances Control Law, static]

3,5-Dimethylaniline

Fish [<i>Oryzias latipes</i>]:	96 h LC ₅₀ = 33.9 mg/L (measured) [OECD TG 203, semi-static]
Invertebrate [<i>Daphnia magna</i>]:	48 h EC ₅₀ = 2.2 mg/L (nominal) [OECD TG 202, static]
Algae [<i>Pseudokirchneriella subcapitata</i>]:	72 h ErC ₅₀ = 29.1 mg/L (growth rate method) (nominal) [OECD TG 201, static]

The following chronic toxicity test results have been determined:

2,3-Dimethylaniline

Invertebrate [<i>Daphnia magna</i>]:	21 d NOEC = 0.1 mg/L (measured) [Provisional procedure proposed by Federal Environmental Agency (Umweltbundesamt), semi-static]
Algae [<i>Pseudokirchneriella subcapitata</i>]:	72 h NOEC = 4.32 mg/L (growth rate method) (measured) [OECD TG 201, static]

2,4-Dimethylaniline

Invertebrate:	No reliable studies were identified. The predicted 21 d NOEC, based on read across from 3,4-dimethylaniline = 0.0095 mg/L
Algae:	No reliable studies were identified. The predicted 72 h NOEC, based on read across from 2,5-dimethylaniline = 2.03 mg/L

2,5-Dimethylaniline

Invertebrate [<i>Daphnia magna</i>]:	21 d NOEC = 0.096 mg/L (measured) [OECD TG 211, semi-static]
Algae [<i>Pseudokirchneriella subcapitata</i>]:	72 h NOEC = 2.0 mg/L (growth rate method) (measured) [OECD TG 201, static]

2,6-Dimethylaniline

Invertebrate [<i>Daphnia magna</i>]:	21 d NOEC = 2.23 mg/L (measured) [OECD TG 211, semi-static]
Algae [<i>Pseudokirchneriella subcapitata</i>]:	72 h NOEC = 32 mg/L (growth rate method) (nominal) [OECD TG 201, static]

3,4-Dimethylaniline

Invertebrate [<i>Daphnia magna</i>]:	21 d NOEC = 0.0095 mg/L (measured) [OECD TG 211, semi-static]
Algae [<i>Pseudokirchneriella subcapitata</i>]:	72 h NOEC = 2.94 mg/L (growth rate method) (measured) [Other Guideline; Chemical Substances Control Law, Japan, static]

3,5-Dimethylaniline

Invertebrate [*Daphnia magna*]: 21 d NOEC = 0.03 mg/L (nominal) [OECD TG 211, semi-static]

Algae [*Pseudokirchneriella subcapitata*]: 72 h NOEC = 5.8 mg/L (growth rate method) (nominal) [OECD TG 201, static]

Acute aquatic toxicity data were available for category members except fish and algae tests on 2,4-dimethylaniline. For fish, LC₅₀ values were generally greater than 100 mg/L except 3,5-dimethylaniline (33.9 mg/L). For daphnids, EC₅₀ values were between 1.09 and 25 mg/L. For algae, EC₅₀ values were between 8.59 and >100 mg/L.

No chronic toxicity data are available on fish. Chronic aquatic toxicity data on daphnids and algae were available for category member substances except 2,4-dimethylaniline. For daphnids, NOEC values were generally less than 0.1 mg/L except 2,6-dimethylaniline (2.23 mg/L). For algae, NOEC values were generally less than 10 mg/L except 2,6-dimethylaniline (32 mg/L).

Chemicals in the category dimethylaniline possess properties indicating a hazard for the environment (acute aquatic toxicity values between 1 and 100 mg/L; chronic aquatic toxicity less than 1.0 mg/L). Chemicals in the category are not readily biodegradable and have 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

2,3-Dimethylaniline

Volume of import into Japan was 30 – 40 tonnes/year around 2005.

2,4-Dimethylaniline

Total volume of production and import in Japan was 512 tonnes in fiscal year of 2009 according to the notification based on the Chemical Substances Control Law in Japan. Production and/or import volume on 2,4-dimethylaniline in USA was 500,000 pounds – 1 million pounds (226.8 tonnes – 453.6 tonnes) in 2006 according to IUR information by US-EPA.

2,5-Dimethylaniline

No detailed information is obtained on the production and import volume in Japan. Production and/or import volume on 2,5-dimethylaniline in USA was less than 500,000 pounds (226.8 tonnes) in 2006 according to IUR information by US EPA.

2,6-Dimethylaniline

According to the notification based on the Chemical Substances Control Law in Japan, total volume of production and import on this chemical in fiscal year 2009 was less than 100 tonnes. Production and/or import volume of 2,6-dimethylaniline in USA was less than 500,000 pounds (226.8 tonnes) in 2006 according to IUR information by US-EPA.

3,4- Dimethylaniline, 3,5-Dimethylaniline

According to the notification based on the Chemical Substances Control Law in Japan, total volume of production and import on 3,5-dimethylaniline in fiscal year 2009 was less than 100 tonnes.

According to the results of the environmental survey and wildlife monitoring and PRTR data in Japan, the release of dimethylanilines to the environment from its manufacturing and formulation plants is minimal.

According to the inquiry survey, employees in the processing site of 2,4-dimethylaniline in a Japanese company wear gloves, protective goggles and other proper protect equipments. Therefore, occupational exposure is thought to be minimal.

All category member substances are used mainly as intermediates for the production of dyes, pigments, pharmaceuticals and agrochemicals. Some are used as intermediate for photographic chemicals, antioxidants, synthetic resins, fragrances and riboflavin. Therefore, consumer exposure is not expected.