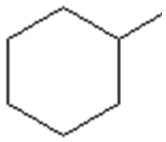
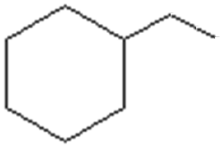
SIDS INITIAL ASSESSMENT PROFILE

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

SUMMARY CONCLUSIONS OF THE SIAR

Category rationale

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

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

1. Similarity of molecular structure and functional group

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

2. Similarity of physical-chemical properties

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

3. Similarity in health effects

   Toxicokinetic properties are similar.

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

   Both chemicals show negative results of genotoxicity.

4. Similarity of environmental fate and distribution

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

5. Similarity of eco-toxicity

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

Analogue rationale

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

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

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

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

X=data available

Physical-chemical properties

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

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

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

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

Human Health

Toxicokinetics

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

Acute toxicity

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

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

Irritation

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

Sensitization

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

Repeated dose toxicity

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

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

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

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

Genotoxicity

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

Carcinogenicity

No guideline study for carcinogenicity was conducted.

Reproductive and developmental toxicity

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

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

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

Environment

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

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

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

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

Biodegradation

Methylcyclohexane

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

Ethylcyclohexane

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

Bioaccumulation

Methylcyclohexane

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

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

Ethylcyclohexane

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

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

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

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

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

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

Exposure

Production volume

Methylcyclohexane

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

Ethylcyclohexane

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

Production methods

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

Ethylcyclohexane is manufactured by hydrogenation of ethylbenzene and purified by distillation

Use pattern

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

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

Occupational exposure

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

Consumer exposure

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

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