FOREWORD INTRODUCTION

6-tert-Butyl-m-Cresol

CAS N°: *88-60-8*

SIDS Initial Assessment Report

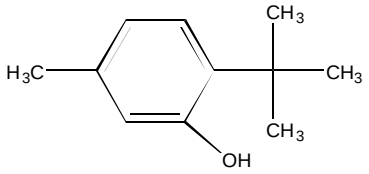
For

SIAM 15

Boston, 22-25th October 2002

1. Chemical Name:	6-*tert*-Butyl-*m*-Cresol
2. CAS Number:	88-60-8
3. Sponsor Country:	Japan National SIDS Contact Point: Mr. Yasuhisa Kawamura, Ministry of Foreign Affairs, Japan
4. Shared Partnership with:	
5. Roles/Responsibilities of the Partners:	
• Name of industry sponsor /consortium	Mr. Naoki Inui Sumitomo Chemical Co. Ltd. E-mail : inuin@sc.sumitomo-chem.co.jp
• Process used	
6. Sponsorship History	
• How was the chemical or category brought into the OECD HPV Chemicals Programme ?	This substance is sponsored by Japan under the ICCA Initiative and is submitted for first discussion at SIAM 15.
7. Review Process Prior to the SIAM:	The industry consortium collected new data and prepared the updated SIDS Dossier, and draft versions of the SIAR and SIAP. The Japanese government peer-reviewed the documents and audited selected studies.
8. Quality check process:	
9. Date of Submission:	
10. Date of last Update:	
11. Comments:	No testing ( ) Testing (X) Micronucleus assay The industry contact point is Mr. Naoki Inui, Sumitomo Chemical Co. Ltd. (consortium members: Honshu Chemical Industry Co. Ltd.)

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	88-60-8
Chemical Name	6-*tert*-Butyl-*m*-cresol
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

There is no available information on toxicokinetics and metabolism of 6-*tert*-Butyl-*m*-cresol. The LD50 values for acute toxicity of this substance were between 320 and 800 mg/kg in males and between 130 and 320 mg/kg in females for rats, and 580 mg/kg in males and 740 mg/kg in females for mice. This substance is corrosive to skin and eyes in rabbits. But no irritation problem has been reported at any production site where workers wear proper clothing and equipment. In a repeated toxicity study in rats (combined repeat dose and reproduction toxicity screening test [OECD TG 422]), suppression of the body weight and decrease in food consumption were observed in females of the 60 mg/kg group. Liver was the primary organ for toxic effect. Hypertrophy of centrilobular hepatocytes was observed in both sexes of the 60 mg/kg group. Based on the above results, the NOAEL for repeated dose toxicity is considered to be 12.5 mg/kg/day for both sexes.

This substance was not genotoxic in a gene reverse mutation test [OECD TG 471,472]. A chromosomal aberration test in CHL/IU cells [OECD TG 473] was positive for short-term treatment with an exogeneous metabolic activation system. However, a mouse micronucleus assay conducted *in vivo* [OECD TG474] was negative.

A reproductive toxicity study in rats [OECD TG 422] revealed that this substance was toxic to the dams at 60 mg/kg, causing depression of body weight gain and a slight decrease in the number of corpora lutea and implantations. This effect in the dams influenced the outcome of pregnancy, seen as a decrease in the number of live births and depression of weight gain in the offspring. These effects were not seen at 12.5 mg/kg/day. No evidence of gross malformations was observed at any dose. Based on these findings, the NOAEL for reproductive toxicity is considered to be 12.5 mg/kg/day for both female parents and pups. Evidence of malformations was not observed at any dose.

Environment

The substance has a solubility in water of 0.42 g/L at 25°C and a vapour pressure of 3.3 Pa at 25°C. The Henry's law constant is 1.3 $Pa \cdot m^3 \cdot mol^{-1}$ at 25°C.

The potential distribution of the substance was estimated using a Fugacity Mackay level III model. The results suggest that the majority of the substance distribute into soil if released to soil or air or equally to each compartment, and into water and sediment if released to the aquatic compartment.

The substance is not readily biodegradable ([OECD TG 301C]; 1% after 28 days). Abiotic degradation by hydrolysis does not occur at pH4, 7 and 9 [OECD TG 111]. The substance has a high logPow (4.11), but the measured BCF is low ([OECD TG 305]; BCF = 41-92 at 10 µg/L and 39-93 at 1 µg/L). The calculated Koc is 3.2×10^3. The acute EC_{50} values for algae were 0.900 mg/L and 1.84 mg/L (24to 48hr, i.e. within the exponential growth phase of the controls) for biomass and growth rate, respectively [OECD TG 203]. The acute EC_{50} for daphnids was 2.77 mg/L [OECD TG 202] and the LC_{50} for fish was 2.72 mg/L [OECD TG 203]. The chronic NOEC values for green algae

were 0.248 mg/L and 0.622 mg/L for biomass and growth rate, respectively [OECD TG 201]. The chronic NOEC for daphnids was 0.241 mg/L [OECD TG 211, draft April, 1997].

Exposure

Production volume of the substance is estimated to be ca. 1,500 tonnes/year in Japan. As the substance is used solely as a chemical intermediate of antioxidants, the exposure of the substance is limited to the production and industrial use in Japan. Although the substance is registered in the EU as a flavoring agent, there is no information to confirm the actual usage in the EU.

Consumer exposure: In consideration of the application of the substance (mostly for industrial use as an intermediate to synthesize antioxidants added to polymers and rubbers.), consumer exposure is considered to be negligible because residual contents of the substance in these products is not expected.

Occupational exposure: During production, processing and use, occupational exposure by inhalation and skin contact at the production and industrial use sites is the only case for consideration. The margin of safety for the exposure by inhalation is very high and workers wear proper protective equipment during these operations.

Exposure to the environment: During production, processing and use in Japan, only the aquatic release of the substance at the production site seems to be possible. But the estimated emission amount at the production site where the greatest amount of release is expected, is practically negligible.

RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

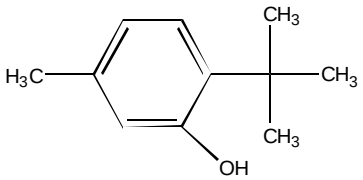
The chemical possesses properties indicating a hazard for human health and the environment. Based on data presented by the Sponsor country, exposure to humans and the environment is anticipated to be low, and therefore this chemical is currently of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 88-60-8
IUPAC Name: 2-*tert*-Butyl-5-methylphenol
Molecular Formula: $C_{11}H_{16}O$
Structural Formula:



Molecular Weight:
Synonyms: (Chemical Name)

6-*tert*-Butyl-3-methylphenol ; 3-Methyl-6- *tert*-butylphenol

5-Methyl-2-*tert*-butylphenol; 1-*tert*- Butyl-2-hydroxy-4-methylbenzene

2-(1,1-Dimethylethyl)-5-methylphenol; 6-tert-Butyl-m-Cresol

(Trade Name)

3M6B

MBMC

1.2 Purity/Impurities/Additives

Purity: = > 97.5% weight / weight**.**

Impurities: 2-*tert*-Butyl-4-methylphenol = < 2.0 % weight / weight

Additives: None**.**

1.3 Physico-Chemical properties

Table 1 Summary of physico-chemical properties

ITEMS	PROTOCOL	RESULTS	REFERENCE
Melting Point	JIS K 4101-5.2	21.3°C	Honshu Chemical (2001)
Boiling Point	JIS K 4101-8.1	244°C (at 101kPa)	Honshu Chemical (2001)
Vapour Pressure	OECD TG 104	3.3 Pa (at 25°C)	METI (1999a)
Partition Coefficient (Log Pow)	OECD TG 107	4.11 (at 25±1°C)	METI (1999b)
Water Solubility	OECD TG 105	0.42 g / L (at 25±1°C)	METI (1999a)
pKa	OECD TG 112	11.21 (at 25±1°C)	METI (1999a)

Note: Based on the vapour pressure and water solubility reported above, a Henry's law constant of 1.3 $Pa.m^3.mol^{-1}$ can be estimated.

2 GENERAL INFORMATION ON EXPOSURE

1) 6-*tert*-Butyl-*m*-cresol is produced in a closed system in Japan. The production volume of the substance is estimated to be ca 1,500 t/year in Japan.

2) This substance is registered in the EU as a flavoring agent used or intended for use in or on foodstuffs, details are unknown to the producers of this substance.

3) In Japan this substance is exclusively used as an intermediate to synthesize antioxidants added to polymers and rubbers. Therefore, the exposure of the substance is limited to the production sites of this substance and the antioxidants.

4) Considering the use pattern of the substance (mostly for industrial use as an intermediate), consumer use is considered to be low.

5) During production, processing and use in Japan, occupational exposure at the production and industrial use sites is the only case for consideration.

6) As for exposure to the environment, the aquatic release of the substance at the production sites seems to be possible. But the estimated emission amount at the production site where the greatest amount of release is expected is practically negligible.

2.1 Environmental Exposure and Fate

The potential distribution of the substance was estimated using a Fugacity level III model. As shown in Table 1 the calculation results suggest that the majority of the substance distributes into soil if released to soil or air or equally to each compartment, and into water and sediment if released to the aquatic compartment.

Table 1. Estimated Distribution under three emission scenarios

Compartment	Release			
	100 % to air	100 % to water	100 % to soil	Equally to each compartment
Air	2.2%	0.0%	0.0%	0.0%
Water	1.8%	67.3%	0.1%	0.4%
Soil	95.0%	1.2%	99.9%	99.4%
Sediment	0.9%	31.5%	0.0%	0.2%

The substance, if released to air, will react with photochemically-produced hydroxy radicals, and decrease with a half-life of 1.2 hours (calculated by AOPWIN). The substance is not readily biodegradable ([OECD TG301C]: 1% after 28 days based on BOD and HPLC analysis) (METI, 1998). Abiotic degradation by hydrolysis does not occur at environmental pHs (METI 1999a). On the other hand, the measured bioaccumulation is low [OECD TG 305; BCF = 41-92 at 10 µg/L and 39-93 at 1 µg/L] (METI, 2000). The partition coefficient between soil/sediment and water (Koc) has been calculated to be 3.2×10^3.

(Note) Appendix 1 shows the Predicted Environmental Concentration (PEC) calculated with a worst case scenario for Japan.

2.2 Human Exposure

2.2.1 Occupational Exposure

1) Occupational exposures in Japan during sampling, loading into a tank truck or container and drum filling at the production sites may occur through inhalation and skin contact.

2) This substance is a liquid having a low vapor pressure (3.3 Pa) and workers wear protective gloves, a face protector, protective mask and protective clothing during the operation.

3) The workplace air concentration was measured at one production site [Sumika Chemical Analysis Service, 2002]. The monitored data are shown in Table 2.

Table2. Workplace monitoring data for 6-*tert*-Butyl-*m*-cresol

Operation	Monitoring Data (mg/m^3)	Working time (hrs/day)	Maximum EHE (mg/kg/day)
Loading	0.029	0.04	2.1×10^{-5}
Sampling	= < 0.05 (analytical limit)	0.04	3.6×10^{-5}
Total			5.7×10^{-5}

[Monitoring method]

Air sample was suctioned and caught by dissolving in the solvent at the breathing zone of the worker at the suction rate of 1 L/min. The suction period is 30 minutes for loading, while 5 minutes for sampling. The analytical limit for loading is 0.005 mg/m^3, and that for sampling is 0.05 mg/m^3. They are analyzed by GC/MS-SIM.

4) The workers may be exposed to the vapour during loading onto a tank truck or container, drum filling and sampling. If the worker (body weight; 70 kg, respiratory volume; 1.25 m^3/hr, exposure period; 0.08 hour) is performing these operations without protection, the highest daily intake (EHE) is calculated to be 5.7×10^{-5} mg/kg/day as a worst case. Normally, workers wear respiratory protective equipment during the operation (Appendix 2).

2.2.2 Consumer Exposure

1) Consumer use is not relevant in Japan because this substance is used as an intermediate to synthesize antioxidants for polymers and rubbers and residues of the parent substance in these products are not expected.

2) Although in the EU this substance is registered as a flavoring substance used or intended for use in or on foodstuffs, details are unknown to the producers of this substance.

3) The consumer exposure through the drinking water was also calculated using the method described in the EU-TGD (1996). The resulting daily intake (EHE) is negligible (3.2×10^{-7} mg/kg/day) (Appendix 3). The default value of drinking water (2 L/day) is mentioned in Appendix 3 of the SIAR.

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

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

3.1.2 Acute Toxicity

Studies in Animals

Available data are shown in Table 3. The studies by MHW, Japan (1999a) [OECD TG401)] and Sumitomo Chemical (1988a) are key studies. These are well conducted and described in detail. The LD_{50} values for this substance were between 320 and 800 mg/kg in males and between 130 and 320 mg/kg in females for the SD rat, and 580 mg/kg in males and 740 mg/kg in females for the ICR mouse.

Toxic signs were found at 800 mg/kg or more in male rats and 130 mg/kg or more in female rats. These were hypoactivity, a prone or lateral position and soiled fur. Bradypnea and Cheyne-Strokes' respiration in moribund animals of both sexes and hypothermia, clonic convulsion, ataxic gait and vocalization in females were observed. In mice, toxic signs were found at 300 mg/kg or more. These were hypoactivity (decrease of spontaneous activity), ataxia, limb paralysis and hyperpnea/dyspnea. Pathological lesions were observed in the digestive organ and kidney in rats, and no remarkable change was observed in mice.

In relation to the acute dermal toxicity, observed toxic signs were decrease of spontaneous activity and pilo-erection at 750 mg/kg or more, and ataxia, hyperpnea and poor appetite at 1000 mg/kg or more. No remarkable change was found in macroscopic observation.

Table 3. Mammalian acute toxicity of 6-*tert*-Butyl-*m*-cresol

Route	Animals	Value	Type	Reference
Oral	Rat	M: 320-800 mg/kg 1) F: 130-320 mg/kg	LD_{50}	MHW, Japan, (1999a)
	Mouse	M: 580 mg/kg F: 740 mg/kg	LD_{50}	Sumitomo Chemical, (1988a)
Dermal	Mouse	M: 1200mg/kg	LD_{50}	Sumitomo Chemical, (1976)

Note: Number of dead animals / Number of dosed animals

M; 130mg/kg: 0/5, 320mg/kg: 0/5, 800mg/kg: 4/5, 2000mg/kg: 3/5

F; 130mg/kg: 0/5, 320mg/kg: 3/5, 800mg/kg: 4/5, 2000mg/kg: 4/5

Studies in Humans

There is no available information on humans.

Conclusion

The LD50 values for acute toxicity of this substance were between 320 and 800 mg/kg in males and between 130 and 320 mg/kg in females for rats, and 580mg/kg in males and 740 mg/kg in females for mice.

3.1.3 Irritation

Studies in Animals

Available data are described below;

Highly irritating to skin in rabbits (Sumitomo Chemical, 1988b)

Highly irritating to eyes in rabbits (Sumitomo Chemical, 1988b)

Two studies performed by Sumitomo Chemical (1988b) are well conducted and described in detail. They are considered to be key studies.

In a skin irritation test with New Zealand white rabbits, slight erythema and severe edema were observed at 4.5 hr after application (0.5 mL/L x 1 inch patch for 4 hr). Moderate erythema, severe edema, eschar and induration of skin were observed from 4.5 hr after aapplication to 2 weeks of post-application.The irritating potency of this substance was judged to be severe.

In an eye irritation test in New Zealand white rabbits, extremely irritating potency was observed after 24 hr with an application of 0.1 ml/eye (unwashed). In the washed group, the irritating potency was moderate at 24 hr. The irritating potency of this substance was judged to be highly irritating.

Conclusion

This substance is corrosive to skin and eyes of rabbits.

3.1.4 Sensitisation

There is no available information.

3.1.5 Repeated Dose Toxicity

Studies in Animals

An OECD combined repeat dose and reproduction toxicity screening test [OECD TG 422] (MHW, Japan, 1999b) was performed for 6-*tert*-Butyl-*m*-cresol. This study was well conducted and reported in detail.

SD (Crj:CD) rats received gavage doses of 0 (vehicle; corn oil), 2.5, 12.5 and 60 mg/kg/day. Males were dosed for 42 days and females were dosed from 14 days before mating, throughout pregnancy until day 3 of lactation. No animal died in any group. No significant clinical sign was observed in any group. Suppression of body weight gain and decrease in food consumption were observed in females of the 60 mg/kg group, along with liver weight increase. Histopathological examination revealed hypertrophy of centrilobular hepatocytes in males and females of the 60 mg/kg group. Whereas an increase in the kidney weight was found in both sexes given 60 mg/kg, there were no adverse effects by histopathological examination. No significant effect was observed in hematology, urinalysis and blood biochemical parameters for males (these endpoints were not tested in females).

NOAEL for repeated dose toxicity is considered to be 12.5 mg/kg/day for both sexes.

Conclusion

This substance causes decrease in body weight gain and food consumption, increase in liver weight and hypertrophy of the liver centrilobular hepatocytes. The NOAEL is considered to be 12.5mg/kg/day for both sexes.

Studies in Humans

There is no available information on human toxicity.

3.1.6 Mutagenicity

In vitro Studies

Genotoxicity studies of 6-*tert*-Butyl-*m*-cresol were performed in the following three tests; gene reverse mutation test in *S.typhimurium* and *E. coli* [OECD TG 471, 472] (MHW, Japan, 1999c), chromosomal aberration test in CHL/IU cells [OECD TG 473] (MHW, Japan, 1999d) and micronucleus test in mice [OECD TG 474] (CERI, Hita Lab., 2002). These studies were all considered to be key studies, because they were well conducted and reported in detail.

This chemical did not induce gene mutation in bacterial systems with or without an exogenous metabolic activation system. In the chromosomal aberration test in CHL/IU cells, structural aberrations including gaps after 6 hr short-term treatment with metabolic activation system were observed at 15 and 30 µg/ml. Cytotoxicity was observed at 120 µg/ml. Polyploidy was not induced in any treatment group.

In vivo Studies

In an *in vivo* micronucleus assay with ICR mice orally administered up to the maximum tolerated dose, 125 mg/kg, no effect on the ratio of micronucleated polychromatic erythrocytes (MNPCE) / polychromatic erythrocytes (PCE) were observed. Therefore, the micronucleus assay was negative.

Conclusion

The substance is clastogenic *in vitro* with metabolic activation; however, no increase in micronucleated polychromatic erythrocytes was observed in an *in vivo* micronucleus test in mice. This substance is not genotoxic in the gene reverse mutation test in bacterial systems. Based on the weight of evidence, it is concluded that this chemical is not genotoxic in vivo.

3.1.7 Toxicity for Reproduction

Studies in Animals

An OECD combined repeat dose and reproductive/developmental toxicity screening study [OECD TG422] (MHW, Japan, 1999b) for 6-*tert*-Butyl-*m*-cresol was considered to be well conducted and reported in detail.

This substance was administered to SD (Crj:CD) rats by gavage at doses of 0 (vehicle ; corn oil), 2.5, 12.5 and 60 mg/kg from 14 days before mating to 14 days after mating in males and from 14 days before mating to day 3 of lactation in females. Maternal body weight gain and food consumption were suppressed in the 60 mg/kg group. No adverse effects were observed on copulation, fertility, delivery and lactation in any group.

Slight effects to the maternal reproductive index, such as a slight decrease in the number of corpora lutea, implants, number of live neonates (statistically significant) at birth and a slight low value of delivery index were observed at 60 mg/kg. In this dose group, the body weight gain of pups was suppressed (statistically significant).

Evidence of malformations was not observed grossly at any dose group.

Based on the above results, the NOAEL for reproductive toxicity is considered to be 12.5 mg/kg for both female parents and pups.

Studies in Humans

There is no available information on humans.

Conclusion

Slight effect to the maternal reproductive index and a decrease of body weight gain in pups was observed. The NOAEL for reproductive toxicity is considered to be 12.5 mg/kg for both female parents and pups.

3.2 Initial Assessment for Human Health

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

The LD50 values for acute toxicity of this substance were between 320 and 800mg/kg in males and between 130 and 320 mg/kg in females for rats, and 580mg/kg in males and 740 mg/kg in females for mice.

In a repeated dose toxicity study in rats, hypertrophy of centrilobular hepatocytes was observed in both sexes of the 60 mg/kg group. The NOAEL for repeated dose toxicity is 12.5 mg/kg.This substance was not genotoxic in a gene reverse mutation test. A chromosomal aberration test in CHL/IU cells was positive for short-term treatment with an exogeneous metabolic activation system (clastogenicity). However, an *in vivo* micronucleus test in mice was negative.

In a reproductive/developmental toxicity screening test with rats, slight effects to the maternal reproductive index were observed in the 60 mg/kg group. Suppression of body weight gain of pups was found in the 60 mg/kg group. The NOAEL for reproductive/developmental toxicity is 12.5 mg/kg for both female parents and pups.

Regarding other human health related information, this substance is corrosive to skin and eyes in rabbits. But no irritation problem has been reported at any production site where workers wear proper clothes and equipments.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

The most relevant results from acute and chronic tests with aquatic organisms are presented in the following table:

Table 4 : Aquatic Toxicity of 6-*tert*-Butyl-*m*-cresol

Organisms	Test duration	Result (mg/L)	Reference
Aquatic plants Green algae (*Selenastrum capricornutum*)	72 hr (static)	Biomass: EC_{50} = 0.900 mg/L NOEC = 0.248 mg/L Growth rate: EC_{50} (24-48 hr) = 1.84 mg/L NOEC (24-48 h) = 0.622 mg/L	EA (1999a)
Invertebrates Daphnids (*Daphnia magna*)	48 hr (static)	Immobility: EC_{50} = 2.77 mg/L EC_0 = 1.23 mg/L	EA (1999b)
	21 day (semi-static)	Parent: LC_{50} = 0.874 mg/L Reproduction: EC_{50} = 0.566 mg/L NOEC = 0.241 mg/L LOEC = 0.490 mg/L	EA (1999c)
Fish Medaka (*Oryzias latipes*)	96 hr (semi-static)	LC_{50} = 2.72 mg/L LC_0 = 2.08 mg/L	EA (1999d)

4.2 Terrestrial Effects

There is no available information.

4.3 Other Environmental Effects

There is no available information.

4.4 Initial Assessment for the Environment

It is possible that the substance would be released into aquatic environment, and show tendencies to distribute into the water and sediment compartment. The substance is not readily biodegradable and the bioaccumulation potential to aquatic organism is low.

Acute toxicity results were obtained from studies with three species (fish, daphnids and algae). Algae were most sensitive and the EC50 values were 0.900 mg/L and 1.84 mg/L for biomass and growth rate, respectively. The chronic NOECs were available from the chronic daphnia and algae tests. The lowest NOEC was 0.241 mg/L for daphnia reproduction. By applying an assessment factor of 100 to this NOEC, the PNEC (aquatic) is estimated as indicated below. The assessment

factor of 100 is applied, because two chronic NOECs from species representing two trophic levels (Daphnia and algae) are available [OECD, 1996].

PNEC (aquatic) = 0.241 / 100 = 0.0024 mg/L

Additionally, by using this PNEC for aquatic environment, the PNEC for the sediment compartment is also estimated tentatively according to the equilibrium partitioning method specified in the EU-TGD (1996). In the equilibrium partitioning method, it is assumed that (1) the sensitivity to the substance is equivalent between sediment-dwelling organisms and water column organisms, and (2) the concentrations in sediment, interstitial water and benthic organisms are thermodynamically equilibrated. This provisional PNEC value can be calculated as follows:

PNEC (sediment) = (K sed-water / RHO sed) × PNEC (aquatic) × 1000:

eq (54) in the EU-TGD

where

K sed-water = F water sed + F solid sed × (Kp sed / 1000) × RHO solid:

eq (10) in the EU-TGD

where F water sed : 0.8 m^3/m^3 (default)

F solid sed : 0.2 m^3/m^3 (default)

Kp sed : 1.6×10^2 L/kg (see Appendix 1)

RHO solid : 2500 kg/m^3 (default)

Thus, K sed-water : 81 m^3/m^3

RHO sed : 1300 kg/m^3 (default)

Thus, PNEC (sediment) = 0.15 mg/kg

The risk quotients (i.e. the ratio of the PEC (Predicted Environmental Concentration) to the PNEC) estimated with the worst case scenario in Japan are shown in Appendix 4.

5 RECOMMENDATIONS

The chemical is currently of low priority for further work.

The chemical possesses properties indicating a hazard for human health and the environment. Based on data presented by the Sponsor country, exposure to humans and the environment is anticipated to be low, and therefore this chemical is currently of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

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Sumitomo Chemical(1988a), unpublished report on acute toxicity in mouse

Sumitomo Chemical(1988b), unpublished report on skin and eye irritation study in rabbits

Appendix 1. The Predicted Environmental Concentration (PEC) with the worst case scenario expected in Japan.

Under conditions of production, processing and use in Japan, the following worst case scenario for emission would be probable:

(1) Life cycle

During production, a release of the substance into the aquatic environment seems to be possible. The use pattern as well as the properties of the substance suggest that a release into the environment at processing site (user's facility) should be negligible. Since the substance is used as an intermediate for antioxidants which are added into or onto matrixes such as rubber, latex and adhesives, the emission into the environment from these matrixes is unlikely.

(2) Environmental compartment receiving the emission

During production, the substance is in contact with the process water. Thus, an emission into the aquatic compartment would be possible. Indirect release through WWTP sludge application into soil compartment is unlikely, since such industrial sludge at production sites will be incinerated. Other than through an accident at the production site, a direct release of the substance to soil and air compartments is unlikely.

Thus, only the aquatic release of the substance at the production sites seems to be possible. In this Appendix, only the local PEC in aquatic and sediment compartments at production sites is estimated. The data utilized for the estimation is the results of analyses of wastewater from one major production site in Japan (Sumika Chemical Analysis Service Ltd., 2002). The wastewater at another major production site in Japan is similarly treated (WWTP and dilution) before being discharged from the production site. The water is further treated at a municipal sewage treatment plant before being released to the environment (Honshu Chemical Industry Co., Ltd. 2002). Therefore, the estimation would represent the worst case scenario in Japan.

1. Local water concentration at a production site

The PEC (local water) is estimated as follows:

PEC (local water) = (concentration in effluent) / (dilution factor)

where concentration in effluent: <0.0018 mg/L (see Note1)

dilution factor: 10 (EU-TGD (1996)).

Thus, PEC (local water) is <0.00018 mg/L.

(Note1)

The concentration of the substance in effluent water was estimated as follows:

(a) The concentration of the substance was <0.01 ppm (detection limit: 0.01 ppm) in the outflow from the WWTP (Waste Water Treatment Plant) at the production site. (Sumika Chemical Analysis Service, 2002)

(b) Before being discharged as effluent from the production site the WWTP outflow is diluted with wastewater not contaminated with the substance. The volumes of WWTP outflow and effluent water were monitored on the days of concentration analyses of WWTP outflow. The monitored volumes were typical at the production site and the dilution factor was 5.6 based on the monitored volumes. (Sumitomo Chemical, 2002)

(c) The concentration in effluent water was estimated to be <0.0018 mg/L (= concentration in WWTP outflow divided by dilution factor).

2. Local sediment concentration at production site

The PEC (local sediment) is estimated as follows:

PEC (local sediment) = (K susp-water / RHO susp) × PEC (local water) × 1000:

eq (35) in the EU-TGD

where

K susp-water = F water susp + F solid susp × (Kp susp / 1000) × RHO solid:

eq (10) in the EU-TGD

where F water susp : 0.9 m^3/m^3 (default)

F solid susp : 0.1 m^3/m^3 (default)

Kp susp : 320 L/kg (see Note 2)

RHO solid : 2500 kg/m^3 (default)

Thus, K susp-water: 81 m^3/m^3

RHO susp: 1150 kg/m^3 (default)

Thus, PEC (local sediment) is <0.013 mg/kg (worst case).

(Note 2)

Based on the Koc 3.2×10^3, the partition coefficient between water and soil, sediment or suspended mater can be estimated by applying the default organic carbon contents specified in the EU-TGD (1996):

System	OC in solid phase	Partition coefficient
Soil-Water	2%	Kp soil = 6.4 × 10 L/kg
Sediment-Water	5%	Kp sed = 1.6×10^2 L/kg
Suspended matter-water	10%	Kp susp = 3.2×10^2 L/kg

Appendix 2. Occupational exposure with the worst case scenario

Based on the highest air concentration at a production site, and the maximum exposure period (0.08 hr/day), the daily intake (EHE) is calculated to be $5.7x10^{-5}$ mg/kg/day as follows;

$EHE = Cair \times IHair \times period \times BW^{-1}$

Where		sampling	loading
Cair	concentration at a site:	= < 0.05 mg/m^3 (analytical limit)	0.029 mg/m^3
IHair	inhalation rate:	1.25 m^3/hr	1.25 m^3/hr
Period	exposure period:	0.04 hr/day	0.04 hr/day
BW	adult body weight (default):	70 kg	70 kg

Thus

EHE = (0.05 mg/m^3 x 0.04 hr/day +0.029 mg/m^3 x 0.04 hr/day) x (1.25 m^3/hr) x (1/70 kg)

= $5.7x10^{-5}$ mg/kg/day

Based on the daily intake (EHE) calculated in the worst case scenario, the margin of safety (MOS) for occupational exposure was estimated as follows:

MOS = NOAEL / EHE

where

NOAEL= 12.5 mg/kg/day based on 28-day oral dose toxicity test

EHE= $5.7x10^{-5}$ mg/kg/day worst case daily intake

Thus

MOS > = 219000

The MOS of 219000 is based on the worst case scenario. The actual MOS is expected to be higher and normally workers wear respiratory protective equipment (mask) during the operation.

(Note)

The exposure period is calculated based on the exposure time per day and the number of days of exposure per year.

Appendix 3. Consumer exposure through the drinking water and risk assessment

The concentration in the surface water (PEC in Appendix 1) is estimated to be 0.00018 mg/L in the worst case scenario. Using the method described in the EU-TGD (1996), the EHE for the drinking water (DOSEdrw) is calculated to be 3.2×10^{-7} mg/kg/day as follows.

DOSEdrw $= C_{drw} \times F_{pur} \times IH_{drw} \times BW^{-1}$: e.g. in the EU-TGD

where

C_{drw}	concentration in drinking water:	0.00018 mg/L
F_{pur}	purification factor (worst case):	1/16
IH_{drw}	drinking water (default):	2 L/day
BW	Adult body weight (default):	70 kg

Thus

DOSEdrw = (0.00018mg/L) x (1/16) x (2 L/day) x (1/70 kg) = 3.2×10^{-7} mg/kg/day

Based on the DOSEdrw, the margin of safety (MOS) for the drinking water was calculated as follows:

MOS = NOAEL / EHE

where

NOAEL= 12.5 mg/kg/day based on 28-day oral dose toxicity test

EHE= 3.2×10^{-7} mg/kg/day (DOSEdrw)

Thus

MOS > = 3.9×10^{7}

Appendix 4. The risk quotient (PEC/PNEC) with the worst case scenario expected in Japan.

For the potential aquatic release of the substance during production in Japan, the quotient PEC (see Appendix 1) / PNEC for aquatic and benthic (sediment) organisms under local conditions can be estimated as indicated below.

Compartment	PEC/PNEC
Aquatic	<0.075 (= <0.00018 / 0.0024)
Sediment	<0.087 (= <0.013 / 0.15)

Thus, even with the worst case scenario, no immediate concern for the aquatic or sediment compartment is suggested. Furthermore, due to the negligible release of the substance to the atmospheric and terrestrial compartments, "no immediate concern" would be also expected in these environments. The secondary poisoning through food-web would be unlikely, because the bioaccumulation potential of the substance is not high.

SIDS Dossier

Existing Chemical	:	ID: 88-60-8
CAS No.	:	88-60-8
EINECS Name	:	6-*tert*-Butyl-*m*-cresol
EC No.	:	201-842-3
Molecular Formula	:	$C_{11}H_{16}O$

Producer related part

Company	:	Sumitomo Chemical Co.,Ltd.
Creation date	:	12.09.2001

Substance related part

Company	:	Honshu Chemical Industry Co.,Ltd.
Creation date	:	12.09.2001
Status	:	
Memo	:	
Printing date	:	12.07.2002
Revision date	:	
Date of last update	:	08.08.2002
Number of pages	:	41
Chapter (profile)	:	Chapter: 1,2,3,4,5,6,7
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Datasheet, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

Type	:	lead organisation
Name	:	Sumitomo Chemical Co.,Ltd.
Contact person	:	Mr. Naoki Inui
Date	:	
Street	:	27-1, Shinkawa 2-chome,Chuo-ku
Town	:	Tokyo 104-8260
Country	:	Japan
Phone	:	81-3-5543-5803
Telefax	:	81-3-5543-5915
Telex	:	
Cedex	:	
Email	:	inuin@sc.sumitomo-chem.co.jp
Homepage	:	

15.01.2002

Type	:	cooperating company
Name	:	Honshu Chemical Industry Co.,Ltd.
Contact person	:	Mr. Shigeharu Moriguchi
Date	:	
Street	:	Yaesu-daibiru Bldg,1-1,Kyobashi,1-Chome Chuou-ku
Town	:	Tokyo 104-0031
Country	:	Japan
Phone	:	81-3-3272-1485
Telefax	:	81-3-3274-3870
Telex	:	
Cedex	:	
Email	:	moriguchi@honshuchemical.co.jp
Homepage	:	

15.01.2002

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

IUPAC Name	:	2-*tert*-Butyl-5-methyphenol
Smiles Code	:	CC1=C(O)C=C(C)C=C1.CC
Molecular formula	:	$C_{11}H_{16}O$
Molecular weight	:	164. 25
Petrol class	:	

15.01.2002

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type : typical for marketed substance
Substance type : organic
Physical status : liquid
Purity : 97.5 % w/w
Colour : yellow
Odour : unique odour that is harmful if swallowed and if inhaled
Remark : Physical status;melting point(21.3°C)
Reliability :
Flag : Material Safety Datasheet
15.01.2002 (30)

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

Synonymus; 3-Methy-6-*tert*-butylphenol
Flag : Material Safety Datasheet
15.01.2002 (11)(31)(32)

Synonymus; 2-*tert*-Butyl-5-methyphenol
Flag : Material Safety Datasheet
15.01.2002 (11)

Synonymus;2-(1,1-Dimetylethyl)-5-methylphenol
Flag : Material Safety Datasheet
15.01.2002 (11)

Synonymus;6-*tert*-Butyl-*m*-cresol
Flag : Material Safety Datasheet
15.01.2002 (11)

Tradenames; 3M6B
Flag : Material Safety Datasheet
15.01.2002 (11) (32)

Tradenames; MBMC
Flag : Material Safety Datasheet
15.01.2002 (31)

1.3 IMPURITIES

CAS -No : 2409-55-4
EINECS -No : 219-314-6
EINECS -Name : 2-*tert*-Butyl-4-methylphenol
Contents : = < 2.0 % weight/weight
Remark : raw material
Source : Sumitomo Chemical Co.,Ltd.
15.01.2002 (30)

1.4 ADDITIVES

None

1.5 TOTAL QUANTITY

Production during the last 12 months	:	
Import during the last 12 months	:	
Quantity produced	:	1,500 tonnes/year in Japan in 2001
Remark	:	We are unable to reseach the world-wide production volume.
Source	:	

17.04.2002 (30)

1.6.1 LABELLING

Labelling	:	Not assigned
Symbols	:	
Nota	:	
Specific limits	:	
R-Phrases	:	
S-Phrases	:	
Source	:	

11.02.2002 (30)

1.6.2 CLASSIFICATION

Classification	:	UN classification
Class of danger	:	8(corrosive)
R-Phrases	:	(21/22) Harmful in contact with skin and if swallowed
Remark	:	UN No: 3145
Source	:	

11.02.2000 (12)

Classification	:	Directive 67/548/EEC and 88/379/ EEC (in Switzerland)
Class of danger	:	4; LD_{50}: (small animals) = 500 - 2000 mg/kg
R-Phrases	:	The Poison Class
Remark	:	Swiss Identification Number; 1530
Source	:	

11.02.2000 (12)

1.6.3 PACKAGING

1.7 USE PATTERN

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

Flag : WGK (DE)
15.01.2002 (13)

Type of use : use
Category : Food/foodstuff additives
Remark :
15.01.2002 (3)

1.7.1 DETAILED USE PATTERN

Type of use : industrial
Remark : Intermediate for other chemical products;the most important use is as an intermediate for antioxidants,4'-Butylidene bis(6-*tert*-butyl-3-methylphenol <CAS No. 85-60-9>, 4,4'-Thio bis(6-*tert*-butyl-3-methylphenol) <CAS No. 96-69-5>, 1,1,3-Tris(5-*tert*-butyl-2-methyl-4-hydroxyphenyl)butane <CAS No. 1843-03-4>, which are applied for mainly rubber, latex and adhesives.

Source
15.01.2002 (13)

Type of use : use
Remark : Although this substance is registered in the EU as a flavoring substance used or intended for use in or on foodstuffs, details are unknown to the producers of this substance.
Source
15.01.2002 (30)

1.7.2 METHODS OF MANUFACTURE

Remark : The alkylation of 3-Methyl phenol with Isobutylene under Acid or Aluminuim catalysis.
Source
15.01.2002 (13)

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

Classified by : VCI (Chemical Company in Germany)
Labelled by : VCI
Class of danger : 2(water-endangering)
WGK Identification Number;1530
Source :
12.11.2001 (12)

1.8.4 MAJOR ACCIDENT HAZARDS

1.8.5 AIR POLLUTION

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

Identification Number 3-521
Remark : Law of the New chemical substance control in Japan
Source

Identification Number 201-842-3
Remark : EINECS
Source

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

Source of exposure : Human: exposure by production
Exposure to the : Substance
Remark : Can be negligible by applying protective measures as written below:
Since this substance is synthesized in a closed reactor, exposure is only possible, other than sampling and loading it onto a tank truck or container;
a worker may be exposed to liquid during such operations, utmost for 0.08 hour a day. The workplace of sampling and loading are outdoor and working place of loading is provided with an air ventilator and the worker is
equipped with the protective gear such as the mask, rubber gloves and goggles to prevent exposure.
Spill or leak is collected and burnt.
Exposure monitoring data
Measured in 2002 at production sites in Japan (producing ca. 500t /year of the substance in 2001):
Method:
Air of workplace atmosphere was suctioned at a ratio of 1 L/min for 2 or 30 minutes, and this substance were collected by the solvent. The substance was caught by dissolving in the solvent and was analyzed by GC/MS-SIM.
Result:
The workplace exposure level near production sites was determined as follows
Sampling workplace : less than 0.05 mg/m^3 (analytical limit)
Loading workplace : 0.029 mg/m^3

17.01.2002 (22)

Source of exposure : Human: exposure through intended use
Exposure to the : Substance
Remark : Since this substance is exclusively used as an intermediate for other chemical products such as antioxidants, exposure is possible during charging a reactor from a tank truck or container and, to lesser probability, sampling and analysis; a worker

may be exposed to liquid for utmost several hours a day. The worker is recommended (by the MSDS) to put on protective gear such as the mask, rubber gloves and goggles to prevent exposure.
Spill and leak is collected and burnt.

17.01.2002

Source of exposure : Environment: exposure from production
Exposure to the : Substance
Remark : Media of release: Process wastewater
Since this substance is synthesized in a closed reactor, no other substantial exposure is probable

13.05.2002

1.11 ADDITIONAL REMARKS

1.12 LAST LITERATURE SEARCH

1.13 REVIEWS

2.1 MELTING POINT

Value : = 21.3 °C
Decomposition : no
Sublimation : no
Method : JIS K 4101-5.2
Year : 2001
GLP : no
Test substance : no data
Reliability : (1) valid without restriction
Flag : Material Safety Datasheet
17.01.2002 (11)

Value : = 21.4 °C
Decomposition : no
Sublimation : no
Method : other; not disclosed
Year :
GLP : no data
Test substance : no data
Reliability : (1) valid without restriction
17.01.2002 (16)

Value : = 23 °C
Decomposition : no data
Sublimation : no data
Method : other; not disclosed
Year :
GLP : no data
Test substance : no data
Reliability : (2) valid with restrictions
17.01.2002 (1)

Value : = 46 - 47 °C
Decomposition : no data
Sublimation : no data
Method : other ;not disclosed
Year :
GLP : no data
Test substance : no data
Method : other; not disclosed
Reliability : (4) not assignable
17.01.2002 (9)

2.2 BOILING POINT

Value : = 244 °C at 101 kPa
Decomposition : no
Method : JIS K 4101-8.1
Year : 2001
GLP : no
Test substance : no data
Reliability : (1) valid without restriction
Flag : Material Safety Datasheet
17.01.2002 (11)

Value : = 224 °C at 101 kPa
Decomposition : ambiguous
Method : other ; not disclosed
Year :
GLP : no data
Test substance : no data
Reliability : (2) valid with restrictions
17.01.2002 (9)

Value : = 127 °C at 1.46 kPa
Decomposition : ambiguous
Method : other ; not disclosed
Year :
GLP : no data
Test substance : no data
Reliability : (2) valid with restrictions
17.01.2002 (9)

Value : = 121 - 122 °C at 21.3 kPa
Decomposition : ambiguous
Method : other ; not disclosed
Year :
GLP : no data
Test substance : no data
Reliability : (2) valid with restrictions
17.01.2002 (1)

Value : = 117 - 118 °C at 1.6 kPa
Decomposition : no
Method : other: not disclosed
Year :
GLP : no data
Test substance : no data
Reliability : (2) valid with restrictions
17.01.2002 (34)

2.3 DENSITY

Type : density
Value : = 0.959 g/cm^3 at 30 °C
Method : JIS K 4101-8.1
Year : 2001
GLP : no
Test substance : no data
Reliability : (1) valid without restriction
Flag : Material Safety Datasheet
17.01.2002 (11)

Type : density
Value : = 0.965 g/cm^3 at 30 °C
Method : other ;not disclosed
Year :
GLP : no data
Test substance : no data
Reliability : (2) valid with restrictions
17.01.2002 (16)

Type : density
Value : = 0.922 g/cm^3 at 80 °C

Method : other; not disclosed
Year :
GLP : no data
Test substance : no data
Reliability : (2) valid with restrictions
17.01.2002 (9)

Type : density
Value : = 0.964 g/cm^3
Method : other ; not disclosed
Year :
GLP : no data
Test substance : no data
Test condition : temperature;not disclosed
Reliability : (2) valid with restrictions
17.01.2002 (34)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : = 3.3 Pa at 25 °C
Decomposition : ambiguous
Method : OECD Guide-line 104 "Vapour Pressure Curve"
Year : 1999
GLP : no
Test substance : other TS; Produced by Tokyo Kasei Kogyo Co., Ltd. Lot No. FHE01,Purity: 98.3%
Reliability : (1) valid without restriction
Well conducted study, carried out by Chemicals Evaluation and Research Institute, Kurume Labo., (Japan)
Flag : Critical study for SIDS endpoint
17.01.2002 (15)

Value : = 13.3 kPa at 171 °C
Decomposition : ambiguous
Method : other (measured); not disclosed
Year : 2001
GLP : no data
Test substance : no data
Reliability : (2) valid with restrictions
Material Safety Datasheet
17.01.2002 (11)

2.5 PARTITION COEFFICIENT

Partition coefficient : octanol-water
Log pow : = 4.11 at 25 °C
pH value : = 6.3
Method : OECD Guide-line 107 "Partition Coefficient (n-octanol/water), Flask-shaking Method"
Year : 1999
GLP : yes
Test substance : other TS; Produced by Tokyo Kasei Kogyo Co., Ltd. Lot No. FHE01,Purity: 98.3%
Remark : After partition equilibrium of the test substance was established between n-octanol

and water at three volume ratios, the concentrations of the test substance of both phase were determined with HPLC.

Reliability : (1) valid without restriction
Well conducted study, carried out by Chemicals Evaluation and Research Institute, Kurume Labo., (Japan)

Flag : Critical study for SIDS endpoint

17.01.2002 (16)

2.6.1 SOLUBILITY IN WATER

Solubility in	:	Water
Value	:	= 0.42 g/L at 25±1 °C
pH value	:	
concentration	:	
Temperature effects	:	
Examine different pol.	:	
pKa	:	
Description	:	moderately soluble (100 - 1000 mg/L)
Stable	:	yes
Deg. product	:	
Method	:	OECD Guide-line 105 "Water Solubility"
Year	:	1999
GLP	:	no
Test substance	:	other TS; Produced by Tokyo Kasei Kogyo Co., Ltd. Lot No. FHE01, Purity: 98.3%
Reliability	:	(1) valid without restriction Well conducted study, carried out by Chemicals Evaluation and Research Institute, Kurume Labo., (Japan)
Flag	:	Critical study for SIDS endpoint

17.01.2002 (15)

2.6.2 SURFACE TENSIO N

2.7 FLASH POINT

Value	:	=114° C
Type	:	closed cup
Method	:	JIS K 2265-7
Year	:	2001
GLP	:	no
Test substance	:	no data
Reliability	:	(1) valid without restriction
Flag	:	Material Safety Datasheet

17.01.2002 (11)

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

Acid-base constant	:	11.21 at 25 °C
Method	:	OECD Guide-line 112 "Dissociation Constants in Water"
Year	:	1999
GLP	:	no
Test substance	:	other TS; Produced by Tokyo Kasei Kogyo Co., Ltd. Lot No. FHE01, Purity: 98.3%
Remark	:	pH value= 10.9 - 11.7, concentration; 10 mg/L at 25 °C
Reliability	:	(1) valid without restriction Well conducted study, carried out by Chemicals Evaluation and Research Institute, Kurume Labo., (Japan)
Flag	:	Critical study for SIDS endpoint

17.01.2002 (15)

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

memo	:	Partition coefficient between soil/sediment and water
Remark	:	Koc was estimated to be 3.2×10^3 according to the method specified in the EU - TGD (1996). The QSAR equation employed in the EU-TGD is for phenols: log Koc = 0.63 log Pow + 0.90. The log Pow value substituted is 4.11.
Flag		Critical study for SIDS endpoint

17.05.2002 (26)

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	
Light spect.	:	nm
Rel. intensity	:	based on Intensity of Sunlight
Indirect photolysis		
Sensitizer	:	OH
Conc. of sens.	:	1.5×10^6 OH/cm^3
Rate constant	:	= 1.051537×10^{-10} cm^3/(molecule-sec)
Degradation	:	= 50 % after 1.2 hour(s)
Deg. Product	:	
Method	:	other (calculated)
Year	:	2001
GLP	:	no
Test substance	:	no data
Method	:	Calculated by using AOPWIN (ver.1.90), based on the Atkinson model recommended in the OECD Guidance.
Conclusion	:	The substance in air is indirectly photodegraded with half-life of 1.2 hours.
Reliability	:	(2) valid with restrictions The value is estimated with the method recommended in the OECD Guidance.

18.07.2001 (24)

3.1.2 STABILITY IN WATER

Type	:	abiotic
$t_{1/2}$ pH4	:	at degree C
$t_{1/2}$ pH7	:	at degree C
$t_{1/2}$ pH9	:	at degree C
Deg. Product	:	
Method	:	OECD Guide-line 111 "Hydrolysis as a Function of pH"
Year	:	1999
GLP	:	no
Result	:	Nominal: ca.100 mg/L Degradation: No hydrolysis at pH 4,7 and 9 at 50±1°C for 5 days.
Test substance	:	other TS; Produced by Tokyo Kasei Kogyo Co., Ltd. Lot No. FHE01, Purity: 98.3%
Conclusion	:	The substance is very stable at pH4, 7 and 9 at 50±1°C for 5 days.
Reliability	:	(1) valid without restriction The data is approved by the Japanese government.

18.07.2001 (15)

3.1.3 STABILITY IN SOIL

3.2 MONITORING DATA

Type of measurement	:	background concentration
Medium	:	surface water
Method	:	Analysis: GC/MS, Extraction: solid-phase extraction method
Concentration	:	
Remark	:	The report describes that plural peaks are detected even in the solvent blank eluted from the cartridge for solid extraction. The detected level is around 0.2 ng/L for the peak corresponding to 6-*tert*-butyl-*m*-cresol.

Result : Tap water: <2 - 6 ng/L (Detection limit: 2 ng/L) in Japan in 1995.
River water: <2 - 21 ng/L (Detection limit: 2 ng/L) in Japan in 1995.
Reliability : (2) valid with restrictions
The site for collecting sample and experimental conditions are not adequately reported.
14.07.2001 (33)

Type of measurement : background concentration
Medium : wastewater
Method : Analysis: GC/ MS
Concentration : < 0.01 mg/L
Result : The concentration of the substance in wastewater was reduced by activated sludge treatment process.
Influent: 0.63–0.80 mg/L, Effluent: <0.01 mg/L (detection limit: 0.01mg/L)
Test condition : Sampling site: Oita plant of Sumitomo Chemical Co. Ltd. (Japan)
Sampling date: February 2002
Reliability : (1) valid without restriction
13.05.2002 (23)

Type of measurement : background concentration
Medium : surface water
Method : Analysis: GC-FID, GC/MS
Concentration : = 0.13 µg/L
Result : The average concentration of the substance was 0.13 µg/L in river water.
Test condition : Sampling site: the Dukou segment of the Jinsha River (China)
Sampling date: July 1982 - Sept. 1983
Reliability : (4) not assignable
18.07.2001 (10)

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type : fugacity model Mackay level III
Media :
Air (level I) :
Water (level I) :
Soil (level I) :
Biota (level II / III) :
Soil (level II / III) :
Method :

Year : 2001
Method : The parameters used are shown in Appendix? .
Result : Estimated Distribution under three emission scenarios

Compartment	Release 100% to air	100% to water	100% to soil	equally to each compartment
Air	2.2%	0.0%	0.0%	0.0%
Water	1.8%	67.3%	0.1%	0.4%
Soil	95.0%	1.2%	99.9%	99.4%
Sediment	0.9%	31.5%	0.0%	0.2%

Attached doc. : Appendix? : Parameters used in calculation of distribution by Mackay level? fugacity model.
Conclusion : The majority of the substance would distribute into soil if released to soil or air compartment, and water and sediment if released to aquatic compartment.

Reliability : (1) valid without restriction
The model employed is developed by the Japanese government.

18.07.2001 (25)

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type	:	aerobic
Inoculum	:	activated sludge
Concentration	:	100 mg/L related to test substance
Contact time	:	28 days
Degradation	:	= 1 % after 28 days based on BOD and HPLC analysis
Result	:	under test conditions no biodegradation was observed
Control substance	:	Aniline
Kinetic	:	7 days = 58 % (BOD) 14 days = 73 % (BOD)
Deg. Product	:	not measured
Method	:	OECD Guide-line 301 C "Ready Biodegradability: Modified MITI Test (I)"
Year	:	1998
GLP	:	Yes
Result	:	1% after 28 days (based on BOD) 1% after 28 days (based on HPLC analysis of the parent)
Test substance	:	other TS; Produced by Tokyo Kasei Kogyo Co., Ltd. Lot No. FHE01, Purity: 98.3%
Conclusion	:	The substance is not readily biodegradable.
Reliability	:	(1) valid without restriction The data is approved by the Japanese government.

18.07.2001 (14)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

Species	:	*Cyprinus carpio* (Fish, fresh water)
Exposure period	:	33 days at 25°C
Concentration	:	
Elimination	:	no
Method	:	OECD Guide-line 305 "Bioaccumulation: Flow-through Fish Test"
Year	:	2000
GLP	:	Yes
Remark	:	The average lipid content of carp was 2.23-2.59%.
Result	:	Bioconcentration Factor:

Exposure conc.	7 day	14 day	21 day	28 day	33 day
10 µg/L	92, 78	88, 56	76, 73	64, 48	74, 41
1 µg/L	93, 72	73, 52	63, 39	52, 50	53, 48

The concentrations of the test substance in water were maintained above 90% of the nominal concentration through the test duration. Steady-state has been reached

within the test duration and the BCF of the subtance at steady-state is 52 at 1 µg/L and 63 at 10 µg/L.

Test condition : Test concentrations: 10 µg/L and 1 µg/L
The stock solution for exposure was prepared by mixing the test substance with 20-fold weight of castor oil (HCO-20). The exposure was conducted under flow-through conditions. No elimination experiment was conducted.
Remark: The use of HCO-20 was to prevent possible adsorption of the substance to the wall of the glass vessels. Since the exposure concentrations of the substance were well below the solubility in water (420mg/L), and since the consentrations of dispersant of 20-200 µg/Lwere well critical micelle concentration of HCO-20 to be around a few hundred mg/L, no bioavailability isuue is expected.

Test substance : other TS; Produced by Tokyo Kasei Kogyo Co., Ltd. Lot No. FHE01, Purity: 98.3%

Conclusion : The BCF of the subtance is 41-92 at 10 µg/L and 39-93 at 1 µg/L.

Reliability : (1) valid without restriction
The data is approved by the Japanese government.

18.07.2001 (17)

3.8 ADDITIONAL REMARKS

Appendix? . Proofs of the calculations for theoretical distribution of 6-*tert*-butyl-*m*-cresol.

Substance: 6-*tert*-butyl-*m*-cresol

Scenario 1

compartment	emission rate	conc.	amount	percent	transfomation rate [kg/h]	
	[kg/h]	[g/m^3]	[kg]	[%]	reaction	advection
air	1000	1.7.E-07	1.7.E+03	2.2	9.8E+02	1.7.E+01
water	0	7.1.E-05	1.4.E+03	1.8	4.1E-03	1.4.E+00
soil	0	4.6.E-02	7.3.E+04	95.0	2.1E-01	
sediment		6.7.E-03	6.7.E+02	0.9	6.4E-04	1.3.E-02
		total amount	7.7.E+04			

Scenario 2

compartment	emission rate	conc.	amount	percent	transfomation rate [kg/h]	
	[kg/h]	[g/m^3]	[kg]	[%]	reaction	advection
air	0	3.3.E-08	3.3.E+02	0.0	1.9.E+02	3.3.E+00
water	1000	4.0.E-02	8.0.E+05	67.3	2.3.E+00	8.0.E+02
soil	0	8.8.E-03	1.4.E+04	1.2	4.1.E-02	
sediment		3.7.E+00	3.7.E+05	31.5	3.6.E-01	7.5.E+00
		total amount	1.2.E+06			

Scenario 3

compartment	emission rate	conc.	amount	percent	transfomation rate [kg/h]	
	[kg/h]	[g/m^3]	[kg]	[%]	reaction	advection
air	0	2.4.E-08	2.4.E+02	0.0	1.4.E+02	2.4.E+00
water	0	9.9.E-03	2.0.E+05	0.1	5.7.E-01	2.0.E+02
soil	1000	1.4.E+02	2.3.E+08	99.9	6.6.E+02	
sediment		9.3.E-01	9.3.E+04	0.0	8.9.E-02	1.9.E+00
		total amount	2.3.E+08			

Scenario 4

compartment	emission rate	conc.	amount	percent	transfomation rate [kg/h]	
	[kg/h]	[g/m^3]	[kg]	[%]	reaction	advection
air	1000	2.3.E-07	2.3.E+03	0.0	1.3.E+03	2.3.E+01
water	1000	5.0.E-02	1.0.E+06	0.4	2.9.E+00	1.0.E+03
soil	1000	1.4.E+02	2.3.E+08	99.4	6.6.E+02	
sediment		4.7.E+00	4.7.E+05	0.2	4.5.E-01	9.3.E+00
		total amount	2.3.E+08			

Appendix? . (continued)

Physico-chemical parameter

molecular weight		164.25	Measured
melting point [°C]		21.3	Measured
vapor pressure [Pa]		3.30E+00	Measured
water solubility [g/m^3]		420	Measured
log Kow		4.11	Measured
half life [h] (Note 1)	in air	1.221	Estimated
	in water	240000	Estimated
	in soil	240000	Estimated
	in sediment	720000	Estimated

Temp. [°C]	25

Environmetal parameter

		volume [m^3]	depth [m]	area [m^2]	organic carbon [-]	lipid content [-]	density [kg/m^3]	residence time [h]
bulk air	air	1.0E+13					1.2	100
	particles	2.0E+03						
	total	1.0E+13	1000	1E+10				
bulk water	water	2.0E+10					1000	1000
	particles	1.0E+06			0.04		1500	
	fish	2.0E+05				0.05	1000	
	total	2.0E+10	10	2E+09				
bulk soil	air	3.2E+08					1.2	
	water	4.8E+08					1000	
	solid	8.0E+08			0.04		2400	
	total	1.6E+09	0.2	8E+09				
bulk sediment	water	8.0E+07					1000	
	solid	2.0E+07			0.06		2400	50000
	total	1.0E+08	0.05	2E+09				

Intermedia Transport Parameters[m/h]

air side air-water MTC	5	soil air boundary layer MTC	5
water side air water MTC	0.05	sediment -water MTC	1E-04
rain rate	1E-04	sediment deposition	5E-07
aerosol deposition	6E-10	sediment resuspension	2E-07
soil air phase diffusion MTC	0.02	soil water runoff	5E-05
soil water phase diffusion MTC	1E-05	soil solid runoff	1E-08

(Note 1) The half life in air is estimated by using AOPWIN (ver.1.90).
The default values are applied for other half lives, as recommended by Chemicals Evaluation and Research Institute, Japan.

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type : semistatic
Species : *Oryzias latipes* (Fish, fresh water)
Exposure period : 96 hour(s)
Analytical monitoring : yes
LC0 : 2.08 mg/L
LC50 : 2.72 mg/L
LC100 : 3.73 mg/L
Method : OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year : 1999
GLP : yes
Test substance : other TS; Produced by Tokyo Kasei Kogyo Co., Ltd. Lot No. FHE01, Purity: 98.3%

Method :
-Test organisms:
a) Size (scaled body length and body weight): 1.8-2.0 cm, 0.083-0.12 g (n=10)
b) Age: not described
c) Pretreatment: Acclimated for more than 12 days at the same conditions of the test
d) Supplier/Source: Nakajima Aquaculture (Kumamoto Prefecture, Japan)
-Test conditions:
a) Dilution water source: Dechlorinated tap water
b) Dilution water chemistry: hardness=52.0 mg/L as CaCO3, pH=7.5
c) Exposure vessel type: 3 L volume glass aquarium (16 cm in diameter x 17 cm depth) with a lid
d) Nominal concentrations: 0, 1.58, 2.05, 2.66, 3.46, 4.50 mg/L
e) Vehicle/solvent and concentrations: Not used
f) Stock solutions preparations and stability: Appropriate amount of test substance was dissolved with dilution water and 100 mg/L stock solution was prepared. Test solution was prepared by mixing appropriate amount of the stock solution and dilution water.
g) Number of replicates: 2
h) Individuals per replicates: 5
i) Loading: Approximately 4.5 L of water was used for 1 g of fish
j) Dosing rate, flow-through rate:
k) Renewal frequency of test water: Semistatic with 48 hours interval
l) Water temperature: 24±1°C
m) Light condition: 16 hours light/8 hours dark (room light)
n) feeding: no
-Method of analytical monitoring: HPLC
-Statistical method:
a) Data analysis: Binomial method
b) Method of calculating mean measured concentrations: Time-weighted mean

Result :
-Measured concentrations:

Nominal concentration (mg/L)	Measured concentration (mg/L) (Percent of nominal)		
	0-hour(a)	48-hour(b)	Mean(c)
control	n.d.	n.d.	–
1.58	1.68 (106)	1.48 (94.0)	1.58 (99.9)
2.05	2.19(107)	1.97(96.0)	2.08(101)
2.66	2.82(106)	2.62(98.7)	2.72 (102)
3.46	3.79(110)	3.67(106)*	3.73(108)
4.50	4.85(108)	4.72(105)*	4.79(106)

*at 24hour
n.d:<0.2mg/L (detection limit)
(a)fresh solution, (b) expired solution

(c)The values are expressed as time-weighted means.

-Water chemistry in test: Water temperature=24.0-24.8°C, pH=7.2-7.5, DO=6.3-8.3 mg/L

-Cumulative mortality:

Nominal concentration (mg/L)	Cumulative number of dead fish (Percent mortality) 24-hour	48-hour	72-hour	96-hour
control	0(0)	0(0)	0(0)	0(0)
1.58	0(0)	0(0)	0(0)	0(0)
2.05	0(0)	0(0)	0(0)	0(0)
2.66	1(10)	3(30)	5(50)	5(50)
3.46	10(100)	10(100)	10(100)	10(100)
4.50	10(100)	10(100)	10(100)	10(100)

-Statistical result: 24, 48, 72 and 96-hour LC_{50}=3.08, 2.92, 2.72 and 2.72 mg/L based on the measured concentrations.

Reliability : (1) valid without restriction
The data is approved by the Japanese government.
Flag : Critical study for SIDS endpoint
14.09.2001 (7)

Type : static
Species : *Lepomis macrochirus* (Fish, fresh water)
Exposure period : 96 hour(s)
Analytical monitoring : no data
LC50 : 2.75 mg/L
Method : other
Year : 1979
GLP : no
Test substance : no data
Remark : Number of fish: 3
Nominal concentrations: 0.5, 1.0, 1.5, 5, 10, 20, 50 mg/L
Temprature range:18.5°C – 21.5°C
PH = 7.0 (time poit of measuring is not described)
D.O. = 7.1-8.1 at the start, 3.2-4.9 at the end
Reliability : (3) invalid. Insufficient documentation for assessment.
(8)

Type : Flow-through
Species : *Lepomis macrochirus* (Fish, fresh water)
Exposure period : 96 hour(s)
Analytical monitoring : no data
LC50 : 3.4 mg/L
Method : no data
Year : 1979
GLP : no data
Test substance : no data
Reliability : (4) not assignable. Insufficient experimantal details.
(8)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	static
Endpoint	:	immobility
Species	:	*Daphnia magna* (Crustacea)
Exposure period	:	48 hour(s)
Analytical monitoring	:	yes
EC_0	:	1.23 mg/L
EC_{50}	:	2.77 mg/L
EC_{100}	:	3.95 mg/L
Method	:	OECD Guide-line 202, part 1 "Daphnia sp., Acute Immobilisation Test"
Year	:	1999
GLP	:	yes
Test substance	:	other TS; Produced by Tokyo Kasei Kogyo Co., Ltd. Lot No. FHE01, Purity: 98.3%
Method	:	-Test organisms: a) Age: <24 hours after hatch b) Pretreatment: c) Supplier/Source: Laboratory cultures maintained at Chemical Inspection and Testing Institute,Japan -Test conditions: a) Dilution water source: Dechlorinated tap water b) Dilution water chemistry: hardness=52.0 mg/L as CaCO3, pH=7.5 c) Exposure vessel type: Petri dish (8.5 cm diameter x 5.7 cm depth) d) Nominal concentrations: 0, 0.762, 1.37, 2.47, 4.44, 8.00 mg/L e) Vehicle/solvent and concentrations: Not used f) Stock solutions preparations and stability: Appropriate amount of test substance was dissolved with dilution water under ultrasonication and 100 mg/L stock solution was prepared. Test solution was prepared by mixing appropriate amount of the stock solution and dilution water and divided into 4 vessels. g) Number of replicates: 4 h) Individuals per replicates: 5 i) Volume of test solution: 200mL/vessel j) Renewal rate of test water: no k) Water temperature: 20±1°C l) Light condition: 16 hours light/8 hours dark (room light) m) feeding: no -Method of analytical monitoring: HPLC (at start and end of test) -Statistical method: a) Data analysis: Probit and binomial methods b) Method of calculating mean measured concentrations: Time-weighted mean
Result	:	-Measured concentrations

Nominal concentration (mg/L)	Measured concentration (mg/L) (Percent of nominal)		
	0-hour(a)	48-hour(b)	Mean(c)
control	n.d.	n.d.	–
0.762	0.725(95.2)	0.685 (89.8)	0.705 (92.5)
1.37	1.27(92.6)	1.20(87.4)	1.23(90.0)
2.47	2.37(95.9)	2.21(89.3)	2.29(92.6)
4.44	4.08(91.8)	3.82(86.0)	3.95(88.9)
8.00	7.57(94.6)	7.40(92.4)	7.48(93.5)

n.d:<0.02mg/L (detection limit)
(a)fresh solution, (b) expired solution
(c)The values are expressed as time-weighted means.

-Water chemistry in test: Water temperature=20.3-20.4°C, pH=7.8-8.1, DO=8.5-8.8 mg/L

-Cumulative immobilization:

Nominal concentration (mg/L)	Cummulative number of Immobilized Daphnia (Percent immobility) 24-hour	48-hour
control	0 (0)	0(0)
0.762	0 (0)	0(0)
1.37	0 (0)	0(0)
2.47	1 (5)	3(15)
4.44	10(50)	20(100)
8.00	20(100)	20(100)

-Statistical result: 24 and 48-hour EC_{50}=3.85 and 2.77 mg/L based on the measured concentrations.

Reliablity : (1) valid without restriction
The data is approved by the Japanese government.

Flag : Critical study for SIDS endpoint

14.09.2001 (5)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species : Selenastrum capricornutum (Algae)
Endpoint : Biomass and growth rate
Exposure period : 72 hour(s)
Analytical monitoring : yes
NOEC (biomass) : 0.248 mg/L
NOEC (growth rate) : 0.622 mg/L
EC_{50} (biomass) : 0.900 mg/L
EC_{50} (growth rate) : 1.84 mg/L
Method : OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year : 1999
GLP : yes
Test substance : other TS; Produced by Tokyo Kasei Kogyo Co., Ltd. Lot No. FHE01, Purity: 98.3%
Method : -Test organisms:
a) Supplier/Source (strain number): Laboratory cultures maintained at Chemical Inspection and Testing Institute, Japan/ATCC 22662
b) Preculture (duration, medium, etc.): 3 days under the same method of test in OECD medium
-Test conditions:
a) Test medium: OECD medium
b) Exposure vessel type: Closed system. Tightly stoppered 500 mL volume glass vessel
c) Nominal concentrations: 0, 0.041, 0.102, 0.256, 0.640, 1.60, 4.00 mg/L
d) Vehicle/Solvent and concentrations: not used
e) Stock solutions preparations and stability: Appropriate amount of test substance was dissolved with OECD medium under ultrasonication and 100 mg/L stock solution was prepared. The stock solution was sterilized by filtration with 0.45 µm membrane filter. Test solution was prepared by mixing appropriate amount of the stock solution and OECD medium.
f) Number of replicates: 3
g) Initial cell number (initial biomass): $1x10^4$ per mL
h) Volume of test solution: 100mL/vessel
i) Water temperature range: 23±2°C
j) Light condition (intensity, duration): 4000-5000 lux, continuous
-Method of analytical monitoring: HPLC (at start: test solution from another vessel

for analysis, and at end: Centrifuged supernatant of mixed test solution from 3 test vessels)
-Statistical method:
a) Data analysis: Comparison of areas under the growth curves and growth rate. NOEC: one-way ANOVA and Dunnett's multiple comparison. EC_{50}: method of least squares
b) Method of calculating mean measured concentrations: Time-weighted mean

Result **:** -Measured concentrations

Nominal concentration (mg/L)	Measured concentration (mg/L) (Percent of nominal)		
	0-hour(a)	72-hour(b)	Mean(c)
control	n.d.	n.d.	–
0.0410	0.0396(96.5)	0.0378 (92.1)	0.0387 (94.3)
0.102	0.102(100)	0.0980(96.1)	0.100(98.1)
0.256	0.260(102)	0.236(92.3)	0.248(96.9)
0.640	0.649(101)	0.596(93.2)	0.622(97.2)
1.60	1.63(102)	1.50(93.6)	1.56(97.6)
4.00	4.06(101)	3.75(93.8)	3.90(97.5)

n.d:<0.05mg/L (detection limit)
(a)fresh solution, (b) expired solution
(c)The values are expressed as time-weighted means.
-Water chemistry in test: Water temperature=22.9-24.9°C, pH=7.9 at the initiation of exposure and 8.3-10.5 at the termination of exposure

-Cell concentration at each flask of each measuring point:

Nominal Concentration (mg/L)	No.	Cell density (x10E+4 cells/mL) 0-hour	24-hour	48-hour	72-hour
Control	1	1.0	5.4	27.8	86.2
	2	1.0	5.8	36.4	85.7
	3	1.0	5.1	24.5	65.4
	Average	1.0	5.5	29.6	79.1
	S.D	0.0	0.4	6.1	11.8
0.0410	1	1.0	5.3	29.7	70.0
	2	1.0	5.1	22.6	60.4
	3	1.0	5.4	30.2	80.4
	Average	1.0	5.3	27.5	70.2
	S.D	0.0	0.1	4.2	10.0
0.102	1	1.0	5.9	31.1	90.2
	2	1.0	5.9	28.9	85.0
	3	1.0	5.2	26.5	80.1
	Average	1.0	5.7	28.8	85.1
	S.D	0.0	0.4	2.3	5.1
0.256	1	1.0	5.3	30.6	63.1
	2	1.0	5.1	26.7	71.8
	3	1.0	5.1	34.4	85.7
	Average	1.0	5.2	30.5	73.5
	S.D	0.0	0.1	3.8	11.4

0.640	1	1.0	4.0	17.6	53.8
	2	1.0	4.3	21.9	54.4
	3	1.0	3.8	20.5	62.8
	Average	1.0	4.0	20.0	57.0
	S.D	0.0	0.3	2.2	5.0
1.60	1	1.0	1.7	6.0	19.2
	2	1.0	1.6	5.2	16.0
	3	1.0	1.7	5.1	18.5
	Average	1.0	1.7	5.4	17.9
	S.D	0.0	0.1	0.5	1.7
4.00	1	1.0	1.4	1.6	1.8
	2	1.0	1.3	1.5	1.8
	3	1.0	1.2	1.4	1.8
	Average	1.0	1.3	1.5	1.8
	S.D	0.0	0.1	0.1	0.0

-Growth inhibition:

Nominal Concentration (mg/L)	No.	Area (X10E+4) 0-72h	Inhibition Rate (%) 0-72h	Inhibition Rate (%) 24-48h	Inhibition Rate (%) 24-72h	Inhibition Rate (%) 24-72h
Control	1	1770	-	0.0680	-	0.0575 -
	2	1980	-	0.0762	-	0.0559 -
	3	1440	-	0.0651	-	0.0530 -
	Average	1730	-	0.0698	-	0.0555 -
0.0410	1	1620	6.34	0.0714	-2.40	0.0536 3.46
	2	1330	23.1	0.0619	11.2	0.0514 7.36
	3	1760	-1.60	0.0720	-3.26	0.0564 -1.62
	Average	1570	9.28	0.0685	1.86	0.0538 3.07
0.102	1	1910	-10.4	0.0694	0.50	0.0569 -2.53
	2	1800	-3.80	0.0664	4.80	0.0556 -0.256
	3	1660	3.92	0.0675	3.23	0.0568 -2.40
	Average	1790	-3.43	0.0678	2.84	0.0565 - 1.73
0.256	1	1560	9.89	0.0730	-4.59	0.0516 7.07
	2	1560	9.58	0.0688	1.41	0.0550 0.859
	3	1920	-10.8	0.0791	-13.4	0.0586 -5.56
	Average	1680	2.90	0.0736	-5.53	0.0551 0.790
0.640	1	1100	36.2	0.0619	11.20	0.0543 2.22
	2	1220	29.3	0.0679	2.66	0.0529 4.74
	3	1280	26.2	0.0703	-0.752	0.0585 -5.32
	Average	1200	30.6	0.0667	4.38	0.0552 0.545
1.60	1	356	79.4	0.0512	26.5	0.0499 10.1
	2	296	82.9	0.0487	30.2	0.0476 14.1

	3	324	81.3	0.0464	33.5	0.0501	9.67
	Average	325	81.2	0.0488	30.1	0.0492	11.3
4.00	1	32.6	98.1	0.00644	90.8	0.00512	90.8
	2	28.9	98.3	0.00431	93.8	0.00637	88.5
	3	23.3	98.7	0.00672	90.4	0.00918	83.5
	Average	28.2	98.4	0.00582	91.7	0.0689	87.6

The control group showed normal growth (more than 65-fold increase after 72hr). The inhibition of growth at 4.00 mg/L was remarkable after 24hr. The growth was also inhibited at 1.60 mg/L and 0.640 mg/L. The lower cocentration groups showed similar growth to the control. The control growth rate is a littel lower during 48 - 72hr than 24 – 48hr.

-Statistical result: EbC_{50}(0-72 h)=0.900 mg/L (95% confidence limits: 0.511 – 1.59 mg/L) and NOEbC=0.248 mg/L.
ErC_{50}(24-48 h)=1.84 mg/L, ErC_{50}(24-72 h)=2.48 mg/L and NOErC=0.622 mg/L.
The statistical results are based on the measured concentrations.

Reliability : (1) valid without restriction
The data is approved by the Japanese government.
Flag : Critical study for SIDS endpoint
14.09.2001 (4)

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
Analytical monitoring : yes
NOEC : 0.241 mg/L
LOEC : 0.490 mg/L
EC_{50} : 0.566 mg/L
LC_{50} : 0.874 mg/L
Method : OECD Guide-line 211 "Daphnia magna reproduction test" (Draft Guideline, April 1997)
Year : 1999
GLP : yes
Test substance : other TS; Produced by Tokyo Kasei Kogyo Co., Ltd. Lot No. FHE01, Purity: 98.3%
Method : -Test organisms:
a) Age: <24 hours after hatch
b) Pretreatment:
c) Supplier/Source: Laboratory cultures maintained at Chemical Inspection and Testing Institute, Japan

-Test conditions:
a) Dilution water source: Dechlorinated tap water
b) Dilution water chemistry: hardness=52.0 mg/L as CaCO3, pH=7.5
c) Exposure vessel type: 500 mL volume glass aquarium (10 cm in diameter x 12 cm height) with a lid
d) Nominal concentrations: 0, 0.125, 0.250, 0.500, 1.00, 2.00 mg/L
e) Vehicle/solvent and concentrations: Not used
f) Stock solutions preparations and stability: Appropriate amount of test substance was dissolved with dilution water under ultrasonication and 100 mg/L stock solution was prepared. Test solution was prepared by mixing appropriate amount of the stock solution and dilution water and divided into 4 vessels.
g) Number of replicates: 4
h) Individuals per replicates: 5
i) Volume of test solution: 500 mL/vessel
j) Renewal frequency of test water: Semistatic with 48 hours interval
k) Water temperature: 20±1°C
l) Light condition: 16 hours light/8 hours dark (room light)
m) feeding: Chlorella vulgaris, 0.1-0.2 mg organic carbon/individual/day
-Method of analytical monitoring: HPLC (just before and after renewal of test water x 3)
-Statistical method:
a) Data analysis: Moving average method for EC_{50}, Bartlett method and Dunnett multiple comparisons method for NOEC and LOEC
b) Method of calculating mean measured concentrations: Time-weighted mean

Result **:** -Measured concentrations:

Nominal concentration (mg/L)	Measured concentration (mg/L) (Percent of nominal)			
	0-day(a)	2-day(b)	8-day(a)	10-day(b)
control	n.d.	n.d.	n.d	n.d.
0.125	0.129(103)	0.122 (97.2)	0.123 (98.5)	0.107(85.9)
0.250	0.254(102)	0.238(95.1)	0.242(96.9)	0.226(90.3)
0.500	0.508(102)	0.490(98.0)	0.497(99.5)	0.447(89.3)
1.00	0.981(98.1)	0.951(95.1)	0.987(98.7)	0.892(89.2)
2.00	1.98(98.9)	1.84(91.8)	1.95(97.6)	1.83(91.7)

(continued)

Nominal concentration (mg/L)	Measured concentration (mg/L) (Percent of nominal)		
	16-day(a)	18-day(b)	Time-weighted mean(c)
control	n.d.	n.d.	n.d
0.125	0.130(104)	0.119 (95.5)	0.122 (97.3)
0.250	0.255(102)	0.232(92.8)	0.241(96.4)
0.500	0.515(103)	0.483(96.6)	0.490(98.0)
1.00	1.02(102)	0.971(97.1)	0.967(96.7)
2.00	2.08(104)	1.97(98.4)	1.94(97.0)

n.d:<0.01mg/L (detection limit)
(a)fresh solution, (b) expired solution
(c)The values are expressed as time-weighted means.

-Water chemistry in test: Water temperature=20.1-20.3°C, pH=7.3-7.6, DO=8.4-9.0 mg/L, hardness=43.0-49.0 mg/L as CaCO3

-Cumulative number of dead parental Daphnia:

Nominal concentration (mg/L)	Exposure time (day) 3	7	14	21
control	0 (0)	0 (0)	0 (0)	2 (10)
0.125	0 (0)	0 (0)	0 (0)	3 (15)
0.250	0 (0)	0 (0)	0 (0)	4 (20)
0.500	0 (0)	0 (0)	0 (0)	1 (5)
1.00	0 (0)	0 (0)	0 (0)	10 (50)
2.00	0 (0)	0 (0)	14 (70)	20 (100)

The values in parentheses express mortality (%) of Daphnia.

-Time of the first production of young: 8 days in all test groups
-Mean cumulative numbers of young production per adult:

Nominal concentration (mg/L)	Exposure time (day) 7	8	9	10	11	12	13	14
control	0	19.5	19.5	21.0	45.7	45.7	45.7	69.7
0.125	0	17.8	17.8	21.5	41.6	41.6	41.6	59.8
0.250	0	18.5	18.5	27.4	42.3	42.3	42.3	65.4
0.500	0	16.7	16.7	17.4	39.8	39.8	39.8	50.0
1.00	0	15.7	15.7	18.2	36.8	36.8	36.8	38.8
2.00	0	3.7	5.3	5.6	7.4	7.4	7.4	7.4

(continued)

Nominal concentration (mg/L)	Exposure time (day) 15	16	17	18	19	20	21
control	69.7	69.7	96.1	98.9	98.9	120	136
0.125	61.1	61.1	85.9	91.4	91.4	108	119
0.250	66.5	66.5	88.3	93.5	93.5	114	126
0.500	50.4	50.4	56.9	59.7	59.8	61.6	68.4
1.00	38.9	38.9	38.9	38.9	38.9	38.9	38.9
2.00	7.4	7.4	7.4	7.4	7.4	7.4	7.4

-Statistical result: 21-day LC_{50} for parental Daphnia = 0.874 mg/L, 21-day EC_{50} for reproduction= 0.566 mg/L, 21-day NOEC and LOEC for reproduction=0.241 and 0.490 mg/L based on the measured concentrations.

Reliability : (1) valid without restriction
The data is approved by the Japanese government.

Flag : Critical study for SIDS endpoint
14.09.2001 (6)

4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO OTHER NON-MAMM. TERRESTRIAL SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

No data available

5.1.1 ACUTE ORAL TOXICITY

Type : LD_{50}
Value : male ; 320-800 mg/kg bw
female ; 130-320 mg/kg bw
Species : rat
Strain : Sprague-Dawley
Sex : male/female
Number of animals : 5/group
Vehicle : other; corn oil
Doses : 130, 320, 800, 2000 mg/kg
Method : OECD Guide-line 401 "Acute Oral Toxicity"
Year : 1999
GLP : yes
Test substance : other TS; Produced by Sumitomo Chemical Co.,Ltd. Purity 99.23%
Remark :

	Male		Female	
Dose(mg/kg)	Cum.Mortal.	Time of death	Cum. Mortal.	Time of death
0	0/5		0/5	
130	0/5		0/5	
320	0/5		3/5	d2:3an
800	4/5	d1:1an, d2:3an	4/5	d1:1an, d2:3an
2000	3/5	d2:2an, d3:1an	4/5	d2:4an

Cum. Mortal.; Cumulative Mortality, No. of animals which dead/ No. of animals used an; animal, d; day

Hypoactivity, a prone or lateral position and soiled fur in 800 mg/kg or more in males and 130 mg/kg or more in females. Bradypnea and Cheyne-Strokes' respiration in moribund animals of both sexes. Hypothermia, clonic convulsion, ataxic gait and vocalization in females. Pathological lesions were observed in the digestive organ and kidney.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
04.02.2002 (18)

Type : LD_{50}
Value : male ; 580 mg/kg bw
female; 740 mg/kg bw
Species : mouse
Strain : ICR
Sex : male/female
Number of animals : 5/group
Vehicle : other; corn oil
Doses : 100, 300, 500, 700, 1000, 1400, 2000 mg/kg
Method : other
Year : 1988
GLP : yes
Test substance : other TS; Produced by Sumitomo Chemical Co.,Ltd.

Remark : Cumulative Daily Mortality (Mouse Oral)

	Male		Female	
Dose(mg/kg)	Cum. Mortal.	Time of death	Cum. Mortal.	Time of death
0	0/5		0/5	
100	0/5		0/5	
300	2/5	d1:2an	0/5	
500	1/5	d1:1an	1/5	d1:1an
700	3/5	d1:2an, d2:1an	4/5	d1:3an, d5:1an
1000	4/5	d1:3an, d2:1an	4/5	d1:4
1400	5/5	d1:3an, d2:2an	3/5	d1:2an, d2:1an
2000	4/5	d1:3an, d8:1an	4/5	d1:3an, d3:1an

Cum. Mortal.; Cumulative Mortality; No. of animals which dead/ No. of animals used an; animal, d; day

Decrease of spontaneous activity, ataxia, limb paralysis, hyperpnea/ dyspnea in 300 mg/kg or more.

Reliability : (1) valid without restriction
Flag : Material Safety Datasheet
04.02.2002 (28)

Type : LD_{50}
Value : = 1080 mg/kg bw
Species : mouse
Strain : no data
Sex : male
Number of animals : 5-10 / group
Vehicle : other;cotton seed oil
Doses : 620, 940, 1400, 2100 mg/kg
Method : other
Year : 1949
GLP : no data
Test substance : no data
Remark : Depression to the point of prostraction, Irritant action on the gastroenteric tract by pathological findings.
Reliability : (4) not assignable
04.02.2002 (34)

5.1.2 ACUTE INHALATION TOXICITY

No data available

5.1.3 ACUTE DERMAL TOXICITY

Type : LD_{50}
Value : = 1200 mg/kg bw
Species : mouse
Strain : no data
Sex : male/female
Number of animals : 10/ group
Vehicle : other;cotton oil

Doses : 500, 750, 1000, 1750, 2500, 5000 mg/kg
Method : other
Year : 1976
GLP : no
Test substance : no data
Remark : Cumulative Daily Mortality (Mouse Dermal)

	Male		Female	
Dose(mg/kg)	Cum.Mortal.	Time of death	Cum. Mortal.	Time of death
500	0/10		0/10	
750	0/10		2/10	d1: 2an
1000	5/10	d1: 5an	4/10	d1: 3an, d6:1an
1750	7/10	d1:6an, d2: 1an	7/10	d1: 7an
2500	10/10	d1: 10an	10/10	d1: 10an
5000	10/10	d1: 10an	10/10	d1: 10an

Cum. Mortal.; Cumulative Mortality; No. of animals which dead/ No. of animals used an; animal, d; day

Decrease of spontaneous activity, ataxia, hyperpnea, poor appetite, pilo-erection, edema in application site. Toxic signs were observed decrease of spontaneous activity and pilo-erection in 750 mg/kg or more, and ataxia, hyperpnea and poor appetite in 1000 mg/kg or more. No remarkable change was found in macroscopic observation.

Reliability : (2) valid with restrictions
28.12.2001 (27)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

No data available

5.2.1 SKIN IRRITATION

Species : rabbit
Strain : New Zealand white
Sex : male/female
Number of animals : 3 (2males,1female)
Vehicle : other; none
Doses : 0.5 ml/1 x1 inch lint patch
Exposure time : 4 hour(s)
Method : Draze's method.
Year : 1988
GLP : yes
Test substance : other TS; Produced by Sumitomo Chemical, Lot No. 80159. Purity 98.5%
Result : irritating
Remark : Slight erythema and severe edema were observed at 4.5 hr after application. Slight to moderate erythema and moderate edema were obseved at 24 hr. Eschar and induration of skin at 72 hr. Irritating potency of the this substance was judged to be severe as primary irritation score was 5.44.
Reliability : (2) valid with restrictions
04.02.2002 (29)

Species : rabbit
Strain : no data
Sex : no data
Number of animals : 1

Vehicle	:	other; none
Doses	:	2.9 ml/kg
Exposure time	:	6 hour(s)
Method	:	Draze's method
Year	:	1949
GLP	:	no
Test substance	:	no data
Result	:	Corrosive Classification: Highly corrosive (cause sever burns)Corrosive
Remark	:	Erythema, Leather-like appearance, Complete necrosis and eventual sloughing and scar formation by cuff exposure (2.9 ml/kg)
Reliability	:	(4) not assignable

04.02.2002 (35)

5.2.2 EYE IRRITATION

Species	:	rabbit
Strain	:	New Zealand white
Sex	:	male/female
Number of animals	:	3/group
Vehicle	:	other: none
Doses	:	0.1 ml/eye
Method	:	Draze's (scoring) and Kay & Calandra's (classification) method
Year	:	1988
GLP	:	yes
Test substance	:	other TS; Produced by Sumitomo Chemical, Lot No. 80159.Purity 98.5%.
Result	:	Highly irritating.Risk of serious damage to eye.
Remark	:	Extreme irritating was observed at 24 hr (MMTS: 58.3) after 0.1 ml/eye application(unwashed). In the washed group, irritating potency was judged to be moderate at 24 hr (MMTS: 36.3).
Reliability	:	(2) valid with restrictions

04.02.2002 (29)

Species	:	rabbit
Strain	:	no data
Sex	:	no data
Number of animals	:	no data
Vehicle	:	other; none
Doses	:	0.03 ml/eye
Method	:	Draze's method
Year	:	1949
GLP	:	no
Test substance	:	no data
Result	:	Highly irritating. Classification:Risk of serious damage to eye
Remark	:	Extreme irritating at 24 hr (Draze score: 80) after 0.03 ml/eye application.
Reliability	:	(4) not assignable

04.02.2002 (35)

5.3 SENSITIZATION

No data available

5.4 REPEATED DOSE TOXICITY

Type	:	Sub-acute
Species	:	rat
Sex	:	male/female
Strain	:	Crj: CD(SD)
Route of admin.	:	oral(gavage)
Exposure period	:	Male: 42 days,Female: from 14 days before mating to day 3 of lactation
Frequency of treatm.	:	7 days/week
Post exposure period	:	no
Doses	:	2.5, 12.5, 60 mg/kg/day (in corn oil)
Control group	:	yes, concurrent vehicle
NOAEL	:	= 12.5 mg/kg bw
LOAEL	:	= 60 mg/kg bw
Method	:	other;OECD Preliminary Reproduct ion Toxicity Screening Test (TG 422)
Year	:	1999
GLP	:	yes
Test substance	:	other TS;Produced by Sumitomo Chemical, Lot No.1271012. Purity 99.23%
Test condition	:	*Age at study initiation: 8 week old for both sexes *Mean weight at study initiation Dose levels(mg/kg) 0 2.5 12.5 60 Body weight (g±SD) Male 291.5±9.0 291.6±9.0 291.7±8.7 291.8±8.1 Female 220.1±7.0 220.1±7.5 219.9±6.7 220.2±7.2 No. of animals per sex per dose: 13 per sexper dose group *Study Design -Terminal killing: Males; day 43, Females; day 4 of lactation -Clinical observations performed and frequency: General condition was observed once a day. Body weight and food consumption were determined once a week. Food consumption in mating period was not.Hematological and serum biochemical examinations, and urinary test were performed for all males. -Organs examined at necropsy: Organ weight: brain, heart, liver, kidneys, spleen, thymus, adrenal glands, testes, epididymides Microscopic: control & all treated groups/ liver, spleen(female only),adrenal glands(female only), control & 60 mg/kg groups/brain, heart, kidneys,spleen, thymus, adrenal glands, testes, epididymides.
Result	:	*LOAEL= 60 mg/kg/day males : histopathological changes in liver females: suppression of body weight gain and histopathological changes in liver * Body weight: Suppression of body weight gain was observed at day 14 of pregnancy and day 4 of lactation in the 60 mg/kg female. <u>Body weight in female</u> Dose level(mg/kg/day) 0 2.5 12.5 60 Body weight (g, mean±SD) y 14 of pregnancy 338.7±15.1 343.8±13.5 335.7±26.7 310.1±24.9** Day 4 of lactation 327.4±20.9 336.5±19.9 311.8±23.9 280.1±29.8** (**P< 0.01) *Food consumption: Decrease in food consumption was observed lactation period in the female group at 60 mg/kg.(Statistical significant was P< 0.01 on the day 4 of lactat ion) *Clinical signs (description, severity, time of onset and duration): No significant effect was observed.

*Mortality and time to death: The death was not observed in any group.
*Hematology and biochemical findings: No significant effect was observed.
*Gross pathology incidence and severity: No significant effect was observed.
*Organ weight changes :
Male: Increase in absolute kidneys weight was observed in the 60 mg/kg group (P<0.05).
Female: Decrease in absolute heart and spleen weights , and increase in relative brain,liver and kidneys weights were observed in the 60 mg/kg group (P< 0.01).
*Histopathology (incidence and severity)
Male & female: Hypertrophy of centrilobular hepatocytes with eosinophilic was observed at 60 mg/kg group. Histopathological change considered to be significant biologically was not observed in other organs.

Histopathological changes in the liver

Sex	Male				Female				
Dose level(mg/kg/day)									
0	2.5	12.5	60	0	2.5	12.5	60	Hypertrophy,eosinophilic Hepatocyte,centrilobular	
0/13	0/13	0/13	5/13*	0/13	0/13	0/13	10/13**	Necrosis	
2/13	1/13	1/13	1/13	4/13	2/13	1/13	6/13	Fibrosis,focal	
1/13	0/13	1/13	0/13	0/13	0/13	1/13	1/13	Fatty hange,periportal	
13/13	13/13	13/13	13/13	3/13	1/13	2/13	7/13		

(* P< 0.05 , ** P< 0.01)

Necrosis, Fibrosis and fatty change in peripotal region are thought to be spontaneous lesion on the liver of male and female rats. Historical control incidence of fifteen Combined Repeated Dose and Reproductive/Developmental Toxicity Studies performed at the same laboratory was checked out. The range of Necrosis, Fibrosis and Fatty change in periportal region were 0-31%, 0-23% and 0-100%, respectively. Especially, the historical incidence of Fatty change, periportal was 100% in all of 15 studies investigated in male rats in the laboratory. In the study of 6-tert-butyl-m-cresol, the incidence of Necrosis, focal (15% in male, 23% in female), Fibrosis, focal (8% in male, 0% in female), Fatty change, periportal (100% in male, 23% in female) in control animals falls within historical control range. Therefore, these lesions in the male and female liver of 6-tert-butyl-m-cresol study were considered to be spontaneous and animals used in the study were normal.

Remark : This study was conducted to examine both repeated dose toxicity and reproductive/developmental toxicity as an OECD screening combined study.Therefore,biochemical and hematological analysis,and urinary for females were not performed.

Conclusions : Toxic effects in this study are suppression of body weight gain and increase of relative liver weight in the 60 mg/kg female, and histopathologica changes of the liver in the 60 mg/kg male and female.
The NOAEL is considered to be 12.5 mg/kg/day for both sexes.

Reliability : (1) valid without restriction
Well conducted study, carried out by Research Institute for Animal Science in Biochemistry and Toxicology (Japan)

Flag : Critical study for SIDS endpoint

04.02.2002 (19)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Bacterial reverse mutation assay

System of testing : *Salmonella typhimurium TA100, TA1535, TA98, TA1537, Escherichia coli WP2uvrA*

Test concentration : -S9 mix: 0, 6.25, 12.5, 25, 50, 100, 200 µg/plate
+S9 mix: 0, 6.25, 12.5, 25, 50, 100, 200 µg/plate

Cycotoxic concentr. : Toxicity was observed at 100 and 200 µg/plate in TA strains with and without S9 mix, and 100 µg/plate without S9 mix and 200 µg/plate with S9 mix in *E. coli WP2 uvrA*
Metabolic activation : S9 from rat liver, induced with Phenobarbital and 5,6-Benzoflavone
Method : Other;OECD Guide-line 471 and 472
Year : 1999
GLP : yes
Test substance : other TS; Produced by Sumitomo Chemical, Lot No.71012, Purity:99.23%

Test condition : Number of replicates: 2,
Plate/test: 3,
Procedure: Pre-incubation,
Solvent: DMSO ;
Positive controls:
-S9 mix; 2-(2-Furyl)-3-(5-nitro-2- furyl) acrylamide(*TA100, TA98, WP2*), Sodium azid (*TA1535*) and 9-Aminoacridine(*TA1537*)
+S9 mix; 2-Aminoanthracene(all strains)

Result : negative
*Genotoxic effects: + ? -
With metabolic activation: [ ] [ ] [X]
Without metabolic activation: [ ] [ ] [X]

Conclusion : Bacteria gene mutation is negative with and without metabolic activation.
Reliability : (1) valid without restriction
Well conducted study, carried out by Research Institute for Animal Science in Biochemistry and Toxicology (Japan)
Flag : Critical study for SIDS endpoint
04.02.2002 (20)

Type : Chromosomal aberration test
System of testing : CHL/IU cell
Test concentration : - S9 mix(continuous treatment) : 0, 10, 20, 40, 60, 80 µg/ml
- S9 mix(short-term treatment) : 0, 7.5, 15, 30, 60, 90, 120 µg/ml
+S9 mix(short-term treatment) : 0, 7.5, 15, 30, 60, 90, 120 µg/ml
[confirmative test]
- S9 mix(6hrs short-term) : 0, 2.5, 5, 7.5, 10, 15 µg/ml
+S9 mix(6hrs shortt-term) : 0, 2.5, 5, 7.5, 10, 15 µg/ml

Cycotoxic concentr. : The concentration of 50% growth inhibition were as follows;
- S9 mix(continuous treatment) : 80 µg/ml
- S9 mix(short-term treatment) : 120 µg/ml
+S9 mix(short-term treatment) : 120 µg/ml

Metabolic activation : S9 from rat liver, induced with Phenobarbital and 5,6-Benzoflavone
Method : OECD Guide-line 473
Year : 1999
GLP : yes
Test substance : other TS ;Produced by Sumitomo Chemical, Lot No. 71012, Purity: 99.23%
Test condition : For continuous treatment, cells were treated for 24 or 48 hrs without S9 mix. For short-term treatment, cells were treated for 6 hrs with and without S9 mix, and cultivated with fresh media for 18 hrs.
Plates/test;2
Solvent;DMSO
Positive controls
continuous treatment; 1-Methyl-3-nitro-1-nitrosoguanidine
short-term treatment; Benzo[a]pyrene

Result : Positive Genotoxic effects: clastogenecity polyploidy

with metabolic activation : positive negative

without activation : negative negative

Remark : After 6hrs short-term treatment, structural chromosomal aberrations including gaps

were induced at 7.5, 15, 30 and 90 µg/ml, respectively with an S9 mix.
In a confirmatory test, structural chromosomal aberretions including gaps were inducedat 15 and 30 µg/ml with an S9 mix. Polyploidy was not induced in any treatment group.Lowest concentration producing cytogenetic effects in Vitro:
With metabolic activation(6hrs short -term treatment): 7.5 µg/ml (cytogenicity)

Chromosome analysis with S9 mix 6hrs short-term treatment
(No. of cells:200)

Concen-tration	No. of strucural aberration						No. cells with aberretions(%)	
(ug/ml)	gap	ctb	cte	cab	cse	oth	total	
0(solvent)	0	0	0	0	1	0	1	1 (0.5)
7. 5	2	5	15	0	0	0	22	17 (8.5) **
15	2	8	10	0	0	0	20	14 (7.0) **
30	0	3	8	0	1	0	12	10 (5.0) *
60	1	1	7	1	0	0	10	8 (4.0)
90	1	1	10	0	0	0	11	11 (5.5) *
120	—		(toxic)	—				
BP,10	2	25	120	2	0	0	149	121 (60.5) ** [Confirmative test]
0(solvent)	2	0	1	0	0	0	3	3 (1.5)
2. 5	1	0	4	0	0	0	5	5 (2.5)
7. 5	0	7	7	0	0	0	14	11 (5.5)
10	2	4	11	0	1	0	18	13 (6.5)
15	3	6	12	0	1	0	22	17(8.5) **
30	4	11	25	0	0	0	40	32(16.5)**
BP, 10	6	33	132	1	0	0	172	139(69.5)** gap:chromatid gap and

chromosome gap, ctb: chromatid break,
cte: chromatid exchange, csb: chromosome break,
cse: chromosome exchange(dicentric and ring), oth: others
(* P< 0.05, ** P< 0.01)

Chromosome analysis with S9 mix 6hrs short-term treatment (Additional Table [a])
(No. of cells:200)

Concen-tration	No. of strucural aberration						No. cells with aberretions(%)	
(ug/ml)	ctb	cte	cab	cse	oth	total	0(solvent)	
0	0	0	1	0	1	1	(0.5)	
7. 5	5	15	0	0	0	20	17 (8.5)	
15	8	10	0	0	0	18	13 (6.5)	
30	3	8	0	1	0	12	10 (5.0)	
60	1	7	1	0	0	9	7(3.5)	
90	1	10	0	0	0	10	10 (5.0)	
120	—		(toxic)	—				
BP,10	25	120	2	0	0	147	121 (60.5)	[Confirmative test]
0(solvent)	0	1	0	0	0	1	1 (0.5)	
2. 5	0	4	0	0	0	4	4 (2.0)	
7. 5	7	7	0	0	0	14	11 (5.5)	
10	4	11	0	1	0	16	13 (6.5)	
15	6	12	0	1	0	19	16(8.0)	
30	11	25	0	0	0	36	31(15.5)	
BP, 10	33	132	1	0	0	166	138(69.0)	

a) Data without gaps. In accordance with OECD guideline, gaps should not be included in stuructural aberration. However, definition of gaps in the study was equivalent to breaks of OECD guideline. Statistical analyses were not conducted with the data.
ctb: chromatid break,
cte: chromatid exchange, csb: chromosome break,
cse: chromosome exchange(dicentric and ring), oth: others

Conclusion : Chromosome aberration in CHL/IU cells is positive(clastogenicity)
Reliability : (1) valid without restriction
Well conducted study, carried out by Research Institute for Animal Science in Biochemistry and Toxicology (Japan).
Flag : Critical study for SIDS endpoint
04.02.2002 (21)

5.6 GENETIC TOXICITY 'IN VIVO'

Type : Micronucleus assay
Species : mouse
Sex : male
Strain : Crj: CD-1 (ICR) SPF
Route of admin. : Oral (gavage)
Exposure period : twice in the interval in 24 hours
Doses : 31.3, 62.5,125 mg/kg (Note1)
Result : negative
Method : OECD Guide-line 474 "Genetic Toxicology: Micronucleus Test"
Year : 2002
GLP : yes
Test substance : other TS: produced by Sumitomo Chemical, Lot No. 20213, Purity:99.0 %
Test condition : No. of animals per dose: 6 (the analysis object:5)
Age : 8 weeks
Vehicle: Olive oil
Positive control:
Mitomycin C (MMC) 2mg/kg in inj. water, single application
Terminal killing: 24 hous after final application
Preparation of specimens: bone marrow cells from the femur
two specimens for each animal
Analysis:
1) Frequency of micronucleated polychromatic erythrocytes (MNPCE) :
MNPCE/Polychromatic erythrocytes(PCE) ratio
(1000 PCE/specimen)
2) Effects to bone marrow cells
PCE/Total erythrocytes(TE) ratio (500 TE/ specimen)
Statistics: MNPCE/PCE: Binomial test with condition
(Kastenbaum & Bowman)
PCE/TE: t-test
Result : Negative

Dose level(mg/kg)	0	31.3	62.5	125	MMC
PCE/TE ratio(%)	45.5±5.12	57.4±5.72*	50.4±8.59	51.6±4.92	46.3±11.0
MNPCE/PCE ratio(%)	0.13±0.09	0.07±0.08	0.17±0.06	0.15±0.05	6.47±1.35**

(* P< 0.05 ** P< 0.01)

Remark (Note1) Since decrease of spontaneous activity, ataxia, hypopnea and the death were observed in a more than 250 mg/kg dose level but not in 125 mg/kg dose level at the preliminary study, 125 mg/kg was taken as the maximum tolerated dose

Conclusion Micronucleus test in mice is negative.
Reliability : (1) valid without restriction
Well conducted study, carried out by Chemicals Evaluation and Research Institute, Hita Labo., (Japan)
Flag : Critical study for SIDS endpoint
07.05.2002 (2)

5.7 CARCINOGENICITY

No data available

5.8.1 TOXICITY TO FERTILITY

No data available

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Remark : An OECD combined repeat dose and reproduction toxicity screening Test [OECD TG 422] was performed.
Conclusion: As for following Section 5.8.3, No adverse effect was observed for reproduction performance of parent males. Reproductive NOAEL is 60 mg/kg for males. Slight effects for female parent were observed for reproductive parameters, such as decrease tendency in number of corpora lutea, implants and live pups at birth. Decrease in body weights of both sexes of pups was noted. The NOAELS are considered to be 12.5mg/kg for female parents and pups toxicity

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

Type : Toxicity to Reproduction
In vitro/in vivo : in vivo
Species : rat
Sex : male/female
Strain : Crj: CD(SD)
Route of admin. : oral(gavage)
Exposure period : Male; for 42 days
Female; for 40-48 days from 14 days prior to mating to the 3 day of lactation
Frequency of treatm. : Daily
Doses : 0, 2.5, 12.5, 60 mg/kg/day (in corn oil)
Control group : yes, concurrent vehicle
Method : Method : OECD Preliminary Reproduction Toxicity Screening Test (TG 422)
*Terminal killing: Male; day 43 Female; day 4 of lactation
*Pre-mating exposure period: 14 days for both males and females
*Statistical methods: Dunnett's or Scheffe's test for continuous data and Chi square test for quantal data
Year : 1999
GLP : yes
Test condition : *Age at study initiation: 8 week old for both sexes
*Mean weight at study initiation:

Dose levels(mg/kg)	0	2.5	12.5	60
Body weight (g±SD)				
Male	291.5±9.0	291.6±9.0	291.7±8.7	291.8±8.1
Female	220.1±7.0	220.1± ± 7.5	219.9± ± 6.7	220.2±7.2

*No. of animals per sex per dose: 13 per sex per dose group

[Study Design]
The animals were sacrificed on the day 4 of lactation for females. Females with no delivery were killed on the day 25 of pregnancy.
*Satellite groups and reason they were added: none
*Mating procedure: Male / female per cage; 1/1, length of cohabitation; at most 14 days, until proof of copulation (formation of vaginal plug or sperm detection in vagina)

*Clinical observations performed and frequency:
Parent: general appearance once a day
Pups: general appearance once a day after birth
*Organs examined at necropsy:
Parent: organ weight: brain, heart, liver, kidneys, spleen, thymus, adrenal glands, testes, epididymis
* Microscopic:
control & all treated groups/ liver, spleen(female only) adrenal glands (female only)
control & 60 mg/kg groups/ brain, heart, kidneys, spleen, thymus, adrenal glands, testes, epididymis
*Pups: full macroscopic examinations on all pups
*Parameters assessed during study: Body weight(once a week), food consumption (once a week), No. of pairs with successful copulation, copulation index(No. of pairs with successful copulation/ No. of pairs mated x 100), pairing days until copulation, No. of pregnant females, fertility index (No. of pregnant animals/ No. of pairs with successful copulation x 100), No. of corpora lutea, No. of implantation sites, implantation index(No. of implantation sites/No. of corpora lutea x 100), No. of living pregnant females, No. of pregnant females with parturition, gestation length, No. of pregnant females with live pups on day 0, gestation index(No. of females with live pups/No. of living pregnant females x 100), No. of pregnant females with live pups on day 4 , delivery index(No. of pups born/ No. of implantation sites x 100), No. of pups alive on day 0 of lactation, live birth index(No. of live pups on day 0/ No. of pups born x 100), sex ratio(Total No. of male pups/ Total No. of female pups), No. of pups alive on day 4 of lactation, viability index(No. of live pups on day 4 / No. of live pups on day 0 x 100), body weight of live pups(on day 0 and 4)

Result : NOAEL;
12.5 mg/kg/day for maternal toxicity
12.5 mg/kg/day for pups toxicity.
*Maternal data with dose level (with NOAEL value):
Decrease tendencies, not significant, in number of corpora lutea and number of implantation sites were observed in the 60 mg/kg group.
*Pups data with dose level (with NOAEL value): Decrease in number of live pups at the day 0 and 4 of lactation were observed at 60 mg/kg group. Decrease in body weights of both sexes on the day 0 and 4 of lactation were noted in the 60 mg/kg group.

Dose level (mg/kg/day)	0	2.5	12.5	60
No. of pairs mated	13	13	13	13
No. of pregnant females	12	13	13	12
Corpora lutea	16.4±1.8	17.0±0.7	16.5±4.6	14.0±2.4
Implantation scars	14.8±3.2	16.2±1.5	15.0±4.6	12.8±3.2
Pups born	13.8±3.0	15.5±1.6	13.8±4.3	10.5±3.1
Delivery index(%)	93.5±6.2	95.2±4.2	92.4±7.4	83.3±17.9
Live pups born	13.8±3.0	15.3±1.6	13.5±4.4	10.3±2.9*
Live birth index (%)	100±0.0	99.0±3.5	91.0±27.8	98.1±3.5
Live pups on day 4 of lactation	13.5±2.8	14.1±4.5	14.4±1.7	8.8±3.7*
Body weight of live pups (g)				
on day 0				
Males	7.0±0.7	6.6±0.4	6.8±0.8	5.8±1.2**
Females	6.7±0.6	6.8±1.4	6.3±0.7	5.6±1.3**
on day 4				
Males	11.3±1.5	10.9±1.0	10.2±1.5	9.6±2.5*
Females	11.0±1.6	10.4±1.0	9.5±1.2	8.8±2.9**

(*P<0.05, **P<0.01)

Remark : *Mortality and day of death: the death was not observed in any group
*Body weight: suppression of body weight gain was observed on the day14 of pregnancy and the day 4 of lactation in the 60 mg/kg group.

		*Food consumption: Decrease in food consumption was observed during lactation period in 60 mg/kg group. *Pups data: Grossly visible abnormalities : no significant effect was observed.
Conclusion	:	No adverse effect was observed for reproductive performance of parent males. Slight effects for female parent were observed for reproductive parameters, such as decrease tendency in number of corpora lutea, implants and live pups at birth. Decrease in body weights of both sexes of pups was noted. The NOAELS are considered to be 12.5 mg/kg/day for female parents and pups toxicity.
Reliability	:	(1) valid without restriction Well conducted study, carried out by Hatano Research Institute, Food and Drug Safety Center(JAPAN)
Flag	:	Critical study for SIDS endpoint
04.02.2002		(19)

5.9 SPECIFIC INVESTIGATIONS

No data available

5.10 EXPOSURE EXPERIENCE

No data available

5.11 ADDITIONAL REMARKS

No data available

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