FOREWORD INTRODUCTION

2-FURANMETHANOL, TETRAHYDRO

CAS N°: 97-99-4

SIDS Initial Assessment Report

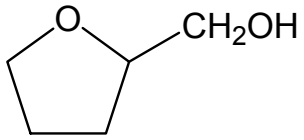
For

SIAM 20

Paris, France, 19-22 April 2005

1. Chemical Name:	2-Furanmethanol, tetrahydro
2. CAS Number:	97-99-4
3. Sponsor Country:	Japan Contact Point: Mr. Motohiko Kato Director Second International Organizations 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	This substance is sponsored by Japan and was submitted for a first discussion at SIAM 20
• How was the chemical or category brought into the OECD HPV Chemicals Programme ?	The original draft documents were prepared by the Japanese government.
7. Review Process Prior to the SIAM:	
8. Quality check process:	An expert committee performed spot checks on randomly selected endpoints and compared the original studies with the data in the SIDS dossier.
9. Date of Submission:	January 21, 2005
10. Date of last Update:	January 21, 2005
11. Comments:	Literature search was performed using the Toxline and Medline, and review articles were looked for in IUCLID, RTECS, IRIS, IARC, EHC, and Toxicological Profile: 27 December, 2004.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	97-99-4
Chemical Name	2-Furanmethanol, tetrahydro-
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

There is no available information on toxicokinetics, metabolism or distribution.

In an acute oral toxicity study [OECD TG 423] of 2-furanmethanol, tetrahydro- in rats, no changes in survival rate, body weight gain or necropsy findings were observed at 2000 mg/kg bw. At this dose, decreased locomotor activity and hypotonia were observed.

This chemical was a moderate eye irritant in rabbits but did not irritate the rabbit skin. Review sources suggest that it might be a moderate skin and eye irritant in humans.

There is no available information on sensitization.

In a repeated oral dose toxicity study [Japanese TG equivalent to OECD TG 407], Crj:CD(SD)IGS rats were administered by gavage at 0 (vehicle: distilled water), 10, 40, 150 or 600 mg/kg bw/day for 28 days. The initial numbers of rats were 10/sex at 0 and 600 mg/kg bw/day, and 5/sex at other doses. Five rats/sex from each group were killed on day 29, and the remaining 5 rats/sex at 0 and 600 mg/kg bw/day were kept without further treatment for another 14 days (recovery period). Increased locomotor activity followed by decreased locomotor activity and adoption of a prone position in males and females, and lowered grip strength of the hindlimb in males were found at 600 mg/kg bw/day. Increased locomotor activity was observed in females at 150 mg/kg bw/day. At 600 mg/kg bw/day, animals showed decreased body weight gain in males, reduced food consumption in males and females, and decreased urinary pH in males. . At this dose, hematological examinations revealed decreases in the mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), leukocyte count and platelet count, and prolonged prothrombin time in males and females and decreases in the reticulocyte count in males and hemoglobin concentration in females. Blood biochemical examinations revealed decreases in the levels of alkaline phosphates (ALP), total protein, albumin, total bilirubin and calcium in males and females, and lactate dehydrogenase (LDH), triglyceride, blood urea nitrogen (BUN) and sodium in males at 600 mg/kg bw/day. At 150 mg/kg bw/day, a decrease in total protein was observed in males. Decreases in the relative weights of the thymus in males and females and pituitary in females, and an increase in the relative weights of the kidney in females were found at 600 mg/kg bw/day. At 150 mg/kg bw/day, a decrease in the relative weight of the pituitary was noted in females. Histopathological examinations revealed atrophy of the thymus in males and females, and atrophy of the red pulp with decreased extramedullary hematopoiesis and inflammation of the capsule of the spleen in males at 600 mg/kg bw/day. Necrosis of seminiferous tubular epithelium of the testes was observed at 150 and 600 mg/kg bw/day. Examination of the spermatogenic cycle showed a decrease in the ratio of the spermatid to Sertoli cell counts at 600 mg/kg bw/day. Histopathological examinations of the testes revealed a tendency for increase in the severity of changes at the end of the 14-day recovery period. Based on these findings, the NOAELs for repeated dose toxicity were 40 mg/kg bw/day in males and females.

In a reverse gene mutation assay [OECD TG 471], this chemical was not mutagenic in *Salmonella typhimurium* TA100, TA1535, TA1537, TA98 or *Escherichia coli* WP2 *uvr*A/ pKM101 with or without an exogenous metabolic activation. In a chromosomal aberration test [OECD TG 473], this chemical did not cause structural chromosomal aberration or polyploidy with or without an exogenous metabolic activation in cultured Chinese

hamster lung (CHL/IU) cells.

There is no available information on carcinogenicity.

In a preliminary reproductive toxicity study [OECD TG 421], Crj:CD(SD)IGS rats (12 animals/sex/dose) were administered by gavage at 0 (vehicle: distilled water), 15, 50, 150 or 500 mg/kg bw/day. Males were dosed for a total of 47 days beginning 14 days before mating. Females were dosed for a total of 42-52 days beginning 14 days before mating to day 4 of lactation throughout the mating and gestation period. Males showed decreased body weight gain at 500 mg/kg bw/day. At 150 mg/kg bw/day and higher, an increased locomotor activity in males and females, and decreased body weight gain in females were observed. At 500 mg/kg bw/day, decreased relative weights of the thymus, testes and epididymides, atrophy of the seminiferous tubule with hyperplasia of the interstitial cell in the testes, and decreased intraluminal sperms with cell debris in the epididymides were noted in males. Prolonged estrous cycles were observed at 500 mg/kg bw/day. At this dose, no females delivered their offspring and examination of the uterus of dams revealed early embryonic resorptions. Prolonged gestation length, decreased gestation index, and lowered delivery index, live birth index, numbers of pups born and live pups on postnatal days (PNDs) 0 and 4, and viability on PND 4 were observed at 150 mg/kg bw/day. No increase in the incidence of morphological abnormalities was found in pups of rats given this chemical. Based on these findings, the NOAEL for reproductive/developmental toxicity was 50 mg/kg bw/day.

Decreased testes weight, low sperm activity and/or testicular atrophy were caused in Beagle dogs fed a diet containing 1000 ppm 2-furanmethanol, tetrahydro- and higher for 90 days.

Rats (eight animals/group) were orally given this chemical at 0, 10, 50, 100, 500 or 1000 mg/kg bw/day on days 6 to 15 of pregnancy. Decreases in maternal body weight gain and food consumption were observed at 500 and 1000 mg/kg bw/day. A 100% incidence of early resorptions at 500 and 1000 mg/kg bw/day and decreased fetal weight at 100 mg/kg bw/day were found. The NOAELs for maternal and developmental toxicity were considered to be 100 and 50 mg/kg bw/day, respectively.

Environment

2-Furanmethanol, tetrahydro- is a colorless and flammable liquid with a water solubility of more than 250 g/L at 20 °C, a melting point of less than – 120 °C, a boiling point of 177.7 °C at 1013 hPa, a vapor pressure of 1.86 hPa at 25 °C and a relative density of 1.0544 at 20/20 °C. Based on the measured log Kow value of -0.11 bio- or geoaccumulation of this chemical is unlikely. Environmental distribution using Mackey level III suggests that when this chemical is released into the environment, it distributes mainly into water and soil. A calculated Henry's Law constant of 4.09^{-9} atm-m^3/mole indicates that only a limited extent of volatilisation from water may occur. 2-Furanmethanol, tetrahydro- is readily biodegradable (10-day window fulfilled) but abiotic degradation is not expected in water. In the atmosphere this chemical is indirectly photodegraded by reaction with OH radicals with a half-life of 0.5 days.

Ecotoxicity data for this substance was available in aquatic species from three trophic levels. In the algal growth inhibition test (OECD TG 201, *Pseudokirchneriella subcapitata*, open system), both the (0-72 h) ErC_{50} and the (0-72 h) EbC_{50} were > 98.9 mg/L. For daphnids, a 48 h EC_{50} of > 91.7 mg/L was reported (OECD TG 202, *Daphnia magna*, semi-static). For fish (OECD TG 203, *Oryzias latipes*, semi-static) a 96 h LC_{50} > 101 mg/L is available.

Regarding chronic toxicity to algae, the (0-72 h) NOEC by growth rate and biomass methods was 98.9 mg/L (OECD TG 201, *Pseudokirchneriella subcapitata*, open system). For daphnids, a 21 d EC_{50} of > 95.1 mg/L for reproduction and a 21 d NOEC of 95.1 mg/L for reproduction are available (OECD TG 211, *Daphnia magna*, semi-static).

Exposure

2-Furanmethanol, tetrahydro- is manufactured by a single manufacture in Japan with an annual production volume of approximately 30 tonnes. Worldwide production capacity outside Japan is not known. The major uses of this chemical are: solvents for various products and uses (fats, waxes, resins, dyes, vegetable oils, cleaners, paints, inks and others: ca 50 to 70% in total) and intermediate in industrial applications (ca. 30 to 50%). Human exposure to this chemical is expected in both occupational settings and consumer sites since some of the applications include open and direct uses (solvents for paints and nail cleaning agents). Such exposure can occur through inhalation and dermal routes. Exposure into the environment may also occur primary through evaporation during the production and down stream user sites.

The routes of occupational exposure are inhalation of vapor and dermal contact to liquid. As a volatile liquid and used as a solvent for various products, workers at production and user sites of this chemical may be exposed.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is a candidate for further work. The chemical possesses a hazard for human health (repeated dose toxicity, irritation, reproductive/developmental toxicity). Exposure to general public is expected through dermal contact and inhalation. This chemical is produced in a closed system in Japan, but used to formulate various products, occupational exposure through inhalation and dermal route is possible in both production and user sites. Therefore, an exposure assessment and, if necessary, a risk assessment for workers and consumers are recommended.

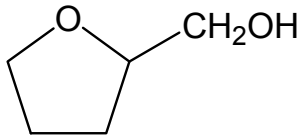
Environment: The chemical is currently of low priority for further work because of its low hazard potential.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 97-99-4
IUPAC Name: 2-Furanmethanol, tetrahydro-
Molecular Formula: $C_5H_{10}O_2$
Structural Formula:



Molecular Weight: 102.13
Synonyms: 2-Furanmethanol, tetrahydro-
Tetrahydro-2-furanmethanol
2-Hydroxymethyl oxolane
Tetrahydro-2-furancarbinol
Tetrahydrofurfuryl alcohol
THFA

1.2 Purity/Impurities/Additives

1.3 Physico-Chemical properties

Table 1 Summary of physico-chemical properties

Property	Value	Reference
Physical state	Liquid	
Melting point	< -120 °C	CERI (2004a)
Boiling point	177.7 °C	CERI (2004a)
Relative density	1.0544 at 20 °C	CRC Handbook
Vapour pressure	1.86 hPa at 25 °C	CERI (2004b)
Water solubility	> 250 g/l at 20 °C	CERI (2004c)
Partition coefficient n-octanol/water (log value)	-0.11 at 20 °C	CERI (2004d)
Henry's law constant	4.09×10^{-9} atm-m3/mole at 25 °C	CERI (2004e)

2-Furanmethanol, tetrahydro- is a colourless, odourless and flammable liquid with a slight ether odour.

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

Production Volumes

2-Furanmethanol, tetrahydro- is manufactured by a single manufacturer in Japan with an annual production volume of approximately 30 tonnes (Koatsu Chemical Industries). The worldwide production capacity is not known.

2-Furanmethanol, tetrahydro- is produced by catalytic hydrogenation of furfuryl alcohol in a closed reactor tank followed by distillation (Koatsu Chemical Industries). Residual non-reacted raw material and the substance are recovered from the reactor tank and applied for re-distillation and/or incineration.

Use Pattern

The major uses of 2-furanmethanol, tetrahydro- are as follows (CERI 2004f):
- Intermediates for industrial raw materials (30-50%: esterification products as a counter compound with various carboxylic acids).
- Solvents for fats, waxes, resins in organic synthesis.
- Solvents for dyes for leather, chlorinated rubber and cellulose esters; solvent-softener for nylon; vegetable oils; coupling agents.
- Plasticizer for synthesis of lysine, paints and varnish ingredient.
- Solvents for specialty uses as nail cleaning agents and paint strippers; replacement for chlorinated solvents; crop sprays; water-based paints; dyeing and finishing of textiles and leathers; intermediate in pharmaceutical applications.
- Coupling solvents for pesticides and textile auxiliaries.

2.2 Environmental Exposure and Fate

2.2.1 Sources of Environmental Exposure

2-Furanmethanol, tetrahydro- is produced and used as an organic solvent in various professional and consumer applications. The compound is also used as a cleaner and paint stripper, and in the dyeing and finishing of textiles and leathers. These applications may result in the emission of the compound into the environment through various waste streams.

Depending on the manufacturing process and wastewater treatment facilities a certain portion of 2-furanmethanol, tetrahydro- may possibly be emitted mainly into the water compartment. In many cases 2-furanmethanol, tetrahydro- present in wastewater streams is eliminated by biological and chemical processes. Since 2-furanmethanol, tetrahydro- is readily biodegradable, the concentration of 2-furanmethanol, tetrahydro- in water should be negligible.

When 2-furanmethanol, tetrahydro- is used as a solvent under open conditions only small amount of 2-furanmethanol, tetrahydro- may be released into air however the extent of the emission should be low taking into account its vapour pressure (1.86 hPa at 25 °C) and boiling point (177.7 °C).

2-Furanmethanol, tetrahydro- may volatilise slowly from dry soil surfaces but volatilisation from water is not expected based on its vapour pressure and Henry’s Law constant.

2.2.2 Photodegradation

The half-life of 2-furanmethanol, tetrahydro- in air by the reaction with photochemically produced OH radicals was calculated to be 0.5 day (rate constant: 2.358 x 10^{-11} cm^3/molecule-sec, OH radical concentration: 1.5 x 10^6 molecule/cm^3, and irradiation time: 12 hours/day) (CERI, 2004e).

2.2.3 Stability in Water

A preliminary study according to OECD TG 111 (50 °C for 5 days at pHs 4.0, 7.0 and 9.0) indicated that 2-furanmethanol, tetrahydro- is stable in water and its half-life is estimated to be more than one year at 25 °C at environmentally relevant pH conditions (CERI, 2004g).

2.2.4 Transport between Environmental Compartments

The distribution modeling using a Mackay fugacity model, Level III calculated with the values of molecular weight of 102.13, vapour pressure of 1.395 mmHg, water solubility of 250 g/L, melting point of -80 °C and partition coefficient (LogKow) of -0.11, indicates that water (54.3%) and soil (44%) are the main target compartments at a temperature of 25 °C (CERI, 2004e).

The Henry's law constant of $4.09 \cdot 10^{-9}$ atm-m3/mole (CERI, 2004e) indicates that 2-furanmethanol, tetrahydro- has a low potential for volatilisation from aqueous solution.

The estimated soil sorption coefficient Koc = 1 (CERI, 2004e) suggest a very low potential for sorption to soil.

2.2.5 Biodegradation

A ready biodegradation study was conducted according to OECD Guideline 301 C "Ready Biodegradability; Modified MITI Test (I)" (CERI, 2004h). Rates of biodegradation were determined by a BOD meter, GC and TOC analysis. All measurements showed more than 90 % degradation after 28 days. Based on the biodegradation curve by BOD analysis, the 10-day window was fulfilled.

Under aerobic conditions it is concluded that 2-furanmethanol, tetrahydro- is readily biodegradable according to OECD criteria.

2.2.6 Bioaccumulation

Using a measured log Kow value of -0.11, a bioconcentration factor (BCF) of 3.16 was calculated by BCFWIN v2.14 (CERI, 2004e). This result indicates that the bioaccumulation of 2-furanmethanol, tetrahydro- in aquatic organisms is expected to be low.

2.3 Human Exposure

2.3.1 Occupational Exposure

This chemical is synthesized by hydrogenation of furfuryl alcohol using hydrogen in a closed system in Japan. Workers may be exposed to this chemical during packaging at the production site. Since this chemical is used as a plasticizer, cleaner, an intermediate for esters, a solvent for various products, downstream users may also be exposed. The routes of exposure are inhalation of vapour and dermal contact to liquids. Actual work practice or workplace monitoring data were not available.

No occupational exposure standard value is assigned, but the AIHA 2001 Emergency Response Planning Guidelines suggested a Workplace Environmental Exposure Level of 8.36 mg/$m^3$for this chemical.

2.3.2 Consumer Exposure

The general population may be exposed through dermal contact and inhalation of vapour through the use of 2-furanmethanol, tetrahydro- as a solvent in various applications. In addition multiple applications including end use products also suggest that exposure to consumers are expected.

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

There is no available information.

3.1.2 Acute Toxicity

Studies in Animals

Inhalation

The LC50 for 6 hr exposure and lowest observed no effect concentration over 6 hr are reported to be 12650 ppm and 655 ppm, respectively [Patty, 1963]. However, no detailed information on this study is available.

Dermal

The acute dermal LD50 in guinea pigs is reported to be less than 5 mL/kg [Patty, 1963]. However, no detailed information on this study is available.

Oral

One reliable study is available for acute oral toxicity in rats [MHLW, Japan, 2004]. This study was conducted according to an OECD acute oral toxicity test [TG423, Acute Oral Toxicity - Acute Toxic Class Method.] under GLP using female Crj:CD(SD)IGS rats.

A dose of 2000 mg/kg bw was given to a total of 6 rats and none died. Clinical signs, such as decreased locomotor activity and hypotonia, were observed. Body weight gain was not affected by administration of this chemical. Necropsy revealed no abnormality related to this chemical.

Other Routes of Exposure

One early study is available for acute toxicity after intraperitoneal injection in groups of up to 4 rats [Sanderson ,1959]. Approximately average lethal dose, maximum symptomless dose and maximum dose without macroscopic pathology were estimated to be 1000 mg/kg bw, 750 mg/kg bw and 750 mg/kg bw, respectively. Observations induced respiratory disturbance, urinary incontinence and necrosis of unspecified tissues.

Studies in Humans

No studies in humans are available for this chemical.

Conclusion

The acute oral lethal dose was considered to be greater than 2000 mg/kg bw in rats, suggesting a low acute oral toxicity. The approximate average lethal dose by intraperitoneal injection was estimated to be 1000 mg/kg bw in rats.

3.1.3 Irritation

Skin Irritation

Studies in Animals

An unspecific volume of neat 2-furanmethanol, tetrahydro- was not irritating to the skin of three nude mice after 24-hr covered contact [Lashmar, Hadgraft and Thomas, 1989]. This chemical did not cause any significant changes in the histology over 24 hr at concentration of 100%.

Studies in Humans

A standard text indicates that this chemical was a moderate irritant to the skin and mucous membranes [Budavari, 2001].

Eye Irritation

Studies in Animals

Evaluation of ocular irritation of 2-furanmethanol, tetrahydro- was performed by measurement of Draize score, corneal thickness, corneal and conjunctival water content, and conjunctival and aqueous humor concentrations of a dye bound to plasma proteins after dye injection in rabbits [Conquest et al, 1977]. The neat test material (0.1 ml) was instilled into one eye of each of four rabbits, with scoring at 2 and 24 hr for all the above parameters and daily until 11th day for Draize scores and corneal thickness. This chemical was found to be irritant and to induce corneal damage in rabbits.

100 ul of undiluted 2-furanmethanol, tetrahydro- was placed into one eye of each of six rabbits [Jacobs et al, 1998]. The eyes were not washed following instillation. The eyes were examined and the grade of ocular reaction was recorded at 4, 24, 48, 72, 96 and 186 hours. Erythema, chemosis, iritis and corneal opacity were scored according to the Draize scores. Redness and swelling were observed, but the mean scores were below the EEC criteria

Studies in Humans

No reliable report is available. One reference cites this chemical as a severe eye irritant in humans [Lewis, 1996].

Respiratory Tract Irritation

There is no available information.

Conclusion

This chemical was a moderate eye irritant in rabbits but did not irritate the rabbit skin. Review sources suggest that it might be a moderate skin and eye irritant in humans.

3.1.4 Sensitisation

There is no available information.

3.1.5 Repeated Dose Toxicity

Studies in Animals

Inhalation

Rats (14 males and 10 females/group) were exposed to this chemical by inhalation at 0, 50, 150 or 500 ppm, six hr/day, five days a week for at least 65 exposures [TSCA Section 8(e), 1995a]. After six weeks, the reproductive tissue of four males from each group were examined. The remaining 20 animals per group were terminated after 13 weeks of treatment. Hypoactivity and intermittent whole spasms occurred and hyperactivity followed in both sexes at 500 ppm. Body weight gains, overall, did not reveal significant changes in either sex. At 150 and 500 ppm, decreased platelet count in both sexes and increased serum levels of chloride and sodium in males were found.

Rats (14 males and females/group) were exposed to this chemical via whole body inhalation at 0, 50, 150 or 500 ppm for six hr/day, five days a week, for at least 65 exposures [TSCA Section 8(e), 1995c]. After 34 exposures four males per group were terminated for assessment of spermatogenic endpoints. The remaining 10 animals per sex per group were terminated following 65 exposures. Frequent intermittent whole-body spasm and hyperactivity were observed at 50 ppm and higher. Male body weights at 150 and 500 ppm were 9.2% and 13.3% lower, respectively. Decreased platelet, hemoglobin and MCH were observed at 500 ppm in males and females. Decreased epididymal sperm number and sperm motility, and increased incidence of abnormal sperm were found at 500 ppm. Absolute and relative weights of the prostate at 150 ppm and higher, and epididymides at 500 ppm were decreased.

Dermal

Rats (17 males and 12 females/group) were administered with this chemical dermally at 0, 100, 300 or 1000 mg/kg bw/day, five days a week for at least 65 applications [TSCA Section 8(e), 1995a]. After seven weeks, the reproductive tissue of five males from each group were examined. The remaining 24 animals per group were terminated after 13 weeks . No effects were found in survival, clinical observations, ophthalmic examinations, haematology or serum chemistry parameters, organ weights, or food consumption. Decreases in weekly body weights were observed in males at 1000 mg/kg bw/day.

Rats (17 males and 12 females/group) were administered with this chemical dermally at 0, 100, 300 or 1000 mg/kg bw/day, five a week for at least 65 applications [TSCA Section 8(e), 1995b]. After 37 applications, five males from each group were sacrificed. The remaining 24 animals per group were terminated after 13 weeks on study. All males were examined for spermatogenic endpoints. No effects were observed in food consumption, haematology and serum chemistry parameters, macro- or microscopic findings or organ weights. Lower body weights were found in both sexes at 1000 mg/kg bw/day. Testicular sperm number and sperm production rate at 300 and 1000 mg/kg bw/day, and percentage of motile sperm at 1000 mg/kg bw/day were lowered.

Oral

Table 2 Repeated oral dose toxicity studies

Species	Administration	NOAEL	Toxicological effect	Reference
Crj:CD(SD)IGS rat	0, 10, 40, 150, 600 mg/kg bw/day by gavage for 28 days	NOAELs: 40 mg/kg bw/day in males and females	Increased locomotor activity, decreased body weight gain, decreased relative weight of pituitary, atrophy of thymus, necrosis of seminiferous tubular epithelium of testes, decreases in MCH, MCHC, leukocyte, ALP and LDH	MHLW, Japan, 2004
Rat	0, 1000, 3000, 10000 ppm in diet for 90 days	NOAELs: 1000 ppm in males and females	Decreased body weight gain, decrease relative weight of testes, degeneration of testes	TSCA Section 8 (e), 1991
Rat	0, 500, 1000, 5000, 10000 ppm in diet for 90 days	LOAEL:500 ppm in males NOAEL:1000 ppm in females	Decreased body weight gain, decreased relative weight of liver, testes and epididymides in males, decreases in globulin, MCH, MCHC and platelets	TSCA Section 8 (e), 1992a
Beagle dog	0, 1000, 3000, 6000 ppm in diet for 90 days	NOAEL: >1000 ppm in males	Decreased weight of testes, testicular atrophy, decreased sperm activity	TSCA Section 8 (e), 1991
Beagle dog	0, 200, 400, 800 ppm in diet for 90 days	NOAEL: >200 ppm in males	no clear-cut dose correlation	TSCA Section 8 (e), 1991
Rabbit	0, 30, 100, 300, 1000 mg/kg bw/day by gavage for five days	NOAEL: 100 mg/kg bw/day	Death, decreased locomotor activity, unsteady walk	TSCA Section 8 (e), 1992b

There are six reliable studies regarding oral toxicity of 2-furanmethanol, tetrahydro-. The 28-day repeated oral dose toxicity test [MHLW, Japan, 2004] was the most reliable and well conducted according to a Japanese test guideline equivalent to OECD TG 407 under GLP and described in details. Details of this study are as follows.

Crj:CD(SD)IGS male and female rats were given 2-furanmethanol, tetrahydro- by gavage at doses of 0 (vehicle: distilled water), 10, 40, 150 or 600 mg/kg bw/day for 28 days. The initial number of rats were 10/sex at 0 and 600 mg/kg bw/day, and five/sex at other doses. Five rats/sex from each group were killed on day 29, and the remaining five rats/sex at 0 and 600 mg/kg bw/day were kept without treatment for another 14 days (recovery period).

Increased locomotor activity followed by decreased locomotor activity and adoption of a prone position in males and females, and lowered grip strength of the hindlimb in males were found at 600 mg/kg bw/day. Increased locomotor activity was observed in females at 150 mg/kg bw/day. At 600 mg/kg bw/day, animals showed decreased body weight gain in males, food consumption in males and females, and decreased urinary pH in males. At this dose, hematological examinations revealed decreases in the mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), leukocyte count and platelet count and prolonged prothrombin time in males and females and decreases in the reticulocyte count in males and hemoglobin concentration in females. Blood biochemical examinations revealed decreases in the levels of alkaline phosphatase (ALP), total protein, albumin, total bilirubin and calcium in males and females, and lactate dehydrogenase (LDH), triglyceride, blood urea nitrogen (BUN) and sodium in males at 600 mg/kg

bw/day. At 150 mg/kg bw/day, a decrease in total protein was observed in males. Decreases in the relative weights of the thymus in males and females and pituitary in females, and an increase in the relative weight of the kidney in females were found at 600 mg/kg bw/day. At 150 mg/kg bw/day, a decreased relative weight of the pituitary was noted in females. Histopathological examinations revealed atrophy of the thymus in males and females, and atrophy of the red pulp with decreased extramedullary hematopoiesis and inflammation of the capsule of the spleen in males at 600 mg/kg bw/day. Necrosis of seminiferous tubular epithelium of the testes was observed at 150 and 600 mg/kg bw/day. Examination of the spermatogenic cycle revealed a decrease in the ratio of the spermatid to Sertoli cell counts at 600 mg/kg bw/day. Histopathological examination of the testes showed a tendency for increase in the severity of changes at the end of the 14-day recovery period. There was a decrease in the ratio of pachytene spermatocyte counts to Sertoli cell counts in addition to that of spermatid to Sertoli cell counts.

Based on these findings, the NOAELs for repeated dose toxicity were considered to be 40 mg/kg bw/day in males and females.

Rats (15 animals/sex/group) were fed a diet containing this chemical at 0, 1000, 3000 or 10000 ppm for 90 days [TSCA Section 8(e), 1991]. Body weight gain was depressed at 3000 and 10000 ppm. There was a decrease in absolute and relative weights of the testes at 10000 ppm. Moderate testicular degeneration was observed in 14 animals at 10000 ppm. These animals exhibited complete loss of spermatogenic activity and their seminiferous tubules were partially to completely lined with a single layer of Sertoli cells. Tubules were also reduced in size.

Rats (20 animals/sex/group) were fed a diet containing this chemical at 0, 500, 1000, 5000 or 10000 ppm for 90 days [TSCA Section 8(e), 1992a]. A decrease in body weight gains was noted in males at 1000, 5000 and 10000 ppm and in females at 10000 ppm. A decreased relative weight of the liver was observed in males at 500 ppm and higher. Increase in relative weights of the brain and kidney were found in males at 5000 and 10000 ppm. Decreases in relative weight of the epididymides at 5000 and 10000 ppm, and testes at 10000 ppm were observed. Increases in relative weight of the kidney at 5000 ppm, liver at 5000 and 10000 ppm, and ovary at 10000 ppm were found in females. Decreases in haemoglobin, MCH, MCHC and platelets were observed in males at 5000 ppm and higher. There is no available information on necropsy and histopathological examination.

Beagle dogs (four animals/sex/group) were fed a diet containing this chemical at 0, 1000, 3000 or 6000 ppm for 90 days [TSC Section 8(e), 1991]. Testes weight was lowered at 1000 ppm and higher. Atrophy of the testes and prostate at 6,000 ppm and decreased spermatogenic activity at 3,000 ppm were observed. There is no available information on females.

Beagle dogs (four males/group) were fed a diet containing this chemical at 0, 200, 400 or 800 ppm for 90 days to examine the testicular maturation [TSCA Section 8(e), 1991]. One animal each at 200 and 400 ppm exhibited lower absolute and relative weights of the testes. These two animals had relatively little to no spermatogenesis. However, no clear-cut dose correlation was observed and animals at 800 ppm exhibited normal testicular development, these depressions were not reported as significant.

Rabbits (three females/group) received this chemical at 0, 30, 100, 300 or 1,000 mg/kg bw/day by gavage for five days [TSCA Section 8(e), 1992b]. At 1000 mg/kg bw/day, two animals were sacrificed moribund after receiving one dose and the remaining animal died on study day 2. Decreased motor activity, unsteady walk, and prostration were observed at 300 and 1000 mg/kg bw/day.

Studies in Humans

There is no available information.

Conclusion

In the repeated inhalation toxicity study for 13 weeks in rats, the NOAELs were considered to be 50 ppm in males and females. In the repeated dermal toxicity study for 13 weeks in rats, the NOAELs were considered to be 100 mg/kg bw/day in males and 300 mg/kg bw/day in females.

In the 28-day repeated oral dose toxicity test in rats, the NOAELs were considered to be 40 mg/kg bw/day in males and females.

3.1.6 Mutagenicity

Studies in Animals

In vitro Studies

Bacterial test

A reverse gene mutation assay was conducted according to a current protocol [OECD TG 471 and Japanese Guideline for Screening Mutagenicity Testing of Chemicals (Chemical Substances Control Law of Japan)] [MHLW, Japan: 2004] under GLP. This study was well conducted.

Growth inhibition was not observed at any of the five tested concentrations up to 5 mg/plate with or without S9 mix. This chemical was not mutagenic in *Salmonella typhimurium* TA100, TA1535, TA98, TA1537 or *Escherichia coli* WP2 *uvr*A/pKM101 at concentrations up to 5000 ug/plate with or without S9 mix.

Non-bacterial in vitro test

A chromosomal aberration test was conducted according to a current protocol [OECD TG 473 and Japanese Guideline for Screening Mutagenicity Testing of Chemicals (Chemical Substances Control Law of Japan)] in cultured Chinese hamster lung (CHL/IU) cells [MHLW, Japan, 2004] under GLP. This study was well conducted.

Even at the highest concentration tested (1.03 mg/mL: 10 mmol/L), there was no effect on growth, polyploidy or the incidence of chromosome aberrations after 6- or 24-hr incubation, with or without S9 mix.

In vivo Studies

There is no available information.

Studies in Humans

There is no available information.

Conclusion

This chemical was not genotoxic with or without an exogenous metabolic activation system in bacterial tests or clastogenic in a chromosomal aberration test *in vitro*.

3.1.7 Carcinogenicity

There is no available information.

3.1.8 Toxicity for Reproduction

The preliminary reproduction toxicity screening test was well conducted according to an OECD TG 421 [MHLW, Japan, 2004] under GLP. This study was the most reliable and described in details. Details of this study are as follows.

Crj:CD(SD)IGS rats (12 animals/sex/dose) were given 2-furanmethanol, tetrahydro- by gavage at 0 (vehicle: distilled water), 15, 50, 150 or 500 mg/kg bw/day. Males were dosed for a total of 47 days beginning 14 days before mating. Females were dosed for a total of 42-52 days beginning 14 days before mating to day 4 of lactation throughout the mating and gestation period.

Males showed decreased body weight gain at 500 mg/kg bw/day. At 150 mg/kg bw/day and higher, an increased locomotor activity and reduced food consumptions in males and females, and decreased body weight gain in females were observed. At 500 mg/kg bw/day, decreased relative weights of the thymus, testes and epididymides, atrophy of the seminiferous tubule with hyperplasia of the interstitial cell of the testes, and decreased intraluminal sperms with cell debris in the epididymides were noted in males. The prolongation of estrous cycles was observed at 500 mg/kg bw/day. At this dose, no females delivered their offspring and examination of the uterus of dams revealed early embryonic resorptions. Prolonged gestation length, decreased gestation index, lowered delivery index, live birth index, numbers of pups born and live pups on postnatal days (PNDs) 0 and 4, and viability on PND 4 were observed at 150 mg/kg bw/day. No significant increase in the incidence of morphological abnormalities was found in pups of rats. Based on these findings, the NOAEL for reproductive/developmental toxicity was considered to be 50 mg/kg bw/day in rats.

Studies in Humans

There is no available information.

Conclusion

This chemical showed adverse effects on the male reproductive organs at 500 mg/kg bw/day and on reproduction/development at 150 mg/kg bw/day and higher. The NOAEL for reproductive/developmental toxicity was considered to be 50 mg/kg bw/day in rats. In a 28-day repeated oral dose toxicity test with rats, necrosis of the seminiferous tubular epithelium of the testes was observed at 150 mg/kg bw/day and higher. Adverse effects on the male reproductive organs were also found at high doses in the repeated oral dose toxicity study in dogs.

3.1.9 Developmental Toxicity/Teratogenicity

In a dose range-finding developmental toxicity study [TSCA Section 8(e):8EHQ-1092-8576S, 1992c], rats (eight animals/group) were orally given this chemical at doses of 0, 10, 50, 100, 500 or 1000 mg/kg bw/day on days 6 to 15 of pregnancy. In maternal rats, impaired mobility, decreased muscle tone and absence of pain response at 1000 mg/kg, and decreases in body weight gain and food consumption at 500 and 1000 mg/kg bw/day were observed. A 100% incidence of early resorptions at 500 and 1000 mg/kg bw/day and decreased fetal weight at 100 mg/kg bw/day were found. Although not significant statistically, fetuses with tail anomaly at 100 mg/kg bw/day were observed. The NOAELs for maternal and developmental toxicity were considered to be 100 and 50 mg/kg bw/day.

Conclusion

In a rat developmental toxicity study, decreases in maternal body weight gain and food consumption were observed at 500 and 1000 mg/kg bw/day. A 100% incidence of early resorptions

at 500 and 1000 mg/kg bw/day and decreased fetal weights at 100 mg/kg bw/day were found. The NOAELs for maternal and developmental toxicity were considered to be 100 and 50 mg/kg bw/day.

3.2 Initial Assessment for Human Health

There is no available information on toxicokinetics, metabolism or distribution.

In an acute oral toxicity study [OECD TG 423] in rats, gavage administration of 2-furanmethanol, tetrahydro- at 2000 mg/kg bw caused hypotonia and reduced locomotor activity, but did not affect growth or the appearance of the tissues, and no deaths occurred. Thus, acute oral toxicity was low.

This chemical was a moderate eye irritant in rabbits but did not irritate the rabbit skin. Review sources suggest that it might be a moderate skin and eye irritant in humans.

There is no available information on sensitisation.

In a repeated inhalation toxicity study for 13 weeks in rats, hypoactivity and intermittent whole spasms occurred and hyperactivity followed at 500 ppm and a decreased platelet count was observed at 150 and 500 ppm in both sexes. Decreased epididymal sperm number and sperm motility, and increased incidence of abnormal sperm were found at 500 ppm. Absolute and relative weights of the prostate at 150 ppm and higher, and epididymides at 500 ppm were decreased. The NOAELs were considered to be 50 ppm in males and females.

In a repeated dermal toxicity study for 13 weeks in rats, lower body weights at 1000 mg/kg bw/day in both sexes and testicular sperm number and sperm production rate at 300 and 1000 mg/kg bw/day in males were found. The NOAELs were considered to be 100 mg/kg bw/day in males and 300 mg/kg bw/day in females.

In a 28-day repeated oral dose toxicity study in rats, behavioural changes were found in males at 600 mg/kg bw/day and females at 150 mg/kg bw/day. Changes in haematological, blood biochemical and urinary parameters were detected in males at 150 mg/kg bw/day and higher and females at 600 mg/kg bw/day. Decreases in the relative weights of the thymus in males and females and pituitary in females, and an increase in the relative weight of the kidney in females were found at 600 mg/kg bw/day. At 150 mg/kg bw/day, a decreased relative weight of the pituitary was noted in females. Histopathological changes were noted in the thymus in males and females and spleen in males at 600 mg/kg bw/day. Abnormalities in the male reproductive organs were observed at 150 and 600 mg/kg bw/day. The NOAELs were considered to be 40 mg/kg bw/day in males and females.

Growth inhibition was not observed at any of the five tested concentrations up to 5 mg/plate with or without S9 mix. This chemical was not mutagenic in *Salmonella typhimurium* TA100, TA1535, TA98, TA1537 or *Escherichia coli* WP2 *uvr*A/pKM101 at concentrations up to 5000 ug/plate with or without S9 mix.

Even at the highest concentration tested (1.03 mg/mL: 10 mmol/L), there was no effect on growth, polyploidy or the incidence of chromosome aberrations after 6- or 24-hr incubation, with or without S9 mix.

There is no available information on carcinogenicity.

In a preliminary reproductive toxicity study [OECD TG 421] with rats, toxicity which was reported in the 28-day oral repeated dose toxicity study with rats was also observed in males and females. At 500 mg/kg bw/day, no females delivered their offspring and examination of the uterus of dams

revealed early embryonic resorptions. Prolonged gestation length and decreased gestation index were found at 150 mg/kg bw/day. Delivery index, live birth index, numbers of pups born and live pups on postnatal days (PNDs) 0 and 4, and viability on PND 4 were also lowered at 150 mg/kg bw/day. No significant increase in the incidence of morphological abnormalities was found in pups of rats. The NOAEL for reproductive/developmental toxicity was considered to be 50 mg/kg bw/day in rats.

In a rat developmental toxicity study, decreases in maternal body weight gain and food consumption were observed at 500 and 1000 mg/kg bw/day. A 100% incidence of early resorptions at 500 and 1000 mg/kg bw/day and decreased fetal weights at 100 mg/kg bw/day were found. The NOAELs for maternal and developmental toxicity were considered to be 100 and 50 mg/kg bw/day.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Acute Toxicity Test Results

Acute toxicity of 2-furanmethanol, tetrahydro- to aquatic species from three trophic levels has been investigated experimentally as shown in Table 3. These toxicity results were obtained from GLP compliance tests.

Table 3 Acute toxicity of 2-furanmethanol, tetrahydro- to aquatic organisms

Species	Method	Exposure	Result	Reference
Medaka *Orizias latipes*	OECD TG 203 Limit test GLP	96 h semi-static open system	LC_{50} > 101 mg/L (measured,mean)	MOE, Japan (2003)
Daphnia magna	OECD TG 202 Limit test GLP test	48 h semi-static	EC_{50}> 91.7 mg/L (measured, mean)	MOE, Japan (2003)
Pseudokirchneriella subcapitata	OECD TG 201 Limit test GLP test	72 h static, open	(rate method) ErC_{50} > 98.9 mg/L (biomass method) EbC_{50} > 98.9 mg/L (measured, mean)	MOE, Japan (2003)

Fish

A semi-static toxicity test with 2-furanmethanol, tetrahydro- to a freshwater fish, *Orizias latipes*, reported a 96h LC_{50} was >101 mg/L (MOE, Japan, 2003). According to a result from a preliminary test, a limit test was carried out (OECD TG 203).Fish were exposed only to 100 mg/L and a control, the number of fish was 10 in each. No mortality and no toxic signs were observed at the end of the test in the exposed and control group. Analytical monitoring was performed and the concentration of the test substance was kept during the exposure period.

Invertebrate

For daphnids, *Daphnia magna,* an acute toxicity test with 2-furanmethanol, tetrahydro- resulted in a 48 h EC_{50} of > 91.7 mg/L (OECD TG 202, MOE, Japan, 2003). A limit test was undertaken at 100 mg/L together with a dilution water (Elendt M4 medium) control. The test was a semi-static test with analytical monitoring showing that the measured concentrations at 0 h and 24 h were 91.6 and 91.8 mg/L, respectively. No immobilisation or toxic effects were observed.

Aquatic plant, e.g. Algae

For a freshwater alga, *Pseudokirchneriella subcapitata*, the ecotoxicity of 2-furanmethanol, tetrahydro- was available (MOE, Japan, 2003). The algal growth inhibition test (OECD TG 201) was carried out with a nominal concentration of 100 mg/L and a control. A (0-72 h) ErC50 of >98.9 mg/L (by a growth rate method) and a (0-72 h) EbC50 of > 98.9 mg/L (by a biomass method, area under growth curve) were reported based on a measured mean concentration. The test showed that the inhibition rate by the growth rate method and the biomass method was 0.3 % and 3 %, respectively.

The pH of the test water changed more than 1 unit in both exposure and control groups. The increase of pH may have occurred due to the shortage of buffer capacity of CO_2. Although there were some deviations from the test guideline 201, the test was regarded to be valid.

Chronic Toxicity Test Results

Test results on chronic toxicity which were regarded to be reliable are summarised in table 4.

Table 4 Chronic toxicity of 2-furanmethanol, tetrahydro- to aquatic organisms

Species	Method	Exposure	Result	Reference
Daphnia magna	OECD TG 211 Limit test GLP	21 d semi-static	(Reproduction) 21d EC_{50} > 95.1 mg/L 21 d NOEC = 95.1 mg/L (measured, time-weighted mean)	MOE, Japan (2003)
Pseudokirchneriella subcapitata	OECD TG 201 Limit test GLP	72 h static, open	(growth rate and biomass method) (0-72h)NOEC= 98.9 mg/L	MOE, Japan (2003)

Invertebrates

Chronic toxicity results with daphnids were reported (MOE, Japan. 2003). According to the result of a preliminary test, a limit test was conduced. In the test parent daphnids were exposed to 2-furanmethanol, tetrahydro- at a nominal concentration of 100 mg/L together with a control. No individuals died among exposed and control daphnids. The mean cumulative numbers of juveniles per adult for 21 days in the control and exposed were 115.3 and 113.9, respectively. Therefore no inhibition by this substance was observed, and the 21-d NOEC to daphnids was 95.1 mg/L based on the time weighted mean of measured concentrations.

Aquatic plant, e.g. Algae

Based on the algal growth inhibition test (MOE, Japan. 2003), the chronic NOECs of 2-furanmethanol, tetrahydro- were determined to be 98.9 mg/L by both the growth rate method and the biomass method.

Toxicity to Microorganisms

There are no data available.

4.2 Terrestrial Effects

There are no data available.

4.3 Other Environmental Effects

There are no data available.

4.4 Initial Assessment for the Environment

2-Furanmethanol, tetrahydro- is a colourless and flammable liquid with a water solubility of more than 250 g/L at 20 °C, a melting point of less than – 120 °C, a boiling point of 177.7 °C at 1013 hPa, a vapour pressure of 1.86 hPa at 25 °C and a relative density of 1.0544 at 20/20 °C. Based on the measured log Kow value of -0.11 bio- or geoaccumulation of this chemical is unlikely. Environmental distribution using Mackey level III suggests that when 2-furanmethanol, tetrahydro- is released into the environment, it distributes mainly into water and soil. A calculated Henry's Law constant of 4.09×10^{-9} atm-m^3/mole indicates that only a limited extent of volatilisation from water may occur. 2-Furanmethanol, tetrahydro- is readily biodegradable (10-day window fulfilled) but abiotic degradation is not expected in water. In the atmosphere 2-furanmethanol, tetrahydro- is indirectly photodegraded by reaction with OH radical with a half-life of 0.5 days.

Eco-toxicity data for this substance were available in aquatic species from three trophic levels. In the algal growth inhibition test (OECD TG 201, *Pseudokirchneriella subcapitata,* open system), both the (0-72 h) ErC_{50} and the (0-72 h) EbC_{50} were > 98.9 mg/L. For daphnids, the 48 h EC_{50} of > 91.7 mg/L was reported (OECD TG 202, *Daphnia magna*, semi-static). For fish (OECD TG 203, *Oryzias latipes,* semi-static) a 96 h LC_{50} > 101 mg/L is available.

Regarding chronic toxicity to algae, the (0-72 h) NOEC by growth rate and biomass methods was 98.9 mg/L (OECD TG 201, *Pseudokirchneriella subcapitata*, open system). For daphnids, a 21 d EC_{50} of > 95.1 mg/L for reproduction and a 21 d NOEC of 95.1 mg/L for reproduction are available (OECD TG 211, *Daphnia magna,* semi-static).

5 RECOMMENDATIONS

Human Health: The chemical is a candidate for further work.

The chemical possesses a hazard for human health (repeated dose toxicity, irritation, reproductive/developmental toxicity). Exposure to general public is expected through dermal contact and inhalation. This chemical is produced in a closed system in Japan, but used to formulate various products, occupational exposure through inhalation and dermal route is possible in both production and user sites. Therefore, an exposure assessment and, if necessary, risk assessment for workers and consumers are recommended.

Environment: The chemical is currently of low priority for further work because of its low hazard potential.

6 REFERENCES

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- Log Pow with KOWWIN v.1.67, 2000
- Water solubility with WSKOW v1.40, 2000
- Indirect Photodegradation with AOPWIN v.1.91, 2000
- Henry's Law Constant with HENRYWIN v.3.10, 2000
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TSCA Section 8(e):8EHQ-0992-1381 (1992b)

TSCA Section 8(e):8EHQ-1092-8576S (1992c)

TSCA Section 8(e):8EHQ-0195-13310 (1995a)

TSCA Section 8(e):8EHQ-0995-13505 (1995b)

TSCA Section 8(e):8EHQ-0995-13504 (1995c)

I U C L I D

Data Set

Existing Chemical	:	ID: 97-99-4
CAS No.	:	97-99-4
EINECS Name	:	2-Furanmethanol, tetrahydro-
EC No.	:	202-625-6
Molecular Formula	:	C5H10O2

Producer related part

Company	:	National Institute of Health & Sciences
Creation date	:	27.12.2004

Substance related part

Company	:	National Institute of Health & Sciences
Creation date	:	27.12.2004
Status	:	
Memo	:	OECD HPV Chemicals programme, SIDS Dossier, approved at SIAM 20 (19-21 April 2005)
Printing date	:	17.11.2005
Revision date	:	
Date of last update	:	17.11.2005
Number of pages	:	1
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

Type : lead organisation
Name : National Institute of Health & Sciences
Contact person :
Date :
Street : 1-18-1, Kamiyoga, Setagaya-ku
Town : 158-8501 Tokyo
Country : Japan
Phone : +81-3-3700-9878
Telefax :
Telex : 03-3700-1408
Cedex :
Email :
Homepage :

27.12.2004

Type : cooperating company
Name : National Institute of Environmental Studies, Environment Agency
Contact person :
Date :
Street : 16-2, Onogawa
Town : 305-0053 Tsukuba-Ibaraki
Country : Japan
Phone : +81-29-850-2458
Telefax : +81-29-850-2920
Telex :
Cedex :
Email :
Homepage :

27.12.2004

Type : cooperating company
Name : Chemicals Evaluation and Research Institute (CERI)
Contact person :
Date :
Street : 1-4-25 Koraku, Bunkyo-ku
Town : 112-0004 Tokyo
Country : Japan
Phone : +81-3-5804-6134
Telefax : +81-3-5804-6140
Telex :
Cedex :
Email :
Homepage :

27.12.2004

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

Type : manufacturer
Name of plant : Koatsu Chemical Industries, Ltd.
Street : 1-12, Tsurumachi 5-chome, Taisyou-ku
Town : 551-0023 Osaka
Country : Japan

Phone : +81-6-6552-0153
Telefax : +81-6-6552-0226
Telex :
Cedex :
Email :
Homepage :

27.12.2004

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

IUPAC Name : 2-Furanmethanol, tetrahydro-
Smiles Code : O(C(CC1)CO)C1
Molecular formula : C5H10O2
Molecular weight : 102.13
Petrol class :

Remark : Reference for Smiles Code: EPIWIN
27.12.2004

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type : measured for specific batch
Substance type : organic
Physical status : liquid
Purity : = 99.3 % w/w
Colour : Colourless transparent liquid
Odour :

27.12.2004 (1)

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

Tetrahydro-2-furanmethanol

27.12.2004 (2)

2-Furanmethanol, tetrahydro-

Remark : IUPAC name
27.12.2004 (3)

2-Hydroxymethyl oxolane

27.12.2004 (4)

Tetrahydro-2-furancarbinol

27.12.2004 (4)

Tetrahydro-2-furylmethanol

27.12.2004 (2)

Tetrahydrofurfuryl alcohol

27.12.2004 (2)

Tetrahydrofurfuryl alcohol

27.12.2004 (4)

THFA

27.12.2004 (2)

1.3 IMPURITIES

Purity	:	measured for specific batch
CAS-No	:	7732-18-5
EC-No	:	231-791-2
EINECS-Name	:	water
Molecular formula	:	H2O
Value	:	= .1 % w/w
Remark	:	Supplier: Wako Pure Chemical Ltd. Lot No. SEF4748 Purity: 99.3 % Impurity: water=0.1% Unknown=0.6%

05.01.2005 (1)

1.4 ADDITIVES

1.5 TOTAL QUANTITY

Quantity	:	ca. 30 - tonnes produced in 2003
Remark	:	A global production volume is unknown. Annual production volume in Japan is ca. 30/tonnes (2003).

27.12.2004 (5)

1.6.1 LABELLING

Labelling	:	as in Directive 67/548/EEC
Specific limits	:	
Symbols	:	Xi, , ,
Nota	:	, ,
R-Phrases	:	(36) Irritating to eyes
S-Phrases	:	(39) Wear eye/face protection

Remark : Labelling data were based on ICSC 27.12.2004 (4)

1.6.2 CLASSIFICATION

1.6.3 PACKAGING

1.7 USE PATTERN

Type of use : industrial
Category : Basic industry: basic chemicals

01.07.2005 (5)

Type of use : industrial
Category : Chemical industry: used in synthesis

27.12.2004 (5)

Type of use : industrial
Category : Paints, lacquers and varnishes industry

01.07.2005 (5)

Type of use : use
Category : Intermediates

01.07.2005 (5)

Type of use : type
Category : Use resulting in inclusion into or onto matrix

01.07.2005 (5)

Type of use : type
Category : Wide dispersive use

01.07.2005

Type of use : use
Category : Solvents

01.07.2005

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

1.8.4 MAJOR ACCIDENT HAZARDS

1.8.5 AIR POLLUTION

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

1.11 ADDITIONAL REMARKS

1.12 LAST LITERATURE SEARCH

Type of search : Internal and External
Chapters covered : 1
Date of search : 27.12.2004

27.12.2004

Type of search : Internal and External
Chapters covered : 2
Date of search : 27.12.2004

27.12.2004

Type of search : Internal and External
Chapters covered : 3
Date of search : 27.12.2004

27.12.2004

1.13 REVIEWS

2.1 MELTING POINT

Value : < -120 °C
Decomposition : no, at °C
Sublimation :
Method : OECD Guide-line 102 "Melting Point/Melting Range"
Year : 2004
GLP : yes
Test substance :

Remark : A study was conducted according to OECD Test Guideline 102 "Melting point/Melting range: Differential Scanning Carolimetry (DSC)".
No clear melting point was observed in a range of 100 to -120 degree C.
Test substance : Supplier: Wako Pure Chemical Ltd.
Lot No. SEF4748
Purity: 99.3 %
Impurity: water=0.1%
Unknown=0.6%
Reliability : (2) valid with restrictions
Guideline study conducted under GLP condition.
No clear melting point/range was reported.
06.01.2005 (6)

Value : = -20.9 °C
Sublimation :
Method : other: Calculated by MPBPWIN v.1.41, 2000
Year : 2000
GLP :
Test substance :

Method : Mean or Weighted MP.
Reliability : (2) valid with restrictions
Accepted calculation method.
05.01.2005 (7)

Value : < -80 °C
Sublimation :
Method : other: Not specified
Year : 2003
GLP :
Test substance : other TS: Not specified.

Source : CRC Handbook of Chemistry and Physics.
Reliability : (2) valid with restrictions
Data from peer reviewed data source.
Flag : Critical study for SIDS endpoint
05.01.2005 (8)

2.2 BOILING POINT

Value : = 177.7 °C at 1013 hPa
Decomposition :
Method : OECD Guide-line 103 "Boiling Point/boiling Range"
Year : 2004
GLP : yes
Test substance :

Method : A study was conducted according to Siwoloboff method.
Result : 177.6, 177.7 degree C. (Av. 177.7 degree C)
Test substance : Supplier: Wako Pure Chemical Ltd.
Lot No. SEF4748
Purity: 99.3 %
Impurity: water=0.1%
Unknown=0.6%
Reliability : (1) valid without restriction
Guideline study conducted under GLP cndition.
Flag : Critical study for SIDS endpoint
06.01.2005 (9)

Value : = 172.4 °C at
Decomposition :
Method : other: Calculated by MPBPWIN v.1.41 (2000)
Year : 2000
GLP :
Test substance :

Method : Adapted Stein & Brown method.
Reliability : (2) valid with restrictions
Accepted calculation method.
06.01.2005 (7)

Value : = 178 °C at 1013
Decomposition :
Method : other: not specified
Year : 2003
GLP :
Test substance : other TS: not specified

Source : CRC Handbook of Chemistry and Physics.
Reliability : (2) valid with restrictions
Data from peer reviewed data source.
05.01.2005 (8)

2.3 DENSITY

Type : relative density
Value : = 1.0544 at 20 °C
Method : other: not specified
Year : 2003
GLP :
Test substance : other TS: not specified

Source : CRC Handbook of Chemistry and Physics.
Reliability : (2) valid with restrictions
Data from peer reviewed data source.
Flag : Critical study for SIDS endpoint
05.01.2005 (8)

Type : relative density
Value : = 1.0558 at 20 °C

Reliability : (4) not assignable
Manufacture data without proof.
Flag : Material Safety Dataset
05.01.2005 (1)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : = 1.86 hPa at 25 °C
Decomposition :
Method : OECD Guide-line 104 "Vapour Pressure Curve"
Year : 2004
GLP : yes
Test substance :

Method : Measured according to static method.
Result : Measurements were carried out at 40, 50 and 60 degree C (n=3).

	C	VP (hPa)
Temp.	40	3.99, 3.99, 3.99
	50	5.99, 5.99, 5.99
	60	9.98, 9.98, 9.31

A vapour pressure at 25 degree C was obtained by extrapolation.
Test substance : Supplier: Wako Pure Chemical Ltd.
Lot No. SEF4748
Purity: 99.3 %
Impurity: water=0.1%
Unknown=0.6%
Reliability : (1) valid without restriction
Guideline study conducted under GLP condition.
Flag : Critical study for SIDS endpoint
06.01.2005 (10)

Value : = .3625 hPa at 25 °C
Decomposition :
Method : other (calculated): MPBPWIN v.1.41, 2000
Year :
GLP :
Test substance :

Reliability : (2) valid with restrictions
Accepted calculation method.
05.01.2005 (7)

Value : = 1.066 hPa at 25 °C

Source : Physical and Thermodynamic Properties of Pure Chemicals Data Compilation.
Reliability : (2) valid with restrictions
Data from reliable handbook or collection of data.
05.01.2005 (11)

2.5 PARTITION COEFFICIENT

Partition coefficient : octanol-water
Log pow : = -.11 at 20 °C
pH value :
Method : OECD Guide-line 107 "Partition Coefficient (n-octanol/water), Flask-shaking Method"
Year : 2004

GLP : yes
Test substance :

Test condition : Condition:

Octanol (ml)	Water (ml)	Test substance (mg)
5	30	5.0
10	25	5.0
20	15	5.0

Analytical method:
Gas chromatography with external standard.

Result: (log value)

Condition-1	Condition-2	Condition-3
-0.11	-0.11	-0.11
-0.11	-0.11	-0.11

Overall average value = -0.11

Test substance : Supplier: Wako Pure Chemical Ltd.
Lot No. SEF4748
Purity: 99.3 %
Impurity: water=0.1%
Unknown=0.6%

Reliability : (1) valid without restriction
Guideline study conducted under GLP condition.

Flag : Critical study for SIDS endpoint

06.01.2005 (12)

Partition coefficient : octanol-water
Log pow : = -.11 at °C
pH value :
Method : other (calculated): KOWWIN v.1.66
Year : 2004
GLP :
Test substance :

Reliability : (2) valid with restrictions
Accepted calculation method.

05.01.2005 (7)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in : Water
Value : > 250 g/l at 20 °C
pH value : = 4.6 - 4.7
concentration : 250 g/l at 20 °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :
Deg. product :
Method : OECD Guide-line 105
Year : 2004
GLP : yes
Test substance :

Method : 1.25 g of test substance was added in 5 ml of distilled water (n=3).
Test solutions were shaken at 20 degree C for one hours and left standing for another 2 hours.
Visually confirmed the complete dissolution and checked by GC analysis
Test substance : Supplier: Wako Pure Chemical Ltd.
Lot No. SEF4748
Purity: 99.3 %
Impurity: water=0.1%
Unknown=0.6%
Reliability : (1) valid without restriction
Guideline study conducted under GLP condition.
Flag : Critical study for SIDS endpoint
06.01.2005 (13)

Solubility in : Water
Value : = 463.4 g/l at 25 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :
Deg. product :
Method : other: calculated by WSKOW v1.40. (2000)
Year : 2004
GLP :
Test substance :

Reliability : (2) valid with restrictions
Accepted calculation method.
06.01.2005 (7)

Solubility in : other
Value : at °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :

Remark : Miscible with water, alcohol, ether, acetone, chloroform and benzene
Source : The Merck Index.
Reliability : (2) valid with restrictions
Data from peer reviewed data source.
06.01.2005 (14)

2.6.2 SURFACE TENSION

Test type : other: not specified
Value : = .037 mN/m at 25 °C
Concentration :
Method : other: not specified
Year :
GLP :
Test substance :

Source : The Merck Index

Reliability : (2) valid with restrictions
Data from peer reviewed data source.
Flag : Critical study for SIDS endpoint
06.01.2005 (14)

2.7 FLASH POINT

Value : = 75 °C
Type : open cup
Method :
Year : 1997
GLP :
Test substance :

Source : Fire Protection Guide to Hazardous Materials.
Reliability : (2) valid with restrictions
Data from peer reviewed data source.
Flag : Critical study for SIDS endpoint
06.01.2005 (15)

2.8 AUTO FLAMMABILITY

Remark : Autoignition Temperature = 282 degree C.
Source : Fire Protection Guide to Hazardous Materials. 12 ed
Reliability : (2) valid with restrictions
Data from peer reviewed data source.
Flag : Critical study for SIDS endpoint
06.01.2005 (15)

2.9 FLAMMABILITY

Result : flammable
Method :
Year : 1997
GLP :
Test substance :

Remark : Flammable Limits:
Lower flammable limit = 1.5% by volume, Upper flammable limit = 9.7% by volume.
Reliability : (2) valid with restrictions
Data from peer reviewed data source.
Flag : Critical study for SIDS endpoint
06.01.2005 (15)

2.10 EXPLOSIVE PROPERTIES

Result : explosive under influence of a flame
Method :
Year : 1996
GLP :
Test substance :

Remark : Lower explosive limit: 1.5% Upper explosive limit: 9.7% @

22.2 to 50 degree C.

Source : Lewis, R.J. Sax's Dangerous Properties of Industrial Materials.

Reliability : (2) valid with restrictions
Data from peer reviewed data source.

Flag : Critical study for SIDS endpoint

06.01.2005 (16)

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

Value : = 6.24 - mPa s (dynamic) at 20 °C

Result :

Method :

Year : 1996

GLP :

Test substance :

Source : The Merck Index

Reliability : (2) valid with restrictions
Data from peer reviewed data source.

Flag : Critical study for SIDS endpoint

06.01.2005 (14)

2.14 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
INDIRECT PHOTOLYSIS		
Sensitizer	:	OH
Conc. of sensitizer	:	1500000
Rate constant	:	= .00000000002358 cm^3/(molecule*sec)
Degradation	:	= 50 % after .5 day(s)
Deg. product	:	
Method	:	other (calculated): AOPWIN v1.90
Year	:	2004
GLP	:	
Test substance	:	
Remark	:	Calculated by SRC-AOPWIN v1.90. Based on 12hrs/day irradiation.
Reliability	:	(2) valid with restrictions Valid calculation method.
Flag	:	Critical study for SIDS endpoint

06.01.2005 (7)

3.1.2 STABILITY IN WATER

Type	:	abiotic
t1/2 pH4	:	> 1 year at 25 °C
t1/2 pH7	:	> 1 year at 25 °C
t1/2 pH9	:	> 1 year at 25 °C
Deg. product	:	no
Method	:	OECD Guide-line 111 "Hydrolysis as a Function of pH"
Year	:	2004
GLP	:	yes
Test substance	:	
Method	:	20 mg/l of test substance solutions at pHs 4, 7 and 9 were incubated at 50 degree C for 5 days (n=2). Concentrations after incubation were determined by gas chromatography. More than 90 % of the initial concentration was maintained in all vessels.
Result	:	The test substance was stable in water and its half-life at 25 degree C was calculated more than 1 year at pHs 4, 7 and 9.
Reliability	:	(1) valid without restriction Guideline study conducted under GLP condition.
Flag	:	Critical study for SIDS endpoint

06.01.2005 (17)

Type	:	abiotic
t1/2 pH4	:	at °C
t1/2 pH7	:	at °C
t1/2 pH9	:	at °C
Deg. product	:	
Method	:	other
Year	:	1990
GLP	:	
Test substance	:	

Remark : 2-Furanmethanol, tetrahydro- is not expected to undergo hydrolysis in the environment due to the lack of hydrolyzable functional groups.
Source : Handbook of Chemical Property Estimation Methods.
Reliability : (2) valid with restrictions
Data from peer reviewed data source.

04.07.2005 (18)

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type : volatility
Media : water - air
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method : other: calculated by HENRYWIN v3.10 (Bond Method)
Year : 2000

Remark : The Henry's Law Constant was calculated using a water solubility of 250 g/l, a vapour pressure of 1.395mmHg, a molecular weight of 102.13 and a temperature of 25 degree C.
Result : The calculated Henry's Law constant was 4.09x10-9 atm-m3/mole.
Reliability : (2) valid with restrictions
Accepted calculation method.
Flag : Critical study for SIDS endpoint
06.01.2005 (7)

3.3.2 DISTRIBUTION

Media : air - biota - sediment(s) - soil - water
Method : other (calculation): Level III Fugacity Model
Year : 2004

Remark : The following input parameters were used for the calculation.
Molecular weight: 102.13
Melting point (degree C): -80 (measured)
Vapour pressure (mmHG): 1.395 (measured)
Water solubility (g/l): 250 (measured)
Log Kow: -0.11 (calculated)
Temperature (degree C): 25

Result :

	Mass amount (%)	Half-life (h)	Emission (kg/h)
Air	1.67	10.9	1000
Water	54.3	360	1000
Soil	44	360	1000
Sediment	0.091	1440	0

Reliability : (2) valid with restrictions
Accepted calculation method.
Flag : Critical study for SIDS endpoint
12.08.2005 (7)

Media : water - soil
Method : other (calculation): PCKOCWIN v1.66
Year : 2004

Result : Calculated Koc value is 1 (log Koc = 0.0)
Reliability : (2) valid with restrictions
Accepted calculation method.
Flag : Critical study for SIDS endpoint
06.01.2005 (7)

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic
Inoculum : activated sludge, non-adapted
Concentration : 100 mg/l related to Test substance
related to
Contact time : 28 day(s)
Degradation : = 90 - 94 (±) % after 28 day(s)
Result : readily biodegradable
Kinetic of testsubst. : 7 day(s) = 15 - 67 %
14 day(s) = 72 - 92 %
21 day(s) = 87 - 92 %
28 day(s) = 90 - 94 %
%
Control substance : Aniline
Kinetic : 7 day(s) = 70 %
14 day(s) = 75 %
Deg. product : no
Method : OECD Guide-line 301 C "Ready Biodegradability: Modified MITI Test (I)"
Year : 2004
GLP : yes
Test substance :

Result : Following resuts were reported.

Biodegradation rates (28 days)
---
by BOD 92% 94% 90% (Av. 92%)
by TOC 97% 98% 98% (Av. 98%)
by GC 100% 100% 100% (Av. 100%)

Three measurement methods (BOD, TOC and GC) suggested complete degradation. 10-day window was also met.
Oxygen uptake in the inoculum blank was 2.9 mg-O2/L in 28 days.
Test condition : 30 mg of the test substance (n=3) or aniline (n=1) and 9 mg of activated sludge (as MLSS) were added into 300 ml of test medium.
The test and control vessels were incubated for 28 days at 25 dgree C.
Biodegradabilities of the test and the control substance were continuously measured by BOD meter. After 28 days cultivation, residual amount of the test substance was determined by DOC and GC analysis.

Test substance	:	Supplier: Wako Pure Chemical Ltd. Lot No. SEF4748 Purity: 99.3 % Impurity: water=0.1% Unknown=0.6%
Reliability	:	(1) valid without restriction Guideline study under GLP condition.
Flag	:	Critical study for SIDS endpoint

12.08.2005 (19)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

BCF	:	= 3.16
Elimination	:	
Method	:	other: calculated by BCFWIN v2.14
Year	:	2004
GLP	:	
Test substance	:	
Remark	:	Calculation was conducted based on a log Pow value of -0.11.
Reliability	:	(2) valid with restrictions Accepted calculation method.
Flag	:	Critical study for SIDS endpoint

06.01.2005 (7)

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	semistatic
Species	:	Oryzias latipes (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC0	:	> 101 measured/nominal
LC50	:	> 101 measured/nominal
Limit test	:	yes
Analytical monitoring	:	yes
Method	:	OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year	:	2003
GLP	:	yes
Test substance	:	other TS: E and E solutions Inc., Lot. No.;2002-4, Purity = 99.480%

Method :

-Test Organisms:
a) Supplier: Test organisms were obtained from private reproduction in Japan.
b) Size (length and weight): 2.29cm (2.19 - 2.40cm) in length; 0.197 g (0.161 - 0.229 g) in weight.
c) Age: About 1 year old.
d) Any pretreatment: Test organisms were acclimated for 18 days before testing. During acclimination, test fishes were fed with TETRAMINE.The mortality of the test organisms for 7 days before testing was below 5%. LC50(96 hr) for a reference substance (copper sulfate pentahydrate) was 1.2 mg/L.

-Test substance: tetrahydrofurfurylalkohol
a) Empirical Formula:C5H10O2
b) Molecular Weight: 102.13
c) Purity: = 99.480 %
d) Boiling Point: 178 C
e) Water Solubility: High

-Test Conditions:
a) Dilution Water Source: Tap water in Yokohama, Japan treated activate carbone, dechlorinated and fully aerated.
b) Dilution Water Chemistry: pH: 7.6 (21 C)
Total hardness (as CaCO3): 73 mg/L
c) Exposure Vessel Type: 5 L glass beaker
d) Nominal Concentrations: control and 100 mg/L (limit test)
e) Vehicle/Solvent and Concentrations: Not used.
f) Stock Solutions Preparations and Stability: Test substance was diluted with dilution water. Test substance was stored in desiccator (room temperature, dark place, nitrogen inclusion). The stability of the chemical was confirmed by IR absorption spectrum. Under the stock condition, IR spectrum of the test substance at the end of test was same at the start.
g) Number of Replicate: 1
h) Fish per Replicates: 10
i) Renewal Rate of Test Water: 24 - hour intervals
j) Water Temperature: 24+/1C
k) Light Condition: 16:8 hours, light-darkness cycle
l) Feeding: None
m) Aeration : None

-Analytical Procedure: The test concentrations were measured at the start, 48th and 96th hours using GC.

-Statistical Method:
a) Data Analysis:None
b) Method of Calculating Mean Measured Concentrations (i.e. arithmetic mean, geometric mean, etc.):Geometric mean

-

Result : - Measured Concentrations: The test concentrations were measured at the start and before water replacemnt (24-hour) for the test using GC.

Nominal Conc.	Measured Conc. (mg/L)			Percent of Nominal (%)	
mg/L	0 Hour	24 Hour	Geo mean	0 Hour	24 Hour
Control	<0.3	<0.3	---	---	---
100	102	99.8	101	102	100

- Water chemistry (pH, DO and temperature in test): Water chemistry were measured for each concentration everyday.
pH: 7.4 - 7.8
DO: 6.1 - 8.5 mg/L
Water Temperature: 23.6 - 24.1 C

-Effect Data(mortality):
LC50 (96hr) > 101 mg/L (mc)
LC0 (96hr) > 101 mg/L (mc)
The LC50 value and its 95% confidence limits could not be determined because the test was conducted as a limit test.

- Cumulative Mortality: None of test organisms were killed during exposure period at both control and 100mg/L.

Measured Conc.	Cumulative Number of Dead (Percent Mortality)			
mg/L	24 Hour	48 Hour	72 Hour	96Hour
Control	0 (0)	0 (0)	0 (0)	0 (0)
101	0 (0)	0 (0)	0 (0)	0 (0)

-Other Effect: Symptoms of toxicity was not observed during test period.

- Calculation of toxicity values: The calculation of toxicity values was the measured concentration.

Source : National Institute for Environment Studies Ibaraki
Reliability : (1) valid without restriction
12.08.2005 (20)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type : semistatic
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
NOEC : > 91.7 measured/nominal

EC50	:	> 91.7 measured/nominal
Limit Test	:	yes
Analytical monitoring	:	yes
Method	:	OECD Guide-line 202
Year	:	2003
GLP	:	yes
Test substance	:	other TS:E and E solutions Inc., Lot. No.;2002-4, Purity = 99.480%

Method :

-Test Organisms:
a) Age: < 24 hours old
b) Supplier/Source: Test organisms were obtained from the National Institute of Environmental Studies (Japan).
c) Any pretreatment: Parental daphnids were acclimated for 3 weeks on test condition before testing. During acclimatization, test daphnids were fed with Chlorella vulgaris, 0.2 mg carbon/day/individual. Juveniles in batches of high mortality and contain resting eggs and males were not used as test indivisuals. EC50 (48hr, immobility) for reference substance (potassium dichromate) was 0.75 mg/L.

-Test substance: tetrahydrofurfurylalkohol
a) Empirical Formula:C5H10O2
b) Molecular Weight: 102.13
c) Purity: = 99.480 %
d) Boiling Point: 178 C
e) Water Solubility: High

-Test Conditions:
a) Dilution Water Source: Elendt M4
b) Dilution Water Chemistry:
c) Exposure Vessel Type: 100 mL test solution in a 100 mL glass beaker coverd with teflon sheet on surface and cap.
d) Nominal Concentrations: control and 100 mg/L
e) Vehicle/Solvent and Concentrations: Not used.
f) Stock Solutions Preparations and Stability: Test substance was diluted with Elendt M4. Test substance was stored in desiccator (room temperature, dark place, nitrogen inclusion). The stability of the chemical was confirmed by IR absorption spectrum. Under the stock condition, IR spectrum of the test substance at the end of test was same at the start.
g) Number of Replicates: 4
h) Individuals per Replicates: 5
i) Water Temperature: 20+/-1C
j) Light Condition: 16:8 hours, light-darkness cycle
k) Feeding: None
l) Aeration : None

- Analytical Procedure: Test concentrations were measured at the start and the end of test using GC.

- Statistical Method:
a) Data Analysis: None
b) Method of Calculating Mean Measured Concentrations:Geometric mean.

Result :

- Measured Concentrations: The test concentrations were measured at the start and before water replacement (24th hour).

Nominal Conc.	Measured Conc., mg/L		Percent of Nominal, %	
mg/L	0 Hour	24 Hour	0 Hour	24 Hour

	New	Old	Geomean	New	Old
Control	<0.3	<0.3	---	---	---
100	91.6	91.8	91.7	92	92

new: freshly prepared test solution.
old: test solution after 48 hours exposure

- Water chemistry (pH, DO, temperature and total hardness in test): Water chemistry were measured for control and 100 mg/L at the start and before water replacement during test period.
pH: 8.2 - 8.3
DO: 8.5 - 8.8 mg/L
Water Temperature: 19.6 - 20.0 C
Total hardness (as CaCO3): 260 mg/L

-Effect Data:
EC50 (48hr) > 91.7 mg/L (mc)
NOEC (48hr) > 91.7 mg/L (mc)

-Mortality or Immobility:None of test organisms were immobilized the behavior both control and 100mg/L.

Measured Conc.	Cumulative Number of Immobilized Daphnia (Percent Immobility)	
mg/L	24 Hour	48 Hour
Control	0 (0)	0 (0)
91.7	0 (0)	0 (0)

- Calculation of toxic values: Measured concentration.

Source : National Institute for Environment Studies Ibaraki
Reliability : (1) valid without restriction
12.08.2005 (20)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species : other algae: Pseudokirchneriella subcapitata
Endpoint : growth rate
Exposure period : 72 hour(s)
Unit : mg/l
NOEC : > 98.9 measured/nominal
EC50 : > 98.9 measured/nominal
Limit test : yes
Analytical monitoring : yes
Method : OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year : 2003
GLP : yes
Test substance : other TS:E and E solutions Inc., Lot. No.;2002-4, Purity = 99.480%

Method : -Test Organisms:
a) Supplier/Source: Obtained from American Type Culture Collection.
b) Method of Cultivation: Sterile
c) Strain Number:ATCC22662

d) Any pretreatment: Acclimated for 5 days before testing.

-Test substance: tetrahydrofurfurylalkohol
a) Empirical Formula:C5H10O2
b) Molecular Weight: 102.13
c) Purity: = 99.480 %
d) Boiling Point: 178 C
e) Water Solubility: High

- Test Conditions:
a) Medium: OECD medium
b) Exposure Vessel Type: 100 mL Medium in a 300mL glass Erlenmeyer flask with breathable silicon cap.
c) Nominal Concentrations: control and 100 mg/L
d) Vehicle/Solvent and Concentrations:Not used
e) Sock Solution Preparations and Stability: Test substance was diluted with OECD medium. Test substance was stored in desiccator (room temperature, dark place, nitrogen inclusion). The stability of the chemical was confirmed by IR absorption spectrum. Under the stock condition, IR spectrum of the test substance at the end of test was same at the start.
f) Number of Replicates: 3
g) Initial Cell Number: 10,000 cells/mL
h) Water Temperature: 23+/-2C
i) Light Condition: 4000 lux, continuously
j)Shaking: 100 rpm

- Analytical Procedure: Test concentrations were measured at the start and the end of test using by GC after removing algal cells by a centrifuge.

- Statistical Method:
a) Data Analysis: Student's t-test (a=0.05, both side) for NOEC, after homoscedastic test (F-test).
b) Method of Calculating Mean Measured Concentrations (i.e. arithmetic mean, geometric mean, etc.):The measured concentration at start of the test was used for calculation.
-

Result **:** - Measured Concentrations : Test concentrations were measured at the start and the end of test using by GC. All of them, the deviation from the nominal were less than +/- 10%.

Nominal Conc.	Measured Conc. mg/L		Percent of Nominal conc. %	
mg/L	0 Hour	72 Hour	0 Hour	72 Hour
Control	<0.2	<0.2	---	---
100	98.9	91.0	99	91

- Water chemistry (pH and temperature in test): pH was measured for control and 100mg/L at the start and the end of test. At the start and the end of test, the pH was 7.8 - 7.9 and 9.8- 10.2 respectively.
Temperature in algal culture cabinet was measured at least once per day and maintained 23.0 C during test period.
pH: 7.8 - 10.2
temperature: 23 +/-2 C

-Effect Data: Rate Method
EC50 (0 - 72 hr) :> 98.9 mg/L

NOEC (0 - 72 hr) : > 98.9 mg/L

- Growth Inhibition (%) of Pseudokirchneriella subcapitata

Growth rate, Inhibition and Cell density Measured

Conc. mg/L	Rate (Average) u(0-72hr)	Inhibition(%) Im(0-72hr)	Cell density(72hr)
Control	1.87	---	2752333
98.9	1.87	0.33	2702333

- Growth Curves: Exponential growth phase during 72 hours.

- Calculation of toxic value:Measured concentration at start of the test.

Source : National Institute for Environment Studies Ibaraki
Reliability : (1) valid without restriction
12.08.2005 (20)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

Species : Daphnia magna (Crustacea)
Endpoint : reproduction rate
Exposure period : 21 day(s)
Unit : mg/l
NOEC : > 95.1 measured/nominal
LOEC : > 95.1 measured/nominal
EC50 : > 95.1 measured/nominal
Analytical monitoring : yes
Method : OECD Guide-line 211
Year : 2003
GLP : yes
Test substance : other TS: E and E solutions Inc., Lot. No.;2002-4, Purity = 99.480%

Method : -Test Organisms:
a) Age: < 24 hours old
b) Supplier/Source: Test organisms were obtained from the National Institute of Environmental Studies (Japan).
c) Any pretreatment: Parental daphnids were acclimated for 4 weeks on test condition before testing. During acclimatization, test daphnids were fed with Chlorella vulgaris, 0.2 mg carbon/day/individual. Mothers of test individuals were selected from batches which were not observed death individuals and any resting-eggs and maledaphnia. EC50 (48hr, immobility) for reference substance (potassium dichromate) was 0.75 mg/L.

-Test substance: tetrahydrofurfurylalkohol
a) Empirical Formula:C5H10O2
b) Molecular Weight: 102.13
c) Purity: = 99.480 %
d) Boiling Point: 178 C
e) Water Solubility: High

-Test Conditions:
a) Dilution Water Source: Elendt M4
b) Dilution Water Chemistry:
c) Exposure Vessel Type: 80 mL test solution in a 100 mL glass beaker coverd with teflon sheet on surface and cap.
d) Nominal Concentrations: control and 100 mg/L
e) Vehicle/Solvent and Concentrations: Not used.
f) Stock Solutions Preparations and Stability: Test substance was diluted with Elendt M4. Test substance was stored in desiccator (room temperature, dark place, nitrogen inclusion). The stability of the chemical was confirmed by IR absorption spectrum. Under the stock condition, IR spectrum of the test substance at the end of test was same at the start.
g) Number of Replicates: 10
h) Individuals per Replicates: 1
i) Water Temperature: 20+/-1C
j) Light Condition: 16:8 hours, light-darkness cycle
k) Feeding: 0.15 mg carbon/day/individual (Chlorella vulgaris: Green Algae)
l) Aeration : None

- Analytical Procedure: The test concentrations were measured 3 times during test period for both renewal and old test solution using GC.
- Statistical Method:
a) Data Analysis:
LC50 and EC50: LC50 , EC50 and their 95%c.l. cannot be calculated.
NOEC and LOEC: The cumulative number of juveniles produced per adult in control and 100mg/L after 21days was tested by Student's t-test (show homoscedasticity on F-test) or Welch's t-test (show nonhomoscedasticity on F-test) (Statlight, Yukms Corp., Tokyo).
b) Method of Calculating Mean Measured Concentrations (i.e. arithmetic mean, geometric mean, etc.): Time-weighted Mean

-

Result **:** - Effect: reproduction- Measured Concentrations: The test concentrations were measured for both renewal and old test solution at the start of the test and 1st, 7th, 8th, 14th and 15th day.

Nominal Conc.	Measured Concentration, mg/L						
mg/L Date	0	1	7	8	14	15	TWM*
	New	Old	New	Old	New	Old	(mg/L)
Control	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3	---
100	96.1	95.4	96.1	95.2	94.6	93.5	95.1

new: freshly prepared test solution.
old: test solutions 24 hours before water renewal.
*: Time-weighted mean measured concentration during 21days.

Nominal	Percent of Nominal Conc. (%)

Conc.

mg/L	Date	0 New	0 Old	1 New	1 Old	7 New	7 Old	8 New	8 Old	14 New	14 Old	15	TWM* (mg/L)
Control		---	---	---	---	---	---	---	---	---	---	---	---
100		96	95	96	95	95		94				95	

new: freshly prepared test solution.
old: test solutions 24 hours before water renewal.
*: Time-weighted mean measured concentration during 21days.

- Water chemistry (pH, DO, temperature and total hardness in test): Water chemistry and temperature were measured for control and 100mg/L at 4 times (before and after water renewal).
pH: 7.6 - 8.3
DO: 7.3 - 8.8 mg/L
Water Temperature: 19.6 - 20.4 C
Total hardness (as CaCO3): 245 - 270 mg/L

-Effect Data(Reproduction):
LC50 (21days) > 95.1 mg/L (parental mortality) (mc)
EC50 (21days) > 95.1 mg/L (mc)
NOEC (21days) > 95.1 mg/L
LOEC (21days) > 95.1 mg/L
mc: based on Time-weighted mean of measured concentrations

- Cumulative Number of Died Parental Daphnia: Mortality rate of parental daphnia both control and 100mg/L were 0%.

-Time (days) to First Brood Production: All parental daphnia first brood at 8 days.

-Cumulative numbers of juveniles produced per adult

Measured Conc. mg/L	Mean Cumulative Numbers of Juveniles Produced per Adult for 21 days 0 --- 7	8	9	10	11	12	13	14
Control	0 --- 0	9.9	9.9	9.9	33.7	33.7	33.7	41.0
95.1	0 --- 0	7.7	7.7	7.7	27.5	29.1	29.2	43.7

Measured Conc. mg/L	Mean Cumulative Numbers of Juveniles Produced per Adult for 21 days 15	16	17	18	19	20	21
Control	58.6	58.6	58.6	88.6	88.6	88.6	115.3
95.1	55.7	55.7	58.5	85.7	85.7	85.7	113.9

-Cumulative numbers of juveniles produced per adult alive for 21 days

Vessel No.	Nominal Concentration, mg/L (Measured Concentration, mg/L) Control	100 (95.1)

1	114	117
2	118	119
3	112	116
4	114	113
5	104	116
6	117	110
7	122	108
8	122	121
9	118	117
10	112	102
Mean	115.3	113.9
S.D.	5.4	5.7
Inhibition ratio (%)		1.2
Significant difference		---

--- : Indicate a no-significant difference.

- Calculation of toxicity values: The calculation of toxicity values was the Time weighted mean of measured concentrations.

Source : National Institute for Environment Studies Ibaraki
Reliability : (1) valid without restriction
12.08.2005 (20)

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Value	:	
Species	:	rat
Strain	:	other:Crj:CD(SD)IGS
Sex	:	female
Number of animals	:	6
Vehicle	:	water
Doses	:	
Method	:	other:OECD Test Guideline 423
Year	:	2004
GLP	:	yes
Test substance	:	other TS:KOATSU CHEMICAL INDUSTRIES, LTD., purity,99.5% containing 0.34% 5-methyltetrahydrofuryl alcohol as impurity.
Remark	:	This test was carried out based on the OECD test guideline 423, Acute Oral Toxicity - Acute Toxic Class Method. Although the starting dose level was selected 2000 mg/kg bw, no mortality was detected. Therefore, the same dose level was selected for a second step and a limit test of one dose level of 2000 mg/kg bw was carried out with six animals(three animals per step).
Result	:	The acute toxicity was classified on category 5 in the GHS. Clinical signs such as decreased locomotor activity and hypotonia were observed. Body weight gain and necropsy revealed no abnormality.
Source	:	National Institute of Health Sciences
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

27.04.2005 (21)

Type	:	LD50
Value	:	
Species	:	rat
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	no data
Doses	:	
Method	:	other
Year	:	1967
GLP	:	no data
Test substance	:	no data
Result	:	LD50: 1.6-3.2 g/kg
Source	:	National Institute of Health Sciences
Reliability	:	(4) not assignable

27.04.2005 (22)

Type	:	LD50
Value	:	
Species	:	guinea pig
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	no data

Doses :
Method : other
Year : 1963
GLP : no data
Test substance : no data

Result : LD50: 0.8-1.6 g/kg
Source : National Institute of Health Sciences
Reliability : (4) not assignable
27.04.2005 (22)

5.1.2 ACUTE INHALATION TOXICITY

Type : LC50
Value :
Species : rat
Strain : no data
Sex : no data
Number of animals :
Vehicle : no data
Doses :
Exposure time : 6 hour(s)
Method : other
Year : 1963
GLP : no data
Test substance : no data

Result : LC50(6 hr) inhalation: 12650 ppm
Lowest observed no effect concentration over the 6 hr period: 655 ppm
Source : National Institute of Health Sciences
Reliability : (3) invalid
28.04.2005 (22)

5.1.3 ACUTE DERMAL TOXICITY

Type : LD50
Value :
Species : guinea pig
Strain : no data
Sex : no data
Number of animals :
Vehicle : no data
Doses : no data
Method :
Year :
GLP : no data
Test substance :

Result : The acute dermal LD50 was less than 5 ml/kg.
Reliability : (3) invalid
20.05.2005 (22)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

Type : LDLo
Value :
Species : rat

Strain	:	other: albino or Glaxo-Wistar
Sex	:	male/female
Number of animals	:	
Vehicle	:	no data
Doses	:	
Route of admin.	:	i.p.
Exposure time	:	
Method	:	
Year	:	1959
GLP	:	no data
Test substance	:	no data
Remark	:	Number of animals: one or 3-4 Initial test were on single animals at each dose, which were then made up to groups of 3-4 near the threshold of effects. Animals were observed for mortality and toxic effects for seven days. Survivors were killed by decapitation and examined macroscopically.
Result	:	Estimated approximately average lethal dose: 1000 mg/kg bw Estimated maximum symptomless dose: 750 mg/kg bw Estimated maximum dose without macroscopic pathology: 750 mg/kg bw Necrosis, urinary incontinence and respiratory distress were observed.
Source	:	National Institute of Health Sciences
Reliability	:	(2) valid with restrictions

27.04.2005 (23)

Type	:	LDLo
Value	:	
Species	:	rabbit
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	no data
Doses	:	
Route of admin.	:	i.v.
Exposure time	:	
Method	:	
Year	:	1949
GLP	:	no data
Test substance	:	no data
Result	:	LDL0 intravenous: 725 mg/kg
Source	:	Research Institute for Animal Science in Biochemistry and Toxicology Sagamihara Kanagawa
Reliability	:	(4) not assignable

21.12.2004 (24)

5.2.1 SKIN IRRITATION

Species	:	mouse
Concentration	:	100 %
Exposure	:	no data
Exposure time	:	24 hour(s)
Number of animals	:	3
Vehicle	:	
PDII	:	
Result	:	not irritating
Classification	:	not irritating
Method	:	other
Year	:	1989
GLP	:	no data

Test substance	:	other TS:BDH CHERMICALS, reagent grade
Remark	:	Strain:nude Sex:male TS was filled into a PVC cup. One cup was fastened to the dorsal side of the animals with surgical tape. TS was kept in contact with the skin for 24h. Treated skin area was histologically examined. Three sections were selected and examined using a scoring system modified from Ingram and Grasso.
Result	:	Any significant changes were not observed in histology over 24 h at 100%.
Source	:	Research Institute for Animal Science in Biochemistry and Toxicology Sagamihara Kanagawa
Test substance	:	other TS:BDH CHERMICALS, reagent grade.
Reliability	:	(2) valid with restrictions

13.06.2005 (25)

Species	:	human
Concentration	:	
Exposure	:	
Exposure time	:	
Number of animals	:	
Vehicle	:	
PDII	:	
Result	:	moderately irritating
Classification	:	irritating
Method	:	other
Year	:	1989
GLP	:	no
Test substance	:	no data
Result	:	Moderate irritant to skin and mucous membranes.
Source	:	Research Institute for Animal Science in Biochemistry and Toxicology Sagamihara Kanagawa
Reliability	:	(3) invalid

27.04.2005 (26)

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Dose	:	.1 ml
Exposure time	:	
Comment	:	not rinsed
Number of animals	:	4
Vehicle	:	
Result	:	irritating
Classification	:	irritating
Method	:	Draize Test
Year	:	1977
GLP	:	no data
Test substance	:	no data
Remark	:	The test compares the subjective Draize score to several objective procedures, namely, corneal thickness measurement, evaluation of corneal and conjunctival water content, and conjunctival and aqueous humor concentrations of a dye bound to plasma proteins after intravenous injection. After a single instillation of 0.1 mL of undiluted compound in the rabbit eye, evaluation of the above parameters was made at 2 and 24 hours. Draize score and corneal thickness were further determined daily for 10 additional days.

Result	:	With the modified Draize procedure, the test material was found to be irritant. After intravenous injection, the animals were sacrificed for sampling of ocular tissues 2 hours and 24 hours after injection. The test material was found to increase the corneal thickness.
Source	:	Research Institute for Animal Science in Biochemistry and Toxicology Sagamihara Kanagawa
Reliability	:	(2) valid with restrictions
13.06.2005		(27)

Species	:	other:NZW rabbit
Concentration	:	100 %
Dose	:	.1 ml
Exposure time	:	
Comment	:	other: Ocular irritation recorded at 4, 24, 48, 72, 96 and 168 hr.
Number of animals	:	6
Vehicle	:	
Result	:	not irritating
Classification	:	not irritating
Method	:	other: experimental protocols in European Cmmunity on dangerous substances
Year	:	1988
GLP	:	no data
Test substance	:	other TS:Fluka A.G.,purity 99%

Remark	:	100 ul of the undiluted test substance was placed into one eye of each rabbit by gently pulling the lower lid away from the eyeball to form a cup into which the test substance was dropped. The lids were then gently held together for one second and the rabbit was replaced in its cage. The other, untreated, eye served as a control. The eyes were not washed following instillation of the test substance. The eyes were examined and the grade of ocular reaction was recorded at 4, 24, 48, 72, 96 and 186 hours. Erythema, chemosis, iritis and coreal opacity were scored according to the Draize scores. The test substance was classified according to the EEC Directive 83/467/EEC.
Result	:	This chemical was not irritant to the rabbit eye
Source	:	Research Institute for Animal Science in Biochemistry and Toxicology Sagamihara Kanagawa
Reliability	:	(2) valid with restrictions
28.04.2005		(28)

Species	:	rabbit
Concentration	:	100 %
Dose	:	20 other: mg
Exposure time	:	24 hour(s)
Comment	:	
Number of animals	:	
Vehicle	:	
Result	:	irritating
Classification	:	irritating
Method	:	other
Year	:	1972
GLP	:	no data
Test substance	:	no data

Result	:	20 mg instilled into rabbit eye(24 hr) caused moderate to severe irritation.
Source	:	Research Institute for Animal Science in Biochemistry and Toxicology Sagamihara Kanagawa
Reliability	:	(4) not assignable
27.04.2005		(29)

Species	:	human

Concentration	:	
Dose	:	
Exposure time	:	
Comment	:	
Number of animals	:	
Vehicle	:	
Result	:	
Classification	:	
Method	:	other
Year	:	1996
GLP	:	no
Test substance	:	no data
Result	:	A severe eye irritant.
Source	:	Research Institute for Animal Science in Biochemistry and Toxicology Sagamihara Kanagawa
Reliability	:	(4) not assignable

27.04.2005 (16)

5.3 SENSITIZATION

5.4 REPEATED DOSE TOXICITY

Type	:	
Species	:	rat
Sex	:	male/female
Strain	:	other:Crj:CD(SD)IGS
Route of admin.	:	gavage
Exposure period	:	28 days
Frequency of treatm.	:	once a day
Post exposure period	:	14 days (recovery period)
Doses	:	10, 40, 150 and 600 mg/kg bw/day
Control group	:	yes, concurrent vehicle
Method	:	other: Guideline for the 28-Day Repeated Dose Toxicity Test in Mammalian Species (Chemical Substances Control Law of Japan)
Year	:	2004
GLP	:	yes
Test substance	:	other TS:KOATSU CHEMICAL INDUSTRIES, LTD., purity,99.5% containing 0.34% 5-methyltetrahydrofuryl alcohol as impurity.
Remark	:	Study design: Vehicle: Distilled water Number of animals/groups: Males, 5; females, 5 Administration period: Males and females, 28 days Recovery period: Males and females at doses of 0 and 600 mg/kg bw/day, 14 days Terminal killing: Males and females, day 29 or 43 Clinical observation and measurement: General conditions were observed once a day during administration and recovery periods. Detailed clinical signs in FOB(Functional Observation Batteries) were observed for all animals on day 7, 14, 21 and 28 of administration period and on day 7 and 14 of recovery period. Sensory/reflex test: Responses in sensory/reflex test were determined for all animals on day 28 of administration period and on day 14 of recovery period. Determinations of landing foot splay, grip strength and spontaneous motor activity were carried out for all animals on day 23 of administration period

and on day 13 of recovery period.
Body weights were determined on day 1 (before dosing), 3, 7, 10, 14, 17, 21, 24 and 28 of administration period and on day 3, 7, 10 and 14 of recovery period.
Food consumption was determined for 24 hours at once a week of administration and recovery periods for both sexes.

Urinalysis was carried out on day 26 of administration period, on day 12 of recovery period for both sexes.

Hematological and biochemical examinations were carried out at time of necropsy after administration period and recovery periods for both sexes.

Organ weights were measured in five animals/group/sex at necropsy after administration and recovery periods.
Organ weights measured: Brain, heart, thymus, liver, kidney, spleen, adrenal, testis and epididymus in males and brain, heart, thymus, liver, kidney, spleen, adrenal and ovary in females.

Microscopic examination: Brain, pituitary, thyroid, parathyroid, thymus, heart, lung, trachea, liver, kidney, spleen, adrenal, stomach, intestine, urinary bladder, spinal cord, lymph node, sciatic nerve, bone marrow, testis, epididymus, prostate, ovary and uterus for all animals of 0 and 600 mg/kg bw/day groups killed after 28 days of administration period, thymus for both sexes, testis and spleen for males of 10, 40 and 150 mg/kg bw/day groups killed after recovery period.

Statistical methods: Dunnett's test for data of administration period, and t-test or U-test for data of recovery period and Fisher's exact test for quantal data.
Significance level is 5%.

Result : NOAEL: 40 mg/kg bw/day
NOEL: 40 mg/kg bw/day
Mortality: There was no mortality related to the test substance treatment.

Clinical signs: Increased locomotor activity followed by decreased locomotor activity and adoption of a prone position in males and females of the 600 mg/kg bw/day group.
Increased locomotor activity without any other sign was observed in females of the 150 mg/kg bw/day group.
Determination of grip strength: Decreased grip strength of the hindlimb was observed in males of the 600 mg/kg bw/day.
No effects on sensory/reflex, landing foot splay and spontaneous motor activity were observed.

Body weight: Statistically significant suppression of body weight gain was noted in males of the 600 mg/kg bw/day group.
Food consumption: Food consumption was statistically significantly decreased throughout the administration period in males of the 600 mg/kg bw/day group. In females of the same dose group, food consumption was statistically significantly decreased only in the 1st week of the administration period.

Urinalysis: Statistically significant decreased urinary pH was detected in males of 600 mg/kg bw/day group.

At the examination of a 28-day administration period
Male

Dose(mg/kg bw/day)	0	10	40	150	600
No.of animals	10	5	5	5	10

PH	6.0	0	0	0	0	4
	6.5	0	0	0	0	1
	7.0	0	0	0	0	3
	7.5	4	4	3	1	2**
	8.0	1	1	0	0	0
	8.5	5	0	2	4	0

Note: **:P<0.01

Hematology: At the examination after a 28-day administration period, statistically significant decreases in MCH, MCHC, leukocyte count and platelet count and prolongation of prothrombin time in males and females, in addition to decreases in reticulocyte count in males and hemoglobin concentration in females of the 600 mg/kg bw/day group.
At the examination after a 14 recovery period, the changes observed at the examination after a 28-day administration period were not observed.

At the examination after a 28-day administration period
Male

Dose (mg/kg bw/day)		0	10	40	150	600
No.of animals		5	5	5	5	5
MCH(pg)	Mean	19.4	19.8	19.4	19.3	18.3*
	SD	0.5	0.6	0.4	0.4	0.8
MCHC(%)	Mean	33.8	33.9	33.2	33.1	32.3**
	SD	0.3	0.4	0.7	0.5	0.5
Leukocyte	Mean	63	63	61	54	37*
(10e+2/uL)	SD	15	11	16	12	9
Platelet	Mean	152	151	159	134	87**
(10e+4/uL)	SD	6	12	18	15	12
Reticulocyte	Mean	37	42	41	30	21**
(0/00)	SD	6	5	3	5	6
PT(sec)	Mean	12.9	12.8	12.7	13.2	13.9*
	SD	0.5	0.2	0.3	0.6	0.1

Note: *:P<0.05; **:P<0.01

Female

Dose (mg/kg bw/day)		0	10	40	150	600
No.of animals		5	5	5	5	5
Hemoglobin(g/dL)	Mean	15.7	15.8	15.4	15.8	14.6**
	SD	0.4	0.6	0.7	0.3	0.4
MCH(pg)	Mean	19.1	19.7	18.8	18.9	18.0*
	SD	0.3	1.2	0.5	0.4	0.5
Leukocyte	Mean	50	52	50	40	23*
(10e+2/uL)	SD	19	15	11	13	7
Platelet	Mean	141	153	145	134	85**
(10e+4/uL)	SD	22	14	9	22	15
PT(sec)	Mean	13.3	13.2	13.8	13.6	14.6**
	SD	0.6	0.3	0.6	0.2	0.6

Note: *:P<0.05; **:P<0.01

Blood biochemistry: At the examination after a 28-day administration period, statistically significant decrease of ALP, total protein, albumin, total bilirubin and calcium in males and females, and LDH, triglyceride and sodium in males of the 600 mg/kg bw/day group. Additionally, statistically significant increase in BUN in males of the 600 mg/kg bw/day. In the 150 mg/kg bw/day, statistically significant decrease in total protein was observed in males.

At the examination after a 14 recovery period, a statistically significant decrease in calcium was observed in males and females of the 600 mg/kg bw/day.

At the examination after a 28-day administration period
Male

Dose (mg/kg bw/day)		0	10	40	150	600
No.of animals		5	5	5	5	5
LDH(IU/L)	Mean	251	421	242	186	134*
	SD	65	212	41	38	32
T.protein(g/dL)	Mean	5.89	5.74	5.77	5.51**	5.20**
	SD	0.12	0.10	0.12	0.20	0.17
Albumin(g/dL)	Mean	2.89	2.84	2.85	2.69	2.59*
	SD	0.12	0.09	0.15	0.16	0.16
Triglyceride	Mean	50	61	49	28	26*
(mg/dL)	SD	11	11	26	6	8
BUN(mg/dL)	Mean	13.0	15.6	13.5	14.8	17.0*
	SD	1.0	2.4	1.1	1.8	3.1
T. bilirubin	Mean	0.34	0.32	0.34	0.30	0.25*
(mg/dL)	SD	0.04	0.04	0.04	0.01	0.01
Ca(mg/dL)	Mean	10.2	10.0	10.1	9.9	9.7**
	SD	0.3	0.2	0.1	0.1	0.2
Na(mEq/L)	Mean	148	147	148	146	145**
	SD	1	1	1	1	1

Note: *:P<0.05; **:P<0.01

Female

Dose (mg/kg bw/day)		0	10	40	150	600
No.of animals		5	5	5	5	5
ALP(IU/L)	Mean	485	414	459	375	277**
	SD	97	144	70	56	43
T.protein(g/dL)	Mean	6.16	6.14	5.83	5.76	5.30**
	SD	0.41	0.14	0.23	0.16	0.23
Albumin(g/dL)	Mean	3.20	3.08	2.82*	3.02	2.58**
	SD	0.31	0.11	0.26	0.14	0.22
T.bilirubin	Mean	0.23	0.22	0.22	0.21	0.17**
(mg/dL)	SD	0.01	0.02	0.03	0.04	0.01
Ca(mg/dL)	Mean	10.1	9.9	9.7*	9.9	9.7*
	SD	0.3	0.1	0.0	0.2	0.0

Note: *:P<0.05; **:P<0.01

At the examination after a 14-day recovery period
Male

Dose (mg/kg bw/day)		0	600
No.of animals		5	5
Ca(mg/dL)	Mean	9.7	9.3*
	SD	0.1	0.2

Note: *:P<0.05

Female

Dose (mg/kg bw/day)		0	600
No.of animals		5	5
Ca(mg/dL)	Mean	9.9	9.4*
	SD	0.4	0.3

Note: *:P<0.05

Necropsy: At the examination after a 28-day administration period, a small-sized thymus was observed in five males and four females of the 600 mg/kg bw/day group. At the examination after a 14-day recovery period, a small-sized thymus was observed in two males and small-sized testes were observed in three males of the 600 mg/kg bw/day group.

Organ weight
At the examination after a 28-day administration period, there were statistically significant decreases in final body weight in males, absolute and relative thymus weights in males and females and absolute and relative pituitary weights in females of the 600 mg/kg bw/day group.
A statistically significant decrease in absolute weights of brain, liver, heart, pituitary, adrenals, testes and epididymides in males and increase in relative kidney weight in females were also observed in the 600 mg/kg bw/day group. In the 150 mg/kg bw/day group, a statistically significant decrease in relative pituitary weight was observed in females.
At the examination after a 14-day recovery period, statistically significant decrease in absolute and relative thymus weights in males and increase in absolute and relative thyroid weight in females, and decreases in final body weight, absolute weights of liver, kidneys, spleen, adrenals, testes and epididymides and increases in relative weight of heart and pituitary in males of the 600 mg/kg bw/day group were observed.

At the examination after a 28-day administration period
Male

Dose (mg/kg bw/day)		0	10	40	150	600
No.of animals		5	5	5	5	5
Body weight(g)	Mean	357	348	362	326	290**
	SD	30	28	43	16	28
Absolute weight						
Brain(g)	Mean	1.94	1.87	1.99	1.82	1.77**
	SD	0.07	0.04	0.07	0.08	0.08
Liver(g)	Mean	10.11	10.24	10.32	8.76	7.32**
	SD	1.34	0.54	1.32	0.70	0.60
Heart(g)	Mean	1.24	1.24	1.21	1.15	1.04*
	SD	0.08	0.23	0.08	0.04	0.09
Thymus(g)	Mean	0.64	0.56	0.61	0.42	0.25**
	SD	0.14	0.05	0.16	0.04	0.04
Pituitary(mg)	Mean	12.6	11.8	11.8	10.8	9.1**
	SD	1.6	1.6	0.9	0.8	0.6
Adrenals(mg)	Mean	58.0	59.1	56.0	52.2	41.9**
	SD	9.6	10.1	6.6	4.9	4.0
Testes(g)	Mean	3.50	3.17	3.49	3.21	2.78**
	SD	0.33	0.28	0.33	0.20	0.24
Epididymides(g)	Mean	0.85	0.89	0.83	0.78	0.68**
	SD	0.05	0.11	0.08	0.03	0.06
Relative weight						
Thymus(g%)	Mean	0.18	0.16	0.17	0.13	0.09**
	SD	0.03	0.01	0.04	0.01	0.01

Note: *:P<0.05; **:P<0.01

Female

Dose (mg/kg bw/day)		0	10	40	150	600
No.of animals		5	5	5	5	5
Absolute weight						
Thymus(g)	Mean	0.42	0.43	0.52	0.42	0.25**
	SD	0.04	0.07	0.11	0.10	0.04
Pituitary(mg)	Mean	13.2	13.6	14.0	12.1	10.3**
	SD	1.0	1.1	2.5	1.1	1.1
Relative weight						
Kidney(g%)	Mean	0.78	0.76	0.79	0.80	0.87*
	SD	0.08	0.04	0.05	0.03	0.05
Thymus(g%)	Mean	0.20	0.21	0.23	0.19	0.12*

	SD	0.01	0.04	0.05	0.06	0.02
Pituitary(mg%)	Mean	6.4	6.4	6.3	5.5*	5.1*
	SD	0.7	0.3	0.8	0.4	0.4

Note: *:P<0.05; **:P<0.01

At the examination of a 14-day recovery period
Male

Dose(mg/kg bw/day)		0	600
No.of animals		5	5
Body weight(g)	Mean	420	355**
	SD	10	39
Absolute weight			
Liver(g)	Mean	11.97	9.81**
	SD	0.58	1.12**
Kidney(g)	Mean	2.87	2.57**
	SD	0.05	0.15
Thymus(g)	Mean	0.50	0.34**
	SD	0.06	0.06
Adrenals(mg)	Mean	66.5	49.8**
	SD	8.5	2.7
Testes(g)	Mean	3.33	2.47**
	SD	0.12	0.52
Epididymides(g)	Mean	1.05	0.79**
	SD	0.07	0.09
Relative weight			
Heart(g%)	Mean	0.33	0.37**
	SD	0.01	0.01
Thymus(g%)	Mean	0.12	0.10*
	SD	0.01	0.02
Pituitary(mg%)	Mean	2.8	3.2*
	SD	0.3	0.2

Note: *:P<0.05; **:P<0.01

Female

Dose(mg/kg bw/day)		0	600
No.of animals		5	5
Absolute weight			
Thyroids(mg)	Mean	19.4	24.7*
	SD	2.7	3.0
Relative weight			
Thyroids(mg%)	Mean	8.2	10.3*
	SD	1.3	1.1

Note: *:P<0.05; **:P<0.01

Histopathology: At the examination after a 28-day administration period, atrophy of the thymus in males and females, and atrophy of the red pulp with decreased extramedullary hematopoiesis and inflammation of the capsule in the spleen and necrosis of seminiferous tubular epithelium in males of the 600 mg/kg bw/day group were observed. Necrosis of the seminiferous tubular epithelium of the testes was also observed in males of the 150 mg/kg bw/day group. Examination of the spermatogenic cycle revealed a decrease in the ratio of the spermatid to Sertoli cell counts in the 600 mg/kg bw/day group. At the examination after a 14-day recovery period, the testes showed a tendency for increase in severity of the changes. There was a decrease in the ratio of pachytene spermatocyte counts to Sertoli cell counts in addition to that of spermatid to Sertoli cell counts. The other changes observed during or at the examination after a 28-day administration period showed a tendency for recovery or complete

recovery. There were no changes in females.

Incidence of histopathological findings at the examination after a 28-day administration period
Male

Dose(mg/kg bw/day)		0	10	40	150	600
No.of animals		5	5	5	5	5
Spleen: Hematopoiesis, Extramedullary	-,+	0	2	1	3	5**
	++	5	3	4	2	0
Testis: Necrosis, seminiferous Epithelium	-	5	5	5	3	0
	+	0	0	0	2	5**
Thymus: Atrophy	-	5	5	5	5	0
	+	0	0	0	0	5**

Female

Dose(mg/kg bw/day)		0	10	40	150	600
No.of animals		5	5	5	5	5
Thymus: Atrophy	-	5	5	5	5	0
	+	0	0	0	0	5**

Note: -:Negative; +:Slight; ++:Moderate; **:P<0.01

Incidence of histopathological findings at the examination after a 14-day recovery period
Male

Dose(mg/kg bw/day)		0	600
No.of animals		5	5
Testis: Necrosis, seminiferous Epithelium	-	5	0
	+	0	5**

Note: -:Negative; +:Slight; **:P<0.01

Source : Research Institute for Animal Science in Biochemistry and Toxicology Sagamihara Kanagawa
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
16.08.2005 (21)

Type :
Species : rat
Sex : male/female
Strain : no data
Route of admin. : oral feed
Exposure period : 90 days
Frequency of treatm. : feed ad libitum
Post exposure period : no
Doses : 1000, 3000 and 10000 ppm
Control group : yes, concurrent no treatment
Method : other:no data
Year : 1991
GLP : no data
Test substance : no data

Remark : Study design: Sub-chronic Oral Toxicity in rats.
Groups of rats(15/sex/group) were provided diets which contained 0, 1000, 3000, or 10000 ppm of the test material for 90 days.
Result : There was a slight depression in body weight gain in the 1000 ppm group

and a statistically significant depression in the 3000 and 10000 ppm groups. There was a statistically significant decrease in testes weights in the 10000 ppm group. There was also a significant decrease in the testes to body and testes to brain weight ratios. Moderate testicular degeneration was observed in 14 animals of the 10000 ppm group. These animals exhibited complete loss of spermatogenic activity and their seminiferous tubules were partially to completely lined with a single layer of Sertoli cells. Tubules were also reduced in size.

Source : Research Institute for Animal Science in Biochemistry and Toxicology Sagamihara Kanagawa

Reliability : (2) valid with restrictions

27.04.2005 (30)

Type :
Species : dog
Sex : male/female
Strain : Beagle
Route of admin. : oral feed
Exposure period : 90 days
Frequency of treatm. : feed ad libitum
Post exposure period : no
Doses : 1000, 3000 and 6000 ppm
Control group : yes, concurrent no treatment
Method : other:no data
Year : 1991
GLP : no data
Test substance : no data

Remark : Study design: Sub-chronic oral toxicity in dogs.
Groups of beagle dogs (4/sex/group) were provided diets which contained 0, 1000, 3000, or 6000 ppm of the test material for 90 days.

Result : There was a significant reduction in the body weight gains of 2 male and female animals in the 6000 ppm group. However, the submitter stated "it is difficult to conclude if this is truly a test related effect, since the animals were housed together in groups of four throughout the study. When dogs are group housed, generally one or two animals will dominate the others; thus limiting the intake of water and food of the non-aggressive animals." Testes weights of males in all treated groups were significantly lower than controls. Severe testicular atrophy was reported in all males at the dosage level of 6000 ppm. Decreased spermatogenic activity was noted at 3000 ppm and interpreted as a prodromal sign of atrophy. There was occasional prostatic atrophy in the 6000 ppm group. The submitter stated "it is difficult to conclude whether or not the lower testes weights and atrophy are a result of test compound administration or sexually immature dogs. Because it appears randomization was not done and therefore the larger, older male dogs were assigned to the untreated control group, it is believed these findings in the group males are associated with sexual immaturity."

Source : Research Institute for Animal Science in Biochemistry and Toxicology Sagamihara Kanagawa

Reliability : (2) valid with restrictions

27.04.2005 (30)

Type :
Species : dog
Sex : male
Strain : Beagle
Route of admin. : oral feed
Exposure period : 90 days
Frequency of treatm. : feed ad libitum
Post exposure period : no
Doses : 200, 400 and 800 ppm
Control group : yes, concurrent no treatment

Method	:	other
Year	:	1991
GLP	:	no data
Test substance	:	no data
Remark	:	Study design: Sub-chronic testicular maturation study in dogs. Groups of 4 male beagle dogs were provided with diets containing 0, 200, 400, or 800 ppm of the test material for 90 days.
Result	:	One animal each at 200 and 400 ppm groups exhibited lower testes weights and testes to body weight ratios than controls. Also, these two animals had relatively little to no spermatogenesis. Sexual immaturity was reported as the probable cause for these findings.However, since no clear-cut dose correlation was observed and animals at 800 ppm exhibited normal testicular development, these depressions were not reported as significant.
Source	:	Research Institute for Animal Science in Biochemistry and Toxicology Sagamihara Kanagawa
Reliability	:	(2) valid with restrictions

27.04.2005 (30)

Type	:	
Species	:	rat
Sex	:	male/female
Strain	:	no data
Route of admin.	:	oral feed
Exposure period	:	90 days
Frequency of treatm.	:	feed ad libitum
Post exposure period	:	no
Doses	:	500, 1000, 5000 and 10000 ppm
Control group	:	yes, concurrent no treatment
Method	:	other
Year	:	1991
GLP	:	no data
Test substance	:	no data
Remark	:	Study design: Sub-chronic dietary toxicity study in rats. Groups of rats (20/sex/group) were provided with diets containing 0, 500, 1000, 5000, or 10000 ppm of the test material for 90 days.
Result	:	A statistically significant depression in mean body weight gains was noted in male rats in the 5000 and 10000 ppm groups during weeks 1-13. Male rats in the 1000 ppm group showed a statistically significant depression in mean body weight gains for study weeks 5, 6, 7 and 8-13. Females in the 10000 ppm group had a statistically significantly depressed mean body weight gains during study weeks 8-13. The mean weights of brain, kidneys, liver, seminal vesicles, epididymides, prostate, testes and adrenal glands were all statistically significantly decreased for male rats in the 10000 ppm group. Except for kidneys, the same observation was noted for males in the 5000 ppm group. Only the brain and liver, and liver mean weights of males in the 1000 and 500 ppm groups, respectively, were statistically significantly decreased. The females in the 10000 ppm group showed only a significant decrease in mean brain weight. The mean brain and kidney to final body weight ratios were statistically significantly increased for males in the 5000 ppm and 10000 ppm groups. Mean liver to final body weight ratios were decreased in males in all treated groups. Other statistically significant decreases in males for mean relative organ weights were epididymides, and testes at the dosage levels of 5000 to 10000 ppm, and 10000 ppm respectively. The mean kidneys; liver; and ovaries to final body weight ratios were statistically significantly increased for females in the 5000, 5000 and 10000, and 10000 ppm groups, respectively.

There were significant decreases in the glucose, total protein, globulin and calcium at dosage levels of 1000, 5000, and 10000 ppm at 13 weeks in the males. In the females, there were significant decreases in the hemoglobin, MCV, MCH, MCHC, and platelets.

Source : Research Institute for Animal Science in Biochemistry and Toxicology Sagamihara Kanagawa

Reliability : (2) valid with restrictions

27.04.2005 (31)

Type :
Species : rabbit
Sex : female
Strain : no data
Route of admin. : gavage
Exposure period : 5 days
Frequency of treatm. : once aday
Post exposure period : no
Doses : 30, 100, 300 and 1000 mg/kg bw/day
Control group : yes
Method : other
Year : 1991
GLP : no data
Test substance : no data

Remark : Study design: Sub-acute oral toxicity study in rabbits.
The test material was administered to groups of three female rabbits at dosage levels of 0, 30, 100, 300, or 1000 mg/kg bw/day for five days.

Result : Two of the animals in the 1000 mg/kg bw/day group were sacrificed moribund after receiving one dose. The remaining animals in the group died on study day 2.
Animals in the 100 and 300 mg/kg bw/day groups elected not to eat after receiving their first dose of the test material. In the 30 mg/kg bw/day group, diet consumption ceased after receiving the fourth dose. Mean body weight gain decreased 6.3%, 7.3%, and 8.5% for the 30, 100, and 300 mg/kg bw/day groups, respectively. Clinical signs seen in one or two animals from the 300 and 1000 mg/kg bw/day groups included decreased motor activity, unsteady walk, and prostration. Two animals in the 1000 mg/kg bw/day group had labored respirations.
Other clinical observations were either dried brown matting of the anogenital area, and/or wet yellow, dried tan or wet brown staining of the urogenital or anogenital area.
Necropsy of the 1000 mg/kg bw/day group revealed dark red areas on the lungs and red foci of the stomach.

Source : Research Institute for Animal Science in Biochemistry and Toxicology Sagamihara Kanagawa

Reliability : (2) valid with restrictions

27.04.2005 (32)

Type :
Species : rat
Sex : male/female
Strain : no data
Route of admin. : dermal
Exposure period : for 13 weeks
Frequency of treatm. : five a week
Post exposure period : no
Doses : 100, 300, 1000mg/kg bw/day
Control group : yes
Method : other
Year : 1995
GLP : no data
Test substance :

Remark	:	The test material was administered dermally the dorsal regions of male and female rats at the dosages of either 100, 300, or 1000mg/kg bw/day, five a week for at least 65 applications.The study was designed whereby the number of animals being evaluated was 17 males and 12 females per group. After seven weeks on study, five males from each group were randomly selected for termination as required by a specific section of the protocol for an interim evaluation of reproductive tissue. The remaining 24 animals per group were terminated after 13 weeks.
Result	:	No treatment-related effects with respect to survival, clinical observations, ophthalmic examinations, hematology values and serum chemistries, absolute and relative organ weights, or food consumption were observed. However, statistically significant decreases in weekly body weights were noted at 5% level of probability for week 9 through 12 and at 1% level of probability for week 13 in the high dose males (1000mg/kg bw/day).
Reliability	:	(2) valid with restrictions
13.06.2005		(33)

Type	:	
Species	:	rat
Sex	:	male/female
Strain	:	no data
Route of admin.	:	inhalation
Exposure period	:	90 days
Frequency of treatm.	:	6 hours per day, five per week
Post exposure period	:	no
Doses	:	50, 150, or 500 ppm
Control group	:	yes
Method	:	other
Year	:	1995
GLP	:	no data
Test substance	:	no data

Remark	:	The test material administration was by inhalation using male and female rats. Concentrations being administered were at either 50, 150, or 500 ppm, 6 hours per day, five days a week for at least 65 exposures. The study was designed whereby the number of animals being evaluated was 14 males and 10 females per group. After six weeks on study, four males from each group were randomly selected for termination as required by a specific section of the protocol for an interim evaluation of reproductive tissue. The remaining 20 animals per group were terminated after 13 weeks on study.
Result	:	Clinical observation: Hypoactivity and intermittent whole spasms were observed in both sexes. The spasms were concentration-related. At one-hour post-exposure, hypoactivity ceased and intermittent whole spasms became less noticeable. However, hyperactivity was noted instead and was being noted in both sexes at 500 ppm during the one-hour post-exposure observation period. Statistically significant decreases in weekly body weights were noted beginning study week one in the high concentration males(500 ppm). Significant difference from the control group was at 1% level of probability for week one through four and seven through 11, at 5% level of probability for weeks five and six. In the case of the high concentration females, statistically significant increases in weekly body weights were recorded during weeks three through nine. However, body weight gains, overall, did notreveal significant changes in either sex. Although statistically significant decreases in weekly food consumption were noted in the high concentration males, the decreases were minimal and sporadic. At four week into the study, the platelet count was statistically significantly decreased (5% level of probability) at 150 and 500 ppm in both sexes. This affect appeared to be concentration related at this time in the

study. The only serum chemistry parameters related to treatment was significant increases in chloride and sodium values in males at 150 and 500 ppm.

Reliability : (2) valid with restrictions
16.08.2005 (33)

Type	:	
Species	:	rat
Sex	:	male/female
Strain	:	no data
Route of admin.	:	inhalation
Exposure period	:	90 days
Frequency of treatm.	:	6 hours per day, five per week
Post exposure period	:	no
Doses	:	50, 150, or 500 ppm
Control group	:	other:filtered air
Method	:	other
Year	:	1995
GLP	:	no data
Test substance	:	no data

Remark : The test material was administered via whole body inhalation to three test groups, each comprised of 14 male and 10 female rats. Exposures were for six hours per day, five days per week, for 13 weeks (at least 65 exposures). Exposure concentrations were 50, 150, and 500 ppm. After 34 exposures four males per group were terminated for assessment of spermatogenic endpoints. The remaining 10 animals per sex per group were terminated following 65 exposures(13 weeks on study). The animals were observed for clinical signs of toxicity and effects on body weight, food consumption, and clinical pathology parameters. Spermatogenic endpoints were evaluated for all males. Necropsies were performed on all animals and selected organs were weighed. A microscopic examination was conducted on selected tissues from all animals at the terminal necropsy.

Result : All animals survived to the scheduled necropsies, except for one female animal(50 ppm) that expired during the first week of exposure due to finding unrelated to the test material exposure.
The predominant clinical finding was intermittent whole-body spasma, which were observed frequently, in a dose-related manner in all exposed groups. Occasional incidences of hypoactivity and excessive grooming were observed for a few animals of each sex in the high exposure group. One-hour post-exposure clinical examinations revealed hyperactivity in a dose-related manner in all test groups. Wet yellow urogenital matting and a low incidence of salivation were noted in the high exposure group as well. Mean body weight gains in the high exposure group males decreased several times throughout the study and, therefore, resulted in decreased mean body weights as well. Results were similarly noted in the mid-exposure group males beginning study week eight. At the end of study week 13, mean body weights in both the mid-and high-exposure group males were 9.2 and 13.3% lower, respectively, than the control group male value. In addition, mean food consumption in both the mid-and high-exposure group males was lower than the control group males throughout the study. Test females revealed body weight and food consumption means that were similar to those of the control group females values. Test material related changes in hematology parameters consisted of decreased platelet and hemoglobin means in the high exposure group males and females at study weeks three and 13. Also a decrease in MCH values was noted in the high exposure group males at study week three and in the high exposure group males and females at study week 13. At both study weeks six and 13 (interim and terminal necropsied, respectively), decreased incidence of morphologically abnormal sperm were observed in the high exposure group males. Mean absolute and relative prostate weights were decreased in both the mid- and high-exposure groups. Mean absolute

seminal vesicle weight, and absolute and relative epididymides weights were also decreased in the high exposure group males. The only microscopic lesion suggestive of a test material related effect was mild multifocal atropy of the testes in a single high exposure group male. Based on the data obtained, NOEL could not be established via whole body inhalation after 13 weeks of exposure.

Reliability : (2) valid with restrictions
13.06.2005 (34)

Type	:	
Species	:	rat
Sex	:	male/female
Strain	:	no data
Route of admin.	:	dermal
Exposure period	:	90 days
Frequency of treatm.	:	five days per week
Post exposure period	:	no
Doses	:	100, 300, 1000 mg/kg bw/day
Control group	:	yes, concurrent vehicle
Method	:	other
Year	:	1995
GLP	:	no data
Test substance	:	no data

Remark : Each groups consisted of 17 males and 12 females. The test substance was administered undiluted five days per week for 13 consecutive weeks for at least 65 applications to shaved intact dorsal skin. Application sites were wrapped for six hours using an occlusive wrap/binder. Selected dosage levels were 100, 300, and 1000 mg/kg bw/day. A concurrent control group of identical design received 0.9% saline on a comparable regiment at a dose volume (0.95 mL/kg) equivalent to the highest dose level. After 37 applications, five males per group were terminated from the study for assessment of spermatogenic endpoints. The remaining 12 animals per sex per group were terminated following 13 weeks of study (65 applications). All animals were observed for signs of overt toxicity, dermal irritation, effects on body weight, food consumption, and hematology and serum chemistry parameters. Spermatogenic endpoints were evaluated for all males. Complete necropsies were performed on all animals and selected organs were weighed. Microscopic examination was conducted on selected tissues from all animals terminated at 13 weeks.

Result : There were no mortalities in the study.
No test substance related clinical signs were observed at any dose level and only very limited dorsal irritation occurred. Mean food consumption and hematology and serum chemistry parameters were unaffected by test substance treatment. In addition, no test substance related macroscopic or microscopic lesions were observed. Organ weights were unaffected by the dorsal application as well.

Mean body weights and body weight gains resulted in both males and females at the dose level of 1000 mg/kg bw/day. Also, an adverse effect on spermatogenesis was noted following 13 consecutive weeks of test substance administration. The mean number of sperm in the testis and the mean sperm production rate were decreased in both the 300 and 1000 mg/kg bw/day group males. In addition, a decrease in the mean percentage of motile sperm was noted in the 1000 mg/kg bw/day group males. No histopathological lesions were observed in the testis, epididymis, seminal vesicles, vas deferens, prostate, or coagulating gland.

Reliability : (2) valid with restrictions
13.06.2005 (35)

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Ames test
System of testing	:	Test species/strain :Salmonella typhimurium TA100, TA1535, TA98, TA1537, Escherichia coli WP2 uvrA/pKM101
Test concentration	:	0, 313, 625, 1250, 2500, 5000 ug/plate(all strains)
Cycotoxic concentr.	:	The chemical did not induce cytotoxicity.
Metabolic activation	:	with and without
Result	:	negative
Method	:	other: Guideline for Screening Mutagenicity Testing of Chemicals(Chemical Substances Control Law of Japan) and OECD Test Guideline 471
Year	:	2004
GLP	:	yes
Test substance	:	other TS:KOATSU CHEMICAL INDUSTRIES, LTD., purity,99.5% containing 0.34% 5-methyltetrahydrofuryl alcohol as impurity.
Remark	:	Solvent:Water for injection Procedures: Pre-incubation method Dosage of each strain with or without S9 -S9 mix:0, 313, 625, 1250, 2500, 5000 ug/plate(TA100, TA1535, TA98, TA1537, WP2 uvrA/pKM101) +S9 mix:0, 313, 625, 1250, 2500, 5000 ug/plate(TA100, TA1535, TA98, TA1537, WP2 uvrA/pKM101) S9:Rat liver, induced with phenobarbital and 5,6-benzoflavone Positive control: -S9 mix; 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide (TA100, TA98), Sodium azide (TA1535) and 9-Aminoacridine hydrochloride (TA1537) and N-Ethyl-N'-nitro-N-nitro-soguanidine (WP2uvrA/pKM101) +S9 mix; 2-Aminoanthracene (all strains) Plates/test:3 Number of replicates:2
Result	:	There were no precipitation in any test concentration. Cytotoxic concentration: Growth inhibition was not observed up to 5000 ug/plate for any stains, with or without S9 mix. Genotoxic effects: Positive control: With metabolic activation: positive Without metabolic activation: positive Salmonella typhimurium TA100, TA98, TA1535, TA1537 With metabolic activation: negative Without metabolic activation: negative Escherichia coli WP2 uvrA/pK101 With metabolic activation: negative Without metabolic activation: negative
Source	:	Research Institute for Animal Science in Biochemistry and Toxicology Sagamihara Kanagawa
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

26.04.2005 (21)

Type	:	Chromosomal aberration test
System of testing	:	Type of cell used: Chinese hamster lung(CHL/IU) cells
Test concentration	:	257.5, 515, 1030 ug/mL
Cycotoxic concentr.	:	
Metabolic activation	:	with and without
Result	:	negative
Method	:	other:Guideline for Screening Mutagenicity Testing of Chemicals(Chemical Substances Control Law of Japan) and OECD Test Guideline 473

Year : 2004
GLP : yes
Test substance : other TS:KOATSU CHEMICAL INDUSTRIES, LTD., purity,99.5% containing 0.34% 5-methyltetrahydrofuryl alcohol as impurity.

Remark : Solvent: Isotonic sodium chloride solution
S9: Rat liver, induced with phenobarbital and 5,6-benzoflavone
Positive control: Cyclophosphamide (with S9), Mitomycin C (without S9)
Plates/test: 2
The maximum concentration was established, based on the growth inhibition test. In this test, growth inhibition was not observed at concentration of 1030 ug/mL (10 mmol/L) with or without S9 mix.
Dosage:
-S9 mix(6 hr short-term treatment):257.5, 515, 1030 ug/mL
+S9 mix(6 hr short-term treatment):257.5, 515, 1030 ug/mL
-S9 mix(24 hr continuous treatment):257.5, 515, 1030 ug/mL

Result : The chemical did not induce structural chromosomal aberrations or polyploidy under the conditions of this experiment.

Genotoxic effects:

	clastogenicity			polyploidy		
	+	?	-	+	?	-
Without metabolic activation:	[ ]	[ ]	[*]	[ ]	[ ]	[*]
With metabolic activation:	[ ]	[ ]	[*]	[ ]	[ ]	[*]

	clastogenicity			polyploidy		
Positive control	+	?	-	+	?	-
Without metabolic activation:	[*]	[ ]	[ ]	[ ]	[ ]	[*]
With metabolic activation:	[*]	[ ]	[ ]	[ ]	[ ]	[*]

Source : Research Institute for Animal Science in Biochemistry and Toxicology Sagamihara Kanagawa
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
16.08.2005 (21)

5.6 GENETIC TOXICITY 'IN VIVO'

5.7 CARCINOGENICITY

5.8.1 TOXICITY TO FERTILITY

Type : other:Preliminary Reproduction Toxicity Screening Test
Species : rat
Sex : male/female
Strain : other:Crj:CD(SD)IGS
Route of admin. : gavage
Exposure period : 47 days for males; 42-52 days from 14 days before mating to 4 days after delivering for females
Frequency of treatm. : once a day
Premating exposure period
Male : 14 days
Female : 14 days
Duration of test : 47 days for males; 42-52 days for females

No. of generation studies	:	
Doses	:	15, 50, 150, 500 mg/kg bw/day
Control group	:	yes, concurrent vehicle
Method	:	other:OECD Test Guideline 421
Year	:	2004
GLP	:	yes
Test substance	:	other TS:KOATSU CHEMICAL INDUSTRIES, LTD., purity,99.5% containing 0.34% 5-methyltetrahydrofuryl alcohol as impurity.

Remark :

Study design:
Vehicle: Distilled water
Terminal killing: Males, day 47; females, day 4 of lactation
Clinical observation performed and frequency: General condition was observed once a day, body weights were determined once a week during treatment period for males and once a week before mating and on day 0, 7, 14 and 20 of gestation period and on day 0 and 4 of lactation period for females, food consumption was determined once a week during treatment period for males and once a week before mating and on day 0,7,14 and 20 of gestation period and on day 0 and 4 of lactation for females. For all males and all females after parturition, necropsy was carried out after 48 days for males and at 5 days after delivery for females.

Organ weights measured: Kidneys, thymus and pituitary for both sexes, and testes and epididymides for males. In males, the organs were weighed in all animals survived; 12 animals in the 0, 50, 150 and 500 mg/kg bw/day groups and in 11 males in 15 mg/kg bw/day group. In females, the organs were weighed in all pregnant rats with parturition; 12 animals in the 0 and 50 mg/kg bw/day groups, in 10 animals in 15 mg/kg bw/day group and in 9 animals in 150 mg/kg bw/day group. In the 500 mg/kg bw/day group, all animals did not delivery.

Microscopic examination: Pituitary, thymus, testes and epididymides for 12 males and pituitary, thymus and ovary for 12 females in 0 and 5000 mg/kg bw/day groups, and spleen for 5 males and females in 0, 15, 50 and 150 mg/kgbw/day groups and 12 males and females in 500 mg/kg bw/day group. Additionally, the dead male in the 15 mg/kg bw/day group was examined for testis, epididymis, pituitary, brain, spinal cord, stomach, intestine, adrenal, spleen, heart, liver, kidney, thyroid, trachea, lung, urinary bladder, sciatic nerve, bone marrow and lymph node. Each one no-pregnant female in the 15 and 150 mg/kg bw/day groups and the one female paired with the dead male in the 15 me/kg bw/day group examined for ovary, uterus and pituitary. The two males without fertility in the 15 and 150 mg/kg bw/day groups were examined for testis, epididymis, prostate and seminal vesicle.

Reproductive and developmental parameters: Estrous cycle, no.of successful copulation, copulation index, paring days until copulation, no.of pregnant females, fertility index, no.of corpora lutea, no.of implantation sites, implantation index[(no.of implantations/no.of corpora lutea)x100], no.of pregnant females with parturition, gestation length, no.of pregnant females with live pups, gestation index[(no.of dam with live newborns/no.of pregnant females)x100], and no.of pregnant females with live pups on day 4, no.of pups born, delivery index, no.of pups alive on day 0 of lactation, live birth index[(no.of live newborns/no.of implantations)x100], sex ratio, no.of pups alive on day 4 of lactation, viability index[(no.of live newborns on day 4 after birth/no.of live newborns)x100], body weight of live pups, no.of external anomalies and internal variations.

Statistical methods: Dunnett's or Scheffe's test for continuous data, Chi square test for reproductive parameters, and Fischer's exact test for pathological findings.

Result : NOAEL: 50 mg/kg bw/day for repeated dose toxicity of males and females, 150 mg/kg bw/day for parent males and 50 mg/kg bw/day for parent females in reproductive performance and 50 mg/kg bw/day for offspring development.

Mortality: There was no mortality related to the test material treatment.
Clinical signs, body weight and food consumption: Increased locomotor activity or increased locomotor activity followed by decreased locomotor activity was observed in males and females of the 150 and 500 mg/kg bw/day groups. Suppression of body weight gain in males at 500 mg/kg bw/day and in females at 150 mg bw/dat and higher, and decreased food consumption in males and females at 150 mg/kg bw/day and higher were also noted.

Necropsy:
Male: A small-sized testis and epididymis were observed in one in the 0, 15 and 150 mg/kg bw/day groups and ten in the 500 mg/kg bw/day group. In spleen, rough of surface was observed in six in the 500 mg/kg bw/day group, and white spot/area in the surface was observed in one in the 150 mg/kg bw/day group and four in the 500 mg/kg bw/day group.
Female: A small-sized thymus was observed in five, and rough of surface and white spot/area in the surface in spleen was observed in eleven and five, respectively, in the 500 mg/kg bw/day group. In two females in the 150 mg/kg bw/day group and twelve females in the 500 mg/kg bw/day group with embryonic death, early/late resorption of embryo was observed.

Organ weights: Statistically significant decreases in body weight, absolute weights of kidneys, thymus, pituitary, testes and epididymides, and relative weight of thymus, testes and epididymides in males in the 500 mg/kg bw/day group and absolute pituitary weight in the 150 mg/kg bw/day group were detected. Statistically significant decreases in body weight and absolute pituitary weight and increase in relative kidney weight in females in the 150 mg/kg bw/day group were detected.

Males:

Dose(mg/kg bw/day)		0	15	50	150	500
No.of animals		12	11	12	12	12
Body weight(g)	Mean	550	535	538	517	489**
	SD	40	30	28	22	33
Absolute:						
Kidneys(g)	Mean	3.10	3.15	3.09	2.90	2.71**
	SD	0.18	0.32	0.20	0.20	0.20
Thymus(g)	Mean	0.36	0.32	0.35	0.31	0.19**
	SD	0.07	0.06	0.06	0.07	0.05
Pituitary(mg)	Mean	15.6	15.6	14.2	13.4*	12.2**
	SD	1.5	2.0	1.3	1.5	1.2
Testes(g)	Mean	3.41	3.18	3.52	3.40	1.77**
	SD	0.50	0.83	0.29	0.45	0.44
Epididymides(g)	Mean	1.40	1.30	1.38	1.26	0.87**
	SD	0.20	0.30	0.15	0.17	0.15
Relative:						
Thymus(g%)	Mean	0.07	0.06	0.07	0.06	0.04**
	SD	0.01	0.01	0.01	0.01	0.01
Testes(g%)	Mean	0.63	0.60	0.66	0.66	0.36**
	SD	0.11	0.15	0.07	0.10	0.09
Epididymides	Mean	0.26	0.24	0.26	0.24	0.18**
(g%)	SD	0.04	0.05	0.03	0.04	0.03

Female

Dose(mg/kg)		0	15	50	150	500
No.of animals		12	10	12	9	0
Body weight(g)	Mean	363	350	339	313	-
	SD	25	35	24	27**	
Absolute:						
Pituitary(mg)	Mean	20.1	18.3	17.6	16.0*	-
	SD	3.8	1.7	1.8	1.9	
Relative:						
Kidneys(g%)	Mean	0.57	0.57	0.61	0.63*	-
	SD	0.04	0.06	0.05	0.05	

Note: *:P<0.05; **:P<0.01

Microscopic examination: There were atrophy of the thymus in both sexes and atrophy of the seminiferous tubule with hyperplasia of the interstitial cell in the testes and decreased intraluminal sperm with cell debris in the epididymides of the 500 mg/kg bw/day group. Atrophy of the red pulp with decreased extramedullary hematopoiesis in the spleen in the 150 and 500 mg/kg bw/day groups, and inflammation of the spleen capsule in the 500 mg/kg bw/day group were also observed in both sexes.

Incidence of histopathological findings

Male

Dose(mg/kg bw/day)	0	15	50	150	500
Thymus: Atrophy	-	12	5	5	4	3
	+,++,+++	0	0	0	1	9**
		(12)	(5)	(5)	(5)	(12)
Testis: Atrophy, seminiferous tubule	-	11	5	5	4	0
	+,++,+++	1	0	0	1	12**
		(12)	(5)	(5)	(5)	(12)
Hyperplasia, interstitial cell	-	11	5	5	5	2
	+,++	1	0	0	0	10**
		(12)	(5)	(5)	(5)	(12)
Epididymides: Decrease, sperm	-	11	5	5	4	0
	+,++,+++	1	0	0	1	12**
		(12)	(5)	(5)	(5)	(12)
Cell debris, lumen	-	11	5	5	4	0
	+,++	1	0	0	1	12**
		(12)	(5)	(5)	(5)	(12)
Spleen: Inflammation, capsule	-	5	5	5	2	1
	+,++,+++	0	0	0	3	11**
		(5)	(5)	(5)	(5)	(12)

Note:(n):No.of animals examined.
- :Negative; +:Slight; ++:Moderate; +++:Severe
**:P<0.01

Female

Dose(mg/kg bw/day)	0	15	50	150	500
Spleen: Hematopiesis, extramedullary	-,+	0	0	1	5	11
	++,+++	5	5	4	0**	1**
		(5)	(5)	(5)	(5)	(12)
Inflammation, capsule						

-	5	5	5	3	0
+,++,+++	0	0	0	2	12**
	(5)	(5)	(5)	(5)	(12)

Note:
(n):No.of animals examined.
- :Negative; +:Slight; ++:Moderate; +++:Severe
**:P<0.01

Reproductive and developmental parameters: Prolongation of gestation length and lowering of the gestation index in female parents, and decreases in numbers of born pups and live pups on day 0 of lactation and indexes for delivery, live birth and viability were observed in the 150 mg/kg bw/day group. In the 500 mg/kg bw/day group, no females delivered because of early resorptions of embryos. No increases in the incidence of fetuses with external and internal abnormalities were detected in pups of any dose groups.

Reproduction results:

Dose(mg/kg bw/day)		0	15	50	150	500
No.of pairs mated		12	12	12	12	12
Estrous cycle(days)	Mean	4.3	4.0	4.1	4.5	4.8*
	SD	0.6	0.1	0.3	0.6	0.5
No.of pairs with successful copulation		12	11	12	12	12
Copulation index(%)		100	91.7	100	100	100
Pairing days until copulation(day)	Mean	2.7	2.5	2.9	2.3	3.7
	SD	1.2	1.4	1.2	1.4	2.7
No.of pregnant females		12	10	12	11	12
Fertility index(%)		100	90.9	100	91.7	100
No.of corpora lutea	Mean	17.7	16.5	17.8	16.4	17.0
	SD	2.1	2.7	1.5	2.0	2.8
No.of implantation sites	Mean	15.6	15.3	16.1	13.7	14.5
	SD	1.3	1.9	1.8	2.1	3.7
Implantation index(%)	Mean	88.8	93.5	90.7	84.5	87.9
	SD	7.4	7.4	8.0	13.1	23.7
No.of pregnant females with parturition		12	10	12	9	0
Gestation length(days)	Mean	22.6	22.7	22.9	24.0**	-
	SD	0.5	0.5	0.3	0.0	-
No.of pregnant females with live pups		12	10	12	4	-
Gestation index(%)		100	100	100	36.4**	-
No.of pregnant females with live pups on day 4		12	10	12	1	-

Note:*:P<0.05; **:P<0.01

Litter results:

Dose(mg/kg bw/day)		0	15	50	150	500
No.of pups born	Mean	14.8	14.5	14.8	7.0**	-
	SD	1.6	2.1	1.7	1.4	
Delivery index(%)	Mean	95.3	94.7	91.9	46.4*	-
	SD	7.1	6.2	5.9	14.0	

No.of pups alive on day 0 of lactation
Total Mean 14.8 14.5 14.6 3.0** -
SD 1.6 2.1 1.8 2.2
Male Mean 7.2 7.2 6.8 1.5** -
SD 2.1 1.9 2.5 1.7
Female Mean 7.7 7.3 7.8 1.5** -
SD 1.8 1.6 3.0 1.9
Live birth index Mean 100 100 98.8 43.1* -
(%) SD 0 0 2.8 29.3
Sex ratio(Male/Female) 0.93 0.99 0.90 1.15 -
No.of pups alive on day 4 of lactation
Total Mean 14.7 14.4 14.3 1.3** -
SD 1.6 2.1 2.0 2.3
Male Mean 7.0 7.2 6.7 0.7** -
SD 2.3 1.9 2.7 1.2
Female Mean 7.7 7.2 7.6 0.7** -
SD 1.8 1.7 3.1 1.2
Viability index Mean 98.9 99.3 97.7 26.7 -
(%) SD 2.6 2.1 3.5 46.2
Body weight of live pups(g)
on day 0
Male Mean 7.3 7.4 7.1 5.9 -
SD 0.7 0.5 0.6 0.6
Female Mean 7.0 7.0 6.9 6.3 -
SD 0.6 0.5 0.6 0.1
on day 4
Male Mean 11.8 11.5 11.0 9.1 -
SD 1.0 0.7 1.1
Female Mean 11.2 10.9 10.7 8.4 -
SD 1.0 0.7 0.9
Note:*:P<0.05; **:P<0.01

Source : Research Institute for Animal Science in Biochemistry and Toxicology Sagamihara Kanagawa
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
16.08.2005 (21)

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species : rat
Sex : female
Strain : no data
Route of admin. : oral unspecified
Exposure period : gestation days 6 through 15
Frequency of treatm. : once a day
Duration of test : no data
Doses : 10, 50, 100, 500, 1000 mg/kg bw/day
Control group : yes
Method : other
Year : 1992
GLP : no data
Test substance : no data

Remark : This study was carried out as a dose range-finding developmentaltoxicity study. Group of eight females (confirmed cohabitation with a male) were administered a single, daily, oral dose of either deinonized water (control vehicle) or the test substance at 10, 50, 100, 500, or 1000 mg/kg/day during the period of major organogenesis (gestation days 6 through 15).
Result : No maternal mortality or abortions were recorded. However, a 100 % incidence of early resorptions was recorded for the two highest dose levels

(500 and 1000 mg/kg bw/day). Females at 0, 10, 50 and 100 mg/kg bw/day did not exhibit any early or late resportions. Thus, fetuses of litters at these dosage levels were all viable.
Statistically significant depression in mean maternal body weight gains were noted during gestation days 8 and 15 for test groups receiving 1000 and 500 mg/kg bw/day, respectively($p<0.05$). Mean body weight gains for these two groups continued to exhibit depression throughout the remainder of the study, but statistical significance increased ($p<0.01$). Statistically significant($p<0.05$ or $p<0.01$) decreases in mean food consumption were also noted specifically in the two highest dose levels. The onset of decreased food consumption was observed first during gestation day seven and such observations continued for the most part throughout the remainder of the study.
Clinical findings associated with oral administration of 1000 mg/kg bw/day were described as impaired mobility, decreased muscle tone of hindlimbs, absence of pain response of hindlimbs, and exophthalmus of both eyes. Transient clinical findings included lacrimation of eyes, dried red material around one eye, and/or dried red material around nose.
Mean body weights per litter for both male and female fetuses at 100 mg/kg bw/day were statistically significantly lower($p<0.01$) when compared to the control group. Although not significant statistically, 5 of 124 fetuses(4 of 8 litters) at 100 mg/kg bw/day exhibited an external malformation known as filamentous tail.

Reliability : (2) valid with restrictions
17.11.2005 (36)

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

5.11 ADDITIONAL REMARKS

Type : other:

Remark : This study was undertaken to study the antagonistic effects of 2-furanmethanol, tetrahydro- (THFA) on induced digitalis toxicity in dogs. Experiments in dogs were divided into four categories. Those in the initial study were used for the establishment of levels of digitalis toxicity. Those in the second study received digoxin to excess and then were treated with THFA. Those in the third study received THFA alone. Finally the fourth study included animals that were pretreated with THFA and then were given digoxin to excess.
For the results of THFA toxicity, each dog received a tenth of mg/kg of digoxin and then an additional 0.1 mg every 10 to 15 minutes until the criterion for digitalis toxicity was met. THFA was added so that each dog received 500 mg/kg bw, intravenously over a 5- to 10-minute period in the second study included 4 animals. In none of the 4 dogs was there recovery of sinus rhythm. Within 12 hours all dogs had expired. The third study included 3 dogs each of whom received THFA at a concentration of 500 mg/kg bw. The all animals were dead within 12 hours. In the fourth study, 2 dogs were pretreated with THFA at a concentration of 500 mg/kg bw and then made toxic with digoxin, 0.1 mg/kg. There was no obvious benefit in correction of the resulting arrhythmia, nor did the dogs survive 24 hours.

27.04.2005 (37)

Type : Cytotoxicity

Remark : The cellular protein content measured in cultured Hep G2 cells was used as the endpoint for determining the cytotoxicity of a rage of 114 chemical compounds. The relative toxicity of the test compounds was quantified by the determination of the PI50, which is the concentration of xenobiotic required to produce a 50% reduction in proteincontent pf the culture after 24 hr. Surfactants and heavy metals consistently had low PI50(ex.Benzalkonium chloride, 0.003mM; Sodium dodecyl sulphate, 0.018mM; Tween 20, 1.2mM; Tween 80, 1.3mM; Cadmium chloride, 0.019mM; Mercuric chloride, 0.087mM. The PI50 of 2-furanmethanol, tetrahydro- was 178.

04.07.2005 (38)

Type : other

Remark : The effect of adding solvents to the pre-incubation mixture in the Salmonella/mammalian microsome assay was examined in tests of the tryptophan-pyrolysate mutagens, 3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole (Trp-P-1) and 3-amino-1-methyl-5H-pyrido[4,3-b]indole (Trp-P-2). The mutagenicity assay was carried out by using the Ames test system with the pre-incubation modification. The strain of Salmonella was TA98. S9 was obtained from livers of SD rats induced with polychlorinated biphenyl. The pre-incubation mixture was prepared by mixing the components in the following order: the solvent to be tested; 500 uL of S9 mix; 100 uL of bacterial culture; and 25 uL of a mutagen solution. After the pre-incubation for 20 min. at 37 degree C, soft agar was added and the mixtures were poured onto the minimal agar plates. The plates were incubated for 48 h, and the revertant colonies were counted. The ratio of the number of His+ revertants found in the presence of 2-furanmethanol, tetrahydro-(THFA) to that found in the absence of solvent(control) was 5.8-5.9 adding 25 uL of THFA or 3.1-4.5 adding 50 uL of THFA. Adding 75 uL of THFA caused to kill the bacteria. Therefore, THFA showed enhancing mutagenic activity of Trp-P-1.

27.04.2005 (39)

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