FOREWORD INTRODUCTION

1,4-Dimethyl-2-(phenylethyl)benzene

CAS N°: 6165-51-1

SIDS Initial Assessment Report

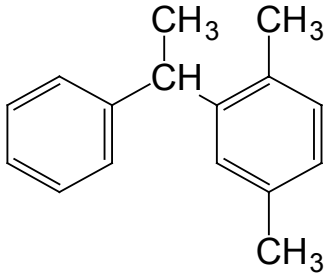
For

SIAM 17

Arona, Italy, 11-14th November 2003

1. Chemical Name:	1,4-Dimethyl-2-(phenylethyl)benzene
2. CAS Number:	6165-51-1
3. Sponsor Country:	Japan Contact Point: Mr. Yasuhisa Kawamura 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	
• How was the chemical or category brought into the OECD HPV Chemicals Programme ?	
7. Review Process Prior to the SIAM:	Expert committee performed spot checks on randomly selected endpoints and compared original studies with data in SIDS dossier.
8. Quality check process:	
9. Date of Submission:	August 15, 2003
10. Date of last Update:	
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.	6165-51-1
Chemical Name	1,4-dimethyl-2-(1-phenylethyl)benzene
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

There are no available data on toxicokinetics, metabolism, or distribution.

In the acute toxicity study [OECD TG 401] with 1,4-dimethyl-2-(1-phenylethyl)benzene in Crj:CD(SD)IGS rats (5 animals/sex/dose), deaths were found in one male and two females at 2000 mg/kg bw. Soiled perianal region, decreased locomotor activity, bradypnea, and lateral position were observed in both sexes at 2000 mg/kg bw. The body weight gain was decreased at 1000 mg/kg bw and higher. The oral LD_{50} values were considered to be more than 2000 mg/kg bw in rats of both sexes.

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 1,4-dimethyl-2-(1-phenylethyl)benzene by gavage at 0 (vehicle: olive oil), 12.5, 50, or 200 mg/kg bw/day. Males were dosed for 47 days from day 14 before mating and females were dosed for 42-45 days from day 14 before mating to day 3 of lactation throughout the mating and pregnancy period. The body weight gain was decreased at 200 mg/kg bw/day in both sexes (5-8%). In urinalysis, increases in the volume and crystals and decreases in the osmotic pressure and specific gravity were detected at 200 mg/kg bw/day in males. Extension of the blood clotting time was observed at 50 mg/kg bw/day and higher in males. An increase in the total cholesterol levels was found at 50 mg/kg bw/day and higher in males. Increases in the γ-GTP and phospholipids levels of males and increase in the glucose levels of females were detected at 200 mg/kg bw/day. The liver weight was increased at 50 mg/kg bw/day and higher in males and at 200 mg/kg bw/day in females. The adrenal weight was decreased at 12.5 mg/kg bw/day and higher in males. In histopathological examinations, hypertrophy of the hepatocytes was observed at 50 mg/kg bw/day and higher in males and at 200 mg/kg bw/day in females. In the adrenals of male rats, atrophy of the zona fasciculate and an increase in the incidence of hypertrophy of the zona glomerulosa were found at 12.5 mg/kg bw/day and higher and at 200 mg/kg bw/day, respectively. Based on the pathological findings in the adrenals in males and in the liver in females, no NOAEL could be derived in male rats for repeated dose toxicity and the LOAEL for repeated dose toxicity was considered to be 12.5 mg/kg bw/day in male rats. In female rats, the LOAEL for repeated dose toxicity was 200 mg/kg bw/day and the NOAEL for repeated dose toxicity was considered to be 50 mg/kg bw/day.

In a reverse gene mutation assay [OECD TG 471], 1,4-dimethyl-2-(1-phenylethyl)benzene was not mutagenic in *Salmonella typhimurium* TA100, TA1535, TA1537, and TA98 or in *Escherichia coli* WP2 *urv*A either with or without an exogenous metabolic activation. In the chromosomal aberration test [OECD TG 473], 1,4-dimethyl-2-(1-phenylethyl) benzene did not induce structural chromosomal aberrations or polyploidy either with or without an exogenous metabolic activation in cultured Chinese hamster lung (CHL/IU) cells.

The above-mentioned combined study [OECD TG 422], showed that the reproduction/developmental parameters, i.e., mating, pregnancy, delivery, lactation, and viability and body weight of pups, were not affected by administration of 1,4-dimethyl-2-(1-phenylethyl)benzene at up to 200 mg/kg bw/day. The NOAEL for reproduction/developmental toxicity was considered to be 200 mg/kg bw/day in rats. At 200 mg/kg/day, some

parameters, number of implantations, implantation index, and numbers of newborns and live newborns (24%), were decreased, but not statistically significant. These values are within the range of historical control data for the performing laboratory.

No information on carcinogenicity is available.

Environment

1,4-Dimethyl-2-(1-phenylethyl)benzene is a colourless liquid with a melting point of $\leq$ -50 °C (OECD TG 102), boiling point of 305.9 °C (MPBPWIN v. 1.40), vapour pressure of 2.1 x 10^{-4} hPa (OECD TG 104) and water solubility of 0.96 mg/L at 25 °C (OECD TG 105). The measured log Kow is 5.39 (OECD TG107).
1,4-Dimethyl-2-(1-phenylethyl)benzene is photodegraded in the atmosphere by reaction with OH radicals with a half-life of 0.5 days. The hydrolysis rate of the substance is slow and no degradation was observed in a preliminary test (pH conditions of 4, 7 and 9, at 50 °C for 5 days) (OECD TG 111). 1,4-Dimethyl-2-(1-phenylethyl)benzene is not readily biodegradable (OECD TG301C). A generic fugacity model (Mackey level III) indicates that the substance mainly partitions to soil if released into soil or air and mainly to sediment if released into water. Experimentally derived BCF values of 760 and 620 (OECD TG 305) showed that the substance has a potential for bioaccumulation.

The ecotoxicity of 1,4-dimethyl-2-(1-phenylethyl)benzene have been studied by using aquatic species among three trophic levels. For fish an acute toxicity result 96 h LC50 of 0.31 mg/L (OECD TG 203, *Orizias latipes*, semistic test with analytical monitoring) is available. For daphnids an acute toxicity result on immobility, a 48 h EC50 of 0.25 mg/L (OECD TG 202 part 1, *Daphnia magna*) was reported. For aquatic plants an algal growth inhibition test (OECD TG 201, *Selenastrum capricornutum*) resulted in a 72 h ErC50 (growth rate) and a 72 h EbC50 (biomass) of >1.54 mg/L and 0.93 mg/L, respectively.
On chronic effects of this substance to aquatic organisms, two toxicity tests were carried out. For daphnids, a 21 d reproduction test (OECD TG211, *Daphnia magna*) showed a NOEC of 0.009 mg/L. For an aquatic plant, NOECs on algal growth inhibition were available. Those were (growth rate) NOEC (24-48 hr) of 0.37 mg/L, (growth rate) NOEC (0-72 hr) of 0.73 mg/L and (biomass method) NOEC (0-72 hr) of 0.047 mg/L based on the mean measured concentration (OECD TG 201, *Selenastrum capricornutum*). Results from chronic tests with fish are not available.

Exposure

In the year 2002 in Japan, only one company, produced 1,4-dimethyl-2-(1-phenylethyl)benzene as a mixture consisting of four homologue chemicals (CAS Nos. 6169-95-8, 6165-53-2, 64800-83-5 and 6416-39-3) with a total production volume of ca. 8000 tonnes (purity in a commercial product ca. 10%). It is assumed that few companies in Korea and China produce this substance as one component of a commercial product with a total production volume of a mixture ca. 1000 and 1500 tonnes in each country. No information on production volumes in other OECD countries is available.
1,4-Dimethyl-2-(1-phenylethyl)benzene is produced in a closed system by alkylation of styrene and xylene isomers in the presence of a solid acid catalysis. In Japan, 1,4-dimethyl-2-(1-phenylethyl)benzene is used as a substitute substance of PCBs and its main usage are as a solvent for pressure sensitive dyes (ca. 60%) and condenser oil (ca. 40%) for industrial use. Small amounts of 1,4-dimethyl-2-(1-phenylethyl)benzene are also used as a plasticizer for epoxy and uretane polymers, and a solvent as a substitute for trichloroethane.

Occupational exposure through inhalation of mist and dermal route is possible. Inhalation of vapor is expected to be minimal because the vapor pressure of this chemical is low.

RECOMMENDATION

The chemical is a candidate for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

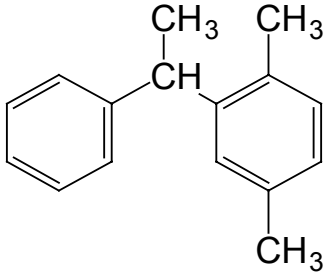
The chemical possesses properties indicating a hazard for human health, including repeated dose toxicity and uncertainty regarding reproductive toxicity in a screening test, and the environment (aquatic toxicity). It is recommended that an exposure assessment be performed to address possible exposure levels to the environment, workers and consumers based due to its use as a solvent, an alternative to PCBs and due to the recycling process of papers containing this chemical. Furthermore, a hazard assessment to sediment organisms and plants is also recommended and if necessary an environmental risk assessment should be performed.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 6165-51-1
IUPAC Name: 1,4-Dimethyl-2-(phenylethyl)benzene
Molecular Formula: $C_{16}H_{18}$
Structural Formula:



Molecular Weight: 210.31
Synonyms: 1-Phenyl-1-xylylethane

2-(1-phenylethyl)-p-xylene

Benzene, 1,4-dimethyl –2-(1-pheylethyl)-

Phenyl xylylethane

1.2 Purity/Impurities/Additives

1,4-Dimethyl-2-(1-phenylethyl)benzene is commercially produced as a mixture consisting of the following four analogue chemicals;

1,2-Dimethyl-4-(1-phenylethyl)benzene: CAS No. 6196-95-8,

2,4-Dimethyl-1-(1-phenylethyl)benzene: CAS No. 6165-52-2,

Ethyl-(phenylethyl)benzene: CAS No. 64800-83-5.

1-Methyl-3-phenylindan: CAS No. 6416-39-3.

A typical purity of 1,4-Dimethyl-2-(1-phenylethyl)benzene in the commercial product is ca. 10%.

Critical studies for physical-chemical properties, environmental fate and toxicity tests were preformed using the test substance with a purity of 99.0 % (Lot no. PPXE000204). Critical studies for ecotoxicity tests were preformed using the substance with a purity of 98.8 % (Lot no. 99S151C).

1.3 Physico-Chemical properties

Table 1 Summary of physico-chemical properties

Property	Value	Protocol (reference) or comment
Physical state	Colourless liquid	MSDS (Nippon Petrochemical Co., Ltd)
Melting point	≤ -50 °C	OECD TG 102 (CERI, 2000a)
Boiling point	305.9 °C (1013 hPa)	Calculated, MPBPWIN (CERI 2003)
Relative density	0.987	Density: 0.989 g/cm3 at 15 °C (MSDS, Nippon Petrochemical Co., Ltd)
Vapour pressure	2.1 x 10^{-4} hPa at 25 °C	OECD TG 104 (CERI, 2000a)
Water solubility	0.96 mg/L at 25 °C	OECD TG 105 (CERI, 2000a)
Partition coefficient n-octanol/water (log value)	5.39 at 25 °C	OECD TG 107 (CERI, 2000b)
Henry's law constant	4.60 Pa·m^3/mol	Calculated (CERI 2003)

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

In the year 2002 in Japan, only one company produced 1,4-dimethyl-2-(1-phenylethyl)benzene as a mixture consisting of four homologue chemicals (CAS Nos. 6169-95-8, 6165-52-2, 64800-83-5 and 6416-39-3) with a total production volume of ca. 8000 tonnes (purity in a commercial product is ca. 10%). It is assumed that few companies in Korea and China produce this substance as one component of a commercial product with a total production volume of the mixture of ca. 1000 and 1500 tonnes in each country. No information on production volumes and use patterns in other OECD countries is available.

1,4-Dimethyl-2-(1-phenylethyl)benzene is produced in a closed system by an alkylation reaction of styrene and xylene isomers in the presence of a solid acid catalysis.

1,4-Dimethyl-2-(1-phenylethyl)benzene is used an a substitute substance of PCBs and its main use is as a solvent for thermal paper dyes (ca. 60%) and as a condenser oil (ca. 40%) for industrial use. A small amount of 1,4-dimethyl-2-(1-phenylethyl)benzene is also used as a plasticizer for epoxy and urethane polymers, and as a substitute solvent for trichloroethane.

2.2 Environmental Exposure and Fate

2.2.1 Sources of Environmental Exposure

Although no monitoring data are available, it is assumed that emissions of 1,4-dimethyl-2-(1-phenylethyl)benzene to waste water and air from production sites and downstream use are low in Japan because the substance is produced in a closed system and adequate measures to prevent any leakage is taken throughout the production and transport.

Based on the use patterns of the substance, a small amount of exposure to the environment is expected during the end-use, transport and disposal.

2.2.2 Photodegradation

An indirect photodegradation of 1,4-dimethyl-2-(1-phenylethyl)benzene with OH radicals in the atmosphere is expected to occur. The half-life of 1,4-dimethyl-2-(1-phenylethyl)benzene is calculated as 0.5 days assuming an OH radical concentration of 1.5 x 10^6 molecules/cm^3 and 12 hours/day irradiation time (CERI, 2003).

2.2.3 Stability in Water

A stability test in water was performed according to OECD Test Guideline 111 (CERI, 2000a). In a preliminary test under the three pH conditions (4, 7 and 9) at 50 °C for 5 days, no hydrolysis was observed. It is therefore concluded that the half-life of the substance at 25 °C is longer than one year.

2.2.4 Transport between Environmental Compartments

Using the fugacity model, Mackay level III, it is estimated that the substance is distributed in the environment compartments as shown in the table below. According to the estimation results, the substance mainly partitions to soil if released to soil or air, and mainly to sediment if released into water.

Table 2 Environmental Distribution Patterns of 1,4- dimethyl-2-(1-phenylethyl)benzene

Target Compartment	Release		
	100% to air	100% to water	100% to soil
Air	6.8%	0.2%	0.0%
Water	1.4%	18.9%	0.0%
Soil	86.0%	3.1%	100.0%
Sediment	5.8%	77.7%	0.0%

Input data; Melting point (Measured): <= -50 degree C.
Boiling point (Measured): 290 degree C.
Vapour pressure (Measured): 0.00021 hPa.
Water solubility (Measured): 0.96 mg/l
log Pow (Measured): 5.39
Temperature: 25 degree C.
Half-life (hours): 12 in air (estimated), 24000 in water (estimated), 24000 in soil (estimated), 72000 in sediment (estimated).

A calculated log Koc value of 5.24 suggests that the chemical has a strong potential to adsorb onto soil and sediment in the aquatic environment (CERI, 2003).

2.2.5 Biodegradation

A biodegradation study according to OECD Test Guideline 301 C (CERI, 2000c) was conducted. Based on the BOD analysis no biodegradation was observed in 28 days whilst 6, 5 and 3 % of primary degradation rates were determined by HPLC analysis. Taking into account the above results, it is concluded that the substance is not readily biodegradable. No data on inherent biodegradation test is available.

2.2.6 Bioaccumulation

1,4-Dimethyl-2-(1-phenylethyl)benzene was tested in a flow-through system in accordance with OECD Test Guideline 305 for 42 days with two concentration levels (1 ppb and 0.1 ppb) (CERI, 2002). A stock solution used in the test was prepared without dispersant but direct dissolution in the test water. BCF values at steady state were determined as 540 for the higher and 620 for the lower concentration level.

2.3 Human Exposure

2.3.1 Occupational Exposure

This chemical is made by catalytic condensation of styrene and xylenes in closed systems. The commercial product is a distilled fraction of the reaction mixture containing this chemical and several closely related chemicals (content of this chemical in a product SAS-296 is about 10 %).

The product is used as condenser oil (40% of the total production) and a solvent for pressure sensitive paper ink (60% of the total production). Occupational exposure through inhalation of the mist and dermal route is possible. Inhalation of vapor is expected to be minimal because the vapor pressure of this chemical is low (2.1×10^{-4}hPa). Workers who operate sampling and analysis, drum filling, lorry tank filling or condenser production may be exposed to this chemical. At production site, currently no protective equipment is used, because this chemical is handled at room temperature only, and mist generation during production is unlikely. Workers at downstream user sites, condenser production and copy paper production, may be exposed to this chemical. Monitoring data at production sites or user sites are not available. No exposure standard value for this chemical was located.

2.3.2 Consumer Exposure

Since the chemical is used as a solvent for pressure sensitive dyes and as a substitute for trichloroethylene, consumer exposure to the chemical is expected.

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

There is no available information.

3.1.2 Acute Toxicity

Studies in Animals

Inhalation

There is no available information.

Dermal

There is no available information.

Oral

One study on acute toxicity in rats is reported [MHLW, Japan, 2002]. This study was conducted according to an OECD acute oral toxicity test guideline [TG401] under GLP. This study was identified as a key study because it was well conducted. Details of the study by MHLW (2002) are as follows.

Crj:CD(SD)IGS rats (five animals/sex/dose) were given 1,4-dimethyl-2-(1-phenylethyl)benzene by gavage at a dose of 0, 500, 1000, or 2000 mg/kg bw. Deaths occurred in one male and two females at 2000 mg/kg bw. The dead animals were found on days 1-2 after administration. Soiled perianal area, decreased locomotor activity, bradypnea, and lateral position were observed at 2000 mg/kg bw in both sexes (5-8%). A decrease in the body weight gain was observed at 1000 and 2000 mg/kg bw in both sexes. At necropsy, light gray spots in the kidney, dark red spots on the thymus or dark red urine in the urinary bladder was observed in a dead male, and dark red coloration in the lung in a dead female. There were no abnormalities in surviving rats at necropsy. The oral LD_{50} values were considered to be more than 2000 mg/kg bw in rats of both sexes.

Studies in Humans

There is no available information.

Conclusion

The oral LD_{50} values were considered to be more than 2000 mg/kg bw in rats of both sexes.

3.1.3 Irritation

There is no available information.

3.1.4 Sensitisation

There is no available information.

3.1.5 Repeated Dose Toxicity

Studies in Animals

Inhalation

There is no available information.

Dermal

There is no available information.

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 guideline [TG 422][MHLW, Japan, 2002] under GLP. This study was identified as a key study because it was well conducted. Details of the study by MHLW (2002) are as follows.

Crj:CD(SD)IGS rats (12 animals/sex/dose) were given 1,4-dimethyl-2-(1-phenylethyl)benzene by gavage at a dose of 0 (vehicle: olive oil), 12.5, 50, or 200 mg/kg bw/day. Males were dosed for 47 days from day 14 before mating and females were dosed for 42-45 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 or clinical signs related to this chemical. A decrease in the body weight gain was observed at 200 mg/kg bw/day in both sexes (5-8%). A tendency to decrease in the food consumption was observed at 200 mg/kg bw/day in males. In urinalysis, increases in the urine volume and crystals and decreases in the osmotic pressure and specific gravity were detected at 200 mg/kg bw/day in males. Extension of the blood clotting time was observed at 50 mg/kg bw/day and higher in males. An increase in the total cholesterol levels was observed at 50 mg/kg bw/day and higher in males. Increases in the γ-GTP and phospholipids levels of males and an increase in the glucose levels of females were detected at 200 mg/kg bw/day. At necropsy, slight enlargement of the liver was observed in 2 of 12 females at 200 mg/kg bw/day. The liver weight was increased at 50 mg/kg bw/day and higher in males and at 200 mg/kg bw/day in females. The adrenal weight was decreased at 12.5 mg/kg bw/day and higher in males. In histopathological examinations, hypertrophy of the hepatocytes at 50 mg/kg bw/day and higher in males and at 200 mg/kg bw/day in females was observed. In the adrenals of male rats, atrophy of the zona fasciculate and an increase in the incidence of hypertrophy of the zona glomerulosa were found at 12.5 mg/kg bw/day and higher and at 200 mg/kg bw/day, respectively. Based on the pathological findings in the adrenals in males and in the liver in females, no NOAEL could be derived in males for repeated dose toxicity and the LOAEL for repeated dose toxicity was considered to be 12.5 mg/kg bw/day in male rats. In female rats, the LOAEL for repeated dose toxicity was 200 mg/kg bw/day and the NOAEL for repeated dose toxicity was considered to be 50 mg/kg bw/day. The overall NOAEL is lower than 12.5 mg/kg bw/day and the LOAEL is 12.5 mg/kg bw/day.

Studies in Humans

There is no available information.

Conclusion

Pathological findings in the adrenal in males at 12.5 mg/kg bw/day and higher and in the liver in females at 200 mg/kg bw/day were found. The LOAEL for repeated dose toxicity was considered to be 12.5 mg/kg bw/day in male rats and the NOAEL for repeated dose toxicity was considered to be 50 mg/kg bw/day in female rats.

3.1.6 Mutagenicity

In vivo Studies

There is no available information.

In vitro Studies

A reverse gene mutation assay was conducted according to a current protocol [OECD TG 471 and Japanese Guideline for Screening Mutagenicity Testing of Chemicals, Chemical Substances Control Law of Japan] [MHLW, Japan:2002] under GLP. This study was identified as a key study because it was well conducted. Toxicity and growth inhibition were not observed at up to the highest dose in any strain of the bacteria either with or without S9 mix (in *Salmonella typhimurium* TA100, TA1535, TA98, and TA1537, or in *Escherichia coli* WP2 *rvr*A; Concentration: 0, 156, 313, 625, 1250, 2500, 5000 μg/plate). Therefore, the chemical was not mutagenic in *Salmonella typhimurium* TA100, TA1535, TA98, and TA1537 or in *Escherichia coli* WP2 *uvr*A at concentrations of up to 5000 μg/plate either with or without S9 mix.

A chromosomal aberration test was conducted according to a current protocol [OECD TG 473] in cultured Chinese hamster lung (CHL/IU) cells [MHLW, Japan: 2002] under GLP. This study was identified as a key study because it was well conducted. The 50% growth inhibition was observed at 125 μg/mL and higher for 6 hr short-term treatment without S9 mix. The 50% growth inhibition was not observed at up to 2100 μg/mL for 6 hr short-term treatment with S9 mix. The concentration inducing 50% growth inhibition was between 31.3 and 62.5 μg/mL for 24 hr continuous treatment without S9 mix. Based on the concentration of the 50% growth inhibition, maximum concentrations of 500 μg/mL for 6 hr short-term treatment without S9 mix, 2100 μg/mL for 6 hr short-term treatment with S9 mix, and 125 μg/mL for 24 hr continuous treatment without S9 mix were chosen. This substance did not induce structural chromosomal aberrations or polyploidy either with or without exogenous metabolic activation in cultured CHL/IU cells at up to the highest dose. Cytotoxicity was observed at 125 μg/mL after 24 hr continuous treatment without S9 mix.

Conclusion

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

3.1.7 Carcinogenicity

There is no available information.

3.1.8 Toxicity for Reproduction

Effects on Fertility

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 guideline [TG 422] [MHLW, Japan, 2002] under GLP. This study was identified as a key study because it was well conducted. Details of the study by MHLW (2002) are as follows.

Crj:CD(SD)IGS rats (12 animals/sex/dose) were given 1,4-dimethyl-2-(1-phenylethyl)benzene by gavage at a dose of 0 (vehicle: olive oil), 12.5, 50, or 200 mg/kg bw/day. Males were dosed for 47 days from day 14 before mating and females were dosed for 42-45 days from day 14 before mating to day 4 of lactation throughout the mating and pregnancy period.

No chemical-related effects on the estrous cycle, copulation index, fertility index, gestation length, number of corpora lutea, or number of implantation sites were found in dams. Pathological changes were not noted in the male and female reproductive organs. No chemical-related effects on the number, sex ratio, body weight, or viability were found in pups. No external or internal malformations were found in pups at any doses. Based on these findings, the NOAEL for reproductive/developmental toxicity was considered to be 200 mg/kg bw/day in rats. At 200 mg/kg/day, some parameters, number of implantations, implantation index, and numbers of newborns and live newborns (24%), were decreased, but not statistically significant. These values are within the range of historical control data.

Developmental Toxicity

See the section of “Effects on Fertility”.

Conclusion

In an OECD combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test, there were no evidences of the chemical-related effects on reproduction/developmental parameters. The NOAEL for reproduction/developmental toxicity was considered to be 200 mg/kg bw/day in rats.

3.2 Initial Assessment for Human Health

In the acute toxicity study [OECD TG 401] with 1,4-dimethyl-2-(1-phenylethyl)benzene in Crj:CD(SD)IGS rats (5 animals/sex/dose), deaths were found in one male and two females at 2000 mg/kg bw. Soiled perianal region, decreased locomotion activity, bradypnea, and lateral position were observed at 2000 mg/kg bw in both sexes. A decrease in the body weight gain was observed at 1000 mg/kg bw and higher in both sexes. The oral LD_{50} values were considered to be more than 2000 mg/kg bw in rats of both sexes.

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 1,4-dimethyl-2-(1-phenylethyl)benzene by gavage at a dose of 0 (vehicle: olive oil), 12.5, 50, or 200 mg/kg bw/day. Males were dosed for 47 days from day 14 before mating and females were dosed for 42-45 days from day 14 before mating to day 4 of lactation throughout the mating and pregnancy period. There were no deaths or clinical signs related to this chemical. A decrease in the body weight gain was observed at 200 mg/kg bw/day in both sexes (5-8%). A decrease in the food consumption was observed at 200 mg/kg bw/day in males. In urinalysis, increases in the urine volume and crystals and decreases in the osmotic pressure and specific gravity were detected at 200 mg/kg bw/day in males. Extension of the blood clotting time was observed at 50 mg/kg bw/day and higher in males. An increase in the total cholesterol levels was observed at 50 mg/kg bw/day and higher in males. Increases in the γ-GTP and phospholipids levels of males and an increase in the glucose levels of females were detected at 200 mg/kg bw/day. At necropsy, slight enlargement of the liver was observed in 2 of 12 females at 200 mg/kg bw/day. The liver weight was increased at 50 mg/kg bw/day and higher in males and at 200 mg/kg bw/day in females. The adrenal weight was decreased at 12.5 mg/kg bw/day and higher in males. In histopathological examinations, hypertrophy of the hepatocytes at 50 mg/kg bw/day and higher in males and at 200 mg/kg bw/day in females was observed. In the adrenals of male rats, atrophy of the zona fasciculate and an increase in the incidence of hypertrophy of the zona glomerulosa were found at 12.5 mg/kg bw/day and higher and at 200 mg/kg bw/day, respectively. Based on the pathological findings in the adrenals in males and in the liver in females, no NOAEL could be derived in males for repeated dose toxicity and the LOAEL for repeated dose toxicity was considered to be 12.5 mg/kg bw/day in male rats. In female rats, the LOAEL for repeated dose toxicity was 200 mg/kg bw/day and the NOAEL for repeated dose toxicity was considered to be 50 mg/kg bw/day. The overall NOAEL is lower than 12.5 mg/kg bw/day and the LOAEL is 12.5 mg/kg bw/day.

In a reverse gene mutation assay [OECD TG 471], 1,4-dimethyl-2-(1-phenylethyl)benzene was not mutagenic in *Salmonella typhimurium* TA100, TA1535, TA1537, and TA98 and *Escherichia coli* WP2 *uvr*A with and without an exogenous metabolic activation. In a chromosomal aberration test [OECD TG 422], 1,4-dimethyl-2-(1-phenylethyl)benzene did not cause structural chromosomal aberration or polyploid with and without an exogenous metabolic activation in cultured Chinese hamster lung (CHL/IU) cells.

The above-mentioned combined study [OECD TG 422], showed that the reproduction/developmental parameters, i.e., mating, pregnancy, delivery, lactation, and viability and body weight of pups, were not affected by administration of 1,4-dimethyl-2-(1-phenylethyl) benzene at up to 200 mg/kg bw/day. The NOAEL for reproduction/developmental toxicity was

considered to be 200 mg/kg bw/day in rats. At 200 mg/kg/day, some parameters, number of implantations, implantation index, and numbers of newborns and live newborns (24%), were decreased, but not statistically significant. These values are within the range of historical control data.

No information is available for irritation, sensitisation and carcinogenicity.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Acute Toxicity Test Results

Acute toxicity of Benzene, 1,4-dimethyl-2-(1-phenylethyl) to aquatic species belonging to three trophic levels have been investigated experimentally, and the data is summarised in Table 3.

Table 3 Acute toxicity of 1,4-dimethyl-2-(1-phenylethyl) to aquatic organisms

Species	Method	Exposure	Result	Reference
Medaka *Orizias latipes*	OECD TG 203 GLP test	96 h semistatic	LC50 = 0.31(0.22-0.40) mg/L	EA, Japan (2000a)
Daphnia magna	OECD TG 202 GLP test	48 h semistatic	EC50 = 0.25(0.13-0.48) mg/L	EA, Japan (2000b)
Selenastrum capricornutum	OECD TG 201 GLP test	72 h static, open system	(rate method) ErC50 > 1.54 mg/L (biomass method) EbC50 = 0.93(0.77-1.15) mg/L	EA, Japan (2000c)

Fish:

The toxicity of 1,4-dimethyl-2-(1-phenylethyl) was determined in a freshwater fish, *Orizias latipes*. A 96h LC50 of 0.31 mg/L was reported (EA, Japan, 2000a). In the test, fish were exposed to concentrations ranging from 0.21 to 3.51 mg/L (mean measured concentrations), and the lowest 96hLC100 was 0.83 mg/L but the highest concentration of no mortality was not available. Based on the OECD guidance document on aquatic toxicity testing of difficult substances and mixtures (OECD Series on Testing and Assessment Number 23), the toxicity value is regarded to be a reliable with restrictions, even though the test was carried out by using a dispersant at 40 mg/L HCO-50 (in final concentration), since the toxicity and the exposure concentrations used to estimate the value were lower than the water solubility. The LC50 of the test substance was calculated based on measured mean concentrations.

Invertebrates:

For daphnids, a 48 h EC50 of 0.25 mg/L was reported for *Daphnia magna* (EA, Japan, 2000b). The test was also performed using a dispersant. The concentration of the dispersant was 10 mg/L of HCO-50. The exposure concentrations of the test substance ranged up to 0.84 mg/L (mean measured concentrations). Therefore, the toxicity value seems to be reliable but it must be considered with restrictions. In the test, the highest concentration showing no immobility (48 h EC0), and the lowest concentration showing 100 % immobility was reported to be 0.13 mg/L and 0.48 mg/l, respectively.

Aquatic plant, e.g. Algae:

For a species of freshwater algae, *Selenastrum capricornutum*, only one ecotoxicity test with 1,4-dimethyl-2-(1-phenylethyl) is available(EA, Japan, 2000c).The test was undertaken using a dispersant (HCO-50) at a concentration of 40 mg/L. In the test, the highest exposure concentration was 0.32 mg/L in the first experiment. At this concentration a weak effect (a growth inhibition of 13.51 % according to the biomass method and – 2.56 % according to the rate method) was observed on the algal growth. Therefore a second experiment was needed at higher concentrations ranging from 0.64 mg/L to 3.72 mg/L i.e. close to or higher than the water solubility (MOE, Japan, 2000). The second experiment showed that the algal growth inhibition at the highest concentration was 49.14 % and 73.65 % according to the rate method and the biomass method, respectively. From the results of the second experiment, a 72 h ErC50 of 3.72 mg/L or more was estimated by the rate method and a 72 h EbC50 of 2.68 (2.23 – 3.33) mg/L by the biomass method, tentatively, based on the initial measured concentration. During the test period the concentrations of the test substance decreased to 34.6 (32.7-41.5) % of the initial concentrations. The toxicity values based on mean measured concentrations were >1.54 mg/L and 0.93 mg/L, respectively. For safety reasons, the lower values should be regarded as the ecotoxicity of the test substance, taking into account thatthese values should be treated carefully to assess an ecological hazard as they are above or close to the water solubility of the substance.

Chronic Toxicity Test Results

For daphnids and algae chronic toxicity of 1,4-dimethyl-2-(1-phenylethyl) test results are available. These are shown in the Table 4.

Table 4 Chronic toxicity of 1,4-dimethyl-2-(1-phenylethyl) to aquatic organisms

Species	Method	Exposure	Result	Reference
Daphnia magna	OECD TG 211 GLP test	21 d semistatic	(Mortality of parent daphnia) 21 d LC50 > 0.174 mg/L (Effect on reproduction) 21 d EC50 = 0.077 (0.064 – 0.096) mg/L 21 d NOEC = 0.009 mg/L 21 d LOEC = 0.015 mg/L	EA, Japan (2000d)
Selenastrum capricornutum	OECD TG 201 GLP test	72 h static, open system	(rate method) NOEC(24-48h)=0.37 mg/L NOEC (0-72h) = 0.73 mg/L (biomass method) NOEC (0-72h) = 0.047 mg/L	EA, Japan (2000c)

Fish:

No information is available.

Invertebrates:

An experimental result from a Daphnia magna reproduction test (OECD test guideline 211) with 1,4-dimethyl-2-(1-phenylethyl) is available (EA, Japan, 2000d). However a dispersant HCO-50 was used at a final concentration of 100 mg/L. The report showed that the mortality of parent daphnids at the highest concentration of 0.174 mg/L was 40 % during the 21 day exposure period, and no mortality was observed at the lower concentrations.

Among the controls and different exposures concentrations, the largest productivity was recorded in the dispersant control. The cumulative numbers of juveniles produced per adult in the dispersant control was 20 % higher than that of the control. Therefore the inhibition rate was calculated based on the result from the dispersant control instead of that of the control. From the reproduction inhibition rates a LOEC and a NOEC of 0.015 mg/L and 0.009 mg/L were determined respectively. At the LOEC the inhibition rate was 24.6 % of the dispersant control. These chronic toxicity values seem to be reliable because the concentration to response curve was well fitted, but the toxicity value should be treated carefully since the test was carried out using a dispersant.

Aquatic plant, e.g. Algae:

In the same test shown above (EA, Japan, 2000c), chronic toxicity values could be derived. The original report described two experiments. From the original test result a NOEC by the biomass method was estimated and from the supplemental test NOECs by both growth rate and biomass method are available.

The LOEC and NOEC by the growth rate method were 2.16 mg/L and 1.15 mg/L, respectively, based on the initial measured concentrations. Based on the time weighted mean concentrations between the start and the end of the exposure duration, these values are 0.735 mg/L and 0.371 mg/L, respectively. By the biomass method the LOEC and NOEC were 0.32 mg/L and 0.14 mg/L, respectively, based on the initial measured concentration. Based on the mean measured concentration these were 0.11 mg/L and 0.047 mg/L, respectively. For safety reasons, the lower values should be selected as the chronic toxicity values, however the original report demonstrated only the values based on the initial measured concentration.

4.2 Terrestrial Effects

No information was available.

4.3 Other Environmental Effects

No information was available

4.4 Initial Assessment for the Environment

1,4-Dimethyl-2-(1-phenylethyl) is a colourless liquid with a melting point of ≤ -50 °C (OECD TG 102), boiling point of 305.9 °C (MPVPWIN v. 1.40), vapour pressure of 2.1 x 10^{-4} hPa (OECD TG 104) and water solubility of 0.96 mg/l (OECD TG 105). The measured log Kow is 5.39 (OECD Test Guideline 107).

1,4-Dimethyl-2-(1-phenylethyl) is photodegraded in the atmosphere by reaction with OH radicals with a half-life of 0.5 days. The hydrolysis rate of the substance is slow and no degradation was observed in a preliminary test (pH conditions of 4, 7 and 9, at 50 °C for 5 days) (OECD TG 111). 1,4-Dimethyl-2-(1-phenylethyl) is not readily biodegradable (OECD Test Guideline 301C). A generic fugacity model (Mackay level III) indicates that the substance mainly partitions to soil if released into soil or air (86% and 100% of the substance is distributed to soil when released into air and soil, respectively) and mainly to sediment if released into water (77.7% of the substance is distributed to sediment when released into water). Experimentally derived BCF values of 540 (1 ppb) and 620 (0.1 ppb) (OECD Test Guideline 305) showed that the substance has a potential for bioaccumulation.

The ecotoxicity of 1,4-dimethyl-2-(1-phenylethyl) has been studied by using aquatic species among three trophic levels. For fish an acute toxicity result 96 h LC50 of 0.31 mg/L (OECD TG 203, *Orizias latipes*, semistic test with analytical monitoring) is available. For daphnids an acute toxicity

result on immobility, a 48 h EC50 of 0.25 mg/L (OECD TG 202 part 1, Daphnia magna) was reported. For an aquatic plant an algal growth inhibition test (OECD TG 201, *Selenastrum capricornutum*, EA, Japan 2000c) resulted in a 72 h ErC50 (growth rate) and a 72 h EbC50 (biomass) of >1.54 mg/L and 0.93 mg/L, respectively. From these acute toxicities, daphnids seemed to be the most sensitive species to 1,4-dimethyl-2-(1-phenylethyl).

On chronic effects of this substance to aquatic organisms, two toxicity tests were carried out. For daphnids, a 21 d reproduction test (OECD TG211, *Daphnia magna*) showed a NOEC of 0.009 mg/L. For an aquatic plant, 72 h NOECs on algal growth inhibition by the growth rate method and by the biomass method were 0.37 mg/L and 0.047 mg/L, respectively, based on the mean measured concentrations (OECD TG 201, *Selenastrum capricornutum*). Results from chronic tests with fish are not available.

No information on effects to other species are available.

5 RECOMMENDATIONS

The chemical is a candidate for further work.

The chemical possesses properties indicating a hazard for human health, including repeated dose toxicity and uncertainty regarding reproductive toxicity in a screening test, and the environment (aquatic toxicity). It is recommended that an exposure assessment be performed to address possible exposure levels to the environment, workers and consumers based due to its use as a solvent, an alternative to PCBs and due to the recycling process of papers containing this chemical. Furthermore, a hazard assessment to sediment organisms and plants is also recommended and if necessary an environmental risk assessment should be performed.

6 REFERENCES

Chemicals Evaluation and Research Institute (CERI), Japan. (2000a) Unpublished data. Report Number 80015BK.

Chemicals Evaluation and Research Institute (CERI), Japan. (2000b) Unpublished data. Report Number K-15B.

Chemicals Evaluation and Research Institute (CERI), Japan. (2000c) Unpublished data. Report Number 20015B.

Chemicals Evaluation and Research Institute (CERI), Japan. (2002) Unpublished data. Report Number 43780.

EA, Japan (2000a) Test report on the acute toxicity test of 1,4-dimethyl-2-(1-phenylethyl) to Medaka (*Orizias latipes*). 31pp.

EA, Japan (2000b) Test report on the acute immobility test of 1,4-dimethyl-2-(1-phenylethyl) to *Daphnia magna*. 30pp.

EA, Japan (2000c) Test report on the growth inhibition test of 1,4-dimethyl-2-(1-phenylethyl) to algae (*Selenastrum capricornutum*).36pp.

EA, Japan (2000d) Test report on the reproduction inhibition test of 1,4-dimethyl-2-(1-phenylethyl) to *Daphnia magna*. 49pp.

MHLW(Ministry of Health, Labour and Welfare), Japan(2002) Toxicity Testing Reports of Environmental Chemicals, 9, 413-442.

Nippon Oil Corporation. Material Safety Data Sheet on SAS-296.

I U C L I D

Data Set

Existing Chemical	:	ID: 6165-51-1
CAS No.	:	6165-51-1
EINECS Name	:	2-(1-phenylethyl)-p-xylene
EC No.	:	228-201-0
Molecular Formula	:	C16H18

Producer related part

Company	:	National Institute of Health & Sciences
Creation date	:	17.02.2004

Substance related part

Company	:	National Institute of Health & Sciences
Creation date	:	17.02.2004
Status	:	
Memo	:	dest
Printing date	:	17.02.2004
Revision date	:	
Date of last update	:	17.02.2004
Number of pages	:	1
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

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

28.11.2003

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

Purity type	:	
Substance type	:	organic
Physical status	:	liquid
Purity	:	ca. 40 - 60 % w/w
Colour	:	
Odour	:	
Remark	:	1,4-Dimethyl-2-(1-phenylethyl)benzen is commercially produced as a mixture consisting of three analogue chemicals.1,2-dimethyl-4-(1-phenylethyl)benzene: CAS No. 6196-95-8,2,4-dimethyl-1-(1-phenylethyl)benzene: CAS No. 6165-52-2,Ethyl-(phenylethyl)benzene: CAS No. 64800-83-5.A typical purity of 1,4-Dimethyl-2-(1-phenylethyl)benzene is between 40 to 60 %. Both commercial and purified grades of the chemical are a colourless liquid at an ambient temperature and pressure.
Source	:	Nippon Petrochemicals Co., Ltd.

04.02.2004

Purity type	:	
Substance type	:	organic
Physical status	:	liquid
Purity	:	= 99 % w/w

Colour :
Odour :

Remark : Critical studies for phisical-chemical and environmental fate tests were performed using the substance with a purity of 99.8% (GC analysis).

28.11.2003

Purity type :
Substance type : organic
Physical status : liquid
Purity : = 98.8 % w/w
Colour :
Odour :

Remark : Critical studies for ecotoxicity tests were performed using the substance with a purity of 98.8%.

04.02.2004

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

1-phenyl-1-xylylethane

28.11.2003

2-(1-phenylethyl)-p-xylene

28.11.2003

Benzene, 1-4-dimethyl-2-(1-phenylethyl)-

28.11.2003

phenyl xylylethane

28.11.2003

1.3 IMPURITIES

Purity :
CAS-No : 6196-95-8
EC-No : 228-249-2
EINECS-Name : 4-(1-phenylethyl)-o-xylene
Molecular formula :
Value : = 30 % w/w

Remark : 1,4-Dimethyl-2-(1-phenylethyl)benzene is commercially produced as a mixture consisting of four analogue chemicals. 1,2-dimethyl-4-(1-phenylethyl)benzene: CAS No. 6196-95-8,2, 4-dimethyl-1-(1-phenylethyl)benzene: CAS No. 6165-52-2, Ethyl-(phenylethyl)benzene: CAS No. 64800-83-5, 1-methyl-3-phenylindan: CAS No. 6416-39-3. A typical purity of 1,4-Dimethyl-2-(1-phenylethyl)benzene in a commercial product is ca. 10%.

28.11.2003

Purity :
CAS-No : 64800-83-5
EC-No : 265-241-8
EINECS-Name : ethyl(phenylethyl)benzene
Molecular formula :
Value : = 30 % w/w

Source : Nippon Petrochemicals Co., Ltd.
28.11.2003

1.4 ADDITIVES

1.5 TOTAL QUANTITY

Quantity : 5000 - 10000 tonnes produced in 2002

Remark : Approx. 8000 tonnes produced in Japan by one company (2002). Production volumes of ca. 1000 tonnes in Korea and 1500 tonnes in China were assumed in 2002.
Flag : Critical study for SIDS endpoint
28.11.2003

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.6.3 PACKAGING

1.7 USE PATTERN

Type of use : type
Category : Use in closed system

Flag : Critical study for SIDS endpoint
28.11.2003

Type of use : industrial
Category : Electrical/electronic engineering industry

28.11.2003

Type of use : use
Category : Absorbents and adsorbents

Flag : Critical study for SIDS endpoint
28.11.2003

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

Remark : No occupational exposure limit values.
Flag : Critical study for SIDS endpoint
28.11.2003

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

1.8.4 MAJOR ACCIDENT HAZARDS

1.8.5 AIR POLLUTION

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

1.11 ADDITIONAL REMARKS

1.12 LAST LITERATURE SEARCH

1.13 REVIEWS

2.1 MELTING POINT

Value	:	<= -50 °C
Sublimation	:	
Method	:	OECD Guide-line 102 "Melting Point/Melting Range"
Year	:	2000
GLP	:	no
Test substance	:	
Source	:	Chemicals Evaluation and Research Institute (CERI), Japan
Test substance	:	Supplied by Nippon Petrochemicals Co., Ltd. Lot Number: PPXE000204 Purity: 99.0% (GC analysis) Impurity: Dialyle alkanes: 0.6% Indan, 1-methyl-3-phenyl 0.3% Unknown 0.1%
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint
04.02.2004		(1)

2.2 BOILING POINT

Value	:	= 290 - 291 °C at 1013 hPa
Decomposition	:	
Method	:	other
Year	:	
GLP	:	no
Test substance	:	
Remark	:	Scientifically reliable data source for physical chemicals properties.
Source	:	Beilstein Handbook of Organic Chemistry
Reliability	:	(2) valid with restrictions
03.02.2004		(2)
Value	:	= 305.9 °C at 1013 hPa
Decomposition	:	
Method	:	other: MPBPWIN v1.40
Year	:	
GLP	:	no
Test substance	:	
Remark	:	Reliable calculation method.
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint
28.11.2003		(3)
Value	:	= 290 - 305 °C at
Remark	:	Manufacturer's MSDS data without proof.
Reliability	:	(4) not assignable
28.11.2003		(4)

2.3 DENSITY

Type	:	density

Value : = .989 g/cm³ at 15 °C
Method : OECD Guide-line 109 "Density of Liquids and Solids"
Year : 2000
GLP : no
Test substance :

Source : Nippon Petrochemicals Co., Ltd. (2003) Material Safety Data Sheet on SAS-296.
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
04.02.2004 (1)

Type : relative density
Value : = .987 at °C

Remark : Manufacturer's MSDS data without proof.
Reliability : (4) not assignable
28.11.2003 (4)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : = .00021 hPa at 25 °C
Decomposition :
Method : OECD Guide-line 104 "Vapour Pressure Curve"
Year : 2000
GLP : no
Test substance :

Method : OECD Test Guideline 104, Gas saturation method.
Remark : The vapour pressure at 25 degree C was determined by extrapolation based on measured data at 40, 50 and 60 degree C (n=3 for each temperature).
Saturated vapour in a column was transferred with nitrogen gas and trapped in acetnitrile solution.
Exact amount of transferred substance was determined by HPLC analysis.
Test substance : Supplied by Nippon Petrochemicals Co., Ltd.
Lot Number: PPXE000204
Purity: 99.0% (GC analysis)
Impurity: Dialyle alkanes: 0.6%
Indan, 1-methyl-3-phenyl 0.3%
Unknown 0.1%
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
28.11.2003 (1)

Value : = .00085 hPa at 25 °C
Decomposition :
Method : other (calculated): MPBPWIN v1.40
Year : 2003
GLP :
Test substance :

Remark : MPBPWIN v1.40.
Reliability : (2) valid with restrictions
28.11.2003 (3)

Value : = .00067 at 25 °C

Remark : Manufacturer's MSDS data without proof.
Reliability : (4) not assignable
28.11.2003 (4)

2.5 PARTITION COEFFICIENT

Partition coefficient :
Log pow : = 5.39 at 25 °C
pH value :
Method : OECD Guide-line 107 "Partition Coefficient (n-octanol/water), Flask-shaking Method"
Year : 2000
GLP : yes
Test substance :

Remark : Three octanol/water ratios were investigated (Octanol/water=5/30, 10/25, 20/15 ml).
After shaking 5 minutes, concentrations of the substance in each phase were measured by HPLC analysis.
The measured log Pow values ranged from 5.34 to 5.39 with a s.d. of 0.08.
Test substance : Supplied by Nippon Petrochemicals Co., Ltd.
Lot Number: PPXE000204
Purity: 99.0% (GC analysis)
Impurity: Dialyle alkanes: 0.6%
Indan, 1-methyl-3-phenyl 0.3%
Unknown 0.1%
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
28.11.2003 (5)

Partition coefficient :
Log pow : = 5.24 at °C
pH value :
Method : other (calculated): KOWWIN v1.66
Year : 2003
GLP :
Test substance :

Remark : Reliable calculation method.
Reliability : (2) valid with restrictions
28.11.2003 (3)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in :
Value : = 96 mg/l at 25 °C
pH value : = 6.2 - 6.4
concentration : 96 mg/l at 25 °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description : slightly soluble (0.1-100 mg/L)
Stable :
Deg. product :

Method	:	OECD Guide-line 105
Year	:	2000
GLP	:	no
Test substance	:	
Remark	:	Duplicate glass vessels contained approx. 100 mg of the substance and 50 ml of water were shaken for 24, 48 and 72 hours at 30 degree C followed by 24 hours shaking at 25 degree C. After centrifugation, supernatant was subjected to HPLC analysis. Measured concentrations were 0.9 to 1.0 mg/l with a C.V. of 6.0 %, and no variance was observed in each shaking time.
Test substance	:	Supplied by Nippon Petrochemicals Co., Ltd. Lot Number: PPXE000204 Purity: 99.0% (GC analysis) Impurity: Dialyle alkanes: 0.6% Indan, 1-methyl-3-phenyl 0.3% Unknown 0.1%
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

28.11.2003 (1)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Value	:	= 425 °C
Type	:	
Remark	:	Cleveland Open Cup (COC). Manufacturer's MSDS data without proof.
Reliability	:	(3) invalid

28.11.2003 (4)

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

Memo : Calculation of Henry's law constant from the water solubility (0.96 mg/l) and vapour pressure (2.1 x 10-4 hPa) and M.W. 210.31.
A Henry's Law Constant was calculated to be 4.60 Pa m3/mol at 25 degree C.

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
04.02.2004 (6)

Memo : Calculated Henry's law constant of the substance is 78.61 Pa-m*3/mol.

Calculation has been made based on the bond estimation method (HENRYWIN v1.90.).

Remark : Reliable calculation method.
Reliability : (2) valid with restrictions
04.02.2004 (7)

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	= based on intensity of sunlight
INDIRECT PHOTOLYSIS		
Sensitizer	:	OH
Conc. of sensitizer	:	1500000 molecule/cm³
Rate constant	:	= .000000000000218092 cm³/(molecule*sec)
Degradation	:	= 50 % after .5 day(s)
Deg. product	:	
Method	:	
Year	:	2003
GLP	:	
Test substance	:	

Method	:	Based on 12 hrs/day irradiation.
Remark	:	Calculated with SRC-AOPWIN v1.90.
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

04.02.2004 (8)

3.1.2 STABILITY IN WATER

Type	:	abiotic
t1/2 pH4	:	> 5 day(s) at 50 °C
t1/2 pH7	:	> 5 day(s) at 50 °C
t1/2 pH9	:	> 5 day(s) at 50 °C
Deg. product	:	
Method	:	OECD Guide-line 111 "Hydrolysis as a Function of pH"
Year	:	2000
GLP	:	no
Test substance	:	

Remark	:	0.4 mg/l of test substance solutions (n=2) at pH 4, 7 and 9 were shaked for 5 days at 50 degree C. The remaning concentrations were determined by HPLC analysis. More than 90% of initial concantration was maintained in all vessels. The half life of the substance in the environmental condition is longer than one year at 25 degree C.
Test substance	:	Supplied by Nippon Petrochemicals Co., Ltd. Lot Number: PPXE000204 Purity: 99.0% (GC analysis) Impurity: Dialyle alkanes: 0.6% Indan, 1-methyl-3-phenyl 0.3% Unknown 0.1%
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

28.11.2003 (1)

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type : fugacity model level III
Media :
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method :
Year : 2003

Remark : Input data:
Melting point (Measured): <= -50 degree C.
Boiling point (Measured): 290 degree C.
Vapour pressure (Measured): 0.00021 hPa.
Water solubility (Measured): 0.96 mg/l
log Pow (Measured): 5.39
Temperature: 25 degree C.
Half-life (hours): 12 in air (estimated), 24000 in water (estimated), 24000 in soil (estimated), 72000 in sediment (estimated).

Compartment	Release		
	100% to air	100% to water	100% to soil
Air	6.8%	0.2%	0.0%
Water	1.4%	18.9%	0.0%
Soil	86.0%	3.1%	100%
Sediment	5.8%	77.7%	0.0%

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
28.11.2003 (9)

3.3.2 DISTRIBUTION

Media : water - soil
Method : other (calculation)
Year : 2003

Result : Binding to soil organic matter has been calculated with the WPIWIN v3.10.
log Koc = 5.24.
Reliability : (2) valid with restrictions
04.02.2004 (10)

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type	:	aerobic
Inoculum	:	activated sludge, non-adapted
Concentration	:	100 mg/l related to Test substance related to
Contact time	:	28 day(s)
Degradation	:	= 0 (±) % after 28 day(s)
Result	:	under test conditions no biodegradation observed
Kinetic of testsubst.	:	7 day(s) = 0 % 14 day(s) = 0 % 21 day(s) = 0 % 28 day(s) = 0 % %
Control substance	:	Aniline
Kinetic	:	7 day(s) = 75 % 14 day(s) > 85 %
Deg. product	:	no
Method	:	OECD Guide-line 301 C "Ready Biodegradability: Modified MITI Test (I)"
Year	:	2000
GLP	:	yes
Test substance	:	
Remark	:	30 mg of the test substance (n=3) or aniline (n=1) and 9 mgof activated sludge (as MLSS) were added into 300 ml of atest medium. The test and control vessels were cultivatedfor 28 days at 25 degree C. Biodegradability of the testsubstance and control (aniline) were continuously measuredby BOD meter. After 28 days of cultivation, residual amountof the test substance in each test solution was determinedby HPLC analysis.
Result	:	0,0,0% of degradation by BOD after 28 days. 6,5,3% of degradation by HPLC analysis after 28 days.
Test substance	:	Supplied by Nippon Petrochemicals Co., Ltd. Lot Number: PPXE000204 Purity: 99.0% (GC analysis) Impurity: Dialyle alkanes: 0.6% Indan, 1-methyl-3-phenyl 0.3% Unknown 0.1%
Conclusion	:	The substance is not readily biodegradable.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

04.02.2004 (11)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

Species	:	Cyprinus carpio (Fish, fresh water)
Exposure period	:	42 day(s) at 25 °C
Concentration	:	
BCF	:	= 620 - 760
Elimination	:	no
Method	:	OECD Guide-line 305 E "Bioaccumulation: Flow-through Fish Test"

Year	:	2002
GLP	:	yes
Test substance	:	
Remark	:	Test concentrations: 1 and 0.1 ppb without dispersant. Average lipid content in the test fish was 3% (v/v). More than 84% of nominal concentration was maintained in the test tanks throughout the test. Bioconcentration factors (BCF) at a steady state were 760 for high concentration (1 ppb) and 620 for lower concentration (0.1 ppb).
Test substance	:	Supplied by Nippon Petrochemicals Co., Ltd. Lot Number: PPXE000204 Purity: 99.0% (GC analysis) Impurity: Dialyle alkanes: 0.6% Indan, 1-methyl-3-phenyl 0.3% Unknown 0.1%
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

04.02.2004 (12)

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	semistatic
Species	:	Oryzias latipes (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC0	:	< .21
LC50	:	= .31
LC100	:	= .83
Limit test	:	
Analytical monitoring	:	yes
Method	:	OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year	:	2000
GLP	:	yes
Test substance	:	other TS: TORAY Research Center Inc. (Japan), Lot. No.: 99S151C, Purity = 98.8%, Test substance was not distributed in commerce. Therefore test substance was synthesized at the test lab.

Method :

-Test Organisms:
a) Supplier: Test organisms were obtained from a private fish farm in Japan, before ten months of the test.
b) Size (length and weight): 2.17cm (1.92 - 2.38 cm) in length; 0.1503 g (0.1026 - 0.1825 g) in weight
c) Age: Not described
d) Any pretreatment: Test organisms were acclimated for 12 days before testing to the test condition. During acclimination, test fishes were fed with TETRAMINE. These test organisms were not fed for 24 hours before exposure. The mortality of the test organisms for 7 days before testing was less than 3%. A LC50(96 hr) for a reference substance (copper sulfate pentahydrate) was 0.59 mg/L.

-Test substance: Benzene, 1,4-dimethyl-2-(1-phenylethyl)
a) Empirical Formula: C16H18
b) Molecular Weight: 230.35 g/mol
c) Purity: =98.8 %
d) Boiling Point: = 130- 138°C/3mmHg
e) Water Solubility: .96 mg/l at 25 °C

-Test Conditions:
a) Dilution Water Source: Dilution water was prepared from tap water (Nagoya city, Japan), was dechlorinated and treated by activated carbon.
b) Dilution Water Chemistry:
pH: = 6.8
Total hardness (as CaCO3): = 41.0 mg/L
c) Exposure Vessel Type: 3 L test solution in a large glass beaker
d) Nominal Concentrations: control, solvent control, 0.38, 0.69, 1.20, 2.20 and 4.00 mg/L of test substance
e) Vehicle/Solvent and Concentrations: HCO-50 40mg/L was used in all exposure. Vehichle concentrations are same in all vessels.
f) Stock Solutions Preparations and Stability: The test substancel was refrigerated. The stability of the chemical was confirmed by IR spectrum, NMR spectrum and HPLC. Under the stock condition the IR spectrum, NMR Spectrum and the chromatogram 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 per beaker
i) Renewal Rate of Test Water: Every 24 hours
j) Water Temperature: 24+/-1°C
k) Light Condition: 16:8 hours, light-darkness cycle
l) Feeding: None m) Aeration : Test solution was not aerated during the test period.

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

-Statistical Method:
a) Data Analysis: LC50 and its 95% confidence intervals were calculated by Moving average method and Binomial method using TOXDAT Multi-Method Program (US EPA).
b) Method of Calculating Mean Measured Concentrations (i.e. arithmetic mean, geometric mean, etc.): Geometric mean

Result : -
- Measured Concentrations: The test concentrations were measured at start of the test and at 24 h. At 24 h, the concentration of the test substance used acute toxicity test for fish was decreased 34.2 - 81.0% as the concentration of the start of the test.

Nominal Conc. mg/L	Measured Conc., mg/L 0 Hour	24 Hour	Mean*	Percent of Nominal 0 Hour	24Hour
Control	<0.006	<0.006	---	---	---
Solvent Control	<0.006	<0.006	---	---	---
0.38	0.33	0.13	0.21	86.8	34.2
0.69	0.62	0.26	0.40	89.9	37.7
1.20	1.07	0.64	0.83	89.2	53.3
2.20	2.06	1.53	1.78	93.6	69.5
4.00	3.81	3.24	3.51	95.3	81.0

*: Mean measured concentration (Geometric Mean)

- 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: 6.8 - 7.1
DO: 6.0 - 11.6 mg/L
Water Temperature: 23.6 - 24.1°C

-Effect Data(mortality):
LC50 (96hr) = 0.31 mg/L (mc) (95% cl: 0.22 - 0.40 mg/L)

LC0 (96hr) < 0.21 mg/L (mc)
LC100 (96hr) = 0.83 mg/L (mc)
mc: based on measured concentration

- Cumulative Mortality: None of test organisms were killed during exposure period at control and solvent control. The lowest concentration from which the test organisms were killed (1 of 10) was 0.21mg/L at 96th hr. At 0.83, 1.78 and 3.51 mg/L, all test organisms were killed untill the end of the test.

Measured Conc.	Cumulative Number of Dead (Percent Mortality)			
-mg/L	24hr	48hr	72hr	96hr
Control	0 (0)	0 (0)	0 (0)	0 (0)
Solvent Control	0 (0)	0 (0)	0 (0)	0 (0)
0.21	0 (0)	0 (0)	0 (0)	1 (10)
0.40	2 (0)	4 (40)	7 (70)	8 (80)
0.83	6 (60)	9 (90)	10 (100)	---
1.78	10 (0)	---	---	---
3.51	10 (0)	---	---	---

---: No observation was made because all Medaka were killed at this observation time.

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

Measured Conc.	Symptoms			
mg/L	24hr	48hr	72hr	96hr
Control	n	n	n	n
Solvent Control	n	n	n	n
0.21	n	n	n	n
0.40	n	B(1)	B(1)	n
0.83	B(1)	n	---	---
1.78	---	---	---	---
3.51	---	---	---	---

n: No abnormalities are detected
B: Abnormal swimming behavior
(n): Numbers of fish
---: No observation was made because all Medaka were dead at this observation time.

- Calculation of toxicity values: The calculation of toxicity values was the measured concentration. The reason is that some of the deviations from the nominal concentration were not less than +/-20%.

-

Source : Environmental Agency, Japan (2000a)
Reliability : (2) valid with restrictions
This test was conducted using a detergent HCO-50 of 40 mg/L since it had been regarded that the test substance had a very low water solubility which was determined as 0.93 mg/L later. The toxicity was reliable because the exposure concentrations except the highest one were lower than the water solubility and no effects were observed in the vehicle control on the fish mortality and their behavior.
Flag : Critical study for SIDS endpoint
17.02.2004 (11)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type : semistatic
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
EC0 : = .13
EC50 : = .25
EC100 : = .48
Analytical monitoring : yes
Method : OECD Guide-line 202
Year : 2000
GLP : yes
Test substance : other TS: TORAY Research Center Inc. (Japan), Lot. No.: 99S151C, Purity = 98.8%, Test substance was not distributed in commerce. Therefore test substance was synthesized at the test lab.

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 daphnid were acclimated for 23 days on test condition before testing. During acclimatization, test daphnid were fed with Chlorella vulgaris, 0.1 - 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 0.6mg/L.

-Test substance: Benzene, 1,4-dimethyl-2-(1-phenylethyl)
a) Empirical Formula: C16H18
b) Molecular Weight: 230.35 g/mol
c) Purity: =98.8 %
d) Boiling Point: = 130- 138°C/3mmHg
e) Water Solubility: .96 mg/l at 25 ° C

-Test Conditions:
a) Dilution Water Source: Elendt M4 (OECD Guide-line 211 "Daphnia magna reproduction test") was used as dilution water for the test.
b) Dilution Water Chemistry:
pH: = 8.0

Total hardness (as CaCO3): = 250 mg/L
c) Exposure Vessel Type: 100 mL test solution in a glass beaker
d) Nominal Concentrations: control, solvent control, 0.05, 0.10, 0.17, 0.31, 0.56 and 1.00 mg/L
e) Vehicle/Solvent and Concentrations: HCO-50 10mg/L was used in all vessels except control.
f) Stock Solutions Preparations and Stability: The test substance was stored at room temperature and dark condition. The stability of the chemical was confirmed by IR spectrum, NMR spectrum and HPLC. Under the stock condition the IR spectrum, NMR Spectrum and the chromatograms of the test substance at the end of the test were the same at the start of test.
g) Number of Replicates: 4
h) Individuals per Replicates: 5 per beaker
i) Renewal Rate of Test Water: Every 24 hours
j) Water Temperature: 20+/-1°C
k) Light Condition: 16:8 hours, light-darkness cycle
l) Feeding: None m) Aeration: Test solution was not aerated during the test period

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

- Statistical Method:
a) Data Analysis: EiC50 and its 95% confidence intervals were calculated by moving average method and binomial method using TOXDAT Multi-Method Program (US EPA).
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 0 Hour Fresh	Measured Conc., mg/L 24 Hour Old	Mean* mg/L	Percent of Nominal 0 Hour Fresh	Percent of Nominal 24 Hour Old
Control	<0.006	<0.006	---	---	---
Solvent Control	<0.006	<0.006	---	---	---
0.05	0.0054	0.0035	0.04	108.0	70.0
0.10	0.091	0.062	0.08	91.0	62.0
0.17	0.147	0.113	0.13	86.5	66.5
0.31	0.288	0.222	0.25	92.9	71.6
0.56	0.535	0.439	0.48	95.5	78.4
1.00	0.947	0.744	0.84	94.7	74.4

Fresh: freshly prepared test solution.

Old: test solution after 24 hours exposure
*: Mean measured concentration (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 the end of the test.
pH: 7.4 - 7.8
DO: 7.9 - 8.8 mg/L
Water Temperature: 19.9 - 20.6°C

-Effect Data: Effect on the immobility
EiC0 (48hr) = 0.13 mg/L (mc)
EiC50 (48hr) = 0.25 mg/L (mc) (95% cl: 0.13 - 0.48 mg/L)
EiC100 (48hr, immobility) = 0.48 mg/L (mc)
mc: based on the mean measured concentrations

-Mortality or Immobility: Any of the test organisms was not dead or immobilized at control, solvent control, 0.04, 0.08, and 0.13 mg/L at the end of the test. All of the test organisms were died at 0.48 and 0.84 mg/L untill the end of the test.

Measured Conc.	Cumulative Number of Dead or Immobilized Daphnids (Percent Mortality or Immobility)	
mg/L	24 Hour	48 Hour
Control	0 (0)	0 (0)
Solvent Control	0 (0)	0 (0)
0.04	0 (0)	0 (0)
0.08	0 (0)	0 (0)
0.13	0 (0)	0 (0)
0.25	2 (10)	10 (50)
0.48	6 (30)	20 (100)
0.84	18 (90)	20 (100)

- Calculation of toxic values: Mean measured concentration

-

Source : Environmental Agency, Japan (2000b)
Reliability : (2) valid with restrictions

-This test was conducted using a detergent HCO-50 of 10 mg/L in all vessels except the control since it had been regarded that the test substance had a very low water solubility which was determined as 0.93 mg/L later. The toxicity was reliable because the exposure concentrations were lower than the water solubility and no effects were observed in the vehicle control on the daphnid immobility and their behavior

Flag : Critical study for SIDS endpoint
17.02.2004 (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
Limit test	:	
Analytical monitoring	:	yes
Method	:	OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year	:	2000
GLP	:	yes
Test substance	:	other TS: TORAY Research Center Inc. (Japan), Lot. No.: 99S151C, Purity = 98.8%, Test substance was not distributed in commerce. Therefore test substance was synthesized at the test lab.

Method :

- Test Organisms:
a) Supplier/Source: Obtained from American Type Culture Collection and reproduced in aseptic culture.
b) Method of Cultivation: Sterile
c) Stain Number: ATCC22662
d) Pre-culture (duration, medium, etc.): Test alga was pre-incubated for 3 days under the same condition of the test in OECD medium. After the pre-incubated, any deformity and abnormal cell of the algae was not observed by microscopy. EbC50 (0-72 hr) for a reference substance (potassium dichromate) was 0.52 mg/L.

-Test substance: Benzene, 1,4-dimethyl-2-(1-phenylethyl)
a) Empirical Formula: C16H18
b) Molecular Weight: 230.35 g/mol
c) Purity: =98.8 %
d) Boiling Point: = 130- 138°C / 3 mmHg
e) Water Solubility: .96 mg/l at 25 ° C

- Test Conditions:
a) Medium: OECD medium
b) Exposure Vessel Type: 100 mL Medium in a 300 mL Erlenmeyer Flask with silicon cap (open system)
c) Nominal Concentrations: Original test: control, solvent control, 0.020, 0.036, 0.065, 0.12, 0.22 and 0.40 mg/L Supplemental test: control, solvent control, 0.72, 1.30, 2.34 and 4.21 mg/L
d) Vehicle/Solvent and Concentrations: HCO-50 100 mg/L was used in all vessels except the control.
e) Stock Solutions Preparations and Stability: HCO-50 was used as 40 mg/L.
f) Stock Solutions Preparations and Stability: Test substance was not distributed in commerce. Therefore test substance was synthesized at the test lab. The test substrate was refrigerated. The stability of the chemical was confirmed by IR spectrum, NMR spectrum and HPLC. Under the stock condition the IR spectrum, NMR Spectrum and the chromatogram of the test substance at the end of the test was the same as at the start of test. Stability in the test condition was monitored analytically, but the preliminary or supplementary tests were not conducted to confirm the stability under the test conditions
g) Number of Replicates: 3

h) Initial Cell Number: 10,000 cells/mL
i) Water Temperature: 23+/-2°C
j) Light Condition: 4,000 - 5,000 lux, continuously
k) Shaking: 100 rpm

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

- Statistical Method:
a) Data Analysis: The calculated inhibition rate at the highest concentration based on growth rate inhibition and biomass were less than 50%, therefore the EC50 was more than the highest concentration. The NOEC values were determined by analysis of variance (ANOVA).
b) Method of Calculating Mean Measured Concentrations (i.e. arithmetic mean, geometric mean, etc.): time-weighted mean

-

Remark : Toxicity effect to algae was not observed at the original test. Therefore, supplemental test was performed by concentration higher than the original test.

Result : NOEC =0.37mg/L (rate method, 24-48hr.)
=0.047 mg/L (biomass method, 0-72hr.)
EC50 >1.54 mg/L (rate method, 0-72hr.)
=0.93 mg/L (biomass method 0-72hr.)

- Measured Concentrations: The tested concentrations were measured at the start and the 72nd hour. For some of them, the deviations from the nominal concentration were not less than +/-20%. Toxic values were calculated by measured concentration at the start of the test.

Original Test

Nominal conc.	Measured Conc., mg/L		Mean	Percent of nominal	
mg/L	0 Hour	72 Hour		0 Hour	72 Hour
Control	<0.006	<0.006	---	---	---
Solvent Control	<0.006	<0.006	---	---	---
0.020	---**	<0.006	---	---	
0.036	0.030	<0.006	---	83.3	---
0.065	0.036	<0.006	---	55.4	---
0.12	0.075	0.008	0.0024	62.5	6.7
0.22	0.14	0.016	0.047	63.6	7.3
0.40	0.32	0.035	0.11	80.0	8.8

**: Failed in the measurement.

Supplemental Test

Nominal conc.	Measured Conc., mg/L		Mean	Percent of nominal	
mg/L	0 Hour	72 Hour		0 Hour	72 Hour
Control	<0.006	<0.006	---	---	---

Solvent Control	<0.006	<0.006	---	---	---
0.72	0.64	0.080	0.23	88.9	11.1
1.30	1.15	0.12	0.37	88.5	9.2
2.34	2.16	0.25	0.73	92.3	10.7
4.21	3.72	0.64	1.54	88.4	15.2

- Water chemistry (pH) and temperature in test: pH and water temperature were measured for controls and each concentration at the start and the end of test period.
Original Test
pH: 7.3 - 7.5 (at the start of the test)
7.7 - 8.5 (at the end of the test)
water temperature: 22.0 - 23.0°C
Supplemental Test
pH: 7.5 - 7.7 (at the start of the test)
7.9 - 8.1 (at the end of the test)
water temperature: 22.2 - 23.1°C

-Effect Data: biomass (based on time-weighted mean measured concentration)
Area Method
EbC50(0-72hr) = 0.93 mg/L (95% cl: 0.77- 1.15)
NOEbC (0-72hr) = 0.047 mg/L
Rate Method
ErC50(24-48hr) > 1.54 mg/L
NOErC (24-48hr) = 0.37 mg/L
ErC50(0-72hr) > 1.54 mg/L
NOErC (0-72hr) = 0.73 mg/L

- Cell density of the Selenastrum capricornutum
Original Test

Initial Conc.	Cell Density (x 10,000 cells/mL) (Average)			
mg/L	0 hr	24 hr	48 hr	72 hr
Control	1.00	6.3	33.9	188.4
Solvent Control	1.00	5.1	30.2	184.5
(0.020)	1.00	5.9	32.5	196.2
0.030	1.00	5.7	31.1	191.5
0.036	1.00	5.8	29.8	179.7
0.075	1.00	5.8	30.4	205.2
0.14	1.00	5.9	27.9	184.7
0.32	1.00	5.1	28.3	166.2

The concentration was the initial measured concentration however the lowest concentration was less than the detection limit of 0.006 mg/L(0.020 mg/L in nominal). The concentrations after 72 h were decreased as shown in the table above.
Each value of cell density represents the mean of three sample counts.

Supplemental Test

Mean Conc.	Cell Density (x 10,000 cells/mL) (Average)			
mg/L	0 hr	24 hr	48 hr	72 hr
Control Solvent	1.00	6.5	39.9	224.1
Control	1.00	6.2	34.3	220.3
0.23	1.00	5.6	27.4	199.4
0.37	1.00	5.2	27.0	192.9
0.73	1.00	5.3	18.6	131.6
1.54	1.00	4.8	12.1	53.5

The concentration of test substance is geometric mean of measured

- Percent Growth Inhibition of Selenastrum capricornutum
Original Test

Initial Conc. mg/L	Area under the growth curves (Average) Area x 10,000 A (0-72hr)	Inhibition (%)* IA (0-72hr)
Control Solvent	3163	---
Control	3002	5.10
(0.020)	3217	-1.69
0.030	3119	1.39
0.036	2951	6.71
0.075	3272	-3.42
0.14	2968	6.18
0.32	2736*	13.51*

* significant difference (a=0.05) by t-test

Initial Conc.	Growth rates and percent inhibition (Average)			
Measured Conc.	Rate	Inhibition(%)	Rate	Inhibition(%)
mg/L	u(24-48hr)	Im(24-48hr)	u(0-72hr)	Im(0-72hr)
Control Solvent	0.0703	---	0.0709	---
Control	0.0739	-5.09	0.0747	-5.29
(0.020)	0.0709	-0.77	0.0729	-2.79
0.030	0.0706	-0.44	0.0732	-3.27
0.036	0.0678	3.53	0.0714	-0.61
0.075	0.0688	2.18	0.0742	-4.59
0.14	0.0651	7.43	0.0719	-1.36
0.32	0.0716	-1.78	0.0727	-2.56

( ): Nominal concentration

Supplement Test

Mean Conc. mg/L	Area under the growth curves (Average) Area x 10,000 A (0-72hr)	Inhibition (%)* IA (0-72hr)
Control Solvent	3742	---
Control	3556	4.96
0.23	3126	16.47
0.37	3026	19.12
0.73	2091	44.13
1.54	986	73.65

The concentration of test substance is geometric mean of measured

Mean Conc. mg/L	Growth rates and percent inhibition (Average) Rate u(24-48hr)	Inhibition(%) Im(24-48hr)	Rate u(0-72hr)	Inhibition(%) Im(0-72hr)
Control Solvent	0.0759	---	0.0739	---
Control	0.0715	5.84	0.0745	-0.77
0.23	0.0650	14.15	0.0744	-0.62
0.37	0.0687	9.49	0.0754	-2.06
0.73	0.0526	30.79	0.0671	9.24
1.54	0.0386	49.14	0.0497	32.71

The concentration of test substance is geometric mean of measured

- Growth Curves: During the test period algae grew almost linearly(log scale) in each concentration.

-

Source : Environmental Agency, Japan (2000c)
Reliability : (2) valid with restrictions
This test was conducted using a detergent HCO-50 of 40 mg/L since it had been regarded that the test substance had a very low water solubility which was determined as 0.93 mg/L later.
The toxicity was as low as water solubility, growth inhibition was observed significantly.
Flag : Critical study for SIDS endpoint
17.02.2004 (13)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

Species	:	Daphnia magna (Crustacea)
Endpoint	:	reproduction rate
Exposure period	:	21 day(s)
Unit	:	mg/l
NOEC	:	= .009
LOEC	:	= .015
EC50	:	= .077
Analytical monitoring	:	yes
Method	:	OECD Guide-line 202, part 2 "Daphnia sp., Reproduction Test"
Year	:	2000
GLP	:	
Test substance	:	other TS: TORAY Research Center Inc. (Japan), Lot. No.: 99S151C, Purity = 98.8%, Test substance was not distributed in commerce. Therefore test substance was synthesized at the test lab.

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 15 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 0.70mg/L.

-Test substance: Benzene, 1,4-dimethyl-2-(1-phenylethyl)
a) Empirical Formula: C16H18
b) Molecular Weight: 230.35 g/mol
c) Purity: =98.8 %
d) Boiling Point: = 130- 138C°/3mmHg
e) Water Solubility: .96 mg/l at 25°C

- 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:
pH: = 7.5
Total hardness (as CaCO3): = 249 mg/L
c) Exposure Vessel Type: 80 mL test solution in a 100mL glass beaker
d) Nominal Concentrations: control, solvent control, 0.013, 0.024, 0.043, 0.077, 0.140 and 0.250 mg/L
e) Vehicle/Solvent and Concentrations: HCO-50 was used as 100 mg/L.
f) Stock Solutions Preparations and Stability: Test substance was not distributed in commerce. Therefore test substance was synthesized at the test lab. The test substancel was refrigerated. The stability of the chemical was confirmed by IR spectrum, NMR spectrum and HPLC. Under the stock condition the IR spectrum, NMR Spectrum and the chromatogram 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: 1
i) Renewal Rate of Test Water: 3 times per week
j) Water Temperature: 20+/-1°C

k) Light Condition: 16:8 hours, light-darkness
l) Feeding: 0.1 - 0.2 mg carbon/day/individual (Chlorella vulgaris: Green Algae)
m) Aeration: not described

- Analytical Procedure: The test concentrations were measured for both renewal and old test solution at the start of the test and 2nd, 7th, 9th, 14th and 16th day using HPLC.

- 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%cl were calculated by Logit method using Eco Tox-Statistics ver.1.1 (Oita University, Japan) and Stat Light #3 (Yukms). NOEC and LOEC: The cumulative number of juveniles produced per adult in control and test vessels after 21days was tested by F and t-test using Eco Tox-Statistics ver.1.1 (Oita University, Japan) and Stat Light #3 (Yukms).
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 2nd, 7th, 9th, 14th and 16th 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	2 Old	7 Fresh	9 Old	14 Fresh	16 Old	TWM* mg/L	% of Nominal
Control	<0.006	<0.006	<0.006	<0.006	<0.006	<0.006	---	---
Solvent Control	<0.006	<0.006	<0.006	<0.006	<0.006	<0.006	---	---
0.013	0.0012	0.008	0.012	<0.006	0.011	0.006	0.009	69.2
0.024	0.021	0.014	0.021	0.008	0.021	0.010	0.015	62.5
0.043	0.035	0.024	0.035	0.019	0.035	0.023	0.028	65.1
0.077	0.069	0.045	0.067	0.037	0.066	0.043	0.053	68.8
0.140	0.119	0.090	0.119	0.070	0.120	0.069	0.096	68.6
0.250	0.221	0.145	0.217	0.135	0.220	0.128	0.174	69.6

Fresh: Start of renewal period
Old: End of renewal period*: Time-weighted mean of measured concentration during 21 days

- Measured Concentration as a Percentage of Nominal

Nominal Conc.	Measured Concentration as a Percentage of Nominal					
mg/L	Date	0	2	7	9	14	16
		Fresh	Old	Fresh	Old	Fresh	Old
0.013		92.3	61.5	92.3	---	84.6	46.2
0.024		87.5	58.3	87.5	33.3	87.5	41.7
0.043		81.4	55.8	81.4	44.2	81.4	53.5
0.077		89.6	58.4	87.0	48.1	85.7	55.8
0.140		85.0	64.3	85.0	50.0	85.7	49.3
0.250		88.4	58.0	86.8	54.0	88.0	51.2

Fresh: Start of renewal period
Old: End of renewal period

- Water chemistry (pH and DO) 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 of the test solutions.
pH: 6.8 - 7.8
DO: 7.8 - 9.0 mg/L
Water Temperature: 19.7 - 20.8°C

- Total hardness: 233 - 255 mg/L

-Effect Data:
LC50 (21day) > 0.174 mg/L (mc)
EC50 (21day) = 0.077 mg/L (mc) (95%cl: 0.064 - 0.096 mg/L)
NOEC (21day) = 0.009 mg/L (mc)
LOEC (21day) = 0.015 mg/L (mc)
mc: based on the mean measured concentrations

- Cumulative Number of Died Parental Daphnids: No test organism was killed at control solvent control, 0.009, 0.015, 0.028, 0.053, and 0.096 mg/L. The lowest concentration that test organisms were dead was at 0.174 mg/L after 16days.

Measured Conc. (mg/L)	Cumulative Number of Dead Parental Daphnids (days)									
	1	2	3	4	5	6	7	8	9	10
Control	0	0	0	0	0	0	0	0	0	0
0.009	0	0	0	0	0	0	0	0	0	0
0.015	0	0	0	0	0	0	0	0	0	0
0.028	0	0	0	0	0	0	0	0	0	0
0.053	0	0	0	0	0	0	0	0	0	0
0.096	0	0	0	0	0	0	0	0	0	0

0.174	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	0	0	0	0	0	0	0	0	0	0	0
0.009	0	0	0	0	0	0	0	0	0	0	0
0.015	0	0	0	0	0	0	0	0	0	0	0
0.028	0	0	0	0	0	0	0	0	0	0	0
0.053	0	0	0	0	0	0	0	0	0	0	0
0.096	0	0	0	0	0	0	0	0	0	0	0
0.174	0	0	0	0	0	1	1	2	3	4	4

-Effect Data(reproduction):Juveniles were first produced on the 8th day at every concentration.

Measured Conc. mg/L	Mean Cumulative Numbers of Juveniles Produced per Adult (days)							
	0 ---	7	8	9	10	11	12	13	14
Control Solvent	0 ---	0	0.2	0.2	0.2	6.1	6.2	6.9	20.6
Control	0 ---	0	2.1	2.1	2.1	10.7	10.7	19.1	30.8
0.009	0 ---	0	2.5	2.5	2.5	9.2	9.2	9.2	27.4
0.015	0 ---	0	2.5	2.5	2.5	6.0	6.0	8.0	16.9
0.028	0 ---	0	3.2	3.3	3.3	4.9	4.9	15.7	15.7
0.053	0 ---	0	5.0	5.0	5.0	7.2	7.2	7.8	19.7
0.096	0 ---	0	0.9	1.3	1.3	1.3	1.3	1.3	6.9
0.174	0 ---	0	0.0	0.8	0.8	0.8	0.8	1.2	1.2

Measured Conc. mg/L	Mean Cumulative Numbers of Juveniles Produced per Adult (days)						
	15	16	17	18	19	20	21
Control Solvent	20.6	24.4	51.5	51.5	57.3	77.3	77.3
Control	30.8	53.2	59.3	59.3	83.1	92.6	92.6
0.009	27.4	30.3	55.2	55.2	62.0	88.8	89.0
0.015	16.9	24.2	43.0	43.0	49.6	69.6	69.8
0.028	15.7	16.6	37.3	37.3	37.3	61.5	62.3
0.053	19.7	29.2	44.2	44.2	60.6	72.5	72.5
0.096	7.7	7.7	21.8	22.9	22.9	43.4	43.5
0.174	4.0	6.0	6.0	9.5	12.8	12.8	19.3

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

	Measured Conc.1), mg/L						
Vessel No.	Solvent Control	Control	0.009	0.015	0.028	0.053	0.096	0.174
1	79	72	78	63	81	79	25	10
2	98	111	84	81	93	53	50	---
3	79	106	98	53	50	72	52	---
4	63	99	113	80	54	43	44	10
5	78	100	93	94	63	59	40	28
6	52	85	109	65	49	80	37	---
7	72	87	85	65	68	63	58	---
8	73	92	86	55	74	79	37	18
9	104	103	96	62	18	91	43	24
10	75	71	48	80	73	106	49	26
Mean	77.3	92.6	89.0	69.8	62.3	72.5	43.5	19.3
S. D.	15.1	13.8	18.2	13.2	20.9	18.6	9.4	8.0
Inhibition rate(%) Against Control	-19.8	-15.1	9.7	19.4	6.2	43.7	75.0	
Significantdifference*1				*		**	**	
Inhibition rate(%) Against Solvent Control		3.9	24.6	32.7	21.7	53.0	79.1	
Significantdifference*2			**	**	*	**	**	

1): Time-weighted mean measured concentration.
---: Were not calculated because the parental Daphnia was dead during a 21 days testing period.
*1: Indicates a significant difference by F and t-test procedure, Two side test.
*2: Indicates a significant difference by Dunnett multiple comparison procedure, Two-sided test.

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

-

Source : Environmental Agency, Japan (2000d)

Reliability : (2) valid with restrictions
This test was conducted with a dispersant, HCO-50 since it had been regarded that the test substance had a very low water solubility which was determined as 0.93 mg/L later. The final concentration of the dispersant was 100 mg/L in all vessels except the control. This test seemed reliable because the exposure concentrations were lower than the water solubility, however the reproductivity in the solvent control was greater than that of

the control(blank, dilution water only) significantly.The chronic toxicity of NOEC was estimated based on the inhibition rates against both the control and the solvent control.

Flag : Critical study for SIDS endpoint
17.02.2004 (14)

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Value	:	-
Species	:	rat
Strain	:	other:CrjCD(SD)IGS
Sex	:	male/female
Number of animals	:	5
Vehicle	:	other: Olive oil
Doses	:	
Method	:	OECD Guide-line 401 "Acute Oral Toxicity"
Year	:	2002
GLP	:	yes
Test substance	:	other TS:Purity, 99.0%; Lot No. PPXE00204
Remark	:	Doses were 0, 500, 1000 and 2000mg/kgbw for both sexes.
Result	:	LD50 values were more than 2000mg/kgbw for both sexes. Deaths occured one male and two females of the 2000 mg/kgbw group. The dead animals were found 1 to 2 dayw after administration. Perprocal soiling, hypoactivity, bradypnea and adoption for a prone or lateral position were observed in botrh sexes at 2000 mg/kg bw. Depression or inhibition of body weight gain was observed in both sexes at 2000 mg/kg bw, and inhibition in both sexes at 1000 mg/kg bw. At necropsy, light gray spots on the kidney, dark red spots on the thymus or retension of dark red urine in the urinary bladder was observed in the dead male, and dark red coloration in the lung in the dead female, and there were no changes in the other dead female and the surviving animals.
Source	:	Research Institute for Animal Science in Biochemistry and Toxicology Sagamihara Kanagawa
Reliability	:	(1) valid without restriction

07.08.2003 (15)

5.1.2 ACUTE INHALATION TOXICITY

5.1.3 ACUTE DERMAL TOXICITY

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

5.2.2 EYE IRRITATION

5.3 SENSITIZATION

5.4 REPEATED DOSE TOXICITY

Type	:	
Species	:	rat
Sex	:	male/female
Strain	:	other:Crj:CD(SD)IGS
Route of admin.	:	gavage
Exposure period	:	Males:47 days. Females:42-45 days from 14 days before mating to day of 4 of lactation.
Frequency of treatm.	:	once a day
Post exposure period	:	
Doses	:	12.5, 50, 200 mg/kgbw:/day
Control group	:	yes, concurrent vehicle
Method	:	OECD combined study TG422
Year	:	2002
GLP	:	yes
Test substance	:	other TS:Purity, 99.0%; Lot No. PPXE000204

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: Olive oil
Terminal killing: Males, day 50; females, day 4 of lactation.
Clinical observation performed and frequency: General condition was observed once a day, body weights were determined twice a week during treatment period for males and twice a week before mating and during maiting period and at days 0, 4, 7, 10, 14, 17 and 21 of gestation period and at days 0 and 4 of lactation period for females, food consumption was determined twice a week during treatment period for males and twice a week before mating and at days 1,4,7,10,14,17 and 21 of gestation period and at days 1 and 4 of lactation for females, but food consumption was not determined during mating period for males and females. For all males, urinalysis was carried out at last week of administration period. For all males and all females after childbirth, hematology and biochemistry were carried out at time of necropsy after 50 days for males and at 4 days after delivery for females. The males were fasted overnight before blood sampling for blood examination. Organs examined at necropsy.

Organ weights measured: Brain, heart, lung, thymus, liver, spleen, kidney, adrenal, testis and epididymus in males, and brain, heart, lung, thymus, liver, spleen, kidney, adrenal, thymus, ovary in females.
Organ weight was determined in 12 males and 12 females in all dose groups.

Microscopic examination: Brain, pituitary, spinal cord, stomach, thyroid, parathyroid, submaxillary lymph node, heart, lung, trachea, thymus, liver, spleen, kidney, adrenal, stomach, duodenum, jejunum, ileum, pancreas, cecum, colon, rectum, mesentery lymph node, urinary bladder, seminal vesicle, prostate gland, testis, epididymis, femur, mammary gland, ovary, uterus, vagina, ischiadic nerve, bone marrow, femoral biceps
muscle for 12 males and 12 females in 0 and

200 mg/kg bw:/day groups, and for liver and adrenal for 12 males and 12 females in 12.5 and 50 mg/kg bw:/day groups.

Statistical methods: Dunnett's test for continuous data, steel test for quantal data and Mann-Whitney's test for histopathological findings.

Result : NOAEL:less than 12.5 mg/kg bw/day for males; 50 mg.kg bw/day for females.
Mortality: There was no mortality related to the test substance treatment.
Clinical signs: No effects related to the test chemical were apparent on clinical observation.
Body weight: Depression of body weight gain was observed in both sexes at 200 mg/kg bw/day.
Food consumption: A tendency to decrease in food consumption was observed in males at 200 mg/kg bw/day.
Urinalysis: Increases in urine volume and crystals, and decreases in osmotic pressure and specific gravity in males at 200 mg/kg bw/day.
Hematology: Extension of prothrombin time was observed in males at 50 mg/kg bw/day or more.

Dose (mg/kg bw/day)		0	12.5	50	200
No.of animals		12	12	12	12
Prothrombin time(sec.)	Mean	14.5	15.9	17.4	18.9
	SD	1.4	1.9	2.6**	2.2**

Note: **,p<0.01

Blood biochemistry: An increase in total cholesterol in males at 50 mg/kg bw/day or more, and an increase in gamma GTP and phospholipids, and a decrease in chlorine in males at 200 mg/kg bw/day, and an increase in glucose in females at 200 mg/kg bw/day.

Dose (mg/kg bw/day)		0	12.5	50	200
Males					
No.of animals		12	12	12	12
Total cholesterol(mg/dL)	Mean	53.0	61.0	69.0	90.0
	SD	12	11	12*	17**
gamma GTP(IU/L)	Mean	0.5	0.6	0.7	1.0
	SD	0.3	0.2	0.2	0.5*
Phospholipids(mg/dL)	Mean	99	109	114	150
	SD	20	18	14	26**
Chlorine	Mean	106.6	105.8	106.3	103.7
	SD	1.2	1.5	1.3	12.6**
Females					
No.of animals		12	12	12	12
Glucose(mg/dL)	Mean	103	103	107	126
	SD	19	15	16	18**

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

Necropsy: Enlargement of liver was observed in 2 of 12 females at 200 mg/kg bw/day.

Organ weights: Liver weights increased in males at 50 mg/kg bw/day or more and in females at 200 mg/kg bw/day. Adernal weights decreased in males at 12.5 mg/kg bw/day or more.

Dose(mg/kg bw/day)		0	12.5	50	200
Males					
No.of animals		12	12	12	12
Absolute liver weight(g)	Mean	14.67	14.26	15.97	17.89

SD 2.17 1.32 1.42 1.16**
Relative liver weight(g/100gbw)
Mean 2.79 2.73 3.04 3.59
SD 0.23 0.20 0.16** 0.13**

Absolute adrenal weight(mg)
Mean 64.6 57.9 57.1 56.3
SD 7.5 4.7* 6.1** 5.1**
Relative adrenal weight(mg/100gbw)
Mean 12.4 11.1 10.9 11.3
SD 1.6 1.0* 0.8** 1.2

Females
No.of animals 12 12 12 12
Absolute liver weight(g) Mean 13.65 14.44 14.98 15.85
SD 2.28 1.32 1.43 1.54**
Relative liver weight(g/100gbw)
Mean 4.06 4.28 4.41 4.93
SD 0.40 0.30 0.38 0.49**
Note: *.p<0.05; **,p<0.01

Histopathology
LIver:Centrilobular hypertrophy of hepatocytes in males at 50 mg/kg bw/day or more and in females at 200 mg/kg bw/day, and decreases in incidence of perportal fatty change of hepatocytes in males at 200 mg/kg bw/day.
Adrenal:Atrophy of zona fasciculata in males at 12.5 mg/kg bw/day or more, and an increase in the incidence of hypertrophy of zona glomerulosa in males at 200 mg/kg bw/day.

Dose(mg/kg bw/day) 0 12.5 50 200
Males
No.of animals examined 12 12 12 12
Liver
Fatty change, hepatocyte, perportal
- 8 10 11 12
+ 4 2 1 0*
Hypertrophy, hepatocyte, centrilobular
- 12 12 10 3
+ 0 0 2 9**
Adrenal
Atrophy, zona fasciculata
- 12 10 10 9
+ 0 2 2 3
Hypertrophy, zona glomerulosa
- 11 11 10 4
+ 1 1 2 8**
Females:
No.of animals examined 12 12 12 12
Liver
Hypertrophy, hepatocyte, centrilobular
- 12 12 12 6
+ 0 0 0 6**

Note:-, Not detected; +,slight; **,P<0.01; *,P<0.05

Source : Research Institute for Animal Science in Biochemistry and Toxicology Sagamihara Kanagawa
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
17.02.2004 (15)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Ames test
System of testing : Test secies/strain:Salmonella typhimurium TA100, TA1535, TA98, TA1537, Escherichia coli WP2 urvA
Test concentration : 0, 156, 313, 625, 1250, 2500, 5000 ug/plate
Cycotoxic concentr. :
Metabolic activation : with and without
Result : negative
Method : other:Chemical Substances Control Law of Japan and OECD Test Guideline 471
Year : 2002
GLP : yes
Test substance : other TS:Purity, 99.0%; Lot No. PPXE000204

Remark : Solvent:Dimethyl sulfoxide
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)
S9:Rat liver, induced with phenobarbital and 5,6-benzoflavone
Positine control:
-S9 mix; 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide (TA100, TA98, WP2 uvrA), sodium azide (TA1535) and 9-Aminoacridine (TA1537)
+S9 mix; 2-Amonoanthracene (all strains)
Plates/test:3
Number of replicates:2

Result : Cytotoxic concentration:Toxicity and growth inhibition were not observed up to the highest dose in any strain with or without S9. Precipitate was observed on the surface of agar plates in the concentrations of 1250 ug/plate or more.
Genotoxic effects:
Positive control
Without metabolic activation: positive
With metabolic acivation: positive

Salmonella typhimurium TA100, TA1535, TA98, TA1537
Without metabolic sactivation: negative
With metabolic activation: negative

Escherichia coli WP2 uvrA
Without metabolic activation: negative
With 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
07.08.2003 (15)

Type : Chromosomal aberration test
System of testing : Type of cell used: Chinese hamster lung(CHL) cell
Test concentration : 0, 15.6, 31.3, 62.5, 125, 250, 500 ug/mL without S9mix(6 hr short-term treatment), 0, 65.6, 131, 263, 525, 1050, 2100 ug/mL with S9 mix(6hr short-term treatment), 0, 7.812, 15.6, 31.3, 62.5, 125 ug/mL(24hr continuous treatment)
Cycotoxic concentr. : 187.5 and 250 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:Purity, 99.0%; Lot No. PPXE000204.

Remark : Solvent:Dimethl sulfoxide
Dosage:
-S9 mix(6 hr short-term treatment):0, 15.6, 31.3, 62.5, 125, 250, 500 ug/mL
+S9 mix(6 hr short-term treatment):0, 65.6, 131, 263, 525, 1050, 2100 ug/mL
-S9 mix(24 hr continuous treatment):0, 7.81, 15.6, 31.3, 62.5, 125 ug/mL
S9 mix:Rat liver, induced with phenobarbital and 5,6-benzoflavone
Positive control:
-S9 mix;1-Methyl-3-nitro-1-niterosoguanidine
+S9 mix;3,4-Benzo[a]pyrene
Plates/test:2
50% growth inhibition was observed at 125 ug/mL or more for 6 hr short-term treatment without S9 mix and more than 2000 ug/mL with S9 mix, and between 31.3 and 62.5 ug/mL for 24 hr continuous term treatment without S9 mix.

Result : No increase in chromosomal aberrations was observed after 6 hr short-term or continous treatment with or without S9 mix, and after 24 hr continuous treatment without S9 mix.
Cytotoxicity was observed at 125 ug/mL ater 24 hr continuous treatment wothout S9 mix.
Genotoxic effects:

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

Positive control	clastogenicity			polyploid		
	+	?	-	+	?	-
Without metabolic activtion:	[*]	[ ]	[ ]	[ ]	[ ]	[*]
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
17.02.2004 (15)

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 admin.	:	gavage
Exposure period	:	Males:47 days. Females:42-45 days from 14 days before mating to day 4 of lactation.
Frequency of treatm.	:	Once a day
Premating exposure period		
Male	:	14 days
Female	:	14 days
Duration of test	:	Males: 48 days. Females:from 14 days before mating to day 5 of lactation
No. of generation studies	:	
Doses	:	
Control group	:	yes, concurrent vehicle
Method	:	OECD combined repeated dose and reproductive/developmental toxicity screening test
Year	:	2002
GLP	:	yes
Test substance	:	other TS:Purity, 99.0%; Lot No.PPXE000204

Remark : his 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: Olive oil
Terminal killing: Males, day 50; females, day 4 of lactation.
Clinical observation performed and frequency: General condition was observed once a day, body weights were determined twice a week during treatment period for males and twice a week before mating and during maiting period and at days 0, 4, 7, 10, 14, 17 and 21 of gestation period and at days 0 and 4 of lactation period for females, food consumption was determined twice a week during treatment period for males and twice a week before mating and at days 1,4,7,10,14,17 and 21 of gestation period and at days 1 and 4 of lactation for females, but food consumption was not determined during mating period for males and females. For all males, urinalysis was carried out at last week of administration period. For all males and all females after childbirth, hematology and biochemistry were carried out at time of necropsy after 50 days for males and at 4 days after delivery for females. The males were fasted overnight before blood sampling for blood examination. Organs examined at necropsy.

Organ weights measured: Brain, heart, lung, thymus, liver, spleen, kidney, adrenal, testis and epididymus in males, and brain, heart, lung, thymus, liver, spleen, kidney, adrenal, thymus, ovary in females.
Organ weight was determined in 12 males and 12 females in all dose groups.

Microscopic examination: Brain, pituitary, spinal code, stomach, thyroid, parathyroid, submaxillary lymph node, heart, lung, trachea, thymus, liver, spleen, kidney, adrenal, stomach, duodenum, jejunum, ileum, pancreas, cecum, colon, rectum, mesentery lymph node, urinary bladder, seminal vesicle, prostate gland, testis, epididymis, femur, mammary gland, ovary, uterus, vagina, ischiadic nerve, bone marrow,

femoral biceps muscle for 12 males and 12 females in 0 and 200 mg/kg bw:/day groups, and for liver and adrenal for 12 males and 12 females in 12.5 and 50 mg/kg bw:/day groups.

Reproductive and developmental parameters:Count of estrus, estrus cycle, No.of copulated, No.of pregnants, duration of mating, gestational days, No.of corpora lutea, No.of implantations, implantation index[(No.of implanttations/No.of corpora lutea)x100], No.of newborns, gestation index[(No.of dam with live newborns/No.of pregnant females)x100], No.of stillborns, No.of live newborns, birth index[(No.of live newborns/No.of implantations)x100], sex ratio of live newborns, body weight of live newborns, viability ibdex[(No.of live newborns on day 4 after birth/No.of live newborns)x100], and No.of external anomalis.

Statistical methods: Dunnett's or Scheffe's test for continuous data, Chi square test for No.of copulated, No.of impregnated, gestation index and sex ratio, Wilcoxon' test for implantation index, No.of stillborns, birth index and viability index.

Result : NOAEL: 200mg/kg bw/day for reproductive perfrmance of parental animals and for offspring development.
Mortality: There was no mortality related to the test substance treatment.
Clinical signs: No effects related to the test article were apparent on clinical observation.
groups.
Body weight: Depression of body weight gain was observed in both sexes at 200 mg/kg bw/day.
Food consumption: A tendency to decrease in food consumption was observed in males at 200 mg/kg bw/day.

Urinalysis: Increases in urine volume and crystals, and decreases in osmotric pressure and specific gravity in males at 200 mg/kg bw/day.
Hematology: Extension of prothrombin time was observed in males at 50 mg/kg bw/day or more.
Blood biochemistry: An increase in total cholesterol in males at 50 mg/kg bw/day or more, and an increase in gamma GTP and phospholipids, and a decrease in chlorine in males at 200 mg/kg bw/day, and an increase in glucose in females at 200 mg/kg bw/day.

Necropsy: Enlargement of liver was observed in 2 of 12 females at 200 mg/kg bw/day.

Organ weights: Liver weights increased in males at 50 mg/kg bw/day or more and in females at 200 mg/kg bw/day. Adernal weights decreased in males at 12.5 mg/kg bw/day or more.

Histopathology:
LIver:Centrilobular hypertrophy of hepatocytes in males at 50 mg/kg bw/day or more and in females at 200 mg/kg bw/day, and decreases in incidence of perportal fatty change of hepatocytes in males at 200 mg/kg bw/day.
Adrenal:Atrophy of zona fasciculata in males at 12.5 mg/kg bw/day or more, and an increase in the incidence of hypertrophy of zona glomerulosa in males at 200

mg/kg bw/day.

Reproductive and developmental parameters: No effects of this substance were observed on reproductive performance in males and females or on viability and body weight of offspring. No malformations were found in offsprings in any groups.

Dose(mg/kg bw/day)		0	12.5	50	200
No.of females examined		12	12	12	12
Count of estrus	Mean	3.58	3.33	3.75	3.58
	SD	0.67	0.65	0.45	0.51
Estrus cycle(days)	Mean	4.00	4.13	4.00	4.13
	SD	0.00	0.43	0.00	0.31
No. of mated		12	12	12	12
No. of copulated		12	12	12	12
No.of impregnated(%)		100	100	100	100
No. of pregnants		12	12	12	12
Duration of mating(day)	Mean	2.17	2.17	2.67	1.83
	SD	1.34	1.03	1.30	0.83
No.of dams		12	12	12	12
Gestation days(day)	Mean	22.17	22.42	22.17	22.42
	SD	0.39	0.51	0.39	0.51
No.of corpora lutea	Mean	16.50	16.83	15.58	15.67
	SD	1.38	2.55	1.00	1.56
No.of implantation	Mean	15.42	15.83	14.67	12.42
	SD	1.56	1.80	1.50	4.06
Implantation index		93.43	94.06	94.12	79.26
No.of newborns	Mean	14.42	15.00	13.75	11.00
	SD	2.15	2.22	2.01	4.41
Gestation index		100	100	100	100
No.of stillborns(Total)		1	1	0	1
No.of live newborns	Mean	14.33	14.92	13.75	10.92
	SD	2.19	2.27	2.01	4.29
Birth index		92.97	94.21	93.75	87.92
Sex ratio(Male/female)		1.21	0.85	1.14	1.11
Viability index		98.84	100	99.39	99.24
No.of external anomalis		0	0	0	0

Historical control data
No. of implantations 11.6-17.7
Implantation index(%) 76.0-96.0
No. of newborns 13.0-15.7
No. of live newborns 12.8-15.7

-

Source : Research Institute for Animal Science in Biochemistry and Toxicology Sagamihara Kanagawa
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
17.02.2004 (15)

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 : other: Information on distribution and disappearanse of the analogue in rats.

Remark : 1-phenyl-1-xylyl-ethanes, an analogue of 1,4-dimethyl-2-(1-phenylethyl)benzene, contains two isomer, 1-phenyl-1-orthoxylyly-ethane and 1-phenyl-1-metaxylyl-ethane.
One group of male rats received 0.1g/kg bw orally, and were killed at 0, 2, 4, 24 and 48 hours later.another group of male rats received 0.1g/kg bw every day for a month, and were killed at 2, 4, and 24 hours, and 7 and 30 days after final dose.
In the single dose study, the chemical was found in large quantities in fat 2 hours after the dose, and increased with time until 24 hours. Nearly the same amount was present in the liver as in fat at 2 hours, but the disappearance rates were fairly large.The concentrations in the blood were smaller than those in the heart, the kidneys, and the brain.

In the continuous dose study, the amount of the chemical in the organs 2 hours after the final dose were of nearly the same order as those after a single dose. Although a little accumulation was observed in fat, the amount in the fat did not affect the distribution and the amount in the other organs. The metabolism of the chemical was investigated by using liver homogenate. The result in vitro showed rapid disappearnace in the liver.
Source : Research Institute for Animal Science in Biochemistry and Toxicology Sagamihara Kanagawa
Reliability : (2) valid with restrictions
14.08.2003 (16)

Type : other: Information on irritant effects of the analogue on rabbit skin.

Remark : Test chemical: SAS-296 is a commercial preparation which contains two isomers, 1-phenyl-1-orthoxylyl-ethane and

1-phenyl-1-metaxylyl-ethane. These chemicals are analogues of 1,4-dimethyl-2-(1-phenylethyl)benzene.
Test method: This study was designed to assess skin irritation potential using New Zealand White strain rabbits. Immediately prior to application of the test chemical, an area of skin approximately 2.5 cm square on the right side of the spine was abraded using the tip of a scalpel blade to make minor incisions through the stratum corneum. A similar site on the left side remained intact.
A 0.5 mL aliquot of SAS-296 was applied under a 2.5 square gauze pad to one intact and one abraded skin site on each animal.
Results: Very slight or well-defined erythema or with or without very slight edema was observed at both sites of all the animals at the 24 hours after application.
Conclusion: SAS-296 was considered to be a moderate irritant to rabbit skin.

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

Reliability : (2) valid with restrictions
14.08.2003 (17)

Type : other: Information on acute toxicity of the analogue in rats.

Remark : Test chemical: SAS-296 is a commercial preparation which contains two isomers, 1-phenyl-1-orthoxylyl-ethane and 1-phenyl-1-metaxylyl-ethane. These chemicals are analogues of 1,4-dimethyl-2-(1-phenylethyl)benzene.
Test method: SAS-296 was administered orally to male and female Fischer strain rats at a dose of 1157, 1388, 1660, 2000, 2400, 2880, or 3456 mg/kg bw. The obervation period was 14 days after administration.
Results: LD50 values(95% confidence limits),1940(1640-2289) mg/kg bw for male; 2200(1897-2252)mg/kg bw for female.

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

Reliability : (2) valid with restrictions
14.08.2003 (18)

Type : other: Information on chronic toxicity and carcinogenicity of the analogue in rats

Remark : Test chemical: SAS is 1-phernyl-1-xylyl-ethane[containe two isomers, 1-phenyl-1-orthxylyl-ethane and 1-phenyl-1-metaxylyl-ethane, which are analoges of 1,4-dimethyl-2-(1-phenylethyl)benzene] produced by Nippon Petrochemicals Co.LTD..
Test method: SAS was administered to male and female Fischer strian rats at a dose of 30, 100, or 300 ppm in feed for 24 months to evaluate the chronic toxicity and carcinogenicity.
Results: No chronic toxicity was detectd at any doses. SAS was to judged to be negative for carcinogenic potential.

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

Reliability : (2) valid with restrictions
14.08.2003 (19)

Type : other: Information on delayed contact hypersensitivity of the analogue in guinea pigs.

Remark : Test chemical: SAS-296 is a commercial preparation which

contains two isomers, 1-phenyl-1-orthoxylyl-ethane and 1-phenyl-1-metaxylyl-ethane. These chemicals are analogues of 1,4-dimethyl-2-(1-phenylethyl)benzene.
Test method: This study was designed to assess skin sensitisation potential using Hartley/Dunkin strain guinea-pigs. The procedure consists of two parts, induction and challenge.
1. Induction method: Prior to each induction application, the skin on the left shoulder region of the animal was clipped free of hair. A 2 x 2 cm patch of surgical guaze was saturated with approximately 0.5 mL of SAS-296, as supplied. The patch was placed on the skin and covered by a length of impermeable plastic adhesive tape. Contact with the skin was maintained for approximately 6 hours for each induction exposure. Nine induction application were made in this manner three times a week during a three week period.
2. Challenge method: The test and control animals were challenged topically eighteen days after the ninth induction application using SAS-296, 50% and 25% v/v in liquid paraffin.
Results. SAS-296 did not produce any evidence of delayed contact hypersensitivity.

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

Reliability : (2) valid with restrictions

14.08.2003 (20)

(1) Chemicals Evaluation and Research Institute (CERI), Japan (2000), Report number 80015BK, Unpublished data.

(2) Beilstein Handbook of Organic Chemistry (Online). Last updated May 1999. Searched data 31.07.2003.

(3) Chemicals Evaluation and Research Institute (CERI), Japan. Product data sheet. MPBPWIN v1.40, 31.07.2003.

(4) Nippon Petrochemicals Co., Ltd. (2003). Material Safety Data Sheet on SAS-296.

(5) Chemicals Evaluation and Research Institute (CERI), Japan (2000), Report on partition coefficient of K-15B, Unpublished data.

(6) Chemicals Evaluation and Research Institute (CERI), Japan. (2003). Calculation of Henry's Law Constant with SRC-HENRYWIN v.3.10.

(7) Chemicals Evaluation and Research Institute (CERI), Japan. Product data sheet. HENRYWIN v1.90, 05.08.2003.

(8) Chemicals Evaluation and Research Institute (CERI), Japan. Product data sheet. AOPWIN v1.90, 31.07.2003.

(9) Chemicals Evaluation and Research Institute (CERI), Japan. Product data sheet. 05.08.2003.

(10) Chemicals Evaluation and Research Institute (CERI), Japan. (2003). Calculation of water-soil partition coefficient with SRC-EPIWIN v.3.10.

(11) Chemicals Evaluation and Research Institute (CERI), Japan (2000), Report number 20015B, Unpublished data.

(12) Chemicals Evaluation and Research Institute (CERI), Japan (2002), Report number 43780, Unpublished data.

(13) Environmental Agency, Japan (2000c)

(14) Environmental Agency, Japan (2000d)

(15) MHLW(Ministry of Health, Labour and Welfare),Japan,Toxicity Testing Reports of Environmental Chemicals,9,413-442(2002)

(16) Hiromichi HASEGAWA, et al., Industrial Health, 20, 237-246 (1982)

(17) Michael P.Liggett, et al., Huntingdon Research Centre, Report No.82384D/NPC 2/SE, unpublished data(1982)

(18) Shouji Saitou, et al., Department of pharmacology, Faculty of Medicine, Nihon University, unpublished data(1980)

(19) Shouji Saitou, et al., Bozo Research Center Inc., unpublished data(1984)

(20) Michael P.Liggett, et al., Huntiongdon Research Centre, Report No.82509D/NPC 4/SS, unpublished data(1982)