FOREWORD INRODUCTION

3-Methoxy-3-methyl-1-butanol

CAS N°: 56539-66-3

SIDS Initial Assessment Report

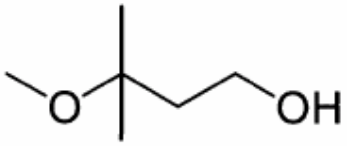
For

SIAM 18

Paris, France, 20-23 April 2004

1. Chemical Name:	3-Methoxy-3-methyl-1-butanol
2. CAS Number:	56539-66-3
3. Sponsor Country:	Japan Contact Point: Mr. Motohiko Kato Director Second International Organizations Division Ministry of Foreign Affairs, Japan
4. Shared Partnership with:	
5. Roles/Responsibilities of the Partners:	
• Name of industry sponsor /consortium	
• Process used	
6. Sponsorship History	
• How was the chemical or category brought into the OECD HPV Chemicals Programme ?	The original draft documents were prepared by the Japanese government.
7. Review Process Prior to the SIAM:	Expert committee performed spot checks on randomly selected endpoints and compared original studies with data in SIDS dossier.
8. Quality check process:	
9. Date of Submission:	23 January 2004
10. Date of last Update:	08 December 2004
11. Comments:	

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	56539-66-3
Chemical Name	3-Methoxy-3-methyl-1-butanol
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

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

In an acute dermal toxicity study with 3-methoxy-3-methyl-1-butanol (MMB) at 2000 mg/kg bw, there was no death, clinical sign or abnormality at necropsy in SD rats. The acute dermal LD_{50} was considered to be more than 2000 mg/kg bw. In an acute oral toxicity study [OECD TG 401], Crj:CD SD rats (5 animals/sex/dose) were given MMB by gavage at 0, 2000, 3200, 4000 or 5000 mg/kg bw for males and females. Deaths were found in males and females at 4000 mg/kg and higher. No changes in body weight were recorded for rats that died. The LD_{50} values were estimated to be 4500 and 4300 mg/kg bw in males and females, respectively. There is no available information on acute inhalation toxicity.

The undiluted MMB showed slight irritation to the skin after prolonged exposure in rabbits. MMB was moderately irritant to rabbit eyes. There was no evidence of sensitisation of MMB in guinea pigs.

In a repeated dose toxicity study, Crj:CD(SD)IGS rats (5 animals/sex/dose) were given MMB by gavage at 0 (vehicle: distilled water), 15, 60, 250 or 1000 mg/kg bw/day. The administration period was 28 days and the recovery period was 14 days after administration. There were no MMB-induced changes in general condition, body weight gain, food consumption, hematological findings, necropsy findings and histopathological findings. A decrease in chloride in males and females at 1000 mg/kg bw/day and increases in A/G ratio and inorganic phosphorus in males at 1000 mg/kg bw/day were detected. An increase in relative weight of the kidneys in males at 250 (11%) and 1000 mg/kg bw/day (15%) and in females at 1000 mg/kg bw/day (16%), and an increase in relative weight of the liver in males (10%) and females (13%) at 1000 mg/kg bw/day after the administration period and in males at 1000 mg/kg bw/day (7%) after the recovery period were detected. The NOAELs for repeated dose toxicity were considered to be 60 mg/kg bw/day for males and 250 mg/kg bw/day for females.

In a reverse gene mutation assay [OECD TG 471], MMB was not mutagenic in *Salmonella typhimurium* TA100, TA1535, TA98, TA1537, and TA 1538 or in *Escherichia coli* WP2 uvrA either with or without an exogenous metabolic activation. In a chromosomal aberration test [OECD TG 473], MMB did not induce structural chromosomal aberrations or polyploidy either with or without an exogenous metabolic activation.
There is no available information on carcinogenicity.

In the reproduction/developmental toxicity screening test [OECD TG 421], Crj:CD(SD)IGS rats (12 animals/sex/dose) were given MMB by gavage at 0 (vehicle: distilled water), 8, 40, 200 or 1000 mg/kg bw/day. Males were dosed for 47 days and females were dosed from day 14 before mating to day 4 of lactation throughout the mating and pregnancy period. Increases in absolute and relative weights of the kidney in males at 200 mg/kg bw/day and higher and relative weight of the liver and kidney in females at 1000 mg/kg bw/day were detected. No effects of MMB on reproductive and developmental parameters were observed. No external or internal malformation was found in pups at any dose. The NOAELs were considered to be 40 mg/kg bw/day in males and 200 mg/kg bw/day in females for general toxicity and 1000 mg/kg bw/day for reproductive and developmental toxicity in rats.

In a developmental toxicity study, Crj:CD(SD) female rats (25 animals/dose) were given MMB by gavage at 0

(vehicle: deionized water), 250, 500 or 2000 mg/kg bw/day on days 6-15 of gestation. Decreased motor activity, excess salivation, ataxia, muscle flaccidity and loss of righting reflex at 2000 mg/kg bw/day and decreases in body weight gains and food consumption at 250 mg/kg bw/day and higher were observed in dams. Fetal body weights were decreased at 2000 mg/kg bw/day. No increases in embryonic/fetal deaths and fetal malformations were detected after administration of MMB. Increases in skeletal variations and delayed ossification were found at 2000 mg/kg bw/day. The NOAELs were considered to be less than 250 mg/kg bw/day for maternal toxicity and 500 mg/kg bw/day for developmental toxicity in rats.

Environment

3-Methoxy-3-methyl-1-butanol (MMB) is a colourless liquid with a water solubility of 100 g/l at 25 °C, a melting point of lower than –50 °C, a boiling point of 173 °C at 1013 hPa, a vapour pressure of 1.25 hPa at 25 °C and a density of 0.927 g/cm^3 at 25 °C. Based on the measured log Kow value of 0.18 bio- or geoaccumulation of this chemical is unlikely. Environmental distribution using a Mackay level III fugacity model suggests that when MMB is released into air or water, it remains in the original compartment whereas when released into soil, 29.4 % is distributed into air, 9.3 % into water and 61.3 % remains in soil. A ready biodegradability test showed that MMB failed to meet a criterion for ready biodegradability (biodegradation rate = 50% after 28 days), however complete biodegradation was observed in an inherent biodegradation test. A study on hydrolysis indicates that MMB is stable in water. In the atmosphere MMB is indirectly photodegraded by reaction with OH radicals with a half-life of 1.1 days.

Ecotoxicity data on this substance are available for aquatic species from three trophic levels. In an algal growth inhibition test (OECD TG 201, *Selenastrum capricornutum,* open system), acute toxicity results of 72 h ErC_{50} >1,000 mg/L and 72 h EbC_{50} >1,000 mg/L were obtained. For daphnids, a 48 h EC_{50} of > 1000 mg/L was reported (OECD TG 202, *Daphnia magna*, static). For fish (OECD TG 203, *Oryzias latipes,* semi-static) a 96 h LC_{50} > 100 mg/L is available.

Regarding chronic toxicity to algae, a 72 h NOEbC of 1,000 mg/L (OECD TG 201, *Selenastrum capricornutum*, open system) was reported. In daphnids, an 21 d EC_{50} of >100 mg and a 21 d NOEC of 100 mg/L were reported (OECD TG 211, *Daphnia magna,* semi-static).

Exposure

The annual production volume of 3-methoxy-3-methyl-1-butanol (MMB) in Japan is ca. 10,000 tonnes in 2002. In 2002, ca. 2000 tonnes of this substance were exported from Japan.

MMB is synthesized from methanol and iso-butylene (C4 fraction of cracked naphtha) in a closed system in the Sponsor country. MMB is used as a solvent for paints, inks, fragrances (ca. 70%), and as a synthetic intermediate for detergents for industrial use (ca. 30%).

Although no monitoring data for MMB at the production site is available, significant emission of MMB into the environment is unlikely because well-controlled waste water treatment is in place and measures to prevent exposure to air are being taken during the production process.

Since MMB has a moderate vapour pressure and is miscible with water or organic solvents, occupational exposure through inhalation of the vapour and dermal route is possible. At the production site, workers who operate sampling and analysis, drum filling, lorry tank filling may be exposed to this chemical. The workers wear protective gloves and goggles during these operations. At user sites where this chemical is used as a solvent occupational exposure is possible, although no information is available. Since end-use products (paint, detergents) contain MMB, exposure to consumers and the environment is expected. Monitoring data at production site or user sites are not available.
No exposure standard value for this chemical was located.

RECOMMENDATION

The chemical is currently of low priority for further work

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health:

The chemical possesses properties indicating a hazard for human health (eye irritation, skin irritation after prolonged exposure). Although these hazards do not warrant further work (as they are related to reversible effects), they should nevertheless be noted by chemical safety professionals and users.

Environment:

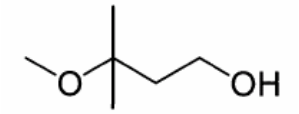
The chemical is currently of low priority for further work based on its low hazard profile.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 56539-66-3
IUPAC Name: 3-Methoxy-3-methyl-1-butanol
Molecular Formula: $C_6H_{14}O_2$
Structural Formula:



Molecular Weight: 118.17
Synonyms: Butanol, 3-methoxy-3-methyl
3-Methoxy-3-methylbutan-1-ol
1-Butanol, 3-methoxy-3-methyl
3-Methyl-3-methoxybutanol
Solfit

1.2 Purity/Impurities/Additives

Purity: > 98 %

Impurity: water < 0.04%

1.3 Physico-Chemical properties

Table 1 Summary of physico-chemical properties

Property	Value	Protocols (Reference) or comments
Physical state	Liquid	
Melting point	≦ -50°C	OECD TG 102 (CERI, 2001b)
Boiling point	173.0 °C (1013 hPa)	OECD TG 103 (CERI, 2001c)
Relative density	0.926 (25°C)	(Sigma-Aldrich-Fluka MSDS 1998)
Vapour pressure	125 Pa (25°C)	OECD TG 104 (CERI, 2001d)
Water solubility	> 100 g/l (25°C)	OECD TG 105 (CERI, 2001f)
Partition coefficient n-octanol/water (log value)	0.18 (25°C)	OECD TG 107 (CERI, 2001e)
Henry's law constant	0.148 Pa m^3/mol (25°C)	

3-Methoxy-3-methyl-1-butanol (MMB) is a colourless liquid with a slight ether odour.

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

Production Volumes

Annual production volume of 3-methoxy-3-methyl-1-butanol (MMB) in Japan is ca. 10,000 tonnes in 2002 by one producer. In 2002, ca. 2000 tonnes of this substance was exported from Japan (Kuraray, 2002). No information on a worldwide production volume is available.

MMB is synthesized from methanol and iso-butylene (C4 fraction of cracked naphtha) in a closed system in sponsor country.

Use Pattern

MMB is used as a solvent for paints, inks, fragrances (ca. 70%), and a raw material for detergents for industrial use (ca. 30%) (Kuraray, 2002).

2.2 Environmental Exposure and Fate

2.2.1 Sources of Environmental Exposure

Although no monitoring data for MMB at the production site is available, significant emission of MMB into the environment is unlikely because a well-controlled waste water treatment and a measure to prevent exposure to air are being taken during the production process at a production site in Japan (Kuraray, 2002).

Since some end use products contain MMB (e.g. paints and detergents), there is a potential for environmental exposure from these products.

2.2.2 Photodegradation

The half-life of MMB in air by the reaction with photochemically produced OH radical was calculated as 1.1 days (rate constant: 9.96 x 10^{-12} cm^3/molecule/sec, OH radical concentration: 1.5 x 10^6 molecule/cm^3, and irradiation time: 12 hrs/day) (CERI, 2004b)

2.2.3 Stability in Water

A preliminary study according to OECD TG 111 (50 °C for 5 days at pH 4.0, 7.0 and 9.0) showed that MMB was stable in water and its half-life was estimated to be more than one year at 25°C (CERI, 2001g).

2.2.4 Transport between Environmental Compartments

Based on a measured vapour pressure value of 125 Pa at 25 °C and a water solubility of 100 g/l at 25 °C, the Henry's Law constant is calculated to be 0.148 Pa x m^3/mole indicating that volatilisation of MMB is not significant but can be expected to some extent.

Using the following parameters, environmental distribution patterns of MMB were estimated with a fugacity-based Mackay level III model (CERI, 2004a).

Input parameter: Molecular weight: 118.17, Melting Point: < -50 °C, Vapour pressure: 125 Pa, Water solubility: 100 g/l, log Kow: 0.18 and Temperature 25 °C.

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

Compartment	Release			
	100% to air	100% to water	100% to soil	Equal to air/water/soil
Air	97.2%	10.1%	29.4%	0.616%
Water	2.7%	89.5%	9.3%	45.8%
Soil	0.1%	0.0%	61.3%	53.5%
Sediment	0.0%	0.4%	0.0%	0.0782%

The model predicted that when MMB is released into air and water, it mainly remains in the original compartment whereas when released into soil 29.4% is distributed into air, 9.3% into water and 61.3% remains in the soil compartment. When MMB is released at equal amounts into air, water and soil, it will partition into water and soil to an equal extent.

2.2.5 Biodegradation

A ready biodegradability test was conducted in accordance with OECD TG 301 (CERI, 2001a). Biodegradation rates were determined by a BOD meter and GC analysis. Out of three replicates, inconsistent results were obtained. One vessel showed almost complete biodegradation by both BOD and GC analysis, whereas only partial biodegradation was observed in the other two vessels (21% by BOD, 13-18% by GC analysis). Average biodegradation rates by BOD and GC analysis were 50 % and 44 %, respectively.MMB failed to meet the criterion for ready biodegradation (60% of pass level and 10-day window).

An inherent biodegradability test was performed according to OECD TG 302C under GLP conditions (CERI, 2002). In this test, complete biodegradation was observed by both BOD and GC analysis in all test solutions (n=3) after 28 days.

2.2.6 Bioaccumulation

A bioconcentration factor of MMB was estimated to be 3.16 using a measured log Kow value of 0.18 (CERI, 2004c). The result indicates that bioaccumulation of MMB in aquatic organisms is unlikely to occur.

2.3 Human Exposure

2.3.1 Occupational Exposure

Since MMB has a moderate vapour pressure and is miscible with water or organic solvents, occupational exposure through inhalation of the vapour and dermal route is possible. At one production site in Japan, workers who operate sampling and analysis, drum filling, lorry tank filling may be exposed to this chemical. Currently, sampling and analysis is conducted once a day, and drum filling every three days. At the production site, workers wear protective gloves and goggles during these operations. At user sites where this chemical is used as a solvent or a raw material, occupational exposure is possible, although further information is not available.

Monitoring data at production site or user sites are not available.

No exposure standard value for this chemical was located.

2.3.2 Consumer Exposure

Since end-use products (paint, detergents) contain MMB, consumer exposure via dermal and inhalation routes to MMB is possible (Kuraray, 2002).

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

There is no available information.

3.1.2 Acute Toxicity

Inhalation

There is no available information.

Dermal

One study on acute dermal toxicity in Crj: CD(SD) rats is reported [IRI, 1991g]. This study was conducted according to Test Guideline of Japanese MAFF under GLP. Details of this study are as follows.

Rats were prepared by clipping the hair of their back and free of hair approximately 24 hours before application [IRI, 1991g]. MMB was applied at 2000 mg/kg bw evenly onto gauze dressing which was applied to the shaved back of each rat. Care was taken to avoid abrading the skin. After a contact period of 24 hours following dosing, the dressing was removed, and the skin was wiped with a water dampened tissue to remove excess test material. Neither death nor clinical sign was noted during the 14-day observation period. No abnormalities were detected at necropsy. The LD_{50} was considered to be more than 2000 mg/kg bw.

Oral

Reliable studies on acute oral toxicity are reported in rats [HRC, 1989a; MHLW, Japan, 2003] and mice [OHSC, 1973] (Table 3). The studies by MHLW and HRC were identified as key studies because these were well conducted according to an OECD Test Guideline [TG 401] under GLP. The mouse study was considered to be insufficient as a key study because it was not conducted under GLP and no detailed information was available.

Crj:CD SD rats (5 animals/sex/dose) were given MMB by gavage at doses of 0, 2000, 3200, 4000 or 5000 mg/kg bw for males and females [HRC, 1989a]. Deaths were found in males and females at 4000 mg/kg and higher. No change in body weight or body weight losses were recorded for rats that died. Slightly pale cortex (kidney) was observed post-mortem in three males and three females at 5000 mg/kg bw and one female at 4000 mg/kg bw that died. The LD_{50} values were estimated to be 4500 and 4300 mg/kg bw in males and females, respectively.

Crj:CD(SD)IGS rats (5 animals/sex/dose) were given MMB by gavage at doses of 0 (vehicle: distilled water), 1000 or 2000 mg/kg bw for males and females [MHLW, Japan, 2003]. There were no deaths during the study. Spontaneous locomotor activity was slightly decreased at 2000 mg/kg bw. No changes were detected in body weight gains and necropsy findings. The LD_{50} value was estimated to be more than 2000 mg/kg bw for both sexes.

Based on the results of these studies in rats, the values of LD_{50} for acute oral toxicity were considered to be 4500 mg/kg bw in males and 4300 mg/kg bw in females.

Table 3 Acute oral toxicity of MMB in rats and mice.

Species	Type	Value	Reference
Rat	LD_{50}	more than 2000mg/kg bw for males and females	MHLW Japan, 2003
Rat	LD_{50}	4500 mg/kg bw for males 4300 mg/kg bw for females	HRC, 1989a
Mouse	LD_{50}	5380 mg/kg bw for males	OHSC, 1973

Conclusion

The dermal LD_{50} was considered to be more than 2000 mg/kg bw for both sexes in rats. The oral LD_{50} values were estimated to be 4500 and 4300 mg/kg bw for male and female rats, respectively.

3.1.3 Irritation

Skin Irritation

Two studies on skin irritation were conducted in New Zealand white rabbits under GLP [IRI, 1991ab]. Details of these studies are as follows.

The hair of the dorsal area of the trunk of rabbits (6 animals) were clipped and MMB was applied to the intact skin using a patch of gauze for 4 hours [IRI, 1991a]. In the shaved area 4 sites were designated and 2 sites were designated as test sites. MMB was applied at a concentration of 100 or 50% v/v in distilled water (2 test sites). Triethyl citrate or distilled water was applied as control (2 control sites). Four patches were applied to each rabbit and the patches were covered with tape. The gauze was then removed, and the skin was wiped with damp tissues. Skin reactions were assessed at 1, 24, 48 and 72 hours after removing the patch. At a concentration of 100%, very slight erythema was noted in one animal at the 24 hours assessment only. No skin reactions were noted at a concentration of 50%. No skin reactions were noted with the control materials, triethyl citrate and distilled water.

The dermal irritation potential of MMB following repeated application was investigated in 6 rabbits [IRI, 1991b]. Treatment comprised 28 consecutive 23 hours exposures with skin assessment 1 hour after patch removal. In the shaved area 4 sites, 2 on either side of the vertebral column, were designated as test sites. MMB was applied at a concentration of 100 or 50% v/v in distilled water (2 test sites). Triethyl citrate or distilled water was applied as control (2 control sites). Four patches were applied to each rabbit and the patches were covered with tape. Very slight to well defined erythema was noted at a concentration of 100% with a score of 3 (moderate to severe erythema) in one rabbit at day 9 of the assessment only. Very slight to slight edema was also noted at a concentration of 100%. No skin reactions were noted following repeated application of MMB at a

concentration of 50%. No skin reactions were noted with the control materials, triethyl citrate and distilled water.

Eye Irritation

The eye irritation potential of MMB was investigated in New Zealand white rabbits [IRI, 1991c]. This study was conducted according to an EPA test guideline [EPA OPP 81-4] under GLP. Details of this study are as follows.

Three rabbits had MMB instilled into the right eye which was then rinsed 30-60 sec. later with 100 mL of distilled water. Ocular reactions were recorded 1, 24, 48 and 72 hours after instillation and then again at 4, 7 and 11 days. The 3 rinsed eyes showed slight to moderate corneal opacity, moderate conjunctival redness and chemosis, slight iritis and slight discharge. By day 7, 2 of the 3 rinsed eyes returned to normal, and the third showed complete recovery by 11 days post-instillation.

A further six rabbits had MMB instilled into the right eye but were not subjected to rinsing. Ocular reactions were recorded at 1, 24, 48 and 72 hours after instillation and then again at 7, 9 and 10 days. The non-rinsed eyes showed slight corneal opacity, slight iritis, moderate to severe conjunctival responses and slight to severe discharge. By day 7, 4 of the 6 treated eyes returned to normal, and the remaining 2 showed complete recovery by 9-10 days post-instillation.

MMB had moderate irritation effect to rabbit eyes and rinsing for 30-60 sec. after instillation with distilled water did not reduce the irritancy.

Conclusion

The undiluted MMB showed light irritation to the skin in rabbits. MMB had moderate irritation effects to rabbit eyes.

3.1.4 Sensitisation

Skin Sensitisation

A photosensitisation test [IRI, 1991f] and a maximization test [IRI, 1991d] with MMB in Dunkin-Hartley guinea pigs were conducted under GLP. Details of these studies are as follows.

Immediately prior to the first induction application, 4 x 0.1 mL of Freund's Complete Adjuvant were intradermally injected at the corners of the shaved area. Approximately 0.1 mL of MMB at 100% was applied open epicutaneously to the test site of each test group of guinea pigs. Approximately 30 min later, the test group guinea pigs were placed in an exposure chamber and exposed to UVA radiation. Immediately prior to application and 24 hours after the application/UV exposure the test sites were assessed for irritation. This procedure, application/UV exposure and assessment, was repeated further 4 times. Twenty days after the final induction exposure, the dorso lumbar area of each group guinea pig was clipped and closely shaved. Four test sites were marked on the test group. Twenty four hours later 0.1 mL of MMB at 100% was applied on the prepared sites. The lower dorso lumbar area test sites on each animal were then covered with light-proof tapes. Thirty minutes after application of test material, the test group and control group guinea pigs were exposed to UVA radiation. The test sites were assessed at 24, 48 and 72 hours after irradiation for evidence of erythema and/or oedema. None of the 10 test group animals showed a positive response to MMB with or without UVA. There is no evidence that MMB shows photosensitisation in guinea pigs.

The sensitisation potential of MMB was investigated by means of the Magnusson-Kligman Maximisation Test [IRI, 1991d] in Dunkin-Hartley guinea pigs. Animals were given intradermal injections (0.1 mL of Freund's Adjuvant, MMB at 10% v/v in distilled water or distilled water, or 50:50 emulsion of MMB in Freund's Adjuvant). One hour and 24 hours after injection, the treated sites were assessed for irritation. Six days after the injection, the injection sites of animals was shaved again and then wetted with 10% sodium lauryl sulphate to provoke a mild inflammatory response to enhance he possibility of sensitisation. After 24 hours, charge with MMB at 10% in distilled water or distilled water was applied to the pretreated area and the patch covered by an overlapping piece. One hour and 4 hours after patch removal, the treated sites were assessed for irritation. Two weeks after the start of topical induction, animals were challenged with MMB at 100% or distilled applied on pieces of filter paper. The patches were held in place for 24 hours. The response was determined at 24 and 48 hours after removal of the challenge patch. At challenge, none of the test or control group animals treated with MMB at a concentration of 100% showed a positive response. There is no evidence from the test results that MMB is a sensitiser in guinea pigs.

Respiratory Tract Sensitisation

There is no available information.

Conclusion

There is no evidence of MMB-induced sensitisation in guinea pigs.

3.1.5 Repeated Dose Toxicity

Studies in Animals

Inhalation

A repeated inhalation toxicity study was reported [OHSC, 1976]. SD rats (10 males/dose) were exposed to MMB in vapor by whole-body inhalation at a concentration of 0, 100, 300 or 500 ppm for 4 hours/day, 5days/week, for 4 weeks. The observation of general condition, body weight gain, food and water consumption, urinalysis, hematological, blood biochemical, and pathological examinations were performed. There were no changes in general condition, body weight gain, food consumption, hematological findings, necropsy findings and histopathological findings. Although increases in GOT at 100 and 500 ppm and in absolute and relative weight of the kidneys at 100 ppm and higher were observed, no histopathological changes in the liver and kidney was detected. The LOAEL for repeated inhalation toxicity was considered to be 100 ppm in male rats.

Dermal

There is no available information.

Oral

A repeated dose toxicity study was reported [MHLW, Japan, 2003]. This study was conducted according to a Guideline for the 28 days repeated dose toxicity test in mammalian species (Japan) under GLP (MHLW, Japan, 2003). Details of this study are as follows.

Crj:CD(SD)IGS rats (5 animals/sex/dose) were given MMB by gavage at doses of 0 (vehicle: distilled water), 15, 60, 250 or 1000 mg/kg bw/day. The administration period was 28 days and the

recovery period was 14 days after administration in males and females. Animals were sacrificed on day 29 (end of the administration period) or day 43 (end of the recovery period). The observation of general condition, body weight gain, food consumption, urinalysis, hematological, and blood biochemical were performed in both sexes of all groups. Histopathological examinations were performed in both sexes in the control and highest dose groups. No deaths were found in any group. There were no changes in general condition, body weight gain, food consumption, hematological findings, necropsy findings and histopathological findings. A decrease in chloride in males and females at 1000 mg/kg bw/day and increases in A/G ratio and inorganic phosphorus in males at 1000 mg/kg bw/day were detected. No differences in these blood chemical parameters from the control values were found after the recovery period. An increase in relative weight of the kidney in males at 250 (11%) and 1000 mg/kg bw/day (15%) and in females at 1000 mg/kg bw/day (16%), and an increase in relative weight of the liver in males (10%) and females (13%) at 1000 mg/kg bw/day after the administration period and in males at 1000 mg/kg bw/day (7%) after the recovery period were detected. Based on the increase of relative weight of the kidney in males at 250 mg/kg bw/day and higher and increases of relative weights of the kidney and liver in females at 1000 mg/kg bw/day, the LOAELs/NOAELs for repeated dose toxicity were considered to be 250/60 mg/kg bw/day for males and 1000/250 mg/kg bw/day for females.

Conclusion

In an oral repeated dose toxicity study in rats, increases of relative weight of the kidney in males at 250 mg/kg bw/day and higher and of relative weight of the kidney and liver in females at 1000 mg/kg bw/day were detected. The NOAELs for repeated dose toxicity were considered to be 60 mg/kg bw/day for males and 250 mg/kg bw/day for females.

3.1.6 Mutagenicity

In vitro Studies

Bacterial test

The results of two reverse gene mutation assays are reported. [MHLW, Japan, 2003; HRC, 1989b]. Both studies were conducted according to a current protocol [OECD TG 471] under GLP.

Cytotoxicity and growth inhibition of MMB were not observed up to the highest concentration in any strain with or without S9 mix in *Salmonella typhimurium* TA100, TA1535, TA98, TA1537, *Escherichia coli* WP2 uvrA in the study by MHLW (2003) and *S. typhimurium* TA 1535, TA 1537, TA 1538, TA 98, TA 100, *E. coli* WP2 uvrA in the study by HRC (1989b). The highest concentration tested was 5000 ug/plate in both studies. Therefore, MMB was not mutagenic in *S. typhimurium* TA 1535, TA 1537, TA 1538, TA 98, TA 100 or *E. coli* WP2 uvrA at concentrations of up to 5000 ug/plate with or without S9 mix.

Non-bacterial in vitro test

A chromosomal aberration test was conducted according to a current protocol [OECD TG 473] in cultured Chinese hamster lung (CHL/IU) cells [MHLW, Japan, 2003] under GLP.

The maximum concentration was established, based on the growth inhibition test in which growth inhibition was not observed at a concentration of 1.2 mg/mL (10 mmol/L) dissolved in distilled water for 6 hours short-term treatment with or without S9 mix and for 24 hours continuous term treatment with S9 mix. The maximum concentration was decided to be 1.2 mg/mL for 6 hours short-term treatment with or without S9 mix and for 24 hours continuous term treatment without S9

mix. Structural chromosomal aberrations and polyploidy were not induced up to the highest concentration in any treatment.

In vivo Studies

There is no available information.

Conclusion

MMB was not genotoxic with or without an exogenous metabolic activation system in bacterial tests and in a chromosomal aberration test in mammalian cells *in vitro*.

3.1.7 Carcinogenicity

There is no available information on carcinogenicity.

3.1.8 Toxicity for Reproduction

Studies in Animals

Two studies are available for reproductive and developmental toxicity. One study was conducted according to an OECD TG 421, reproduction/developmental toxicity screening test [MHLW, Japan, 2003] under GLP. The other study was conducted according to an FDA TG, guidelines for reproduction studies for safety evaluation of drugs for human use [ARL, 1991] under GLP. Details of these studies are as follows.

In the reproduction/developmental toxicity screening test [MHLW, Japan, 2003], Crj:CD(SD)IGS rats (12 animals/sex/dose) were given MMB by gavage at doses of 0 (vehicle: distilled water), 8, 40, 200 or 1000 mg/kg bw/day. Males were dosed for 47 days from day 14 before mating and females were dosed for 42-52 days from day 14 before mating to day 4 of lactation throughout the mating and pregnancy period. No deaths were observed in both sexes of any groups. No effects of MMB on clinical signs, body weight gains, food consumption and necropsy findings, were observed. Increases of absolute and relative weights of the kidney in males at 200 mg/kg bw/day and higher and relative weight of the liver and kidney in females at 1000 mg/kg bw/day were detected. No histopathological changes were found in any organs including the reproductive organs in any rats of the highest dose group.

No effects of MMB were detected on reproductive parameters such as estrous cycle, number of pairs mated, number of pairs with successful copulation, copulation index, precoital interval, number of pregnant females, fertility index, number of corpora lutea, number of implantation sites, implantation index, number of pregnant females with parturition, gestation length, number of pregnant females with live pups, gestation index and number of pregnant females with live pups on day 4 of lactation. No effects of MMB were detected on developmental parameters such as number of pups born, delivery index, number and weight of pups on postnatal days 0 and 4, live birth index, sex ratio and viability of pups. No external or internal malformation was found in pups at any dose. Based on these findings, the NOAELs were considered to be 40 mg/kg bw/day in males and 200 mg/kg bw/day in females for general toxicity and 1000 mg/kg bw/day for reproductive and developmental toxicity in rats.

Crj:CD(SD) female rats (25 animals/dose) were given MMB by gavage at a dose of 0 (vehicle: deionized water), 250, 500 or 2000 mg/kg bw/day [ARL, 1991]. Pregnant females were dosed on days 6 through 15 of gestation. On day 20 of gestation, rats were sacrificed to examine pregnancy

outcome. Fetuses were weighed, sexed and examined for external anomalies. Approximately one-half of the fetuses in each litter were examined for internal anomalies. The remaining fetuses in each litter were examined for skeletal anomalies. Decreased motor activity, excess salivation, ataxia, muscle flaccidity and loss of righting reflex were observed in dams at 2000 mg/kg bw/day. Decreases in maternal body weight gains and food consumption were detected at 250, 500 and 2000 mg/kg bw/day. No MMB-related changes in necropsy findings were detected. Fetal body weights were decreased at 2000 mg/kg bw/day. No effects of MMB on the number of implantation sites, resorptions and live and dead fetuses were found. No increase in the incidence of fetal malformation was detected after administration of MMB. Increases in the incidences of skeletal variations and delayed ossification were detected at 2000 mg/kg bw/day. The NOAELs were considered to be less than 250 mg/kg bw/day for maternal toxicity and 500 mg/kg bw/day for developmental toxicity in rats.

Studies in Humans

There is no available information.

Conclusion

In the rat reproduction/developmental toxicity screening test, no effects of MMB on reproductive and developmental parameters were observed at doses up to 1000 mg/kg bw/day. In parent rats, increases of absolute and relative weights of the kidney in males at 200 mg/kg bw/day and higher and relative weight of the liver and kidney in females at 1000 mg/kg bw/day were detected. The NOAELs were considered to be 40 mg/kg bw/day in males and 200 mg/kg bw/day in females for general toxicity and 1000 mg/kg bw/day for reproductive and developmental toxicity in rats. In the rat developmental toxicity study, decreases in body weight gains and food consumption at all doses of MMB in maternal rats and a decrease in the body weight and increase in the incidences of skeletal variations and delayed ossifications at 2000 mg/kg bw/day in fetal rats were detected. The NOAELs were considered to be less than 250 mg/kg bw/day for maternal toxicity and 500 mg/kg bw/day for developmental toxicity in rats.

Similar toxicity to rats were observed in the above stated 28 days repeated dose toxicity study in which rats were given MMB by gavage for 28 days. An increase in relative weight of the kidneys in males at 250 mg/kg bw/day and in males and females at 1000 mg/kg bw/day and an increase in relative weight of the liver in males and females at 1000 mg/kg bw/day were found. The NOAELs for repeated dose toxicity were considered to be 60 mg/kg bw/day for males and 250 mg/kg bw/day for females.

3.2 Initial Assessment for Human Health

There is no available information on toxicokinetics, metabolism or distribution of 3-methoxy-3-methyl-1-butanol (MMB).

In a dermal acute toxicity study in rats, no death, clinical sign or abnormality was noted and the dermal LD_{50} value was more than 2000 mg/kg bw. In acute oral toxicity studies in rats [OECD TG 401], the oral LD_{50} values were 4500 and 4300 mg/kg bw for males and females, respectively.

In studies on skin irritation, the undiluted MMB showed light irritation to the skin in rabbits. In eye irritation studies, MMB had moderate irritation effect to rabbit eyes. In photosensitization and maximization tests in guinea pigs, MMB has no sensitizing potential.

In a repeated inhalation toxicity study in male rats, increases in GOT at 100 and 500 ppm and in absolute and relative weight of the kidneys at 100 ppm and higher. The LOAEL for repeated

inhalation toxicity was 100 ppm. In a repeated oral dose toxicity study, a decrease in chloride in males and females at 1000 mg/kg bw/day and increases in A/G ratio and inorganic phosphorus in males at 1000 mg/kg bw/day were detected. An increase in relative weight of the kidney in males at 250 and 1000 mg/kg bw/day and in females at 1000 mg/kg bw/day, and in relative weight of the liver in males and females at 1000 mg/kg bw/day after the administration period and in males at 1000 mg/kg bw/day after the recovery period were detected. The LOAELs/NOAELs were 250/60 mg/kg bw/day for males and 1000/250 mg/kg bw/day for females.

In reverse gene mutation assays [OECD TG 473], MMB was not mutagenic in *S. typhimurium* TA 1535, TA 1537, TA 1538, TA 98, TA 100 or *E. coli* WP2 uvrA at concentrations of up to 5000 μg/plate with or without S9 mix. In a chromosomal aberration test in cultured Chinese hamster lung (CHL/IU) cells [OECD TG 473], MMB did not induce structural chromosomal aberrations or polyploidy either with or without an exogenous metabolic activation.

There is no available information on carcinogenicity.

In the rat reproduction/developmental toxicity screening test [OECD TG 421], no effects of MMB on reproductive and developmental parameters were observed at doses up to 1000 mg/kg bw/day. In parent rats, increases of absolute and relative weights of the kidney in males at 200 mg/kg bw/day and higher and relative weight of the liver and kidney in females at 1000 mg/kg bw/day were detected. The NOAELs were 40 mg/kg bw/day in males and 200 mg/kg bw/day in females for general toxicity and 1000 mg/kg bw/day for reproductive and developmental toxicity. In the rat developmental toxicity study, decreases in body weight gains and food consumption at all doses in maternal rats and a decrease in the body weight and increase in the incidences of skeletal variations and delayed ossifications at 2000 mg/kg bw/day in fetal rats were detected. The NOAELs were less than 250 mg/kg bw/day for maternal toxicity and 500 mg/kg bw/day for developmental toxicity in rats.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Acute Toxicity Test Results

Acute toxicity of MMB to aquatic species from three trophic levels has been investigated experimentally as shown in Table 4. These toxicity data were obtained from GLP compliance tests and the analytical monitoring showed the test substance was stable in each test conditions. Therefore these data were considered reliable without any restrictions.

Table 4 Acute toxicity of MMB to aquatic organisms

Species	Method	Exposure	Result	Reference
Medaka *Orizias latipes*	OECD TG 203 GLP test	96 h semi-static	LC_{50} > 100 mg/L	MOE, Japan (2002)
Daphnia magna	OECD TG 202 GLP test	48 h static	EC_{50}> 1,000 mg/L	MOE, Japan (2002)
Selenastrum capricornutum	OECD TG 201 GLP test	72 h static, open system	(rate method) ErC_{50} > 1,000 mg/L (biomass method) EbC_{50} > 1,000 mg/L	MOE, Japan (2002)

Fish

The toxicity test result of MMB to freshwater fish, *Orizias latipes*, was reported to be 96h LC_{50} >100 mg/L (MOE, Japan, 2002). In the test (OECD TG 203), fish were exposed only at a concentration of 100 mg/L and the control, and no individuals were killed and showed no toxicological symptoms.

Invertebrate

For daphnids, *Daphnia magna,* an acute toxicity result of 48 h EC_{50} > 1000 mg/L was reported (OECD TG 202, MOE, Japan, 2002). The exposure of the substance to daphnids was undertaken at the concentration of 1,000 mg/L with dilution water (Elendt M4 medium) and a control. No individuals were immobilised.

Aquatic plant, e.g. Algae

One test with a species of freshwater algae, *Selenastrum capricornutum*, is available (MOE, Japan, 2002). The algal growth inhibition test (OECD TG 201) was carried out with one concentration of 1,000 mg/L and one control. A (0-72 h) ErC_{50} of >1000 mg/L and a (0-72 h) EbC_{50} of > 1,000 mg/L were reported.

Chronic Toxicity Test Results

Test results on chronic toxicity which are regarded reliable are summarised in the table 5.

Table 5 Chronic toxicity of MMB to aquatic organisms

Species	Method	Exposure	Result	Reference
Daphnia magna	OECD TG 211 GLP test	21 d semi-static	(Reproduction) 21 NOEC = 100 mg/L	MOE, Japan (2002)
Selenastrum capricornutum	OECD TG 201 GLP test	72 h static, open system	(biomass method) (0-72 h) NOEC = 1,000 mg/L	MOE, Japan (2002)

A chronic toxicity test result with daphnids was reported (MOE, Japan, 2002). In the test parent daphnids were exposed at nominal concentrations of MMB ranging from 10 to 100 mg/L (4 different concentrations) with one control. No individuals were killed at any concentration. The

mean cumulative numbers of juveniles per adult for 21 days in the control, 10, 22, 46 and 100 mg/L were 64.9, 71.2, 90.0, 73.9, and 70.0, respectively. Therefore no inhibition by this substance was observed, and the 21-d NOEC to daphnids was 100 mg/L.

From the study on algal toxicity (MOE, Japan, 2002), a chronic value of NOEC = 1,000 mg/L (OECD TG 201, biomass method) was derived. The exposure was undertaken at only one concentration of 1,000 mg/L. The statistic calculation showed that the growth rate (0-72 h) at 1,000 mg/L was significantly different to that of the control however the inhibition rate (growth rate) was only 3.2 % of the control. Therefore the NOEC by the growth rate method could not be determined.

4.2 Initial Assessment for the Environment

MMB is a colourless liquid with a water solubility of 100 g/l at 25 °C and vapour pressure of 125 Pa at 25 °C. Based on the measured log Kow of 0.18, bioaccumulation is not expected. Environmental distribution using a Mackay level III fugacity model indicates when MMB is released into air or water, it remains in the original compartment whereas when released into soil, 29.4 % is distributed into air, 9.3 % into water and 61.3 % remains in soil. A ready biodegradability test showed that MMB failed to meet a criterion for ready biodegradability (pass level and 10-day window), however, complete biodegradation was observed in an inherent biodegradation test. A study on hydrolysis indicates that MMB is stable in water. In the atmosphere MMB is indirectly photodegraded by reaction with OH radicals with a half-life of 1.1 days.

Ecotoxicity data on this substance are available in aquatic species from three trophic levels. In an algal growth inhibition test (OECD TG 201, *Selenastrum capricornutum,* open system), acute toxicity results of 72 h ErC_{50} > 1,000 mg/L and 72 h EbC_{50} >1,000 mg/L were obtained. For daphnids, a 48 h EC_{50} of > 1,000 mg/L was reported (OECD TG 202, *Daphnia magna*, static). For fish (OECD TG 203, *Oryzias latipes,* semi-static) a 96 h LC_{50} > 100 mg/L is available.

Regarding chronic toxicity to algae, a 72 h NOEbC of 1,000 mg/L (OECD TG 201, *Selenastrum capricornutum*, open system) was reported. In daphnids, a 21 d EC_{50} of >100 mg and a 21 d NOEC of 100 mg/L were reported (OECD TG 211, *Daphnia magna,* semi-static).

There is no available information on toxicity to neither terrestrial nor other organisms.

5 RECOMMENDATIONS

The chemical is currently of low priority for further work.

Human health: The chemical possesses properties indicating a hazard for human health (eye irritation, skin irritation after prolonged exposure). Although these hazards do not warrant further work (as they are related to reversible effects), they should nevertheless be noted by chemical safety professionals and users.

Environment: The chemical is currently of low priority for further work based on its low hazard profile.

6 REFERENCES

Argus Research Laboratories, Inc. (ARL). (1991). Developmental toxicity (embryo-fetal toxicity and teratogenic potential) study of 3-methoxy-3-methyl-1-butanol(MMB) administered orally via gavage to Crl:CD BR VAF/Plus presumed pregnant rats, Protocol211-001. Unpublished Report.

Chemicals Evaluation and Research Institute (CERI). (2001a). Ready Biodegradation Study on MMB, Report Number 13675. Unpublished Report.

Chemicals Evaluation and Research Institute (CERI). (2001b). Report of Melting Point Measurement of MMB, Report Number 81944. Unpublished Report.

Chemicals Evaluation and Research Institute (CERI). (2001c). Report of Boiling Point Measurement of MMB, Report Number 81945. Unpublished Report.

Chemicals Evaluation and Research Institute (CERI). (2001d). Report of Vapour Pressure Measurement of MMB, Report Number 81946. Unpublished Report.

Chemicals Evaluation and Research Institute (CERI). (2001e). Report of Partition Coefficient Measurement of MMB, Report Number 81947. Unpublished Report.

Chemicals Evaluation and Research Institute (CERI). (2001f). Report of Water Solubility Measurement of MMB, Report Number 81948. Unpublished Report.

Chemicals Evaluation and Research Institute (CERI). (2001g). Report of Hydrolysis rate of MMB, Report Number 81949. Unpublished Report.

Chemicals Evaluation and Research Institute (CERI). (2002). Biodegradation Study on MMB, Report Number 13847. Unpublished Report.

Chemicals Evaluation and Research Institute (CERI). (2004a). Internal Data

Chemicals Evaluation and Research Institute (CERI). (2004b). SRC-AOPWIN v1.90.

Chemicals Evaluation and Research Institute (CERI). (2004c). BCFWIN v2.14

Huntingdon Research Center, Ltd. (HRC). (1989a). Acute oral toxicity to rats of Solfit. Unpublished Report.

Huntingdon Research Center, Ltd. (HRC). (1989b). Microbial Metabolic Activation test to Assess the potential mutagenic effect of Solfit. Unpublished Report.

Inveresk Research International (IRI). (1991a).Primary skin irritation test in rabbits. Report No.6915. Unpublished Report.

Inveresk Research International (IRI). (1991b). Dermal irritation test in rabbits-28day repeated application. Report No.6916. Unpublished Report.

Inveresk Research International (IRI). (1991c). Primary eye irritation test in rabbits. Report No.6917. Unpublished Report.

Inveresk Research International (IRI). (1991d). Magnsson-Kligman maximisation test in Guinea pigs. Report No.6918. Unpublished Report.

Inveresk Research International (IRI). (1991e). Determination of photoirritation potential in Guinea pigs. Report No.6919. Unpublished Report.

Inveresk Research International (IRI). (1991f). Determination of photoirritation potential in Guinea pigs. Report No.6920. Unpublished Report.

Inveresk Research International (IRI). (1991g). Acute dermal Toxicity (LD50) test in rats. Report No.8025. Unpublished Report.

Kuraray. (2002). Material Safety Data Sheet on 3-methoxy-3-methyl-butanol

Ministry of the Environment (MOE), Japan (2002). Unpublished data.

Ministry of Health, Labour and Welfare (MHLW), Japan. (2003). Toxicity Testing Reports of Environmental Chemicals,10, 571-605.

Occupational Health Service Center, Japan. (1973)

Occupational Health Service Center, Japan. (1976)

Sigma-Aldrich-Fluka. (1998) Material Safety Data Sheet on 3-methoxy-3-methyl-butanol

I U C L I D

Data Set

Existing Chemical	:	ID: 56539-66-3
CAS No.	:	56539-66-3
EINECS Name	:	3-methoxy-3-methylbutan-1-ol
EC No.	:	260-252-4
Molecular Formula	:	C6H14O2

Producer related part

Company	:	National Institute for Environment Studies
Creation date	:	04.10.2004

Substance related part

Company	:	National Institute for Environment Studies
Creation date	:	04.10.2004
Status	:	
Memo	:	
Printing date	:	25.03.2005
Revision date	:	
Date of last update	:	08.12.2004
Number of pages	:	
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

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

Source : National Institute of Health & Sciences Tokyo
16.07.2004

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

Source : National Institute of Health & Sciences Tokyo
16.07.2004

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

Source : National Institute of Health & Sciences Tokyo
07.12.2004

Type : cooperating company
Name : National Institute of Industrial Health
Contact person :
Date :
Street : 6-21-1, Nagao, Tama-ku, Kawasaki-shi

Town : 214-8585 Kanagawa
Country : Japan
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Source : National Institute of Health & Sciences Tokyo
16.07.2004

Type : cooperating company
Name : National Institute of Industrial Health
Contact person :
Date :
Street : 6-21-1, Nagao, Tama-ku, Kawasaki-shi
Town : 214-8585 Kanagawa
Country : Japan
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Source : National Institute of Health & Sciences Tokyo
07.12.2004

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

Source : National Institute of Health & Sciences Tokyo
16.07.2004

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

Source : National Institute of Health & Sciences Tokyo

07.12.2004

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type :
Substance type : organic
Physical status : liquid
Purity : >= 98 % w/w
Colour :
Odour :

Remark : Colourless liquid with slight ether odour.
Source : Kuraray, Co., Ltd.
National Institute of Health & Sciences Tokyo
16.07.2004 (1)

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

1-Butanol, 3-methoxy-3-methyl-

Source : National Institute of Health & Sciences Tokyo
16.07.2004

3-Methoxy-3-methyl-1-butanol

Source : National Institute of Health & Sciences Tokyo
16.07.2004

3-Methyl-3-methoxybutanol

Source : National Institute of Health & Sciences Tokyo
16.07.2004

Butanol. 3-methoxy-3-methyl-

Source : National Institute of Health & Sciences Tokyo
16.07.2004

Solfit

Source : National Institute of Health & Sciences Tokyo
16.07.2004 (1)

1.3 IMPURITIES

Purity :
CAS-No : 7732-18-5
EC-No : 231-791-2
EINECS-Name : water
Molecular formula :
Value : <= .04 % w/w

Source : Kuraray Co., Ltd.
National Institute of Health & Sciences Tokyo
16.07.2004 (2)

1.4 ADDITIVES

1.5 TOTAL QUANTITY

Quantity : - tonnes in 2002

Remark : ca. 10,000 tonnes produced in Japan by one company (2002).
ca. 2,000 tonnes exported from Japan to the rest of the world (2002).
World-wide production is unknown.
Source : Kuraray Co., Ltd.
National Institute of Health & Sciences Tokyo
07.12.2004

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.6.3 PACKAGING

1.7 USE PATTERN

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

Source : National Institute of Health & Sciences Tokyo
16.07.2004

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

Source : National Institute of Health & Sciences Tokyo
16.07.2004

Type of use : use
Category : Cleaning/washing agents and disinfectants

Source : National Institute of Health & Sciences Tokyo
16.07.2004

Type of use : use
Category : Solvents

Source : National Institute of Health & Sciences Tokyo
16.07.2004

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

Remark : No occupational limit value has been set in Japan.
Source : National Institute of Health & Sciences Tokyo
16.07.2004

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

1.8.4 MAJOR ACCIDENT HAZARDS

1.8.5 AIR POLLUTION

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

Remark : Exposure to consumers and the environment is expected because this substance is used as a solvent for paints, raw material for a cleaner and fregrance.
Source : National Institute of Health & Sciences Tokyo
16.07.2004

1.11 ADDITIONAL REMARKS

1.12 LAST LITERATURE SEARCH

Type of search : Internal and External
Chapters covered : 3, 4, 5
Date of search : 05.01.2004

Source : National Institute of Health & Sciences Tokyo
07.12.2004

Type of search : Internal and External
Chapters covered : 2
Date of search : 06.12.2004

Source : National Institute of Health & Sciences Tokyo
07.12.2004

1.13 REVIEWS

2.1 MELTING POINT

Value : <= -50 °C
Sublimation :
Method : OECD Guide-line 102 "Melting Point/Melting Range"
Year : 2001
GLP : no
Test substance :

Source : National Institute of Health & Sciences Tokyo
Test substance : Source: Tokyo Kasei Kogyo Co., Ltd.
Purity: 99.3 %
Lot No.: GG01
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
07.12.2004 (2)

2.2 BOILING POINT

Value : = 173 °C at 1013 hPa
Decomposition :
Method : OECD Guide-line 103 "Boiling Point/boiling Range"
Year : 2001
GLP : no
Test substance :

Remark : A study was performed according to OECD TG 103 (Siwoloboff method).
Measured values were 173.0, 173.1 and 173.0 degree C (average 173.0).
Source : National Institute of Health & Sciences Tokyo
Test substance : Source: Tokyo Kasei Kogyo Co., Ltd.
Purity: 99.3 %
Lot No.: GG01
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
07.12.2004 (3)

Value : = 173 - 175 °C at 1013 hPa

Source : National Institute of Health & Sciences Tokyo
Reliability : (2) valid with restrictions
Scientifically acceptable data source.
16.07.2004

Value : = 174 °C at

Source : Kuraray Co., Ltd., Material Safety Data Sheet on
3-Methoxy-3-methyl-1-butanol, 20 August 2002.
National Institute of Health & Sciences Tokyo
Reliability : (4) not assignable
Data from producer without proof.
07.12.2004 (1)

2.3 DENSITY

Type : relative density

Value : = .926 at 20 °C

Source : National Institute of Health & Sciences Tokyo
Reliability : (2) valid with restrictions
Scientifically acceptable data source.
Flag : Critical study for SIDS endpoint
07.12.2004 (4)

Type : density
Value : = .927 g/cm³ at 25 °C

Source : Kuraray Co., Ltd., Material Safety Data Sheet on 3-Methoxy-3-methyl-1-butanol, 20 August 2002.
National Institute of Health & Sciences Tokyo
Reliability : (4) not assignable
Producer's MSDS without proof.
Flag : Material Safety Dataset
07.12.2004 (1)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : = 1.25 hPa at 25 °C
Decomposition :
Method : OECD Guide-line 104 "Vapour Pressure Curve"
Year : 2001
GLP : no
Test substance :

Remark : Result was extrapolated using three measured values by dynamic method.

Temperature (degree C)	V.P. (hPa)
40	3.33
50	7.32
60	11.3

Source : National Institute of Health & Sciences Tokyo
Test substance : Source: Tokyo Kasei Kogyo Co., Ltd.
Purity: 99.3 %
Lot No.: GG01
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
07.12.2004 (5)

Value : = 1.03 hPa at °C
Decomposition :
Method : other (calculated)
Year :
GLP :
Test substance :

Remark : SRC-MPBPWIN v1.40
Source : National Institute of Health & Sciences Tokyo
Reliability : (2) valid with restrictions
Valid calculation method.
16.07.2004 (6)

Value : = .67 hPa at °C

Source : National Institute of Health & Sciences Tokyo
Reliability : (4) not assignable
Manufacturer / producer data without proof.
Flag : Material Safety Dataset
16.07.2004 (1)

2.5 PARTITION COEFFICIENT

Partition coefficient :
Log pow : = .18 at 25 °C
pH value :
Method : OECD Guide-line 107 "Partition Coefficient (n-octanol/water), Flask-shaking Method"
Year : 2001
GLP : yes
Test substance :

Remark : Condition:

	Condition-1	Condition-2	Condition-3
Octanol (ml)	5	10	20
Water (ml)	30	25	15
Test substance (mg)	10.3	10.3	10.3

Analytical method:
Gas chromatography with external standard.

Result:

Condition-1	Condition-2	Condition-3
0.18	0.20	0.20
0.17	0.17	0.17

Source : National Institute of Health & Sciences Tokyo
Test substance : Source: Tokyo Kasei Kogyo Co., Ltd.
Purity: 99.3 %
Lot No.: GG01
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
07.12.2004 (7)

Partition coefficient :
Log pow : = .46 at 25 °C
pH value :
Method : other (calculated)
Year :
GLP :
Test substance :

Remark : SRC-KOWWIN v1.66
Source : National Institute of Health & Sciences Tokyo
Reliability : (2) valid with restrictions
Valid calculation method.
07.12.2004 (8)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in	:	
Value	:	>= 100 g/l at 25 °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	miscible
Stable	:	
Deg. product	:	
Method	:	OECD Guide-line 105
Year	:	2001
GLP	:	no
Test substance	:	
Remark	:	500 mg of the substance was added in 5 ml of distilled water (n=3). Visually confirmed the complete dissolution.
Source	:	National Institute of Health & Sciences Tokyo
Test substance	:	Source: Tokyo Kasei Kogyo Co., Ltd. Purity: 99.3% Lot No.: GG01
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

07.12.2004 (9)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Value	:	= 71 °C
Type	:	
Source	:	Sigma-Aldrich-Furuka, Material Safety Data Sheet on 3-Methoxy-3-methyl-1-Butanol. Searched on 5-Jan-2004. National Institute of Health & Sciences Tokyo
Reliability	:	(2) valid with restrictions Scientifically acceptable data source.

07.12.2004 (4)

Value	:	= 68 °C
Type	:	
Source	:	Kuraray Co., Ltd., Material Safety Data Sheet on 3-Methoxy-3-methyl-1-butanol, 20 August 2002. National Institute of Health & Sciences Tokyo
Reliability	:	(4) not assignable Manufacturer / producer data without proof.
Flag	:	Material Safety Dataset

07.12.2004 (1)

2.8 AUTO FLAMMABILITY

Value	:	= 395 °C at

Source : Kuraray Co., Ltd., Material Safety Data Sheet on 3-Methoxy-3-methyl-1-butanol, 20 August 2002. National Institute of Health & Sciences Tokyo
Reliability : (4) not assignable Manufacturer/ producer data without proof.
Flag : Material Safety Dataset
07.12.2004 (1)

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

Result : explosive under influence of a flame

Remark : Range of explosion is 1.2 to 13.1 %.
Source : Kuraray Co., Ltd., Material Safety Data Sheet on 3-Methoxy-3-methyl-1-butanol, 20 August 2002. National Institute of Health & Sciences Tokyo
Reliability : (4) not assignable Manufacturer / producer data without proof.
Flag : Material Safety Dataset
07.12.2004 (1)

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
INDIRECT PHOTOLYSIS		
Sensitizer	:	OH
Conc. of sensitizer	:	1500000 molecule/cm³
Rate constant	:	= .00000000000996 cm³/(molecule*sec)
Degradation	:	= 50 % after 1.1 day(s)
Deg. product	:	
Method	:	other (calculated)
Year	:	
GLP	:	
Test substance	:	
Remark	:	Based on 12 hrs/day irradiation. Calculated with SRC-AOPWIN v1.90.
Source	:	National Institute of Health & Sciences Tokyo
Reliability	:	(2) valid with restrictions Valid calculation method.
Flag	:	Critical study for SIDS endpoint

16.07.2004 (10)

3.1.2 STABILITY IN WATER

Type	:	abiotic
t1/2 pH4	:	> 1 year at 25 °C
t1/2 pH7	:	> 1 year at 25 °C
t1/2 pH9	:	> 1 year at 25 °C
Deg. product	:	
Method	:	OECD Guide-line 111 "Hydrolysis as a Function of pH"
Year	:	2001
GLP	:	no
Test substance	:	
Remark	:	Approx. 200 mg/l of the test substance solutions at pHs 4, 7 and 9 were incubated at 50 degree C for 5 days (n=2). More than 90% of the initial concentrations were maintained in all vessels. Concentrations were determied by gas chromatograph.
Result	:	The substance was stale in water and its half-life at 25 degree C was greater than 1 year at pHs 4, 7 and 9.
Source	:	National Institute of Health & Sciences Tokyo
Test substance	:	Source: Tokyo Kasei Kogyo Co., Ltd. Purity: 99.3 % Lot No.: GG01
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

07.12.2004 (11)

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type : volatility
Media : water - air
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method :
Year :

Method : The Henry's Law Constant was calculated using a water solubility of 100 g/l, a vapour pressure of 125 Pa and a molecular weight of 118.17.
Result : The calculated Henry's Law Constant was 0.148 Pa x m3/mol.
Source : National Institute of Health & Sciences Tokyo
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
16.07.2004

3.3.2 DISTRIBUTION

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

Remark : The following input parameters were used for the calculation.
Molecular weight: 118.17
Melting point (degree C): -50 (Measured)
Vapour pressure (Pa): 125 (Measured)
Water solubility (g/l): 100 (Measured)
log Kow: 0.18 (Measured)
Temperature: 25 degree C
Halh life (h) in air: 25 (Calculated)
in water: 360 (Estimated)
in soil: 360 (Estimated)
in sediment: 1440 (Estimated)
Emission rate (kg/h) in air: 1000 (Estimated)
in water: 1000 (Estimated)
in soil: 1000 (Estimated)
in sediment: 0 (Estimated)

Result :

Compartment	100% to Air	100% to water	Release 100% to soil	equal to a/w/s
Air	97.2%	10.1%	29.4%	0.616%
Water	2.7%	89.5%	9.3%	45.8%
Soil	0.1%	0.0%	61.3%	53.5%
Sediment	0.0%	0.4%	0.0%	0.0782%

Source : National Institute of Health & Sciences Tokyo
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
07.12.2004 (12)

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic
Inoculum : activated sludge, non-adapted
Concentration : 100 mg/l related to Test substance
related to
Contact time : 28 day(s)
Degradation : = 50 (±) % after 28 day(s)
Result :
Kinetic of testsubst. : 7 day(s) = 2 - 3 %
14 day(s) = 7 - 72 %
21 day(s) = 10 - 100 %
28 day(s) = 21 - 100 %
%
Control substance : Aniline
Kinetic : 7 day(s) = 40 %
14 day(s) = 78 %
Deg. product : no
Method : OECD Guide-line 301 C "Ready Biodegradability: Modified MITI Test (I)"
Year : 2001
GLP : yes
Test substance :

Remark : 30 mg of the test substance (n=3) or aniline (n=1) and 9 mg of activated sludge (as MLSS) were added into 300 ml of a test medium.
The test and control vessels were cultivated for 28 days at 25 degree C.
Biodegradability of the test substance and contol (aniline) were continuously measured by BOD meter.
After 28 days of caltivation, residual amount of the test substance in each test solution were detemined by GC analysis.
Result : Biodegradation rates after 28 days were 21, 21 and 100% by BOD, and 18, 13 and 94% by GC analysis.
Average biodegradation rates by BOD and GC analysis were 50 and 44%, respectively.
Based on the results by BOD and GC analysis, this substance was failed to meet the criteria for ready biodegradability (pass level and 10 day window).
Source : National Institute of Health & Sciences Tokyo
Test substance : Source: Tokyo Kasei Kogyo Co., Ltd.
Purity: 99.3 %
Lot No.: GG01
Reliability : (2) valid with restrictions
Although the study was conducted in accordance with the GLP compliance, a significant difference was observed in test results without discussion.
Flag : Critical study for SIDS endpoint
07.12.2004 (13)

Type : aerobic
Inoculum : activated sludge, non-adapted
Concentration : 30 mg/l related to Test substance
related to
Contact time : 28 day(s)

Degradation	:	(±) % after
Result	:	inherently biodegradable
Kinetic of testsubst.	:	7 day(s) = 17 - 24 % 14 day(s) = 100 - 100 % 21 day(s) = 100 - 100 % 28 day(s) = 100 - 100 % %
Control substance	:	Aniline
Kinetic	:	7 day(s) = 53 % 14 day(s) = 72 %
Deg. product	:	
Method	:	OECD Guide-line 302 C "Inherent Biodegradability: Modified MITI Test (II)"
Year	:	2002
GLP	:	yes
Test substance	:	
Remark	:	9 mg of the test substance (n=3) or aniline (n=1) and 30 mg of activated sludge (as MLSS) were added into 300 ml of a test medium. The test and control vessles were cultivated for 28 days at 25 degree C. Biodegradabilities of the test and control (aniline) were continuously measured by BOD meter. After 28 days of cultivation, residual amount of the test substance in each test solution was determined by GC analysis.
Result	:	Biodegradation rates in test solutions after 28 days were 100% in all vessels by BOD and GC analysis. No metabolite was detected in all test solutions.
Source	:	National Institute of Health & Sciences Tokyo
Test substance	:	Source: Tokyo Kasei Kogyo Co., Ltd. Purity: 99.3 % Lot No.: GG01
Reliability	:	(1) valid without restriction

07.12.2004 (14)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

BCF	:	= 3.16
Elimination	:	
Method	:	other
Year	:	
GLP	:	
Test substance	:	
Remark	:	Calculated by BCFWIN v2.14 based on the measured log Kow value of 0.18.
Source	:	National Institute of Health & Sciences Tokyo
Reliability	:	(2) valid with restrictions

16.07.2004

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	semistatic
Species	:	Oryzias latipes (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
NOEC	:	> 100
LC50	:	> 100
Limit test	:	yes
Analytical monitoring	:	yes
Method	:	OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year	:	2002
GLP	:	yes
Test substance	:	other TS:3-Methoxy-3-methylbutanol (CAS No.: 56539-66-3, KURARAY Co., Ltd. (Japan), Lot. No.: 22517, Purity = 99.19 wt%

Method :

-Test Organisms:
a) Supplier: Test organisms were reproduced at the testing laboratory.
b) Size (length and weight): 2.2 cm (1.9 - 2.4 cm) in length; 0.16 g (0.09 - 0.24 g) in weight
c) Age: Not described
d) Any pretreatment: Test organisms were acclimated for one month before testing. During acclimination, test fishes were fed with TETRAMINE equivalent to 2% of weight per day. These test organisms were not fed for 24 hours before the test started. The mortality of the test organisms for 7 days before testing was less than 5%. LC50(96 hr) for a reference substance (copper sulfate pentahydrate) was 0.40 mg/L.

-Test substance:
a) Empirical Formula: C6H14O2
b) Molecular Weight: 118 g/mol
c) Purity: =99.19 wt%

-Test Conditions:
a) Dilution Water Source: Dilution water was prepared from tap water. The tap water was dechlorinated and treated by activated carbon. Before using the dilution water, aeration was fully carried out.
b) Dilution Water Chemistry:
pH: = 7.7
Total hardness (as CaCO3): = 28 mg/L
c) Exposure Vessel Type: 3 L test solution in a 3 L glass beaker
d) Nominal Concentrations: control and 100 mg/L. Test concentration was determined based on preliminary test result.
e) Vehicle/Solvent and Concentrations: Any solvent was not used.
f) Stock Solutions Preparations and Stability: Test chemical was refrigerated. 1,000mg/L test solution was prepared by the following method. 500mg test chemical was dissolved in 500mL dilution water. Infrared absorption spectrum of the refrigerated test chemical was detected at the start and the end of the test, and both spectrums are

not contradictory to each other.
g) Number of Replicates: 1
h) Fish per Replicates: 10
i) Change Rate of Test Water: Test medium was renewed every 2 days.
j) Water Temperature: 24+/-1 C
k) Light Condition: 16:8 hours, light-darkness cycle
l) Feeding: None
m) Aeration : Test solution was not aerated during the test period.

-Analytical Procedure: The tested concentrations were measured at the start and the 48th hour using GC.

-Statistical Method:
a) Data Analysis: All of test organisms were lived at the end of the test period, therefore the LC50 is more than the highest concentration.
b) Method of Calculating Mean Measured Concentrations (i.e. arithmetic mean, geometric mean, etc.): Mean measured concentration was not calculated.

-

Result **:** - Measured Concentrations: The test concentrations were measured at 0 h and 48 h. For all of them, the deviations from the nominal were less than +/-20%.

Nominal Conc.	Measured Conc., mg/L		Percent of Nominal Conc.	
mg/L	0 Hour	48 Hours	0 Hour	48 Hours
Control	< 2	< 2	---	---
100	95.9	103	95.9	103

- Water chemistry (pH and DO) and temperature in test:
Water chemistry and temperature were measured for old and renewal solution with control and each concentration at the start of test and every 24 hours.
pH: 7.2 - 7.8
DO: 5.2 - 8.2 mg/L
Water Temperature: 23.9 - 24.0C

-Effect Data(mortality):
LC50 (96hr) >= 100 mg/L (nc)
LC100 (96hr) >= 100 mg/L (nc)
mc: based on nominal concentration

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

Nominal Conc.	Cumulative Number of Dead (Percent Mortality)			
-mg/L	24hr	48hr	72hr	96hr

Control	0 (0)	0 (0)	0 (0)	0 (0)
100	0 (0)	0 (0)	0 (0)	0 (0)

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

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

-n: No abnormalities are detected

- Calculation of toxicity values: The calculation of toxicity values was the nominal concentration. The reason is that all of the deviations from the nominal concentration were less than +/-20%.

Source : Ministry of Environment, Japan (2002)
National Institute of Environmental Studies, Environment Agency
Tsukuba-Ibaraki

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint

04.10.2004 (15)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type : static
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
EC0 : = 1000
EC50 : >= 1000
Limit Test : yes
Analytical monitoring : yes
Method : OECD Guide-line 202
Year : 2002
GLP : yes
Test substance : other TS:3-Methoxy-3-methylbutanol (CAS No.: 56539-66-3, KURARAY Co., Ltd. (Japan), Lot. No.: 22517, Purity = 99.19 wt%

Method : - Test Organisms:
a) Age: < 24 hours old
b) Supplier/Source: Test organisms were obtained from National Institute for Environmental Studies and had been reproduced in the testing laboratory for 5 years.
c) Any pretreatment: Parental daphnids were acclimated for 27 days on test condition before testing. During acclimination, test daphnids were fed with Chlorella vulgaris, 0.15 - 0.2 mg carbon/day/individual. The

mortality of the daphnids was less than 5% for 2 weeks before testing. Any resting-egg and male daphnia was not observed. EC50(48hr, immobility) for reference substance (potassium dichromate) was 0.67mg/L.

-Test substance:
a) Empirical Formula: C6H14O2
b) Molecular Weight: 118 g/mol
c) Purity: =99.19 wt%

-Test Conditions:
a) Dilution Water Source: Elendt M4 recommended by OECD TG 211 was used as dilution water.
b) Exposure Vessel Type: 100 mL test solution in a 100 mL glass vessel with screw cap
c) Nominal Concentrations: control and 1,000 mg/L
d) Vehicle/Solvent and Concentrations: Any solvent was not used.
e) Stock Solutions Preparations and Stability: Test chemical was refrigerated. 500mg test chemical was dissolved in 500mL dilution water and which was used as 1,000mg/L test solution. Infrared absorption spectrum of the refrigerated test chemical was detected at the start and the end of the test, and both spectrums are not contradictory to each other.
f) Number of Replicates: 4
g) Individuals per Replicates: 5
h) Water Temperature: 20+/-1C
i) Light Condition: 16:8 hours, light-darkness cycle
j) Feeding: None k) Aeration : not described

- Analytical Procedure: Test concentrations were measured at the start and the end of the test using gas chromatography with flame ionization detector.

- Statistical Method:
a) Data Analysis: During test period the immobility of test organisms was not observed in any concentration, therefore the EC 50 is more than the highest concentration.
b) Method of Calculating Mean Measured Concentrations (i.e. arithmetic mean, geometric mean, etc.): Mean measured concentration was not calculated.

Result : -
- Measured Concentrations: The test concentrations were measured at the start and the end of the test. For all of them, the deviations from the nominal were less than +/-20%.

Nominal Conc.	Measured Conc., mg/L		Percent of Nominal	
mg/L	0 Hour Fresh	48 Hour Old	0 Hour Fresh	24 Hour Old
Control	<2	<2	---	---

1,000	1,040	1,020	104	102

Fresh: freshly prepared test solution.
Old: test solution after 48 hours exposure

- Water chemistry (pH and DO) and temperature in test:
Water chemistry and temperature were measured for control and each concentration at the start and the end of the test.
pH: 8.1
DO: 8.0- 8.2mg/L
Water Temperature: 20.4 - 20.6C

-Effect Data:
EC0 (48hr) = 1,000 mg/L (nc)
EC50 (48hr) >= 1,000 mg/L (nc)
nc: based on the nominal concentrations

-Mortality or Immobility: No test organism was Immobilized at any concentration.

Daphnids Nominal Conc.	Cumulative Number of Dead or Immobilized (Percent Mortality or Immobility)	
mg/L	24 Hour	48 Hour
Control	0 (0)	0 (0)
1,000	0 (0)	0 (0)

- Calculation of toxic values: Nominal concentration

Source : Ministry of Environment, Japan (2002)
National Institute of Environmental Studies, Environment Agency
Tsukuba-Ibaraki

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint

04.10.2004 (15)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Selenastrum capricornutum (Algae)
Endpoint	:	growth rate
Exposure period	:	72 hour(s)
Unit	:	mg/l
NOEC	:	= 1000
EC50	:	> 1000
Limit test	:	yes
Analytical monitoring	:	yes
Method	:	OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year	:	2002
GLP	:	yes
Test substance	:	other TS:3-Methoxy-3-methylbutanol (CAS No.: 56539-66-3, KURARAY Co., Ltd. (Japan), Lot. No.: 22517, Purity = 99.19 wt%
Method	:	- Test Organisms:

a) Supplier/Source: Obtained from American Type Culture Collection and reproduced in aseptic culture at 13th November 1997.
b) Method of Cultivation: Sterile
c) Stain Number: ATCC22662
d) Pre-culture (duration, medium, etc.): Test alga was pre-incubated for 4 days under the same method of test in OECD medium. EbC50 (0-72 hr) for a reference substance (potassium dichromate) was 0.82 mg/L.

-Test substance:
a) Empirical Formula: C6H14O2
b) Molecular Weight: 118 g/mol
c) Purity: =99.19 wt%

- Test Conditions:
a) Medium: OECD medium
b) Exposure Vessel Type: 300mL Erlenmeyer flask
c) Nominal Concentrations: control and 1000 mg/L
d) Vehicle/Solvent and Concentrations: Any solvent was not used.
e) Stock Solutions Preparations and Stability: Test chemical was refrigerated. 500mg test chemical was dissolved in 50mL OECD medium and which was used as 10,000mg/L test solution. Infrared absorption spectrum of the refrigerated test chemical was detected at the start and the end of the test, and both spectrums are not contradictory to each other.
f) Number of Replicates: 3
g) Initial Cell Number: 10,000 cells/mL
h) Water Temperature: 23+/-2C
i) Light Condition: 4,000 - 5,000 lux, continuously
j) Shaking: 100 rpm

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

- Statistical Method:
a) Data Analysis: The calculated inhibition rate at the highest concentration based on growth rate inhibition and biomass were less than 50%, therefore the EC50 was more than the highest concentration. The NOEC values were determined by analysis of variance (ANOVA).
b) Method of Calculating Mean Measured Concentrations (i.e. arithmetic mean, geometric mean, etc.): Mean measured concentration was not calculated.

-

Result **:** - Measured Concentrations: The tested concentrations were measured at the start and the 72nd hour. For all of them, the deviations from the nominal concentration were less than +/-20%.

Nominal conc.	Measured Conc., mg/L		Percent of nominal	
mg/L	0 Hour	72 Hour	0 Hour	72 Hour

Control	<2	<2	---	---
1,000	1,050	1,040	105	104

- Water chemistry (pH) and temperature in test: pH and water temperature were measured for control and each concentration at the start and the end of test period.
pH: 8.8 - 8.9 (at the start of the test)
9.9 - 10.0 (at the end of the test)
water temperature: 23.0 - 23.1C

-Effect Data: biomass
Area Method
EbC50(0-72hr) >1,000 mg/L (nc)
NOEbC (0-72hr) = 1,000 mg/L (nc)

Rate Method
ErC50(24-48hr) > 1,000 mg/L (mc)
NOErC (24-48hr) = 1,000 mg/L (mc)
ErC50(0-72hr) > 1,000 mg/L (mc)
NOErC (0-72hr) = 1,000 mg/L (mc)
nc: nominal concentration

- Percent Growth Inhibition of Selenastrum capricornutum

Nominal Conc. mg/L	Area under the growth curves (Average) Area A (0-72hr)	Inhibition (%)* IA (0-72hr)
Control	1,596.0	---
1,000	1,519.0	4.82

Nominal Conc. mg/L	Growth rates and percent inhibition (Average) Rate u(0-72hr)	Inhibition(%) Im(0-72hr)
Control	1.43	---
1,000	1.38	0.03246

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

-

Source : Ministry of Environment, Japan (2002)
National Institute of Environmental Studies, Environment Agency
Tsukuba-Ibaraki
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
04.10.2004 (15)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

Species	:	Daphnia magna (Crustacea)
Endpoint	:	reproduction rate
Exposure period	:	21 day(s)
Unit	:	mg/l
NOEC	:	= 100
LOEC	:	> 100
EC50	:	> 100
Analytical monitoring	:	yes
Method	:	OECD Guide-line 211
Year	:	2002
GLP	:	yes
Test substance	:	other TS:3-Methoxy-3-methylbutanol (CAS No.: 56539-66-3, KURARAY Co., Ltd. (Japan), Lot. No.: 22517, Purity = 99.19 wt%

Method :

-Test Organisms:
a) Age: < 24 hours old
b) Supplier/Source: Test organisms were obtained from National Institute for Environmental Studies and had been reproduced in the testing laboratory for 5 years.
c) Any pretreatment: Parental daphnids were acclimated for 25 days on test conditions before testing, any groups showing high mortality were not used for testing. The mortality of the daphnids was less than 5% for 2 weeks before testing. EC50(48 hr, immobility) for a reference substance (potassium dichromate) was 0.67 mg/L.

-Test substance:
a) Empirical Formula: C6H14O2
b) Molecular Weight: 118 g/mol
c) Purity: =99.19 wt%

- Test Conditions:
a) Dilution Water Source: Elendt M4 medium (Water hardness = 250 mg/L as CaCO3) recommended by OECD TG 211 was used as dilution water.
b) Exposure Vessel Type: 80 mL test solution in a 100mL glass beaker
c) Nominal Concentrations: control, 10, 22, 46 and 100 mg/L
d) Vehicle/Solvent and Concentrations: Any solvent was not used.
e) Stock Solutions Preparations and Stability: Test chemical was refrigerated. 200mg test chemical was dissolved in 200mL dilution water and which was used as 1,000mg/L test solution. Infrared absorption spectrum of the refrigerated test chemical was detected at the start and the end of the test, and both spectrums are not contradictory to each other.
f) Number of Replicates: 10
g) Individuals per Replicates: 10
h) Renewal Rate of Test Water: three time per week
i) Water Temperature: 20+/-1C
j) Light Condition: 16:8 hours, light-darkness
k) Feeding: 0.15 - 0.2 mg carbon/day/individual (Chlorella

vulgaris: Green Algae)
l) Aeration: not described

- Analytical Procedure: The test concentrations were measured for fresh test solution at the start , 10th and 9th day and old test solution at the start of test and 3rd, 12th and 21st day using GC.

- Statistical Method:
a) Data Analysis: LC50 and EC50: During test period the any test organism was not killed in any concentration. The significant difference of reproduction was not shown . From these reason LC50 and EC50 is more than highest concentration. NOEC and LOEC: The cumulative number of juveniles produced per adult in control and test vessels after 21days was tested by Dunnett's Multicomparison Test
b) Method of Calculating Mean Measured Concentrations (i.e. arithmetic mean, geometric mean, etc.): Time-weighted Mean

-

Remark : Mean cumulative numbers of juveniles per adult alive for 21 days at control were 64.9. But 3 pearent daphnids at control produced less than 60 juveniles for 21 days.

-

Result : - Effect: reproduction- Measured Concentrations: The test concentrations were measured for both renewal and old test solution at the start of test and 1st, 8th, 9th, 16th and 17th day. For all of them, the deviations from the nominal were less than +/-20%.

Nominal Conc.	Measured Conc., mg/L							
mg/L	Date	0 Fresh	3 Old	10 Fresh	12 Old	19 Fresh	21 Old	TWM* mg/L	% of Nominal
Control		<2	<2	<2	<2	<2	<2	---	---
10		9.3	9.4	8.6	10.8	10.8	11.9	10.3	103
22		21.9	21.1	20.8	22.5	21.8	23.8	22.1	100
46		45.6	47.1	46.4	49.0	44.6	47.4	46.5	101
100		102	97.0	101	100	102	96.1	99.5	100

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

- Measured Concentration as a Percentage of Nominal

Nominal Conc.	Measured Concentration as a Percentage of Nominal					
mg/L	Date	0 Fresh	3 Old	10 Fresh	12 Old	19 Fresh	21 Old
10		93	94	86	108	108	119

22	100	96	95	102	99	108
46	99	102	101	107	97	103
100	102	97	101	100	102	96

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

- Water chemistry (pH and DO) and temperature in test: Water chemistry and temperature were measured for control and each concentration at the start of test and before and after renewal of the test solutions.

pH: 7.2 - 8.3
DO: 7.0 - 8.2 mg/L
Water Temperature: 20.3 - 20.8C
Total hardness: 249 - 281 mg/L

-Effect Data:

LC50 (21day) >100 (nc)
EC50 (21day) >100 (nc)
NOEC (21day) = 100 (nc)
LOEC (21day) > 100 (nc)
nc: based on the nominal concentrations

- Cumulative Number of Died Parental Daphnids: No test organism was killed at each concentration.

Nominal Conc. (mg/L)	Cumulative Number of Dead Parental Daphnids (days) 1	2	3	4	5	6	7	8	9	10
Control	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0	0
100	0	0	0	0	0	0	0	0	0	0

Nominal Conc. (mg/L)	Cumulative Number of Dead Parental Daphnids (days) 11	12	13	14	15	16	17	18	19	20	21
Control	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0	0	0
100	0	0	0	0	0	0	0	0	0	0	0

-Effect Data(reproduction):Juveniles were first produced between the 8th to 10th day at every concentration.

Nominal Conc. mg/L	Mean Cumulative Numbers of Juveniles Produced per Adult (days) 0 --- 7	8	9	10	11	12	13	14
Control	0 --- 0	0	1.3	7.2	8.5	10.5	20.8	24.4
10	0 --- 0	1.6	3.5	5.3	10.2	13.0	15.3	26.2
22	0 --- 0	2.6	3.6	6.8	12.8	14.6	21.2	34.3
46	0 --- 0	1.0	1.4	7.7	10.2	11.2	22.7	27.8

100	0 --- 0	0	0.4	7.4	8.7	9.6	22.1	25.8

Nominal Conc. mg/L	Mean Cumulative Numbers of Juveniles Produced per Adult (days) 15	16	17	18	19	20	21
Control	25.2	36.4	43.1	44.9	54.2	63.6	64.9
10	26.8	29.6	48.4	50.4	53.6	66.7	71.2
22	34.3	42.6	63.4	63.4	72.2	88.3	90.0
46	28.7	43.1	50.7	52.1	66.1	72.4	73.9
100	25.8	41.5	47.0	47.0	64.9	69.4	70.0

-Cumulative numbers of juveniles produced per adult alive for 21days in each test vessels and results of statistical comparison of the mean values (by Dunnett's Multicomparison Test)

	Nominal Conc., mg/L				
Vessel No.	Control	10	22	46	100
1	52	102	84	73	90
2	41	93	120	59	27
3	32	78	74	83	106
4	60	56	104	93	86
5	80	31	61	52	85
6	80	98	96	78	86
7	82	41	80	87	94
8	55	63	98	108	27
9	71	55	96	77	64
10	96	95	87	29	35
Mean	64.9	71.2	90.0	73.9	70.0
S.D.	20.3	25.5	16.6	22.4	29.8
Inhibition rate(%)		-9.7	-38.7	-13.9	-7.9
Significant difference		N.S.	N.S.	N.S.	N.S.

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

Source : Ministry of Environment, Japan (2002)
National Institute of Environmental Studies, Environment Agency Tsukuba-Ibaraki

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint

04.10.2004 (15)

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Value	:	
Species	:	rat
Strain	:	other:Crj:CD(SD)IGS
Sex	:	male/female
Number of animals	:	5
Vehicle	:	other:distilled water
Doses	:	
Method	:	OECD Guide-line 401 "Acute Oral Toxicity"
Year	:	2003
GLP	:	yes
Test substance	:	other TS:KURARAY Co., Ltd.; Purity, 99.19%
Remark	:	Doses were 0, 1000 and 2000mg/kgbw for both sexes.
Result	:	There were no mortalities during the study. As a clinical sign, decreased locomotor activity was observed in 2000 mg/kgbw females. No abnormalities were detected in body weight gain and necropsy findings. The LD50 value was estimated to be more than 2000 mg/kgbw for both sexes.
Source	:	Research Institute for Animal Science in Biochemistry and Toxicology Sagamihara Kanagawa National Institute of Health & Sciences Tokyo
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

21.01.2004 (16)

Type	:	LD50
Value	:	
Species	:	rat
Strain	:	Crj: CD(SD)
Sex	:	male/female
Number of animals	:	5
Vehicle	:	other:None
Doses	:	
Method	:	OECD Guide-line 401 "Acute Oral Toxicity"
Year	:	1989
GLP	:	yes
Test substance	:	other TS:Batch No.L-754148, Purity:99.9%u.p.
Remark	:	Dose(mg/kg): 2000, 3200, 4000, 5000 Dose volume(mL/kg): 2.16, 3.45, 4.31, 5.39 No.of rats: 5 rats/group/sex Observation period:14 days after administration. Necropsy:Day 15 after administration(The day of dosing was designated Day 1)
Result	:	LD50 values: Males and females combined: 4400(3900 to 5200)mg/kgbw Males only: 4500(3900 to 5600)mg/kgbw Females only: 4300(3600 to 5300)mg/kgbw Mortality: Deaths occurred amongst male and female rats dosed at 4000 mg/kg and above. Deaths occurred from within

two hours until day 3.
No change in body weight or body weight losses were recorded for rats that died.
Slightly pale cortex(kidney) was observed post-mortem in three males and three females(5000 mg/kg) and one female(4000 mg/kg)that died. Autopsy of rats that died revealed no other macroscopic.

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

National Institute of Health & Sciences Tokyo

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
08.12.2004 (17)

Type : LD50
Value : = 5830 mg/kg bw
Species : mouse
Strain : ICR
Sex : male
Number of animals : 10
Vehicle : other:Non
Doses :
Method : other
Year : 1973
GLP : no
Test substance : no data

Remark : Dose: 2520, 3010, 3620, 4340, 5220, 6260, 7510, 9020, 10820, 12980 mg/kg
Observation period: For 7 days after administration
Result : LD50 value :5830(5280-6420)mg/kgbw
Source : Research Institute for Animal Science in Biochemistry and Toxicology Sagamihara Kanagawa

National Institute of Health & Sciences Tokyo

Reliability : (2) valid with restrictions
05.04.2004 (18)

5.1.2 ACUTE INHALATION TOXICITY

5.1.3 ACUTE DERMAL TOXICITY

Type : LD50
Value :
Species : rat
Strain : Crj: CD(SD)
Sex : male/female
Number of animals : 5
Vehicle :
Doses :
Method : other:Testing Guideline for Toxicity Studies of Japanese MAFF(28 January 1985)
Year : 1991
GLP : yes
Test substance : other TS:Batch No.024141, Specific gravity:0.96

Remark : Dose:2000 mg/kgbw

Animal:5 males and 5 females
Rats were prepared by clipping the hair of back and approximately 24 hours before application of the test material. Care was taken to avoid abrading the skin. The test material was applied evenly onto gauze dressing which was applied to the shaved back of each rat. Approximately 23 cm2 of the body surface was in contact with the test material. The trunk of the rat was then encircled with a strip of non-irritating taps.
After a contact period of 24 hours following dosing the dressing was removed and the skin was wiped with a water dampened tissue to remove excess test material.
The rats were observed frequently on the day of dosing and for 14 days following dosing. They were weighed immediately prior to dosing, 7 days after dosing and at sacrifice at the end of the 14 day observation period.
At the end of the obsevation period, each animal was subjected to necropsy.

Result : LD50:More than 2000 mg/kgbw
No deaths and no clinical signs were noted. No abnormalities were detected at necropsy.

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

National Institute of Health & Sciences Tokyo

Reliability : (2) valid with restrictions
05.04.2004 (19)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

Species : rabbit
Concentration :
Exposure : Occlusive
Exposure time : 4 hour(s)
Number of animals : 6
Vehicle :
PDII :
Result : not irritating
Classification : not irritating
Method : EPA OPP 81-5
Year : 1991
GLP : yes
Test substance : other TS:BatchNo.024141

Remark : Concentration:100% and 50% in distilled water
Animal:Six New Zealand White rabbits
The hair was clipped from the dorsal area of the trunk of each rabbit approximately 24 hours before treatment.
The test material(0.5 mL) was applied to intact skin on each rabbit using a 2.5 x 2.5 cm patch of gauze. In the shaved area 4 sites, 2 sites were designated as test sites. MMB was applied at a concentration 100 or 50% (2 test sites). Triethyl citrate or distilled water was applied as control (2 control sites). Four patches were applied to each rabbit and the patches were covered with tape.
The test material was applied for 4 hours. At the end of application period, the test material was removed and the skin was wiped with damp tissues

without altering the existing response or the integrity of the epidermis.
Skin reactions of six animals were assessed 1, 24, 48 and 72 hours after patch removal using the scoring system.

Result : At a concentration of 100% very slight erythema was noted at one animal at 24 hours assessment only. No skin reactions were noted at a concentration of 50% v/v in distilled water.
No skin reactions were noted with the control materials, triethyl citrate and distilled water.

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

National Institute of Health & Sciences Tokyo

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
05.04.2004 (20)

Species : rabbit
Concentration :
Exposure : Occlusive
Exposure time :
Number of animals : 6
Vehicle :
PDII :
Result : slightly irritating
Classification : irritating
Method : other
Year : 1991
GLP : yes
Test substance : other TS:Batch No.024141

Remark : Concentration:100% and 50% in distilled water
Animal:Six New Zealand White rabbits
Exposure time: For 28 consecutive days at 23 h/day
The hair was clipped from the dorsal area of the trunk of each rabbit approximately 24 hours before first patch application.
The test material(0.5 mL) was applied to intact skin on each rabbit using a 2.5 x 2.5 cm patch of gauze. In the shaved area 4 sites, 2 on either side of the vertebral column, were designated as test sites. The test material was applied at concentrations of 100% and 50% (2 test sites). Triethyl citrate oe distilled water was applied as control (2 control sites). Four patches were applied to each rabbit and the patches were covered with tape.
The test material was applied at concentrations of 100% and 50% v/v in distilled water. After the 23 h exposure period of the last treatment, the patch was removed and the skin was wiped to remove residual test material.
Skin reactions of six animals were assessed and recorded 1 hour after patch removal using the scoring system.
This procedure of patch application was repeated further 27 times on successive days with the final assessment on day 29, 24 h after the last patch removal.

Result : Very slight to well defined erythema was noted with the test material at a concentration of 100% and moderate to severe erythema was noted in one animal at the 9th day assessment only. Very slight to slight oedema was also noted at a concentration of 100%. No skin reactions were noted at a concentration of 50% v/v in distilled water.
No skin reactions were noted with the control materials, triethyl citrate and distilled water.

Source : Research Institute for Animal Science in Biochemistry and Toxicology

Sagamihara Kanagawa

National Institute of Health & Sciences Tokyo

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
05.04.2004 (21)

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	
Dose	:	.1 ml
Exposure time	:	
Comment	:	
Number of animals	:	9
Vehicle	:	
Result	:	moderately irritating
Classification	:	irritating
Method	:	EPA OPP 81-4
Year	:	1991
GLP	:	yes
Test substance	:	other TS: Batch No.024141

Remark : Nine male young adult New Zealand White rabbits were used.
The quantity of material instilled into the treated eye was 0.1 mL.

Rinsed group:
Three rabbits were treated. The test material was instilled,

and 30-60 sec. post-instillation, the treated eye was rinsed with circa 100 mL of distilled water.
The eyes were examined for irritation, using a hand held magnifier and pen torch and ocular reactions were recorded 1, 24, 48 and 72 hours after administration. Further assessment was carried out on 4, 7 and 11 day until reversibility was established.

Non rinsed group:
Six rabbits were treated.
The eyes were examined for irritation, using a hand held magnifier and pen torch and ocular reactions were recorded 1, 24, 48 and 72 hours after administration. Further assessment was carried out on 7, 9 and 10 day until reversibility was established.

Result : Rinsed group:
The 3 rinsed eyes showed slight to moderste corneal opacity, moderate conjunctival redness and
chemosis, slight iritis and slight discharge. By 7 days 2 of the 3 rinsed eyes returned to normal and the remain showed complete recovery by 11 days post-instillation.

Non-rinsed group:
The 6 non-rinsed eyes showed slight corneal opacity, slight iritis, moderate to severe conjunctival responses and slight to severe discharge. By 7 days 4 of the 6 treated eyes returned to normal and the remaining 2 eyes showed complete recovery by 9-10 days post-instillation.

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

National Institute of Health & Sciences Tokyo

Reliability : (2) valid with restrictions
05.04.2004 (22)

5.3 SENSITIZATION

Type	:	other: Photosensitization
Species	:	guinea pig
Concentration	:	1st: Induction 100 % open epicutaneous 2nd: Challenge 100 % open epicutaneous 3rd:
Number of animals	:	10
Vehicle	:	
Result	:	not sensitizing
Classification	:	not sensitizing
Method	:	other:Method based on that of Harber, Armstrong and Ichikawa(JNCI, 1982,69,1)
Year	:	1991
GLP	:	yes
Test substance	:	other TS: KURARAY Co.LTD, Batch No.024141

Remark : Induction:
All guinea pigs (Dunkin-Hartley strain) had the hair removed from a 3 cm x 3 cm area
of the scapular region by clipping followed by a close shaving using a shaving cream and a safety razor. Twenty four hours later a 2.5 cm2 test site was delineated on the prepared back of each animal.
Immediately prior to the first induction application, 4 x 0.1 mL intradermal injections of Freund's Complete Adjuvant (50% v/v emulsion with distilled water) were administered at the corners of the shaved area.
Approximately 0.1 mL of the test material was applied open epicutaneously to the test site of each test group guinea pigs. Approximately 30 min later, the test group guinea pigs were placed in a wire mesh exposure chamber and exposed to 10.2 J.cm-2 of UVA radiation through a 3 mm thick window glass.
Immediately prior to application and 24 hours after the application/UV exposure the test sites were assessed for irritation.
This procedure, application/UV exposure and assessment, was repeated further 4 times.

Challenge:
Twenty days after the final induction exposure, the dorso lumber area of each group guinea pig was clipped and closely shaved. Four 2.5 cm2 test sites were marked on the test group.Twenty four hours later 0.1 mL of the test material was applied on the prepared sites. The lower dorso lumbar area test sites on each animal were then covered with light proof tapes.
Thirty minutes after application of test material, the test group and control group guinea pigs were exposed to 10.2 J.cm-2 of UVA radiation through a 3 mm thick window glass.

The test sites were assessed at 24, 48 and 72 hours after irradiation for evidence of erythema and/or oedema.

Result : Following challenge, non of the 10 test group animals showed

a positive response to the test material with or without UVA.
There is no evidence from the test result that the test material is a photosensitiser in guinea pigs.

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

National Institute of Health & Sciences Tokyo

Reliability : (2) valid with restrictions
05.04.2004 (23)

Type : Guinea pig maximization test
Species : guinea pig
Concentration : 1st: Induction 10 % intracutaneous
2nd: Induction 100 % open epicutaneous
3rd: Challenge 100 % open epicutaneous
Number of animals : 20
Vehicle : other:Distilled water
Result : not sensitizing
Classification : not sensitizing
Method : other:Magnusson-Kligman Maximization Test(Magnusson, B.,Kligman,A.M.,J.Invest.Dermat.,52,268-276,1969
Year : 1991
GLP : yes
Test substance : other TS:Batch No.024141

Remark : Animal:Less than one year old guinea pigs (Dunkin-Hartley strain)
The induction procedure consists of an intradermal injection of the test material and a topical application after the one week. The challenge procedure, which consists of a topical application, was carried out 3 weeks after commencement of the induction procedure.
Test group (10 animals) were each given 6 intradermal injections, 3 in a line each side of and parallel to the mid-line in the shaved region (0.1 mL of Freund's Adjuvant, test material or 50:50 emulsion of test material in Freund's Adjuvant). The test material was injected at 10% v/v in distilled water. The 10 control group animals were simiarly treated but with distilled water replacing test material. One hour and 24 hours after injection, the treated sites of both test and control groups were assessed for irritation. Six days after the injection, the injection sites of each of the test and control group animals was shaved again and then wetted with 10% sodium lauryl sulphate to provoke a mild inflammatory response to enhansce the possibility of sensitisation. After 24 hours, charge with the test material at 10% was applied to the pretreated area of each of the test group animals and the patch covered by an overlapping piece. The control group animals were similarly treated, but with distilled water replacing the test material. One hour and 4 hours after patch removal, the treated sites of both test and control groups were assessed for irritation. Two weeks after the start of topical induction, both the test and control animals were challenged with the test material at a concentration of 100% and with distilled water. The test and control material were applied to the prepared test site on pieces of filter paper. The patches were held in place for 24 hours using the same method as topical induction. The response was determined 24 and 48 hours after removal of the challenge patch.

Result : Induction: Slight irritation was noted in the test group.
Challenge: Following challenge with the test material at a concentration of 100%, none of the 10 test group showed positive reactions to this application.

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

National Institute of Health & Sciences Tokyo

Reliability : (2) valid with restrictions
05.04.2004 (24)

5.4 REPEATED DOSE TOXICITY

Type	:	
Species	:	rat
Sex	:	male/female
Strain	:	other:Crj:CD(SD)IGS
Route of admin.	:	gavage
Exposure period	:	28 days
Frequency of treatm.	:	once a day
Post exposure period	:	14 days
Doses	:	15, 60, 250, 1000 mg/kgbw/day
Control group	:	yes, concurrent vehicle
Method	:	other: Guideline for the 28-Day Repeated Dose Toxicity Test in Mammalian Species(Chemical Substances Control Law of Japan)
Year	:	2003
GLP	:	yes
Test substance	:	other TS:KURARAY Co., Ltd.; Purity, 99.19%

Remark : Study design:
Vehicle: Distilled water
Number of animals/groups: Males, 5; females, 5
Treatment period: Males and females, 28 days
Recovery period: Males and females, 14 days
Terminal killing: Males and females, day 29 or 43
Clinical observation performed and frequency: General condition was observed once a day, body weights were determined on day 1(before dosing),3,7,10,14,17,21,24 and 28 of treatment period and on day 3, 7, 10 and 14 of recovery period, food consumption was determined for 24 hours at once a week of treatment and recovery periods for both sexes.

Urinalysis was carried out on day 26 of treatment period, on day 13 of recovery period for males; on day 25 of treatment period and on day 12 of recovery period for females.

Hematological and biochemical examinations were carried out at time of necropsy after 28 days of treatment period and after 14 days of recovery period for both sexes.

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

Microscopic examination: Brain, heart, lung, liver, kidney, spleen, adrenal, stomach, urinary bladder, spinal code, isciadic nerve, bone marrow, small intestine, large intestine, lymph node, testis, epididymus, ovary and uterine for all animals in 0 and 1000 mg/kgbw/day groups.

Statistical methods: Dunnett's or Scheffe's test for continuous data and Fisher's exact test for quantal data. Significance level is 5%.

Result : NOAEL:60 mg/kgbw/day for males and 250 mg/kgbw/day for

females
Mortality: There was no mortality related to the test substance treatment.
Clinical signs: No clinical signs were observed in males and females.
Body weight: No statistically significant changes for males and females.
Food consumption: No statistically significant changes for males and females.
Urinalysis: No statistically significant changes.
Hematology: No effects for males and females.

Blood biochemistry: A decrease in chloride in males and females, and increases in A/G ratio and inorganic phosphorus in males of 1000 mg/kgbw/day at examination after administration period.

At examination after administration period:
Males

Dose(mg/kgbw/day)		0	15	60	250	1000
No. of animals		5	5	5	5	5
Chloride(mEq/L)	Mean	105	105	106	105	102*
	SD	2	1	1	2	1
A/G ratio	Mean	1.00	1.04	1.03	1.11	1.17*
	SD	0.09	0.10	0.06	0.08	0.04
I.P.(mg/dL)	Mean	8.3	8.5	8.9	9.1	9.5*
	SD	0.7	0.7	0.6	0.3	0.8

Females

Dose(mg/kgbw/day)		0	15	60	250	1000
No. of animals		5	5	5	5	5
Chloride(mEq/L)	Mean	106	106	106	106	104*
	SD	1	1	1	1	1

Note: *,P<0.05

Necropsy: No effect for males and females

Organ weights: An increase in relative weight of kidneys in males of 250 mg/kgbw/day, and males and females of 1000 mg/kgbw/day and an increase in relative weight of liver in males of 1000 mg/kgbw/day at examination after administration period, and an increase in relative weight of liver in males of 1000 mg/kgbw/day.

Males

Dose(mg/kgbw/day)		0	15	60	250	1000
No. of animals		5	5	5	5	5
Relative weight:Kidney(g%)	Mean	0.81	0.82	0.87	0.90*	0.93**
	SD	0.03	0.04	0.03	0.05	0.06
:Liver(g%)	Mean	2.97	3.00	2.98	3.03	3.27*
	SD	0.10	0.22	0.24	0.08	0.10

Females

Dose(mg/kgbw/day)	0	15	60	250	1000
No. of animals	5	5	5	5	5

Relative weight:Kidney(g%)

Mean	0.82	0.79	0.87	0.88	0.95**
SD	0.02	0.02	0.04	0.05	0.07

:Liver(g%)

Mean	2.88	2.96	3.02	3.02	3.25**
SD	0.10	0.11	0.19	0.09	0.21

At examination after recovery period
Males

Dose(mg/kgbw/day)	0	1000
No. of animals	5	5

Relative weight:Liver(g%)

Mean	2.72	2.91*
SD	0.13	0.13

Note: *,P<0.05; **,P<0.01
Females: No effect

Histopathology: No effects for males and females.

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

National Institute of Health & Sciences Tokyo

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
15.04.2004 (16)

Type :
Species : rat
Sex : male
Strain : other:JCL-SD
Route of admin. : inhalation: vapour
Exposure period : 4 weeks
Frequency of treatm. : 4 hours/day, five times/week
Post exposure period : None
Doses : 100, 300, 500 ppm
Control group : yes
Method : other
Year : 1976
GLP : no
Test substance : other TS

Remark : Air volume:10 L/min
Ventilation:10 time/hour
Whole-body inhalation
Observation and measurement:
general condition, body weight, food consumption, water consumption, hematology, blood biochemistry, urinalysis, necropsy, organ weight, histopathology(liver, kidney, adrenal, spleen, heart, lung, brain, spinal cord, testis)

Result : Clinical sign: No effects were observed.
Body weight:No statistically significant changes
Food consumption:No statistically significant changes
Water consumption:No statistically significant changes
Blood chemistry: An increase of GOT in 100 and 500 ppm.
Urinalysis: No statistically significant changes
Necropsy: No effect
Organ weight:Increases of absolute and relative weights of kidney in all treated group.
Histopathology: No effect related to the test material

Source : Research Institute for Animal Science in Biochemistry and Toxicology

Sagamihara Kanagawa

National Institute of Health & Sciences Tokyo

Reliability : (2) valid with restrictions
05.04.2004 (25)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Ames test
System of testing : Test species/strain:Salmonella typhimurium TA100, TA1535, TA98, TA1537, Escherichia coli WP2 uvrA
Test concentration : 0, 313, 625, 1250, 5000 ug/plate
Cycotoxic concentr. : The chemical did not induce cytotoxicity.
Metabolic activation : with and without
Result : negative
Method : other: Guideline for Screening Mutagenicity Testing of Chemicals(Chemical Substances Control Law of Japan) and OECD Test Guideline 471
Year : 2003
GLP : yes
Test substance : other TS: KURARAY Co., Ltd.; Purity, 99.19%

Remark : Solvent:Water for injection
Procedures: Pre-incubation method
Dosage of each strain with or without S9 mix
-S9 mix:0, 313, 625, 1250, 2500, 5000 ug/plate(TA100, TA1535, TA98, TA1537, WP2 uvrA)
+S9 mix:0, 313, 625, 1250, 2500, 5000 ug/plate(TA100, TA1535, TA98, TA1537, WP2 uvrA)
S9 mix:Rat liver, induced with phenobarbital and 5,6-benzoflavone
Positive control:
-S9 mix; 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide (TA100, TA98, WP2 uvrA), sodium azide (TA1535) and 9-Aminoacridine (TA1537)
+S9 mix; 2-Amonoanthracene (all strains)
Plates/test:3(1 for cytotoxicity test)
Number of replicates:2 (plus 1 cytotoxicity test)

Result : There was no precipitation in any test concentration.
Cytotoxic concentration: Growth inhibition was not observed up to 5000 ug/plate for any stains, with or without S9 mix.
Genotoxic effects:
Positive control:
With metabolic activation: positive
Without metabolic activation: positive

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

Escherichia coli WP2 uvrA
With metabolic activation: negative
Without metabolic activation: negative

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

National Institute of Health & Sciences Tokyo

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
21.01.2004 (16)

Type : Chromosomal aberration test
System of testing : Type of cell used: Chinese hamster lung(CHL/IU) cell
Test concentration : 0.30, 0.60, 1.2 mg/mL
Cycotoxic concentr. :
Metabolic activation : with and without
Result : negative
Method : other:Guideline for Screening Mutagenicity Testing of Chemicals(Chemical Substances Control Law of Japan) and OECD Test Guideline 473
Year : 2003
GLP : yes
Test substance : other TS: KURARAY Co., Ltd.; Purity, 99.19%

Remark : Solvent: Water for injection
S9 mix: Rat liver, induced with phenobarbital and 5,6-benzoflavone
Positive control: Cyclophosphamide (with S9 mix), Mitomycin C (without S9 mix)
Plates/test: 2
The maximum concentration was established, based on the growth inhibition test. In this test, growth inhibition was not observed at a concentration of 1.2 mg/mL (10 mmol/L) for 6 hours short-term treatment with or without S9 mix and for 24 hours continuous term treatment with S9 mix.
Dosage:
-S9 mix(6 hr short-term treatment):0, 0.30, 0.60, 1.2 mg/mL
+S9 mix(6 hr short-term treatment):0, 0.30, 0.60, 1.2 mg/mL
-S9 mix(24 hr continuous treatment):0, 0.30, 0.60,1.2 mg/mL

Result : The incidence of cells with structural chromosomal aberrations and polyploidy was not significantly altered at any doses.

Genotoxic effects:

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

Positive control

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

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

National Institute of Health & Sciences Tokyo
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
22.01.2004 (16)

Type : Ames test
System of testing : Salmonella typhimurium TA 1535, TA1537, TA 1538, TA 98, TA 100 and E.coli WP uvrA
Test concentration : 312.5, 625, 1250, 2500, 5000 ug/plate
Cycotoxic concentr. :
Metabolic activation : with and without
Result : negative
Method : OECD Guide-line 471
Year : 1989

GLP	:	yes
Test substance	:	other TS:Batch No.L-754148, >99.9%
Remark	:	Solvent: Water Dose finding test:Dose levels:5000, 500, 50, 5 ug/plate No. of plates: 1 plate for dose finding test Main test: No.of plates: 3 plates for Ames test Repetition: 2 Positive control: With S9 mix: 2-Aminoanthracene for all strains Without S9 mix: 9-Aminoacridine for TA 1537, N-Ethyl-N'-nitro-N-nitrosoguanidine for TA 100, TA 1535 and WP2 uvrA, 2-Nitrofluorene for TA 98 and TA 1538
Result	:	Dose finding test: The test material was not toxic towards the tester strains. Therefore 5000 ug/plate was chosen as the top dose level in the mutation tests Ames test: No substantial increases in revertant colony numbers of all tester strains were observed at any dose levels, either in the presence or absence of metabolic activation. Positive control:positive for all strains
Source	:	Research Institute for Animal Science in Biochemistry and Toxicology Sagamihara Kanagawa National Institute of Health & Sciences Tokyo
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

08.12.2004 (26)

5.6 GENETIC TOXICITY 'IN VIVO'

5.7 CARCINOGENICITY

5.8.1 TOXICITY TO FERTILITY

Type	:	other:Preliminary Reproduction Toxicity Screening Test
Species	:	rat
Sex	:	male/female
Strain	:	other:CrjCD(SD)IGS
Route of admin.	:	gavage
Exposure period	:	47 days for males; 42-52 days from 14 days before mating to day 4 of lactation for females
Frequency of treatm.	:	once a day
Premating exposure period		
Male	:	14 days
Female	:	14 days
Duration of test	:	47 days for males; 42-52 days for females
No. of generation studies	:	
Doses	:	8, 40, 200, 1000 mg/kgbw:/day
Control group	:	yes, concurrent vehicle
Method	:	other:OECD Test Guideline 421
Year	:	2003
GLP	:	yes
Test substance	:	other TS:KURARAY Co., Ltd.; Purity, 99.19%

Remark : Study design:
Vehicle: Distilled water
Terminal killing: Males, day 47; females, day 4 of lactation
Clinical observation performed and frequency: General condition was observed once a day, body weights were determined once a week during treatment period for males and once a week before mating and on day 0, 7, 14 and 20 of gestation period and on day 0 and 4 of lactation period for females, food consumption was determined once a week during treatment period for males and once a week before mating and on day 0,7,14 and 20 of gestation period and on day 0 and 4 of lactation for females.

Body weight gains of male rats (g)

Dose (mg/kg)		Days of treatment 1-8	8-22	22-29	29-36	36-43	43-47	1-47
0	Mean	26	47	25	21	17	10	145
	SD	9	9	7	7	4	3	24
8	Mean	31	50	25	22	19	11	158
	SD	10	12	8	6	10	8	32
40	Mean	31	48	28	24	14	10	155
	SD	11	12	7	8	5	6	37
200	Mean	29	49	27	19	16	13	154
	SD	12	12	6	7	5	4	27
1000	Mean	28	43	24	18	16	6	135
	SD	10	10	6	9	11	6	30

Total food consumption of male rats (g)

Dose (mg/kg)		Days of treatment 1-8	8-22	22-29	29-36	36-43	43-47	1-47
0	Mean	220	459	226	233	238	133	1509
	SD	19	45	22	16	26	12	130
8	Mean	230	481	247	253	258	138	1608
	SD	28	54	27	31	37	14	167
40	Mean	224	485	251	249	243	139	1588
	SD	19	57	20	29	33	19	154
200	Mean	214	471	242	246	243	140	1556
	SD	29	47	25	29	22	16	143
1000	Mean	196	485	244	239	250	135	1543
	SD	27	34	21	18	28	18	114

Body weight gains of female rats (g)

Dose (mg/kg)		Days of premating 1-8	8-15	1-15	Days of pregnancy 0-7	7-14	14-20	0-20	Days of lactation 0-4
0	Mean	17	15	33	42	41	86	169	20
	SD	8	5	11	9	12	19	32	11
8	Mean	17	12	29	46	42	90	179	25
	SD	6	8	8	9	5	10	14	16

40	Mean	17	17	34	46	38	86	170	12
	SD	8	5	10	7	5	11	21	21
200	Mean	13	12	25	41	45	85	172	18
	SD	8	6	9	9	7	13	21	15
1000	Mean	11	14	25	36	38	83	157	14
	SD	6	9	10	7	6	12	12	11

Total food consumption of female rats (g)

Dose (mg/kg)		Days of premating			Days of pregnancy			Days of lactation		
		1-8	8-15	1-15	0-7	7-14	14-20	0-20	0-4	Total
0	Mean	157	146	302	147	205	173	525	150	978
	SD	29	21	33	27	24	21	60	28	97
8	Mean	146	171*	316	160	229	190	579	159	1054
	SD	31	15	42	20	32	28	67	13	102
40	Mean	167	156	323	144	211	181	536	154	1010
	SD	18	26	33	29	20	20	63	26	83
200	Mean	146	150	296	141	208	180	529	165	989
	SD	22	12	24	25	18	24	50	17	71
1000	Mean	142	143	285	132	204	179	516	143	943
	SD	15	23	33	45	25	33	83	16	117

* Significantly diffrent from control at 5% level of probability

For all males and all females after childbirth, necropsy was carried out after 48 days for males and at 5 days after delivery for females.

Organ weights measured: Liver and kidney in both sexes, and testis and epididymus in males.
Organ weight was determined in 12 males in all dose groups and in 12 females in 0, 8, 200 and 1000 mg/kgbw/day groups and in 11 females in 40 mg/kgbw/day group.

Microscopic examination: Liver, kidney, testis and epididymus for 12 males in 0 and 1000 mg/kgbw/day groups, and liver, kidney and ovary for 12 females in 0 and 1000 mg/kg bw/day groups.

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

Statistical methods: Dunnett's or Scheffe's test for

continuous data, Chi-square test for reproductive parameters, and Fischer's exact test for pathological findings.

Result : NOAEL:40 mg/kgbw/day for repeated dose toxicity of males and 200 mg/kg bw/day for repeated dose toxicity of females, and 1000 mg/kgbw/day for reproductive performance of parents and for offspring development.

Mortality: There was no mortality related to the test material treatment.
Clinical signs: No effects related to the test material were apparent on clinical observation.
Body weight: No statistically significant changes.
Food consumption: No statistically significant changes.
Necropsy: No effect for males and females.
Organ weights: Absolute and relative weights of kidneys increased in males at 200 mg/kg bw/day or more and relative weights of liver and kidneys increased in females at 1000 mg/kg bw/day.

Males:

Dose(mg/kg)		0	8	40	200	1000
No.of animals		12	12	12	12	12
Kidneys	Absolute weight(g)					
	Mean	3.10	3.26	3.25	3.50*	3.68**
	SD	0.28	0.35	0.32	0.23	0.47
	Relative weight(g%)					
	Mean	0.59	0.59	0.60	0.65*	0.70**
	SD	0.04	0.05	0.06	0.04	0.04

Females:

Dose(mg/kg)		0	8	40	200	1000
No.of animals		12	12	12	12	12
Liver	Relative weight(g%)					
	Mean	4.62	4.72	4.84	4.70	5.13**
	SD	0.25	0.26	0.24	0.40	0.25
Kidney	Relative weight(g%)					
	Mean	0.57	0.59	0.60	0.59	0.64**
	SD	0.05	0.04	0.03	0.03	0.05

Histopathology: No effect for males and females.

Reproductive and developmental parameters: The parent animals exhibited no alterations in reproductive parameters. There were no significant differences in offspring parameters.

Reproduction results:

Dose(mg/kgbw/day)		0	8	40	200	1000
No.of females examined		12	12	12	12	12
Estrous cycle(days)						
	Mean	4.0	4.0	4.0	4.0	4.0
	SD	0.0	0.1	0.1	0.0	0.1
No.of pairs mated		12	12	12	12	12
No.of pairs with successful copulatation		12	12	11	12	12
Copulation index(%)		100	100	91.7	100	100
Pairing days until copulation(day)						
	Mean	2.3	3.2	2.0	2.3	3.3
	SD	0.9	0.8	1.0	1.2	1.8

No.of pregnant females		12	12	11	12	12
Fertility index(%)		100	100	100	100	100
No.of corpora lutea						
	Mean	18.7	19.5	18.2	17.8	18.3
	SD	2.7	2.2	1.9	2.1	2.1
No.of implantation sites						
	Mean	17.0	18.1	16.6	16.4	16.7
	SD	2.6	1.8	3.0	1.2	2.4
Implantation index(%)						
	Mean	91.4	93.0	90.9	92.7	91.7
	SD	9.0	6.2	8.9	6.5	11.5
No.of pregnant females with parturition		12	12	11	12	12
Gestation length(days)						
	Mean	22.5	22.4	22.5	22.2	22.4
	SD	0.5	0.5	0.5	0.4	0.5
No.of pregnant females with live pups		12	12	11	12	12
Gestation index(%)		100	100	100	100	100
No.of pregnant females with live pups on day 4		12	12	11	12	12
Litter results:						
Dose(mg/kgbw/day)		0	8	40	200	1000
No.of pups born						
	Mean	15.2	16.7	15.4	15.3	14.9
	SD	3.9	2.3	3.3	1.7	2.1
Deliver index(%)						
	Mean	89.5	92.1	92.0	93.3	89.9
	SD	19.8	8.6	7.4	7.1	8.1
No.of pups on day 0 of lactaion						
	Mean	15.2	16.7	15.3	15.3	14.5
	SD	3.9	2.3	3.2	1.7	2.5
Live birth index(%)						
	Mean	100	100	99.5	100	97.2
	SD	0	0	1.6	0	9.6
Sex ratio(male/female)		1.04	0.82	1.04	1.16	1.01
No.of pups alive on day 4 of lactation						
	Mean	14.9	16.3	14.9	15.0	14.1
	SD	3.7	2.3	3.2	2.0	2.6
Viability(%)						
	Mean	98.6	98.1	97.6	97.7	97.1
	SD	2.6	4.4	4.9	4.5	4.5
Body weight of live pups on day 0 : Male						
	Mean	7.2	7.1	7.3	7.0	6.7
	SD	0.6	0.8	0.8	0.5	0.6
: Female						
	Mean	6.9	6.7	7.0	6.4	6.5
	SD	0.8	0.9	0.8	0.5	0.4
on day 4 : Male						
	Mean	11.7	11.7	11.6	11.5	11.0
	SD	1.7	1.7	2.3	0.8	1.1
: Female						
	Mean	11.4	11.0	11.0	10.8	10.7
	SD	1.8	1.6	1.9	0.7	1.1

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

National Institute of Health & Sciences Tokyo
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
16.04.2004 (16)

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species : rat
Sex : female
Strain : Crj: CD(SD)
Route of admin. : gavage
Exposure period : day 6 through 15 of gestation
Frequency of treatm. : once a day
Duration of test : for 15 days from 6 to 20 days of gestation
Doses : 250, 500, 2000 mg/kgbw/day
Control group : yes, concurrent vehicle
Method : other:Guidelines for Reproduction Studies for Safety Evaluation of Drugs for Human Use(FDA:1966)
Year : 1991
GLP : yes
Test substance : other TS:Lot No.023849, Purity, 100%

Remark : Methods:
There were 25 presumed pregnant rats randomly assigned to each dosage group.
The test material was administered orally via gavage once daily to the female rats on day 6 through 15 of gestation at doses of 0(vehicle:deionized water), 250, 500 and 2000 mg/kgbw/day. The dosage volume was 10 mL/kgbw, which was adjusted daily on the basis of the individual body weights recorded immediately prior to intubation.
The rats were examined daily during the dosage and postdosage periods for clinical observations of test material effects, abortions, premature deliveries and death.
Body weights and food consumption values in the rats were recorded on day 0 of gestation and daily during the dosage and postdosage periods.

Maternal body weight changes(g)

Dose (mg/kg)		Days 0-6	Days 6-12	Days 16-20
0	Mean	39.6	64.1	63.7
	SD	8.9	10.2	13.4
250	Mean	41.9	59.1	64.1
	SD	7.0	10.9	17.9
500	Mean	40.6	57.9*	64.2
	SD	7.6	10.0	12.8
2000	Mean	40.9	35.8**	68.1
	SD	7.2	9.2	11.6

Maternal absolute feed consumption values (g/day)

Dose (mg/kg)		Days 0-6	Days 6-12	Days 16-20
0	Mean	25.3	27.3	29.4
	SD	2.4	2.0	2.2
250	Mean	25.8	25.9*	30.2
	SD	2.4	2.5	3.6

500	Mean	25.3	25.5**	30.4
	SD	1.8	1.8	3.3
2000	Mean	25.4	20.3**	30.7
	SD	2.2	2.0	2.6

* significantly different from the vehicle control group value (P=<0.05)
** significantly different from the vehicle control group value (P=<0.01)

On day 20 of gestaion, the rats were sacrificed to examine for the number and placement of implantations, early and late resorptions, live and dead fetuses and the number of corpora lutea in each ovary. Fetuses were weighed, individually identified, sexed and examined for external alterations. Live fetuses were sacrificed by immersion in the appropriate fixative.
Approximately one-half of the fetuses in each litter were examined for soft tissue alterations. The remaining fetuses in each litter were examined for skeletal alternations.

Result : NOEL for pregnant females: Less than 250 mg/kgbw/day
NOEL for development of fetuses: 500 mg/kgbw/day

Clinical signs: Decreased mortor activity, excess salivation, ataxia, muscle flaccidity and loss of righting reflex were observed in the 2000 mg/kgbw/day group.
Body weights: Decreases of body weight gains in pregnant females of 250, 500 and 2000 mg/kgbw/day.
Food consumption: The 250, 500 and 2000 mg/kgbw/day groups had significant reductions in absolute (g/day) and relative(g/kg/day) maternal feed consumption values for the entire dosage period.
Necropsy: No gross lesions were caused by the test material.
Fetal parameters: The 2000 mg/kgbw/day group reduced fetal body weight. No other Caesarean-sectioning or litter observations were attributable to the test material.
Malformations and variations: The test material did not cause fetal malformations. The 2000 mg/kgbw/day group had significant increases in the litter and fetal incidences of variations in skeletal ossification of the ribs, sternum and pelvis.

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

National Institute of Health & Sciences Tokyo

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
15.04.2004 (27)

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

5.11 ADDITIONAL REMARKS

Type : other:Patch test

Remark : Subject: 20 men and 21 women of 20-53 years old
Method: Test subustance was attached to the humeral skin for 48 hours. The test substance was removed from the skin. Examinations for reaction in patch test were judged at 30 minutes and 24 hours after removing.
The test substance was judged to be negative at examinations of 30 minutes and 24 hours after removing the test substance.

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

National Institute of Health & Sciences Tokyo

Reliability : (4) not assignable
24.12.2003 (28)

Type : other:Photoirritation

Remark : Determination of photoirritation potential in guinea pigs
GLP:Yes
The photoirritation potential of the test material was investigated in guinea pigs. The test material was applied dermally at concentrations of 100%, 50%, 25% and 10%V/V in distilled water to test and control groups followed by exposure to UVA in the test group only.
No photoirritation responses were noted in the test and control groups.
There is no evidence from the results that the test material is a photoirritant in guinea pigs.

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

National Institute of Health & Sciences Tokyo

Reliability : (4) not assignable
05.04.2004 (29)

(1) Kuraray Co., Ltd.(2004), Material Safety Data Sheet on 3-Methoxy-3-methyl-1-butanol

(2) Chemicals Evaluation and Research Institute (CERI). (2001). Report of Melting Point Measurement of MMB, Report Number 81944. Unpublished Report.

(3) Chemicals Evaluation and Research Institute (CERI). (2001). Report of Boiling Point Measurement of MMB, Report Number 81945. Unpublished Report.

(4) Sigma-Aldrich-Furuka, Material Safety Data Sheet on 3-Methoxy-3-methyl-1-Butanol. Searched on 5-Jan-2004.

(5) Chemicals Evaluation and Research Institute (CERI). (2001). Report of Vapour Pressure Measurement of MMB, Report Number 81946. Unpublished Report.

(6) Chemicals Evaluation and Research Institute (CERI), (2004). SRC-MPBPWIN v1.40.

(7) Chemicals Evaluation and Research Institute (CERI). (2001). Report of Partition Coefficient Measurement of MMB, Report Number 81947. Unpublished Report.

(8) Chemicals Evaluation and Research Institute (CERI), (2004). SRC-KOWWIN v1.66.

(9) Chemicals Evaluation and Research Institute (CERI). (2001). Report of Water Solubility Measurement of MMB, Report Number 81948. Unpublished Report.

(10) Chemicals Evaluation and Research Institute (CERI), (2004). SRC-AOPWIN v1.90.

(11) Chemicals Evaluation and Research Institute (CERI). (2001). Report of Hydrolysis rate of MMB, Report Number 81949. Unpublished Report.

(12) Chemicals Evaluation and Research Institute (CERI), (2004). Internal data.

(13) Chemicals Evaluation and Research Institute (CERI). (2001). Ready Biodegradation Study on MMB, Report Number 13675. Unpublished Report.

(14) Chemicals Evaluation and Research Institute (CERI). (2002). Biodegradation Study on MMB, Report Number 13847. Unpublished Report.

(15) Ministry of the Environment(MOE), Japan.(2001), Unpublished data.

(16) Ministry of Health, Labour and Welfare(MHLW), Japan.(2003),
571-605

(17) Huntingdon Research Center Ltd.(1989a),Acute oral toxicity to rats of Solfit. Unpublished report

(18) Occupational Health Service center.(1973), Unpublished report

(19) Inversk Resarch International(IRI).(1991g), Acute dermal Toxicity (LD50) test in rats. Report No.8025, Unpublished report

(20) Inversk Resarch International(IRI).(1991a), Primary skin irritation test in rabbits. Report No.6915, Unpublished report

(21) Inversk Resarch International(IRI).(1991b), Dermal irritation test in rabbits-28day repeated application. Report No.6916, Unpublished report

(22) Inversk Resarch International(IRI).(1991c), Primary eye irritation test in rabbits. Report No.6917, Unpublished report

(23) Inversk Resarch International(IRI).(1991f), Determination of photoirritation potential in Guinea pigs. Report No.6920, Unpublished report

(24) Inversk Resarch International(IRI).(1991d), Magnsson-Kligman maximization test in Guinea pigs. Report No.6918, Unpublished report

(25) Occupational Health Service center.(1976), Unpublished report

(26) Huntingdon Research Center Ltd.(1989b),Microbial Metabolic Activation test to Assess the potential mutagenic effect of Solfit. Unpublished report

(27) Argus Research Laboratories, Inc.(ARI),(1991). Developmental toxicity (embryo-fetal toxicity and teratogenic potential) study of 3-methoxy-3-methyl-1-butanol(MMB) administered orally via gavage to Crl:CD BR VAF/Plus presumed pregnant rats, Protocol211-001. Unpublished report

(28) KURARAY Co.Ltd, in-house report

(29) Inversk Resarch International(IRI).(1991e), Determination of photoirritation potential in Guinea pigs. Report No.6919, Unpublished report