FOREWORD INTRODUCTION

2,2'6,6'-TETRAMETHYLPIPERIDIN-4-OL

CAS N°: 2403-88-5

SIDS Initial Assessment Report for SIAM 14

(Paris, 26-28th March 2002)

Chemical Name: 2,2,6,6-Tetramethylpiperidin-4-ol

CAS No: 2403-88-5

Sponsor Country: Japan

National SIDS Contact Point in Sponsor Country:

Mr. Koji Tomita
Ministry of Foreign Affair, Economic Affairs Bureau, Second International Organizations Division.

Industry:

Mr. Mutsuo Tokuwame
Mitsui Chemicals Inc,
E-mail: Mutsuo.Tokuwame@mitsui-chem.co.jp

HISTORY:

This substance was sponsored by Japan under the ICCA Initiative and was submitted for first discussion at SIAM 14.

PEER REVIEW PROCESS:

The industry consortium collected new data and prepared the draft versions of the SIAR and SIAP. Japanese government peer-reviewed the documents, audited selected studies.

TESTING:

No testing ( )
Testing (X)
A micronucleus assay with bone marrow cells of rats according to OECD TG 474.

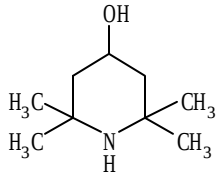
COMMENTS:

The industry contact point is Mr. Mutsuo Tokuwame, Mitsui Chemicals Inc. acting on behalf of the Manufacturing Association (consortium members: Ciba Specialty Chemicals, Degussa A G).

Deadline for circulation: 1/2/02

Date of circulation: 1/2/02

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	2403-88-5
Chemical Name	2,2,6,6-Tetramethylpiperidin-4-ol
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

There is no available information on toxicokinetics and metabolism of this substance. Oral LD_{50} of rats was 1482 mg/kg for males and 1564 mg/kg for females [OECD TG 401]. The major toxic signs were decreased locomotor activity, mydriasis and blepharoptosis, and tissue damages in the stomach and duodenum in both sexes. Dermal LD_{50} of rats was more than 2000 mg/kg. This substance is highly irritating to skin in rabbits [OECD TG 404], and it can be expected to cause serious damage to eyes but the study has not been performed. It has a moderate to strong grade of skin-sensitizing (contact allergenic) potential in guinea pigs [OECD TG 406].

In a (oral) combined repeat dose and reproductive/developmental study [OECD TG 422] rats received 0, 60, 200 or 600 mg/kg for at least 41-days. Animals died at 600 mg/kg (3/12 male, 1/12 female). Pathological changes were only observed in these animals; tissue damage to the gastro-intestinal tract, stomach and kidneys. The only effects seen at 60 and 200 mg/kg were drooping of the upper eyelid and dilation of the pupil in a dose related manner. A LOAEL of 60 mg/kg is identified for these clinical signs of toxicity. A NOAEL could not be identified.

In the above screening test [OECD TG 422], the substance was given from 14 days before mating to 20 days after mating in males, and to day 3 of lactation in females. In the 600 mg/kg group, the mean estrous cycle was prolonged with continuous diestrous in three females. With regard to the effects on neonates, viability and body weight on day 4 of lactation were decreased in the 600 mg/kg group. These effects are secondary non-specific consequence of systemic toxicity. The NOEL for reproductive /developmental toxicity was considered to be 200 mg/kg/day.

As for the genotoxicity, this substance was not mutagenic in bacteria [OECS TG 471 and 472]. An increase in chromosome aberrations in Chinese hamster lungs cells without S9 [OECD TG 473], were considered to be due to cytotoxicity and the study was considered to be "equivocal." A negative result was obtained in a rat bone marrow micronucleus assay [OECD TG 474]. Thus, on the basis of the available data, 2,2,6,6-tetramethylpiperidin-4-ol is not considered to be an *in vivo* genotoxicant, as the questionable genotoxicity observed *in vitro* is not expressed *in vivo*.

Environment

The generic fugacity model (Mackey level III) shows that if this substance is released into water, ca. 100% of this substance is expected to stay in water due to the high solubility in water (> 100 g/L at 25°C, pKa 9.92 at 25°C). However as the substance is cationic form in the environment, it is likely that a certain portion of the substance is adsorbed in the sediment. This substance is not readily biodegradable (OECD TG 301C: 0 - 2% after 28 days) or hydrolyzed at pH 4, 7 and 9 at 50°C. But, it is expected to have low potential for bioaccumulation based on a low Log Pow (0.24) and a measured BCF of less than 5.7.

This substance has been tested in a limited number of aquatic species including fish, daphnia and algae. LC_{50} of the acute toxicity (96 h) for fishes (Medaka and Zebrafish) are 237 mg/L and > 1000 mg/L, respectively. A prolonged toxicity test using Medaka resulted in a LC_{50} (14 d) of 88.1 mg/L. The acute (immobility) and chronic data (reproduction) for daphnia were 100.1 mg/L for EC_{50} (48 h), and 46.2 mg/L for EC_{50} (21 d) and 3.7 mg/L for NOEC (21 d reproduction). The toxicity to *Selenastrum capricornutum* and *Scendedesmus subspicatus* of aquatic plants (algae) were 155 mg/L for EC_{50} (72 h) and 76 mg/L for NOEC (72 h), and 158 mg/L for EC_{50} (72 h) and 10 mg/L for NOEC (72 h), respectively. A predicted no-effect concentration (PNEC) of 0.037 mg/L for the aquatic organisms was calculated from the chronic NOEC for daphnia using an assessment factor of 100, because two chronic data (daphnia and algae) were available.

Exposure

This substance is used exclusively as an intermediate in synthesis of light stabilizer 'HALS' (Hindered Amine Light-Stabiliser) for plastics. The production volume in Japan was ca. 2,500 tons/year, while estimated global production was ca. 8,000 tons/year in 1999.

Workers may be exposed to this substance at production sites and user sites in industries. The production process is fully closed, but in packing and unpacking work, inhalation and dermal exposure is possible. Since this substance may cause irritation, corrosion and sensitization to the skin, a worker is allowed to work only after being equipped with appropriate protection implements at the workplace. Therefore, the amounts of exposure to a worker of this substance in the workplace would be practically low.

Consumer exposure is considered as follows. The amount of HALS in final consumer products, e.g. plastics is estimated to be less than 1.0%. The content of the substance itself in the consumer products should be far below that. Then exposure by the residues to a consumer through product surfaces would be very low.

During production and use in Japan, only the aquatic release of this substance from the production site seems to be possible. Although this substance is not readily biodegradable or hydrolysable, the bioaccumulation potential of this substance is low.

NATURE OF FURTHER WORK RECOMMENDED

No recommendation based on the prerequisite of negligible human exposure and environmental release.

FULL SIDS SUMMARY

CAS NO: 2403-88-5		SPECIES	PROTOCOL	RESULTS
PHYSICAL-CHEMICAL				
2.1	Melting Point		Unknown	130.6°C
2.2	Boiling Point		Unknown	212 - 215 °C (at 1,013 hPa)
2.3	Density		JIS K 7112-1980	1.062 g/cm^3 (at 25°C)
2.4	Vapour Pressure		OECD TG 104	2.6×10^{-1} Pa (at 25°C)
2.5	Partition Coefficient (Log Pow)		OECD TG 107	0.24 (at 25°C)
2.6 A.	Water Solubility		OECD TG 105	> 100 g/L (at 25°C)
B.	pH			0.01 % solution = 10.22 0.1 % solution = 10.93 1.0 % solution = 11.47
	pKa		OECD TG 112	9.92 (at 25 °C)
2.12	Oxidation: Reduction Potential			No data available
ENVIRONMENTAL FATE AND PATHWAY				
3.1.1	Photodegradation		Calculated	$T_{1/2}$ = 5 hr.
3.1.2	Stability in Water		OECD TG 111	Stable at pH 4, 7 and 9 at 50 °C after 5 days (exposure time)
3.2	Monitoring Data			None
3.3	Transport and Distribution		Fugacity Model (Mackay level III)	(Release 100% to air) Air Water Soil Sediment 0.4% 32.5% 67.0% 0.1% (Release 100% to water) Air Water Soil Sediment 0.0% 99.7% 0.0% 0.3% (Release 100% to soil) Air Water Soil Sediment 0.0% 20.4% 79.6% 0.1%
3.5	Biodegradation		OECD TG 301C	Not readily biodegradatble.
3.7	Bioaccumulation	*Cyprinus carpio*	OECD TG 305C	BCF (4 weeks): < 5.7
ECOTOXICOLOGY				
4.1	Acute/Prolonged Toxicity to Fish	*Oryzias latipes*	OECD TG 203 OECD TG 204	LC_{50} (96 hr) 237 mg/L LC_{50} (14 d) 88.1 mg/L NOEC 25.0 mg/L
4.2	Acute Toxicity to Aquatic Invertebrates (*Daphnia*)	*Daphnia magna*	OECD TG 202	EC_{50} (24 hr) 130.1 mg/L EC_{50} (48 hr) 100.1 mg/L
4.3	Toxicity to Aquatic Plants e.g. Algae	*Selenastrum capricornutum* (ATCC22662)	OECD TG 201	EC_{50} (biomass, 72 hr) 107 mg/L NOEC (biomass, 72 hr) 76 mg/L EC_{50} (growth rate, 72 hr) 155 mg/L NOEC (growth rate, 72 hr) 76 mg/L
4.5.2	Chronic Toxicity to Aquatic Invertebrates (*Daphnia*)	*Daphnia magna*	OECD TG 211	EC_{50} (21 d) 46.2 mg/L (Reproduction) NOEC 3.7 mg/L (Reproduction)
4.6.1	Toxicity to Soil Dwelling Organisms			No data available
4.6.2	Toxicity to Terrestrial Plants			No data available
4.6.3	Toxicity to Other Non-Mammalian Terrestrial Species (Including Birds)			No data available

TOXICOLOGY				
5.1.1	Acute Oral Toxicity	Rat	OECD TG 401	LD_{50} 1482 mg/kg (male) LD_{50} 1564 mg/kg (female)
5.1.2	Acute Inhalation Toxicity			No data available
5.1.3	Acute Dermal Toxicity			LD_{50} > 2000 mg/kg (male) LD_{50} > 2000 mg/kg (female)
5.2.1	Skin Irritation	Rabbit	OECD T G 404	Highly irritating
5.2.2	Eye Irritation			No data available
5.3	Skin Sensitisation	Guinea pig	OECD TG 406	Sensitising
5.4	Repeated Dose Toxicity	Rat	OECD TG 422	NOAEL < 60 mg/kg/day (male) NOAEL < 60 mg/kg/day (female)
5.5	Genetic Toxicity *in vitro*			
A.	Bacterial Test (Gene mutation)	*S.typhimurium, E. coli*	OECD TG 471 & 472	- (With metabolic activation) - (Without metabolic activation)
B.	Non-Bacterial *in vitro* Test (Chromosomal aberrations)	CHL cells	OECD TG 473	- (With metabolic activation) + (Without metabolic activation)
5.6	Genetic Toxicity *in vivo* (Micronucleus assay)	Rat	OECD TG 474	negative
5.7	Carcinogenicity			None
5.8	Toxicity to Reproduction	Rat	OECD TG 422	NOEL Parental > 600 mg/kg/day (male) NOEL Parental 200 mg/kg/day (female) NOEL F_1 Offspring 200mg/kg/day
5.9	Developmental Toxicity/ Teratogenicity	Rat	OECD TG 422	Teratogenicity > 600 mg/kg/day
5.11	Experience with Human Exposure			No data available

SIDS INITIAL ASSESSMENT REPORT

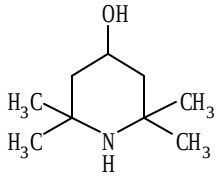
1. IDENTITY

IUPAC name: 2,2,6,6-Tetramethylpiperidin-4-ol

CAS number: 2403-88-5

Molecular formula: $C_9H_{19}NO$

Structural formula:



Synonyms:

2,2,6,6-Tetramethyl-4-hydroxypiperidine
2,2,6,6-Tetramethyl-4-piperidinol
4-Hydroxy-2,2,6,6-tetramethylpiperidine
4-Piperidinol 2,2,6,6-tetramethyl-
HTMP
Hydoroxytetramethypiperidine
Triacetoneaminoalcohol

Purity:

>= 98.0 % weight/weight.

Impurities: 2,2,6,6-Tetramethyl- 4-aminopiperidine
2,2,6,6-Tetramethyl-4-oxopiperidine
2,2,6,6-Tetramethyltetrahydrofuran-4-ol

Physical and chemical properties:

ITEMS	PROTOCOL	RESULTS
Melting Point	Unknown	130.6 °C
Boiling Point	Unknown	212 - 215 °C (at 1,013 hPa)
Density	JIS K 7112-1980	1.062 g/cm^3 (at 25 °C)
Vapour Pressure	OECD TG 104	2.6×10^{-1} Pa (at 25 °C)
Partition Coefficient (Log Pow)	OECD TG 107	0.24 (at 25 °C)
Water Solubility	OECD TG 105	> 100.0 g/L (at 25 °C)
pKa	OECD TG 112	9.92 (at 25 °C)
Oxidation:Reduction Potential		No data

2. GENERAL INFORMATION ON EXPOSURE

- 2,2,6,6-Tetramethylpiperidin-4-ol is produced in a closed system. The production volume of the substance is estimated ca. 2,500 tons/year in Japan, and ca. 5,500 tons/year in the EU; major producers are located in Switzerland and Germany.
- The substance is used exclusively as an intermediate for the synthesis of light stabilizer 'HALS' (Hindered Amine Light-Stabiliser) for plastics. Therefore, the exposure of the substance is limited to industrial use.
- As for the application of the substance (mostly for industrial use), consumer use is not relevant.
- During production of the substance and the use for the synthesis of 'HALS' in Japan, workers may be exposed to this substance only at the production sites and industrial use sites, since use of this substance is limited to industries. As for exposure to the environment, the aquatic release of the substance from production site seems to be possible. But the estimated emission amount is low, and thus, exposure to environmental organisms is considered unlikely.

2.1 Environmental Fate

- A generic fugacity model (Mackay level III) suggests that if released to air, water or soil, the majority of the substance would distribute into the compartment of soil and/or water as shown in Table 1.

Table 1: Environmental distribution of 2,2,6,6-tetramethylpiperidin-4-ol using a generic fugacity model (Mackey level III) under three emission scenario

	Release: 100% to air	Release: 100% to water	Release: 100% to soil
Air	0.4%	0.0%	0.0%
Water	32.5%	99.7%	20.4%
Soil	67.0%	0.0%	79.6%
Sediment	0.1%	0.3%	0.1%

The calculation revealed that in the case of 100 % release into water, ca. 100 % of this substance is expected to stay in water due to the high water solubility. But, if this substance is released into air and/or soil, it is likely to be distributed into water and/or soil compartments, ca. 20 - 30 % and ca. 70 - 80 %, respectively.

- The substance is not readily biodegradable (MITI I - test, corresponding to the OECD 301C: 0% after 28 days based on BOD and 0 - 2% based on GC analysis). However, at the drainage treatment process of the manufacture factory, this substance's concentration in drainage was reduced to 0.06 mg/L and/or less than 0.06 mg/L. The substance, if released to the air compartment, will react with photochemically-produced hydroxyl radicals with the half life of 4.0 hours (estimated with the Atkinson model).
- The substance has low hydrophobicity (e.g. log Pow = 0.24), and low bioconcentration potential to aquatic organisms is shown experimentally (BCF < 5.7).

2.2 Human Exposure

2.2.1 Occupational Exposure

- Occupational exposure at the production sites to the dust of this substance may occur by inhalation and dermal routes.
- The atmospheric concentration was measured at production sites (Packing, Sampling, Analysis). These results are shown in Table 2.

Table 2: Available workplace monitoring data for 2,2,6,6-Tetramethylpiperidin-4-ol

	Frequency Times/day	Working hr/day	Maximum Concentration mg/m^3	Maximum Concentration mg/m^3	Average EHE inh mg/kg/day	Maximum EHE der mg/kg/day
Packing	1	4.0	1.263	0.879	0.090	0.600
Sampling	1	0.5	3.599	1.807	0.032	0.075
Analysis	1	0.5	0.338	0.203	0.003	0.075

EHE: Estimated Human Exposure
Source: Japan Industrial Safety and Health Association Report (2000)

Monitoring method: Air sample was suctioned at the breathing zone (1.5 m in height) of a worker at the suction rate of 500L/min for 30 min and was passed through a filter. The substance collected on the filter was dissolved in a solvent and analyzed quantitatively by a GC method. The identity of the substance was confirmed by GC/MS.

- The workers are exposed to the substance through the dust during the production at production sites, and the loading (packing) operation is expected to create the most dust and expected to result in the highest exposure level (1.263 mg/m^3). If a worker (body weight; 70 kg, respiratory volume; 1.25 m^3/h, exposure period; 4 h) is assigned to equipment without protection, the maximum estimated human exposure (EHE inh) is calculated to be 0.09 mg/kg/day as the worst case. For the dermal exposure of this substance, as well, if a worker (body weight; 70 kg, exposure volume; 0.1 mg/cm^2/day, exposure period; 4 h, exposed skin surface area; 840 cm^2 for hands) is assigned to this equipment without protection (hands), the dermal maximum estimated human exposure (EHE der) is calculated to be 0.60 mg/kg/day.
- Occupational exposure of this substance to a worker is considered to occur through the respiratory system and dermal routes. Since this substance may cause irritation, corrosion and sensitization to the skin, a worker is allowed to work only, after being equipped with a appropriate protection implements at the workplace. Therefore, the level of exposure to a worker of this substance at the workplace would be practically negligible.

2.2.2 Consumer exposure

As for the consumer products, this substance is used as an intermediate for the production of light stabilizers (HALS) for plastics in Japan. The amount of HALS in final consumer product, e.g. plastics is estimated to be less than 1.0 %. The content of the substance itself in the consumer products should be far below that. Then exposure by residues to a consumer through product surfaces would be very low.

2.2.3 Indirect exposure via the environment

Some of the substance might be released from the facilities through the wastewater. But, since the substance concentration in drainage was reduced by the drainage treatment process of the manufacture factory in Japan, the estimated emission amount would be practically negligible.

3. HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

a) Toxicokinetics and metabolism

There is no available information on toxicokinetics and metabolism of this substance.

b) Acute toxicity

Acute toxicity via oral and dermal were located. They are summarized in Table 3.

Table 3: Acute toxicity of 2,2,6,6-Tetramethylpiperidin-4-ol.

Route	Animal	Values	Type	References
Oral				
	Rat	1,482 mg/kg for male	LD_{50}	Ministry of Health & Welfare, Japan (1998)
		1,564 mg/kg for female	LD_{50}	
	Rat*	2,413 mg/kg	LD_{50}	Ciba additiveds GmbH Lampertheim
	Rat	> 2,000 mg/kg for male	LD_{50}	Degussa AG (1973)
		> 2,000 mg/kg for female	LD_{50}	
Dermal	Rat	> 2,000 mg/kg for male	LD_{50}	Ciba additiveds GmbH Lampertheim
		> 2,000 mg/kg for female	LD_{50}	(1992)

*: species is not specified,

Among the above, the studies by MHW (Japan, 1998) and Ciba additives GmbH Lampertheim (1992) were identified as the key studies because they were well conducted and described in detail. Details of the study are as follows:

As for the oral LD_{50} for rats, male and female Crj:CD (SD) rats were administered orally at doses of 590, 769, 1000, 1300, 1690 and 2197 mg/kg and observed for two weeks. In all groups, clinical signs of decreased locomotor activity, mydriasis and blepharoptosis were observed in both sexes. Prone position, hypothermia and tremors were observed at 1300 mg/kg or higher doses in both sexes. Moreover, wasting, abdominal distension and pallor of the auricles at 1300 mg/kg and piloerection in the males at 1690 mg/kg, as well as abdominal distension, pallor of auricles and loss of fur in the females at 1690 mg/kg were observed. Pathological examination was conducted in the male and female rats which died, hemorrhage, necrosis, and vacuolar degeneration were seen in the stomach gland, and edema, hemorrhage, necrosis and vacuolar degeneration were observed in the duodenum. LD_{50} was established at 1482 mg/kg for male and 1564 mg/kg for female rats, respectively.

Dermal acute toxicity study of rat was conducted at a dose of 2000 mg/kg only. Piloerection and hunched posture were seen, being common symptoms in both sexes. At the application site erythema was seen in all animals. Necrosis was observed in one male and one female. The animals recovered within 8 to 13 days. Death of rats was not observed during the examination. The LD_{50} was more than 2000 mg/kg for both sexes.

There is no available information on human.

Conclusions:

The acute oral LD_{50} values are 1482 mg/kg and 1564 mg/kg for male rats and female rats, respectively. The acute dermal LD_{50} is more than 2,000 mg/kg for both sexes in rats.

c) Repeated dose toxicity

There is only one report of a repeated oral toxicity study using rats. In an oral (via gavage) rat study according to the OECD combined repeated dose and reproductive/development toxicity screening test [OECD TG 422], organ weight and histopathological changes were observed (MHW, Japan, 1998). This MHW study was identified as the key study because it was well conducted and used a current protocol. Details of the study are as follows.

The study was conducted at doses of 0, 60, 200, and 600 mg/kg/day. In males of the 600 mg/kg group, 1 and 2 rats died after 6 and 9 days, respectively. In females of the 60 mg/kg and 600 mg/kg groups, 1 and 1 rat died after 16 and 3 days, respectively. In male rats and female rats (during the gestation period) at 200 mg/kg, a tendency for low body weight gain during the administration period was observed and a statistically significant difference from controls was noticed. In both sexes at 600 mg/kg, a remarkable body weight decrease was observed. Blepharoptosis and mydriasis were observed in all dose groups of both sexes, and their changes were dose-related. In the minimum dose (60 mg/kg/day) group, mydriasis was observed only in 1 male and 1 female, on the other hand blepharoptosis was observed in eight of 12 males (8/12) and all females (12/12). But both clinical signs were observed slightly and only sporadically. There were no dose-related changes in haematology and biochemistry. Relative adrenal weights in the 600 mg/kg group of both sexes were slightly increased, and relative liver weights in the 600 mg/kg group of females were increased moderately. Abnormalities of the surviving rats were not observed in histopathological examination. In males of the 600 mg/kg group, 1 and 2 rats died after 6 and 9 days, respectively. In females of the 60 mg/kg and 600 mg/kg groups, 1 and 1 rat died after 16 and 3 days, respectively. As for the dead female rat at 60 mg/kg/day, the cause of death was not determined since no histopathological change related to death was observed. However, in the dead rats of the 600 mg/kg/day group, reddish spots in the digestive tracts, abnormal foci with gastric ulcer and vacuolar degeneration in the renal tubular epithelium were observed. These results suggested that the NOAEL for toxicity in rats of both sexes was less than 60 mg/kg/day.

There is no available information on humans.

Conclusions:

Death caused by the test substance was observed in one female of the 60 mg/kg group, and three males and one female of the 600 mg/kg group. In the dead female rat at 60 mg/kg/day, the cause of death was not determined since no histopathological change related to death was observed. But reddish spots of the digestive tracts, abnormal foci with gastric ulcer and vacuolar degeneration of the renal tubular epithelium were observed in the dead rats of the 600 mg/kg group. On the basis of clinical signs (blepharoptosis) in the 60, 200 and 600 mg/kg /day groups, a NOAEL of less than 60 mg/kg/day was established for both sexes of rats exposed to this substance.

e) Genetic Toxicity or Mutagenicity

This substance has been investigated in *in vitro* tests, gene mutation in bacterial systems and chromosomal aberration in mammalian cultured cells, with and without an exogenous

metabolic activation systems (MHW, Japan, 1998). Also a micronucleus assay using rats was performed, because this substance induced chromosome aberrations in mammalian cultured cells, without S9mix. These were identified as the key studies because they were well conducted and used a current protocol. Details of the studies are as follows.

Bacterial test

Two reverse gene mutation assay were reviewed (MHW, Japan, 1998. Ciba additive GmbH Lampertheim), and the MHW study was identified to be a key study because it was conducted according to OECD TG 471 and well reported.
The substance was not mutagenic in *Salmonella typhimurium* TA100, TA1535, TA98, TA1537 and *Escherichia coli* WP2 *uvr*A at concentrations of up to 5000 ug/plate, with and without an exogenous metabolic activation system (MHW, Japan, 1998). The other study showed negative results as well.

Non-bacterial in vitro test

Only one report was reviewed (MHW, Japan, 1998). This study was a reliable study, because the test was conducted according to OECD TG 473 (MHW, Japan, 1998).
An *in vitro* chromosomal aberration study with this substance was conducted using CHL/IU cells derived from lungs of female Chinese hamsters. In the cell growth inhibition test, the 50% cell growth inhibitory concentrations in the continuous treatment assay were estimated to be 572 μg/mL in the 24-hour treatment and 683 μg/mL in the 48-hour treatment. Those for the short-term treatment assay (6-hour exposure and 18 hour recovery) were estimated to be 726 μg/mL with S9 mix and 565 μg/mL without S9 mix. From these results, the concentration which was higher than the 50% cell growth inhibitory concentration was selected as the highest concentration in the chromosomal aberration test. The concentrations in the chromosomal aberration test were set at 4 concentrations including 1/2, 1/4, and 1/8 of the highest concentration. As a result, structural or numerical chromosome aberration was not induced at any treatment conditions. However, in the short-term treatment assay without S9 mix, the mitotic index at the highest concentration was 6.6 and it was considered that chromosome analysis at higher concentrations would be possible. Therefore, the additional test (the short-term treatment assay without S9 mix) was conducted at up to 2000 ug/mL. As a result, structural chromosome aberration was induced at 2000 ug/mL. Numerical chromosome aberration was also induced at 2000 ug/mL, but the reproducibility was not recognized.

In conclusion, as 2,2,6,6-Tetramethyl-4-hydroxypiperidine induced structural chromosomal aberration without S9 mix only at concentrations higher than the 50 % cell growth inhibitory concentration, which was considered to be due to cytotoxicity, the result was considered to be equivocal.

Genetic in vivo test

Since this substance showed positive results i the chromosome aberration test (MHW, Japan, 1998), a micronucleus assay was performed (Mitsui Chemical Inc., 2001). This assay with bone marrow cells of rats was performed in accordance with the OECD TG 474. This substance was administered twice orally (during a 24 hour interval) to male Crj:CD(SD)IGS rats at 250, 500, 1000 and 1500 mg/kg. The incidence of micronucleated immature erythrocytes was evaluated in rat bone marrow 22 to 24 hours after the final administration. Distilled water was used as a negative control, and cyclophosphamide monohydrate (CP) 20 mg/kg as a positive control.

The result of this assay was as follows. 1) No significant increase was noted in the frequency of micronucleated immature erythrocytes in any test article group, in comparison with the negative control group. A significant low value was noted in the immature erythrocyte ratio of all doses compared to the negative control group. 1 of 6 animal died at 1500 mg/kg. 2) A significant difference was noted in the frequency of micronucleated immature erythrocytes and in the ratio of immature erythrocytes in the positive control group compared to the negative control group. 3) After exposure of the test article to bone marrow erythrocytes in rats, it was confirmed that a significant decrease in the immature erythrocyte ratio occurred at all doses compared to the negative control group. Therefore, it was concluded from the results described above, that under the conditions of this study, this substance did not induce clastogenic activity in the bone marrow erythrocytes of rats.

Conclusions:

This substance was not mutagenic with or without an exogenous metabolic activation in bacteria [OECD TG 471 & 472]. It induced chromosomal aberration in CHL/IU cells in vitro, without metabolic activation system, which were considered to be due to cytotoxicity and the study was considered to be "equivocal" [OECD TG 473]. A negative result was obtained in a rat bone marrow micronucleus assay [OECD TG 474]. Thus, on the basis of the available data, this substance is not considered to be an *in vivo* genotoxicant, as the questionable genotoxicity observed *in vitro* is not expressed *in vivo*.

f) Carcinogenicity

There is no available information.

g) Reproduction/developmental toxicity

Only the results from one study are available. The OECD repeat dose and reproductive toxicity study [OECD TG 422] was reported (MHW, Japan, 1998). This study was identified to be well conducted and reported.

As for the reproductive ability of parent animals, no effects were detected in males but on estrous cycle examination, continuous diestrous was observed in three females of the 600 mg/kg group and the mean estrous cycle of this group showed extension compared with the control group. There were no effects of the test substance on the copulation or fertility indices. Pathological examination hardly showed abnormalities in the reproductive organs of animals. With regard to the effects on neonates, viability on day 4 of lactation was decreased in the 600 mg/kg group, and male and female pups of the 600 mg/kg group showed lower body weights on day 4 of lactation. There are no significant differences in the delivery index and live birth index. Also, no external and visceral abnormalities related to the test substance were detected in any of the offspring.

There is no available information on humans.

Conclusions:

On the basis of these findings, the NOEL of 2,2,6,6-Tetramethylpiperidin-4-ol for reproductive toxicity to parental rats was considered to be 600 mg/kg/day for males, and 200 mg/kg/day for females. Moreover, the NOEL of the test substance to F1 offspring was established to be 200 mg/kg/day.

h) Other: Irritation; Sensitization; Corrosivity

Animal data

There was only one report from a study on acute dermal irritation/corrosion [OECD TG 404] in the rabbit (Ciba additive GmbH Lampertheim). This study was identified as the key study because it was well conducted and used a current protocol. This substance induced moderate to severe skin irritation when applied to the clipped albino rabbits skin. In one animal the skin reactions were not reversible within 14 days after patch removal.
There was only one report from a study on skin sensitization in guinea pigs (Ciba additive GmbH Lampertheim). This study was identified as the key study because it was well conducted and used a current protocol [OECD TG 406]. Test substance showed a moderate to strong grade of skin-sensitizing (contact allergenic) potential according to the grading of Magnusson and Kligman in albino guinea pigs.

Human data

There is no available information on humans.

Conclusion

This chemical is highly irritating to skin, and it showed a moderate to strong grade of skin-sensitizing (contact allergenic) potential in albino guinea pigs.

3.2 Initial Assessment for Human Health

There is no available information on toxicokinetics and metabolism of this substance. Oral LD_{50} of the substance are 1482 mg/kg and 1564 mg/kg for male rats and female rats, respectively. The major toxic signs were decreased locomotor activity, mydriasis and blepharoptosis, and tissue damages in the stomach and duodenum in both sexes. Dermal LD_{50} of rats was more than 2000 mg/kg. This substance is highly irritating to skin in rabbits, and it can be expected to cause serious damage to eyes but the study has not been performed. It has a moderate to strong grade of skin-sensitizing (contact allergenic) potential in guinea pigs [OECD TG 406].

In the repeated dose toxicity studies, blepharoptosis and mydriasis as the clinical signs were observed in all dose groups of both sexes, and the changes were dose-related. In the minimum dose (60 mg/kg/day) group, mydriasis was observed only in one male and one female, and on the other hand blepharoptosis was observed in eight of 12 males (8/12) and all females (12/12). But, both clinical signs were observed slightly and only sporadically. On the basis of clinical signs (blepharoptosis) in the 60, 200 and 600 mg/kg /day groups, a NOAEL of less than 60 mg/kg/day was established for both sexes of rats exposed to this substance.

In a reproductive/developmental toxicity study, the substance caused significant reproductive /developmental effects in rats of the 600 mg/kg/day dose group. The NOEL for reproductive /developmental in animal is 200 mg/kg/day. As for the genotoxicity, this substance was not mutagenic in bacteria. An increase in chromosome aberrations in Chinese hamster lung cells was considered to be due to cytotoxicity and the study was considered to be “equivocal”. This equivocal effect could not be confirmed *in vivo* micronucleus assay using rat bone marrow. These results suggest that this substance can be considered not to be genotoxic *in vivo*.

4. HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

In the following table, the most relevant results from acute and chronic tests with aquatic organisms are presented.

Table 4: Summary of effects of aquatic organisms

Organism	Test duration	Result (mg/L)	Reference
Aquatic plants Green algae (*Selenastrum capricornutum*)	72 hr (cl)	EC_{50} (bms) 107 (nc*) NOEC (bms) 76 (nc*) EC_{50} (gr) 155 (nc*) NOEC (gr) 76 (nc*)	EA, Japan (1997)
(*Scendedesmus subspicatus*)	72 hr (cl)	EC_{50} (gr) 158 (nc*) NOEC (gr) 10 (nc*)	Ciba additive GmbH Lampertheim
Invertebrates Water flea (*Daphnia magna*)	24 hr (op, s) 48 hr (op, s) 21 d (op, ss)	EC_{50} (imm) 130.1 (nc*) EC_{50} (imm) 100.1 (nc*) EC_{50} (rep) 46.2 (nc*) NOEC (rep) 3.7 (nc*)	EA, Japan (1997)
Fish Zebrafish (*Brachydanio rerio*)	96 h (-, s)	LC_{50} > 1000 (nc*)	Ciba additive GmbH Lampertheim
Medaka (*Oryzias latipes*)	96 h (op, ss)	LC_{50} 237 (nc)	MITI, Japan (1998)
	14 d (op, f)	(a) no adjusting pH of the test solution LC_{50} 88.1 (nc*) NOEC 25.0 (nc*) (b) adjusting pH of the test solution LC_{50} > 100.0 (nc*) NOEC 25.0 (nc*)	EA, Japan (1997)

cl ; closed system, op ;open system
s ; static, ss ;semi-static, f ; flow through
nc; nominal concentration
nc; nominal concentration (actual concentration measured and greater than 80% of the nominal)*
bms ; biomass, gr ; growth rate, imm ;immobility, rep ;reproduction

This substance has been tested in a limited number of aquatic species including fish, daphnia and algae. All the data shown in this Table are derived from experiments conducted under GLP. LC_{50} of the acute toxicity (96 h) for fishes (Medaka and Zebrafish) are 237 mg/L and more than 1000 mg/L, respectively (MITI, Japan, 1998: Ciba additive GmbH). And the prolonged toxicity test result using Medaka was 88.1 mg/L for LC_{50} (14 d). But when the prolonged toxicity (14 d) test was conducted using neutralized test solution, because the non-adjusted test solution showed

alkalinity, the LC_{50} for prolonged toxicity (14 d) for Medaka was more than 100 mg/L (EA, Japan, 1997).
Consequently, this substance showed stronger toxicity to Medaka in non-adjusted solution than neutralized solution. The acute (mortality or immobility) and chronic data (reproduction) for daphnia were 100.1 mg/L for EC_{50} (48 h) and 46.2 mg/L for EC_{50} (21 d), and 3.7 mg/L for NOEC (21 d reproduction), respectively (EA, Japan, 1997). The toxicity to the aquatic plants (algae) *Selenastrum caricornutum* and *Scenedesmus subspicatus* were 107 mg/L for EC_{50} (72 h) and 158 mg/L for EC_{50} (72 h), respectively. A NOEC (72 h) of 10 mg/L is reported for *Scenedesmus subspicatus* (EA, Japan, 1997: Ciba additive GmbH, Test No. 928326).
The lowest value obtained from acute and chronic toxicity studies in three species is 3.7 mg/L (NOEC 21 d) with Daphnia (reproduction). The PNEC is calculated to be 0.037 mg/L by applying anassessment factor of 100.

4.2. Terrestrial Effects

There is no available information.

4.3. OtherEnvironmental Effects

There is no available information.

4.4. Initial Assessment for the Environment

The potential environmental distribution of this substance was obtained from a generic fugacity model (Mackay level III) under three emission scenarios. The calculation revealed that in the case of 100 % release to water, ca. 100 % of this substance is expected to stay in water due to the high water solubility. This substance is not readily biodegradable (OECD TG 301C: 0 - 2% after 28 days) nor hydrolyzed at pH 4, 7 and 9 at 50 °C after 5 days. But, it was expected to have a low potential for bioaccumulation based on a low Log Pow (0.24) and a measured BCF of less than 5.7.

A predicted no-effect concentration (PNEC) was determined from the following toxicity data in a limited number of aquatic species. LC_{50} values for acute toxicity (96 h) for fishes (Medaka and Zebrafish) are 237 mg/L and more than 1000 mg/L, respectively. The prolonged toxicity test result using Medaka was 88.1 mg/L for LC_{50} (14 d). But when the prolonged toxicity test was conducted using neutralized test solution, the LC_{50} (14 d) for Medaka was more than 100 mg/L. These results suggest that the non-adjusted test solution of this substance develop stronger toxicity in fishes. The acute (mortality or immobility) and chronic data (reproduction) for daphnia were 100.1 mg/L for EC_{50} (48 h) and 46.2 mg/L for EC_{50} (21 d), and 3.7 mg/L for NOEC (21 d reproduction), respectively. The toxicity to *Selenastrum caricornutum* and *Scendedesmus subspicatus* of aquatic plants (algae) were 107 mg/L for EC_{50} (72 h) and 158 mg/L for EC_{50} (72 h), respectively. A NOEC (72 h) of 10 mg/L is reported for *Scendedesmus subspicatus*.

A predicted no-effect concentration (PNEC) of 0.037 mg/L for the aquatic organisms was calculated from the NOEC (21 d) for *Daphnia magna* using an assessment factor of 100, because two chronic data (Daphnia magna and algae) were available.

5. CONCLUTIONS AND RECOMMENDATIONS

5.1 Conclusions

Exposure

The production volume of the substance is estimated to be ca. 2,500 tons/year in Japan, and ca. 5,500 tons/year in the EU; major producers are located in Switzerland and Germany. Generally, the chemical produced in Japan is used in the polymers industry as an intermediate for the production of plastic antioxidants and/or stabilizers (HALS). A worker may be exposed to this substance at production sites and user sites in industries. The production process is fully closed. Even at the packing site where maximum inhalation exposure to workers is expected if a worker (exposure period; 4 h) is assigned to equipment without protection, the maximum estimated human exposure (EHE inh) would be calculated to be 0.090 mg/kg/day. Regarding the dermal exposure of this substance, without personal protective equipment (hands), the dermal estimated human exposure (EHE der) is calculated to be 0.60 mg/kg/day. Since this substance may cause irritation and sensitization to the skin, a worker is allowed to work only with appropriate protection implements. Therefore, the levels of exposure to a worker of this substance at the workplace would be very low.

Consumer exposure is considered as follows. The amount of HALS in final consumer products, e.g. plastics is estimated less than 1.0 %. The content of the substance itself in the consumer products should be far below that. Then exposure by residues to a consumer through product surfaces would be very low.

During production and use in Japan, only the aquatic release of this substance from the production sites seems to be possible. Although this substance is not readily biodegradable or hydrolysable, the bioaccumulation potential of this substance is low.

Hazards to the Environment

This substance is not readily biodegradable (OECD TG 301C: 0 - 2% after 28 days) and it is not hydrolyzed at pH 4, 7 and 9 at 50 °C after 5 days. The generic fugacity model (Mackay level III) shows that if this substance is released into water, it is unlikely to be migrated into other compartments, because it shows high solubility in water. However as the substance is present in a cationic form in the environment, it is likely that a certain portion of the substance is adsorbed in the sediment. It was expected to have a low potential for bioaccumulation based on a low Log Pow (0.24) and a measured BCF of less than 5.7.
This substance has been tested in a limited number of aquatic species including fish, daphnia and algae. The lowest acute test result was 88.1 mg/L (Medaka 14 d LC_{50}), and the lowest chronic test result was 3.7 mg/L (Daphnia 21 d NOEC, reproduction). A predicted no-effect concentration (PNEC) of 0.037 mg/L for the aquatic organisms was calculated from the chronic NOEC for daphnia using an assessment factor of 100, because two chronic data (daphnia and algae) were available.

Human Health Hazards

Oral (gavage) LD_{50} values of 2,2,6,6-Tetramethylpiperidin-4-ol for rats are 1482 mg/kg for males and 1564 mg/kg for females. This substance is highly irritating to skin in rabbits. According to the grading of Magnusson and Kligman this substance showed a moderate to strong grade of skin-sensitizing (contact allergenic) potential in albino guinea pigs.

As for the repeated dose toxicity studies, in males and females (during the gestation period) at 200 mg/kg, a tendency of low body weight gain during the administration period was observed and a statistically significant difference from controls was noticed in body weight. In both sexes at 600 mg/kg, a remarkable body weight decrease was observed. Blepharoptosis and mydriasis were observed in all groups of both sexes, and their changes were also dose-related. Both clinical signs were observed even in the minimum dose group (60 mg/kg/day) but both clinical signs were observed slightly and only sporadically. Thus, on the basis of clinical signs (blepharoptosis) in the 60, 200 and 600 mg/kg /day groups, a NOAEL of less than 60 mg/kg/day was established for both sexes of rats exposed to this substance.

As for the reproductive ability of parent animals, no effects were detected in males. But on estrous cycle examination, continuous diestrous was observed in three females of the 600 mg/kg group and the mean estrous cycle of this group showed extension compared with the control group. There were no effects of the test substance on the copulation or fertility indices. With regard to the effects on neonates, viability on day 4 of lactation decreased in the 600 mg/kg group, and male and female pups of the 600 mg/kg group showed lower body weights on day 4 of lactation. There are no significant differences in the delivery index and live birth index. Also, no external and visceral abnormalities related to the test substance were detected in any of the offspring. On the basis of these findings, the NOEL of this substance for reproductive toxicity in parental rats was considered to be 600 mg/kg/day for males, and 200 mg/kg/day for females. Moreover, NOEL of the test substance to F1 offspring was judged to be 200 mg/kg/day.

This substance is not genotoxic with and without an exogenous metabolic activation system in bacterial test, but induced structural chromosomal aberration in CHL/IU cells without S9 mix *in vitro*, which were considered to be due to cytotoxicity and the study result was considered to be "equivocal." A micronucleus assay according to OECD TG 474 showed negative results *in vivo*. Thus, this substance is considered not to be an *in vivo* genotoxicant.

5.2 Recommendations

The chemical is currently of low priority for further work, on the prerequisite of negligible human exposure and environmental release.

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SIDS DOSSIER

2,2,6,6-Tetramethylpiperidin-4-ol

CAS No. 2403-88-5

Sponsor Country : Japan

DATE: 1 February, 2002

1. GENERAL INFORMATION

1.01 SUBSTANCE INFORMATION

A. CAS Number 2403-88-5

B. Name *(IUPAC name)* 2,2,6,6-Tetramethylpiperidin-4-ol

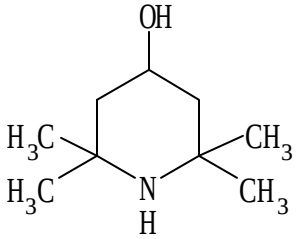
C. Name *(OECD name)*

D. CAS Descriptor Not applicable in this case

E. EINECS-Number 219-292-2

F. Molecular Formula $C_9H_{19}NO$

G. Structural Formula



H. Substance Group Not applicable

I. Substance Remark None

J. Molecular Weight 157.26

1.02 OECD INFORMATION

A. Sponsor Country: Japan

B. Lead Organisation:

Name of Lead Organisation:	Mitsui Chemicals Inc.
Contact person:	Mr. Katsutoshi Ishikawa
Address:	3-2-5, Kasumigaseki, Chiyoda-ku, Tokyo 100-6070, Japan Tel: +81-3-3592-4131, Fax: +81-3-3592-4222 E-mail: Katsutoshi.Ishikawa@mitsui-chem.co.jp
Contact person of Japan:	Mr. Koji Tomita Ministry of Foreign Affairs Economic Affairs Bureau Second International Organisations Div.
Address:	2-2-1 Kasumigaseki, Chiyoda-ku, Tokyo 100, Japan Tel: +81-3-3581-0018, Fax: +81-3-3581-9470 E-mail: seiichi.urauchi@mofa.go.jp

C. Name of responder: the same as above

1.1 GENERAL SUBSTANCE INFORMATION

A. **Type of Substance**

element [ ]; inorganic [ ]; natural substance [ ]; organic [**X**]; organometallic [ ]; petroleum product [ ]

B. Physical State (at 20°C and 1,013 hPa)

gaseous [ ]; liquid [ ]; solid [**X**]

C. Purity Test Substance: ≥ 99.8 % weight/weight
Industrial Product: ≥ 98.0 % weight/weight

Reference: Mitsui Chemicals Inc. (1999a), unpublished data

1.2 SYNONYMS (Chemical Name)

2,2,6,6-Tetramethyl-4-hydroxypiperidine
2,2,6,6-Tetramethyl-4-piperidinol
4-Hydroxy-2,2,6,6-tetramethylpiperidine
4-Piperidinol 2,2,6,6-tetramethyl-
HTMP
Hydoroxytetramethypiperidine
Triacetoneaminoalcohol

1.3 IMPURITIES

2,2,6,6-Tetramethyl-4-aminopiperidine
2,2,6,6-Tetramethyl-4-oxopiperidine
2,2,6,6-Tetramethyltetrahydrofuran-4-ol

Reference: Mitsui Chemicals Inc. (1999b), unpublished data

1.4 ADDITIVES None

1.5 QUANTITY

Remarks: Estimated global production was 8,000 tons in 1999.
There are five companies in the world.
The production volume was 5,500 tons by three companies in EU and 2,500 tons by two companies in Japan.

Reference: Mitsui Chemicals Inc. (1999c), unpublished data

1.6 LABELLING AND CLASSIFICATION

Labelling: Not assigned according to the EC Directive 67/548/EEC

Classification: Not classified

1.7 USE PATTERN

A. General

Type of Use:	Category:
main	Chemical industry
industrial use	Use as an intermediate in synthesis of the light stabiliser. 'HALS' (Hindered Amine Light-Stabiliser) for plastics.

Remarks: In Japan, all of this substance is used in the factories.

Reference: Mitsui Chemicals Inc. (1999d), unpublished data

B. Uses in Consumer Products

The consumer does not use directly this substance, since this is an intermediate of the plastic stabiliser.

Remarks: All of this substance is used as an intermediate of the plastic stabiliser in Japan.

Reference: Mitsui Chemicals Inc. (1999d), unpublished data

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUE

Exposure limit value: None

Short term exposure limit value: None

1.9 SOURCES OF EXPOSURE

A. Potential human exposure: Exposure can be neglected by applying protective measures, since the production process is closed.

(a) At a production site:

A worker may be exposed when sampling and analysis. But, it's a short time. However a worker in the packing site may be exposed to it for eight hours a day. The workplace is provided with an air ventilator and a worker is equipped with protective gear such as mask, rubber gloves, rubber boots, goggles and a chemical suit to prevent exposure (by Mitsui Chemicals Inc., MSDS, 2000). Spill is collected and burnt.

Exposure monitoring data:

Measured in 2000 at a production site in Japan.

Method:

The air of atmosphere was suctioned at a ratio of 3.0 L/min. for 30 min, and airborne particles were collected by a filter. The collected dust was dissolved in solvent which it was analysed by HPLC.

Result:

The exposure level of a worker at the following workplace was measured as follows

Analysis: 0.203 mg/m^3
Sampling: 1.807 mg/m^3
Packing: 0.879 mg/m^3

Reference: Ministry of Labour in Japan (2000), unpublished data

(b) At a user's facility:

The substance is used as an intermediate of the plastic stabilizer. Potential exposure is controlled by the use of efficient exhaust ventilation. Exposure is possible during dispensing the substance from packing bag into a container at user's facility.

A worker may be exposed the vapour. A worker is recommended to put on protective gear such as mask, rubber gloves, rubber boots, goggles and a chemical suit to prevent exposure (by the MSDS Mitsui Chemicals, 2000). Spill is collected and burnt.

B. Potential environmental exposure:

(a) At a production site:

Source: Media of release: waste water from a production site.
Quantities per media: Estimated max. ca. 17.5 kg/year in a production site in Japan (2001), in which ca. 1600 tons/year of the chemical substance was produced.

Remarks: Data use for the estimation: estimated by Mitsui Chemicals Inc.
Waste water released: ca.800 m^3/day
Content of the substance: 0.06 mg/L

Reference: Mitsui Chemicals Inc. (2001a), unpublished data

(b) At a user's facility:

Potential exposure is controlled by the use of efficient exhaust ventilator.
The waste water from the production site was treated by the waste water treatment equipment. Spill is collected and burnt.

Remarks: When the wastewater (influent) of the manufacturing factory containing this substance and the wastewater (effluent) treated at the drainage treatment process with activated sludge of this factory are analyzed. The influent and effluent concentrations of this substance were 1526 mg/L and 0.633 mg/L, respectively. Furthermore, after the effluent is processed in the final sewage disposal plant of Wakayama Prefecture in Japan (a public drainage processing facility), it is released to the river. The concentration of this substance contained in the effluent that released to the river was 0.06 mg/L and/or less than 0.06 mg/L. (Minimum detection limit ; 0.015 mg/L).

Reference: Mitsui Chemicals Inc. (2001a), unpublished data

1.10 ADDITIONAL REMARKS

A. Options for disposal

Incineration; release to sewage system for waste water treatment.

B. Other remarks

None.

2. PHYSICAL-CHEMICAL DATA

2.1 MELTING POINT

(a)
Preferred result

Value:	130.6 °C
Decomposition:	Yes **[ ]** No **[ ]** Ambiguous **[ ]**
Sublimation:	Yes **[ ]** No **[ ]** Ambiguous **[ ]**
Method:	Not specified
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Remarks:	Not stated
Reference:	Ministry of International Trade and Industry, Japan (1998a). Report No. K-1364 (5-0776), unpublished data.

(b)

Value:	128 - 130 °C
Decomposition:	Yes **[ ]** No **[X]** Ambiguous **[ ]**
Sublimation:	Yes **[ ]** No **[X]** Ambiguous **[ ]**
Method:	Not specified
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Remarks:	Not stated
Reference:	Ciba additive GmbH Lampertheim (Ciba, Untersuchung)

(c)

Value:	127.5 - 128.5 °C
Decomposition:	Yes **[ ]** No **[ ]** Ambiguous **[ ]**
Sublimation:	Yes **[ ]** No **[ ]** Ambiguous **[ ]**
Method:	Not specified
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Remarks:	Not stated
Reference:	Nathan Kornblum and Harold W Pinnick (1972) J.Org.Chem.; 37, 2050-

2.2 BOILING POINT

Value:	212 - 215 °C
Pressure:	at 1,013 hPa
Decomposition:	Yes **[ ]** No **[ ]** Ambiguous **[ ]**
Method:	Not specified
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Remarks:	Not stated
Reference:	Ministry of International Trade and Industry, Japan (1998b). Report No. K-1364 (5-0776), unpublished data.

2.3 DENSITY (relative density)

(a)
Preferred result

Type:	Bulk density **[ ]**; Density **[X]**; Relative Density **[ ]**
Value:	1.062 g/cm^3
Temperature:	25 °C
Method:	JIS K 7112-1980
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Remarks:	Not stated

Reference: Ministry of International Trade and Industry, Japan (1998c). Report No. K-1364 (5-0776), unpublished data.

(b)
Type: Bulk density **[ ]**; Density **[ ]**; Relative Density **[X]**
Value: 1.09 g/cm^3
Temperature: 20 °C
Method: Not specified
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Remarks: Not stated
Reference: Ciba additive GmbH Lampertheim (Ciba, Untersuchung)

(c)
Type: Bulk density **[X]**; Density **[ ]**; Relative Density **[ ]**
Value: 730 kg /m^3
Temperature: 20 °C
Method: Not specified
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Remarks: Not stated
Reference: Ciba additive GmbH Lampertheim (Ciba, Untersuchung)

2.4 VAPOUR PRESSURE

Value: 2.6×10^{-1} Pa
Temperature: 25 °C
Method: OECD TG 104
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Remarks: Not stated
Reference: Ministry of International Trade and Industry, Japan (1998d). Report No. K-1364 (5-0776), unpublished data.

2.5 PARTITION COEFFICIENT $\log_{10}P_{ow}$

(a)
Preferred result
Log P_{OW}: 0.24
Temperature: No data
Method: OECD TG 107
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Remarks: Shake flask method.
Reference: Ministry of International Trade and Industry, Japan (1998e). Report No. K-1364 (5-0776), unpublished data.

(b)
Log P_{OW}: 0.544
Temperature: No data
Method: calculated **[X]**; measured **[ ]**
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: calculated using the ClogP program "MacLogP", version 2.0.0., Biobyte Corporation
Reference: Mitsui Chemicals Inc. (2001b), unpublished data

2.6 WATER SOLUBILITY

A. Solubility

(a)
Preferred result

Value:	> 100 g/L
Temperature:	25 °C
Description:	Miscible **[ ]**; Of very high solubility **[X]**; Of high solubility **[ ]**; Soluble **[ ]**; Slightly soluble **[ ]**; Of low solubility **[ ]**; Of very low solubility **[ ]**; Not soluble **[ ]**
Method:	OECD TG 105
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Remarks:	Not stated
Reference:	Ministry of International Trade and Industry, Japan (1998f). Report No. K-1364 (5-0776), unpublished data.

(b)

Value:	> 149 g/L
Temperature:	20 °C
Description:	Miscible **[ ]**; Of very high solubility **[X]**; Of high solubility **[ ]**; Soluble **[ ]**; Slightly soluble **[ ]**; Of low solubility **[ ]**; Of very low solubility **[ ]**; Not soluble **[ ]**
Method:	Not specified
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Remarks:	Not stated
Reference:	Ciba additive GmbH Lampertheim (Ciba, Untersuchung)

B. pH Value, pKa Value

pH Value:	11.47
Concentration:	1 % solution
Temperature:	20 °C
Method:	Glass Electrodes method
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Remarks:	The examination result related to concentration is as follows: pH value of 0.01%, 0.02, 0.03, 0.05, 0.1, 0.5, 1.0, 5.0 and 8.45 is 10.22, 10.54, 10.58, 10.72, 10.93, 11.32, 11.47, 11.83 and 11.94, respectively.
Reference:	Mitsui Chemicals Inc. (2001c), unpublished data

pKa value:	9.92
Temperature:	25 °C
Method:	OECD TG 112
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Remarks:	Not stated
Reference:	Ministry of International Trade and Industry, Japan (1998g). Report No. K-1364 (5-0776), unpublished data.

2.7 FLASH POINT

Value:	85 °C
Type of test:	Open cup
Method:	Not specified
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Remarks:	Not stated
Reference:	Ciba additive GmbH Lampertheim (Ciba, Test No. S-7770674)

2.8 AUTO FLAMMABILITY *(solid/gases)*

Value:	> 130 °C
Pressure:	No data
Method:	Not specified
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Remarks:	Not stated
Reference:	Ciba additive GmbH Lampertheim (Ciba, Untersuchung)

2.9 FLAMMABILITY

No data available

2.10 EXPLOSIVE PROPERTIES

Result:	UEL: 2.4 %
Method:	No specified
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Reference:	Ciba additive GmbH Lampertheim (Ciba, Untersuchung)

2.11 OXIDISING PROPERTIES

No data available

2.12 OXIDATION: REDUCTION POTENTIAL

No data available

3. ENVIRONMENTAL FATE AND PATHWAYS

3.1 STABILITY

3.1.1 PHOTODEGRADATION

Type:	Air **[X]**; Water **[ ]**; Soil **[ ]**; Other **[ ]**
Temperature:	25 °C
Type of sensitizer:	OH radical
Concentration of sensitizer:	5×10^{5} molecule/cm^{3}
Rate constant (radical):	7.69078×10^{-11} cm^{3}/molecule-sec
Degradation:	50 % after 5.00 hours
Method:	calculated **[X]**; measured **[ ]**
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Remarks:	The rate constant for gas-phase reaction between OH radical and the test substance was calculated by using AOP Win (ver.1.86) and the half-life time of 5.00 hours was calculated with the daily average concentration of OH radical of 5×10^{5} molecule/cm^{3} in atmosphere.
Reference:	Mitsui Chemicals Inc. (2001d), unpublished data

3.1.2 STABILITY IN WATER

Type:	Abiotic (hydrolysis) **[X]**; biotic (sediment)**[ ]**
Half life:	> 1 year
Degradation:	No degradation at pH 4, 7 and 9 at 50 °C after 5 days (exposure time)
Method:	OECD TG 111
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:, purity:	Wako Pure Chemical Industries, Ltd., 99.2 %
Remarks:	
Reference:	Ministry of International Trade and Industry, Japan (1998h). Report No. K-1364 (5-0776), unpublished data.

3.1.3 STABILITY IN SOIL

No data available

3.2 MONITORING DATA (ENVIRONMENTAL)

No data available

3.3 TRANSPORT AND DISTRIBUTION BETWEEN ENVIRONMENTAL COMPARTMENTS INCLUDING ESTIMATED ENVIRONMENTAL CONCENTRATIONS AND DISTRIBUTION PATHWAYS

3.3.1 TRANSPORT

No data available

3.3.2 THEORETICAL DISTRIBUTION (FUGACITY CALCULATION)

Media:	Air-biota **[ ]**; Air-biota-sediment-soil-water **[X]**; Soil-biota **[ ]**; Water-air **[ ]**; Water-biota **[ ]**; Water-soil **[ ]**; Other **[ ]**
Method:	Fugacity level I **[ ]**; Fugacity level II **[ ]**; Fugacity level III **[X]**; Fugacity level IV **[ ]**; Other (calculation) **[ ]**; Other (measurement)**[ ]**

Results: Predicted distribution of 2,2,6,6-Tetramethylpiperidin-4-ol using Fugacity model (Mackay level III)

Compartment	Release 100% into air	Release 100% into water	Release 100% into soil
Air	0.4 %	0.0 %	0.0 %
Water	32.5 %	99.7 %	20.4 %
Soil	67.0 %	0.0 %	79.6 %
Sediment	0.1 %	0.3 %	0.1 %

Remarks: See Appendix 1.
Reference: Mitsui Chemicals Inc. (2001e), unpublished data

3.4 MODE OF DEGRADABILITY IN ACTUAL USE

No data available

3.5 BIODEGRADATION

(a)
Preferred result
Type: aerobic **[X]**; anaerobic **[ ]**
Inoculum: adapted **[ ]**; non-adapted **[X]**;
Activated sludge, 30 mg/L as suspended solid
Concentration of the chemical: 100 mg/L related to COD **[ ]**; DOC **[ ]**; test substance **[X]**
Medium: water **[X];** water-sediment **[ ];** soil **[ ];** sewage treatment **[ ]**
Degradation: (percentage reduction/exposure time)
0 % after 28 days (based on BOD)
1 % after 28 days (based on TOC)
2 % after 28 days (based on GC)
Results: readily biodeg.**[ ];** inherently biodeg.**[ ]**; under test condition no biodegradation observed **[X]**, other **[ ]**
Kinetic Not stated
Method: OECD TG 301C (1992)
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance:. purity: 99.2 %
Remarks: The results indicate that the chemical is not biodegradable.
Reference: Ministry of International Trade and Industry, Japan (1998i). Report No. K-1364 (5-0776), unpublished data.

(b)
Type: aerobic **[X]**; anaerobic **[ ]**
Inoculum: adapted **[ ]**; non-adapted **[X]**;
Activated sludge, 30mg/L as suspended solid
Concentration of the chemical: 100 mg/L related to COD **[ ]**; DOC **[ ]**; test substance **[X]**
Medium: water **[X];** water-sediment **[ ];** soil **[ ];** sewage treatment **[ ]**
Degradation: (percentage reduction/exposure time)
1 % after 28 days (based on BOD)
0 % after 28 days (based on TOC)
1 % after 28 days (based on GC)

Results: readily biodeg.**[ ];** inherently biodeg.**[ ]**; under test condition no biodegradation observed **[X]**, other **[ ]**
Kinetic: 0 % after 7 days BOD
1 % after 14 days BOD

1 % after 21 days BOD
1 % after 28 days BOD
Method: OECD TG 301C (1992)
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance:. purity: 100 %
Remarks: The results indicate that the chemical is not biodegradable.
Reference: Mitsui Chemicals Inc. (1997), unpublished data

(c)
Type: aerobic **[X]**; anaerobic **[ ]**
Inoculum: adapted **[ ]**; non-adapted **[X]**;
Domestic sewage
Concentration of the chemical: 10.4 mg/L related to COD **[ ]**; DOC **[ ]**; test substance **[X]**
Medium: water **[X];** water-sediment **[ ];** soil **[ ];** sewage treatment **[ ]**
Degradation: (percentage reduction/exposure time)
3 % after 28 days
Results: readily biodeg. **[ ];** inherently biodeg. **[ ]**; under test condition no biodegradation observed **[X]**, other **[ ]**
Method: Directive 84/449/EEC, C.5 "Biotic degradation-modified Sturm test"
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance:. Not stated
Remarks: The results indicate that the chemical is not biodegradable.
Reference: Ciba additive GmbH Lampertheim (Test No. 894485)

(d)
Type: aerobic **[X]**; anaerobic **[ ]**
Inoculum: adapted **[ ]**; non-adapted **[X]**;
Domestic sewage
Concentration of the chemical: 20.4 mg/L related to COD **[ ]**; DOC **[ ]**; test substance **[X]**
Medium: water **[X];** water-sediment **[ ];** soil **[ ];** sewage treatment **[ ]**
Degradation: (percentage reduction/exposure time)
4 % after 28 days
Results: readily biodeg. **[ ];** inherently biodeg. **[ ]**; under test condition no biodegradation observed **[X]**, other **[ ]**
Method: Directive 84/449/EEC, C.5 "Biotic degradation-modified Sturm test"
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance:. Not stated
Remarks: The results indicate that the chemical is not biodegradable.
Reference: Ciba additive GmbH Lampertheim (Test No. 894485)

3.6 BOD_5, COD OR RATIO BOD_5/COD

No data available

3.7 BIOACCUMULATION

Species: Carp (*Cyprinus carpio*)
Exposure period: 4 weeks
Temperature: 25 °C
Concentration: 1.0 mg/L and 0.1 mg/L
BCF: < 5.7 (1.0 mg/L)
< 0.57 (0.1 mg/L)
Elimination: Yes **[ ]** No **[X]** ? **[ ]**
Method: MITI method (1974), corresponding to the previous OECD TG 305C (1981).

Type of test:	calculated **[ ]**; measured **[X]** static **[ ]**; semi-static **[ ]**; flow-through **[X]**; other *(e.g. field test)* **[ ]**
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	purity: 99.2 %
Remarks:	The stock solution for exposure was prepared with castor oil (HCO-40) according to the guideline. The exposure was conducted under flow-through conditions. The average lipid content of carp was 2.15 %. No elimination experiment was conducted.
Reference:	Ministry of International Trade and Industry, Japan (1998j). Report No. K-1364 (5-0776), unpublished data.

4. ECOTOXICITY

4.1 ACUTE/PROLONGED TOXICITY TO FISH

4.1.1 ACUTE TOXICITY TO FISH

(a)
Preferred result

Type of test:	static **[ ]**; semi-static **[X]**; flow-through **[ ]**; other *(e.g. field test)* **[ ]** open-system **[X]**; closed-system **[ ]**; ? **[ ]**
Species:	Medaka (*Oryzias latipes*)
Exposure period:	96 h
Results:	LC_{50} 237 mg/L
Analytical monitoring:	Yes **[ ]** No **[X]** ? **[ ]**
Method:	OECD TG 203
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance: purity:	99.9 %
Remarks:	Not stated.
Reference:	Ministry of International Trade and Industry, Japan (1998k). Report No. K-1364 (5-0776), unpublished data.

(b)

Type of test:	static **[ ]**; semi-static **[X]**; flow-through **[ ]**; other *(e.g. field test)* **[ ]** open-system **[X]**; closed-system **[ ]**
Species:	Medaka (*Oryzias latipes*)
Exposure period:	96 h
Results:	(a) LC_{50} > 100 mg/L (b) LC_{50} > 100 mg/L
Analytical monitoring:	Yes **[X]** No **[ ]** ? **[ ]**
Method:	OECD TG 203
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance: purity:	> 99.0 %,
Remark:	Tap water was used after dechlorinated by passing through activated carbon. Test was conducted at the nominal concentrations of 0, 9.5, 17.1, 30.9, 55.6, 100.0 mg/L. The test solution was replaced every 24 hours by newly prepared ones. When the test solution was analysed after 24 hours, the measured concentrations showed more than 80 % of the nominal concentrations. At the nominal concentrations of 0, 9.5, 17.1, 30.9, 55.6, 100.0 mg/L, 100 % of fishes survived until 96 hours were normal. The examination was performed on two conditions, (a) test was carried out without adjusting pH of test solution, and (b) test was carried out after adjusting test solution to neutrality, since the test solution of 2,2,6,6-Tetramethylpiperidin-4-ol was alkalinity. As for the test, only 100 mg/L concentration was examined. At 72 hours, one fish showed abnormal swimming behaviour.
Reference:	Environmental Agency of Japan, (1997). Ecotoxicity testing report, Test No. NMMP/E09/4070, unpublished data.

(c)

Type of test:	static **[X]**; semi-static **[ ]**; flow-through **[ ]**; other *(e.g. field test)* **[ ]** open-system **[ ]**; closed-system **[ ]**; ? **[X]**
Species:	Zebrafish (*Brachydanio rerio*)
Exposure period:	(96 h)
Results:	LC_0 1000 mg/L

	LC_{50} > 1000 mg/L
	LC_{100} > 1000 mg/L
Analytical monitoring:	Yes **[ ]** No **[X]** ? **[ ]**
Method:	Directive 84/449/EEC, C.1 "Acute toxicity to fish"
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance: purity:	Not stated.
Remarks:	Not stated.
Reference:	Ciba additive GmbH Lampertheim (Ciba, eigene Untersuchung)

4.1.2 PROLONGED TOXICITY TO FISH

Type of test:	static **[ ]**; semi-static **[ ]**; flow-through **[X]**; other *(e.g. field test)* **[ ]**; open-system **[X]**; closed-system **[ ]**
Species	Medaka (*Oryzias latipes*)
Endpoint:	Length of fish **[ ]**; Weight of fish **[ ]**; Reproduction rate **[ ]**; Other **[X]**
Exposure period:	14 days
Results:	test-A LC_{50} 88.1 mg/L NOEC 25.0 mg/L test-B LC_{50}> 100.0 mg/L NOEC 25.0 mg/L
Analytical monitoring:	Yes **[X]** No **[ ]** ? **[ ]**
Method:	OECD TG 204
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:purity:	> 99.0 % (Wako Pure Chemical Industries, LTD. Lot No. WTK0815)
Remarks:	The examination was performed on two conditions, test-A and test-B were conducted at the nominal concentration of 0, 6.3, 12.5, 25.0, 50.0, 100.0 mg/L and 25.0, 50.0, 100.0 mg/L, respectively. Test-A was carried out without adjusting pH of test solution, and test-B was carried out after test solution was adjusted to neutrality, since the test solution of 2,2,6,6-Tetramethyl-4-piperidin-4-ol was alkalinity.
Reference:	Environmental Agency of Japan, (1997). Ecotoxicity testing report, Test No. NMMP/E09/5070, unpublished data.

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

4.2.1 Daphnia

(a)

Preferred result

Type of test:	static **[X]**; semi-static **[ ]**; flow-through **[ ]**; other *(e.g. field test)* **[ ]**; open-system **[X]**; closed-system **[ ]**
Species:	Daphnia (*Daphnia magna*)
Exposure period:	48 h
Results:	EC_{50} (24 h) 130.1 mg/L EC_{50} (48 h) 100.1 mg/L NOEC (48 h) 61.7 mg/L
Analytical monitoring:	Yes **[X]** No **[ ]** ? **[ ]**
Method:	OECD TG 202
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance: purity:	> 99.0 % (Wako Pure Chemical Industries, LTD. Lot No. WTK0815)
Remarks:	Test was conducted at the nominal concentraion of 0, 10.6, 19.1, 34.3, 61.7, 111.1, 200.0 mg/L. When the test solution was analysed at start and end of the test, the measured concentrations showed more than

90 % of the nominal concentrations. The EC_{50} values was calculated based on nominal concentrations value.

Reference: Environmental Agency of Japan, (1997). Ecotoxicity testing report, Test No. NMMP/E09/2070, unpublished data.

(b)

Type of test: static **[X]**; semi-static **[ ]**; flow-through **[ ]**; other *(e.g. field test)* **[ ]**; open-system **[X]**; closed-system **[ ]**

Species: Daphnia (*Daphnia magna*)

Exposure period: 24 h

Results: EC_0 100 mg/L
EC_{50} 560 mg/L
EC_{100} > 1000 mg/L

Analytical monitoring: Yes **[ ]** No **[X]** ? **[ ]**

Method: Directive 84/449/EEC, C.2 "Acute toxicity for Daphnia"

GLP: Yes **[ ]** No **[X]** ? **[ ]**

Test substance: purity: > 99.0 %

Remarks: Not stated.

Reference: Ciba additive GmbH Lampertheim (Ciba-Geigy, Test No. 894486)

4.2.2 Other aquatic organisms

No data available.

4.3 TOXICITY TO AQUATIC PLANTS, e.g. algae

(a)

Preferred result

Species: *Selenastrum caricornutum* ATCC 22662

Endpoint: Biomass **[X]**; Growth rate **[X]**; Other **[ ]**

Exposure period: 72 h

Results:

Biomass EC_{50} 107 mg/L
NOEC 76 mg/L

Growth rate EC_{50} (24 - 48) 127 mg/L
EC_{50} (24 - 72) 155 mg/L
NOEC (24 - 72) 76 mg/L

Analytical monitoring: Yes **[X]** No **[ ]** ? **[ ]**

Method: OECD TG 201
open-system **[ ]**; closed-system **[X]**

GLP: Yes **[X]** No **[ ]** ? **[ ]**

Test substance: purity: > 99.0 % (Wako Pure Chemical Industries, LTD. Lot No. WT K0815)

Remarks: Static system. The EC_{50} value for biomass was calculated based on nominal concentrations (42, 76, 137, 247, 444, 800 mg/mL).

Reference: Environmental Agency of Japan, (1997). Ecotoxicity testing report, Test No. NMMP/E09/1070, unpublished data.

(b)

Species: Algae (*Scenedesmus subspicatus*)

Endpoint: Biomass **[ ]**; Growth rate **[X]**; Other **[ ]**

Exposure period: 72 h

Results: EC_{50} 158 mg/L
NOEC 10 mg/L

Analytical monitoring: Yes **[ ]** No **[X]** ? **[ ]**

Method: Directive 87/307/EEC, part C. P. 89 "Algae inhibition test"
open-system **[ ]**; closed-system **[X]**

GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: purity: Not stated.
Remarks: Not stated.
Reference: Ciba additive GmbH Lampertheim (Ciba-Geigy, Test No. 928326)

4.4 TOXICITY TO BACTERIA

Type: Aquatic **[X]**; Field **[ ]**; Soil **[ ]**; Other **[ ]**
Species: activated sludge, domestic
Exposure Period: 3 h
Results: EC_{50} > 100 mg/L
EC_{20} > 100 mg/L
EC_{80} > 100 mg/L
Analytical monitoring: Yes **[ ]** No **[X]** ? **[ ]**
Method: Directive 87/302/EEC, part C, P. 118 "Biodegradation: Activated sludge Respiration inhibition test"
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: purity: Not stated.
Remarks: Not stated.
Reference: Ciba additive GmbH Lampertheim (Ciba-Geigy, Test No. intener test)

4.5 CHRONIC TOXICITY TO AQUATIC ORGANISMS

4.5.1 CHRONIC TOXICITY TO FISH

No data available.

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

Type of test: static **[ ]**; semi-static **[X]**; flow-through **[ ]**; other *(e.g. field test)* **[ ]**; open-system **[X]**; closed-system **[ ]**
Species: Daphnia (*Daphnia magna*)
Endpoint: Mortality **[X]**; Reproduction rate **[X]**; Other **[ ]**
Exposure period: 21 days
Results: Mortality: LC_{50} > 70.0 mg/L
Reproduction: EC_{50} 46.2 mg/L
NOEC 3.7 mg/L
LOEC 6.7 mg/L
Analytical monitoring: Yes **[X]** No **[ ]** ? **[ ]**
Method: OECD TG 211
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance:purity: > 99.0 % (Wako Pure Chemical Industries, LTD. Lot No. WTK0815)
Remarks: Ten daphnia (Ten replicates; One organism per replicate) were exposed to the nominal concentrations of 0, 3.7. 6.7, 12.0, 21.6, 38.9, 70.0 mg/L. Measured concentrations were within 91.0 to 100.5 % of the nominal concentration throughout the 21 d test period. The LC_{50} value was calculated based on nominal concentrations (42, 76, 137, 247, 444, 800 mg/ml). The water analysis was not determined, since reconstituted water (M4) was used for the examination.
Reference: Environmental Agency of Japan, (1997). Ecotoxicity testing report, Test No. NMMP/E09/3070, unpublished data.

4.6 TOXICITY TO TERRESTRIAL ORGANISMS

4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

No data available.

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

No data available.

4.6.3 TOXICITY TO OTHER NON MAMMALIAN TERRESTRIAL SPECIES (INCLUDING AVIAN)

No data available.

4.7 BIOLOGICAL EFFECTS MONITORING (INCLUDING BIOMAGNIFICATION)

No data available.

4.8 BIOTRANSFORMATION AND KINETICS

No data available.

4.9 ADDITIONAL REMARKS

None.

5. TOXICITY

5.1 ACUTE TOXICITY

5.1.1 ACUTE ORAL TOXICITY

(a)
Preferd result

Type:	LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain:	Rat/Crj: CD (SD)
Value:	Male: 1482 (1239 - 1774) mg/kg b.w.: Female: 1564 (1326 - 1842) mg/kg b.w.: Discriminating dose: 590, 769, 1000, 1300, 1690, 2197
Method:	OECD TG 401
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:. purity:	> 99.8 %
Remarks:	Death of animals was observed in 1300 mg/kg and more groups of the both sexes, and sex difference was not seen. Death of animals was mostly observed at the next day of treatment. In all groups, clinical signs of decreased locomotor activity, mydriasis and blepharoptosis were observed in both sexes. Prone position, hypothermia and tremors were observed in 1300 mg/kg or higher groups of the both sexes. Moreover wasting, abdominal distension and pallor of the auricles in 1300 mg/kg and piloerection in the male of 1690 mg/kg, as well as abdominal distension, pallor of auricles and loss of fur in the females of 1690 mg/kg were observed. The change of main clinical signs (decreased locomotor activity, mydriasis, blepharoptosis) were almost recovered after 24 hours. Degree of the mydriasis at 2197 mg/kg was severe. Pathological lesions due to 2,2,6,6-Tetramethylpiperidin-4-ol were observed in stomach and duodenum of the both sexes. Pathological examination was conducted using the male and female rat which died, haemorrhage, necrosis, and vacuolar degeneration were seen in the stomach, and oedema, haemorrhage, necrosis, and vacuolar degeneration were observed in the duodenum. The cause of death was considered to be haemorrhage of digestive tract.
Reference:	Ministry of Health and Welfare, Japan (1998a): Toxicity Testing Reports of Environmental Chemicals, vol. 6, 513 - 515.

(b)

Type:	LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain:	Rat
Value:	Male > 2000 m/kg b.w. Female > 2000 m/kg b.w.
Method:	Not stated.
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Test substance:. purity:	Not stated.
Remarks:	Not stated.
Reference:	Degussa AG, Germany (1973), unpublished report (No. AO-92/ 0079)

(c)

Type:	LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain:	Rat
Value:	2413 mg/kg b.w.
Method:	OECD TG 401
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Test substance:. purity:	Not stated.

Remarks: Not stated.
Reference: Ciba additive GmbH Lampertheim (Ciba-Geigy, Test No. 831053)

5.1.2 ACUTE INHALATION TOXICITY

No data available.

5.1.3 ACUTE DERMAL TOXICITY

Type: LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain: Rat
Value: Male > 2000 mg/kg b.w.
Female > 2000 mg/kg b.w.
Method: OECD TG 402
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance:. purity: 99.7%
Remarks: Piloerecton and hunched posture were seen, being common symptoms in acute dermal tests. At the application site erythema was seen in all animals. Necrosis was observed in one male and one female. The animals recovered within 8 to 13 days.
Reference: Ciba additive GmbH Lampertheim (Ciba-Geigy, Test No. 924124)

5.1.4 ACUTE TOXICITY, OTHER ROUTES OF ADMINISTRATION

No data available.

5.2 CORROSIVENESS/IRRITATION

5.2.1 SKIN IRRITATION/CORROSION

Species/strain: Rabbit
Results: Highly corrosive **[ ]**; Corrosive **[ ]**; Highly irritating **[X]**; Irritating **[ ]**; Moderate irritating **[ ]**; Slightly irritating **[ ]**; Not irritating **[ ]**
Classification: Highly corrosive (causes severe burns) **[ ]**; Corrosive (causes burns) **[ ]**; Irritating **[ ]**; Not irritating **[ ]**
Method: OECD TG 404
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: 99.7%.
Remarks: This substance induced moderate to severe skin irritation that was not reversible after patch removal.
Reference: Ciba additive GmbH Lampertheim (Ciba-Geigy, Test No.924125)

5.2.2 EYE IRRITATION/CORROSION

No data available

5.3 SKIN SENSITIZATION

Type: Maximization test.
Species/strain: Guinea pig.
Results: Sensitizing **[X]**; Not sensitizing **[ ]**; Ambiguous **[ ]**
Classification: Sensitizing **[X]**; Not sensitizing **[ ]**
Method: OECD TG 406
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: 99.7 %

Remarks: This substance is classified as a moderate to strong sensitizer in albino guinea pigs according to the grading of Magunusson and Kligman.
Reference: Ciba additive GmbH Lampertheim (Ciba-Geigy, Test No.924127)

5.4 REPEATED DOSE TOXICITY

Species/strain: Rat/Crj: CD (SD)
Sex: Female **[ ]**; Male **[ ]**; Male/Female **[X]**; No data **[ ]**
Route of Administration: Oral (gavage)
Exposure period: Male: 48 days
Female: 41 - 52 days (from 14 days before mating to day 3 of lactation)
Frequency of treatment: daily
Post exposure observation period: None.
Dose: 0, 60, 200, 600 mg/kg/day
Control group: Yes **[X]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment; **[ ]**; Concurrent vehicle;**[X]**; Historical; **[ ]**
NOAEL: Male: < 60 mg/kg/day, Female: < 60 mg/kg/day
LOAEL: Not determined
Results: Death caused by the test substance was observed in one female of the 60 mg/kg group and three males and one female of the 600 mg/kg group.
Blepharoptosis and mydriasis in the 60 mg/kg or more groups of both sexes were observed. But, both clinical signs were observed slightly and only sporadically in 60 mg/kg/day. And spontaneous locomotor activity reduction in the 600 mg/kg group of male rats were observed.
Body weight gain was decreased in the 200 mg/kg or more groups and food consumption was increased only in the 600 mg/kg group of the both sexes. Increase of the organ weight in 600 mg/kg group was observed in adrenal of the both sexes and in liver of the male.
Pathological examination showed no abnormalities in the survival rats. However, the reddish spots of digestive tracts, the glandular mucous membrane of the stomach and the vacuolar degeneration of renal tubular epithelium were observed in the dead rats of 600 mg/kg group. These results suggest that the NOAEL for toxicity in rats of both sexes was considered to be less than 60 mg/kg/day.

Method: OECD TG 422
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance:purity: 99.8 %
Remark: None.
Reference: Ministry of Health and Welfare, Japan (1998b): Toxicity Testing Reports of Environmental Chemicals, vol. 6, 516 - 529.

5.5 GENETIC TOXICITY IN VITRO

A. BACTERIAL TEST

(a)
Preferd result
Type: Bacterial reverse mutation assay
System of testing: *Salmonella typhimurium* TA100, TA1535, TA98, TA1537
Escherichia coli WP2 *uvr*A
Concentration: - S9mix; 0, 156, 313, 625, 1250, 2500, 5000 ug/plate
+S9mix; 0, 156, 313, 625, 1250, 2500, 5000 ug/plate
Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**
Results:

Cytotoxicity conc: With metabolic activation: 2500 ug/plate; TA100, TA1537
5000 ug/plate; TA98, TA 1535, WP2 uvrA
Without metabolic activation: 2500 ug/plate; TA100, TA98, TA1537
5000 ug/plate; TA1535, WP2 uvrA

Precipitation: None.

Genotoxic effects:

	+	?	-
With metabolic activation:	[ ]	[ ]	[X]
Without metabolic activation:	[ ]	[ ]	[X]

Method: Guidline for Screening Mutagenicity Testing of Chemicals (Japan) and OECD TG 471 and TG 472

GLP: Yes **[X]** No **[ ]** ? **[ ]**

Test substance:purity: > 99.8 %

Remarks: The examination was carried out on the following test conditions.
Procedures: Pre-incubation method.
Solvent: Distilled water.
Positive control: -S9 mix; AF-2 (TA100, TA98), Sodium azide(TA1535)
ENNG (WP2 uvrA) and 9-Aminoanthracene (TA1537)
+S9 mix; 2-Aminoanthracene (all strains)
S9: Rat liver, induced with phenobarbital and 5, 6-benzoflavone.
Plates/test: 3
Number of replicates: 2

Reference: Ministry of Health and Welfare, Japan (1998c), Toxicity Testing Reports of Environmental Chemicals, vol. 6, 530 - 533.

(b)

Type: Bacterial reverse mutation assay

System of testing: *Salmonella typhimurium* TA100, TA1535, TA98, TA1537

Concentration: 20, 80, 320, 1280, 5120 ug/0.1 ml

Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**

Results:

Genotoxic effects:

	+	?	-
With metabolic activation:	[ ]	[ ]	[X]
Without metabolic activation:	[ ]	[ ]	[X]

Method: other: Ames, B.N., Lee, F.D., Durston, W.E., Proc, Natl. Acad. Sci. USA 70, 782 - 786

GLP: Yes **[ ]** No **[X]** ? **[ ]**

Test substance: purity: Not stated.

Remarks: The examination was performed in 1973.

Reference: Ciba additive GmbH Lampertheim (Ciba-Geigy, Test No.8331054)

B. NON-BACTERIAL IN VITRO TEST

Type: *In vitro* mammalian chromosomal aberration test

System of testing: Chinese Hamster lung (CHL/IU) cells

Concentration: -S9 mix (24 and 48 h continuous treatment): 0, 100, 200, 400, 800 ug/ml
-S9 mix (6h short treatment): 0, 100, 200, 400, 800 ug/ml
-S9 mix (6h short treatment): 0, 800, 1000, 1200 ug/ml
-S9 mix (6h short treatment): 0, 1000, 1500, 2000 ug/ml
+S9 mix (6h short treatment):0, 100, 200, 400, 800 ug/ml

Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**

Results:

Cytotoxicity conc: With metabolic activation: (6h short treatment): 726 ug/ml
Without metabolic activation: (6h short treatment): 565 ug/ml
Without metabolic activation: (24h continuous treatment): 572 ug/ml
Without metabolic activation: (48h continuous treatment): 683 ug/ml

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

Method: Guidline for Screening Mutagenicity Testing of Chemicals (Japan) and OECD 473
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance:purity: > 99.8 %
Remarks: Test condition and the results were as follows;
Solvent: JP saline
Positive control: -S9 mix; Mitomycin C
+S9 mix; Benzo[a]pyrene
S9 from rat liver was induced with phenobarbital and 5,6-benzoflavone.
Plates/test: 2
Structural chromosomal aberrations (17.5 %, including gaps) were induced in 2000 ug/ml of the 6 h short-term treatment without S9 mix (-S9).
Polyploidy was not induced in any treatment groups of with or without S9 mix.
The additional examination of the substance in high concentration was performed from the results of mitotic index. The substance induced structural chromosomal aberrations in 2000 ug/ml of without S9 mix (6 h short treatment).
See Appendix 2.
Reference: Ministry of Health and Welfare, Japan (1998d), Toxicity Testing Reports of Environmental Chemicals, vol. 6, 534 - 538.

5.6 GENETIC TOXICITY IN VIVO

Type: Micronucleus assay
Species/strain: Rat /Crj:CD(SD)
Sex Male
Route of Administration: Oral (by gavage)
Exposure period: 2 days
Doses: 0, 250, 500, 1000, 1500 mg/kg b.w.
Results: negative
Method: OECD TG 474
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance:. purity: > 99.92 %
Remarks: This examination was performed to used only the male rats, since the difference hardly showed between male and female in the single oral acute toxicity test.
Reference: Mitsui Chemicals Inc. (2001f): unpublished data

5.7 CARCINOGENICITY

No data available

5.8 TOXICITY TO REPRODUCTION

Type: Fertility **[ ]**; One-generation study **[ ]**; Two-generation study **[ ]**; Other **[X]**
Species/strain: Rat/Crj: CD (SD)
Sex: Female **[ ]**; Male **[ ]**; Male/Female **[X]**; No data **[ ]**
Route of Administration: Oral (gavage)

Exposure period:	Male: 48 days Female: 41 - 52 days (from 14 days before mating to day 3 of lactation)
Frequency of treatment:	daily
Post exposure observation period:	None.
Premating exposure period:	Male: 14 days, Female: 14 days
Duration of the test:	Male: 49 days, Female: 42 - 53 days
Doses:	0, 60, 200, 600 mg/kg/day
Control group:	Yes **[X]**; No **[ ]**; No data **[ ]**; Concurrent no treatment **[ ]**; Concurrent vehicle **[X]**; Historical **[ ]**
NOEL Parental:	Male: > 600 mg/kg/day, Female: 200 mg/kg/day
NOEL F1 Offspring:	200 mg/kg/day
Results:	As for the reproductive ability of parent rats, no effects were detected in males but on estrous cycle examination, continuous diestrus was observed in three females of the 600 mg/kg group and the mean estrous cycle of this group showed extension compared with the control group.

There were no effects of the test substance on the copulation or fertility indices. With regard to the effects on neonates, viability on day 4 of lactation was decreased in the 600 mg/kg group, and male and female pups of the 600 mg/kg group showed lower body weights on day 4 of lactation. There are no significant differences in the delivery index and live birth index. Also, no external and visceral abnormalities related to the test substance were detected in any of the offspring. On the basis of these findings, NOEL of 2,2,6,6-Tetramethylpiperidin-4-ol for reproductive toxicity to parental rats were considered to be 600 mg/kg/day for males, and 200 mg/kg/day for females, respectively. Moreover, NOEL of the test substance to F1 offspring was considered to be 200 mg/kg/day.

Method:	OECD TG 422, combined repeat dose and reproductive/developmental toxicity screening test.
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance: purity:	> 99.8 %
Remarks:	External or visceral abnormalities related to the test substance were not observed in any of the offspring.
Reference:	Ministry of Health and Welfare, Japan (1998e), Toxicity Testing Reports of Environmental Chemicals, vol. 6, 513 - 515.

5.9 DEVELOPMENTAL TOXICITY/ TERATOGENICITY

See 5.8

5.10 OTHER RELEVANT INFORMATION

A. Specific toxicities:

No data available.

B. Toxicodynamics, toxicokinetics:

No data available.

5.11 EXPERIENCE WITH HUMAN EXPOSURE

No data available.

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APPENDIXES

Appendix I. Parameters used in calculation of distribution by Mackay level III Fugacity model.

Substance: 2,2,6,6-Tetramethylpiperidin-4-ol

Scenario 1

Compartment	Emission rate [kg/h]	Concentration [g/m^3]	Amount [kg]	Percent [%]	Transformation rate [kg/h]	
					Reaction [kg/h]	Advection [kg/h]
Air	1000	1.3 E-07	1.3 E+03	0.4	1.8 E+02	1.3 E+01
Water	0	5.8 E-03	1.2 E+05	32.5	2.2 E+02	1.2 E+02
Soil	0	1.5 E+01	2.4 E+05	67.0	4.6 E+02	
Sediment		3.8 E+03	3.8 E+02	0.1	2.4 E-01	7.5 E-03
		Total amount	3.6 E+05			

Scenario 2

Compartment	Emission rate [kg/h]	Concentration [g/m^3]	Amount [kg]	Percent [%]	Transformation rate [kg/h]	
					Reaction [kg/h]	Advection [kg/h]
Air	0	3.7 E-12	3.7 E-02	0.0	5.2 E-03	3.7 E-04
Water	1000	1.7 E-02	3.4 E+05	99.7	6.6 E+00	3.4 E+02
Soil	0	4.2 E-06	6.8 E+01	0.0	1.3 E-02	
Sediment		1.1 E-02	1.1 E+03	0.3	7.1 E-01	2.2 E-02
		Total amount	3.4 E+05			

Scenario 3

Compartment	Emission rate [kg/h]	Concentration [g/m^3]	Amount [kg]	Percent [%]	Transformation rate [kg/h]	
					Reaction [kg/h]	Advection [kg/h]
Air	0	5.6 E-12	5.6 E+00	0.0	7.8 E-01	5.6 E-02
Water	0	4.8 E-03	9.6 E+04	20.4	1.8 E+02	9.6 E+01
Soil	1000	2.3 E-01	3.7 E+05	79.6	7.2 E+00	
Sediment		3.1 E-03	3.1 E+02	0.1	2.0 E-01	6.2 E-03
		Total amount	4.7 E+05			

Scenario 4

Compartment	Emission rate [kg/h]	Concentration [g/m^3]	Amount [kg]	Percent [%]	Transformation rate [kg/h]	
					Reaction [kg/h]	Advection [kg/h]
Air	600	7.9 E-08	7.9 E+02	0.2	1.1 E+02	7.9 E+00
Water	300	9.1 E-03	1.8 E+05	49.9	3.5 E+02	1.8 E+02
Soil	100	1.1 E-01	1.8 E+05	49.8	3.5 E+02	
Sediment		5.9 E-03	5.9 E+02	0.2	3.8 E-01	1.2 E-02
		Total amount	3.6 E+05			

(Continued)

Appendix I. (Continued)

Physico-chemical parameter

Molecular weight		157.26	Calculated
Melting point[°C]		130.6	Measured
Vapour pressure [Pa]		2.60E-01	Measured
Water solubility [g/m^3]		100000	Temporary
log P_{OW}		0.24	Measured
Half lives [h] (Note 1)	In air	5	Estimated
	In water	360	Estimated
	In soil	360	Estimated
	In sediment	1080	Estimated

Temperature [°C]	25

Environmental parameter

		Volume [m^3]	Depth [m]	Area [m^2]	Organic carbon content [-]	Lipid content [-]	Density [kg/m^3]	Residence Time [h]
Bulk air	Air	1.0E+13					1.2	100
	Particles	2.0E+03						
	Total	1.0E+13	1000	1E+10				
Bulk water	Water	2.0E+10					1000	1000
	Particles	1.0E+06			0.04		1500	
	Fish	2.0E+05				0.05	1000	
	Total	2.0E+10	10	2E+09				
Bulk soil	Air	3.2E+08					1.2	
	Water	4.8E+08					1000	
	Solid	8.0E+08			0.04		2400	
	Total	1.6E+09	0.2	8E+09				
Bulk Sediment	Water	8.0E+07					1000	
	Solid	2.0E+07			0.06		2400	50000
	Total	1.0E+08	0.05	2E+09				

Intermedia transport parameter
[m/h]

Air side air-water MTC	5	Soil air boundary layer MTC	5
Water side air-water MTC	0.05	Sediment-water MTC	1E-04
Rain rate	1E-04	Sediment deposition	5E-07
Aerosol deposition	6E-10	Sediment resuspension	2E-07
Soil air phase diffusion MTC	0.02	Soil water runoff	5E-05
Soil water phase diffusion MTC	1E-05	Soil solid runoff	1E-08

(Note 1) The half life in air is estimated by using AOP Win (ver.1.86). See section 3.1.1. Other half lives are estimated according to the method specified in the EU-TGD (European Commission, 1996).

Appendix ? Results of the chromosomal aberration test (continuous treatment assay) [main test]

Test substance: 2,2,6,6-Tetramethyl-4-hydroxypiperidine

Treatment	Exposure time (h)	Concentration (μg/mL)	Number of cells analyzed	Number of polyploid cells		Number and incidence of structural aberrant cells[1]								
				(%)	Judge-ment[2]	gap	Chromatid type		Chromosome type		frg	Total		Judge-ment[2]
						gap	ctb	cte	csb	cse		-gap	+gap	
Solvent (Saline)	24	0	100	0		0	0	0	0	0	0	0	0	
			100	0		0	0	0	0	0	0	0	0	
			200	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	48	0	100	0		0	0	0	0	0	0	0	0	
			100	0		0	0	0	2	0	0	2	2	
			200	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0)	0 (0.0)	0 (0.0)	2 (1.0)	2 (1.0)	
Test substance	24	100	100	0		0	0	0	0	0	0	0	0	
			100	0	-	0	1	0	0	0	0	1	1	-
			200	0 (0.0)		0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	
		200	100	0		0	1	1	0	0	0	2	2	
			100	0	-	0	0	0	1	0	0	1	1	-
			200	0 (0.0)		0 (0.0)	1 (0.5)	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)	3 (1.5)	3 (1.5)	
		400	100	0		0	0	0	1	0	0	1	1	
			100	0	-	0	0	0	0	0	0	0	0	-
			200	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	
		800	100	1		0	0	0	0	0	0	0	0	
			76	0	-	0	0	0	0	0	0	0	0	-
			176	1 (0.6)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	48	100	100	0		0	1	0	0	0	0	1	1	
			100	0	-	1	0	0	1	0	0	1	2	-
			200	0 (0.0)		1 (0.5)	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	2 (1.0)	3 (1.5)	
		200	100	0		0	0	0	0	0	0	0	0	
			100	0	-	1	0	0	1	0	0	1	2	-
			200	0 (0.0)		1 (0.5)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.5)	2 (1.0)	
		400	100	0		0	0	0	0	0	0	0	0	
			100	0	-	0	0	0	0	0	0	0	0	-
			200	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
		800	100	3		0	0	3	2	0	0	4	4	
			100	1	-	0	0	0	0	0	0	0	0	-
			200	4 (2.0)		0 (0.0)	0 (0.0)	3 (1.5)	2 (1.0)	0 (0.0)	0 (0.0)	4 (2.0)	4 (2.0)	
Positive control (MMC)	24	0.03	100	0		0	7	19	0	0	0	24	24	
			100	0	-	0	8	22	3	1	0	34	34	+
			200	0 (0.0)		0 (0.0)	15 (7.5)	41 (20.5)	3 (1.5)	1 (0.5)	0 (0.0)	58 (29.0)	58 (29.0)	
	48	0.03	100	0		2	9	22	4	0	0	33	34	
			100	0	-	0	5	28	2	0	0	31	31	+
			200	0 (0.0)		2 (1.0)	14 (7.0)	50 (25.0)	6 (3.0)	0 (0.0)	0 (0.0)	64 (32.0)	65 (32.5)	

[1] gap: chromatid type gap or chromosome type gap, ctb: chromatid type break, cte: chromatid type exchange, csb: chromosome type break, cse: chromosome type exchange, frg: fragmentation

[2] The ability of the test substance to induce chromosomal aberrations was judged to be negative (-) when both structural and numerical aberrations are observed at an incidence of lower than 5% (+gap), inconclusive (±) when the structural or numerical aberrations are observed at an incidence of 5% or higher, but lower than 10%, and positive (+) when the structural or numerical aberrations are observed at an incidence of 10% or higher.

Saline: Japanese Pharmacopoeia saline, MMC: Mitomycin C

Appendix ? (Continued) Results of the chromosomal aberration test (short-term treatment assay) [main test]

Test substance: 2,2,6,6-Tetramethyl-4-hydroxypiperidine

Treatment	With or without S9 mix	Concentration (μg/mL)	Number of cells analyzed	Number of polyploid cells		Number and incidence of structural aberrant cells[1]								
				(%)	Judge-ment[2]	gap	Chromatid type		Chromosome type		frg	Total		Judge-ment[2]
						gap	ctb	cte	csb	cse		-gap	+gap	
Solvent (Saline)	-	0	100	0		0	0	0	0	1	0	1	1	
			100	0		0	1	0	0	0	0	1	1	
			200	0 (0.0)		0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	2 (1.0)	2 (1.0)	
	+	0	100	1		0	0	0	0	0	0	0	0	
			100	0		0	0	0	0	0	0	0	0	
			200	1 (0.5)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Test substance	-	100	100	0	-	0	0	0	0	0	0	0	0	-
			100	0		0	1	0	0	0	0	1	1	
			200	0 (0.0)		0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	
		200	100	1	-	0	0	0	1	0	0	1	1	-
			100	0		0	0	0	0	0	0	0	0	
			200	1 (0.5)		0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	
		400	100	0	-	0	0	0	0	1	0	1	1	-
			100	0		0	1	0	0	0	0	1	1	
			200	0 (0.0)		0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	2 (1.0)	2 (1.0)	
		800	100	1	-	0	0	0	0	0	0	0	0	-
			100	0		0	0	0	0	1	0	1	1	
			200	1 (0.5)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)	1 (0.5)	
	+	100	100	0	-	0	0	0	0	0	0	0	0	-
			100	0		0	0	0	0	0	0	0	0	
			200	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
		200	100	0	-	0	0	0	0	0	0	0	0	-
			100	0		0	0	0	1	0	0	1	1	
			200	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	
		400	100	0	-	0	1	0	0	0	0	1	1	-
			100	0		0	0	0	1	0	0	1	1	
			200	0 (0.0)		0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	2 (1.0)	2 (1.0)	
		800	100	0	-	0	0	0	0	0	0	0	0	-
			100	0		0	1	0	0	0	0	1	1	
			200	0 (0.0)		0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	
Positive control (BP)	-	20	100	0	-	0	0	0	1	0	0	1	1	-
			100	0		0	0	0	0	0	0	0	0	
			200	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	
	+	20	100	0	-	1	9	79	1	0	0	80	80	+
			100	0		1	10	78	0	0	0	80	80	
			200	0 (0.0)		2 (1.0)	19 (9.5)	157 (78.5)	1 (0.5)	0 (0.0)	0 (0.0)	160 (80.0)	160 (80.0)	

[1] gap: chromatid type gap or chromosome type gap, ctb: chromatid type break, cte: chromatid type exchange, csb: chromosome type break, cse: chromosome type exchange, frg: fragmentation

[2] The ability of the test substance to induce chromosomal aberrations was judged to be negative (-) when both structural and numerical aberrations are observed at an incidence of lower than 5% (+gap), inconclusive (±) when the structural or numerical aberrations are observed at an incidence of 5% or higher, but lower than 10%, and positive (+) when the structural or numerical aberrations are observed at an incidence of 10% or higher.
Content of S9: 5%, Test substance exposure time: 6 hours, Recovery time after exposure: 18 hours

Saline: Japanese Pharmacopoeia saline, BP: Benzo [a] pyrene

Appendix ? (Continued) Results of the chromosomal aberration test (short-term treatment assay) [additional test 1]

Test substance: 2,2,6,6-Tetramethyl-4-hydroxypiperidine

Treatment	With or without S9 mix	Concentration (Hg/mL)	Number of cells analyzed	Number of polyploid cells		Number and incidence of structural aberrant cells[1]								
				(%)	Judge-ment[2]	gap	Chromatid type		Chromosome type		frg	Total		Judge-ment[2]
						gap	ctb	cte	csb	cse		-gap	+gap	
Solvent (Saline)	-	0	100	0		0	0	0	0	0	0	0	0	
			100	0		0	0	0	0	0	0	0	0	
			200	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Test substance	-	800	100	1	-	0	0	0	0	0	0	0	0	-
			100	0		0	0	1	0	0	0	1	1	
			200	1 (0.5)		0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	
		1000	100	1	-	0	0	0	0	0	0	0	0	-
			100	1		0	0	0	0	0	0	0	0	
			200	2 (1.0)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
		1200	100	1	-	0	0	0	0	1	0	1	1	-
			100	0		0	0	1	0	0	0	1	1	
			200	1 (0.5)		0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)	2 (1.0)	2 (1.0)	
Positive control (BP)	-	20	100	0	-	0	0	0	1	0	0	1	1	-
			100	0		0	1	0	0	0	0	1	1	
			200	0 (0.0)		0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	2 (1.0)	2 (1.0)	

[1] gap: chromatid type gap or chromosome type gap, ctb: chromatid type break, cte: chromatid type exchange, csb: chromosome type break, cse: chromosome type exchange, frg: fragmentation

[2] The ability of the test substance to induce chromosomal aberrations was judged to be negative (-) when both structural and numerical aberrations are observed at an incidence of lower than 5% (+gap), inconclusive (±) when the structural or numerical aberrations are observed at an incidence of 5% or higher, but lower than 10%, and positive (+) when the structural or numerical aberrations are observed at an incidence of 10% or higher.

Content of S9: 5%, Test substance exposure time: 6 hours, Recovery time after exposure: 18 hours

Saline: Japanese Pharmacopoeia saline, BP: Benzo [a] pyrene

Appendix ? (Continued) Results of the chromosomal aberration test (short-term treatment assay) [additional test 2]

Test substance: 2,2,6,6-Tetramethyl-4-hydroxypiperidine

Treatment	With or without S9 mix	Concentration (μg/mL)	Number of cells analyzed	Number of polyploid cells		Number and incidence of structural aberrant cells[1]								
				(%)	Judge-ment[2]	gap	Chromatid type		Chromosome type		frg	Total		Judge-ment[2]
						gap	ctb	cte	csb	cse		-gap	+gap	
Solvent (Saline)	-	0	100	0		0	0	0	0	0	0	0	0	
			100	0		0	0	0	0	0	0	0	0	
			200	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Test substance	-	1000	100	1	-	0	0	0	0	0	0	0	0	-
			100	0		0	0	0	0	0	0	0	0	
			200	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
		1500	100	6	-	0	1	0	0	0	0	1	1	-
			100	2		2	0	0	0	0	0	0	2	
			200	8 (4.0)		2 (1.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	3 (1.5)	
		2000	100	7	±	1	0	4	0	1	0	5	6	±
			Toxic			Toxic								
			100	7 (7.0)		1 (1.0)	0 (0.0)	4 (4.0)	0 (0.0)	1 (1.0)	0 (0.0)	5 (5.0)	6 (6.0)	
Positive control (BP)	-	20	100	0	-	0	0	0	0	0	0	0	0	-
			100	0		0	0	0	0	0	0	0	0	
			200	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	

[1] gap: chromatid type gap or chromosome type gap, ctb: chromatid type break, cte: chromatid type exchange, csb: chromosome type break, cse: chromosome type exchange, frg: fragmentation

[2] The ability of the test substance to induce chromosomal aberrations was judged to be negative (-) when both structural and numerical aberrations are observed at an incidence of lower than 5% (+gap), inconclusive (±) when the structural or numerical aberrations are observed at an incidence of 5% or higher, but lower than 10%, and positive (+) when the structural or numerical aberrations are observed at an incidence of 10% or higher.

Content of S9: 5%, Test substance exposure time: 6 hours, Recovery time after exposure: 18 hours

Saline: Japanese Pharmacopoeia saline, BP: Benzo [a] pyrene

Appendix ? (Continued) Results of the chromosomal aberration test (short-term treatment assay) [additional test 3]

Test substance: 2,2,6,6-Tetramethyl-4-hydroxypiperidine

Treatment	With or without S9 mix	Concentration (μg/mL)	Number of cells analyzed	Number of polyploid cells		Number and incidence of structural aberrant cells[1]								
				'	Judge-ment[2]	gap	Chromatid type		Chromosome type		frg	Total		Judge-ment[2]
						gap	ctb	cte	csb	cse		-gap	+gap	
Solvent (Saline)	-	0	100	0		1	2	0	0	0	0	2	3	
			100	0		0	1	0	0	0	0	1	1	
			200	0 (0.0)		1 (0.5)	3 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.5)	4 (2.0)	
Test substance	-	1000	100	0	-	1	0	0	0	0	0	0	1	-
			100	0		0	0	0	0	0	0	0	0	
			200	0 (0.0)		1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	
		1500	100	1	-	0	1	2	1	0	0	4	4	-
			100	0		0	0	2	0	0	0	2	2	
			200	1 (0.5)		0 (0.0)	1 (0.5)	4 (2.0)	1 (0.5)	0 (0.0)	0 (0.0)	6 (3.0)	6 (3.0)	
		2000	100	0	-	0	5	15	0	0	0	18	18	+
			100	0		1	0	17	0	0	0	17	17	
			200	0 (0.0)		1 (2.5)	5 (2.5)	32 (16.0)	0 (0.0)	0 (0.0)	0 (0.0)	35 (17.5)	35 (17.5)	
Positive control (BP)	-	20	100	0	-	0	0	0	0	0	0	0	0	-
			100	0		0	0	0	0	0	0	0	0	
			200	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	

[1] gap: chromatid type gap or chromosome type gap, ctb: chromatid type break, cte: chromatid type exchange, csb: chromosome type break, cse: chromosome type exchange, frg: fragmentation
[2] The ability of the test substance to induce chromosomal aberrations was judged to be negative (-) when both structural and numerical aberrations are observed at an incidence of lower than 5% (+gap), inconclusive (±) when the structural or numerical aberrations are observed at an incidence of 5% or higher, but lower than 10%, and positive (+) when the structural or numerical aberrations are observed at an incidence of 10% or higher.
Content of S9: 5%, Test substance exposure time: 6 hours, Recovery time after exposure: 18 hours

Saline: Japanese Pharmacopoeia saline, BP: Benzo [a] pyrene

Appendix ? (Continued) Mitotic index (continuous treatment assay) [main test]

Treatment	Exposure time (h)	Concentration (μg/mL)	Number of cells analyzed	Number of mitotic cells	Mitotic index (%)	Mitotic activity (%)
Negative control (Saline)	24	0	2000	178	8.9	100
2,2,6,6-tetramethyl-4-hydroxypiperidine	24	100	2000	151	7.6	85
	24	200	2000	157	7.9	88
	24	400	2000	144	7.2	81
	24	800	2000	18	0.9	10
Positive control (MMC)	24	0.03	2000	86	4.3	48
Negative control (Saline)	48	0	2000	111	5.6	100
2,2,6,6-tetramethyl-4-hydroxypiperidine	48	100	2000	90	4.5	81
	48	200	2000	102	5.1	92
	48	400	2000	91	4.6	82
	48	800	2000	26	1.3	23
Positive control (MMC)	48	0.03	2000	75	3.8	68

Saline: Japanese Pharmacopoeia saline
MMC: Mitomycin C

Appendix ? (Continued) Mitotic index (short-term treatment assay) [main test]

Treatment	With or without S9 mix	Concentration (μg/mL)	Number of cells analyzed	Number of mitotic cells	Mitotic index (%)	Mitotic activity (%)
Negative control (Saline)	-	0	2000	135	6.8	100
2,2,6,6-tetramethyl-4-hydroxypiperidine	-	100	2000	142	7.1	105
	-	200	2000	167	8.4	124
	-	400	2000	141	7.1	104
	-	800	2000	132	6.6	98
Positive control (BP)	-	20	2000	159	8.0	118
Negative control (Saline)	+	0	2000	199	10.0	100
2,2,6,6-tetramethyl-4-hydroxypiperidine	+	100	2000	183	9.2	92
	+	200	2000	195	9.8	98
	+	400	2000	188	9.4	94
	+	800	2000	188	9.4	94
Positive control (BP)	+	20	2000	30	1.5	15

Saline: Japanese Pharmacopoeia saline

BP: Benzo [a] pyrene

Appendix ? (Continued) Mitotic index (short-term treatment assay) [additional test 1]

Treatment	With or without S9 mix	Concentration (μg/mL)	Number of cells analyzed	Number of mitotic cells	Mitotic index (%)	Mitotic activity (%)
Negative control (Saline)	-	0	2000	74	3.7	100
2,2,6,6-tetramethyl-4-hydroxypiperidine	-	800	2000	155	7.8	209
	-	1000	2000	152	7.6	205
	-	1200	2000	125	6.3	169
Positive control (BP)	-	20	2000	59	3.0	80

Saline: Japanese Pharmacopoeia saline

BP: Benzo [a] pyrene

Appendix ? (Continued) Mitotic index (short-term treatment assay) [additional test 2]

Treatment	With or without S9 mix	Concentration (μg/mL)	Number of cells analyzed	Number of mitotic cells	Mitotic index (%)	Mitotic activity (%)
Negative control (Saline)	-	0	2000	90	4.5	100
2,2,6,6-tetramethyl-4-hydroxypiperidine	-	1000	2000	109	5.5	121
	-	1500	2000	68	3.4	76
	-	2000	2000	32	1.6	36
Positive control (BP)	-	20	2000	99	5.0	110

Saline: Japanese Pharmacopoeia saline

BP: Benzo [a] pyrene

Appendix ? (Continued) Mitotic index (short-term treatment assay) [additional test 3]

Treatment	With or without S9 mix	Concentration (μg/mL)	Number of cells analyzed	Number of mitotic cells	Mitotic index (%)	Mitotic activity (%)
Negative control (Saline)	-	0	2000	101	5.1	100
2,2,6,6-tetramethyl-4-hydroxypiperidine	-	1000	2000	145	7.3	144
	-	1500	2000	73	3.7	72
	-	2000	2000	66	3.3	65
Positive control (BP)	-	20	2000	104	5.2	103

Saline: Japanese Pharmacopoeia saline
BP: Benzo [a] pyrene

ROBUST STUDY SUMMARIES

For 2,2,6,6-Tetramethylpiperidin-4-ol
CAS No. 2403 - 88 - 5

Sponsor Country: Japan

DATE: 1 February, 2002

PHYSICAL/CHEMICAL ELEMENTS

MELTING POINT

TEST SUBSTANCE

- **Identity:** 2,2,6,6-Tetramethylpiperidin-4-ol (CAS No. 2403-88-5)
- **Remarks:** Source: Wako Pure Chemical Industries, Ltd.

METHOD

- **Method/guideline:** Unspecified.
- **GLP:** Not stated.
- **Year:** Not stated.
- **Remarks:** Not stated

RESULTS

- **Melting point value:** 130.6 °C
- **Decomposition:** Not stated.
- **Sublimation:** Not stated.
- **Remarks:** Not stated.

CONCLUSIONS

Melting point is 130.6 °C.

DATA QUALITY

- **Reliabilities:** Key study
- **Remarks:** Not stated

REFERENCES (Free Text)

Ministry of International Trade and Industry, Japan (1998). Report No. K-1364 (5-0776), unpublished data.

OTHER

- **Last changed:**
- **Order number for sorting**
- **Remarks:**

BOILING POINT

TEST SUBSTANCE

- **Identity:** 2,2,6,6-Tetramethylpiperidin-4-ol (CAS No. 2403-88-5)
- **Remarks:** Source: Aldrich Chemical co., Inc.

METHOD

- **Method:** Not specified.
- **GLP:** Not stated.
- **Year:** Not stated.
- **Remarks:** Not stated.

RESULTS

- **Boiling point value:** 212 - 215 °C
- **Pressure:** Not stated.
- **Pressure unit:** Not stated.
- **Decomposition:** Not stated.
- **Remarks:** Not stated.

CONCLUSIONS

Boiling point is 212 - 215 °C

DATA QUALITY

- **Reliabilities:** Key study
- **Remarks:** Not stated

REFERENCES

Ministry of International Trade and Industry, Japan (1998). Report No. K-1364 (5-0776), unpublished data.

OTHER

- **Last changed:**
- **Order number for sorting**
- **Remarks:**

DENSITY

TEST SUBSTANCE

- **Identity:** 2,2,6,6-Tetramethylpiperidin-4-ol (CAS No. 2403-88-5)
- **Remarks:** Source: Tokyo Kasei Kogyo co., Ltd.
  Purity: 99.9 %

METHOD

- **Method:** JIS K 7112-1980
- **GLP:** Yes
- **Year:** 1998
- **Remarks:** Not stated.

RESULTS

- **Density of the crystal:** 1.062 g/cm^3
- **Temperature:** 25 °C
- **Decomposition:** Not stated.
- **Remarks:** Not stated.

CONCLUSIONS

The density is 1.062 g/cm^3 at 25 °C

DATA QUALITY

- **Reliabilities:** Key study
- **Remarks:** Well conducted study, carried out by Chemicals Evaluation and **Research**
  Institute (Japan).

REFERENCES

Ministry of International Trade and Industry, Japan (1998). Report No. K-1364 (5-0776), unpublished data.

OTHER

- **Last changed:**
- **Order number for sorting**
- **Remarks:** Bulk density is 730 kg/m^3 (IUCLID, 2000: Ciba additive GmbH Lampertheim)

VAPOUR PRESSURE

TEST SUBSTANCE

- **Identity:** 2,2,6,6-Tetramethylpiperidin-4-ol (CAS No. 2403-88-5)
- **Remarks:** Source: Tokyo Kasei Kogyo co., Ltd.
  Purity: 99.9 %

METHOD

- **Method:** OECD TG 104
- **GLP:** Yes
- **Year:** 1998
- **Remarks:** Not stated.

RESULTS

- **Vapour Pressure value:** 2.6×10^{-1} Pa
- **Temperature:** 25 °C
- **Decomposition:** Not stated.
- **Remarks:** Not stated.

CONCLUSIONS

Vapour Pressure is 2.6×10^{-1} Pa at 25 °C

DATA QUALITY

- **Reliabilities:** Key study
- **Remarks:** Well conducted study, carried out by Chemicals Evaluation and **Research**
  Institute (Japan).

REFERENCES

Ministry of International Trade and Industry, Japan (1998). Report No. K-1364 (5-0776), unpublished data.

OTHER

- **Last changed:**
- **Order numbe r for sorting**
- **Remarks:**

PARTITION COEFFICIENT

TEST SUBSTANCE

- **Identity:** 2,2,6,6-Tetramethylpiperidin-4-ol (CAS No. 2403-88-5)
- **Remarks:** Source: Tokyo Kasei Kogyo co., Ltd.
  Purity: 99.9 %

METHOD

- **Method/guideline:** OECD TG 107.
- **GLP:** Yes
- **Year:** 1998.
- **Remarks field for Test Conditions**
  Shake Flask method.

RESULTS

- **Log P_{ow} :** 0.24
- **Temperature:** 25 °C
- **Remarks:** Not stated.

CONCLUSIONS

Log P_{ow} is 0.24 at 25 °C

DATA QUALITY

- **Reliabilities:** Key study
- **Remarks:** Well conducted study, carried out by Chemicals Evaluation and **Research**
  Institute (Japan).

REFERENCES

Ministry of International Trade and Industry, Japan (1998). Report No. K-1364 (5-0776), unpublished data.

OTHER

- **Last changed:**
- **Order number for sorting**
- **Remarks:**

WATER SOLUBILITY

TEST SUBSTANCE

- **Identity:** 2,2,6,6-Tetramethylpiperidin-4-ol (CAS No. 2403-88-5)
- **Remarks**: Source: Tokyo Kasei Kogyo co., Ltd.
  Purity: 99.9 %.

METHOD

- **Method:** OECD TG 105
- **GLP:** Yes
- **Year:** 1998.
- **Remarks:** Not stated.

RESULTS

- **Value :** > 100 g/L at 25 °C
- **Description of solubility:** Very soluble
- **pH value:** Not stated.
- **pKa value:** 9.92

Remarks: The pKa value was determined by Titration method (OECD TG 112).

CONCLUSIONS

This chemical is very soluble (> 100 g/L at 25 °C) in water.

DATA QUALITY

- **Reliabilities:** Key study
- **Remarks:** Well conducted study, carried out by Chemicals Evaluation and **Research**
  Institute (Japan).

REFERENCES

Ministry of International Trade and Industry, Japan (1998). Report No. K-1364 (5-0776), unpublished data.

OTHER

- **Last changed:**
- **Order number for sorting**
- **Remarks:**

ENVIRONMENTAL FATE AND PATHWAYS ELEMENTS

STABILITY IN WATER

TEST SUBSTANCE

- **Identity:** 2,2,6,6-Tetramethylpiperidin-4-ol (CAS No. 2403-88-5)
- **Remarks:** Source: Wako Pure Chemical Industries, Ltd.
  Purity: 99.2 %

METHOD

- **Method/guideline:** OECD TG 111
- **Type :** Hydrolysis as a function of pH
- **GLP:** Yes
- **Year:** 1998
- **Remarks:** No hydrolysis at pH 4, 7, 9

RESULTS

- **Nominal:** Not specified.
- **Measured value:** Not specified
- **Degradation:** No degradation at pH 4 pH 7 and pH 9 at 50 °C after 5 days (exposure time)
- **Half-life ($t_{(1/2)}$):** > 1 year.
- **Breakdown products:** None.
- **Remarks:**
  The half-life value was not calculated since no hydrolysis of test substance was observed.

CONCLUSIONS

This test substance is stable in aqueous water at pH 4, pH 7, and pH 9 under the condition studied.

DATA QUALITY

- **Reliabilities:** Key study
- **Remarks:** Well conducted study, carried out by Chemicals Evaluation and Research Institute (Japan).

REFERENCES

Ministry of International Trade and Industry, Japan (1998). Report No. K-1364 (5-0776), unpublished data.

OTHER

- **Last changed:**
- **Order number for sorting**
- **Remarks:**

TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS (FUGACITY)

TEST SUBSTANCE

- **Identity:** 2,2,6,6-Tetramethylpiperidin-4-ol (CAS No. 2403-88-5)
- **Remarks:** Source: Not applicable.

METHOD

- **Test :** Calculation
- **Method :** Fugacity model (Mackay level III)
- **Year :** 2001
- **Remarks :** The parameters used are shown in Appendix.

RESULTS

- **Media :** Air-Biota-Sediment-Soil-Water
- **Estimated Distribution under three emission scenarios :**

Compartment	Release100 % into air	Release 100 % into water	Release 100 % into soil
Air	0.4 %	0.0 %	0.0 %
Water	32.5 %	99.7 %	20.4 %
Soil	67.0 %	0.0 %	79.6 %
Sediment	0.1 %	0.3 %	0.1 %

Remarks:

CONCLUSIONS

If the test substance is released into water, it is expected to stay in water, but it is released into air, it is likely to be distributed in water (32.5 %) and soil (67.0 %). If it is released into soil, this substance is likely to be distributed in water (20.4 %) and soil (79.6 %).

DATA QUALITY

- **Reliabilities:** Key study
- **Remarks:** Not stated.

REFERENCES

Mitsui Chemicals Inc. (2001), unpublished data.

OTHER

- **Last changed:**
- **Order number for sorting**
- **Remarks:**

Appendix : Prameters used in calculation of distribution by Mackay level III fugacity model.

Physico-chemical parameter

Molecular weight		157.26	Calculated
Melting point [°C]		130.6	Measured
Vapour pressure [Pa]		2.6E-01	Measured
Water solubility [g/m^3]		100000	Temporary
log Kow		0.24	Measured
Half lives [h] (Note 1)	In air	5	Estimated
	In water	360	Estimated
	In soil	360	Estimated
	In sediment	1080	Estimated

Temperature [°C]	25

Environmental parameter

		Volume [m^3]	Depth [m]	Area [m^2]	Organic carbon content [-]	Lipid content [-]	Density [kg/m^3]	Residence Time [h]
Bulk air	Air	1.0E+13					1.2	100
	Particles	2.0E+03						
	Total	1.0E+13	1000	1E+10				
Bulk water	Water	2.0E+10					1000	1000
	Particles	1.0E+06			0.04		1500	
	Fish	2.0E+05				0.05	1000	
	Total	2.0E+10	10	2E+09				
Bulk soil	Air	3.2E+08					1.2	
	Water	4.8E+08					1000	
	Solid	8.0E+08			0.04		2400	
	Total	1.6E+09	0.2	8E+09				
Bulk Sediment	Water	8.0E+07					1000	
	Solid	2.0E+07			0.06		2400	50000
	Total	1.0E+08	0.05	2E+09				

Intermedia transport parameter [m/h]

Air side air-water MTC	5	Soil air boundary layer MTC	5
Water side air-water MTC	0.05	Sediment-water MTC	1E-04
Rain rate	1E-04	Sediment deposition	5E-07
Aerosol deposition	6E-10	Sediment resuspension	2E-07
Soil air phase diffusion MTC	0.02	Soil water runoff	5E-05
Soil water phase diffusion MTC	1E-05	Soil solid runoff	1E-08

(Note 1) The half life in air is estimated by using AOPWIN (ver.1.80). See section 3.1.1. Other half lives are estimated according to the method specified in the EU-TGD (European Commission, 1996).

BIODEGRADATION

TEST SUBSTANCE

- **Identity:** 2,2,6,6-Tetramethylpiperidin-4-ol (CAS No. 2403-88-5)
- **Remarks:** Source: Tokyo Kasei Kogyo co., Ltd.
  Purity: 99.2 %

METHOD

- **Method/guideline:** OECD TG 301C
- **Test Type:** Aerobic
- **GLP:** Yes
- **Year:** 1998
- **Contact time:** 28 days
- **Inoculum:**
  Non adapted standardized activated sludge, prepared as specified in the OECD 301C.

Remarks:
The concentration of the substance is 100 mg/L. The concentration of the inoculum is 30 mg/L, as suspended solid.

RESULTS

Degradation rate: (percentage reduction/exposure time)
0 % after 28 days (based on BOD)
1 % after 28 days (based on TOC)
2 % after 28 days(based on GC)

- **Degradability:** The results indicate that the chemical is not biodegradable.
- **Kinetics:** Not stated.
- **Breakdown products:** Not stated.
- **Remarks:** Not stated.

CONCLUSIONS

This chemical is not readily biodegradable.

DATA QUALITY

- **Reliabilities:** Key study
- **Remarks:** Well conducted study, carried out by Chemicals Evaluation and Research Institute (Japan).

REFERENCES

Ministry of International Trade and Industry, Japan (1998). Report No. K-1364 (5-0776), unpublished data.

OTHER

- **Last changed:**
- **Order number for sorting**
- **Remarks:**

BIOACCUMULATION

TEST SUBSTANCE

- **Identity:** 2,2,6,6-Tetramethylpiperidin-4-ol (CAS No. 2403-88-5)
- **Remarks:** Source: Tokyo Kasei Kogyo co., Ltd.
  Purity: 99.2 %

METHOD

- **Method:** MITI method (1974), corresponding to the previous OECD 305C (1981).
- **GLP:** Yes
- **Year:** 1998
- **Fish Species:** Carp (*Cyprinus carpio*)
- **Exposure Period:** 4 weeks
- **Temperature:** 25 °C
- **Concentrations:** 1.0 mg/L and 0.1 mg/L
- **Remarks:** The exposure was conducted under flow-through conditions. No elimination experiment was conducted.

RESULTS

- **Bioconcentration factor:**

Exposure conc.	5 days	11 days	15 days	21 days	28 days
1.0 mg/L	< 0.57	< 0.57	< 0.57	< 0.57	< 0.57
0.1 mg/L	< 5.7	< 5.7	< 5.7	< 5.7	< 5.7

- **Kinetics:** Not conducted
- **Remarks:** The average lipid content of carp was 2.15 %.

CONCLUSION

The BCF of the substance is less than 5.7.

DATA QUALITY

- **Reliability:** Key study
- **Remarks:** Well conducted study, carried out by Chemicals Evaluation and Research Institute (Japan).

REFERENCES (Free Text)

Ministry of International Trade and Industry, Japan (1998). Report No. K-1364 (5-0776), unpublished data.

OTHER

- **Last changed:**
- **Order number forsorting**
- **Remarks:**

ECOTOXICITY ELEMENTS

ACUTE TOXICITY TO FISH

TEST SUBSTANCE

- **Identity:** 2,2,6,6-Tetramethylpiperidin-4-ol (CAS No. 2403-88-5)
- **Remarks**: Source: Source: Tokyo Kasei Kogyo co., Ltd.
  Purity: > 99.9 %.

METHOD

- **Method/guideline followed:** OECD TG 203
- **Type:** Semi-static.
- **GLP :** Yes.
- **Year :** 1998
- **Species/Strain/Supplier:**
  Medaka (*Oryzias latipes*): Obtained from commercial domestic hatcheries.
- **Analytical monitoring :** No
- **Exposure period (h):** 96
- **Statistical methods:** Doudoroff method
- **Remarks field for Test Conditions:**

  – Test fish:
  · Acclimated for more than 12 days before testing; any groups showing no mortality for 7 days before test started.

  – Test conditions:
  · Details of test: Semi-static (water renewed every 24 hours)
  · Dilution water source: Tap water after dechlorinated by passing through activated carbon.
  Stock and test solution and how they are prepared: No solvent used. Test chemical was diluted to 1.0 wet. % with deionized water and it was diluted with the dechlorinated tap water for testing.
  · Concentrations dosing rate: Concentrations of 0, 87.5, 114, 148, 192, 250, 325, 423 mg/L were tested.
  · Vehicle/solvent and concentrations: Not used.
  Exposure vessel type: 10 fish per group in 4 L glass beaker without aeration under room light.
  · Water chemistry in test (O_2, pH) in the control and one concentration where effects were observed: Dissolved oxygen concentration and pH values were taken daily during 96 h exposure period.
  · Dissolved oxygen concentrations: 6.4 - 8.1 mg/L.
  · pH values: 8.7 - 10.0.

  – Test temperature range:
  · Water temperature at 23.9 - 24.8 °C.

RESULTS

- **Nominal concentrations :**

0, 87.5, 114, 148, 192, 250, 325, 423 (mg/L)

- **Unit :** mg/L.
- **Element value:** 96 hr-LC_{50} 237 mg/L (nominal concentration).
- **Statistical results as appropriate:** Not stated.
- **Remarks field for Results:**

  – Biological observation: Not described.
  – Table showing cumulative mortality:

Percent mortality of *Oryzias latipes* exposed to the test chemical

Nominal concentration (mg/L)	Cumulative number of dead fish (% mortality)			
	24 hour	**48 hour**	**72 hour**	**96 hour**
Control	0(0)	0(0)	0(0)	0(0)
87.5	0(0)	0(0)	0(0)	0(0)
114	0(0)	0(0)	0(0)	0(0)
148	0(0)	0(0)	0(0)	0(0)
192	0(0)	1(10)	1(10)	1(10)
250	5(50)	5(50)	6(60)	6(60)
325	10(100)	-	-	-
423	10(100)	-	-	-

  – Lowest test substance concentration causing 100 % mortality: 325 mg/L
  – Mortality of controls: No mortality observed during test period.
  – Abnormal responses: Not stated.
  – Reference substances (if used) – results: Not described.
  – Any observations: No precipitates and colour formation by the test chemical.

CONCLUSIONS

The 96 hours LC_{50} for Medaka (*Oryzias latipes*) exposed to 2,2,6,6-Tetramethylpiperidin-4-ol is 237 mg/L from the concentration-response curve.

DATA QUALITY

- **Reliabilities:** Klimisch Code: 1 = Reliable without restriction, Key study
- **Remarks field for Data Reliability:** Well conducted study, carried out by Chemicals Evaluation and Research Institute(Japan).

REFERENCES

Ministry of International Trade and Industry, Japan (1998). Report No. K-1364 (5-0776), unpublished data.

OTHER

- **Last changed :**
- **Order number for sorting :**
- **Remarks field for General Remarks :**

PROLONGED TOXICITY TO FISH

TEST SUBSTANCE

- **Identity:** 2,2,6,6-Tetramethylpiperidin-4-ol (CAS No. 2403-88-5)
- **Remarks:** Source: Wako Pure Chemical Industries, LTD. Lot No. WTK0815, Purity > 99.0 %

METHOD

- **Method/guideline followed :** OECD TG 204
- **Type:** Flow-through.
- **GLP:** Yes.
- **Year:** 1997.
- **Species/Strain/Supplier:** Medaka *Oryzias latipes*: Obtained from commercial domestic hatcheries.
- **Analytical monitoring:** Yes. Test solutions were measured by gas chromatography before and after 7 and 14 days exposure period
- **Exposure period:** 14 day.
- **Statistical methods:** Binominal method (TOXDAT MULTI-METHOD PROGRAM, USEPA) and Dunnet method were used for LC_{50} and for fish body weight difference, respectively.
- **Remarks field for Test Conditions:** The test was conducted in two conditions using non-adjusting test solution (test-A) and the neutralised test solution (test-B), since the test solution of 2,2,6,6-Tetramethylpiperidin-4-ol showed alkaline tendency.
  - Test fish:

    Acclimated for more than 12 days before testing; any groups showing no mortality for 7 days before test started. Mean body weight and mean body length of test fish were 0.14 g (0.13-0.16 g) and 2.2 cm (2.1-2.3 cm) in test-A, respectively, and in test-B they were 0.13 g (0.09-0.2 g) and 2.2 cm (2.0-2.4 cm), respectively. Fish were starved for 24 hours before the test started.
  - Test conditions:
    - Details of test: Flow-through (water changed 10 times/day).
    - Dilution water source: Tap water after dechlorinated by passing through activated carbon.
    - Dilution water chemistry: Hardness: 15.3 mg/L as $CaCO_3$, pH: 7.0
    - Stock and test solution and how they are prepared : The working solution was prepared by diluting the stock solution (3, 4 and 5 wt %) with the dilution water. The test solution was supplied continuously by mixing the working solution and the dilution water with the help of a mechanically operated quantitative water-pump.
    - Concentrations dosing rate, flow-through rate, in what medium: Nominal concentration of the test chemical in test-A was set as 0, 6.3, 12.5, 25.0, 50.0 and 100 mg/L, and the concentration in test-B was set to 0, 25.0, 50.0, 100.0 mg/L.
    - Vehicle/solvent and concentration: Not used.

· Stability of the test chemical solutions: Stable, no precipitation and colouration during the exposure period.

Exposure vessel type: 10 fish per group in 3 L glass beaker without aeration under room light.

· Number of replicates, fish per replicate: One replicate was done.

· Water chemistry (O_2, pH) during exposure: Dissolved oxygen concentration and pH values were measured every 2 - 3 days during the exposure period.

· Dissolved oxygen concentration: 7.1 - 8.3 mg/L.

· pH values: test-A; 6.9 - 10.0, test-B; 6.8 - 7.2

– Test temperature range: Water temperature at 23.5 - 24.1°C.

– Method of calculating mean measured concentrations : Geometric mean.

RESULTS

- **Nominal concentrations :** test-A; 0, 6.3, 12.5, 25.0, 50.0 and 100 mg/L.
  test-B; 0, 25.0, 50.0 and 100 mg/L.

- **Measured concentrations :**

  Measured concentration of the test chemical during a 14day exposure of Medaka (*Oryzias latipes*) under flow-through test conditions

Test-A

Nominal conc. (mg/L)	Measured concentration (mg/L) (percent of nominal)			
	0 day	7 day	14 day	Mean
Control	< 0.2	< 0.2	< 0.2	--
6.3	5.4 (85.7)	5.2 (82.5)	5.4(85.7)	5.3 (84.7)
12.5	11.7 (93.6)	10.9 (87.2)	11.5(92.0)	11.4 (90.9)
25.0	23.7 (94.8)	22.0 (88.0)	24.7(98.8)	23.5 (93.9)
50.0	47.7 (95.4)	44.6 (89.2)	46.7(93.4)	46.3 (92.7)
100.0	101.2(101.2)	95.7 (95.7)	95.3(95.3)	97.4 (97.4)

Test-B

Control	< 0.2	< 0.2	< 0.2	----
25.0	28.5(114.0)	24.3 (97.2)	26.0 (104.0)	26.3 (105.1)
50.0	52.4(104.8)	43.6 (87.2)	48.3 (96.6)	48.1 (96.2)
100.0	106.7(106.7)	88.2 (88.2)	93.9 (93.9)	96..3 (96.3)

- **Unit:** mg/L.
- **Element value:** test-A

  LC_{50} (14 d) 88.1 mg/L (nominal concentration)
  NOEC 25.0 mg/L (nominal concentration)

  test-B

  LC_{50} (14 d) > 100.0 mg/L (nominal concentration)
  NOEC 25.0 mg/L (nominal concentration)

- **Statistical results, as appropriate:**
  – Calculated LC_{50} values for fish exposed to the test chemical under flow-through test conditions.

Exposure period (day)	LC_{50} (mg/L)	95 % Confidence limits	Statistical method
Test-A			
7	88.1	65.1- 371.6	Moving average
14	88.1	65.1- 371.6	Moving average
Test-B			
7	> 100.0	-	-
14	> 100.0	-	-

? The mean body weight of fish exposed to the test chemical was not significantly different from controls during the test period (alpha=0.05, Dunnet).

- **Remarks field for Results.:**

  - Biological observations: At nominal concentration of 100.0 mg/L in test-A, reduction of food intake was observed. However, it was not showed shown in test-B.
  - Cumulative mortality:

Percent mortality of Medaka (*Oryzias latipes*)exposed to the test chemical under flow-through test conditions

Test-A

Nominal conc. (mg/L)	Cumulative number of dead fish (% mortality)														
days	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Control	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
6.3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
12.5	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
25.0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
50.0	0 (0)	1 (10)	1 (10)	1 (10)	1 (10)	1 (10)	1 (10)	1 (10)	1 (10)	1 (10)	1 (10)	1 (10)	1 (10)	1 (10)	1 (10)
100.0	0 (0)	5 (50)	6 (60)	6 (60)	6 (60)	6 (60)	6 (60)	6 (60)	6 (60)	6 (60)	6 (60)	6 (60)	6 (60)	6 (60)	6 (60)

Test-B

Nominal conc. (mg/L)	Cumulative number of dead fish (% mortality)														
days	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Control	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (10)	1 (10)	1 (10)	1 (10)	1 (10)	1 (10)	1 (10)
25.0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (10)	1 (10)
50.0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (10)	1 (10)	1 (10)	1 (10)	1 (10)	1 (10)	1 (10)	1 (10)	1 (10)	1 (10)
100.0	0 (0)	0 (0)	0 (0)	1 (10)	1 (10)	1 (10)	1 (10)	1 (10)	1 (10)	1 (10)	1 (10)	1 (10)	1 (10)	2 (20)	2 (20)

Fish body weight:

Test-A

Nominal conc. (mg/L)	Body Weight (g)										
	No.1	**No.2**	**No.3**	**No.4**	**No.5**	**No.6**	**No.7**	**No.8**	**No.9**	**No.10**	**Average**
Control	0.189	0.159	0.174	0.161	0.164	0.139	0.172	0.128	0.178	0.088	0.155
6.3	0.120	0.172	0.161	0.207	0.133	0.144	0.125	0.141	0.161	0.130	0.150
12.5	0.114	0.136	0.183	0.163	0.164	0.178	0.134	0.120	0.125	0.121	0.144
25.0	0.086	0.153	0.120	0.117	0.137	0.182	0.199	0.163	0.155	0.125	0.144
50.0	0.103	0.113	0.132	0.133	0.206	0.136	0.125	0.135	0.131	--- a	0.135
100.0	0.099	0.121	0.158	0.186	--- a	--- a	--- a	--- a	--- a	--- a	0.141

Test-B

Nominal conc. (mg/L)	Body Weight (g)										
	No.1	No.2	No.3	No.4	No.5	No.6	No.7	No.8	No.9	No.10	Average
Control	0.148	0.126	0.166	0.202	0.163	0.116	0.152	0.130	0.154	--- a	0.151
25.0	0.138	0.184	0.161	0.133	0.165	0.105	0.143	0.201	0.119	--- a	0.150
50.0	0.086	0.135	0.103	0.140	0.153	0.129	0.136	0.137	0.124	--- a	0.127
100.0	0.102	0.120	0.157	0.155	0.108	0.172	0.173	0.122	--- a	--- a	0.139

--- a : No measurement was made because the Medaka was dead.

pH values:

pH values during a 14day flow-through exposure of Medaka (*Oryzias latipes*) to test chemical.

Test-A

Nominal conc. (mg/L)	pH values							
	0	2	5	7	9	12	14	(days)
Control	7.2	7.0	7.2	7.0	7.3	6.9	6.7	
6.3	7.9	7.4	7.5	7.5	7.4	7.3	7.2	
12.5	8.7	8.5	8.5	8.5	8.5	8.3	8.4	
25.0	9.2	9.1	9.1	9.1	9.1	9.0	9.1	
50.0	9.6	9.6	9.6	9.6	9.5	9.5	9.6	
100.0	9.9	9.9	9.9	10.0	9.9	9.8	9.9	

Test-B

Nominal conc. (mg/L)	pH values							
	0	2	5	7	9	12	14	(days)
Control	6.9	7.0	7.0	7.1	7.0	7.1	7.1	
25.0	7.0	7.0	7.0	7.1	7.0	7.1	7.1	
50.0	7.1	7.0	7.0	7.1	7.0	7.2	7.2	
100.0	7.2	7.0	7.1	7.1	7.3	6.9	6.8	

– After 14 days, mortality rate at the highest concentration group (100 mg/L) of test-A and test-B were 60 % and 20 %, respectively.

– Mortality of controls: A 10 % mortality was observed during the test period (8 through 14 days) in test-B, but death was not observed in test-A.

– Food intake: Fish was fed with Tetramin® fish food (2 % of fish body weight). In test-A, reduction of food intake was observed in 100.0 mg/L group only, but it was not showed in all treatment groups of test-B.

– Abnormal responses: Toxicological symptom considered to be effected by the test substance was not observed except for reduction of food intake in the test-A.

– Reference substances (if used) – results: Copper (II) sulfate pentahydrate. LC_{50} at 96 h was 0.30 mg/L.

– Any observations, such as precipitation that might cause a difference between measured and nominal values: No precipitation and no coloration.

CONCLUSIONS

The test was conducted in two conditions using non-adjusted test solution test-A or the neutralised test solution test-B. The results were as follows:

test A:

The determined LC_{50} value (14 d) was 88.1 mg/L based on the nominal concentration. The NOEC value for toxicological symptom was evaluated to be 25.0 mg/L.

test B:

The determined LC_{50} value (14 d) was more than 100.0 mg/L on the nominal concentration. The NOEC value for toxicological symptom was evaluated to be 25.0 mg/L.

DATA QUALITY

- **Reliabilities:** Klimisch Code: 1 = Reliable without restriction, Key study
- **Remarks field for Data Reliability:**

Well conducted study, carried out by Toray Research Centre.

REFERENCES

Environmental Agency of Japan, (1997). Ecotoxicity testing report, Test No. NMMP/E09/5070, unpublished data.

OTHER

- **Last changed :**
- **Order number for sorting :**
- **Remarks field for General Remarks :**

ACUTE TOXICITY TO AQUATIC INVERTEBRATES

TEST SUBSTANCE

- **Identity:** 2,2,6,6-Tetramethylpiperidin-4-ol (CAS No. 2403-88-5)
- **Remarks:** Source: Wako Pure Chemical Industries, LTD. Lot No. WTK0815, Purity > 99.0 %

METHOD

- **Method/guideline:** OECD TG 202 (1984)
- **Test type:** Static
- **GLP (Y/N):** Yes.
- **Year (study performed):** 1997
- **Analytical procedures:** Yes. Measured by gas chromatography at start and end of the test.
- **Species/Strain:** *Daphnia magna*
- **Exposure period (h):** 48
- **Statistical methods:** Binomial method.

Remarks field for Test Conditions:

– Test organisms:
  · Source, supplier, any pre-treatment, breeding method: Supplied by NIES (Japan).
  · Age at study initiation: Juveniles within 24h old.
  · Control group: Yes.

– Test conditions
  · Stock solutions preparation and stability: No solvent used. Test chemical was diluted to 0.3 wt.%
  · with diluting water (Elendt M4) and it was diluted with the dilution water for testing.
  · Test temperature range: 20 ± 1 °C (measured: 20.0 - 20.5 °C)
  · Exposure vessel type: 100 ml test solution in a 100 ml glass beaker; 4 beakers per treatment.
  · Dilution water source: Dechlorinated tap water
  · Dilution water chemistry: Hardness: 228 mg/L as $CaCO_3$, pH = 7.4.
  · Lighting: room light, 16h:8h light-darkness cycle
  · Water chemistry in test: DO = 7.9 - 8.7 mg/L; pH = 7.4 - 10.0
  · Feeding: *Chlorella vulgaris*, 0.1 - 0.2 mgC/day/individual

– Element (unit) basis: Mean cumulative numbers of juveniles produced per adult (immobilisation)
– Test design: Number of replicates = 4; individuals per replicate = 5; concentrations; 0, 10.6, 19.1, 34.3, 61.7, 111.1and 200.0 mg/L.
– Method of calculating mean measured concentrations: geometric mean.
– Exposure period: 48 h.
– Analytical monitoring: By GC analysis. 101.0 - 111.4 % of the nominal concentration at preparation; 92.4 - 100.0 % of the nominal concentration at preparation (after 48 hours exposure).

RESULTS

- **Nominal concentrations:** 0, 10.6, 19.1, 34.3, 61.7, 111.1 and 200.0 mg/L
- **Measured concentrations:** < 0.2, 11.3, 19.3, 35.6, 63.7, 119.7 and 222.7 mg/L
- **Measured concentrations after 48 hours:** < 0.2, 10.6, 18.2, 33.5, 59.5, 104.2 and 184.8 mg/L
- **EC_{50}:** EiC_{50} (24 h) 130.1(111.1 - 200.0) mg/L
  EiC_{50} (48 h) 100.1 (61.7 - 200.0) mg/L
  NOECi (48 h) 61.7 mg/L
- **Reference substance/Results:**
  Potassium dichromate. The 48 h-EC_{50} value determined was 0.87 mg/L.
- **Statistical results, as appropriate:** No conducted.

Remarks field for Results.

- **Measured Exposure Concentration**

Nominal Concentration (mg/L)	Measured Concentration (mg/L)			Percent to the Nominal
	0 Hour new	48 Hour old	Geometric Mean	
Control	< 0.2	< 0.2	?	?
10.6	11.3	10.6	10.9	102.8
19.1	19.3	18.2	18.7	97.9
34.3	35.6	33.5	34.5	100.6
61.7	63.7	59.5	61.6	99.8
111.1	119.7	104.2	111.7	100.5
200.0	222.7	184.8	202.9	101.5

New: freshly prepared test solutions.
Old: test solutions after 48 hours exposure period.

(Note) The geometric mean values were corresponding to 97.9 to 102.8% of the nominal concentration. Thus, the results were expressed based on the geometric mean values of the nominal concentration.

- **EC_{50} (Immobility):**

Exposure Period (Hour)	EiC_{50} (mg/L)	95-Percet Confidence Limits (mg/L)	Statistical Method
24	130.1	111.1 - 200.0	Binomial
48	100.0	61.7 - 200.0	Binomial

- **Remarks:**

? Cumulative number of dead or immobilized Daphnia:

Nominal Concentration (mg/L)	Cumulative Number of Dead or Immobilized Daphnia (Percent Mortality or Immobility)	
	24 Hour	48 Hour
Control	0 (0)	0 (0)
10.6	0 (0)	0 (0)
19.1	0 (0)	0 (0)
34.3	0 (0)	0 (0)
61.7	0 (0)	0 (0)
111.1	5 (5)	13 (65)
200.0	20 (100)	20 (100)

? EiC0 and EiC100:

Exposure Period (Hour)	Maximum concentration causing 0% immobility (mg/L)	Lowest Concentration in 100% Mortality or Immobility (mg/L)
24	61.7	200.0
48	61.7	200.0

(Note) Based on the geometric means of the nominal concentration.

CONCLUSIONS

Due to high water solubility of the substance, the results were expressed base on the geometric mean values of the nominal concentration. The determined 24 hr-EC50 and 48 hr-EC50 values were 130.1 mg/L and 100.0 mg/L, respectively. The NOECi value of 48 hr was 61.7 mg/L. Experimental designs and results were well documented and prescribed conditions in the guideline were well satisfied.

DATA QUALITY

- **Reliabilities:** Klimisch Code: 1 = Reliable without restriction, Key study
- **Remarks field for Data Reliability:**

Well conducted study, carried out by Toray Research Centre.

REFERENCES (Free Text)

Environmental Agency of Japan, (1997). Ecotoxicity testing report, Test No. NMMP/E09/2070, unpublished data.

OTHER

- **Last changed :**
- **Order number for sorting :**
- **Remarks field for General Remarks :**

TOXICITY TO AQUATIC PLANTS (E.G., ALGAE)

TEST SUBSTANCE

- **Identity:** 2,2,6,6-Tetramethylpiperidin-4-ol (CAS No. 2403-88-5)
- **Remarks:** Source: Wako Pure Chemical Industries, LTD. Lot No. WTK0815, Purity > 99.0 %.

METHOD

- **Method/guideline followed :** OECD TG 201
- **Test type :** Static
- **GLP :** Yes
- **Year :** 1997
- **Species/strain # and source:** *Selenastrum capricornutum* ATCC22662 (purchased from ATCC)
- **Element basis:** Area under the growth curve.
- **Exposure period:** 72 h.
- **Analytical monitoring:** Yes, measured by gas chromatography at start and end (72 h) of the test.
- **Statistical methods:** Bartlett test for homogeneity in variances and One-way Anova (EcoTox- Statistics Ver.1.0 beta R1.4) were used for EC_{50}, LC_{50} and NOEC determination ($p = 0.05$).

Remarks field for Test Conditions :

– Test organisms
  - Laboratory culture: OECD medium
  - Method of cultivation: Shaking at 100 rpm
  - Controls: OECD medium. EC_{50} of potassium dichromate was 0.41 mg/L.

– Test Conditions
  - Test temperature range: 23 ± 2 °C
  - Growth/test medium: OECD medium.
  - Shaking: 100 rpm
  - Dilution water source: OECD medium.
  - Exposure vessel type: A 100 mL OECD medium in a 300 mL Erlenmeyer flask with a silicon cap which allows ventilation.
  - Water chemistry in test (pH) in at least one replicate of each concentrations (at start and end of the test): pH = 7.7 - 10.4 at start and 8.0 - 8.8 at end of the test (72 h).
  - Stock solutions preparation : No stock solution was prepared. Test chemical was diluted to 2.0 wt.% with OECD medium and sterilised with filter before use.
  - Light levels and quality during exposure: 4,000 - 5,000 Lux, continuous illumination.

– Test design:
  - Number of replicates: Triplicate
  - Concentrations: 0, 42, 76, 137, 247, 444 and 800 mg/L
  - Initial cell number in cells/mL: 1×10^4

– Method of calculating mean measured concentrations:
· Geometric mean.

RESULTS

- **Nominal concentrations :**
  0, 42, 76, 137, 247, 444 and 800 mg/L
- **Measured concentrations :**
  At start of the test (0 h); < 0.2, 40, 71, 130, 221, 400, 707 mg/L
  At end of the test (72 h); < 0.2, 44, 78, 144, 252, 477, 755 mg/L
- **Unit :** Cell density (cells/mL)
- **Results:** (calculated based on nominal concentration)
  (1) Growth inhibition (comparison of area under growth curve)
  EC_{50} (72 h) 107 mg/L
  NOEC 76 mg/L
  (2) Growth inhibition (comparison of growth rates)
  EC_{50} (24 - 48) 127 mg/L
  EC_{50} (24 - 72) 155 mg/L
  NOEC (24 - 72) 76mg/L
- **Was control response satisfactory:**
  Yes: Mean cell density to 2.33×10^6 cells/mL (233-fold increase) after 72 h.
- **Statistical results as appropriate:**
  There was no statistically significant difference in the growth curve between
  values at 76 mg/L and in control.

Remarks field for Results:

– Biological observations
Cell density at each flask at each measuring point:

Nominal Concentration (mg/L)	Cell Density ($x10^4$ cells/mL)			
	0 h	24 h	48 h	72 h
Control	1.0 ± 0.00	9.2 ± 3.18	43.1 ± 7.91	232.6 ± 45.70
42	1.0 ± 0.00	8.0 ± 1.05	46.8 ± 3.33	261.1 ± 17.05
76	1.0 ± 0.00	8.3 ± 0.59	41.8 ± 9.29	186.6 ± 20.65
137	1.0 ± 0.00	3.3 ± 0.38	5.0 ± 0.52	18.5 ± 4.06
247	1.0 ± 0.00	3.4 ± 0.17	3.5 ± 1.09	4.2 ± 1.60
444	1.0 ± 0.00	3.7 ± 0.70	2.8 ± 1.07	3.2 ± 1.26
800	1.0 ± 0.00	2.4 ± 0.17	3.9 ± 0.62	3.2 ± 1.50

(Each value represents the mean of three sample counts.)

· Growth curves: Logarithmic growth until end of the test (72 h).
· Percent biomass/growth rate inhibition per concentration: Not described.
· Observations: 42 - 76 mg/L test groups showed normal and similar growth to that of control after 72 h.

CONCLUSIONS

The determined EC_{50} value for biomass (0 - 72 h) was 107 mg/L based on the nominal concentration. The NOEC value for biomass (0 - 72 h) was evaluated to be 76 mg/L. The EC_{50} for growth rate were 127 mg/L (24 - 48 h) and 155 mg/L (24 - 72 h). The NOEC's for growth rate were 76 mg/L (24 - 48 h) and 76 mg/L (24 - 72 h).

DATA QUALITY

- **Reliabilities:** Klimisch Code: 1 = Reliable without restriction, Key study
- **Remarks field for Data Reliability:**

Well conducted study, carried out by Toray Research Centre.

REFERENCES

Environmental Agency of Japan, (1997). Ecotoxicity testing report, Test No. NMMP/E09/1070, unpublished data

OTHER

- **Last changed :**
- **Order number for sorting :**
- **Remarks field for General Remarks :**

CHRONIC TOXICITY TO AQUATIC INVERTEBRATES (E.G., DAPHNIA)

TEST SUBSTANCE

- **Identity:** 2,2,6,6-Tetramethylpiperidin-4-ol (CAS No. 2403-88-5)
- **Remarks:** Source: Wako Pure Chemical Industries, LTD. Lot No. WTK0815, Purity > 99.0 %.

METHOD

- **Method/guideline:** OECD TG 211.
- **Test type:** Semi-static
- **GLP :** Yes.
- **Year :** 1997.
- **Analytical procedures:** Yes.
  Measured by gas chromatography 2 - 3 times a week (before and after the replacement of the test water.)
- **Species/Strain:** *Daphnia magna*
- **Test details:** Semi-static (water renewal: 3 times a week), open-system.
- **Statistical methods:** EC_{50}, LC_{50} and NOEC values were determined using the calculation program
  (EcoTox-Statistics Ver.1.0 beta R1.4).

Remarks field for Test Conditions :

– Test organisms:
  - Source, supplier, any pretreatment, breeding method: Supplied by NIES (National Institute of Environmental Studies) of Japan.
  - Age at study initiation: Juveniles within 24 h old.
  - Control group: Yes.

– Test conditions
  - Stock solutions preparation and stability: No solvent used. Test chemical was diluted to 0.3 wt.% with dilution water (Elendt M4) and it was diluted with the dilution water for testing.
  - Test temperature range: 19.2 - 20.7 °C.
  - Exposure vessel type: A 80 ml test solution in a 100 ml glass beaker; 10 beakers per treatment.
  - Dilution water source: Dechlorinated tap water
  - Dilution water chemistry: Hardness: 228 - 236 mg/L as $CaCO_3$
  - Lighting: < 1,200 lux, 16 h : 8 h light-dark cycle
  - Water chemistry in test: DO = 8.0 - 8.6 mg/L; pH = 7.1-9.5.
  - Feeding: *Chlorella vulgaris*, 0.1 - 0.2 mgC/day/individual

– Element (unit) basis: Mean cumulative numbers of juveniles produced per adult (reproduction)

– Test design: Number of replicate, individuals per replicate: Ten replicates, One daphnia per replicate concentrations: 0, 3.7, 6.7, 12.0, 21.6, 38.9 and 70.0 mg/L, because 48 h-EiC_{50} for parent Daphnia (Acute immobilisation test) was 100.0 mg/L.

– Method of calculating mean measured concentrations: Geometric mean.
– Exposure period: 21 day
– Analytical monitoring: By GC analysis. A 88.9 - 105.4 % of the nominal concentration at preparation; 84.7 - 118.9 % just before the renewal of the test water (after 2 days exposure).

RESULTS

- **Nominal concentrations:** 0, 3.7, 6.7, 12.0, 21.6, 38.9, 70.0 mg/L
- **Measured concentrations:**

The time-weighted average of measured test chemical concentration during 21-day exposure was as follows.

Measured concentration of test chemical during 21 day exposure of *Daphnia magna*.

Nominal concentration (mg/L)	Measured concentration (mg/L)					
	0 day (new)	2 day (old)	7 day(new)	9 day(old)	16 day(new)	19 day(old)
Control	< 0.2	< 0.2	< 0.2	< 0.2	< 0.2	< 0.2
3.7	3.9	4.4	3.4	3.4	3.7	3.6
6.7	6.3	7.0	6.0	6.0	6.2	6.3
12.0	11.9	11.3	10.1	10.9	11.1	11.7
21.6	19.2	20.4	18.4	20.5	21.2	18.3
38.9	39.7	35.6	34.1	37.1	36.5	38.9
70.0	62.5	62.7	62.3	70.1	66.7	72.9

new: freshly prepared test solutions.
old: test solution after 2 days.

- **Unit :** mg/L
- **Results:** (calculated based on the nominal concentration)
  - LC50 for parental *Daphnia* (21 d) : > 70.0 mg/L
  - EC50 (21 d, reproduction) : 46.2 mg/L
  - NOEC (21 d, reproduction) : 3.7 mg/L
  - LOEC (21 d, reproduction) : 6.7 mg/L

Mean cumulative numbers of juveniles produced per adult during 21 day.

Nominal concentration (mg/L)	Days																				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Control	0.0	0.0	0.0	0.0	0.0	0.0	1.2	11.6	15.9	21.3	35.8	52.5	52.5	80.6	98.3	98.3	118.4	129.8	129.8	156.9	175.4
3.7	0.0	0.0	0.0	0.0	0.0	0.0	2.0	11.8	16.6	18.2	35.2	50.2	50.2	75.2	91.6	91.6	109.6	117.8	121.1	146.4	158.7
6.7	0.0	0.0	0.0	0.0	0.0	0.0	1.7	12.5	15.5	15.5	38.9	38.9	49.4	81.5	81.5	89.6	108.2	108.2	111.9	144.8	144.9
12.0	0.0	0.0	0.0	0.0	0.0	0.0	0.9	8.1	13.7	13.7	30.9	43.3	43.3	66.4	78.7	78.7	96.7	105.7	107.6	125.4	136.9
21.6	0.0	0.0	0.0	0.0	0.0	0.0	2.3	5.1	13.5	13.5	23.4	39.9	39.9	48.6	66.3	66.3	73.0	90.1	92.2	101.5	122.6
38.9	0.0	0.0	0.0	0.0	0.0	0.0	1.3	7.1	8.5	8.5	25.2	30.0	30.0	43.1	51.0	51.4	67.0	74.5	77.3	94.0	103.6
70.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.6	4.6	4.6	13.4	18.0	18.0	26.7	26.9	30.3	38.1	39.1	46.3	56.0	60.9

Cumulative numbers of dead parental Daphnia during 21 day.

Nominal concentration (mg/L)	Days																				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3.7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6.7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
12.0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
21.6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
38.9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
70.0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	3

- **Statistical results as appropriate:**
  There was no statistically significant difference between data from the control and 3.7 - 70.0 mg/L test groups.

Remarks field for Results :

– Biological observations:
  · Cumulative numbers of dead parental *Daphnia* :
  Control - 38.9 mg/L: 0 (mortality: 0 %), 70.0 mg/L: 3 (mortality: 30 %)
  · Time of the first production of juveniles:
  Control: 8 d, 3.7 mg/L: 8 d, 6.7 mg/L: 7.9 d, 12.0 mg/L: 8.2 d, 21.6 mg/L: 7.9 d, 38.9 mg/L: 8.4 d, 70.0 mg/L: 9.2 d
  · Mean cumulative numbers of juveniles produced per adult alive for 21 days.
  Control: 175.4, 3.7 mg/L: 158.7, 6.7 mg/L: 144.9, 12.0 mg/L: 136.9, 21.6 mg/L: 122.6, 38.9 mg/L: 103.6, 70.0 mg/L: 60.9
  · Was control response satisfactory: Yes.

CONCLUSIONS

LC_{50} and EC_{50} values after 21 days exposure were more than 70 mg/L and 46.2 mg/L (38.6 - 57.5 mg/L) based on the nominal concentration. The NOEC and LOEC for reproduction rate were evaluated to be 3.7 mg/L and 6.7 mg/L, respectively. Experimental designs and results were well documented and prescribed conditions in the guideline were well satisfied.

DATA QUALITY

- **Reliabilities:** Klimisch Code: 1 = Reliable without restriction, Key study
- **Remarks field for Data Reliability:**

Well conducted study, carried out by Toray Research Centre.

REFERENCES

Environmental Agency of Japan, (1997). Ecotoxicity testing report, Test No. NMMP/E09/3070, unpublished data.

OTHER

- **Last changed :**
- **Order number for sorting :**
- **Remarks field for General Remarks :**

HEALTH ELEMENTS

ACUTE ORAL TOXICITY

TEST SUBSTANCE

- **Identity:** 2,2,6,6-Tetramethylpiperidin-4-ol (CAS No. 2403-88-5)
- **Remarks:** Source: Mitsui Chemicals Inc., Lot No. 6509051
  Purity > 99.8 %.

METHOD

- **Method/guideline:** OECD TG 401
- **Test type:** Acute Oral Toxicity Test
- **GLP:** Yes
- **Year:** 1998
- **Species:** Rat
- **Strain:** Crj:CD (SD)
- **Route of administration:** Oral (by single-dose gavage)
- **Doses/concentration levels:**

  590, 769, 1000, 1300, 1690 and 2197 mg/kg
- **Sex:** Male & Female
- **Control group and treatment:** No control and vehicle used.
- **Post exposure observation period:** Two weeks.
- **Statistical methods:** LD_{50} was calculated by the Litchfield-Wilcoxon method (1949).

REMARKS FIELD FOR TEST CONDITIONS

– Test Subjects:
  - Age at study initiation: 7 week old for males and females.
  - Weight at study initiation: 177 - 195 g for males, 139 - 153 g for females.
  - No. of animals per sex per dose: 5 per sex per dose group

– Study Design:
  - Vehicle: Distilled water.
  - Satellite groups and reasons they were added: None
  - Clinical observations performed and frequency:
    Each rat was weighed immediately prior to treatment, the day after and weekly thereafter for two-week post-treatment observation period.

The rats were observed periodically during this time for signs of toxicity. All rats were submitted for a gross pathological examination as they died spontaneously, or survivors two weeks post-treatment.

RESULTS

- **LD_{50}:** Male : 1482 mg/kg b.w. (1239 - 1774 mg/kg b.w., 95 % confidence interval)
  Female : 1564 mg/kg b.w. (1326 - 1842 mg/kg b.w., 95 % confidence interval)

REMARKS FIELD FOR RESULTS

– Body weight: In the male and female rats of 1600 mg/kg b.w. group, body weight reduction was observed temporarily. But all surviving rats gained weight during the two-week observation period.
No detailed body weight data available.

– Food/water consumption: No data available.

– Clinical signs :

In all groups, clinical signs of decreased locomotor activity, mydriasis and blepharoptosis were observed in both sexes. Prone position, hypothermia and tremors were observed in 1300 mg/kg or higher groups of the both sexes. Moreover wasting, abdominal distension and pallor of the auricles in 1300 mg/kg and piloerection in the male of 1690 mg/kg, as well as abdominal distension, pallor of auricles and loss of fur in the females of 1690 mg/kg were observed. The change of main clinical signs (decreased locomotor activity, mydriasis, blepharoptosis) were almost recovered after 24 hours. Degree of the mydriasis observed in 2197 mg/kg was severe.

– Haematology: Not done.

– Biochem: Not done.

– Ophthalmologic findings: Not examined.

– Mortality and time to death:

Mortality of male and female rats dosed orally with the undiluted test material

Dose level (mg/kg)	# Dead / # Treated		Time of Death	
	Males	**Females**	**Males**	**Females**
592	0/5	0/5	--	--
769	0/5	0/5	--	--
1,000	0/5	0/5	--	--
1,300	1/5	1/5	1 rat - Day 13	1 rat - Day 6
1,690	4/5	3/5	3 rat - Day 1 1 rat - Day 7	3 rat - Day 1
2,197	5/5	5/6	5 rat - Day 1	5 rat - Day 1

– Gross pathology incidence and severity:

In the male and female rats which died, the diffusional hemorrhage of stomach gland and the red spots of duodenum were observed.

– Organ weight changes: Not done.

– Histopathology: Pathological examination was conducted using the male and female rats which died, hemorrhage, necrosis, and vacuolar degeneration were seen in the stomach gland, and edema, hemorrhage, necrosis, and vacuolar degeneration were observed in the duodenum.

CONCLUSIONS

LD50 was established at 1,482 mg/kg for male and 1,564 mg/kg for female, respectively.

DATA QUALITY

- **Reliabilities:** Klimisch Code: 1 = Reliable without restriction
- **Remarks field for Data Reliability:**

Well conducted study, carried out by Biosafety Research Center, Foods, Drugs and Pesticides (An-Pyo Centre).

REFERENCES

Ministry of Health and Welfare, Japan (1998), Toxicity Testing Reports of Environmental Chemicals, vol. 6, 513 - 515.

GENERAL REMARKS

ACUTE DERMAL TOXICITY

TEST SUBSTANCE

- **Ide ntity:** 2,2,6,6-Tetramethylpiperidin-4-ol (CAS No. 2403-88-5)
- **Remarks:** Source: CIBA-GEIGY Limited, Batch No. HT-92-034
  Purity 99.7 %

METHOD

- **Method/guideline:** OECD TG 402
- **Test type:** Acute Dermal Toxicity Test
- **GLP:** Yes.
- **Year:** 1992
- **Species:** Rat
- **Strain:** Tif : RAI f1
- **Route of administration:** Dermal application
- **Doses/concentration levels:**

  2000 mg/kg body weight (Limit test)
- **Sex:** Male & Female
- **Control group and treatment:** No control and vehicle used.
- **Post exposure observation period:** 14 days.
- **Statistical methods:** LD_{50} was calculated by the Litchfield-Wilcoxon method (1949).

REMARKS FIELD FOR TEST CONDITIONS

– Test Subjects:
  - · Age at study initiation: No data available.
  - · Weight at study initiation: 219 - 252 g
  - · No. of animals per sex per dose: 5 per sex per dose group

– Study Design:
  - · Pretreatment: Approximately 24 hours before treatment an area on the back of the rat of at least 10% of the body surface was shaved with an electric clipper.
  - · Application: This substance was evenly dispersed on the skin. It was covered with a gauze-lined semi-occlusive dressing fastened around the trunk with an adhesive elastic bandage. After 24 hours the dressing was removed and the skin was cleaned with lukewarm water.

Thereafter the skin reaction was appraised repeatedly.
- Frequency of application: One single dose.
- Vehicle: Distilled water.
- Volume (ml/kg body weight) applied: 4
- Clinical observations performed and frequency:
  Each rat was weighed immediately before application and on days 7 and 14. The rats were observed daily for 14 days. All rats were submitted to a gross necropsy at the end of the observation period.

RESULTS

- **LD_{50}:** Male : > 2000 mg/kg b.w.
  Female : > 2000 mg/kg b.w.

REMARKS FIELD FOR RESULTS

– In-life observations are depicted in Table 1.

Table 1 In-life observations

	Animal No.	Observations	Appl. day	Days after application 1	2	3	4	5	6	7	8	9	10
2000 mg/kg, males	**1 - 5**	**piloerection**	+	+									
	1 - 5	**hunched post**		+									
	1 - 5	**erythema a.s.**		+		+		+	+	+			
	2	**necrosis a.s.**			+	+	+	+	+	+	+	+	#
2000 mg/kg, females	**1 - 5**	**piloerection**		+	+								
	1 - 5	**hunched post**		+									
	2 - 5	**erythema a.s.**		+	+								
	1	**erythema a.s.**		+	+	+	+	+	+	+			
	2	**necrosis a.s.**			+	+	+	+	+	+	+	+	#

+ slight
hunched post = hunched posture
a.s. = at the application site
 # = slight until day 12

Piloerection and hunched posture were seen, being common symptoms in acute dermal tests. At the application site erythema was seen in all animals. Necrosis was observed in one male and one female. The animals recoverd within 8 to 13 days.

. Body weight: Individual body weight, their group means and standard deviations are shown in Table 2.

Table 2 Body weight and necropsy findings

	Animal No.	Body Weights (g) d 0	d 7	d 14	*	Gross Necropsy Findings
Males dosed with 2000 mg/kg	**1**	252	305	343	TS	NOA
	2	248	271	300	TS	NOA
	3	249	300	348	TS	NOA
	4	246	290	335	TS	NOA
	5	244	282	326	TS	NOA
	mean	248	290	330		
	S.D.	3.0	13.7	18.9		
Females dosed with 2000 mg/kg	**1**	200	240	253	TS	NOA
	2	227	229	242	TS	NOA
	3	223	228	238	TS	NOA
	4	219	225	226	TS	NOA
	5	228	235	240	TS	NOA
	mean	223	231	240		
	S.D.	4.0	6.0	9.7		

*** terminal sacrifice**
NOA no observable abnormalities

Food/water consumption: No data available.

Organ weight changes: Not done.

CONCLUSIONS

LD50 was established at 1,482 mg/kg for male and 1,564 mg/kg for female, respectively.

DATA QUALITY

- **Reliabilities:** Klimisch Code: 1 = Reliable without restriction
- **Remarks field for Data Reliability:**

Well conducted study, carried out by Chiba Additive GmbH Lampertheim

REFERENCES

Ciba additive GmbH Lampertheim (Ciba-Geigy, Test No.924124)

GENERAL REMARKS

ACUTE SKIN IRRITATION

TEST SUBSTANCE

- **Identity:** 2,2,6,6-Tetramethylpiperidin-4-ol (CAS No. 2403-88-5)
- **Remarks:** Source: CIBA-GEIGY Limited, Batch No. HT-92-034
  Purity 99.7 %

METHOD

- **Method/guideline:** OECD TG 404
- **Test type:** Acute Dermal Irritation/Corrosion
- **GLP:** Yes
- **Year:** 1992
- **Species:** Rabbit
- **Strain:** New Zealand White
- **Route of administration:** Dermal application to the shaved intact dorsal skin
- **Doses/concentration levels:** 0.5 g/patch
- **Sex:** Male
- **No. of animals per dose:** 3
- **Remarks field for Test Condition:**
- **Test Subjects:**

  Age: Not stated
  Weight at study initiation: 2440 - 2710 g
  Doses: 0.5 g/animal
  Doses per time period: 4 hours exposure
  Volume of administration or concentration: Test substance was applied to the flank (approx.12 - 16 cm^2 and then covered with an aluminium foil.
  Post dose observation period: After the 4-hour exposure the patch was removed and the skin sites were evaluated. Scores were taken 1 hours, 1, 2, 3, 7, 10 and 14 days after patch removal.

- **Study Design:**

  Clinical observations performed and frequency:
  The animals were checked daily for systemic symptoms.
  Organs examined at necropsy: Not stated

RESULTS

One hour after patch removal the treated skin of animal No. 1 appeared severely corroded. From 24 hours up to 72 hours after patch removal the treated skin of this animal still appeared necrotic. Additionally, crust formations had developed which were partially sloughing off from day 10 until day 14. In the remaining two animals skin reactions were less prominent. Besides erythema and edema reactions scaling was observed towards the end of the observation period. The skin reactions in animal No. 1 were not reversible within 14 days after patch removal. The skin reactions observed were reversible in two animals until the end of the observation period on day 14.

REMARKS FIELD FOR RESULTS

Examination schedule — **Skin irritation scores**

	Erythema			Edema		
Animal No.	**1**	**2**	**3**	**1**	**2**	**3**
Before dosing	0	0	0	0	0	0
Time after removal of the patch						
60 min	4 n	2	2	2	1	1
24 hrs	4 c, n	2	2	3	1	1
48 hrs	4 c, n	2	2	2	1	1
72 hrs	4 c, n	2 s	2	1	1	0
7 days	4 c	2 s	1 s	1	1	0
10 days	4 c	1 s	0 s	0	0	0
14 days	4 c	0	0	0	0	0

0: no pathological findings
n: necrosis
c: crust
s: scaling

CONCLUSIONS

This substance induced moderate to severe skin irritation when applied to the clipped albino rabbit skin.
The skin reactions in an animal were not reversible within 14 days after patch removal.

DATA QUALITY

- **Reliabilities:** Klimisch Code: 1 = Reliable without restriction
- **Remarks field for Data Reliability**

Well conducted study, carried out by Chiba Additive GmbH Lampertheim

REFERENCES

Ciba additive GmbH Lampertheim (Ciba-Geigy, Test No.924125)

GENERAL REMARKS

SKIN SENSITIZATION

TEST SUBSTANCE

- **Identity:** 2,2,6,6-Tetramethylpiperidin-4-ol (CAS No. 2403-88-5)
- **Remarks:** Source: CIBA-GEIGY Limited, Batch No. HT-92-034
  Purity 99.7 %

METHOD

- **Method/guideline:** OECD TG 406 (Skin Sensitization)
- **Test type:** Guinea pig maximization test
- **GLP:** Yes
- **Year:** 1993
- **Species:** Guinea pig
- **Strain:** Pirbright White
- **Sex:** Male, Female
- **No. of animals per dose:** Control group 10 (5 males and 5 females)
  Test group 20 (10 males and 10 females)
- **Route of administration:** Induction procedure (week 1 and 2).
  First, intradermal injections (into the neck region).
  Second, closed patch exposure over the injection sites.
  Challenge (week 5) and Rechallenge (week 6)
  The animals were tested on the flank with this substance in Vaseline.
- **Induction concentration:** First indubtion week, intradermal injection
  Adjuvant/saline mixture 1 : 1 (v/v)
  1% : this substance in physiological saline (w/v)
  1% : this substance in the adjuvant/saline mixture (w/v)
  Second induction week, epidermal application
  50% : this substance in Vaseline (w/w)
- **Induction vehicle:** Physiological saline (0.9%), sterile solution
  Bacto Adjuvant, Complete, Freund
  Vaseline (white petrolatum)
- **Challenge concentration:** Challenge (week 5)
  30 % : this substance in Vaseline
  Rechallenge (week 6)
  10 % : this substance in Vaseline
- **Grading system used:** The grading of Magnusson and Kligman.

- **Remarks field for test conditions:**

Test Subjects:

Weight at study initiation: 300 - 431 g
No of animals per dose: Test group (10 males and 10 females), Control group (5 males and 5 females

Study Design:

- Induction procedure (week 1 and 2): The induction was a two-stage operation. First, intradermal injections (into the neck region); second, closed patch exposure over the injection sites one week later.
- First induction week, intradermal injection; Three pairs of intradermal injections (0.1 ml per injection) were made simultaneously into the shaved neck of the guinea pigs as follows:
  Adjuvant/saline mixture 1:1 (v/v)
  1% test substance in physiological saline (w/v)
  1% test substance in the adjuvant/saline mixture
- Second induction week, epidermal application: In the second week of induction test substance was incorporated in vaseline (w/w) and applied on a filterpaper patch to the neck of the animals (patch 2×4 cm; approx. 0.4 g paste per patch; occluded administration for 48 hours).
- Rest period: During weeks 3 and 4 no treatments were performed.
- Challenge (week 5) and Rechallenge (week 6): The animals were tested on the flank with this substance in vaseline (w/w) and the vehicle alone.
- Control group: A control group was treated with adjuvant and the vehicle during the induction period. During the challenge period the group was treated with the vehicle as well as with the test substance to check the maximum subirritant concentration of the test substance in adjuvant treated animals.
- The concentration for the intradermal injections and the epidermal applications were as follows;
  Intradermal induction: Test substance 1 %, Vehicle physiological saline
  Epidermal induction: Test substance 50 %, Vehicle vaseline
  Epidermal challenge: Test substance 30 %, Vehicle vaseline
  Rechallenge: Test substance 10 %, Vehicle vaseline
- Observations and records:

Induction reactions;After the intradermal and the epidermal induction application irritant reactions are normally induced by the adjuvant, the high test substance concentration, or the sodium lauryl sulfate pretreatment.
Challenge reactions;Twenty four and forty eight hours after removing the dressings, the challenge reactions were graded according to the Draize scoring scale.
General; The sensitizing potential of test substance was classified according to the grading of Magnusson and Kligman. The body weight was recorded at start and end of the test.
Macropathology; Because of mortality in the test group the surviving animals were sacrificed and necropsied at the end of the study. The necropsy included examination of the external surface of the body, all orifices, and the cranial, thoracic and abdominal cavities and their contents.

RESULTS

Moribund one male and one female were sacrificed on experimental day 11 and 14,

respectively. On experimental day 15, two females were found dead. After the first challenge application 56% of the animals of the test group and 70% of the animals of the control group showed skin reactions. After a second challenge application, using a lower test substance concentration and a new control group, 31% and 69% of the animals of the test group were sensitised 24 and 48 hours after removing the dressings, respectively. None of the animals of the control group showed skin reactions during the second challenge.

Number of positive animals per group after first occlusive epidermal challenge application.

	after 24 hours	after 48 hours
Control group	**# positive/# treated**	**# positive/# treated**
vehicle control	0/10	0/10
test substance	7/10	7/10
Test group		
vehicle control	0/16	0/16
test substance	9/16	9/16

Number of positive animals per group after second occlusive epidermal challenge application.

	after 24 hours	after 48 hours
Control group	**# positive/# treated**	**# positive/# treated**
vehicle control	0/10	0/10
test substance	0/10	0/10
Test group		
vehicle control	0/16	0/16
test substance	5/16	11/16

CONCLUSIONS

2,2,6,6-Tetramethylpiperidin-4-ol is classified as a moderate to strong sensitizer in albino guinea pigs according to the grading of Magnusson and Kligman.

DATA QUALITY

- **Reliabilities:** Klimisch Code: 1 = Reliable without restriction
- **Remarks field for Data Reliability**

  Well conducted study, carried out by Chiba Additive GmbH Lampertheim

REFERENCES

Ciba additive GmbH Lampertheim (Ciba-Geigy, Test No.924127)

GENERAL REMARKS

REPEATED DOSE TOXICITY

TEST SUBSTANCE

- **Identity:** 2,2,6,6-Tetramethylpiperidin-4-ol (CAS No. 2403-88-5)
- **Remarks:** Source: Mitsui Chemicals Inc., Lot No. 6509051
  Purity > 99.8 %.

METHOD

- **Method/guideline:** OECD TG 422
- **Test type:** OECD Combined Repeat Dose and Reproductive/Developmental Toxicity
  Screening Test
- **GLP:** Yes
- **Year:** 1998
- **Species:** Rat
- **Strain:** Crj;CD (SD)
- **Route of administration:** Oral (by gavage)
- **Doses/concentration levels:** 0, 60, 200, 600 mg/kg/day (in distilled water)
- **Sex:** Male & Female
- **Exposure period:** Males; for 48 days from 2 weeks prior to mating
  Females; for 41 - 52 days from 14 days before mating to day 3 of location
- **Frequency of treatment:** Once daily.
- **Control group and treatment:** Concurrent vehicle. (distilled water)
- **Post exposure observation period:** None.
- **Duration of test:** Male; for 48 days
  Female; for 41 - 52 days
- **Statistical methods:** Dunnett's or Scheffe's test for continuous data and Chi square test for quantal data

REMARKS FIELD FOR TEST CONDITIONS

– Test Subjects:

· Age at study initiation: 10 week old for males, 10 week old for females
· Weight at study initiation: 359 - 400 g for males, 227 - 282 g for females
· No. of animals per sex per dose: 12 per sex per dose group

– Study Design:

· Vehicle: Distilled water
· Satellite groups and reasons they were added: None
· Clinical observations performed and frequency:
General condition was observed once a day, body wt. was determined on the first day, the last day of the administration, the day of sacrifice and once a week during the administration period. For pregnant females, body wt. was determined on the day 0, 14 and 20 of gestation and on day 0 and 4 of lactation. Food consumption was determined on the same day when body wt. was determined for 24 hr. For males haematology and biochemistry were conducted only at the time of necropsy after 48 days of test substance exposure.
· Organs examined at necropsy:

Organ weight: For both sexes, brain, pituitary gland, thyroid gland, heart, liver, kidney, spleen, adrenal, thymus, and in addition for males, testes and epididymis.

Microscopic: All animals in control and 600 mg/kg group, and unfertilized animals in other groups: brain, spinal cord, pituitary gland, eyeball, thyroid gland (including parathyroid gland), thymus, heart, trachea, lung, liver, kidney, adrenal, spleen, stomach, small intestine, large intestine, pancreas, urinary bladder, bone marrow, sciatic nerve, lymph node, testes, epididymis, prostate, seminal vesicle, ovary, uterus, vagina, mammary gland. All pregnant males and females in 60 and 200 mg/kg group: kidney and any organs which might be expected to have histopathological changes at the higher doses.

RESULTS

- **NOAEL**

Male : < 60 mg/kg/day
Female : < 60 mg/kg/day

- **LOAEL**

Not determined.

REMARKS FIELD FOR RESULTS.

– Body weight:

For males at 200 mg/kg, a tendency for low body weight gain during administration period was observed and statistically significant difference from controls was noticed for body weight gain 29 - 43 days *(Dunnets test $p \leq 0.05$)*. Low body weight gain during the

gestation period in females at 200 mg/kg was also observed *(Dunnets test $p \leq 0.05$)*.In both sexes at 600 mg/kg, a more remarkable body weight decrease was observed at the same time *(Dunnets test $p \leq 0.01$)*.

Table-1 Body weight change of male rats

Dose level (mg/kg)		0	60	200	600
No. of animals		12 (N)	12 (N)	12 (N)	12 (N)
Days of experiment	1	385±12 (12)	385±11 (12)	385±11 (12)	385±12 (12)
	8	403±17 (12)	399±23 (12)	395±13 (12)	368±41 (11)
	15	422±21 (12)	419±23 (12)	409±20 (12)	402±21 (9)
	22	445±20 (12)	436±28 (12)	428±19 (12)	416±17 (9)*
	29	473±20 (12)	463±29 (12)	448±19 (12)*	441±20 (9)**
	36	493±21 (12)	484±32 (12)	463±23 (12)*	455±22 (9)**
	43	503±18 (12)	494±29 (12)	474±24 (12)*	465±24 (9)**
	49	482±19 (12)	475±32 (12)	450±26 (12)**	438±19 (9)**
Gain	1 - 43	118±14 (12)	109±22 (12)	89±20 (12)**	81±19 (9)**

Significant difference from contraol group; *: P ≤ 0.05 **: P≤ 0.01
Mean ± S.D.
Unit; gram

Table-2 Body weight change of female rats

Dose level (mg/kg)		0	60	200	600
Before mating period					
No. of animals		12 (N)	12 (N)	12 (N)	12 (N)
Days of before mating	1	251±14 (12)	252±13 (12)	253±15 (12)	252±14 (12)
	8	259±16 (12)	257±13 (12)	253±18 (12)	255±12 (11)
	15	268±14 (12)	266±13 (12)	261±19 (12)	270±17 (11)
Gain	1-15	17± 8 (12)	14± 9 (12)	8± 8 (12)	17±14 (11)*
Gestation period					
No. of animals		12 (N)	12 (N)	12 (N)	12 (N)
Day of gestation	0	281±15 (12)	276±22 (11)	274±18 (12)	280±19 (10)
	7	310±16 (12)	310±18 (11)	301±22 (12)	301±22 (10)
	14	350±17 (12)	349±15 (11)	339±23 (12)	336±19 (10)
	21	458±20 (12)	457±22 (11)	432±30 (12)*	418±27 (10)**
Gain	0 - 21	176±12 (12)	181±11 (11)	158±18 (12)**	138±15 (10)**
Lactation period					
No. of dams		12 (N)	11 (N)	12 (N)	10 (N)
Day of Lactation	0	315±21 (12)	323±27 (11)	293±32 (12)	288±25 (10)
	4	332±23 (12)	327±21 (11)	308±26 (12)	312±26 (9)
Gain	0 - 4	18±24 (12)	4±21 (11)	15±24 (12)	20±24 (9)

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01
Mean ± S.D.
Unit; gram

– Food/water consumption:

For males at 600 mg/kg, a tendency for increase in food consumption during administration period was observed and statistically significant differences from controls were noticed on day 8 - 48 *(Dunnets test $p < 0.01$)*. For females at 600 mg/kg, a tendency for increase in food consumption during the premating period *(Dunnets test $p \leq 0.01$)* and gestation period *(Dunnets test $p \leq 0.05$)* was observed However, the statistically significant difference from controls was not observed during the lactation period in all groups.

Table-3 Food consumption change of male rats

Dose level (mg/kg)		0	60	200	600
No. of animals		12 (N)	12 (N)	12 (N)	12 (N)
Days of experiment	1 - 8	28± 2 (12)	29± 4 (12)	28± 2 (12)	24± 7 (12)
	8 - 15	30± 2 (12)	31± 2 (12)	31± 2 (12)	35± 3 (9)**
	22 - 29	31± 2 (12)	31± 2 (11)	31± 2 (12)	34± 3 (9)**
	29 - 36	32± 2 (12)	32± 3 (12)	32± 2 (12)	35± 2 (9)**
	36 - 43	30± 2 (12)	31± 2 (12)	31± 2 (12)	34± 2 (9)**
	43 - 48	30± 2 (12)	31± 2 (12)	30± 3 (12)	34± 3 (9)**
Cumulative consumption					
	1 - 15	410±28 (12)	416±36 (12)	413±30 (12)	428±36 (9)
	22 - 48	798±38 (12)	810±56 (11)	811±49 (12)	889±51 (9)**

Significant difference from contraol group; *: P ? 0.05 **: P ? 0.01
Mean ± S.D.
Unit; gram

Table-4 Food consumption change of female rats

Dose level (mg/kg)		0	60	200	600
Before mating period					
No. of animals		12 (N)	12 (N)	12 (N)	12 (N)
Days of before mating	1 - 8	21± 1 (12)	22± 1 (12)	21± 2 (12)	21± 1 (11)
	8 -10	22± 2 (12)	23± 1 (12)	24± 2 (12)	27± 2 (11)**
Cumulative consumption					
	1-15	305±21 (12)	310± 19 (12)	314±24 (12)	341±25 (11)**
Gestation period					
No. of dams		12 (N)	11 (N)	12 (N)	10 (N)
Day of gestation	0 - 7	27± 2 (12)	28± 1 (11)	28± 2 (12)	29± 4 (10)
	7 -14	28± 2 (12)	31± 1 (11)	31± 3 (12)	31± 3 (10)*
	14 - 21	29±39 (12)	31± 2 (11)	29± 2 (12)	29± 4 (10)
Cumulative consumption					
	0 - 21	593±12 (12)	626±23 (11)	614±41 (12)	627±57 (10)
Lactation period					
No. of dams		12 (N)	11 (N)	12 (N)	10 (N)
Day of Lactation	0 - 4	35±10 (12)	32± 8 (11)	33± 8 (12)	35±10 (9)

Significant difference from contraol group; *: P ≤? 0.05 **: P ≤? 0.01
Mean ± S.D.
Unit; gram

– Clinical signs : Blepharoptosis and mydriasis were observed in all groups of both sexes, and their changes were dose-related. In 60 mg/kg/day group, mydriasis was observed only in one male and one female, on the other hand blepharoptosis was observed in eight of 12 males (8/12) and all females (12/12). But both clinical signs were slight and observed only sporadically.

Table-1 Clinical observations in male rats.

	Dose level	Days experiment							Total
miyriasis(mg/kg)		1 - 7	8 - 14	15 - 21	22 - 28	29 - 35	36 - 42	43 - 49	(1 - 49)
	0	0	0	0	0	0	0	0	0
	60	0	1	0	0	0	1	0	1
	200	4	4	0	0	0	8	2	9
	600	12	11	7	9	9	9	8	12
blepharoptosis	0	0	0	0	0	0	0	0	0
	60	3	2	1	1	0	6	0	8
	200	12	12	12	12	12	12	12	12
	600	12	10	9	9	9	9	9	12

dead	0	0	0	0	0	0	0	0	0
	60	0	0	0	0	0	0	0	0
	200	0	0	0	0	0	0	0	0
	600	1	2	0	0	0	0	0	3
number of group	0	12	12	12	12	12	12	12	12
	60	12	12	12	12	12	12	12	12
	200	12	12	12	12	12	12	12	12
	600	12	11	9	9	9	9	9	9

Table-2 Clinical observations in female rats. (Before and during mating period)

signs	Dose level	Days experiment							Total
miyriasis(mg/kg)		**1 - 7**	**8 - 14**	**15 - 21**	**22 - 28**	**29 - 35**	**36 - 42**	**43 - 49**	**(1 - 49)**
	0	0	0	0	0	0	0	0	0
	60	0	1	0	0	0	0	0	1
	200	3	1	0	0	0	0	0	4
	600	12	11	10	2	1	1	1	12
blepharoptosis	0	0	0	0	0	0	0	0	0
	60	11	12	8	0	0	0	0	12
	200	12	12	12	0	0	0	0	12
	600	12	11	11	2	1	1	1	12
dead	0	0	0	0	0	0	0	0	0
	60	0	0	1	0	0	0	0	1
	200	0	0	0	0	0	0	0	0
	600	1	0	0	0	0	0	0	1
number of group	0	12	12	12	0	0	0	0	
	60	12	12	12	0	0	0	0	
	200	12	12	12	0	0	0	0	
	600	12	11	11	1	1	1	1	

Table-3 Clinical observations in female rats. (Gestation period)

signs	Dose level	Days experiment																							Total
miyriasis	**(mg/kg)**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**0 - 23**
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	60	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1
	200	1	3	2	1	1	3	3	3	0	1	1	1	1	0	0	0	0	1	1	1	2	2	0	0	11
	600	8	7	6	7	8	9	9	8	9	7	7	8	6	5	5	5	4	7	9	9	9	9	4	0	10
blepharoptosis																										
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	60	5	5	5	6	6	4	7	3	4	4	3	2	3	2	1	4	3	2	6	5	0	5	1	0	10
	200	12	12	12	12	12	12	12	11	11	12	12	12	12	12	12	11	12	12	12	12	10	11	6	0	12
	600	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	4	0	10
number of group																										
	0	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	8	
	60	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	3	
	200	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7	
	600	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	4	

Table-4 Clinical observations in female rats. (Lactation period)

signs	Dose level	Days experiment					Total
miyriasis	**(mg/kg)**	**0**	**1**	**2**	**3**	**4**	**0 - 4**
	0	0	0	0	0	0	0
	60	0	0	0	0	0	0
	200	10	10	8	2	0	12
	600	9	8	9	8	0	10
blepharoptosis	0	0	0	0	0	0	0
	60	3	1	1	1	0	3
	200	12	12	12	12	0	12
	600	10	10	9	9	0	10
number of group	0	12	12	12	12	12	
	60	11	11	11	11	11	
	200	12	12	12	12	12	
	600	10	10	10	9	9	

– Haematology :

Males: No dose-related changes in haematology.

– Biochem:

Males*:* No dose-related changes in biochemistry.

– Urinalysis: Not examined
– Ophthalmologic findings: Not examined.
– Mortality and time to death:

Males: In 600 mg/kg group, one and two animals died after 6 and 9 days, respectively.

Female: In 60 mg/kg group, one animal died after 16 days. In 600 mg/kg, one animal died after 3 days.
In the dead female rat at 60 mg/kg/day, the cause of death was not determined. But, in the dead rats at 600 mg/kg/day group, it was diagnosed that the cause of death occurred by test substance.

– Gross pathology incidence and severity:

No changes in gross pathology in the survival rats.
However, the reddish spots of digestive tracts, the abnormal foci with gastric ulcer, and the vacuolar degeneration in renal tubular epithelium were observed in the death rat of 600 mg/kg groups.

– Organ weight changes:

Male : Increase of adrenals weight was observed in 600 mg/kg group
Female : In 600 mg/kg, increase of organ weight were observed in adrenals and liver.

Dose level (mg/kg/day)	0	200	600	0	200	600
Absolute weight						
Liver (g, Mean ± SD)	13.56 ± 0.08	12.94 ± 1.92	11.76 ± 1.09**	14.45 ± 1.82	14.56 ± 1.07	15.43 ± 2.43
Adrenals (mg, Mean ± SD)	66 ± 2	67 ± 12	71 ± 8	80 ± 10	862 ± 8	87 ± 10
Relative weight						
Liver (mg, Mean ± SD)	2.815 ± 0.086	2.867 ± 0.315	2.682 ± 0.206	4.341 ± 0.396	4.741 ± 0.270	4.927 ± 0.535**
Adrenal (mg, Mean ± SD)	13.688 ± 1.934	14.865 ± 2.922	16.250 ± 1.836*	24.142 ± 2.978	26.647 ± 2.910	27.825 ± 2.976*

– Histopathology Abnormalities of the survival rats were not observed in pathological examination. However, the red spots of digestive tracts, abnormal foci with gastric ulcer and the vacuolar degeneration of renal tubular epithelium were observed in the dead rats of 600 mg/kg group.

CONCLUSIONS

Body weight gain was decreased at more than 200 mg/kg/day in both sexes. In clinical signs, blepharoptosis and mydriasis were observed in all groups of both sexes, and their changes were dose-related. In 60 mg/kg/day group, mydriasis was observed only in one male and one female, on the other hand blephraoptosis was observed in eight of 12 males (8/12) and all females (12/12). But, both clinical signs were slightly and observed only sporadically. Dead rats were observed in one female at 60 mg/kg/day, and in three males and one female at 600 mg/kg/day. As for the dead female rat at 60 mg/kg/day, the cause of death was not determined since no histopathological change related to death was observed. However, in the dead rats of 600 mg/kg/day group, the reddish spots in digestive tracts, abnormal foci with gastric ulcer and the vacuolar degeneration in renal tubular epithelium were observed. On the basis of blephraoptosis clinical signs in 60, 200 and 600 mg/kg /day groups, a NOAEL of less than 60 mg/kg/day was established for both sexes of rats exposed to this substance.

DATA QUALITY

- **Reliabilities:** Klimisch Code: 1 = Reliable without restriction

- **Remarks field for Data Reliability**

Well conducted study, carried out by Biosafety Research Centre, Foods, Drugs and Pesticides (An-pyo Centre) (Japan).

REFERENCES

Ministry of Health and Welfare, Japan (1998), Toxicity Testing Reports of Environmental Chemicals, vol. 6, 516 - 529.

GENERAL REMARKS

This study was conducted to examine both repeated dose toxicity and reproductive/developmental toxicity as an OECD screening combined study. Therefore, biochemical and haematological analysis, and urinalysis for females was not performed. Functional observation, estrous cycle length and pattern, and sperm examination were not performed because the test was conducted by the TG adopted in 1990.

TOXICITY TO REPRODUCTION

TEST SUBSTANCE

- **Identity:** 2,2,6,6-Tetramethylpiperidin-4-ol (CAS No. 2403-88-5)
- **Remarks:** Source: MITSUI CHEMICALS INC. Lot No. 6509051
  Purity > 99.8 %.

METHOD

- **Method/guideline:** OECD TG 422
- **Test type:** OECD Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test
- **GLP:** Yes
- **Year:** 1998
- **Species:** Rat
- **Strain:** Crj;CD (SD)
- **Route of administration:** Oral (by gavage)
- **Doses/concentration levels:**
  0, 60, 200, 600 mg/kg/day (in distilled water)
- **Sex:** Male & Female
- **Exposure period:**
  Male: for 48 days from 2 weeks prior to mating
  Female: for 41 - 52 days from 2 weeks prior to mating to day 3 postpartum throughout mating and pregnancy.
- **Frequency of treatment:** Once daily.
- **Control group and treatment:** Concurrent vehicle (distilled water).
- **Post exposure observation period:** None.
- **Duration of the test:** Male: for 49 days
  Female: for 42 - 53 days
- **Statistical methods:** Dunnett's or Scheffe's test for continuous data and Chi square test for quantal data

REMARKS FIELD FOR TEST CONDITIONS

– Test Subjects:
  · Age at study initiation: 10 week old for males, 10 week old for females

· Weight at study initiation: 359 - 400 g for males, 227 - 282 g for females
· No. of animals per sex per dose: 12 per sex per dose group

– Study Design:

The female animals were sacrificed on the day 4 of lactation. Females with no delivery were killed 4 days after the delivery expected date (1/10 in 600 mg/kg group).

· Vehicle: distilled water
· Satellite groups and reasons they were added: None
· Mating procedures: Male/female per cage; 1/1, length of cohabitation; at the most 3 days, until proof of pregnancy (formation of vaginal closing or sperm detection in vagina)
· Clinical observations performed and frequency:
Parent: General appearance once a day
Foetus: General appearance once a day after birth
Haematology and biochemistry for males conducted only at the time of necropsy after 49 days of test substance exposure.
· Organs examined at necropsy:
· Parent: organ weight: brain, thyroid gland, liver, kidney, spleen, adrenal, thymus and for males, testes and epididymis.
Microscopic: Dead animals in 60 and 600 mg/kg group, and the parent from which all pups died in 600 mg/kg group : brain, spinal cord, pituitary gland, eyeball, harderian gland, salivary gland, tongue, thyroid gland (including parathyroid gland), thymus, heart, trachea, bronchus, esophagus, lung, liver, kidney, adrenal, spleen, stomach, duodenum, small intestine, large intestine, pancreas, urinary bladder, sternum, bone marrow, sciatic nerve, lymph node, testes, epididymis, prostate, seminal vesicle, ovary, uterus, vagina, mammary gland, skin.
All pregnant males and females in 60 and 200 mg/kg group: kidney and any organs which might be expected to have histopathological changes at the higher doses.
Foetal: Full macroscopic examinations on all of pups
· Parameters assessed during study:
Body wt. (for males, once a week, the first and the last day of the administration, the sacrificed day : for pregnant females, on day 0, 14 and 20 of gestation, on day 0 and 4 of lactation), food/water consumption (once a week, on the same day when body wt. determined), No. of pairs with successful copulation, copulation index (No. of pairs with successful copulation/No. of pairs mated×100), estrus cycle, No. of pregnant females, fertility index (No. of pregnant animals/No. of pairs with successful copulation×100), No. of corpora lutea, No. of implantation sites, implantation index (No. of implantation sites/No. of corpora lutea×100), No. of living pregnant females, No. of pregnant females with parturition, gestation length, No. of pregnant females with live pups on day 0, gestation index (No. of females with live pups/No. of living pregnant females×100), No. of pregnant females with live pups on day 4, delivery index (No. of pups born/No. of implantation sites×100), No. of pups alive on day 0 of lactation, live birth index

(No. of live pups on day 0/No. of pups born× 100), sex ratio (Total No. of male pups/Total No. of female pups), No. of pups alive on day 4 of lactation, viability index (No. of live pups on day 4/No. of live pups on day 0× 100), body wt. of live pups (on day 0 and 4)

RESULTS

- **NOEL parental toxicity:** NOEL: Male > 600 mg/kg/day Female: 200 mg/kg/day
- **NOEL foetal toxicity:** NOEL: 200 mg/kg/day
- **Actual dose received by dose level by sex if available:**

  0, 60, 200, 600 mg/kg/day for both sexes

- **Maternal data with dose level:**

  Estrous cycle examination, continuous diestrus was observed in three females of the 600 mg/kg group and the mean estrous cycle of this group showed extension compared with the control group ($p < 0.05$).

- **Foetal data with dose level:**

  Male and female pups of the 600 mg/kg group showed lower body weights on day 4 of lactation.

REMARKS FIELD FOR RESULTS

Mortality and day of death :

Deaths caused by the test substance were observed one female (on 16 day) of the 60 mg/kg group, and three males (on 6 - 9 day) and one female (on 3 day) of the 600 mg/kg group.

Body weight : Low body weight gain during the premating period in females at 200 mg/kg was observed *(Dunnets test $p \leq 0.05$)*.

Food/water consumption:

For males, a tendency for increase in food consumption during administration period was observed at 600 mg/kg, and statistical significant difference from controls was noticed on day 8 to 48 of the administration.

For females, statistical significant difference from controls was observed during premating period (on 8 - 15 day) and gestation period (on 7 - 14 day), respectively.

– Reproductive data : No statistical significant difference from controls.
– Fetal data : No statistical significant difference from controls.
– Grossly visible abnormalities, external, soft tissue and skeletal abnormalities :

No statistically significant effects were observed in all groups.

Reproduction results of rats treated orally with 2,2,6,6-Tetramethylpiperidin-4-ol

Dose level (mg/kg/day)	0	60	200	600
No. of pairs mated	12	11	12	10
No. of pairs mated with successful copulation	12	11	12	10
Copulation index (%)	100	100	100	90.9
No. of pregnant females	12	11	12	10
Fertility index (%)	100	100	100	100
Pairing days until copulation (Mean ± S.D.)	2.9 ± 1.1	2.3 ± 0.9	2.4 ± 0.7	3.1 ± 0.8
No. of corpora lutea (Mean ± SD)	18.8 ± 1.5	20.6 ± 2.9	19.6 ± 2.5	18.6 ± 1.7
No. of implantation sites (Mean ± S.D.)	17.6 ± 1.6	17.2 ± 3.3	18.2 ± 1.9	17.0 ± 2.3
Implantation index (%, Mean ± S.D.)	93.4 ± 5.4	83.5 ± 14.3	93.2 ± 7.5	91.3 ± 8.0
No. of pregnant females with parturition (Mean ± S.D.)	12	11	12	10
Gestation length (days, Mean ± SD)	22.7 ± 0.5	22.3 ± 0.5	22.6 ± 0.5	22.4 ± 0.5
Gestation index (%)	100	100	100	100
Estrus cycle (days, Mean ± S.D)	4.1 ± 0.3	4.1 ± 0.3	4.3 ± 0.5	4.5 ± 0.4[?]

Copulation index (%)=(No. of pairs with successful copulation / No. of pairs mated)x100
Fertility index (%)=(No. of pregnant females / No. of pairs with successful copulation)x100
Gestation index (%)=(No. of females with live pups / No. of pregnant females)x100
Significant difference from control group ; [?] : P < 0.05

Litter results of rats treated orally with 2,2,6,6-Tetramethylpiperidin-4-ol

Dose level (mg/kg/day)	0	60	200	600
No. of pups born	16.3 ± 2.0	15.3 ± 3.3	15.4 ± 1.5	15.7 ± 2.7
Delivery index (%)	92.9 ± 7.0	90.3 ± 16.2	85.2 ± 6.9	92.1 ± 6.0
No. of pups alive on day 0 of lactation				
Total	16.3 ± 2.0	15.2 ± 3.3	15.3 ± 1.4	15.7 ± 2.7
Male	8.2 ± 2.2	7.7 ± 2.3	7.9 ± 1.8	7.0 ± 3.0
Female	8.2 ± 1.5	7.5 ± 2.6	7.4 ± 2.2	8.7 ± 2.3
Live birth index (%)	100 ± 0.0	99.5 ± 1.8	99.5 ± 1.7	100 ± 0.0
Sex ratio (Male/Female)	1.05 ± 0.37	1.15 ± 0.46	1.22 ± 0.60	0.90 ± 0.57
No. of pups alive on day 4 of lactation				
Total				
Male	7.8 ± 2.0	7.5 ± 2.2	6.5 ± 2.7	4.3 ± 2.9
Female	7.4 ± 1.1	6.5 ± 2.5	6.3 ± 2.5	6.4 ± 3.7
Viability index (%)				
Total	96.1 ± 7.5	96.8 ± 5.4	82.7 ± 28.4	67.2 ± 39.2
Male	91.9 ± 9.9	86.2 ± 10.4	85.8 ± 20.3	70.7 ± 35.0
No. of total dead pups born (Mean ± S.D.)	0.0 ± 0.0	0.1 ± 0.3	0.1 ± 0.3	0.0 ± 0.0
Stillbirth	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
cannibalism	0.0 ± 0.0	0.1 ± 0.3	0.1 ± 0.3	0.0 ± 0.0

Delivery index (%)=(No. of pups born/ No. of implantation sites)x100
Live birth index (%)=(No. of live pups on day 0 / No. of pups born)x100
Viability index (%)=(No. of live pups on day 4/ No. of live pups on day 0)x100
Sex ratio =Total No. of male pups/ Total No. of female pups
Values are expressed as Mean±S.D. Except sex ratio.

CONCLUSIONS

On the basis of these findings, NOEL of 2,2,6,6-Tetramethyl-4-hydroxypiperidine for reproductive toxicity to parental rats were considered to be more than 600 mg/kg/day for males, and 200 mg/kg/day for females. Moreover, NOEL of the test substance to F1 offspring was established to be 200 mg/kg/day.

DATA QUALITY

- **Reliabilities:** Klimisch Code: 1 = Reliable without restriction

Remarks field for Data Reliability

Well conducted study, carried out by Biosafety Research Centre, Foods, Drugs and Pesticides (An-pyo Centre) (Japan).

REFERENCES

Ministry of Health and Welfare, Japan (1998), Toxicity Testing Reports of Environmental Chemicals, vol. 6, 516 - 529.

GENERAL REMARKS

This study was conducted to examine both repeated dose toxicity and reproductive/developmental toxicity as an OECD screening combined study.

GENETIC TOXICITY IN VITRO (BACTERIAL TEST)

TEST SUBSTANCE

- **Identity:** 2,2,6,6-Tetramethylpiperidin-4-ol (CAS No. 2403-88-5)
- **Remarks:** Source: Mitsui Chemicals Inc. Lot No. 6509051
  Purity > 99.8 %

METHOD

- **Method/guideline:** Guideline for Screening Toxicity Testing of Chemicals (Japan) and OECD TG 471 and 472
- **Test type:** Reverse mutation assay
- **GLP:** Yes
- **Year:** 1998
- **Species/Strain:** *Salmonella typhimurium* TA100, TA1535, TA98, TA1537
  Escherichia coli WP2 *uvr*A
- **Metabolic activation:** with and without S9 from rat liver, induced with phenobarbital and 5,6-benzoflavone.
- **Statistical methods:** No statistical analysis was done.

REMARKS FIELD FOR TEST CONDITIONS

- **Study Design:**
  - Concentration:
    - S9: 0, 156, 313, 625, 1250, 2500, 5000 ug/plate
    +S9: 0, 156, 313, 625, 1250, 2500, 5000 ug/plate
  - Number of replicates: 2
  - Plates/test: 3
  - Procedure: Pre-incubation
  - Solvent: Distilled water
  - Positive controls:
    -S9mix ; 2-(2-furyl)-3-(5-nitro-2-furyl) acrylamide (TA100, TA98), N-ethyl-N'-nitro-N-nitrosoguanidine (WP2 uvrA), sodium azide (TA1535) and 9-aminoacridine(TA1537)
    +S9mix ; 2-aminoanthracene(five strains)

RESULTS

- **Cytotoxic concentration:**

Toxicity was observed as follow:
With metabolic activation: 2500 ug/plate; TA100, TA1537
5000 ug/plate; TA98, TA 1535, WP2 uvrA

Without metabolic activation: 2500 ug/plate; TA100, TA98, TA1537
5000 ug/plate; TA1535, WP2 uvrA

- **Genotoxic effects:**

	+	?	-
– With metabolic activation:	**[ ]**	**[ ]**	**[X]**
– Without metabolic activation:	**[ ]**	**[ ]**	**[X]**

REMARKS FIELD FOR RESULTS

CONCLUSIONS

Bacterial gene mutation is negative with and without metabolic activation.

DATA QUALITY

- **Reliabilities:** Klimisch Code: 1 = Reliable without restriction

Remarks field for Data Reliability

Well conducted study, carried out by Mitsubishi Chemical Safety Institute Ltd., (Japan).

REFERENCES

Ministry of Health and Welfare, Japan (1998), Toxicity Testing Reports of Environmental Chemicals, vol. 6, 530 - 533.

GENERAL REMARKS

None.

GENETIC TOXICITY IN VITRO (NON-BACTERIAL IN VITRO TEST)

TEST SUBSTANCE

- **Identity:** 2,2,6,6-Tetramethylpiperidin-4-ol (CAS No. 2403-88-5)
- **Remarks:** Source: Mitsui Chemicals Inc. Lot No. 6509051
  Purity > 99.8 %

METHOD

Method/guideline: Guideline for Screening Mutagenicity Testing of Chemicals (Japan) and OECD 473

- **Test type**: Chromosomal aberration test
- **GLP**: Yes
- **Year**: 1997 - 1998
- **Species/Strain:** CHL/IU cell
- **Metabolic activation:** with and without S9 from rat liver, induced with phenobarbital and 5,6-benzoflavone.
- **Statistical methods**: Fisher's exact analysis

REMARKS FIELD FOR TEST CONDITIONS

- **Study Design:**

For continuous treatment, cells were treated for 24 or 48 hrs without S9.
For short-term treatment, cells were treated for 6 hrs with and without S9 and cultivated with chemical-free fresh media for 18 hrs.
Based on the results of cell growth inhibition test, the test concentrations were decided as follows:

· ***Concentration*:**
[Main test]
-S9 (continuous treatment) :0, 100, 200, 400, 800 ug/mL
-S9 (short-term treatment) : 0, 100, 200, 400, 800 ug/mL
+S9 (short-term treatment) :0, 100, 200, 400, 800 ug/mL
In the short-term treatment assay without S9 mix, as mitotic index at the highest concentration was 6.6, three additional tests were conducted at up to 2000 ug/mL.
[Additional test 1]

-S9 (short-term treatment) : 0, 800, 1000, 1200 ug/mL
[Additional test 2 & 3]
-S9 (short-term treatment) : 0, 1000, 1500, 2000 ug/mL

· **Plates/test:** 2
· **Solvent:** Distilled water
· **Positive controls:**

Mitomycin C for continuous treatment
Cyclophosphamide for short-term treatment

RESULTS

- **Cytotoxic concentration:**

Toxicity was observed in continuous and short-term treatment with or without S9 mix as follows:

With metabolic activation : (6h short treatment): 726 ug/mL
Without metabolic activation : (6h short treatment): 565 ug/mL
Without metabolic activation :(24h continuous treatment): 572 ug/mL
Without metabolic activation :(48h continuous treatment): 683 ug/mL

- **Genotoxic effects:**

	Clastogenicity			polyploidy		
	+	?	-	+	?	-
– With metabolic activation:	**[ ]**	**[ ]**	**[X]**	**[ ]**	**[ ]**	**[X]**
– Without metabolic activation:	**[X]**	**[ ]**	**[ ]**	**[ ]**	**[ ]**	**[X]**

REMARKS FIELD FOR RESULTS

Structural or numerical chromosome aberration was not induced at any treatment conditions of main study. In additional tests for the short-term treatment assay without S9 mix, structural chromosome aberration was induced at 2000 ug/mL under mitotic index of 1.6 or 3.3. Numerical chromosome aberration was also induced at 2000 ug/mL, but the reproducibility was not recognized.

CONCLUSIONS

Authors concluded that chromosomal aberration of 2,2,6,6-tetramethyl-4-hydroxypiperidine was positive. However, the result was reassessed as described below "General Remarks".

DATA QUALITY

- **Reliabilities:** Klimisch Code: 1 = Reliable without restriction

- Remarks field for Data Reliability

Well conducted study, carried out by Mitsubishi Chemical Safety Institute Ltd., (Japan).

REFERENCES

Ministry of Health and Welfare, Japan (1998), Toxicity Testing Reports of Environmental Chemicals, vol. 6, 534 - 538.

GENERAL REMARKS

As chromosomal aberration was observed only at much higher than 50 % cell growth inhibitory concentration, which was considered to be due to cytotoxicity, this result should be considered to be equivocal

GENETIC TOXICITY IN VIVO

TEST SUBSTANCE

- **Identity:** 2,2,6,6-Tetramethylpiperidin-4-ol (CAS No. 2403-88-5)
- **Remarks:** Source: Mitsui Chemicals Inc. Lot No. 1502081
  Purity > 99.92%.

METHOD

- **Method/guideline:** OECD TG 474
- **Test type:** Micronucleus Test
- **GLP:** Yes.
- **Year:** 2001
- **Species:** Rat
- **Strain:** Crj:CD (SD)
- **Route of administration:** Oral (by gavage)
- **Doses/concentration levels:** 0, 250, 500, 1000 and 1500 mg/kg
- **Sex:** Male
- **Control group and treatment:**
  Negative control substance; Water for injection Positive control group; Cyclophosphamide
- **Exposure period:** 2 days
- **Statistical methods:** The IE ratio, an indicator of suppression of bone marrow cell growth, was analyzed by Student's t-test.
  For the incidence of MNIE 's, tables of Kastenbaum and Bowman were applied.

REMARKS FIELD FOR TEST CONDITIONS

- Test Subjects: Forty male Crj: CD (SD) IGS rats (seven weeks old) were purchased from Charles River Japan, Inc. on March 13, 2001. Healthy rats were used in this study after quarantine and acclimation for six days. They were seven weeks old and weighted from 273 - 299 g on the day of administration.
- Number of animals: Five rats per group were used.
- Body weight: The animals were weighted just before administration and before

preparation of specimen.

– Sampling time: The animals in each group were sacrificed 24-hours after the final administration.

– Experimental design: The test design in the micronucleus test is as follows.

Treatment group	Dose (mg/kg)	Times	Number of animals
Water for injection*	0	2	6
Test substance	250	2	6
Test substance	500	2	6
Test substance	1000	2	6
Test substance	1500	2	6
Cyclophosphamide	20	2	6

– Preparation of specimen:

Animals were euthanized by CO_2 inhalation 22 to 24 hours after the final administration.
The ends of each bone were cut off and the bone marrow was drained into a test tube by injecting 1 mL of fetal bovine (FBS, GIBCO BRL) into the bone.
This mixture of bone marrow and FBS were centrifuged (1000 r.p.m. for 5 min.) and the supernatant was removed. The bone marrow cells suspension was smeared onto a clean slide. The slides were stained with acridine orange solution.

– Observation of slides:

The coded smear slides were observed under a microscope. Two thousand immature erythrocytes (IE) were examined per animal, the number of micronucleated immature erythrocytes (MNIE) per 2000 IE's was determined and the ratio (%) of MNIE calculated.
Five hundred erythrocytes (IE + mature erythrocytes: ME) per animal were observed, and the ration of IE's to all the erythrocytes was determined as an indicator of suppression of the increase in bone marrow cells.

– Statistical analysis:

The IE ratio, an indicator of suppression of bone marrow cell growth, was analyzed by Student's t-test. The incidence of MNIE was applied by Kastenbaum and Bowman's tables.

RESULTS

The MNIE % values of this substance treatment groups were within 0.08 to 0.12% and no significant difference was observed in comparison with the negative control group (0.07%).
The IE % values were 47.30% at 250 mg/kg, 45.47% at 500 mg/kg, 43.90% at 1000 mg/kg and 39.96% at 1500 mg/kg, respectively, and these displayed significant differences in comparison with the negative control group (50.87%).
1 of 6 animals died at 1500 mg/kg.
MNIE % and IE % were 3.50% and 40.20%, respectively in the positive control group, and showed significant differences in comparison with the negative control group.
The negative control incidences of MNIE among tests was within the range of

the laboratory background data and positive control ones showed remarkable increase.
This chemical dose not induce micronuclei under the test conditions employed.

CONCLUSIONS

This chemical does not induce micronuclei under the test conditions employed.

DATA QUALITY

- **Reliabilities:** Klimisch Code: 1 = Reliable without restriction
- **Remarks field for Data Reliability**

Well conducted study, carried out by Shin Nippon Biomedical Laboratories, LTD. (Japan)

REFERENCES

Mitsui Chemicals Inc., Japan (2001), unpublished data.

GENERAL REMARKS