SIDS Initial Assessment Report

For

CoCAM1

**Paris, France, 10-12 October, 2011**

|  |  |
| --- | --- |
| **1. Chemical Name:** | 1,1,1-Tris(hydroxymethyl)ethane |
| **2. CAS Number:** | 77-85-0 |
| **3. Sponsor Country:** | Japan  Contact Point:  Mr. Hiroshi Kamitsuji  Deputy Director  OECD Division  Ministry of Foreign Affairs, Japan |
| **4. Shared Partnership with:** |  |
| **5. Roles/Responsibilities of the Partners:** |  |
| * Name of industry sponsor /consortium |  |
| * Process used |  |
| **6. Sponsorship History** |  |
| • How was the chemical or category brought into the OECD HPV Chemicals Programme? | 1,1,1-Tris(hydroxymethyl)ethane is sponsored by Japan and is submitted for first discussion at CoCAM1  Literature search was conducted by on-line database such as CHRIP, TOXNET and RTECS. |
| **7. Review Process Prior to the SIAM:** | Japanese government peer-reviewed the documents and audited selected studies. |
| **8. Quality check process:** | Japanese government peer-review committee performed spot checks on randomly selected endpoints and compared original studies with data in the SIDS Dossier. |
| **9. Date of Submission:** | 6, July 2011 |
| **10. Date of last Update:** | 30, November 2011 |
| **11. Comments:** | The summaries and evaluations contained in this assessment report may be based on unpublished proprietary data submitted for the purpose of the OECD assessment. In many cases, national/regional regulatory authorities will not accept a regulatory submission based on the summaries and evaluation of unpublished proprietary data contained in this [these] assessment report[s] unless they have received the data on which the summaries and evaluation are based, either from:   * the owner of the data; or * a second party that has obtained permission from the owner of the data for this purpose; or alternatively * the applicant has received permission from the data owner that the summary and evaluation contained in this [these] assessment report[s] may be used in lieu of the data; or * following expiry of any period of exclusive use, mandatory compensation, where required, has been offered unless the period of protection for the proprietary data concerned has expired.   Applicants who wish to use data in this assessment report should ensure that the use is consistent with the legal requirements in the country/region in which it is proposed to use the data. |

**SIDS INITIAL ASSESSMENT PROFILE**

|  |  |
| --- | --- |
| **CAS No.** | 77-85-0 |
| **Chemical Name** | 1,1,1-Tris(hydroxymethyl)ethane |
| **Structural Formula** |  |
| **SUMMARY CONCLUSIONS OF THE SIAR**  **Physical-chemical properties**  1,1,1-Tris(hydroxymethyl)ethane is a white powder with no odour at standard temperature. Melting point and boiling point are 204 °C and 286.7 °C respectively. Vapour pressure is 1.82 x 10-5 Pa at 25 °C, extrapolated from the experimental value. Partition coefficient between octanol and water (log Kow) is -0.95 and water solubility is more than 300 g/L at 20 °C.  **Human Health**  No specific study on toxicokinetics, metabolism and distribution has been identified. The slight liver toxicity seen in rats given 1000 mg/kg bw/day (in the combined repeated dose and reproductive/developmental toxicity screening test) indicates that 1,1,1-tris-(hydroxymethyl)ethane is absorbed through the gastrointestinal tract to some degree.  In an acute oral study conducted in accordance with OECD TG 401, no deaths or signs of toxicity were observed at 2,000 mg/kg bw in rats. Therefore, the oral LD50 value of 1,1,1-tris(hydroxymethyl)ethane was concluded to be > 2,000 mg/kg bw.  Data on acute dermal toxicity are not available. The limited information on dermal toxicity (LD50 > 500 mg/kg bw) in rat of the structurally similar analogue of tris(hydroxymethyl)propane (CAS 77-99-6 assessed at SIAM) suggested to be of low acute dermal toxicity.  Data on inhalation toxicity are not available. The limited information on inhalation studies in rats, mice, rabbits and guinea pigs of the structurally similar analogue tris(hydroxymethyl)propane suggested that LC50 is higher than 0.29 mg/L/4h.  No reliable studies are available on skin irritation or sensitisation. The limited information on skin irritation in rabbits of the structurally similar analogue of tris(hydroxymethyl)propane suggests that there is no irritation.  There is one reliable study for repeated dose toxicity of 1,1,1-tris(hydroxymethyl)ethane. This study was conducted in accordance with OECD TG 422 except for the limited haematological and clinical chemistry examination in males only. The substance was administered via gavage to 13 rats/sex/dose at 0, 100, 300 and 1,000 mg/kg bw/day for 42 days (staring from 14 days before mating) in males and the 14 days pre-mating, mating and gestation periods and the days until day 3 of lactation in females (a total of 49 days). No treatment-related effects were observed in clinical signs, food consumption, hematology (examined only in males), organ weight and the histopathological appearance of tissues from the major organs including the liver. In clinical chemistry (examined only in males), significant but slight increases in GOT and GPT, reflecting an effect on liver function, and a slight decrease in glucose were observed at 1,000 mg/kg bw/day. Based on no histopathological changes in the liver, these changes in clinical chemistry were not considered to be toxicologically important. A significant but slight decrease in body weight gain was observed in pregnant females at 1,000 mg/kg bw/day. However this change was observed only in the late period of pregnancy. Based on the above findings, the NOAEL was considered to be 1000 mg/kg bw/day in both sexes.  In an Ames test with multiple strains of *Salmonella typhimurium* and *Escherichia coli* [OECD TG 471 and 472], 1,1,1-tris(hydroxymethyl)ethane was negative both with and without metabolic activation. An *in vitro* chromosome aberration test using cultured Chinese hamster lung (CHL/IU) cells [OECD TG 473] was negative both with and without metabolic activation. Based on these results, 1,1,1-tris(hydroxymethyl)ethane is considered non genotoxic *in vitro*.  No data are available for the carcinogenicity of 1,1,1-tris(hydroxymethyl)ethane.  The reproductive toxicity of the 1,1,1-tris(hydroxymethyl)ethane has been investigated in the above-mentioned combined repeated oral gavage dose toxicity study with the reproductive/developmental toxicity screening test in rats (OECD TG 422). No adverse effects on reproductive parameters (copulation, fertility, gestation and delivery index, etc.) and on reproductive organ (weight or histopathological changes) were observed, and therefore the oral NOAEL for reproductive toxicity was the maximum tested dose of 1,000 mg/kg bw/day. For developmental effects, there were no treatment-related changes in the number of live pups born, viability index on postnatal day 4, body weight on postnatal day 0 and day 4, and number of external anomalies. The NOAEL for developmental toxicity was considered to be 1,000 mg/kg bw/day (the highest dose).  **1,1,1-tris(hydroxymethyl)ethane 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 Cooperative Chemicals Assessment Programme.**  **Environment**  In the atmosphere, 1,1,1-tris(hydroxymethyl)ethane is expected to be degraded by hydroxyl radicals. A calculated half-life time of 0.85 days is obtained by AOPWIN (version 1.92a) for the indirect photo-oxidation by reaction with hydroxyl radicals in air.  1,1,1-Tris(hydroxymethyl)ethane is not hydrolysed due to the lack of hydrolysable functional groups. A hydrolysis test according to OECD test guideline 111 showed no hydrolysis of 1,1,1-tris(hydroxymethyl)ethane in water at pH 4, 7 and 9 in 50 °C after five days.  An OECD test guideline 301C test was conducted with 1,1,1-tris(hydroxymethyl)ethane 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 3-6 % degradation by BOD. According to the result, 1,1,1-tris(hydroxymethyl)ethane is considered to be not readily biodegradable.  No information was available on the bio-concentration on 1,1,1-tris(hydroxymethyl)ethane. Using an octanol-water partition coefficient (log Kow) of -0.95, a bio-concentration factor of 3.2 was calculated with BCFBAF (version 3.00). This chemical is not expected to bioaccumulate.  Fugacity level III calculations show that 1,1,1-tris(hydroxymethyl)ethane is mainly distributed to the soil compartment (61.0 %) and water compartment (38.7 %) if equally and continuously released to the air, soil and water. A Henry’s law constant of 1.13×10-3 Pa.m3/mole at 25 °C suggests that 1,1,1-tris(hydroxymethyl)ethane is non volatile from water. A soil adsorption coefficient of Log Koc = -0.4 indicates 1,1,1-tris(hydroxymethyl)ethane has low adsorption to soil and sediment.  The following acute and prolonged toxicity test results have been determined for aquatic species;  Fish [*Oryzias latipes,* OECD-TG 203]: 96 h LC50 > 100 mg/L (nominal)  Fish [*Oryzias latipes,* OECD-TG 204]: 14 d LC50 > 99.8 mg/L (nominal)  14 d NOEC > 99.8 mg/L (nominal)  Daphnid [*Daphnia magna,* OECD-TG 202]: 48 h EC50 > 1000 mg/L (nominal)  Algae [*Pseudokirchneriella subcapitata,* OECD-TG 201]:  72 h ErC50 > 1000 mg/L (nominal, growth rate)  72 h EbC50 > 1000 mg/L (nominal, area under  growth curve)  The following chronic toxicity test results have been determined for aquatic species:  Daphnid [*Daphnia magna*, OECD-TG 211]: 21 d NOEC > 88.5 mg/L (measured)  Algae [*Pseudokirchneriella subcapitata* OECD-TG 201]:  72 h NOErC and 72 h NOEbC > 1000 mg/L (nominal)  **1,1,1-Tris(hydroxymethyl)ethane does not present a hazard to the environment due to its low hazard profile. Although this chemical is considered not to be readily biodegradable, it has a low bioaccumulation potential. Adequate screening-level data are available to characterize the environmental hazard for the purposes of the Cooperative Chemicals Assessment Programme.**  **Exposure**  Currently, no production of 1,1,1-tris(hydroxymethyl)ethane is reported in Japan (sponsor country) and import volume in Japan is between 100 and 1,000 tonnes/year. Production and/or import volume of 1,1,1-tris(hydroxymethyl)ethane in the United States was between 1 million and 10 million pounds (454,000 - 4,540,000 tonnes) during 2006 according to Inventory Updated Reporting. Production volume in the world is not available.  1,1,1-Tris(hydroxymethyl)ethane is produced by aldol condensation of propionaldehyde with formaldehyde, followed by reaction of the intermediate 2,2-bis(hydroxymethyl)propanal with excess formaldehyde in the presence of sodium hydroxide or lime as basic component. 1,1,1-Tris(hydroxymethyl)ethane is used as a conditioning agent, manufacture of varnishes, alkyd and polyester resins, synthetic drying oils. This substance is also used as a coating agent for titanium dioxide pigment. According to Inventory Updated Reporting, 1,1,1-tris(hydroxymethyl)ethane is included in consumer products such as paints and coatings.  Occupational inhalation exposure scenarios indicate that this exposure route is of low concern taking into account the very low vapour pressure of this chemical.  As 1,1,1-tris(hydroxymethyl)ethane may be included in consumer products such as paints and coatings, consumer exposure is anticipated. However, no detailed information is obtained for the consumer exposure. | |

SIDS Initial Assessment Report

# identity

## Identification of the Substance

Table Identification of the Substance

|  |  |
| --- | --- |
| CAS Number: | 77-85-0 |
| IUPAC Name: | 1,1,1-Tris(hydroxymethyl)ethane |
| Molecular Formula: | C5H12O3 |
| Structural Formula: |  |
| Molecular Weight: | 120.15 |
| Synonyms: | 1,1,1-tris(hydroxymethyl)ethane  1,1,1-Trimethylolethane  Trimethylolethane  Ethylidynetrimethanol  Ethane, 1,1,1-tris(hydroxymethyl)-  Methriol  Methyltrimethanolmethane  Metriol |

## Purity/Impurities/Additives

As far as available information by our research, purity of 1,1,1-tris(hydroxymethyl)ethane for industrial use is more than 99 % (CERI, 2011a).

## Physico-Chemical properties

1,1,1-Tris(hydroxymethyl)ethane is a white powder with no odour at standard temperature and pressure. Melting point and boiling point are 204 °C and 286.7 °C respectively. Vapour pressure at 25 °C extrapolated from the experimental value is 1.82 x 10-5 Pa. Partition coefficient between octanol and water (log Kow) is -0.95 and water solubility is more than 300 g/L at 20 °C. Physico-chemical properties of 1,1,1-tris(hydroxymethyl)ethane are shown in Table 2.

Table Summary of physico-chemical properties of 1,1,1-tris(hydroxymethyl)ethane

|  |  |  |  |
| --- | --- | --- | --- |
| Property | Value | Reliability | Reference |
| Physical state/appearance | White powder with no odour | 2 | Lide D.R. (ed), 2008 |
| Melting point | 204 °C | 2 | Lide D.R. (ed), 2008 |
| Boiling point | 286.7 °C1) | 1 | CERI, 2010a |
| Density | 1.236 g/cm3 at 25 °C | 2 | CITI, 1993a |
| Vapour pressure | 1.82 x 10-5 Pa at 25 °C2) | 1 | CERI, 2011b |
| Water solubility | ≥ 300 g/L at 20 °C3) | 1 | CERI, 2010b |
| Partition coefficient between octanol and water | log Kow = -0.95 at 25 °C 4) | 1 | CITI, 1994 |
| Soil adsorption coefficient | log Koc = -0.45)  KOCWIN | 2 | USEPA, 2009a |
| Henry’s Law constant | 1.13 x 10-3 Pa.m3/mole at 25 °C  HENRYWIN | 2 | USEPA, 2008a |

1. Test was conducted according to OECD test-guideline 103: “Boiling Point: Photocell detection” in compliance with GLP.
2. Vapour pressure at 25 °C was extrapolated by the following regression expression, which was obtained from the results of a test according to OECD test-guieline104: “Vapour pressure: Gas saturation method” in compliance with GLP.
3. log P (Pa) = -6262.32/T + 16.2640
4. Test was conducted according to OECD test-guideline 105: “Water solubility: flask method”.
5. Test was conducted according to OECD test-guideline 107: “Partition coefficient (n-octanol /water): Shake flask method” in compliance with GLP.
6. The value is calculated with log Kow of -0.95.

## Category Justification

Not applicable for this substance.

# general information on exposure

## Production Volumes and Use Pattern

Production Volumes

Currently, no production of 1,1,1-tris(hydroxymethyl)ethane is reported in Japan (sponsor country) and import volume in Japan is between 100 and 1,000 tonnes/year (CERI, 2011a). Production and/or import volume of 1,1,1-tris(hydroxymethyl)ethane in the United States was between 1 million and 10 million pounds (454,000 - 4,540,000 tonnes) during 2006 according to Inventory Updated Reporting (USEPA, 2011). Production volume in the world is not available.

Production methods

1,1,1-Tris(hydroxymethyl)ethane is produced by aldol condensation of propionaldehyde with formaldehyde, followed by reaction of the intermediate 2,2-bis(hydroxymethyl)propanal with excess formaldehyde in the presence of sodium hydroxide or lime as basic component (HSDB, 2008).

Use Pattern

1,1,1-Tris(hydroxymethyl)ethane is used as a conditioning agent, manufacture of varnishes, alkyd and polyester resins, synthetic drying oils (Lewis R.J., 2001). 1,1,1-Tris(hydroxymethyl)ethane is also used as a coating agent for titanium dioxide pigment (Kirk-Othmer, 2004). According to Inventory Updated Reporting (USEPA, 2011), 1,1,1-tris(hydroxymethyl)ethane is included in consumer products such as paints and coatings.

## Environmental Exposure and Fate

### Sources of Environmental Exposure

No detailed information concerning production of 1,1,1-tris(hydroxymethyl)ethane was obtained in Japan (sponsor country) because this substance seems not to be produced in Japan (sponsor country). No detailed information concerning the release during processing was obtained.

### Photo-degradation

1,1,1-Tris(hydroxymethyl)ethane entering in the atmosphere is expected to be degraded by hydroxyl radicals. Using AOPWIN (version 1.92a), a calculated half-life time of 0.85 days and a rate constant of 12.6×10-12 cm3/molecule-sec are obtained for the indirect photo-oxidation of 1,1,1-tris(hydroxymethyl)ethane by reaction with hydroxyl radicals in air (USEPA, 2008b). Concentration of hydroxyl radicals was assumed to be 1.5×106 OH/cm3 and time frame of hydroxyl radicals is 12 hours/day.

### Stability in Water

1,1,1-Tris(hydroxymethyl)ethane is not hydrolyzed due to the lack of hydrolysable functional groups. A study according to OECD test-guideline 111 showed no hydrolysis of 1,1,1-tris(hydroxymethyl)ethane in water at pH 4, 7 and 9 in 50 °C after five days (CITI, 1998).

### Transport between Environmental Compartments

Fugacity modeling (level III) for 1,1,1-tris(hydroxymethyl)ethane was conducted using EPISUITE, version 4.0 (USEPA, 2008c). Input parameters are melting point of 204 °C, boiling point of 286.7 °C, log Kow of -0.95, vapour pressure of 1.82 x 10-5 Pa, water solubility of 300 g/L (the lowest limit value) and Henry’s Law constant of 1.13 x 10-3 Pa.m3/mole. When equal and continuous release to air, water and soil is assumed, 1,1,1-tris(hydroxymethyl)ethane is mainly distributed in water and soil compartments. If released to the water compartment only, 1,1,1-tris(hydroxymethyl)ethane stays in the water compartment.

Table Environmental distribution of 1,1,1-tris(hydroxymethyl)ethane with Fugacity Level III model

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Release to air, water and soil | Release to air | Release to water | Release to soil |
| Air compartment | 0.3 % | 0.7 % | 0.0 % | 0.0 % |
| Water compartment | 38.7 % | 24.7 % | 99.8 % | 20.9 % |
| Soil compartment | 61.0 % | 74.6 % | 0.0 % | 79.0 % |
| Sediment compartment | 0.1 % | 0.0 % | 0.2 % | 0.0 % |

A Henry’s law constant of 1.13 x 10-3 Pa.m3/mole at 25 °C suggests that 1,1,1-tris(hydroxymethyl)ethane is nonvolatile from water (USEPA, 2009b). A soil adsorption coefficient of log Koc = -0.4 indicates 1,1,1-tris(hydroxymethyl)ethane has low adsorption to soil and sediment.

### Biodegradation

An OECD test guideline 301C test was conducted with 1,1,1-tris(hydroxymethyl)ethane with activated sludge for four weeks (CERI, 1993b). 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 3-6 % degradation by BOD. 1,1,1-Tris(hydroxymethyl)ethane is not likely to be toxic to microorganisms given the absence of toxicity to aquatic organisms. According to the result, 1,1,1-tris(hydroxymethyl)ethane is considered to be not-readily biodegradable.

### Bioaccumulation

No information was available on the bio-concentration on 1,1,1-tris(hydroxymethyl)ethane. Using an octanol-water partition coefficient (log Kow) of -0.95, a bio-concentration factor of 3.2 was calculated with BCFBAF, version 3.00 (USEPA, 2008d). This chemical is not expected to bioaccumulate.

### Other Information on Environmental Fate

## Human Exposure

### Occupational Exposure

According to the vapour pressure of this substance of 1.82 x 10-5 Pa at 25 °C, which corresponds to maximum vapour concentration of less than 0.2 ppb, inahlation of vapor may be negligible, but inhalation of mist of this substance may be a concern where aerosol formation is possible. The log Kow of this chemical is -0.95, so dermal intake is also a concern. To prevent worker exposure to mist, some kind of worker protection measures such as LEV or PPE are necessary at production sites, also proper worker protection measures may be necessary at user sites.

As 1,1,1-tris(hydroxymethyl)ethane is not produced in Japan, no actual exposure data are available.

No occupational exposure limit value are established for 1,1,1-tris(hydroxymethyl)ethane in the sponsor country.

### Consumer Exposure

As 1,1,1-tris(hydroxymethyl)ethane may be included in consumer products such as paints and coatings, consumer exposure is anticipated. However, no detailed information is obtained for the consumer exposure.

# human health hazards

## Effects on Human Health

### Toxicokinetics, Metabolism and Distribution

Studies in Animals

In vitro Studies

No information is available.

In vivo Studies

No information is available for toxicokinetics, metabolism and distribution. The slight liver toxicity seen in rats given 1000 mg/kg bw bw/day (in the repeated dose study described in section 3.1.5) indicates that 1,1,1-tris(hydroxymethyl)ethane is absorbed through the gastrointestinal tract to some degree..

Studies in Humans

In vitro Studies

No information on humans is available.

In vivo Studies

No information on humans is available.

Conclusion

No specific study on toxicokinetics, metabolism and distribution has been identified. The slight liver toxicity seen in rats given 1000 mg/kg bw bw/day (in the repeated dose study described in section 3.1.5) indicates that 1,1,1-tris-(hydroxymethyl)ethane is absorbed through the gastrointestinal tract to some degree.

### Acute Toxicity

Studies in Animals

Oral

One reliable acute oral study is available. This study was conducted in accordance with an acute oral toxicity [OECD TG 401] under GLP [MHW Japan, 1998a]. Details of the study are as follows.

Crj: CD (SD) rats (5 animals/sex) were given 1,1,1-tris(hydroxymethyl)ethane by gavage at 2,000 mg/kg bw (20%(w/v)). The gavage vehicle was distilled water and the observation period was 14 days.

No deaths occurred in either males or females in the treated groups. No effects were found in clinical signs, body weight changes or autopsy findings. The single dose toxicity test revealed an LD50 value of above 2,000 mg/kg bw for both sexes [MHW, Japan, 1998a].

Inhalation

No information is available.

Dermal

No information is available.

Other Routes of Exposure

No information is available.

Studies in Humans

Inhalation

No information on humans is available.

Dermal

No information on humans is available.

Oral

No information on humans is available.

Other Routes of Exposure

No information on humans is available.

Conclusion

In the acute oral toxicity study, no deaths or signs of toxicity were observed at 2,000 mg/kg bw in rats. Therefore, the oral LD50 value of 1,1,1-tris(hydroxymethyl)ethane was concluded to be > 2,000 mg/kg bw. Data on acute dermal and inhalative toxicity are not available, but toxicity via these exposure routes is suggested to be low concern taking into account of low acute oral toxicity and vapour pressure of this chemical.

### Irritation

Skin Irritation

Studies in Animals

No reliable studies are available.

Studies in Humans

No information on humans is available.

Eye Irritation

Studies in Animals

No information is available.

Studies in Humans

No information on humans is available.

Respiratory Tract Irritation

Studies in Animals

No information is available.

Studies in Humans

No information on humans is available.

Conclusion

No reliable studies are available on skin irritation, and no information is available on eye and respiratory tract irritation.

### Sensitisation

Studies in Animals

Skin

No reliable studies are available.

Respiratory Tract

No information is available.

Studies in Humans

Skin

No information on humans is available.

Respiratory Tract

No information on humans is available.

Conclusion

No reliable studies are available on skin sensitisation, and no information is available on respiratory tract sensitisation.

### Repeated Dose Toxicity

Studies in Animals

Oral

One reliable study is available for repeated dose oral toxicity. This study was conducted in accordance with a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [OECD TG 422] under GLP [MHW Japan, 1998b]. Details of the MHW study are as follows. Crj: CD (SD) rats (13 animals/sex/dose) were given 1,1,1-tris(hydroxymethyl)ethane by gavage (in distilled water as a vehicle) at doses of 0, 100, 300 or 1,000 mg/kg bw/day. Males were dosed for 42 days including 14 days pre-mating period and 28 subsequent days. Females were dosed for 14 days pre-mating, mating (up to 14 days) and gestation period and the days until day 3 of lactation (a total of up to 49 days). General clinical observations, measurement of body weight and food consumption, and hematological (male only), clinical chemistry (male only), necropsy and histopathological examinations (tissues from the brain, heart, thymus, liver, kidneys, spleen, adrenals, urinary bladder, uterus and testes were examined microscopically) were performed.

No treatment-related effects were observed in clinical signs, food consumption, hematology, organ weights and histopathological examinations. In clinical chemistry, significant increases in GOT and GPT, and a significant decrease in glucose, were observed at 1,000 mg/kg bw/day, which may indicate adverse effects on the liver. However, histopathological examination revealed no effects on the liver. Statistically significant changes were observed in hematocrit, MCHC, segmented neutrophil, lymphocyte, but these changes are considered unrelated to the test substance. A slight but significant decrease in body weight gain was observed in pregnant females at 1,000 mg/kg bw/day. However this change was observed only in the late period of pregnancy. Based on the above findings, the NOAEL was considered to be 1000 mg/kg bw/day in both sexes.

Inhalation

No information is available.

Dermal

No information is available.

Studies in Humans

Inhalation

No information on humans is available.

Dermal

No information on humans is available.

Oral

No information on humans is available.

Conclusion

In a combined repeated dose toxicity/reproductive toxicity study (OECD TG 422), rats were treated orally for 42-54 days. No treatment-related effects were observed in clinical signs, food consumption, hematology (examined only in males), organ weight and the histopathological appearance of tissues from the major organs including the liver. In clinical chemistry (examined only in males), significant but slight increases in GOT and GPT, reflecting an effect on liver function, and a slight decrease in glucose were observed at 1,000 mg/kg bw/day. Based on no histopathological changes in the liver, these changes in clinical chemistry were not considered to be toxicologically important. A significant but slight decrease in body weight gain was observed in pregnant females at 1,000 mg/kg bw/day. However this change was observed only in the late period of pregnancy. Based on the above findings, the NOAEL was considered to be 1000 mg/kg bw/day in both sexes.

### Mutagenicity

Studies in Animals

In vitro Studies

*Bacterial mutation test*

A reverse gene mutation assay of 1,1,1-tris(hydroxymethyl)ethane was conducted in accordance with the current protocols [OECD TG 471, TG472 and the Japanese Guideline for Screening Mutagenicity Testing of Chemicals (Chemical Substances Control Law of Japan)] under GLP [MHW, Japan: 1998c].

1,1,1-Tris(hydroxymethyl)ethane was not mutagenic at doses of 156-5000 μg/plate in *Salmonella typhimurium* TA100, TA1535, TA98, TA1537 and *Escherichia coli* WP2 uvrA with and without metabolic activation (S9 mix prepared from enzyme-induced rat liver). No toxicity was observed in any of the cases. The positive controls showed expected levels of mutagenicity.

*Chromosomal aberration test*

A chromosomal aberration test of 1,1,1-tris(hydroxymethyl)ethane was conducted in accordance with the current protocol [OECD TG 473 and the Japanese Guideline for Screening Mutagenicity Testing of Chemicals (Chemical Substances Control Law of Japan)] in cultured Chinese hamster lung (CHL/IU) cells [MHW Japan, 1998d].

The CHL/IU cells were treated at 300, 600 and 1,200 μg/ml for 24 or 48 hrs (continuous treatment) without S9 mix, or at 300, 600 and 1,200 μg/ml with and without S9 mix for 6 hrs (short-term treatment).

In either test condition, no increase in structural aberrations or polyploidy was observed. The positive controls [mitomycin C (0.05 μg/ml) for continuous treatment, cyclophosphamide (12.5 μg/ml) for short-term treatment] were effective for induction of chromosome aberrations.

In vivo Studies

No information is available.

Studies in Humans

No information on humans is available.

Conclusion

1,1,1-tris(hydroxymethyl)ethane did not induce gene mutation in bacterial *in vitro* tests (OECD TG 471, OECD TG 472 and Japanese guideline). The substance did not induce chromosome aberrations in cultured Chinese hamster lung (CHL/IU) cells (OECD TG 473 and Japanese guideline). Based on these results, 1,1,1-tris(hydroxymethyl)ethane is considered to be non genotoxic *in vitro*. There is no *in vivo* study on mutagenicity.

### Carcinogenicity

No information on carcinogenicity for 1,1,1-tris(hydroxymethyl)ethane is available.

### Toxicity for Reproduction

Studies in Animals

One reliable study is available for reproductive/developmental toxicity. This study was conducted in accordance with a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [OECD TG 422] under GLP [MHW Japan, 1998b]. Details about the effects on reproductive/developmental parameters in the MHW study are as follows, and other details about the general toxicity parameters are shown in 3.1.5 Repeated Dose Toxicity.

Crj: CD (SD) rats (13 animals/sex/dose) were given 1,1,1-tris(hydroxymethyl)ethane at doses of 0 (vehicle: distilled water for injection), 100, 300 or 1,000 mg/kg bw/day. Males were dosed for 42 days from 14 days before mating, and females were dosed for days including 14 days pre-mating, mating and gestation period and the days until day 3 of lactation.

Effects on Fertility

No treatment-related effects were observed in reproductive parameters, including male and female copulation and fertility index, precoital and gestational days and gestation index. There were also no changes in the weight and histopathology of reproductive organs in either sex. Thus, the NOAEL for reproductive toxicity was considered to be 1,000 mg/kg bw/day.

Developmental Toxicity

No treatment-related effects were observed in developmental parameters, including the number of live pups born, viability index on postnatal day 4, body weight on postnatal day 0 and day 4, and number of external anomalies. Based on the findings, the NOAEL for developmental toxicity was considered to be 1,000 mg/kg bw/day.

Studies in Humans

Effects on Fertility

No information on humans is available.

Developmental Toxicity

No information on humans is available.

Conclusion

In a reproduction/developmental toxicity screening test using rats (OECD TG 422), no adverse effects were seen at the maximum tested oral dose of 1,000 mg/kg bw/day. The NOAEL for reproductive and developmental toxicity was therefore 1,000 mg/kg bw/day.

**Conclusion**

**1,1,1-tris(hydroxymethyl)ethane 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 HPV Chemicals Programme.**

# hazards to the environment

## Aquatic Effects

Acute Toxicity Test Results

Acute and prolonged toxicities of 1,1,1-tris(hydroxymethyl)ethane to aquatic species from three trophic levels are available, and reliable acute aquatic toxicities are shown in Table 5. Acute toxicities for fish (species was not defined), daphnid and green algae were estimated by using the QSAR toolbox software(Version 2.1). The results were also shown in Table 5.

Table Acute and prolonged toxicity of 1,1,1-tris(hydroxymethyl)ethane to aquatic organisms, experimental and estimated values

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Species | Method | Exposure | Result | Reliability | Reference |
| *Oryzias latipes* | OECD TG 203- Limit test, GLP | 96 h semi-static | LC50 >100 mg/L (nominal) | 1 | MOE, Japan (1998) |
| Fish | QSAR prediction | 96 h | LC50=10,400 mg/L |  |  |
| *Oryzias latipes* | OECD TG 204- Limit test, GLP | 14 days  flow-through | LC50 > 99.8 mg/L  NOEC >99.8 mg/L  (nominal ) | 1 | MOE, Japan (1998) |
| *Daphnia magna* | OECD TG 202, limit test, GLP | 48 h static | EC50 > 1000 mg/L (nominal) | 1 | MOE, Japan (1998) |
| Daphnid | QSAR prediction | 48 h | L(E)C50 = 6,770mg/L | - | - |
| *Pseudokirchneriella subcapitata* | OECD TG 201  Limit test  GLP | 72 h static | growth rate  ErC50 > 1000 mg/L  (nominal)  area under growth curve  EbC50 > 1000 mg/L (nominal) | 1 | MOE, Japan (1998) |
| Algae | QSAR prediction | 72h | EC50 = 75 mg/L | - | - |

Fish

An acute toxicity test of 1,1,1-tris(hydroxymethyl)ethane was conducted for Japanese Medaka, *Oryzias latipes*, according to OECD TG 203 in compliance with GLP (MOE Japan, 1998). A limit test with an exposure concentration of 100 mg/L in nominal and control was conducted because no toxicological effects were observed in the preliminary test. Ten fish per concentration were exposed in semi-static system with renewal of test solution every day, under test conditions as water temperature of 23.6– 24.2 degree C, pH of 7.1-7.6, and DO of 6.4 - 8.7 mg/L, more than 60 % of saturation, during test. The measured concentrations at 0 h and 24 h (just before changing test solution) were 97.2 and 82.3 mg/L ( the mean measured concentration was 89.4 mg/L), respectively. No toxicological symptoms and mortality were observed in both exposed and control group. The 96h LC50 of >100 mg/L was determined based on the nominal concentration.

Following to acute toxicity test, a prolonged toxicity test of this chemical was conducted for Japanese Medaka, *Oryzias latipes*, according to OECD TG 204 in compliance with GLP, as a limit test with a control and the treated group at concentration of 99.8 mg/L. Under a flow-through condition, ten fish were exposed to the chemical for 14 days. The concentrations of the test substance in test solution were analysed on 0, 7th, and 14th day. The mean measured concentration was 89.0 mg/L, ranging from 85.4 to 93.5 mg/L. Mortality and toxicological symptom were observed during the test and measurement of body size (both total body length and body weight) was undertaken at the end of test. No mortality was observed during test, a 14 day LC50 was > 99.8 and NOEC was >99.8 mg/L based on nominal concentration.

Invertebrate

An acute toxicity test of 1,1,1-tris(hydroxymethyl)ethane was conducted for daphnids, *Daphnia magna*, according to OECD TG 202 in compliance with GLP (MOE Japan, 1998) as a limit test because no toxicological symptoms were observed in a preliminary test. Twenty daphnids per concentrations were exposed under static condition to the chemical at nominal concentration of 1000 mg/L with a control. The environmental factors were monitored and shown as temperature of 19.4-19.6 degree C, pH of 7.6 - 7.9, and DO of 8.4 - 8.6. The measured concentrations of the 1,1,1-tris(hydroxymethyl)ethane in test solution at 0h and 48h were 945 and 991 mg/L, respectively. No immobility was observed in both the control and the exposed daphnids. The 48h EC50 of > 1000 mg/L was determined based on the nominal concentration.

Aquatic plant, e.g. Algae

For a freshwater algal species, *Pseudokirchneriella subcapitata*, the toxicity of 1,1,1-tris(hydroxymethyl)ethane was studied (MOE, Japan, 1998). An algal growth inhibition test (OECD TG 201) was conducted in compliance with GLP with a nominal concentration of 1000 mg/L as a limit test. The concentration of test substance was measured by using a GC at the initial and the end of test as 973 and 991 mg/L, respectively. There was no significant difference between the cell densities of the control and the exposed groups at the end of test. The 72hErC50 and 72 EbC50 were > 1000 mg/L based on the nominal concentration.

Chronic Toxicity Test Results

Test results on chronic toxicity of 1,1,1-tris(hydroxymethyl)ethane are summarised in the table 6.

Fish

No data available

Invertebrates

A chronic toxicity test of 1,1,1-tris(hydroxymethyl)ethane to *Daphnia magna*, OECD-TG 211, GLP study, on reproduction was reported (MOE, Japan. 1998). The test was conducted as a limit test with an exposure concentration of 100 mg/L in nominal, under semi-static condition in which the test solution was renewed three times per a week. The test substance was measured once a week for both fresh and expired test solution by using a GC. The mean measured concentration was determined as 88.5 mg/L by time-weighted mean because the measured value was ranging 77.6 - 103 % of nominal. In the test number of offspring per female was counted, and no significant difference between the control and treated group was observed. Since toxic symptoms were not observed the 21 day NOEC was determined as > 88.5 mg/L based on the measured mean concentration.

Aquatic plant, e.g. Algae

Corresponding to the algal growth inhibition test (MOE Japan, 1998) described in acute toxicity section, the chronic eco-toxicity of 1,1,1-tris(hydroxymethyl)ethane was also determined. The 72 h NOECs by growth rate method and by area under growth curve method were determined as >1000 mg/L and >1000 mg/L, respectively.

Table Chronic toxicity of 1,1,1-tris(hydroxymethyl)ethane to aquatic organisms

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Species | Method | Exposure | Result | Reliability | Reference |
| *Daphnia magna* | OECD TG 211, limit test, GLP | 21 d semi-static | NOEC > 88.5 mg/L  (measured)  reproduction | 1 | MOE, Japan (1998) |
| *Pseudokirchneriella*  *subcapitata* | OECD TG 201, limit test,  GLP | 72 h static, | (Growth rate method)  NOErC > 1000 mg/L (nominal)  (Area method)  NOEbC > 1000 mg/L (nominal) | 1 | MOE, Japan (1998) |

Toxicity to Microorganisms

No data available

**Conclusion**

**1,1,1-tris(hydroxymethyl)ethane does not present a hazard to the environment due to its low hazard profile. Although this chemical is considered not to be readily biodegradable, it has a low accumulative potential. Adequate screening-level data are available to characterize the environmental hazard for the purposes of the OECD HPV Programme.**

## Terrestrial Effects

No data available

Acute Toxicity Test Results

No data available

Chronic Toxicity Test Results

No data available

## Other Environmental Effects

No data available

# recommendations

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