FOREWORD INTRODUCTION

ETHANOL, 2-TERT-BUTOXY-

CAS N°: 7580-85-0

SIDS Initial Assessment Report

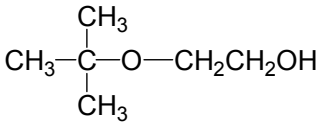
For

SIAM 19

Berlin, 19-22 October 2004

1. Chemical Name:	Ethanol, 2-tert-butoxy-
2. CAS Number:	7580-85-0
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 is submitted for first discussion at SIAM 19
• How was the chemical or category brought into the OECD HPV Chemicals Programme ?	The original draft documents were prepared by Japanese government.
7. Review Process Prior to the SIAM:	
8. Quality check process:	Expert committee performed spot checks on randomly selected endpoints and compared original studies with data in SIDS dossier.
9. Date of Submission:	July 23, 2004
10. Date of last Update:	July 23, 2004
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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	7580-85-0
Chemical Name	Ethanol, 2-tert-butoxy-
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

There is no available information on toxicokinetics.

In an acute oral toxicity study [OECD TG 401, now deleted] with ethanol, 2-tert-butoxy- (ETB), Crj:CD (SD) IGS rats (five animals/sex/dose) were given ETB by gavage at 0, 500, 1000, or 2000mg/kg bw. No deaths occurred in any groups. Anemia and chromaturia at 500 mg/kg bw and higher, abnormal gait at 1000 mg/kg bw, and adoption of a prone position, decreased locomotor activity and irregular respiration at 2000 mg/kg bw were observed. No abnormalities were observed in body weights or necropsy findings. The oral LD_{50} values were more than 2000 mg/kg bw for both sexes. In an acute oral toxicity study of ETB in male ddY mice (four animals/dose), the LD_{50} was 1328 mg/kg bw.

In a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [OECD TG 422], Crj:CD (SD) IGS rats (12 animals/sex/dose) were given ETB by gavage at 0, 4, 20, or 100 mg/kg bw/day. Males were dosed for 37 days from day 14 before mating and females were dosed for 42-47 days from day 14 before mating to day 4 of lactation throughout the mating and pregnancy period. There were no deaths in any groups. Reddish urine was apparent in all animals at 100 mg/kg bw/day. No effects of ETB on body weight, food consumption, or urinalysis were observed. In the hematological examination, decreases in erythrocyte count, hemoglobin, hematocrit, mean corpuscular hemoglobin concentration (MCHC) and leukocyte count, and increases in mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and reticulocytes at 100 mg/kg bw/day were observed in males. Decreases in erythrocyte count, hemoglobin and MCHC, and increases in MCV and reticulocytes at 20 and 100 mg/kg bw/day, and increase in MCH at 100 mg/kg bw/day were found in females. Absolute and relative weights of the spleen were increased in males and females at 100 mg/kg bw/day. Increase in hematopoietic cells, erythrocyte cells, in the bone marrow and hemosiderin deposition in Kupffer cells of the liver and tubular epithelium of the kidney were observed in males and females at 100mg/kg bw/day. Hemosiderin deposition in the spleen was observed in males at 100 mg/kg bw/day. Extramedullary hematopoiesis in the liver was found in females at 100mg/kg bw/day. Extramedullary erythropoietic hematopoiesis in the spleen was found in males at 100 mg/kg bw/day and females at 20 mg/kg bw/day and higher. The NOAELs for repeated dose toxicity were 20 mg/kg bw/day in males and 4 mg/kg bw/day in females.

In a reverse gene mutation assay [OECD TG 471], ETB was not mutagenic in *Salmonella typhimurium* TA100, TA1535, TA98, TA1537 or *Escherichia coli* WP2 *uvr*A with or without an exogeneous metabolic activation. In a chromosomal aberration test [OECD TG 473], ETB did not induce structural chromosomal aberrations or polyploidy with or without an exogeneous metabolic activation in cultured Chinese hamster lung (CHL/IU) cells. Based on these findings, ETB is not anticipated to be genotoxic *in vivo*.

The above-mentioned combined study [OECD TG 422] showed that the reproductive/developmental parameters, i.e., estrous cycle, copulation index, fertility index, gestation length, or number of corpora lutea, or implantations in dams or number, sex ratio, body weight, or viability of pups, were not affected by administration of ETB up to 100 mg/kg bw/day. No external or internal malformations were noted in pups of any groups. The NOAEL for reproductive/developmental toxicity was 100 mg/kg bw/day in rats.

No information is available for irritation, sensitization, or carcinogenicity.

Environment

ETB is a colourless liquid with a water solubility of 100 g/l at 25 °C and a vapour pressure of 1.03 hPa at 25 °C. Based on a measured log Kow of 0.36, bioaccumulation is not expected. Environmental distribution estimated by a level III Fugacity model indicates that almost all of the ETB partitions into water and soil. A ready biodegradation study showed that ETB was not mineralised (6% by BOD) but about 70% of ETB was transformed to 1-tert-butoxy acetic acid (OECD TG 301C). The degradation products may have similar physical chemical properties and less ecotoxicity to ETB. A study on hydrolysis indicates that ETB is stable in water. In the atmosphere ETB is indirectly photodegraded by reaction with OH radicals with a half-life of 0.849 days.

Ecotoxicity data on this substance were available in aquatic species from three trophic levels. In an algal growth inhibition test (OECD TG 201, *Selenastrum capricornutum,* open system, 72 h), acute toxicity was > 866 mg/L for both ErC_{50} and EbC_{50}. For daphnids, a 48 h EC_{50} of > 891 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} > 100 mg/L was available.

Regarding chronic toxicity to algae, a 72 h NOEC (growth rate and biomass) of 291 mg/L (OECD TG 201, *Selenastrum capricornutum*, open system) was reported. For daphnids, a 21 d EC_{50} of > 94.2 mg on reproduction and a 21 d NOEC of 94.2 mg/L on reproduction were reported (OECD TG 211, *Daphnia magna,* semi-static).

Exposure

ETB is produced by a single Japanese manufacturer at one production site. Annual production volume in 2003 was 4,000-5,000 metric tonnes in Japan. ETB is synthesised from butene, isobutylene and ethylene glycol. ETB is used primary as a solvent for dyes and a raw material of inks but also there are many applications including end use products. Exposure to the environment can occur primary through evaporation at production and user sites. Exposure to the general public is expected through dermal contact and inhalation of vapour. 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.

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 properties indicating a hazard for human health (repeated dose toxicity by oral route). Exposure to the general public is expected through dermal contact and inhalation of vapour. 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.

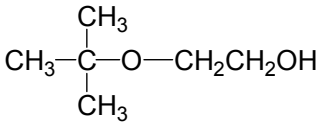
SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 7580-85-0
IUPAC Name: Ethanol, 2-tert-butoxy-
Molecular Formula: $C_6H_{14}O_2$

Structural Formula:



Molecular Weight: 118.17
Synonyms: Ethanol, 2-(1,1-Dimethylethoxy)-
Ethylene glycol mono-tert-butyl ether
2-(1,1-Dimethylethoxy) ethanol
2-tert Butoxyethanol
Ethylene glycol tert-butyl ether
Swasolve ETB
tert-Butyl 2-hydroxyethyl ether
tert-Butyl Cellosolve

1.2 Purity/Impurities/Additives

1.3 Physico-Chemical properties

Table 1 Summary of physico-chemical properties

Property	Value	Protocols (Reference) or comments
Physical state	Liquid	
Melting point	<-50 °C	OECD TG 102 (CERI, 2000b)
Boiling point	152.5 °C	Beilstein Handbook of Organic Chemistry.
Relative density	0.8994 at 20 °C	Beilstein Handbook of Organic Chemistry.
Vapour pressure	1.03 hPa at 25 °C	Calculated (CERI 2004)
Water solubility	> 100 g/l at 25 °C	OECD TG 105 (CERI, 2000b)
Partition coefficient n-octanol/water (log value)	0.36 at 25 °C	OECD TG 107 (CERI, 2000b)
Henry's law constant	9.79 E-8 atm-m3/ mole at 25 °C	Calculated (CERI 2004)

Ethanol, 2-tert-butoxy- (ETB) is a flammable colourless liquid with a slight ether odour.

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

Production Volumes

Ethanol, 2-tert-butoxy- (ETB) is produced by one Japanese manufacturer at one production site. The annual production volume in 2003 was reported to be 4,400 tonnes (Maruzen Petrochemical, 2004). ETB is produced by reacting butene and butanes fraction (RB) included in isobutylene with ethylene glycol (EG) in the presence of a catalyst. This product is separated from non-reacted RB and EG, polymerised oil, water and any impurities by distillation. As a final product, high-purity ETB is obtained.

Use Pattern

ETB is used as a high boiling point solvent for synthetic resin of enamel/lacquer, antibleaching agent for thinner paint and lacquer/vanish and fluidity adjuster. Because of its high water solubility, it is suitable as a high boiling solvent for aqueous paint. ETB is also used in inks, solvent for dye, photocopying ink, antirust, operating oil, brake fluid and lubricant for fiber (Maruzen Petrochemical, 2003).

2.2 Environmental Exposure and Fate

2.2.1 Sources of Environmental Exposure

Although no monitoring data of ETB at the production site are available, since ETB is produced in a continuous closed system and a well-controlled waste water treatment system is in operation at the production site, significant emission into aqueous phase during manufacture is unlikely. Exposure to the atmosphere is expected primary through evaporation at production and user sites. Environmental release during transport and downstream uses is possible in the event of a spill or accident. Since ETB is used as a solvent and other multiple applications including consumer products, ETB may be released into the aquatic environment through industrial waste water.

2.2.2 Photodegradation

The half-life of ETB in air by the reaction with photochemically produced OH radicals was calculated to be 0.8 day (rate constant: 1.26×10^{-11} cm^3/molecule-sec, OH radical concentration: 1.5×10^6 molecule/cm^3, and irradiation time: 12 hours/day) (CERI, 2004).

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) showed that ETB was stable in water and its half-life was estimated to be more than one year at 25 °C at the environmentally relevant pH condition (CERI, 2000b).

2.2.4 Transport between Environmental Compartments

Using the following input parameters, environmental distribution patterns of ETB were estimated with a level III Fugacity model as included in the EPIWIN Programme (CERI, 2004).

Input parameters: melting point = -50 °C, vapour pressure = 0.03 Pa, water solubility = 100 g/l, log Kow = 0.36 and temperature = 25 °C.

Table 2 Estimation of environmental distribution of ETB with a generic Fugacity model, Mackay level III.

	Mass amount (%)	Half-life (h)	Emission (kg/h)
Air	0.00135	20.4	1000
Water	44.4	360	1000
Soil	55.5	360	1000
Sediment	0.0754	1440	0

The Fugacity model predicts that almost all of the substance partitions about equally to water and soil, with a very limited partitioning to air and sediment. A calculated Koc value of 1 supports the estimated distribution patters (CERI 2004).

2.2.5 Biodegradation

A ready biodegradation study was conducted according to OECD Guideline 301 C "Ready Biodegradability; Modified MITI Test (I)" (CERI, 2000a). Rates of biodegradation were determined by a BOD meter, GC and TOC analysis. Whereas only very limited degradation was observed by TOC (0%) and BOD analysis (6%), about 70% of degradation was determined by GC analysis. Conflicting results between GC and BOD or TOC analysis suggested a residue of a metabolic product and 1-tert-butoxy acetic acid was identified by LC-MS. Total mass balance of the identified metabolite and the parent compound were almost equivalent to the initial test substance added.

According to calculation results, the degradation product 1-tertbutoxy acetic acid may have similar physical chemical properties and is estimated to be less toxic to aquatic organisms compared to the parent compound (see table 3).

Table 3 Calculation results of physical chemical properties and ecotoxicity of ETB and degradation product (1-tertbutoxy acetic acid)

Chemical Name	**Ethanol, 2-tert-butoxy- (ETB)**	**1-tertbutoxy acetic acid**	**Calculation method**
CAS Number	7580-85-0		
Molecular formula	C6H14O2	C6H12O3	
Log Kow	0.46	0.68	KOWWIN v1.66 (CERI 2004)
Water solubility (g/L)	195.6	130.5	WSKOW v1.40 (CERI 2004)
Fish 96-h LC50 (g/L)	2.46	17.1	ECOSAR v0.99 (CERI 2004)
Daphnia 48-h LC50 (g/L)	2.37	16.7	ECOSAR v0.99 (CERI 2004)
Algae 96-h EC50 (g/L)	1.35	9.67	ECOSAR v0.99 (CERI 2004)
Fish 30-d MTAC (mg/L)	248	1776	ECOSAR v0.99 (CERI 2004)
Daphnia 16-d EC50 (mg/L)	61.8	480	ECOSAR v0.99 (CERI 2004)
Algae 96-h MTAC (mg/L)	55.6	450	ECOSAR v0.99 (CERI 2004)

2.2.6 Bioaccumulation

Using a measured log Kow value of 0.36, a bioconcentration factor (BCF) of 3.16 was calculated by EPIWIN BCF v2.14 (CERI, 2004). This result indicates that bioaccumulation of ETB in aquatic organisms is not expected.

2.3 Human Exposure

2.3.1 Occupational Exposure

This chemical is produced by the reaction of isobutylene and ethylene glycol and purified by fractional distillation in a closed system in Japan (Maruzen Petrochemical, 2004). Although the actual operational process is not known, worker exposure through inhalation of vapour and dermal route is possible during sampling and drumming at the production site. Since this chemical is used as a solvent, thinner etc, worker exposure through both routes is possible at user sites producing these products. Monitoring data of airborne concentration at the workplace are not available, but the vapour pressure of this chemical is 0.03 Pa at 25°C, which corresponds to an airborne concentration of 3 ppm. Therefore the actual inhalation exposure may be small if this chemical is handled at room temperature.

An occupational exposure limit value is not established for this chemical.

2.3.2 Consumer Exposure

The general population may be exposed through dermal contact and inhalation of vapour through ETB's use in inks or solvent for dye. In addition multiple applications including end use products also suggest that exposure to consumers are expected. The main exposure routes to consumers are dermal and inhalation, and the latter may not be significant because ETB has a relatively low vapour pressure (0.03 Pa at 25 °C).

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

There is no available information.

Dermal

There is no available information.

Oral

An acute oral toxicity study in rats is reported [MHLW, Japan, 2002]. This study was conducted according to an OECD acute oral toxicity test [TG 401] under GLP conditions. Crj:CD (SD) IGS rats (five animals/sex/dose) were given ETB by gavage at a dose of 0 (vehicle: purified water), 500, 1000, or 2000 mg/kg bw. No deaths occurred in any groups. Anemia and chromaturia were observed at 500 mg/kg bw and higher in all males and females. Abnormal gait was found at 1000 mg/kg bw in five males and two females. Adoption of a prone position in two males and one female, decreased locomotor activity in four males and one female, and irregular respiration in one male were observed at 2000 mg/kg bw. No abnormalities were observed in body weights or necropsy findings. The oral LD_{50} values were considered to be more than 2000 mg/kg bw for both sexes.

Male ddY mice (four animals/dose) were orally given ETB at four different doses with pretreatment of intraperitoneal olive oil 24 hours prior to administration of ETB (Tanii, Saito and Hashimoto,1992). The LD_{50} value was1328 mg/kg bw (1084-1620 mg/kg bw).

Other Routes of Exposure

There is no available information.

Conclusion

The oral LD_{50} values were more than 2000 mg/kg bw for both sexes in rats. The oral LD_{50} was 1328 mg/kg bw in male mice.

3.1.3 Irritation

There is no available information.

3.1.4 Sensitisation

There is no available information.

3.1.5 Repeated Dose Toxicity

Oral

One study is available for repeated dose toxicity. This study was conducted according to an OECD combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [TG 422] under GLP conditions [MHLW, Japan, 2002]. Details of the study by MHLW (2002) are as follows.

Crj:CD (SD) IGS rats (12 animals/sex/dose) were given ETB by gavage at doses of 0 (vehicle: purified water), 4, 20, or 100 mg/kg bw/day. Males were dosed for 37 days from day 14 before mating and females were dosed for 42-47 days from day 14 before mating to day 4 of lactation throughout the mating and pregnancy period. Hematological, blood biochemical, and histopathological examinations were performed in both sexes, and urinalysis was conducted in males.

There were no deaths in any groups. Reddish urine was apparent in all animals at 100 mg/kg bw/day for three hours after the first administration. There were no effects of this chemical on body weight or food consumption in males and females. No effects of ETB on the urinalysis were observed. In hematological examination, significant decreases in erythrocyte count, hemoglobin,

hematocrit, mean corpuscular hemoglobin concentration (MCHC) and leukocyte count, and increases in mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and reticulocytes at 100 mg/kg bw/day, and decrease in MCHC at 20 mg/kg bw/day were observed in males. Significant decreases in erythrocyte count, hemoglobin and MCHC, and increases in MCV and reticulocytes at 20 and 100 mg/kg bw/day, and increase in MCH at 100 mg/kg bw/day were observed in females. At necropsy, spleen enlargement and brown colored spleen in six males and spleen enlargement in eight females were observed at 100 mg/kg bw/day. Absolute and relative weights of the spleen were significantly increased in males and females at 100 mg/kg bw/day. Significant increase in hematopoietic cells, erythrocyte cells, in the bone marrow and hemosiderin deposition in Kupffer cells of the liver and tubular epithelium of the kidney were observed in males and females at 100mg/kg bw/day. Hemosiderin deposition in the spleen was observed in males at 100 mg/kg bw/day. Extramedullary hematopoiesis in the liver was found in females at 100mg/kg bw/day. Extramedullary erythropoietic hematopoiesis in the spleen was found in males at 100 mg/kg bw/day and females at 20 mg/kg bw/day and higher. No significant changes in other parameters associated with the change in MCHC at 20 mg/kg bw/day in males were found.

Based on the hematological and histopathological findings, the NOAELs for repeated dose toxicity were considered to be 20 mg/kg bw/day in males and 4 mg/kg bw/day in females.

Conclusion

In an oral repeated dose toxicity study in rats, the chemical had hematological and histopathological effects in males at 100 mg/kg bw/day and in females at 20 and 100 mg/kg bw/day. The NOAELs for repeated dose toxicity were considered to be 20 mg/kg bw/day in males and 4 mg/kg bw/day in 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)] under GLP conditions [MHLW, Japan, 2002].

Growth inhibition was not observed at concentrations up to 5000 μg/plate with or without S9 mix in all strains. This chemical was not mutagenic in *Salmonella typhimurium* TA100, TA1535, TA98, TA1537 or *Escherichia coli* WP2 *uvr*A at concentrations up to 5000 μg/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] in cultured Chinese hamster lung (CHL/IU) cells under GLP conditions [MHLW, Japan, 2002].

Growth inhibition was not observed at 1200 μg/mL after short-term or continuous treatment with or without S9 mix. The maximum concentration was established to be 1200 μg/mL. Structural chromosomal aberrations and polyploidy were not induced up to 1200 μg/mL.

In vivo Studies

There is no available information.

Conclusion

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

3.1.7 Carcinogenicity

There is no available information.

3.1.8 Toxicity for Reproduction

One study was available for reproduction/developmental toxicity. This study was conducted according to an OECD combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [TG 422] under GLP conditions [MHLW, Japan, 2002]. Details of the study by MHLW (2002) are as follows.

Crj:CD (SD) IGS rats (12 animals/sex/dose) were given ETB by gavage at doses of 0 (vehicle: purified water), 4, 20, or 100 mg/kg bw/day. Males were dosed for 38 days from day 14 before mating and females were dosed for 42-47 days from day 14 before mating to day 4 of lactation throughout the mating and pregnancy period.

No effects of ETB on the estrous cycle, copulation index, fertility index, gestation length, number of corpora lutea, or number of implantation sites were found in dams. No ETB-related effects on numbers, sex ratio, body weight, or viability of pups were detected on days 0 and 4 of lactation. No abnormal findings considered to be attributable to administration of ETB were observed in dead pups during lactation and pups at scheduled sacrifice. No external or internal malformations were also noted in pups of any groups. Based on these findings, the NOAEL for reproductive/developmental toxicity was considered to be 100 mg/kg bw/day in rats.

Conclusion

In an OECD combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test conducted according to OECD TG 422, there was no evidence of reproduction/developmental toxicity of ETB. The NOAEL for reproduction/developmental toxicity was considered to be 100 mg/kg bw/day in rats.

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 401, now deleted] of ethanol, 2-tert-butoxy- (ETB), Crj:CD (SD) IGS rats (five animals/sex/dose) were given ETB by gavage at 0, 500, 1000, or 2000 mg/kg bw. No deaths occurred in any groups. Anemia and chromaturia were observed at 500 mg/kg bw and higher. Abnormal gait was found at 1000 mg/kg bw. Adoption of a prone position, decreased locomotor activity, and irregular respiration were observed at 2000 mg/kg bw. No abnormalities were observed in body weights or necropsy findings. The oral LD_{50} values were more than 2000 mg/kg bw for both sexes. In an acute oral toxicity study of ETB in male ddY mice (four animals/dose), the LD_{50} was1328 mg/kg bw (1084-1620 mg/kg bw).

In a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [OECD TG 422], Crj:CD (SD) IGS rats (12 animals/sex/dose) were given ETB by gavage at 0, 4, 20, or 100 mg/kg bw/day. Males were dosed for 37 days from day 14 before mating and females were dosed for 42-47 days from day 14 before mating to day 4 of lactation throughout the mating

and pregnancy period. Hematological, blood biochemical, and histopathological examinations were performed in both sexes, and urinalysis was conducted in males. There were no deaths in any groups. Reddish urine was apparent in all animals at 100 mg/kg bw/day for three hours after the first administration. There were no effects of this chemical on body weight or food consumption in males and females. No effects of ETB on the urinalysis were observed. In hematological examination, decreases in erythrocyte count, hemoglobin, hematocrit, MCHC and leukocyte count, and increases in MCV, MCH and reticulocytes at 100 mg/kg bw/day were observed in males. Decreases in erythrocyte count, hemoglobin and MCHC, and increases in MCV and reticulocytes at 20 and 100 mg/kg bw/day, and increase at MCH in 100 mg/kg bw/day were observed in females. At necropsy, spleen enlargement and brown colored spleen in six males and spleen enlargement in eight females were observed at 100 mg/kg bw/day. Absolute and relative weights of the spleen were increased in males and females at 100 mg/kg bw/day. Increase in hematopoietic cells, erythrocyte cells, in the bone marrow and hemosiderin deposition in Kupffer cells in the liver and tubular epithelium of the kidney were observed in males and females at 100mg/kg bw/day. Hemosiderin deposition in the spleen was observed in males at 100 mg/kg bw/day. Extramedullary hematopoiesis in the liver was found in females at 100mg/kg bw/day. Extramedullary erythropoietic hematopoiesis in the spleen was found in males at 100 mg/kg bw/day and females at 20 mg/kg bw/day and higher. Based on the hematological and histopathological findings, the NOAELs for repeated dose toxicity were considered to be 20 mg/kg bw/day in males and 4 mg/kg bw/day in females.

In a reverse gene mutation assay [OECD TG 471 and Japanese Guideline for Screening Mutagenicity Testing of Chemicals (Chemical Substances Control Law of Japan)], growth inhibition was not observed at concentrations up to 5000 μg/plate with or without S9 mix in all strains. This chemical was not mutagenic in *Salmonella typhimurium* TA100, TA1535, TA98, TA1537 or *Escherichia coli* WP2 *uvr*A at concentrations up to 5000 μg/plate with or without S9 mix.

In a chromosomal aberration test [OECD TG 473] in cultured Chinese hamster lung (CHL/IU) cells, growth inhibition was not observed at 1200 μg/mL after short-term or continuous treatment with or without S9 mix. The maximum concentration was established to be 1200 μg/mL. Structural chromosomal aberrations and polyploidy were not induced up to 1200 μg/mL.

In the above-mentioned combined study [OECD TG 422], no effects of ETB on the estrous cycle, copulation index, fertility index, gestation length, number of corpora lutea, or number of implantation sites were found in dams. No ETB-related effects on numbers, sex ratio, body weight, or viability of pups were detected on days 0 and 4 of lactation. No abnormal findings considered to be attributable to administration of ETB were observed in dead pups during lactation and pups at scheduled sacrifice. No external or internal malformations were also noted in pups of any groups. Based on these findings, the NOAEL for reproductive/developmental toxicity was considered to be 100 mg/kg bw/day in rats.

No information is available for dermal toxicity, irritation, sensitization, or carcinogenicity.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Acute Toxicity Test Results

Acute toxicity of ETB 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 4 Acute toxicity of ETB to aquatic organisms

Species	Method	Exposure	Result	Reference
Medaka *Orizias latipes*	OECD TG 203 GLP test	96 h semistatic	LC_{50} > 100 mg/L	MOE, Japan (2001)
Daphnia magna	OECD TG 202 GLP test	48 h semistatic	EC_{50}> 891 mg/L	MOE, Japan (2001)
*Selenastrum capricornutum**	OECD TG 201 GLP test	72 h static, open system	(rate method) ErC_{50} > 866 mg/L	MOE, Japan (2001)

** Pseudokirchneriella subcapitata*

Fish

The toxicity of ETB towards freshwater fish, *Orizias latipes*, was reported to be 96h LC_{50} >100 mg/L (MOE, Japan, 2001). According to a result from a preliminary test, a limit test was carried out (OECD TG 203). Fish were exposed only to a concentration of 100 mg/L and a control. Although a mortality of 30 % was observed at the end of the test in the exposed group, no further experiment was carried out. The test result was lacking the highest concentration with no mortality. A binomial distribution shows the probability of the toxicity to be LC_{50} > 100 mg/L is less than 95 % (83 %), therefore the test may be insufficient and the test is considered to be reliable with restrictions.

Invertebrates

For daphnids, *Daphnia magna,* an acute toxicity result of 48 h EC_{50} of > 891 mg/L was reported (OECD TG 202, MOE, Japan, 2001). The exposure of the substance to daphnids was undertaken at concentrations ranging from 100 to 1,000 mg/L and dilution water (Elendt M4 medium) control. The test was performed under semi-static conditions with analytical monitoring showing that the concentration of the chemical was decreased by 4 to 11 % of the initial concentrations after 24 hours in the test water. Therefore the result was derived based on measured mean concentrations. Up to 5 % immobilisation was observed at three exposure levels but no individual was immobilized at the highest concentration.

Aquatic plant, e.g. Algae

Results of the toxicity of ETB is available for a species of freshwater algae, *Selenastrum capricornutum* (= *Pseudokirchneriella subcapitata*), (MOE, Japan, 2001). The algal growth inhibition test (OECD TG 201, 1984) was carried out with concentrations ranging from 10 to 1,000 mg/L (nominal) of the test substance and one control. The (0-72 h) ErC_{50} of >866 mg/L was reported

based on measured mean concentration. In the test, growth inhibition was observed only at the highest concentration (12.9 % inhibition compared to the control based on growth rate). The algae in all concentrations kept an exponential growth phase only for 48 hours and the growth rates for 48 to 72 hrs were decreased compared to those for 0 to 48 hrs. Therefore the toxicity was estimated using data taken until 48 hours. And the pH of the test water changed by more than 1.5 units in all concentrations (from pH 7.8 at the start to pH 10.4 at the end of the test). The increase of pH may have occurred because of a shortage of buffer capacity of CO_2. Although there were some deviations from the test guideline 201, the test was regarded to be valid, the reliability of the test was (2) valid with restrictions.

Chronic Toxicity Test Results

Test results on chronic toxicity which are regarded as reliable are summarised in Table 5.

Table 5 Chronic toxicity of ETB to aquatic organisms

Species	Method	Exposure	Result	Reference
Daphnia magna	OECD TG 211 GLP test	21 d semi-static	(Reproduction) 21 NOEC = 94.2 mg/L	MOE, Japan (2001)
*Selenastrum capricornutum**	OECD TG 201 GLP test	72 h static, open system	(growth rate and biomass method) (0-72 h) NOEC = 291 mg/L	MOE, Japan (2001)

** Pseudokirchneriella subcapitata*

A result on chronic toxicity to daphnids was reported by MOE, Japan (2001). In the test, parent daphnids were exposed to ETB at a nominal concentration of 100 mg/L with a control. No individuals were killed among the exposed daphnids. The mean cumulative numbers of juveniles per adult for 21 days in the control and 100 mg/L were 97.1 and 99.5, respectively. Therefore no inhibition by this substance was observed, and the 21-d NOEC to daphnids is considered to be 94.2 mg/L (time weighted mean of measured concentrations).

From the study on algal toxicity (MOE, Japan, 2001), a NOEC = 291 mg/L (OECD TG 201) was derived. At the highest concentration an inhibition of 12.9 % by the growth rate method was observed. This was differing significantly from the control.

Toxicity to Microorganisms

There is no available information..

4.2 Terrestrial Effects

There is no available information.

4.3 Other Environmental Effects

There is no available information.

4.4 Initial Assessment for the Environment

ETB is a colourless liquid with a water solubility of 100 g/l at 25 °C and a vapour pressure of 0.03 Pa at 25 °C. Based on a measured log Kow of 0.36, bioaccumulation is not expected.

Environmental distribution estimated by a level III Fugacity model indicates that almost all of the ETB partitions water and soil. A ready biodegradation study showed that ETB was not mineralised (6% by BOD) but about 70% of ETB was transformed to 1-tert-ethoxy acetic acid (OECD TG 301C). A study on hydrolysis indicates that ETB is stable in water. In the atmosphere ETB is indirectly photodegraded by reaction with OH radicals with a half-life of 0.849 days.

Ecotoxicity data on this substance were available in aquatic species from three trophic levels. In an algal growth inhibition test (OECD TG 201, *Selenastrum capricornutum,* open system), the 72 h ErC_{50} was > 866 mg/L. For daphnids, a 48 h EC_{50} of > 891 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} > 100 mg/L was available.

In chronic toxicity to algae, a 72 h NOEC of 291 mg/L (OECD TG 201, *Selenastrum capricornutum*, open system) was reported. For daphnids, a 21 d EC_{50} of > 94.2 mg on reproduction and a 21 d NOEC of 94.2 mg/L on reproduction were reported (OECD TG 211, *Daphnia magna,* semi-static).

There is no available information on toxicity to terrestrial organisms.

5 RECOMMENDATIONS

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

The chemical possesses a hazard for human health (repeated dose toxicity). Exposure to the general public is expected through dermal contact and inhalation of vapour. 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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-Water solubility with SRC-WSKOWWIN v1.40.
-Henry's Law Constant with SRC-HENRYWIN v3.10.
-Indirect Photodegradation with SRC-AOPWIN v1.90.
-BCF by BCFWIN v2.14.
-Distribution of ETB based on Fugacity model (Level III) with EPIWIN.
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Maruzen Petrochemical Co., Ltd. (2004). Internal data on production and use patterns of MTB.

MHLW (Ministry of Health, Labour and Welfare), Japan (2002). Toxicity Testing Reports of Environmental Chemicals. **9**, 443-471.

MOE (Ministry of the Environment), Japan (2001). Report of eco-toxicity (both acute and chronic toxicities to algae and daphnids, and acute fish toxicity) of ETB. Unpublished data.

Tanii H, Saito S and Hashimoto K (1992). Structure-toxicity relationship of ethylene glycol ethers. Archives of Toxicology. **66**, 368-371.

I U C L I D

D a t a S e t

Existing Chemical	ID: 7580-85-0
CAS No.	7580-85-0
Molecular Formula	C6H14O2
EINECS Name	Ethanol, 2-tert-butoxy
Producer Related Part	
Company:	National Institute of Health & Sciences
Creation date:	06-JUL-2004
Substance Related Part	
Company:	National Institute of Health & Sciences
Creation date:	06-JUL-2004
Memo:	OECD HPV Chemicals Programme, SIDS Dossier, approved at SIAM 19 (19-22 October 2004)
Printing date:	22-MAR-2005
Revision date:	
Date of last Update:	22-MAR-2005
Number of Pages:	48
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
Street: 1-18-1, Kamiyoga, Setagaya-ku
Town: 158-8501 Tokyo
Country: Japan

06-JUL-2004

Type: cooperating company
Name: National Institute of Environmental Studies, Environment Agency
Street: 16-2, Onogawa
Town: 305-0053 Tsukuba-Ibaraki
Country: Japan

06-JUL-2004

Type: cooperating company
Name: National Institute of Industrial Health
Street: 6-21-1, Nagao, Tamaku, Kawasaki-shi
Town: 214-8585 Kanagawa
Country: Japan

06-JUL-2004

Type: cooperating company
Name: Chemicals Evaluation and Research Institute (CERI)
Street: 1-4-25 Koraku, Bunkyo-ku
Town: 112-0004 Tokyo
Country: Japan

06-JUL-2004

1.0.2 Location of Production Site, Importer or Formulator

1.0.3 Identity of Recipients

1.0.4 Details on Category/Template

1.1.0 Substance Identification

1.1.1 General Substance Information

Substance type: organic
Physical status: liquid
Purity: = 99.7 - % w/w

Remark: Colourless liquid with slight ether odour.

Purity is given in a CERI report to be 99.7 % as of a technical grade.
Industrial grade of product is of about 99 % purity.

06-JUL-2004 (2)

1.1.2 Spectra

1.2 Synonyms and Tradenames

2-(1,1-Dimethylethoxy) ethanol

09-JUL-2004

2-tert-Butoxyethanol

09-JUL-2004

Ethanol, 2-(1,1-dimethylethoxy)-

09-JUL-2004

Ethylene glycol mono-tert-butyl ether

09-JUL-2004

Ethylene glycol tert-butyl ether

06-JUL-2004

Swasolve ETB

06-JUL-2004

tert-Butyl 2-hydroxyethyl ether

06-JUL-2004

tert-Butyl Cellosolve

06-JUL-2004

1.3 Impurities

1.4 Additives

1.5 Total Quantity

Quantity: 1000 - 5000 tonnes produced in 2003

Remark: Production volume in Japan was 4400 tonnes in 2003.
ca. 400 tonnes exported to Taiwan in 2003.
No production was reported outside Japan.
Flag: confidential
09-JUL-2004 (9)

1.6.1 Labelling

1.6.2 Classification

1.6.3 Packaging

1.7 Use Pattern

Type: industrial
Category: Basic industry: basic chemicals

06-JUL-2004 (8)

Type: industrial
Category: Paints, lacquers and varnishes industry

06-JUL-2004

Type: use
Category: Fuel additives

Source: Maruzen Petrochemical Co., Ltd.
06-JUL-2004

Type: use
Category: Solvents

06-JUL-2004

1.7.1 Detailed Use Pattern

1.7.2 Methods of Manufacture

1.8 Regulatory Measures

1.8.1 Occupational Exposure Limit Values

Type of limit: other

Remark: Acceptable limit value of 2-n-tert-butoxy ethanol was 25 ppm by ACGIH.
09-JUL-2004 (9)

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

06-JUL-2004

1.11 Additional Remarks

1.12 Last Literature Search

06-JUL-2004

1.13 Reviews

2.1 Melting Point

Value: <= -50 degree C

Method: OECD Guide-line 102 "Melting Point/Melting Range"
Year: 2000
GLP: no

Remark: No freesing was observed down to -50 degree C.
Test substance: CAS No. 7580-85-0
Chemical Name: Ethanol, 2-tert-butoxy-
Source: Tokyo Kasei Kougyou Co., Ltd.
Purity: 99.7%
Lot No.: FGD01
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
10-DEC-2004 (3)

Value: < -120 degree C

Reliability: (4) not assignable
MSDS data without proof.
Flag: Material Safety Dataset
06-JUL-2004 (8)

Value: = -25.3 degree C

Method: SRC-MPBPWIN v1.40.
Test substance: CAS No. 7580-85-0
Chemical Name: Ethanol, 2-tert-butoxy-
Reliability: (2) valid with restrictions
Valid calculation method.
10-DEC-2004 (6)

2.2 Boiling Point

Value: = 152.5 degree C at 1013 hPa
Decomposition: no

Test substance: CAS No. 7580-85-0
Chemical Name: Ethanol, 2-tert-butoxy-
Reliability: (2) valid with restrictions
Peer reviewed data source.
Flag: Critical study for SIDS endpoint
10-DEC-2004 (1)

Value: = 160 degree C at 1013 hPa

Test substance: CAS No. 7580-85-0
Chemical Name: Ethanol, 2-tert-butoxy-
Reliability: (2) valid with restrictions
Valid calculation method.
10-DEC-2004 (6)

2.3 Density

Type: relative density
Value: = .8994 at 20 degree C

Test substance: CAS No. 7580-85-0
Chemical Name: Ethanol, 2-tert-butoxy-
Reliability: (2) valid with restrictions
Scientifically acceptable data source.
Flag: Critical study for SIDS endpoint
10-DEC-2004 (1)

Type: density
Value: = .905 g/cm³ at 20 degree C

Reliability: (4) not assignable
MSDS data without proof.
Flag: Material Safety Dataset
06-JUL-2004 (8)

2.3.1 Granulometry

2.4 Vapour Pressure

Value: = .0003 hPa at 25 degree C
Decomposition: no

Method: OECD Guide-line 104 "Vapour Pressure Curve"
Year: 2000
GLP: no

Remark: Vapour pressure value at 25 degree C was obtained by extraporation using three measured data (at 60, 70 and 80 degree C, n=3).
Test substance: CAS No. 7580-85-0
Chemical Name: Ethanol, 2-tert-butoxy-
Source: Tokyo Kasei Kougyou Co., Ltd.
Purity: 99.7%
Lot No.: FGD01
Reliability: (3) invalid
The reported value may not be reliable because variations between measurement were high and only trace amount of the test substance was detected.
10-DEC-2004 (3)

Value: = 1.026 hPa at 25 degree C

Reliability: (2) valid with restrictions
Valid calculation method.
Flag: Critical study for SIDS endpoint
09-JUL-2004 (5)

Value: = 1.03 hPa at 25 degree C

Method: Calculated with SRC-MPBPWIN v1.40.
Reliability: (2) valid with restrictions

Valid calculation method.
10-DEC-2004 (6)

2.5 Partition Coefficient

log Pow: = .36 at 25 degree C

Method: OECD Guide-line 107 "Partition Coefficient (n-octanol/water), Flask-shaking Method"
Year: 2000
GLP: yes

Remark: Condition:

Octanol (ml)	Water (ml)	Test substance (mg)
5	30	4.88
10	25	4.88
20	15	4.88

Analytical method:
Gas chromatography with external standard.

Result: (log value)

Condition-1	Condition-2	Condition-3
0.36	0.38	0.36
0.36	0.37	0.36

Overall average value = 0.36
Test substance: CAS No. 7580-85-0
Chemical Name: Ethanol, 2-tert-butoxy-
Source: Tokyo Kasei Kougyou Co., Ltd.
Purity: 99.7 %
Lot No.: FGD01
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
10-DEC-2004 (3)

log Pow: = .46

Method: other (calculated)

Reliability: (2) valid with restrictions
Valid calculation method.
10-DEC-2004 (6)

2.6.1 Solubility in different media

Value: >= 100 g/l at 25 degree C
Descr.: very soluble (> 10000 mg/L)

Method: OECD Guide-line 105
Year: 2000
GLP: no

Remark: 200 mg of test substance was added in 1.8 ml of distilled water (n=3).

Visually confirmed the complete dissolution.
Test substance: CAS No. 7580-85-0
Chemical Name: Ethanol, 2-tert-butoxy-
Source: Tokyo Kasei Kougyou Co., Ltd.
Purity: 99.7 %
Lot No.: FGD01
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
10-DEC-2004 (3)

Value: = 153 g/l at 25 degree C

Test substance: CAS No. 7580-85-0
Test Substance Name: Ethanol, 2-tert-butoxy
Reliability: (2) valid with restrictions
Valid calculation method.
10-DEC-2004 (6)

2.6.2 Surface Tension

2.7 Flash Point

Value: = 55 degree C

Test substance: CAS No. 7580-85-0
Test Substance Name: Ethanol, 2-tert-butoxy-
Reliability: (4) not assignable
Producer's MSDS data without proof.
Flag: Material Safety Dataset
10-DEC-2004 (8)

2.8 Auto Flammability

2.9 Flammability

2.10 Explosive Properties

Remark: A range of explosion is 0.6 to 10.5 vol %.
Test substance: CAS No. 7580-85-0
Test Substance Name: Ethanol, 2-tert-butoxy-
Reliability: (4) not assignable
Producer's MSDS data without proof
Flag: Material Safety Dataset
10-DEC-2004 (8)

2.11 Oxidizing Properties

2.12 Dissociation Constant

2.13 Viscosity

2.14 Additional Remarks

3.1.1 Photodegradation

Type: air
INDIRECT PHOTOLYSIS
Sensitizer: OH
Conc. of sens.: 1500000 molecule/cm³
Rate constant: = .0000000000125967 cm³/(molecule * sec)
Degradation: = 50 % after .8 day(s)

Method: other (calculated)

Remark: Calculated by SRC-AOPWIN v1.90.
Based on 12hrs/day irradiation.
Test substance: CAS No. 7580-85-0
Chemical Name: Ethanol, 2-tert-butoxy-
Reliability: (2) valid with restrictions
Valid calculation method.
Flag: Critical study for SIDS endpoint
10-DEC-2004 (6)

3.1.2 Stability in Water

Type: abiotic
t1/2 pH4: > 1 year at 25 degree C
t1/2 pH7: > 1 year at 25 degree C
t1/2 pH9: > 1 year at 25 degree C

Method: OECD Guide-line 111 "Hydrolysis as a Function of pH"
Year: 2000
GLP: no

Remark: 100 mg/l of test substance solutions at pHs 4, 7 and 9 were incubated at 50 degree C for 5 days (n=2).
More than 90 % of the initial concentration was maintained in all vessels.
Concentrations were determined by gas chromatography.
Result: The test substance was stable in water and its half-life at 25 degree C was calculated as more than 1 year at pHs 4, 7 and 9.
Test substance: CAS No. 7580-85-0
Chemical Name: Ethanol, 2-tert-butoxy-
Source: Tokyo Kasei Kougyou Co., Ltd.
Purity: 99.7 %
Lot No.: FGD01
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
10-DEC-2004 (3)

3.1.3 Stability in Soil

3.2.1 Monitoring Data (Environment)

3.2.2 Field Studies

3.3.1 Transport between Environmental Compartments

Type: volatility
Media: water - air

Method: The Henry's Law Constant was calculated using a water solubility of 100 g/l, a vapour pressure of 0.77mmHg and a molecular weight of 118.17.
Result: The calculated Henry's Law constant was 9.79x10-8 atm-m3/mole.
Test substance: CAS No. 7580-85-0
Chemical Name: Ethanol, 2-tert-butoxy-
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
10-DEC-2004 (6)

3.3.2 Distribution

Media: air - biota - sediment(s) - soil - water
Method: Calculation according Mackay, Level III

Remark: The following input parameters were used for the calculation.
Molecular weight: 118.17
Melting point (degree C): -50 (measured)
Vapour pressure (mmHG): 0.000267 (measured)
Water solubility (g/l): 100 (measured)
Log Kow: 0.36
Temperature (degree C): 25
Result:

	Mass amount (%)	Half-life (h)	Emission (kg/h)
Air	0.00135	20.4	1000
Water	44.4	360	1000
Soil	55.5	360	1000
Sediment	0.0754	1440	0

Test substance: CAS No. 7580-85-0
Chemical Name: Ethanol, 2-tert-butoxy-
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
22-MAR-2005 (6)

Media: water - soil

Result: A calculated Koc value is 1 (PCKOCWINv1.66).
Test substance: CAS No. 7580-85-0
Test Substance Name: Ethanol, 2-tert-butoxy-
Reliability: (2) valid with restrictions
Valid calculation method.
10-DEC-2004

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
Contact time: 28 day(s)
Degradation: = 6 % after 28 day(s)
Result: under test conditions no biodegradation observed
Control Subst.: Aniline
Deg. product: yes

Method: OECD Guide-line 301 C "Ready Biodegradability: Modified MITI Test (I)"
Year: 2000
GLP: yes

Remark: 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 cessels were cultivated 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 were determined by GC analysis.
Result: Following resuts were reported.

Biodegradation rates (28 days)

by BOD	7%	5%	6%	(Av. 6%)
by TOC	0%	0%	0%	(Av. 0%)
by GC	62%	74%	67%	(Av. 68%)

Conflicting results of GC and BOD/TOC analysis suggested a residue of metabolic substance and 1-tert-butoxy acetic acid was identified by LC-MS analysis.
Total mass balance of the identified metabolite and parent compound was almost equivalent to the initial test substance added in all test vessels (n=3).
Test substance: CAS No. 7580-85-0
Chemical Name: Ethanol, 2-tert-butoxy-
Source: Tokyo Kasei Kougyou Co., Ltd.
Purity: 99.7 %
Lot No.: FGD01
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
10-DEC-2004 (4)

3.6 BOD5, COD or BOD5/COD Ratio

3.7 Bioaccumulation

BCF: = 3.16

Remark: A BCF value was calculated based no the measured log Kow value of 0.36.
Test substance: CAS No. 7580-85-0
Chemical Name: Ethanol, 2-tert-butoxy-
Reliability: (2) valid with restrictions

Valid calculation method.
Flag: Critical study for SIDS endpoint
10-DEC-2004 (6)

3.8 Additional Remarks

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type: semistatic
Species: Oryzias latipes (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: yes
LC50: > 100 -
Limit Test: yes

Method: OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year: 2001
GLP: yes
Test substance: other TS:TOKYO KASEI KOGYO Co, Ltd., Lot. No.;FGD01, Purity=99.7%

Method: -Test Organisms:
a) Supplier: Test organisms were obtained from private fish farm in Japan, before 1 month of a test.
b) Size (length and weight): 2.43cm (2.26 - 2.49 cm) in length; 0.233 g (0.179 - 0.300 g) in weight
c) Age: Not described
d) Any pretreatment: Test organisms were acclimated for 14 days before testing. During acclimination, test fishes were fed with TETRAMINE. The mortality of the test organisms for 7 days before testing was less than 5%. LC50(96 hr) for a reference substance (copper sulfate pentahydrate) was 1.4 mg/L.

-Test substance: 2-tert-butoxy-ethanol
a) Empirical Formula: C6H14O2
b) Molecular Weight: 118.17g/mol
c) Purity: = 99.7 %
d) Boiling Point: = 171.2C
e) Water Solubility: soluble

-Test Conditions:
a) Dilution Water Source: Dilution water was prepared from tap water (Yokohama in Japan). The tap water was dechlorinated and treated by activated carbon and aerated.
b) Dilution Water Chemistry:
pH: = 7.7
Total hardness (as CaCO3): = 67mg/L
c) Exposure Vessel Type: 5 L test solution in a 5 L glass beaker with teflon sheet cover on the water.
d) Nominal Concentrations: control, 100 mg/L (a limit test)
e) Vehicle/Solvent and Concentrations:Not used.
f) Stock Solutions Preparations and Stability: Not described on the stock solution and stability in the test condition. Test substance was stored in freezer during test period. The stability of the chemical was confirmed by IR spectrum. Under the stock condition the IR spectrum of the test substance at the end of the test was same at the start of test.
g) Number of Replicates: 1
h) Fish per Replicates: 10
i) Renewal Rate of Test Water: Every 24 hours

j) Water Temperature: 24+/-1C
k) Light Condition: 16:8 hours, light-darkness cycle
l) Feeding: None
m) Aeration : None

-Analytical Procedure: The tested concentrations were measured at the start and at 24 hours using GC.

-Statistical Method:
a) Data Analysis:None
b) Method of Calculating Mean Measured Concentrations (i.e. arithmetic mean, geometric mean, etc.): Not described.

-

Result: - Measured Concentrations: The test concentrations were measured at start of the test and at 24 h.

Nominal Conc.	Measured Conc., mg/L		Percent of Nominal Conc.	
mg/L	0 Hour	24 Hour	0 Hour	24Hour
Control	<0.05	<0.05	---	---
100	91.0	103	91	103

- Water chemistry (pH and DO) and temperature in test: Water chemistry and temperature were measured for old and renewal solution with control and each concentration at the start of test and every 24 hours.
pH: 6.9 - 7.4
DO: 5.3 - 8.5 mg/L
Water Temperature: 23.5 - 23.8C

-Effect Data(mortality):
LC50 (96hr) = >100 mg/L (nc)
LC100 (96hr) >100 mg/L (nc)
nc: based on nominal concentration
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 control. The lowest concentration from which the test organisms were killed was 100 mg/L at 96th hr.

Measured Conc.	Cumulative Number of Dead (Percent Mortality)			
mg/L	24hr	48hr	72hr	96hr
Control	0 (0)	0 (0)	0 (0)	0 (0)
100	0 (0)	0 (0)	0 (0)	3 (30)

This test was conducted as a limit test at the concentrations of 100mg/l of the test substance, but three of ten fish died in the treatment group.

Therefore this test was regarded invalid as limit test. It may be true that the toxicity of 96 h LC50 > 100mg/L.

-Other Effect: Toxicological symptom was not observed at any concentration.

Nominal Conc.	Symptoms			
mg/L	24hr	48hr	72hr	96hr
Control	n	n	n	n
100	n	n	as-1	n

n: No toxicological symptom was observed.
as: Abnormal swimming - numbers of indivisuals.

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

-

Source: National Institute for Environment Studies Ibaraki
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
22-MAR-2005 (11)

Type: semistatic
Species: Oryzias latipes (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no
LC0: > 4000 -
LC50: > 4000 -
LC100: > 4000 -

Method: other:JISK0102"Fish, Acute Toxicity Test"(1981)
Year: 1985
GLP: no
Test substance: other TS:Not described

Method: -Test Organisms:
a) Supplier: Test organisms were obtained from private fish farm in Japan,
b) Size (length and weight): 3.2cm (SD=0.12) in length; 0.28 g (SD=0.04) in weight
c) Age: Not described
d) Any pretreatment: Test organisms were acclimated for over than 14 days before testing. During acclimination the mortality of test fish was less than 5 %
-Test substance: 2-tert-butoxy-ethanol
a) Empirical Formula: C6H14O2
b) Molecular Weight: 118.17g/mol
c) Purity: Not described
d) Boiling Point: = 171.2C
e) Water Solubility: Very high

-Test Conditions:
a) Dilution Water Source: Not described
b) Dilution Water Chemistry: Not described

c) Exposure Vessel Type: 5 L test solution in a 5 L glass aquariums
d) Nominal Concentrations: control, 3000, 4000 mg/L (limited test)
e) Vehicle/Solvent and Concentrations:Not used.
f) Stock Solutions Preparations and Stability: Test substance was added to the test aquariums directly
g) Number of Replicates: 1
h) Fish per Replicates: 10
i) Renewal Rate of Test Water: Every 2 days
j) Water Temperature: 25+/1C
k) Light Condition: 14:10 hours, light-darkness cycle
l) Feeding: None
m) Aeration : Not apply during the exposure

-Analytical Procedure: Not described.

-Statistical Method:
a) Data Analysis: Not described
b) Method of Calculating Mean Measured Concentrations (i.e. arithmetic mean, geometric mean, etc.): Not described.
-

Result: - Measured Concentrations: None

- Water chemistry (pH and DO) and temperature in test:
pH: 7..4 at the initial, 7.0-7.3 at the end
DO: 7.9 - 8.0 mg/L at the initial, 6.1-6.3 mg/L at the end mg/L
Water Temperature:

-Effect Data(mortality):
LC50 (96hr) > 4000 mg/L (nc)
LC0 (96hr) > 4000 mg/L (nc)
LC100 (96hr) > 4000 mg/L (nc)
nc: based on nominal concentration

- Cumulative Mortality: None of test organisms were killed during exposure period at the all concentrations of 0(control), 3000 and 4000 mg/L

-Other Effect: Toxicological symptom was not observed at any concentration.

Nominal Conc.	Symptoms			
mg/L	24hr	48hr	72hr	96hr
Control	n	n	n	n
3000	n	n	n	n
4000	n	AS.RA	AS.RA	AS.RA

n: No toxicological symptom was observed.
AS: At the surface(abnormal behavior)
RA: Reduced Activity

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

-

Source: National Institute for Environment Studies Ibaraki
Reliability: (4) not assignable
The details of the test method was not available, and the information on test substance was entirely lacking, therefore the exposure concentration and also the impurity could not be ensured because of no analytical monitoring
22-MAR-2005 (7)

4.2 Acute Toxicity to Aquatic Invertebrates

Type: semistatic
Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: yes
EC50: > 891 - measured/nominal
Limit Test: no

Method: OECD Guide-line 202
Year: 2001
GLP: yes
Test substance: other TS:TOKYO KASEI KOGYO Co, Ltd., Lot. No.;FGD01, Purity=99.7%

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 22 days on test condition before testing. During acclimatization, test daphnids were fed with Chlorella vulgaris, 0.2 mg carbon/day/individual. 24 hours before acute toxicity test, mortality of the test daphnia was low and any resting-egg and male daphnia was not observed. EC50 (48hr, immobility) for reference substance (potassium dichromate) was 0.68mg/L.

-Test substance: 2-tert-butoxy-ethanol
a) Empirical Formula: C6H14O2
b) Molecular Weight: 118.17g/mol
c) Purity: = 99.7 %
d) Boiling Point: = 171.2C
e) Water Solubility: soluble

-Test Conditions:
a) Dilution Water Source: Elendt M4 media (OECD Guide-line 211 "Daphnia magna reproduction test") was used as dilution water for the test.
b) Dilution Water Chemistry: Not described
c) Exposure Vessel Type: 100 mL test solution in a 100 mL glass beaker with teflon sheet cover on the water.
d) Nominal Concentrations: control, 100, 180, 320, 560 and 1000 mg/L
e) Vehicle/Solvent and Concentrations: Not used.

f) Stock Solutions Preparations and Stability:Not described on the stock solution and stability in the test condition. Test substance was stored in freezer during test period. The stability of the chemical was confirmed by IR spectrum. Under the stock condition the IR spectrum of the test substance at the end of the test was same at the start of test.
g) Number of Replicates: 4
h) Individuals per Replicates: 5 per beaker
i) Water Temperature: 20+/-1C
j) Light Condition: 16:8 hours, light-darkness cycle
k) Feeding: None
l) Aeration : Test solution was not aerated during the test period

- Analytical Procedure: Test concentrations were measured at the start and at 24 hour using GC.

- Statistical Method:
a) Data Analysis: EiC50 and 95% confidence intervals were calculated by proper one of three methods, binominal method, moving average method and probit method, when inhibition rate at treatment of highest concentration is more than 50%. If inhibition rate at the highest concentration is less than 50%, EiC50 were determined more than the highest concentration.(>highest concentration)
b) Method of Calculating Mean Measured Concentrations: Geometric mean

-

Result: - Measured Concentrations: The test concentrations were measured at the start and at 24 hour of the test. For some of them, the deviations from the nominal were not less than +/-20%.

Nominal Conc. mg/L	Measured Conc., mg/L		Mean* mg/L	Percent of Nominal	
	0 Hour Fresh	24 Hour Old		0 Hour Fresh	24 Hour Old
Control	<0.09	<0.09	---	---	---
100	92.8	83.2	87.9	93	83
180	174	155	164	97	86
320	353	278	313	110	87
560	574	530	552	103	95
1000	934	850	891	93	85

Fresh: freshly prepared test solution.
Old: test solutions after 24 hours exposure
*: Mean measured concentration during 24 hours.(Geometric mean)

- Water chemistry (pH and DO) and temperature in test: Water chemistry and temperature were measured for control and each concentration at the start and before the water replacement.
pH: 8.0 - 8.2

DO: 8.5 - 8.8 mg/L
Water Temperature: 19.9 - 20.0C

-Effect Data:
NOECi (48hr) =>891 mg/L (mc)
EC50 (48hr) =>891 mg/L (mc)

mc: based on the geometric mean of the measured concentrations
95% C.I. cannot calculated.

-Mortality or Immobility: Most of the test organisms was not dead or immobilized in all treatments at the end of the test.

Nominal Conc.	Cumulative Numbers of Immobilized Daphnia (Percent Immobility)	
mg/L	24 Hour	48 Hour
Control	0 (0)	1 (5)
87.9	0 (0)	1 (5)
164	0 (0)	0 (0)
313	0 (0)	0 (0)
552	0 (0)	1 (5)
891	0 (0)	0 (0)

- Calculation of toxic values: Geometric mean of measured concentrations at the start and 24 hours.

-

Source: National Institute for Environment Studies Ibaraki
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
22-MAR-2005 (11)

4.3 Toxicity to Aquatic Plants e.g. Algae

Species: Selenastrum capricornutum (Algae)
Endpoint: growth rate
Exposure period: 72 hour(s)
Unit: mg/l Analytical monitoring: yes
NOEC: = 291 - measured/nominal
EC10: - measured/nominal
EC50: > 866 -

Method: OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year: 2001
GLP: yes
Test substance: other TS:TOKYO KASEI KOGYO Co, Ltd., Lot. No.;FGD01, Purity=99.7%

Method: - Test Organisms:
a) Supplier/Source: Obtained from American Type Culture Collection
b) Method of Cultivation: Sterile
c) Stain Number: ATCC22662
d) Any pretreatment: Acclimated for 4 days before testing.

-Test substance: 2-tert-butoxy-ethanol
a) Empirical Formula: C6H14O2
b) Molecular Weight: 118.17g/mol
c) Purity: =99.7 %
d) Boiling Point: = 171.2C
e) Water Solubility: soluble

- Test Conditions:
a) Medium: OECD medium
b) Exposure Vessel Type: 100 mL Medium in a 500mL glass Erlenmeyer flask with stopper
c) Nominal Concentrations: control, 10.0,32.0,100,320 and 1000mg/L
d) Vehicle/Solvent and Concentrations: Not used.
e) Sock Solution: 2-tert-butoxy-ethanol was diluted with OECD medium.
f) Number of Replicates: 3
g) Initial Cell Number: 10,000 cells/mL
h) Water Temperature: 23+/-2C
i) Light Condition: 4,000 lux (fluctuation within +/-20%), continuously
j)Shaking: 100 rpm

- Analytical Procedure: Test concentrations were measured at the start and the 72nd hour.

- Statistical Method:
a) Data Analysis: Probit method for EC50. 1-way ANOVA (a=0.05) and Dunnett's method (a=0.05, both side) for NOEC, after Bartlett's homoscedastic test.
b) Method of Calculating Mean Measured Concentrations (i.e. arithmetic mean, geometric mean, etc.):geometric mean

-

Result: - Measured Concentrations : The tested concentrations were measured at the start and the 72nd hour.

Nominal Conc. (mg/L)	Measured Conc. (mg/L)		Percent of nominal (%)		Mean Conc. (mg/L)
mg/L	0 Hour Fresh	72 Hour Old	0 Hour Fresh	72 Hour Old	
Control	<0.05	<0.05	---	---	<0.05
10.0	11.1	10.2	111	102	10.6
32.0	25.0	21.9	78	68	23.4
100	87.5	74.4	88	74	80.7
320	306	276	96	86	291

1000 891 841 89 84 866

Fresh: freshly prepared test solution
Old: test solution after 72 hours exposure

- Water chemistry (pH) and temperature in test: pH was measured for control and each concentration at the start and the end of test. At the start and the end of test, the pH was 7.8 and 10.1 - 10.4, respectively.
Temperature was measured for control and each concentration everyday, and maintained 23+/-2C during test period.
pH: 7.8 - 10.4
temperature: 23 +/- 2 C

Mean Concentration	pH	
mg/L	0 Hour	72 Hour
Control	7.8	10.4
10.6	7.8	10.4
23.4	7.8	10.4
80.7	7.8	10.4
291	7.8	10.4
866	7.8	10.1

At the end of test, pH increased more than 1 unit compared with the start. When carbon dioxide assimilation is active and growth rate is high, pH often increases more than 1 unit.

-Effect Data: Rate Method
EC50 (0-72hr) > 866 mg/L (mc)
NOEC (0-72hr) = 291 mg/L (mc)

mc: based on geometric mean of measured concentration at the start and the end.

- Growth Inhibition (%) of Slenastrum capricornutum

Measured Conc.	Growth rates and inhibition	
mg/L	Rate (Average)	Inhibition(%)
Control	164	----
10.6	159	2.74
23.4	161	1.65
80.7	156	4.59*
291	158	3.75
866	143	12.9**

- Growth Curves: Exponential growth phase kept for 48 hours. Therefore the average growth rate was calculated based on the cell density at 0 and 48 hr after the start of the test.

- Calculation of toxic value: Geometric mean of measured concentration at the start and the end was used.

* Indicates a significant difference (a=0.05) from the control.
** Indicates a significant difference (a=0.01) from the control.

-
Source: National Institute for Environment Studies Ibaraki
Reliability: (2) valid with restrictions
However some deviations from the test guidline this study seemed to be reliable. The exponential growth phase could not keep throughout the test period and the deviation of pH was greater than 1.5 unit at the end of the test.
22-MAR-2005 (11)

4.4 Toxicity to Microorganisms e.g. Bacteria

4.5 Chronic Toxicity to Aquatic Organisms

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 Analytical monitoring: yes
NOEC: >= 94.2 - measured/nominal
LOEC: >= 94.2 - measured/nominal
EC50: >= 94.2 - measured/nominal

Method: OECD Guide-line 211
Year: 2001
GLP: yes
Test substance: other TS:TOKYO KASEI KOGYO Co, Ltd., Lot. No.;FGD01, Purity=99.7%

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 29 days on test conditions before testing. Less than 24 hours old organisms were used for test. The mortality of their parent daphnids were 0.0% and any resting-egg production or male was not observed in their parent daphnids. EC50(48 hr, immobility) for a reference substance (potassium dichromate) was 0.63mg/L.

-Test substance: 2-tert-butoxy-ethanol
a) Empirical Formula: C6H14O2
b) Molecular Weight: 118.17g/mol
c) Purity: = 99.7 %
d) Boiling Point: = 171.2C
e) Water Solubility: soluble

- Test Conditions:
a) Dilution Water Source: Elendt M4 media (OECD Guide-line 211 "Daphnia magna reproduction test") was used as dilution water for the test.
b) Dilution Water Chemistry:Not described.
c) Exposure Vessel Type: 80 mL test solution in a 100mL glass beaker with teflon sheet cover on the water.
d) Nominal Concentrations: control, 100 mg/L (a limit test)
e) Vehicle/Solvent and Concentrations: Not used.
f) Stock Solutions Preparations and Stability: Not described on the stock solution and stability in the test condition. Test substance was stored in freezer during test period. The stability of the chemical was confirmed by IR spectrum. Under the stock condition the IR spectrum of the test substance at the end of the test was same at the start of test.
g) Number of Replicates: 10
h) Individuals per Replicates: 10
i) Renewal Rate of Test Water: everyday
j) Water Temperature: 20+/-1C
k) Light Condition: 16:8 hours, light-darkness
l) Feeding: 0.15 mg carbon/day/individual (Chlorella vulgaris: Green Algae)
m) Aeration: Not described

- Analytical Procedure: The test concentrations were measured three times during test period for both renewal and old test solution using GC.
- Statistical Method:
a) Data Analysis:
LC50: During test period the test organisms were not killed more than 50% in any concentration.
EC50: EC50 and its 95%c.l. were calculated by Logit method.
NOEC and LOEC: The cumulative number of juveniles produced per adult in control and test concentration after 21days was tested by F test and t-test of Student using statistical software 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, 9th, 14th and 15th day. Some of them, the deviation from the nominal concentration were not less than +/-20%.

Nominal Conc.	Measured Conc., mg/L							
mg/L Date	0 Fresh	1 Old	7 Fresh	8 Old	14 Fresh	15 Old	TWM* mg/L	%of Nominal
Control	<0.08	<0.08	<0.08	<0.08	<0.08	<0.08	---	---
100	91.5	83.4	113	96.1	92.3	89.6	94.2	94

Fresh: Freshly prepared test solution.
Old: Old test solution before renewal.
*: Time-weighted mean of measured concentration during 21 days

- Range of Measured Concentration and Percentage of Nominal Concentration

	Measured Concentration (mg/L)			Percentage of Nominal		
	Min.		Max	Min.		Max
New	91.5	-	113	92	-	113
Old	83.4	-	96.1	83	-	96

Fresh: Freshly prepared test solution.
Old: Old test solution before renewal.

- Water chemistry (pH, DO and) and temperature in test:
Water chemistry and temperature were measured for control and each concentration at the start of test and before and after renewal 4 times during exposure.
pH: 7.2 - 8.5
DO: 7.7 - 8.8 mg/L
Water Temperature: 19.7 - 20.1C

- Total hardness(as CaCO3): 235 - 255 mg/L

-Effect Data:
LC50 (21day) > 94.2 mg/L (mc)
EC50 (21day) = > 94.2 mg/L (mc)
NOEC (21day) = > 94.2 mg/L (mc)
LOEC (21day) = > 94.2 mg/L (mc)
mc: based on the time weighted mean of measured concentrations
The LC50 and EC50 values and their associated 95% confidence limits could not be determined by statistical methods because the mortality of parental Daphnia and the reproduction inhibition rate at the maximum concentration level were less than 50%.

- Cumulative Number of Died Parental Daphnia: No test organism was killed at 100 mg/L. At the control, test organisms were dead after 5days. Mortality rate of parental Daphnia at the control was less than 20%.

Nominal Conc. (mg/L)	Cumulative Number of Dead Parental Daphnia (days)									
	1	2	3	4	5	6	7	8	9	10
Control	0	0	0	0	1	1	1	2	2	2
100	0	0	0	0	0	0	0	0	0	0

Measured Conc. (mg/L)	Cumulative Number of Dead Parental Daphnids (days) 11	12	13	14	15	16	17	18	19	20	21
Control	2	2	2	2	2	2	2	2	2	2	2
100	0	0	0	0	0	0	0	0	0	0	0

-Effect Data(reproduction):Juveniles were first produced on the 8th and 9th day at both treatment.
-Cumulative numbers of juveniles produced per adult alive for 21days

Nominal Conc. mg/L	Mean Cumulative Numbers of Juveniles Produced per Adult Alive for 21 days (Days) 0 --- 7	8	9	10	11	12	13	14
Control	0 --- 0	6.5	9.6	9.6	21.0	33.8	33.8	33.8
100	0 --- 0	6.6	10.1	10.1	22.6	32.3	32.3	32.3

Measured Conc. mg/L	Mean Cumulative Numbers of Juveniles Produced per Adult Alive for 21 days (Days) 15	16	17	18	19	20	21
Control	61.1	61.1	61.1	82.9	85.6	85.6	97.1
100	60.5	60.6	60.6	78.7	85.6	85.6	99.5

-Cumulative numbers of juveniles produced per adult alive for 21days in each test vessels and results of statistical comparison of the mean values (by Student's t paired comparison test)

	Nominal Conc., mg/L	
Vessel No.	Control	100
1	88	85
2	D	105
3	109	118
4	104	75
5	104	88
6	110	108
7	D	121
8	93	82
9	73	116
10	96	97
Mean	97.1	99.5
S. D.	12.4	16.4

Inhibition rate(%)	-2.4
Significantdifference	-

D: Were not included for calculation because the parental Daphnia was dead during a 21-days testing period.
- : Indicates 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
Flag: Critical study for SIDS endpoint
22-MAR-2005 (11)

TERRESTRIAL ORGANISMS

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 Toxicity to other Non-Mamm. Terrestrial Species

4.7 Biological Effects Monitoring

4.8 Biotransformation and Kinetics

4.9 Additional Remarks

5.0 Toxicokinetics, Metabolism and Distribution

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type:	LD50
Species:	rat
Strain:	other:Crj:CD(SD)IGS
Sex:	male/female
No. of Animals:	5
Vehicle:	other:Purified water
Method:	OECD Guide-line 401 "Acute Oral Toxicity"
Year:	2002
GLP:	yes
Test substance:	other TS: MARUZEN PETROCHEMICAL CO.,LTD;Purity 99.98%
Remark:	Doses were 0, 500, 1000, and 2000mg/kgbw for both sexes.
Result:	LD50 value was more than 2,000 mg/kg bw for both sexes. No abnormalities were observed in body weight or necropsy finding in any groups. Anemia and chromaturia were observed at 500 mg/kg bw/day and higher in five males and females. Abnormal gait was found at 1000 mg/kg bw/day in five males and two females. Adoption of a prone position in two males and one female, decrease locomotor activity in four males and one female, and irregular respiration in one male were observed at 2000 mg/kg bw/day. No abnormalities were observed in body weights or necropsy findings.
Source:	Research Institute for Animal Science in Biochemistry and Toxicology Sagamihara Kanagawa
Reliability:	(1) valid without restriction
Flag:	Critical study for SIDS endpoint

13-DEC-2004 (10)

Type:	LD50
Species:	mouse
Strain:	other: ddY(Japan SLC Co.)
Sex:	male
No. of Animals:	4
Vehicle:	other: olive oil
Test substance:	other TS: Ethylene glycol mono-t-butyl ether (Tokyo Kasei Co., Tokyo)
Remark:	Male ddY mice weighing about 25 g were used for determining the acute oral toxicity. The animals were given either 2.0 g/kg CCl4 dissolved in olive oil or olive oil only intraperitoneally, in a volume of 0.16 mL per 25 g, 24 h prior to receiving the chemical, intraperitoneally. This dosage of CCl4 alone caused no death to animals during the experiment. The oral LD50 was determined using four animals per dose level, four different doses and 1 week observation period.
Result:	The LD50 with pretreatment of olive oil was 11.24(9.17-13.76) mmol/kg bw, that is, 1328(1084-1615) mg/kg bw.

Reliability: (2) valid with restrictions
13-DEC-2004 (12)

5.1.2 Acute Inhalation Toxicity

5.1.3 Acute Dermal Toxicity

5.1.4 Acute Toxicity, other Routes

Type: LD50
Species: mouse
Strain: other:ddY(Japan SLC Co.)
Sex: male
No. of Animals: 4
Vehicle: other:olive oil
Route of admin.: i.p.

Year: 1992
GLP: no data
Test substance: no data

Remark: Male ddY mice weighing about 25 g were used for determining the acute toxicitry. The animals were given either 2.0 g/kg CCl4 dissolved in olive oil or olive oil only intrapertoneally, in a volume of 0.16 mL per 25 g, 25 h prior to receiving the chemical, intraperitoneally. This dosage of CCl4 alone caused no death to animals during the experiment. The LD50 was determined according to Weil using four animal per dose level, four different doses and 1 week observation period.
Result: The LD50 with preteratment of olive oil was 11.24(9.17-13.76) mmol/kg, that is, 1328(1084-1615) mg/kg. THe LD50 with pertreatment of CCl4 was 8.29 mmol/kg, 980 mg/kg.
Source: Research Institute for Animal Science in Biochemistry and Toxicology Sagamihara Kanagawa
Reliability: (2) valid with restrictions
11-JUL-2004 (12)

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

5.2.2 Eye Irritation

5.3 Sensitization

5.4 Repeated Dose Toxicity

Species: rat Sex: male/female
Strain: other:Crj:CD(SD)IGS
Route of administration: gavage
Exposure period: Males:37 days Females:42-47 days from 14 days before mating to day 4 of lactation
Frequency of treatment: Once a day
Post exposure period: None

Doses: 4, 20, 100 mg/kg bw/day
Control Group: yes, concurrent vehicle

Method: OECD combined study TG422
Year: 2002
GLP: yes
Test substance: other TS:MARUZEN PETROCHEMICAL CO.,LTD;Purity 99.98%

Remark: This study was conducted to examine both repeated dose toxicity and reproductive/developmental toxicity as an OECD screening combined study (Test guideline: 422).
Study design:
Number of animals:12
Vehicle: Purified water
Clinical observation performed and frequency: General condition was observed once a day. Body weights were determined on days 0 (before dosing), 3, 7, 14, 21, 28 and 35 of treatment for males and on days 0, 3, 7 and 14 of treatment and on days 0, 7, 14 and 20 of gestation and on days 0 and 4 of lactation for females and at autopsy in males and females. Food consumption was determined on days 0, 7, 14, 21, 28 and 35 of treatment for males and at days 0, 7 and 14 of treatment and on days 0, 7, 14 and 20 of gestation and at days 0 and 4 of lactation in females, but it was not determined during the mating period for males and females.
In 6 males per group, urinalysis was carried out on 35 days of administration.
In all males and all females after birth of pups, hematology and biochemistry were carried out at time of necropsy after 37 days in males and at 5 days after delivery in females.
Organs were examined at necropsy.
Weighs: The brain, heart, liver, kidney, adrenal, thymus, spleen, testis and epididymis were determined.
Microscopic examination: The spleen, liver, kidney and bone marrow in males and females of all groups, the brain, pituitary, thymus, thyroid, parathyroid, adrenal, heart, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, trachea, lung, urinary bladder, spinal cord, mesentery lymph node, mandibular lymph node, isciadic nerve in males and females at 0 and 100 me/kg bw/day, the testis, epididymis, prostate and seminal vesicle in males at 0 and 100 mg/kg bw/day, the ovary, uterus and vagina in females at 0 and 100 mg/kg bw/day and the skin with alopecia in one male at 4 mg/kg bw/day and one female at 20 mg/kg/day were examined.
Statistical methods: Dunnett's test for continuous data and Steel test for quantal data were used.

Result: Mortality: There was no death in any groups.
Clinical signs: Reddish urine was apparent in all animals at 100 mg/kg bw/day for 3 hours after first administration.
Body weight: No statistically significant changes were found in males and females.
Food consumption: No effects were observed in males and females.
Urinalysis: No statistically significant changes were found.

Hematology
Males: Decreases in erythrocyte count, hemoglobin, hematocrit, MCHC and leukocyte count, and increases in MCV, MCH and reticulocytes in 100 mg/kg bw/day group, and decreases in MCHC in 20 mg/kg bw/day group were observed.

Dose(mg/kg bw/day)		0	4	20	100
No. of animals		12	12	12	12
Erythrocyte count(10^4/uL)					
	Mean	838.0	853.7	819.6	703.3**
	SD	31.8	27.3	55.4	34.5
Hemoglobin(g/dL)	Mean	15.88	15.87	15.44	14.18**
	SD	0.55	0.35	0.98	0.77
Hematocrit(%)	Mean	45.03	45.22	45.15	42.03**
	SD	1.78	1.26	2.55	2.60
Reticulocyte(0/00)	Mean	24.23	23.14	26.89	57.45**
	SD	3.93	3.64	5.56	12.27
MCV(fL)	Mean	53.76	52.97	55.16	59.79**
	SD	2.30	1.14	2.10	3.29
MCH(pg)	Mean	18.97	18.59	18.86	20.17**
	SD	0.75	0.41	0.69	0.77
MCHC(%)	Mean	35.29	35.10	34.18**	33.75**
	SD	0.84	0.35	0.62	0.87
Leukocyte count(10^2/uL)					
	Mean	98.13	93.68	90.40	67.18**
	SD	22.59	17.92	18.45	14.26

Note:**, p<0.01

Females: Decreases in erythrocyte count, hemoglobin and MCHC, and increases in MCV and reticulocytes at 20 and 100 mg/kg/day, and increase in MCH at 100 mg/kg/day were observed.

Dose(mg/kg bw/day)		0	4	20	100
No. of animals		12	10	12	9
Erythrocyte count(10^4/uL)					
	Mean	723.1	699.6	653.7**	554.8**
	SD	31.0	38.2	42.7	43.2
Hemoglobin(g/dL)	Mean	13.87	13.69	12.84**	12.42**
	SD	0.53	0.60	0.73	0.69
Reticulocyte(0/00)	Mean	50.85	57.92	74.88*	143.27**
	SD	8.68	16.62	17.79	32.16
MCV(fL)	Mean	55.90	58.01	59.23*	72.49**
	SD	1.30	2.21	2.91	4.23
MCH(pg)	Mean	19.19	19.60	19.67	22.43**
	SD	0.44	0.63	0.99	0.93
MCHC(%)	Mean	34.33	33.78	33.23**	30.99**
	SD	0.54	0.56	0.69	0.82

**Note: *,p<0.05; **,p<0.01

Blood biochemistry
Males: Increases in total cholesterol at 100 mg/kg bw/day were observed.

Dose (mg/kg bw/day)		0	4	20	100
No.of animals		12	12	12	12
Total cholesterol(mg/dL)	Mean	49.2	55.0	51.6	60.2*
	SD	7.9	6.1	13.0	9.3

Note:*,P<0.05

Females: Decrease in potassium at 100 mg/kg bw/day were observed .

Dose (mg/kg bw/day)		0	4	20	100
No. of animals		10	10	12	9
K(mmol/L)	Mean	4.35	4.34	4.41	4.01*
	SD	0.23	0.21	0.98	0.24

Note:*,p<0.05

Necropsy: Spleen enlargement and brown in color of spleen for 6 males and spleen enlargement in 8 females were observed at 100 mg/kg bw/day .
Organ weights: Increases in absolute and relative weights of the spleen were observed in males and females at 100 mg/kg bw/day.

Dose (mg/kg bw/day)			0	4	20	100
Male						
No.of animals			12	12	12	12
Spleen	Absolute (g)	Mean	0.797	0.782	0.841	1.090*
		SD	0.124	0.133	0.132	0.256
	Relative (g%)	Mean	0.179	0.168	0.186	0.239**
		SD	0.023	0.028	0.022	0.045
Female						
Dose (mg/kg bw/day)			0	4	20	100
No.of animals			10	10	12	9
Spleen	Absolute(g)	Mean	0.745	0.751	0.856	1.114**
		SD	0.069	0.147	0.451	0.222
	Relative(g%)	Mean	0.233	0.235	0.268	0.347**
		SD	0.020	0.035	0.133	0.077

Note:*, p<0.05; **,p<0.01

Histopathology: There were histopathological changes in the spleen, liver, kidneys and bone marrow in both sexes at 20 and/or 100 mg/kg bw/day. The histopathological findings were as follows: Extramedullary hematopoiesis such as erythrocytic cells and hemosiderin deposition in spleen, extramedullary hematopoiesis and hemosiderin deposition in liver, hemosiderin deposition in tubular epithelium of kidney and increase in hematopoietic cells such as erythrocytic cells in bone marrow.

Males

Dose(mg/kg bw/day)		0	4	20	100
No.of animals		12	12	12	12
Spleen:					
Extramedullary hematopoiesis,					
erythrocytic	+	8	8	7	3**
	++	0	0	1	9
hemosiderin deposition	+	2	4	1	0**
	++	8	7	8	4
	+++	2	1	3	8
Liver:					
Hemosiderin deposition,					
kupper cell	+	6	6	5	6**

	++	0	0	2	6
Kidney:					
Hemosiderin deposition,					
tubular epithelium	+	1	0	0	10**
Bone marrow:					
Increase in hematopoietic cell,					
erythrocytic	+	0	0	0	8**

Females

Dose(mg/kg bw/day)		0	4	20	100
No.of animals		12	12	12	12
Spleen:					
Extramedullary hematopoiesis,					
erythrocytic	+	10	9	4*	2**
	++	1	1	6	7
Liver:					
Extramedullary hematopoiesis					
	+	1	1	4	9**
Hemosiderin deposition,					
kupffer cell	+	7	7	10	4**

Note:*, p<0.05; **,p<0.01

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

Conclusion: The NOAELs for repeated dose toxicity were considered to be 20 mg/kg bw/day in males and 4 mg/kg bw/day in females.

Reliability: (1) valid without restriction

Flag: Critical study for SIDS endpoint

22-MAR-2005 (10)

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

Concentration: See "Remark"

Metabolic activation: with and without

Result: negative

Method: OECD Guide-line 471

Year: 2002

GLP: yes

Test substance: other TS:MARUZEN PETROCHEMICAL CO.,LTD;Purity 99.98%

Remark: Procedures: Pre-incubation method
Solvent: Water for injection
Dosage of each strain with or without S9
-S9 mix: 0, 156, 313, 625, 1250, 2500, 5000 ug/plate(all strains)
+S9 mix: 0, 156, 313, 625, 1250, 2500, 5000 ug/plate(all strains)
Maximum concentration was established based on the result of the preliminary test at concentration up to 5000 ug/plate. In this test, the growth inhibition was not observed up to 5000 ug/plate with and without S9 mix in all strains.

Positive control:
without S9 mix:2-(2-Furyl)-3-(5-nitro -2-furyl)acrylamide (TA100, TA98, WP2uvrA), Sodium azide (TA 1535), 9-aminoacridine hydrochloride (TA1537)
with S9 mix: 2-Aminoanthracene (all strains)
S9: Rat liver, induced with phenobarbital and 5,6-benzoflavone
Plates/test: 3
Statistical analysis : no

Result: There were no precipitation in any test concentration. Cytotoxic concentration: Growth inhibition was not observed at concentration up to 5000ug/plate with or without S9 mix in all stains. Genotoxic effects:
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

13-DEC-2004 (10)

Type: Chromosomal aberration test
System of testing: Type of cell used: Chinese hamster lung(CHL/IU) cell
Concentration: 0, 300, 600, 1200 ug/mL
Metabolic activation: with and without
Result: negative

Method: other::Chemical Substances Control Law of Japan and OECD Test Guideline 473
Year: 2002
GLP: yes
Test substance: other TS:MARUZEN PETROCHEMICAL CO.,LTD;Purity 99.98%

Remark: Solvent: Water for injection
S9: Rat liver, induced with phenobarbital and 5,6-benzoflavone
Dosage:
-S9 mix(short-term treatment): 0, 300, 600, 1200 ug/mL
+S9 mix(short-term treatment): 0, 300, 600, 1200 ug/mL
-S9 mix(continuous treatment 24hr): 0, 300, 600, 1200 ug/mL
Positive control: Cyclophosphamide (with S9), Mitomycin C (without S9)
Plates/test: 2
Maximum concentration was established based on the result of the preliminary test up to 1200 ug/plate. In this test, the growth inhibition was not observed at 1200 ug/plate with and without S9 mix in all strains.
Statistical analysis : no

Result: No increase in chromosomal aberrations was observed in the test with either short-term treatment (with S9 and without S9) or continuous treatment.

Genetic effects:	Clastogenicity			Polyploidy		
	+	?	-	+	?	-
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
13-DEC-2004 (10)

5.6 Genetic Toxicity 'in Vivo'

5.7 Carcinogenicity

5.8.1 Toxicity to Fertility

Type: other
Species: rat
Sex: male/female
Strain: other:Crj:CD(SD)IGS
Route of administration: gavage
Exposure Period: Males:37 daysFemales:42-47 days from 14 days before mating to day 4 of lactation
Frequency of treatment: Once a day
Premating Exposure Period
male: 14 days
female: 14 days
Duration of test: Males: 38 days, females: from 14 days before mating to day 5 of lactation
Doses: 4, 20, 100 mg/kgbw/day
Control Group: yes, concurrent vehicle

Method: other:OECD Test guideline 422
Year: 2002
GLP: yes
Test substance: other TS:MARUZEN PETROCHEMICAL CO.,LTD;Purity 99.98%

Remark: This study was conducted to examine both repeated dose toxicity and reproductive/developmental toxicity as an OECD screening combined study (Test guideline: 422).
Study design:
Vehicle: Purified water
Clinical observation performed and frequency: General condition was observed once a day. Body weights were determined on days 0 (before dosing), 3, 7, 14, 21, 28 and 35 of treatment in males and on days 0, 3, 7 and 14 of treatment and on days 0, 7, 14 and 20 of gestation and on days 0 and 4 of lactation in females and at autopsy for both sexes. Food consumption was determined at days 0, 7, 14, 21, 28 and 35 of treatment in males and on days 0, 7 and 14 of treatment and on days 0, 7, 14 and 20 of gestation and on days 0 and 4 of lactation in females, but it was not determined during the mating period in males and females. In 6 males per group, urinalysis was carried out on 35 days of administration. In all males and all females after childbirth per group, hematology and biochemistry were carried out at time of necropsy after 37 days in males and at 5 days after delivery in females.
Organs were examined at necropsy.
Organ weight: weights of the brain, heart, liver, kidney,

adrenal, thymus, spleen, testis and epididymis were determined.
Microscopic examination: The spleen, liver, kidney and bone marrow in males and females of all groups, the brain, pituitary, thymus, thyroid, parathyroid, adrenal, heart, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, trachea, lung, urinary bladder, spinal cord, mesentery lymph node, mandibular lymph node, isciadic nerve in males and females at 0 and 100 me/kg bw/day, the testis, epididymis, prostate and seminal vesicle in males at 0 and 100 mg/kg bw/day, the ovary, uterus and vagina in females at 0 and 100 mg/kg bw/day and skin with alopecia in one male at 4 mg/kg bw/day and one female at 20 mg/kg/day were examined.
Statistical methods: Dunnett's test for continuous data and Steel test for quantal data were used.
Reproductive and developmental parameters: No.of pairs with successful mating, no. of pregnant females, mating index (no. of pairs with successful copulation/no. of pairs mated x 100), fertility index (no. of pregnant animals/no.of animals with successful mating x 100), estrous cycle, no. of females with live pups, gestational length, no.of corpora lutea, no.of implantation sites, no.of pups delivered, no.of live pups delivered, sex ratio, gestation index (no.of females with live pups/no.of pregnant females x 100),implantation index (no.of implants/no.of corpora lutea x100), delivery index (no.of pups born/no. of implants x100), live birth index (no.of live pups born/no. of pups born x 100), and viability index on day 4 (no.of live pups on day 4 after birth/no.of live pups born x 100) were determined.
Statistical methods: Dunnett's test for continuous data and Steel test for quantal data were used.

Result: Result: Mortality: There was no mortality related to the test substance.
Clinical signs: Reddish urine was apparent in all animals at 100 mg/kg bw/day for 3 hours after first administration.
Body weight: No statistically significant changes were found in males and females.
Food consumption: No effects in males and females were found.
Urinalysis: No statistically significant changes.
Hematology:
Males: Decreases in erythrocyte count, hemoglobin, hematocrit, MCHC and leukocyte count, and increases in MCV, MCH and reticulocytes at 100 mg/kg bw/day, and decreases in MCHC at 20 mg/kg bw/day were observed.
Females: Decreases in erythrocyte count, hemoglobin and MCHC, and increases in MCV and reticulocytes at 20 and 100 mg/kg bw/day, and increase in MCH at 100 mg/kg bw/day were observed.
Blood biochemistry:
Males: Increases in total cholesterol at 100 mg/kg bw/day were observed.
Females: Decreases in potassium at 100 mg/kg bw/day were found.
Necropsy: Spleen enlargement and brown in color of spleen in 6 males and spleen enlargement in 8 females at 100 mg/kg bw/day were observed.
Organ weights: Increases in absolute and relative weights of spleen in males and females at 100 mg/kg bw/day were found.

Histopathology: There were histopathological changes in the spleen, liver, kidneys and bone marrow in both sexes at 20 and/or 100 mg/kg bw/day. The histopathological findings were as follows: Extramedullary hematopoiesis such as erythrocytic cells and hemosiderin deposition in the spleen, extramedullary hematopoiesis and hemosiderin deposition in the liver, hemosiderin deposition in tubular epithelium of the kidney and increase in hematopoietic cells such as erythrocytic cells in the bone marrow.
Reproductive and developmental parameters: No effects were observed on reproductive parameters in males and females given each dose, and developmental parameters of the offspring.

Dose(mg/kg bw/day)		0	4	20	100
No. of pairs mated		12	12	12	12
No. of pairs with successful mating		12	12	12	12
No. of pregnant females		11	10	12	9
Fertility index (%)		91.7	83.3	100.0	75.0
No. of females with live pups		10	10	12	9
Gestation length(day)					
	Mean	22.2	22.1	22.2	22.4
	SD	0.4	0.3	0.4	0.5
No. of corpora lutea					
	Mean	19.3	19.2	20.1	19.2
	SD	4.2	2.1	4.2	4.0
No. of implantation sites					
	Mean	15.6	15.8	16.2	14.6
	SD	4.5	2.4	2.5	2.9
No. of pups delivered					
	Mean	16.0	15.2	15.3	13.4
	SD	1.6	2.1	2.8	3.6
Sex ratio(male/female)		0.78	1.11	1.09	1.16
No. of live pups on day 4					
	Mean	15.1	14.8	15.2	13.3
	SD	2.3	2.3	2.8	3.6
Viability index on day 4					
	Mean	94.68	97.90	99.02	99.21
	SD	12.86	3.40	2.30	2.37

Source: Research Institute for Animal Science in Biochemistry and Toxicology Sagamihara Kanagawa
Conclusion: The test substance had no effects on any reproductive and developmental parameters. The NOAEL for reproductive and developmental toxicity was concluded to be 100 mg/kgbw/day for parental animals and offspring.
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
13-DEC-2004 (10)

5.8.2 Developmental Toxicity/Teratogenicity

5.8.3 Toxicity to Reproduction, Other Studies

5.9 Specific Investigations

5.10 Exposure Experience

5.11 Additional Remarks

Type: Cytotoxicity

Remark: Two cell lines, neuroblastoma N18TG-2 and glioma C6, were used. Since the two cell lines are derived from the nervous system, it may be expected that they lack in or have little of the metabolic activating systems found in liver. The two cells were used to evaluate the direct toxic effect in vitro. The cells(0.5x10^6 for both N18TG-2 and C6) were plated in Falcon plastic dishes(3002, 60 mm) and cultured in DMEM supplemented with 5% fetal calf serum, penicillin(100 units/mL) and streptomycin(100 units/mL) at 37 degree C in a humidified atmosphere of 10% CO2. ETB (Tokyo Kasei co., Tokyo) was added at various concentrations to the medium containing the cells, at the beginning of culture. Six days after culturing, cells
were collected from dishes by trituration in calcium and magnesium-free phosphate buffered saline. Maximal cell density was found 6 days after culturing for both types of cells, when the effect of the chemical was examined. The ED50 was calculated after a Probit transformation of the cell viability, obtained at various concentrations.
The cytotoxicity of the chemical was expressed as ED50 values for N18TG-2 and C6, 3.07 mM (363 mg) and 2.03 mM (240 mg), respectively.

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

Reliability: (2) valid with restrictions

13-DEC-2004 (12)

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