FOREWORD **INTRODUCTION**

M-TOLUIC ACID

CAS N°:99-04-7

SIDS Initial Assessment Report

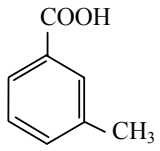
For

SIAM 16

Paris May 27-30, 2003

1. Chemical Name:	*m*-toluic acid
2. CAS Number:	99-04-7
3. Sponsor Country:	Japan Mr. Yasuhisa Kawamura Director Second International Organisations Div. Ministry of Foreign Affairs 2-2-1 Kasumigaseki, Chiyoda-ku Tokyo 100
4. Shared Partnership with:	Mr. Kiichiro Seki Mitsubishi Gas Chemical Company, Inc. E-mail: kiichiro-seki@mgc.co.jp
5. Roles/Responsibilities of the Partners:	Mitsubishi Gas Chemical Company, Inc.
• Name of industry sponsor /consortium	
• 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 16.
7. Review Process Prior to the SIAM:	Japanese government peer-reviewed the documents and audited selected studies.
8. Quality check process:	Japanese government peer-review committee performed spot checks on randomly selected endpoints and compared original studies with data in the SIDS Dossier.
9. Date of Submission:	February 21, 2003
10. Date of last Update:	
11. Comments:	None

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	99-04-7
Chemical Name	*m*-Toluic acid
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

m-Toluic acid is metabolized to methylhippuric acid and rapidly excreted in the urine.

The acute oral toxicity of the substance is relatively low. The oral LD_{50} in rats is greater than 2,000 mg/kg bw. At 2,000 mg/kg no animals died, no clinical signs, no effect on body weight gain, and no macroscopical changes were observed.

This substance is considered to be not irritating to skin. The sensitizing effect of *m*-toluic acid is not clear due to the lack of reliable data, but this substance might potentially be a sensitizer.

A combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [OECD TG 422] was conducted in rats at the doses of 0 (vehicle), 30, 100, 300 and 1,000 mg/kg/day administered by gavage. For males, the adverse effects, such as a decrease in locomotor activity, extension of prothrombin time, decrease in platelet, increase in GOT and increase in relative weight of the pituitary were observed at 1,000 mg/kg/day. For females, an increase in relative and absolute liver weight associated with periportal hepatocellular vacuolar degeneration (7/10) were observed at 1,000 mg/kg/day. Histological changes were observed (3/10) in the 300 mg/kg/day group. The NOAEL for the repeat dose toxicity is considered to be 300 mg/kg/day for males, and 100 mg/kg/day for females based on the adverse effects in the liver.

Two independent bacterial gene mutation tests [OECD TG 471 and 472] gave negative result with and without metabolic activation. In a chromosomal aberration test with Chinese hamster cultured cells (CHL/IU) [OECD TG 473], a little higher incidence of cells with chromosomal aberrations was observed, and this test gave equivocal results. Moreover, an *in vivo* micronucleus assay using rats [OECD TG 474], tested up to 2000 mg/kg, gave negative results. Considering these points, the chromosomal aberrations observed *in vitro* seems not to occur in the animal body.

In the above-described combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [OECD TG 422], there were no signs of reproduction/developmental toxicity on the gestation index, numbers, sex ratio, or viability of pups up to 1,000 mg/kg/day. The NOAEL of the reproduction/developmental toxicity is considered to be 1,000 mg/kg/day.

Environment

m-Toluic acid is white to yellowish crystal, which is soluble in water (1 g/L at 25 °C). Melting point, boiling point, and vapour pressure are 111.7 °C, 263 °C, and 0.00019 hPa (25 °C), respectively. *m*-Toluic acid is readily biodegradable [OECD TG 301C: BOD = 91 % after 28 days] and its bioaccumulation potential seems to be low based on its log Kow (2.37 at 25 °C). Indirect photo-oxidation by hydroxy radicals is predicted to occur with a half-life estimated at 63 hours. Hydrolysis is not expected to occur. Fugacity modeling (Mackay level III) predicts that if *m*-toluic acid is released to water and soil, it is unlikely to distribute into other compartments. When *m*-toluic acid is released to air, 2.1% stays in air and 15.6 % is transported to water and 82.2 % is transported to soil. This substance is weakly acidic (pKa = 4.27) and can be regarded as a non-dissociated molecule for the calculations with the fugacity model.

m-Toluic acid has been tested for the toxicity with species of three trophic levels. Acute toxicity tests were conducted with algae, daphnids and fish. The 72 h EC50 in algae (*Selenastrum capricornutum*) was 10 mg/L (biomass) or 15 mg/L (growth rate) [OECD TG 201]. The 48 h EC50 in daphnids (*Daphnia magna*) was 75 mg/L [OECD TG 202 part 1]. The 96 h LC50 in fish (*Oryzias latipes*) was 82 mg/L [OECD TG 203]. Two chronic toxicity results in algae (*Selenastrum capricornutum*) and daphnids (*Daphnia magna*) were available. For algae, a 72 h NOEC on growth inhibition of 2.2 mg/L (biomass) or 10 mg/L (growth rate), and for daphnids a 21 d NOEC for reproduction of 9.7 mg/L were reported. Algae are the most sensitive aquatic organisms among three trophic levels according to acute values.

Exposure

The production volume of *m*-toluic acid was estimated at approximately 250 t/year in Japan and 2,600 t/year world-wide in 2000. *m*-Toluic acid is produced in a closed system. Normal practice of production/conversion in Japan include sewage treatment to prevent environmental exposure to this substance. This chemical is used almost entirely as a chemical intermediate in the chemical industry to make an insect repellent used by humans. A very small portion of the product (c.a. 1%) is converted to a plastic stabilizer. During production and use of this substance, occupational exposure is possible by inhalation and dermal route.

RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

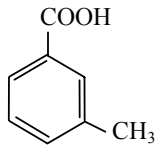
The chemical possesses properties indicating a hazard for the environment. Based on data presented by the Sponsor country, exposure to humans and the environment is anticipated to be low, and therefore this chemical is currently of low priority for further work. Countries may desire to investigate any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

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 99-04-7
IUPAC Name: *m*-Toluic Acid
Molecular Formula: $C_8H_8O_2$
Structural Formula:



Molecular Weight: 136.15
Synonyms: MTA

Benzoic acid, 3-methyl-

beta-Methylbenzoic acid

m-Methylbenzoate

m-Methylbenzoic acid

m-Toluylic acid

1.2 Purity/Impurities/Additives

Substance type: organic

Physical status: solid

Purity: > 97.0 % w/w

Impurities: Benzoic acid 0.4 %

o-Toluic acid 0.1 %

p-Toluic acid 0.05 %

Dimethybenzoic acid 0.05 %

1.3 Physico-Chemical properties

m-Toluic acid is a white to yellowish crystal, which is soluble in water. Other physical-chemical properties are shown in Table 1.

Table 1 Physical and chemical properties

	Protocol	**Results**
Melting Point	Unknown	111.7 °C
Boiling Point	Unknown	263 °C
Density	Unknown	0.996 g/cm^3 (4 and 20 °C)
Vapour Pressure	OECD TG 104	0.00019 hPa (25 °C)
Partition Coefficient (Log Kow)	Unknown	2.37 (25 °C)
Water Solubility	OECD TG 105	1,000 mg/L (25 °C)
pKa	Unknown	4.272 (25°C)

2 GENERAL INFORMATION ON EXPOSURE

Production and import

The production volume of *m*-toluic acid was estimated as approximately 250 t/year in Japan and 2,600 t/year worldwide in 2000. Normal practice of production/conversion in Japan include sewage treatment to prevent environmental exposure to this substance.

Use Pattern

m-Toluic acid is used almost entirely as a chemical intermediate to make the insect repellant (N, N-diethyl-*m*-toluamide: DEET) in the chemical industry. A very small portion of the product (ca. 1%) is converted to a plastic stabilizer.

2.1 Environmental Fate and Pathways

m-Toluic acid is readily biodegradable (OECD TG 301C: BOD = 91% after 28days) [CITI Japan, 1998] and its bioaccumulation potential seems to be low based on its log Kow (2.37 at 25 °C) [CITI Japan, 1999]. Abiotically this chemical is stable to hydrolysis in water. As a result of the hydrolysis test, this chemical was not hydrolyzed in 5 days on at 50ºC, pH 4, 7 and 9 (OECD TG 111) [CITI Japan, 1999]. Indirect photo-oxidation by hydroxy radicals in the atmosphere is predicted to occur with a half-life estimated at 63 hours.

The Mackay level III fugacity model was employed to estimate the environmental distribution of *m*-toluic acid in air, water, soil and sediment. This was considered the key study and the results are shown below. The results show that if *m*-toluic acid is released into water, 99.2% stays in water, it is unlikely to migrate into other compartments. When *m*-toluic acid is released to air, 2.1% stays in air, 15.6 % is transported to water and 82.2 % is transported to soil. When released to soil, 98.3% stays in soil and 1.7% is transported to water. This substance is a weakly acidic and can be regarded as a non-dissociated molecule for the calculation with the fugacity model.

Table 2 Estimated distribution under three emission scenarios

Compartment	Release: 100% to air	Release: 100% to water	Release: 100% to soil
Air	2.1 %	0.0 %	0.0 %
Water	15.6 %	99.2 %	1.7 %
Soil	82.2 %	0.0 %	98.3 %
Sediment	0.1 %	0.8 %	0.0 %

2.2 Human Exposure

2.2.1 Occupational Exposure

Occupational exposures to workers at production sites may occur by the inhalation route and dermal route.

The atmospheric concentration was measured at one production site [Japan Industrial Safety and Health Association (JISHA), 2001]. The monitored data are shown in table 3.

Table 3 Workplace monitoring data for *m*-toluic acid

Operation	Monitoring Data (maximum concentration)	Frequency time/day	Working time hrs/day	Maximum EHEinh mg/kg/day
Sampling work	0.679 mg/m^3	1	0.083	1.01 x 10^{-3}
Drum filling	2.632 mg/m^3	1	0.30	1.41 x 10^{-2}
Analysis work	*0.052 mg/m^3	1	0.025	2.32 x 10^{-5}

*: detection limit Total 1.51 x 10^{-2} mg/kg/day

[Monitoring method]

Air sample was suctioned at the breathing zone of the worker at a suction rate of 1.0 L/min. for ca.1.3 min. and recovered through a collection tube and analyzed by HPLC.

2.2.2 Occupational exposure limit of m-toluic acid

There is no available official recommendation.

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Mode of Action

m-Xylene is identified as a structurally related chemical of m-toluic acid because m-toluic acid is the first-step metabolite (the oxidation of one methyl side chain) of m-xylene. Six reports on the toxicokinetics and metabolism of m-toluic acid and structurally related chemicals such as xylenes, toluene and benzoic acid were reviewed. Four studies reported, in summary, that xylene and toluene were oxidized mainly to methylbenzoic acid and benzoic acid respectively, which in turn were conjugated with glycine to produce methylhippuric acid and hippuric acid, then excreted in the

urine [Riihimaki V. et. al., 1979 b] [Riihimaki V. et. al., 1984] [Amsel et al., 1969] [Sedivec et al., 1976].

One study reported the metabolism of m-methyl benzoic acid (m-toluic acid), benzoic acid, m-methyl hippuric acid and hippuric acid [Riihimaki V. et. al., 1979 a]. This was identified as the key study because it was a well organized study on m-toluic acid. The study is summarized below.

Urine samples from a volunteer weighing 70 kg who was exposed to separate doses of 41 micromoles of benzoic acid, an intermediate metabolite of toluene, and 33.5 micromoles of hippuric acid, a final metabolite of toluene, m-methylbenzoic acid (m-toluic acid), an intermediate metabolite of m-xylene, and m-methyl hippuric acid, a final metabolite of m-xylene, indicated total recovery of the compound through renal excretion via the kidneys. The measured urinary elimination of ingested m-toluic acid was complete in all cases of m-methylbenzoic acid (m-toluic acid), and m-methylhippuric acid. The excretion of both the benzoic acid and methylbenzoic acid conjugates was rapid for some 4-5 hr after the ingestion of the acids, the excretion rate constants being on the order of 1.0 h^{-1}. Only traces of free benzoic acid and methylbenzoic acid were detected in the urine after the compounds were ingested [Riihimaki V. et. al., 1979 a].

Conclusion

m-Toluic acid is rapidly excreted in urine as methylhippuric acid via the glycine conjugate route.

3.1.2 Acute Toxicity

There were limited numbers of reports located on the acute toxicity of *m*-toluic acid by different administration routes. Two studies with variable reliability and validity were reviewed. MHW study [MHW Japan, 1999] was considered to be the most reliable because this study was well conducted according to the OECD TG 401 in compliance with GLP. The details of this study were as follows. The chemical was 98.79 % pure *m*-toluic acid. SD rat (5/sex/dose) were administered by gavage at doses of 0 (vehicle), 1,000 and 2,000 mg/kg bw. No rats died in any of the groups during the 14 days post observation period. No effects of *m*-toluic acid were found on clinical signs, body weight gain and macroscopical findings in any of treated animals by autopsy. The oral LD_{50} was considered to be greater than 2,000 mg/kg bw. The other well-organized study [MGC Japan, 1974] reported much higher values shown in the table 4 below and no rats died at doses of less than 2,000 mg/day bw . The LD_{50} of *m*-toluic acid is considered to be greater than 2,000 mg/kg bw. As to the toxicity via the i.p. route and the acute dermal toxicity, no available reports were found.

Table 4 Acute toxicity of *m*-toluic acid in experimental animals

Route	Animals	Values	Type	References
Oral	Rat	> 2,000 mg/kg bw	LD_{50}	MHW Japan, 1999
Oral	Rat	4,446 mg/kg bw (Male) 4,699 mg/kg bw (Female)	LD_{50}	MGC, 1974

Conclusion

This substance has relatively low acute toxicity.

The acute oral LD_{50} of m-toluic acid in rats is considered to be greater than 2,000 mg/kg bw.

3.1.3 Irritation

The results are summarized in the table 5 below.

Table 5 The summary of other human health information

Species	Method	Result	Reference
Irritation (Skin)			
Rabbit (JW)	Draize method. rabbit.	Not irritating	MGC Japan, 1992b

As to skin irritation, erythema was observed in two animals out of six. In one animal, it was observed on the intact skin and the abraded skin. In the other animal, it was done on the abraded skin only. The erythema on the intact skin observed at 24 hrs had disappeared at 48 hrs.

No study was found on eye irritation.

This substance is considered to be not irritating to skin.

3.1.4 Sensitisation

There were no reports on the sensitizing effect of *m*-toluic acid to animals. Only one report available is on the sensitization effect of toluic acids to humans [Emmett, 1973]. Although a cross-sensitivity was found between three isomers (*o*-, *m*-, *p*-toluic acid), the sensitizing of the single *m*-toluic acid was ambiguous. It should be concluded that the sensitization effect of *m*-toluic acid is not clear at present; this substance might potentially be a sensitizer.

3.1.5 Repeated Dose Toxicity

One study according to the OECD Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening test [OECD TG 422] was conducted by MHW Japan in compliance with GLP and this was identified as the key study [MHW Japan, 1999].

SD (Crj: CD) rats received gavage doses of 0 (vehicle; 1 % methylcellulose solution in water), 30, 100, 300, and 1,000 mg/kg/day once daily. The doses were decided by a preliminary test in which females at 1,000 mg/kg/day showed a body weight gain suppression and a decrease of food consumption, and both males and females showed a decrease of platelets counts at 1,000 mg/kg/day. The dosing period for males was 44 days, and for females were 41 to 45 days from 14 days before mating to day 3 of lactation. The purity of *m*-toluic acid was 98.79 %. There was no mortality for all groups of both sexes. The adverse effects are summarized below.

(Males)

At 1,000 mg/kg/day, the following significant adverse effects were observed. Clinical signs: Four animals showed decreased locomotive activity after 16 days of administration. Hematology: Extension in the prothrombin time, decrease in platelet count, increase of GOT value and increase of sodium (Na) were observed. Organ weight: At 1,000 mg/kg/day, significant increase in the relative weight of pituitary was observed. Along with above mentioned adverse effects, the following effects which were considered to be focal and not dose dependent, were observed: 1) increase of leukocytes, 2) PAS-stained hyaline droplet in proximal tubular epithelium in kidney, 3) extramedually hematopoiesis and Berlin-Blue-stained hemosiderin deposit in spleen, 4) degeneration of the germ cells in testis, 5) inflammation in prostate. At 300 mg/kg/day, there were no significant abnormal findings. The following effects which were considered to be focal and not dose dependent, were observed: 1) loss of fur, 2) increase in alkaline phosphates value. These were

not considered as adverse effects related to the administration of *m*-toluic acid. At 100 mg/kg/day, no effects were observed. At 30 mg/kg/day, there were no significant abnormal findings. The following effects, which were considered to be focal and not dose dependent, were observed: 1) increase of leukocytes. These were not considered as adverse effects related to the administration of *m*-toluic acid.

The NOAEL for males is considered to be 300 mg/kg/day based on the adverse effects on the liver.

(Female)

At 1,000 mg/kg/day, the following significant adverse effects were observed. Organ weight: Increases in the absolute and relative weight of liver were observed. Histopathology: Seven animals showed periportal hepatocellular vacuolar degeneration in the liver. As a non-significant effect, extramedually hematopoiesis and Berlin-Blue-stained hemosiderin deposit in spleen was observed. These effects were observed in all animals of the control group. So this was not considered to be due to the administration of *m*-toluic acid. At 300 mg/kg/day, 3 animals showed periportal hepatocellular vacuolar degeneration in the liver. At 30 and 100 mg/kg/day, there were no abnormal findings.

The NOAEL for females is considered to be 100 mg/kg/day based on the adverse effects on the liver.

Conclusion

For males, the adverse effects, such as a decrease in locomotor activity, extension of prothrombin time, decrease in platelet, increase in GOT and increase in relative weight of the pituitary were observed at 1,000 mg/kg/day. For females, an increase in relative and absolute liver weight associated with periportal hepatocellular vacuolar degeneration (7/10) were observed at 1,000 mg/kg/day. Histological changes were observed (3/10) in the 300 mg/kg/day group. The NOAEL for the repeat dose toxicity is considered to be 300 mg/kg/day for males and 100 mg/kg/day for females.

3.1.6 Mutagenicity

Four reports for tests on genetic toxicity according to OECD TG 471 & 472, TG 473 and TG 474 were reviewed and summarized in the table 6 shown below. These were two bacterial *in vitro* tests, one non-bacterial *in vitro* test and one genetic *in vivo* test.

Table 6 Summary of genetic toxicity studies

Type of test	Test system	Dose	Result	Reference
Bacteria *in vitro* test				
Reverse mutation OECD TG 471 & 472	*Salmonella typhimurium* (strains TA100, TA1535, TA98, TA1537) *Escherichia coli* WP2 *uvrA*	Up to 5,000 ug/plate Toxicity was observed at 2,500 and 5,000 ug/plate in TA100, TA1535, TA1537 and at 5,000 ug/plate TA98, WP2 *uvr*A without S9 mix. At 5,000 ug/plate with S9 mix, precipitates were observed.	Negative (+ & - MA*)	MHW Japan, 1999
	S. typhimurium (strains TA1535, TA1537, TA1538, TA98 and TA100) *E. coli* WP2 *uvrA*	Up to 5,000 ug/plate. The cytotoxicity was observed at 5,000 ug/plate.	Negative (+ & - MA)	MGC Japan, 1992a
Non Bacteria *in vitro* test				
Chromosomal aberration test OECD TG 473	CHL/IU cells	Up to 2,500 mg/mL ** Cytotoxicity (See note)	Positive (- MA)	MHW Japan, 1999
Genetic *in vivo* test				
Micronucleus test OECD TG 474	Male rats [Crj: CD (SD) IGS], oral gavage	500 - 2,000 mg/kg Extended test: 125 -500 mg/kg Two administrations with 24 hr interval.	Negative	MGC Japan, 2002
* MA: Metabolic activation				
** Cytotoxicity: 812 ug/mL (24hr continuous), 455 ug/mL (48 hr continuous) 863 ug/mL (6 hr short treatment with S9), 1,182 ug/mL (6 hr short treatment without S9).				

In vitro Studies

Bacterial test

Two reports were reviewed. The results of these two studies were negative for all S. typhimurium strains (TA1535, TA1537, TA1538, TA98 and TA100) and E. coli WP2 uvrA. Among these two, the study MHW, Japan (1999) was well conducted according to the Japanese Guideline for Screening Mutagenicity Testing of Chemicals and the OECD TG 471 and 472 in compliance with GLP. This was identified as the key reliable study. The purity of the chemical was 98.79 %. The test was conducted two times for all cells with and without S9 at 0 (vehicle), 156, 313, 625, 1,250, 2,500, and 5,000 ug/plate. These doses were decided by a preliminary test to find out cytotoxic concentration with the doses of 1.22, 4.88, 19.5, 78.1, 313, 1,250, and 2,500 ug/plate. Cytotoxicity was observed at 2,500 ug/plate and 5,000 ug/plate without S9 mix except for 2,500 ug/plate of TA 98 and WP2 uvrA. At 5,000 ug/plate with S9 mix, precipitates were observed. The results were negative because m-toluic acid did not induce mutations (number of revertants) more than two times of the control group with and without metabolic activation for all the Salmonella typhimurium strains (TA100, TA1535, TA98, TA1537) and Escherichia coli WP2 uvrA.

Non-bacterial test

There was only one report available on the chromosomal aberration test on cultured Chinese hamster lung (CHL/IU) cells. This study was conducted by MHW, Japan (1999) according to the OECD TG 473 in compliance with GLP and was identified as the key reliable study . The summary of the test was as follows. The purity of the chemical was 98.79 %. A preliminary test for cytotoxicity, the main test, and the confirmation test were conducted. The dose-finding tests were as follows. Preliminary test: 0 (vehicle) up to 2,500 ug/mL, main test: 0 (vehicle) up to 2,000 ug/mL, confirmation test: 0 (vehicle) up to 2000 ug/plate. Cytotoxicity was observed as shown in the note of table 6 above.

In both continuous treatments (24 or 48 hr) without metabolic activation, structural chromosomal aberrations were not induced at any doses except 500 ug/mL for the 48 hr treatment at a level of 5.0 % (within equivocal range). Polyploidy was not induced in any treatment group. In the 6 hr short-term treatment with or without metabolic activation, structural chromosomal aberrations were not induced at any doses except 1,000 ug/mL with metabolic activation at a level of 5.0 % (within equivocal range). In the confirmation test, these aberrations were not induced at any doses with or without metabolic activation. Polyploidy was not induced in any treatment group. These values did not follow a dose-response and were not reproducibe. In all test conditions, some of this substance precipitated in the medium and the color of the growth medium was changed to yellow at the beginning of the treatment for 1,000 ug/mL and higher concentrations. The pH values of the growth media were more than 6.2 at the concentrations where the mutagenicity was observed.

It is concluded that the chromosomal aberrations in cultured Chinese hamster lung cells gave equivocal results.

In vivo Studies

Genetic test

Only one study on the micronucleus assay was reported. This study was conducted by the OECD TG 474 in compliance with GLP [MGC, 2002] and was reliable. This study was identified as the key study. The summary of the test is as follows.

The purity of m-toluic acid was 98.96 %. Five male SD (Crj: CD IGS) rats/group were administered by oral gavage 2 times with 24 hr interval. The doses were set at 500, 1,000, and 2,000 mg/kg bw based on the oral LD_{50}, greater than 2,000 mg/kg bw. At 24 hr after the 2nd administration, animals were sacrificed and samples were prepared for analysis. m-Toluic acid did not induce micronuclei except that there was a separate incidence in one animal in the 500 mg/kg group that showed statistically abnormal value. The additional test was conducted with 3 doses of 125, 250 and 500 mg/kg. As concluded from the main and the additional test combined, the chemical did not induce significant increases in the micronuclei in any treated groups of a wide dose range. The reproducibility of the separate incidence was not established in the duplication of the 500 mg/kg dose. The incidences of micronuclei in the negative and positive control were within the range of the test laboratory's background data.

Conclusion

Two independent bacterial gene mutation tests [OECD TG 471 and 472] gave negative results with and without metabolic activation. In a chromosomal aberration test with Chinese hamster cultured cells (CHL/IU) [OECD TG 473], a little higher incidence of cells with chromosomal aberrations was observed, and this test gave equivocal result. Moreover an in vivo micronucleus assay using rats [OECD TG 474], tested up to 2,000 mg/kg, gave negative results. Considering these results, the chromosomal aberrations observed in vitro in the absence of an exogenous metabolic activation system seems not to occur in the animal body.

3.1.7 Toxicity for Reproduction and Development

There was only one study available.: the OECD Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening test [OECD TG 422]. The study was conducted by MHW, Japan (1999) in compliance with GLP. It is identified as the key reliable study. Details of the study were as follows.

The purity of chemical was 98.79 %. SD (Crj: CD) rats received gavage doses of 0 (vehicle), 30, 100, 300 and 1,000 mg/kg/day, for 14 days before mating for males and from 14 days before mating to day 3 of lactation for females. The parental animals exhibited no alteration in the reproductive parameters although adverse effects, mainly to the liver, were observed at 300 mg/kg/day and greater doses for females and at 1,000 mg/kg/day for males. There were no significant differences in the offspring parameters. Upon external inspection of pups, no abnormalities were found. Also no abnormalities were found in the internal organs.

The NOAEL for the reproduction/developmental toxicity is considered to be 1,000 mg/kg/day.

Conclusion

The NOAEL of *m*-toluic acid for the reproduction/developmental toxicity is considered to be 1,000 mg/kg.

3.1.8 Other Valid and Reliable Information

Information on chemicals which are structurally related to *m*-toluic acid:

***m-Xylene* [CAS No.: 108-38-3] (see also corresponding SIDS Documents)**

Xylene was reported to be oxidized mainly to methylbenzoic acid, which in turn was conjugated with glycine to produce methylhippuric acid and excreted in the urine. The maximum urinary excretion rate of hippuric acid (final metabolite of toluene) was about 190 umol/min and was limited by the mobilization of endogenous glycine for benzoic acid conjugation [Sedivec et al., 1976]. LD_{50} values were reported as follows: oral dose (rat) 5,000 - 6,661 mg/kg, inhalation (LC_{50} mouse, 6 hr) 5,267 - 5,300 ppm, dermal (rabbit) 3,228 - 12,100 mg/kg, intraperitoneal (mouse) 1,330 - 1,346 mg/kg. *m*-Xylene is irritating to skin and eyes. In a repeated oral dose toxicity test (rat, 800 mg/kg/day, 5 days/week x 3.5 weeks), a decrease of cytochrome p-450 in lungs and an increase of plasma ALT as a toxicity to livers were observed. *m*-Xylene is negative in the reverse mutation *in vitro* test with *Salmonella thyphmurium* and *Escherichia coli*. This chemical is negative in chromosomal aberration *in vitro* tests with mammalian cultured cells and human lymphocytes. Also this chemical is negative in the *in vivo* micronucleus test.

3.2 Initial Assessment for Human Health

m-Toluic acid is metabolized to methylhippuric acid and rapidly excreted in the urine. The acute oral toxicity of the substance is relatively low. The oral LD_{50} in rats is greater than 2,000 mg/kg bw. At 2,000 mg/kg no animals died, no clinical signs, no effect on body weight gain, and no macroscopical changes were observed. This substance is considered to be not irritating to skin. The sensitizing effect of *m*-toluic acid is not clear due to the lack of reliable data, but this substance might potentially be a sensitizer.

A combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [OECD TG 422] was conducted in rats at the doses of 0 (vehicle), 30, 100, 300 and 1,000 mg/kg/day administered by gavage. Decreased locomotor activity, increases in prothrombin time and GOT, a decrease in platelet counts and increase in relative weight of the pituitary were

observed at 1,000 mg/kg/bw/day in males. In females, hepatocellular vacuolar degeneration was revealed in the 300 and 1,000 mg/kg groups. Absolute and relative liver weights were increased at 1,000 mg/kg group. The NOAELs for repeat dose toxicity are considered to be 300 mg/kg/day for males and 100 mg/kg/day for females.

Two independent bacterial gene mutation tests [OECD TG 471 and 472] gave negative results with and without metabolic activation. A chromosomal aberration test with Chinese hamster cultured cells (CHL/IU) [OECD TG 473], a little higher incidence of cells with chromosomal aberrations was observed, and this test gave equivocal result. Moreover, an *in vivo* micronucleus assay using rats [OECD TG 474], tested up to 2,000 mg/kg, gave negative results. Considering these points, the chromosomal aberrations observed *in vitro* seems not be able to occur in the animal body.

In the above-described combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [OECD TG 422], there were no signs of reproduction/developmental toxicity on the numbers, sex ratio, or viability of pups up to 1,000 mg/kg/day. The NOAEL of the reproduction/developmental toxicity is considered to be 1,000 mg/kg/day.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

The toxicity data to aquatic organisms is summarized in Table 7.

Environmental Agency of Japan (1998) reported acute toxicity data for three kinds of aquatic organism (algae, invertebrates and fish). The growth inhibition test for algae was performed using *Selenastrum capricornutum* (OECD TG 201). The EC_{50}s for algae were estimated based on biomass and growth rate. The EC_{50} (biomass; 0-72 h) was 10 mg/L and the EC_{50} (growth rate; 24-72 h) was 18 mg/L. The acute toxicity for daphnids (*Daphnia magna*) 24 h EC_{50} was 75 mg/L (OECD TG 202 part 1). And the 96 h LC_{50} for fish (*Oryzias latipes*) was 82 mg/L (OECD TG 203). The lowest acute toxicity of *m*-toluic acid was reported from the algae inhibition test for biomass (72 h EC_{50} of 10 mg/L).

Two chronic toxicity values, for alga (*Selenastrum capricornutum*) and daphnids (*Daphnia magna*) were reported by Environmental Agency of Japan (1998). The NOECs for green alga on growth inhibition were estimated based on biomass and growth rate as in the case of the acute toxicity (OECD TG 201), which were 2.2 mg/L (0-72 h) and 10 mg/L (24-72 h), respectively. In the reproduction test with daphnids, the 21 d NOEC was 9.7 mg/L (OECD TG 211).

All the data shown here were derived from the experiment conducted under GLP, and the *m*-toluic acid concentrations in the testing media were monitored during the course of the experiments.

Other information on the hazard potential of *m*-toluic acid including towards sediment dwellers were not available.

Table 7 Summary of effects of *m*-toluic acid on aquatic organisms

Organism	Test duration	Result (mg/L)	Reference
algae			
Green alga (*Selenastrum capricornutum*)	72 h (op)	EC_{50} (bms, 0-72 h) = 10 (nc) NOEC (bms, 0-72 h) = 2.2 (nc) EC_{50} (gr, 24-48 h) = 15 (nc) EC_{50} (gr, 24-72 h) = 18 (nc) NOEC (gr, 24-72 h) = 10 (nc)	EA, Japan 1998
Invertebrates			
Water flea (*Daphnia magna*)	48 h (op,s)	EC_{50} (imm) = 75 (nc) EC_0 (imm) = 56 (nc)	EA, Japan 1998
	21 d (op,ss)	LC_{50} >= 46 (mc) EC_{50} (rep) = 15 (mc) LOEC (rep) = 22 (mc) NOEC (rep) = 9.7 (mc)	EA, Japan 1998
Fish			
Medaka (*Oryzias latipes*)	96 h (op,ss)	LC_{50} = 82 (nc) LC_0 = 68 (nc)	EA, Japan 1998

op: open system, ss: semi-static, s: static, bms: biomass, gr: growth rate, imm: immobilization,

rep: reproduction, nc: calculated based on nominal concentration (actual concentration measured and greater than 80% of the nominal), mc: calculated based on measured concentrations, because some of the measured concentration were less than 80% of the nominal.

This substance is a weak acid. Nevertheless in these tests the pH values at each EC_{50} or LC_{50} was not significantly reduced and the effects can therefore be considered to relate only to this substance itself.

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

m-Toluic acid is readily biodegradable and its bioaccumulation potential seems to be low based on its Log Kow of 2.37. Indirect photo-oxidation by hydroxy radicals is predicted to occur with a half-life estimated at 63 hours. A generic level III fugacity model shows that if *m*-toluic acid is released to water and soil, it is unlikely to distribute into other compartments. When *m*-toluic acid is released to air, 2.1% stays in air and 15.6 % is transported to water and 82.2 % is transported to soil. This substance is a weakly acidic and can be regarded as a non-dissociated molecule for the calculations with the fugacity model.

Algae are the most sensitive organisms among the three trophic levels according to the results from the acute tests. The values of acute and chronic toxicity for algae (*Selenastrum capricornutum*) have been reported as EC_{50} (0-72 h) of 10 mg/L and 72 h NOEC of 2.2 mg/L on growth inhibition (endpoint biomass). The predicted no effect concentration (PNEC) of 0.022 mg/L for the aquatic organisms is calculated from the 72 h NOEC for *Selenastrum capricornutum* using an assessment factor of 100, because two chronic results (*Daphnia* and *Selenastrum*) are available.

5 RECOMMENDATIONS

The chemical is currently of low priority for further work.

The chemical possesses properties indicating a hazard for 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 Sponsor countries.

6 REFERENCES

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SIDS

Dossier

Existing Chemical	:	ID: 99-04-7
CAS No.	:	99-04-7
EINECS Name	:	m-toluic acid
EINECS No.	:	202-723-9
Molecular Formula	:	C8H8O2

Producer Related Part

Company	:	Mitsubishi Gas Chemical Company, Inc.
Creation date	:	20.08.2002

Substance Related Part

Company	:	Mitsubishi Gas Chemical Company, Inc.
Creation date	:	20.08.2002
Memo	:	SIAM16
Printing date	:	20.11.2002
Revision date	:	
Date of last Update	:	01.11.2002
Number of Pages	:	57
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 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 Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 OECD AND COMPANY INFORMATION

Type : lead organisation
Name : Mitsubishi Gas Chemical Company, Inc.
Partner :
Date :
Street : Mitsubishi Bldg. 5-2, Marunouchi 2 chome, Chiyoda-ku
Town : 100-8324 Tokyo
Country : Japan
Phone : +81-3-3283-4800
Telefax : +81-3-3214-0938
Telex :
Cedex :
Source : Mitsubishi Gas Chemical Company, Inc.
16.07.2002

1.0.2 LOCATION OF PRODUCTION SITE

1.0.3 IDENTITY OF RECIPIENTS

1.1 GENERAL SUBSTANCE INFORMATION

Substance type : organic
Physical status : solid
Purity : > 97 % w/w
Source : Mitsubishi Gas Chemical Company, Inc.
16.07.2002

1.1.0 DETAILS ON TEMPLATE

1.1.1 SPECTRA

1.2 SYNONYMS

Benzoic acid, 3-methyl-
Source : Mitsubishi Gas Chemical Company, Inc.
16.07.2002

beta-Methylbenzoic acid
Source : Mitsubishi Gas Chemical Company, Inc.
16.07.2002

m-Methylbenzoic acid
Source : Mitsubishi Gas Chemical Company, Inc.
16.07.2002

m-Methylbenzoate
Source : Mitsubishi Gas Chemical Company, Inc.
16.07.2002

m-Toluylic acid
Source : Mitsubishi Gas Chemical Company, Inc.
16.07.2002

MTA
Source : Mitsubishi Gas Chemical Company, Inc.
16.07.2002

1.3 IMPURITIES

Benzoic acid : 0.4 %
o-Toluic Acid : 0.1 %
o-Toluic Acid : 0.05 %
dimethybenzoic acid : 0.05 %
Source : Mitsubishi Gas Chemical Company, Inc.
25.04.2003

1.4 ADDITIVES

1.5 QUANTITY

Production during the last 12 months :
Import during the last 12 months :
Quantity produced : tonnes in
Remark : 250 t/y in Japan and 2,600 t/y world-wide in 2000.
Source : Mitsubishi Gas Chemical Company, Inc.
18.07.2002

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.7 USE PATTERN

Type : type
Category : Non dispersive use
Source : Mitsubishi Gas Chemical Company, Inc.
18.07.2002

Type : type
Category : Use in closed system
Source : Mitsubishi Gas Chemical Company, Inc.
18.07.2002

Type : industrial
Category
Source Mitsubishi Gas Chemical Company, Inc.
18.07.2002

Type : use
Category : Intermediates
Source : Mitsubishi Gas Chemical Company, Inc.
18.07.2002

MEMO : This chemical is used almost entirely as a chemical intermediate to make the evasion agent (DEET) for insects in the chemical industry. The very small portion of the product (c.a. 1%) is converted to a plastic stabilizer.
Source : Mitsubishi Gas Chemical Company, Inc.
Flag : Critical study for SIDS endpoint
05.02.2003

1.7.1 TECHNOLOGY PRODUCTION/USE

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUES

Remark : No data available on Occupational Exposure Limit Values
Source : Mitsubishi Gas Chemical Company, Inc.
18.07.2002

1.9 SOURCE OF EXPOSURE

Remark : Occupational exposures at production sites may occur by the inhalation route and dermal route.

The atmospheric concentration was measured at one production site [Japan Industrial Safety and Health Association (JISHA), 2001]. The monitored data are shown in Table 2.

Table 2: Workplace monitoring data for MTA

Operation	Monitoring Data (Maximum Concentration)	Frequenytime/day	Working timehrs/day	MaximumEHEinhmg/kg/day
Sampling work	0.679 mg/m3	1	0.083	1.01 x 10-3
Drum filling	2.632 mg/m3	1	0.30	1.41 x 10-2
Analysis work	0.052 mg/m3	1	0.025	2.32 x 10-5
			Total	1.51 x 10-2 mg/kg/day

[Monitoring method]
Air sample was suctioned at the breathing zone of the worker at the suction rate of 1.0 L/min. for ca.1.3 min. and adsorbed through a collection can and analyzed by HPLC.

As shown in Table 2, the monitored exposure concentrations were below 0.052 - 2.632 mg/m3 at the sampling work, the drum filling work and the analysis work. The highest daily intake (respiratory EHEinh) for a worker (body weight; 70 kg, respiratory volume; 1.25 m3/hr) assigned to the drum filling work without protection is calculated as 1.41 x 10-2 mg/kg/day. The duration of dermal exposure is assumed to be 0.30 hrs/day. EHEder for the worker who implement all daily operation through hands is calculated as *4.50 x 10-2 mg/kg/day, assuming that the work is classified as non-dispersive, direct handling, and contact level is incidental.

* 840x0.3x0.1/8/70
: Mitsubishi Gas Chemical Company, Inc.

18.07.2002

1.10.1 RECOMMENDATIONS/PRECAUTIONARY MEASURES

1.10.2 EMERGENCY MEASURES

1.11 PACKAGING

1.12 POSSIB. OF RENDERING SUBST. HARMLESS

1.13 STATEMENTS CONCERNING WASTE

1.14.1 WATER POLLUTION

1.14.2 MAJOR ACCIDENT HAZARDS

1.14.3 AIR POLLUTION

1.15 ADDITIONAL REMARKS

1.16 LAST LITERATURE SEARCH

1.17 REVIEWS

1.18 LISTINGS E.G. CHEMICAL INVENTORIES

2.1 MELTING POINT

Value : = 111.7 ° C
Sublimation :
Method : other : measured
Year :
GLP : no data
Test substance : other TS: Mitsubishi Gas Chemical Co., Inc.; Purity>=97%
Source : Mitsubishi Gas Chemical Co., Inc.
Reliability : (2) valid with restriction
Flag : Critical study for SIDS endpoint
10.05.2002 (18)

Value : = 111 - 113 ° C
Sublimation :
Method : other
Year :
GLP : no data
Test substance :
Source : Merk Index
Reliability : (2) valid with restriction
05.02.2003 (2)

Value : = 108.7 ° C
Sublimation :
Method : other: measured
Year :
GLP : no data
Test substance :
Source : SRC PhysProp Database
Reliability : (2) valid with restriction
10.05.2002 (25)

Value : = 63.43 ° C
Sublimation :
Method : other: estimated
Year :
GLP : no data
Test substance :
Source : MPBPWIN version 1.40
Reliability : (2) valid with restriction
05.02.2003 (7)

2.2 BOILING POINT

Value : = 263 ° C at 1013.08 hPa
Decomposition :
Method : other
Year :
GLP : no data
Test substance : other TS: Mitsubishi Gas Chemical Co., Inc.; Purity>=97%
Source : Mitsubishi Gas Chemical Co., Inc.
Reliability : (2) valid with restriction
Flag : Critical study for SIDS endpoint
10.05.2002 (18)

Value : = 263 ° C

Decomposition :
Method :
Year :
GLP : no data
Test substance :
Source : Merk Index
Reliability : (2) valid with restriction
05.02.2003 (2)

Value : = 266.57 ° C
Decomposition :
Method : other: estimated
Year :
GLP : no data
Test substance :
Source : MPBPWIN version 1.40
Reliability : (2) valid with restriction
05.02.2003 (7)

2.3 DENSITY

Type : density
Value : = 1.054 g/cm3 at 112° C
Method : other : measured
Year :
GLP : no data
Test substance : other TS: Mitsubishi Gas Chemical Co., Inc.; Purity>=97%
Source : Mitsubishi Gas Chemical Co., Inc.
Reliability : (2) valid with restriction
Flag : Critical study for SIDS endpoint
10.05.2002 (18)

Type : density
Value : = 0.996 g/cm3 at 4 and 20° C
Method : other
Year :
GLP : no data
Source : Merk Index
Reliability : (2) valid with restriction
Flag : Critical study for SIDS endpoint
05.02.2003 (2)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : = .00019 hPa at 25° C
Decomposition :
Method OECD Guide-line 104 "Vapour Pressure Curve", measured
Year : 1999
GLP :
Test substance : other TS: Wako Pure Chemical Industries,Ltd., Purity; 99.1%
Source : CITI, Japan(1999)
Reliability : (2) valid with restriction
Flag : Critical study for SIDS endpoint

10.05.2002 (4)

Value : = .0002364 mmHg at 25° C
Decomposition :
Method : other (calculated)
Year :
GLP : no data
Test substance :
Source : SRC PhysProp Database
10.05.2002 (5)

Value : = 10.66 hPa at 140° C
Decomposition :
Method
Year :
GLP :
Test substance : other TS: Mitsubishi Gas Chemical Co., Inc.; Purity>=97%
Source : Mitsubishi Gas Chemical Co., Inc.
10.05.2002 (18)

Value : = 94.64 hPa at 200° C
Decomposition :
Method
Year :
GLP :
Test substance : other TS: Mitsubishi Gas Chemical Co., Inc.; Purity>=97%
Source : Mitsubishi Gas Chemical Co., Inc.
10.05.2002 (18)

Value : = 0.00191 mm Hg at 25° C
Decomposition :
Method : other: estimated
Year :
GLP : no data
Test substance :
Source : MPBPWIN version 1.40
05.02.2003 (7)

2.5 PARTITION COEFFICIENT

Log pow : = 2.37 at 25 ° C
Source : SRC PhysProp Database, measured
Reliability : (2) valid with restriction
Flag : Critical study for SIDS endpoint
10.05.2002 (9)

Log pow : = 2.42
Source : KOWWIN version 1.66 , estimated
05.02.2003 (7)

2.6.1 WATER SOLUBILITY

Value : = 1000 mg/l at 25 ° C
Qualitative :
Pka : 4.272 at 25 ° C
PH : at and ° C
Method : OECD Guide-line 105 "Water Solubility", measured
Year : 1999

GLP :
Test substance :
Source : CITI, Japan(1999)
Reliability : (2) valid with restriction
Flag : Critical study for SIDS endpoint
10.05.2002 (4)

Value : = 980 mg/l at 25 ° C
Qualitative :
Pka : 4.27 at 25 ° C
PH : at and ° C
Method : other: calculated
Year :
GLP :
Test substance :
Source : SRC PhysProp Database
10.05.2002 (11) (26)

Value : = 980 mg/l at 25 ° C
Qualitative :
Pka : at 25 ° C
PH : at and ° C
Method :
Year :
GLP :
Test substance : other TS: Mitsubishi Gas Chemical Co., Inc.; Purity>=97%
Source : Mitsubishi Gas Chemical Co., Inc.
10.05.2002 (18)

Value : = 19800 mg/l at 100 ° C
Qualitative :
Pka : at 25 ° C
PH : at and ° C
Method :
Year :
GLP :
Test substance : other TS: Mitsubishi Gas Chemical Co., Inc.; Purity>=97%
Source : Mitsubishi Gas Chemical Co., Inc.
10.05.2002 (18)

Value : = 1678 mg/l at 25 ° C
Qualitative :
Pka :
PH :
Method : other: estimated
Year :
GLP :
Test substance :
Source : WSKOW version 1.40
05.02.2003 (7)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Value : = 147 ° C
Type : open cup
Source : Mitsubishi Gas Chemical Co., Inc.

Reliability : (2) valid with restriction
Flag : Critical study for SIDS endpoint
10.05.2002 (18)

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 ADDITIONAL REMARKS

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 E6 molecule/cm3
Rate constant	:	= 2.045 E-12 cm3/(molecule*sec)
Degradation	:	= 50 % after 63 hour(s)
Source	:	AOPWINNT v 1.90
Flag	:	Critical study for SIDS endpoint

10.05.2002 (7)

3.1.2 STABILITY IN WATER

Type	:	abiotic
t1/2 pH4	:	> 5 days at 50 degree C
t1/2 pH7	:	> 5 days at 50 degree C
t1/2 pH9	:	> 5 days at 50 degree C
Deg. Product	:	
Method	:	OECD Guide-line 111 "Hydrolysis as a Function of pH"
Year	:	1999
GLP	:	yes
Test substance	:	other TS: Wako Pure Chemical Industries,Ltd., Purity=99.1%
Method	:	-Preliminary Test a) Water Temperature: 50ºC b) Nominal Concentration: ca. 100 mg/L c) pH: pH4, 7 and 9 d) Number of Replicates: 2 e) Test Period: 5 days f) Exposure Vessel Type: Glass Vial
Result	:	As a result of the preliminary test, this chemical was not hydrolyzed in 5 days on condition of 50ºC, pH 4, 7 and 9.
Source	:	CITI, Japan(1999)
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

13.05.2002 (4)

3.1.3 STABILITY IN SOIL

3.2 MONITORING DATA

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

3.3.2 DISTRIBUTION

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

Year : 2002
Method : Distributions were calculated with following factors.

m-Toluic acid
Molecular Weight: 136.15
Melting Point [C]: 111.7
Vapor Pressure [Pa]: 0.019
Water Solubility [g/m3]: 1,000
log Kow: 2.37
half life [h] in air: 63
in water: 360
in soil: 360
in sediment: 1,080
Temp. [ºC]: 25

Result : The potential environmental distribution of MTA obtained from generic level III fugacity model under three emission scenarios is shown in table. The results show that if MTA is released into water, 99.2% stays in water and 0.8% is transported to sediment. When MTA is released to air, 82.2% is transported in soil and 15.6% is transported to water. If MTA is released to soil, 98.3% stays in soil.

Compartment	Amount %		
	Release 100% to air	Release 100% to water	Release 100% to soil
Air	2.1%	0.0%	0.0%
Water	15.6%	99.2%	1.7%
Soil	82.2%	0.0%	98.3%
Sediment	0.1%	0.8%	0.0%

Flag : Critical study for SIDS endpoint
13.05.2002

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic
Inoculum : predominantly domestic sewage, non-adapted
Concentration : 100 mg/l related to Test substance
related to
Contact time :
Degradation : = 91 % after 28 day
= 75 % after 14 day
= 70 % after 7 day
Result : readily biodegradable
Deg. Product :
Method : OECD Guide-line 301 C "Ready Biodegradability: Modified MITI Test (I)"
Year : 1998
GLP : yes
Test substance : other TS: Wako Pure Chemical Industries,Ltd., Lot. No.; WTJ0974, Purity=99.1%
Test condition : Inoculum added: 30 mg/l; BOD measurementThe inoculum was a mixture of activated sewage whose source was collected from ten different sites in Japan (4 city sewage plant, 3 river water samples, 1 lake water sample and 2 bay water samples). Test temperature: 25±1ºC Test period: 28 days

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
10.05.2002 (3)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	Semistatic
Species	:	Oryzias latipes (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	Yes
LC0	:	= 68
LC50	:	= 82
LC100	:	= 100
Method	:	OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year	:	1998
GLP	:	Yes
Test substance	:	other TS: Wako Pure Chemical Industries, Ltd., Lot. No.; PAJ0644, Purity = 99.9 %
Method	:	-Test Organisms: a) Supplier: Test organisms(Lot. No.; F039811) were obtained from Takizawa Yougyo-jo (Private Fish Farm, Japan). b) Size (length and weight): 2.2 cm (2.0 - 2.4 cm) in length; 0.14 g (0.11 - 0.20 g) in weight c) Age: Not described d) Any pretreatment: Acclimated for at least 7 days before testing, any groups showing > 5 % mortality were not used for testing. During acclimation, test fishes were fed withTETRAMIN. These test organisms were not fed for 24hours before the test started. -Test substance: m-Toluic Acid a) Empirical Formula: C8H8O2 b) Molecular Weight: 136.15 c) Purity: 99.9 % -Test Conditions: a) Dilution Water Source: Dechlorinated tap water b) Dilution Water Chemistry: pH: = 7.8 Total hardness (as CaCO3): = 44 mg/L c) Exposure Vessel Type: 3 L test solution in a 5 L Glass Tank d) Nominal Concentrations: control, 22, 32, 46, 68 and 100 mg/L e) Vehicle/Solvent and Concentrations: No solvent was used. f) Number of Replicates: 1 g) Fish per Replicates: 10 h) Renewal Rate of Test Water: Every 48 hours i) Water Temperature: 24±1ºC j) Light Condition: 16:8 hours, light-darkness cycle k) Feeding: None l) Aeration : None -Analytical Procedure: The tested concentrations were measured at start and just before renewal of test water. -Statistical Method: Binomial a) Data Analysis: Binominal method for LC50 b) Method of Calculating Mean Measured Concentrations (i.e. arithmetic mean, geometric mean, etc.): Arithmetic mean or Time-weighted mean
Result	:	- The test concentrations were measured at the start and the 48th hour.All the error ranges of measured concentration were suited to less than±20% of nominal concentration.

Nominal Conc. mg/L	Measured Conc., mg/L: 0 Hour Fresh	48 Hours Old	Mean mg/L	Percent of Nominal: 0 Hour Fresh	48 Hours Old
Control	<0.05	<0.05	---	---	---
22	22.6	22.6	22.6a	103	103
32	32.7	32.0	32.3 t	102	100
46	45.6	46.3	46.0a	99	101
68	71.4	70.7	71.0 t	105	104
100	105	104d	104 t	105	104d

a: Arithmetic Mean
t: Time-Weighted Mean
d: Test Solutions after 3 hours because all Oryzias latipes were dead at this period.
Fresh: Start of renewal period
Old: End of renewal period

- Water chemistry (pH and DO) and temperature in test:
Water chemistry and temperature were measured for control and each concentration at the start of test and every 24 hours. Almost all pH was between 6 - 8. In the tank of 100mg/L, pH was 4.7.
pH: 4.7 - 7.6
DO: 6.2 - 9.4 mg/L
Water Temperature: 23.5 - 24.2ºC

pH

Hours	Nominal Conc. (mg/L) Control	22	32	46	68	100
0 Fresh	7.6	7.0	6.8	6.5	5.8	4.7
24	7.3	7.0	6.9	6.7	6.1	4.7d)
48 Old	7.5	7.2	7.1	7.0	6.7	-----a)
48 Fresh	7.6	6.9	6.7	6.3	5.6	-----a)
72	7.4	7.2	7.1	7.0	6.5	-----a)
96 Old	7.4	7.5	7.4	7.4	6.9	-----a)

Fresh: start of renewal period, Old: End of renewal period
a): No measurement was made because every fish was dead at this period.
d): Test solutions after 3 hours because every fish was dead at this period.
-Effect Data(mortality):
LC50 (96hr) = 82mg/L (nc)
LC0 (96hr) = 68mg/L (nc)
LC100 (96hr) = 100mg/L (nc)
nc: based on nominal concentration

- Cumulative Mortality: None of test organisms were killed during exposure period at control, 22, 32, 46 and 68 mg/L, however all test organisms were killed at 100mg/L on and after 24 hours.

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

Control	0 (0)	0 (0)	0 (0)	0 (0)
22	0 (0)	0 (0)	0 (0)	0 (0)
32	0 (0)	0 (0)	0 (0)	0 (0)
46	0 (0)	0 (0)	0 (0)	0 (0)
68	0 (0)	0 (0)	0 (0)	0 (0)
100	10 (100)	10 (100)	10(100)	10(100)

-Other Effect:Toxicological symptom was first observed at 100 mg/L (24 hr)

Nominal Conc. mg/L	Symptoms 24hr	48hr	72hr	96hr
Control	n	n	n	n
22	n	n	n	n
32	n	n	n	n
46	n	n	n	n
68	n	n	n	n
100	---a	---a	---a	---a

n: No abnormalities are detected
a: No observation was made because all Oryzias latipes were dead at this period.

- Calculation of toxic values: Calculated based on nominal concentration (actual concentration measured and greater than 80% of the nominal).

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
16.07.2002 (19)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type : Static
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
Analytical monitoring : Yes
NOEC : = 56
EC50 : = 75
Method : OECD Guide-line 202, part 1 "Daphnia sp., Acute Immobilisation Test"
Year : 1998
GLP : Yes
Test substance : other TS: Wako Pure Chemical Industries, Ltd., Lot. No.; PAJ0644, Purity= 99.9 %
Method : - Test Organisms:
a) Age: < 24 hours old
b) Supplier/Source: Test organisms were obtained from National Institute for Environmental Studies (JAPAN).
-Test substance: m-Toluic Acid
a) Empirical Formula: C8H8O2
b) Molecular Weight: 136.15
c) Purity: 99.9 %

- Test Conditions:
a) Dilution Water Source: Dechlorinated tap water
b) Dilution Water Chemistry: pH: = 7.8
Total hardness (as CaCO3): = 72 mg/L

c) Exposure Vessel Type: 100 mL test solution in a 270 mLGlass Beaker with glass cap
d) Nominal Concentrations: control , 10, 18, 32, 56, 100, 180 and 320 mg/L
e) Vehicle/Solvent and Concentrations: No solvent was used.
f) Number of Replicates: 4
g) Individuals per Replicates: 5
h) Water Temperature: 20±1ºC
i) Light Condition: 16:8 hours, light-darkness cycle
j) Feeding: None

- Analytical Procedure: Test concentrations were measured at the start and the 48th hour.

- Statistical Method:a) Data Analysis: Binomial method for LC50b) Method of Calculating Mean Measured Concentrations:
Time-Weighted Mean or Arithmetic Mean

Result : - Measured Concentrations : The test concentrations were measured at the start and the 48th hour.All the error ranges of measured concentration were suited to less than±20% of nominal concentration.

Nominal Conc. mg/L	Measured Conc., mg/L		Mean	Percent of Nominal	
	0 Hour	48 Hour	mg/L	0 Hour	48 Hour
Control	<0.05	<0.05	---	---	---
10	11.9	11.6	11.7t	119	116
18	21.0	20.7	20.8t	117	115
32	26.5	26.5*	26.5a	83	83
56	58.6	59.6	59.1a	105	106
100	107	106	106t	107	106
180	188	178d	183t	104	99d
320	318	328d	323a	99	103d

a: Arithmetic Mean
t: Time-Weighted Mean
d: Test solusions after 24 hours because all Daphnia magna were dead at this period.

- Water chemistry (pH and DO) and temperature in test:
Water chemistry and temperature were measured for control and each concentration at the start and end of test. In control, 10, 18, 32 and 56mg/L, the pH was between 6.7 -7.8. In 100, 180 and 320mg/L, the pH was between 3.9 - 6.3.
pH: 3.9 - 7.8
DO: 8.6 - 9.5 mg/L
Water Temperature: 19.6 - 20.9ºC

Nominal Concentartion (mg/L)	pH 0 Hour Fresh	pH 48 Hours Old
Control	7.8	7.7
10	7.3	7.7
18	7.1	7.7
32	7.0	7.6
56	6.7	7.5
100	5.4	6.3
180	4.4	4.4d)

320 4.0 3.9d)

Fresh: start of test, Old: End of test
d): Test solutions after 24 hours because every Daphnia magna was dead at this period.

-Effect Data:
EC50 (48hr) = 75 mg/L (nc)
EC100 (48hr) = 100 mg/L (nc)
EC0 (48hr) = 56 mg/L (nc)
nc: based on nominal concentration

-
- Mortality or Immobility: No test organism was affected at control, 10, 18, 32 and 56mg/L. All test organisms were afected at 100, 180 and 320mg/L on and after 24th hour.

Nominal Conc.	Cumulative Number of Dead or Immobilized Daphnids (Percent Mortality or Immobility)	
mg/L	24Hour	48 Hour
Control	0 (0)	0 (0)
10	0 (0)	0 (0)
18	0 (0)	0 (0)
32	0 (0)	0 (0)
56	0 (0)	0 (0)
100	20 (100)	20 (100)
180	20 (100)	20 (100)
320	20 (100)	20 (100)

- Calculation of toxic values: Calculated based on nominal concentration (actual concentration measured and greater than 80% of the nominal).

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
16.07.2002 (19)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species : Selenastrum capricornutum (Algae)
Endpoint : biomass
Exposure period : 72 hour(s)
Unit : mg/l
Analytical monitoring : Yes
NOEC : = 2.2 (0-72 hr, biomass), 10 (24-72 hr, growth rate)
EC50 : = 10 (0-72 hr, biomass), 15 (24- 47 hr, growth rate)
Method : OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year : 1998
GLP : Yes
Test substance : other TS: Wako Pure Chemical Industries, Ltd., Lot. No.; PAJ0644, Purity=99.9 %
Method : - Test Organisms:
a) Supplier/Source: Obtained from American Type Culture Collection
b) Method of Cultivation: Sterile
c) Strain Number: ATCC22622

-Test substance: m-Toluic Acid
a) Empirical Formula: C8H8O2
b) Molecular Weight: 136.15
c) Purity: 99.9 %

- Test Conditions:
a) Medium: OECD medium
b) Exposure Vessel Type: 100 mL Medium in an Erlenmeyer flask
c) Nominal Concentrations: control, 1.0, 2.2, 4.6, 10, 22, 46 and 100mg/L
d) Vehicle/Solvent and Concentrations: No solvent was used.
e) Stock Solutions Preparations and Stability: Not described.
f) Number of Replicates: 3
g) Initial Cell Concentration: 10,000 cells/mL
h) Water Temperature: 23±2ºC
i) Light Condition: 4,000 - 5,000 lux, continuously
j)Shaking: 100 rpm

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

- Statistical Method:
a) Data Analysis: regression analysis for EC50
Dunnett multiple comparison
b) Method of Calculating Mean Measured Concentrations (i.e. arithmetic mean, geometric mean, etc.): Time-weighted Mean

Remark : NOEC was determined based on growth inhibition.

Result : - Calculated based on nominal concentration (actual concentration measured and greater than 80% and less than 120 % of the nominal)

Nominal conc. mg/L	Measured Conc., mg/L 0 Hour	72 Hour	Mean mg/L	Percent of nominal 0 Hour	72 Hour
Control	<0.05	<0.05			
1.0	1.13	1.08	1.10	113	108
2.2	2.53	2.41	2.47	115	110
4.6	5.33	5.01	5.17	116	109
10	11.3	10.8	11.0	113	108
22	25.2	23.9	24.5	115	109
46	52.3	47.8	50.0	114	104
100	114	105	109	114	105

Mean: Time-weighted Mean

- Water chemistry (pH) in test: pH was measured for control and each concentration at the start and end of test. In control and exposure except 100mg/L, at the strat and end of test, the pH was 7.3 - 8.0 and 7.5 - 10.4, respectively. In high concentration, i.e., 100mg/L, at the start and end of test, the pH was 6.4 and 6.7, respectively.

Nominal Concentartion (mg/L)	pH 0 Hour	72 Hours
Control	7.9	9.9
1.0	8.0	10.4
2.2	7.9	10.3
4.6	7.9	9.8
10	7.8	9.3
22	7.6	7.8

46	7.3	7.5
100	6.4	6.7

-Effect Data:
Area Method (Biomass)
EbC50(0-72hr) =10 mg/L (95% C. I.: 8.4 - 12 mg/L) (nc)
NOEC = 2.2 mg/L (nc)

Rate Method (Growth rate)
ErC50(24-48hr) = 15 mg/L (95% C. I.: 13 - 18 mg/L) (nc)
NOEC : Not estimeted
ErC50(24-72hr) = 18 mg/L (95% C. I.: 15 - 21 mg/L) (nc)
NOEC = 10 mg/L (nc)
nc: based on nominal concentration

-
- Percent Growth Inhibition of Selenastrum capricornutum

Nominal Conc. mg/L	Area under the growth curves (Average) Area A (0-72hr)	Inhibition (%)*1 IA (0-72hr)
Control	13,459,200	---
1.0	14,202,000	-5.52
2.2	12,980,800	3.55
4.6	11,004,000	18.24*
10	8,309,600	38.26*
22	861,600	93.60*
46	278,000	97.93*
100	32,000	99.76*

* Indicates a significant difference from the control.

Growth rates and percent inhibition (Average)

Nominal Conc. mg/L	Rate u(24-48hr)	Inhibition(%) Im(24-48hr)	Rate u(24-72hr)	Inhibition(%) Im(24-72hr)
Control	0.075408	---	0.062407	---
1.0	0.069116	8.34	0.056821	8.95
2.2	0.070408	6.63	0.059278	5.01
4.6	0.060089	20.31*	0.058183	6.77
10	0.057121	24.25*	0.058177	6.78
22	0.016646	77.92*	0.014564	76.66*
46	0.003825	94.93*	0.001659	97.34*
100	0.003055	95.95*	0.003452	94.47*

* Indicates a significant difference from the control.

- Growth Curves: Log phase during the test period
- Calculation of toxic value: Calculated based on nominal concentration (actual concentration measured and greater than 80% of the nominal).

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
16.07.2002 (19)

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
Unit	:	mg/l
Analytical monitoring	:	Yes
NOEC	:	= 9.7
LCEC	:	= 22
Method	:	OECD Guide-line 202, part 2 "Daphnia sp., Reproduction Test"
Year	:	1998
GLP	:	Yes
Test substance	:	other TS: Wako Pure Chemical Industries, Ltd., Lot. No.; PAJ0644, Purity=99.9 %
Method	:	-Test Organisms: a) Age: < 24 hours old b) Supplier/Source: Test organisms were obtained from National Institute for Environmental Studies (JAPAN). -Test substance: m-Toluic Acid a) Empirical Formula: C8H8O2 b) Molecular Weight: 136.15 c) Purity: 99.9 % - Test Conditions: a) Dilution Water Source: : Dechlorinated tap water b) Dilution Water Chemistry: pH: = 7.6 - 8.2 Total hardness (as CaCO3): = 87 - 88 mg/L c) Exposure Vessel Type: 80 mL test solution in a 100 mL glass jar with glass screw cap d) Nominal Concentrations: control, 1.0, 2.2, 4.6, 10, 22 and 46 mg/L e) Vehicle/Solvent and Concentrations: No solvent was used. f) Stock Solutions Preparations and Stability: Not described. g) Number of Replicates: 1 h) Individuals per Replicates: 10 i) Renewal Rate of Test Water: Every 48 hours j) Water Temperature: 20±1° C k) Light Condition: 16:8 hours, light-darkness l) Feeding: 0.15 mg carbon/day/individual (Chlorella vulgaris: Green Algae) - Analytical Procedure: The test concentrations were measured for both renewal and old test solution at the start of test and 2nd, 6th 8th, 14th and 16th day. - Statistical Method: a) Data Analysis: Dunnett multiple comparison for NOEC and LOEC b) Method of Calculating Mean Measured Concentrations (i.e. arithmetic mean, geometric mean, etc.): Arithmetic Mean or Time-weighted Mean
Remark	:	NOEC or LOEC was determined based on the cumulative number of juveniles produced per adult alive for 21 days. 1.0 and 2.2 mg/L indicate a significant difference from the control by Dunnet type multiple comparisons procedure, one-side test. However these results were judged that there was nothing under the influence by this substance because no significant

difference at 4.6 and 10 mg/L.

Result : - Effect: reproduction
- Measured Concentrations : Calculated based on measured concentrations, because some of the measured concentration were less than 80% of the nominal.

Nominal Conc. mg/L	Measured Conc., mg/L 0 day Fresh	2 days Old	Mean mg/L	Percent of nominal Mean 0 day Fresh	2 days Old
Control	<0.05	<0.05	---	---	---
1.0	0.967	1.01	0.993a	98	101
2.2	2.24	2.24	2.24a	102	102
4.6	4.63	4.59	4.61t	101	100
10	10.0	10.2	10.1a	100	102
22	21.8	22.2	22.0a	99	101
46	45.6	45.4	45.5	99	99

Nominal Conc. mg/L	Measured Conc., mg/L 6 days Fresh	8 days Old	Mean mg/L	Percent of nominal Mean 6 days Fresh	8 days Old
Control	<0.05	<0.05	---	---	---
1.0	1.01	0.115	0.412	101	12
2.2	2.25	1.49	1.84	102	68
4.6	4.65	4.19	4.42	101	91
10	9.86	9.99	9.93a	99	100
22	21.8	22.1	22.0a	99	100
46	45.0	46.6	45.8a	98	101

Nominal Conc. mg/L	Measured Conc., mg/L 14 days Fresh	16 days Old	Mean mg/L	Percent of nominal Mean 14 days Fresh	16 days Old
Control	<0.05	<0.05	---	---	---
1.0	1.04	<0.05	0.222	104	---
2.2	2.28	<0.05	0.418	104	---
4.6	4.76	2.24	3.34	103	49
10	10.2	8.24	9.19	102	82
22	22.4	22.3	22.3	102	101
46	46.4	46.2	46.3	101	100

a: Arithmetic Mean
t: Time-Weighted Mean
Fresh: Start of renewal period
Old: End of renewal period

- Water chemistry (pH and DO) and temperature in test:
Water chemistry and temperature were measured for control and each concentration at the start of test and before and after renewal of the test solusions.
pH: 6.8 - 8.5
DO: 7.6 - 9.7 mg/L
Water Temperature: 19.2 - 20.8ºC

pH

Days	Nominal Conc. (mg/L)	Control	1.0	2.2	4.6	10	22	46
0	Fresh	7.9	8.0	7.9	7.8	7.5	7.2	6.8
2	Old	8.5	8.5	8.5	8.5	8.5	8.4	8.3
2	Fresh	8.0	8.0	7.9	7.8	7.7	7.4	6.9
4	Old	8.2	8.4	8.3	8.4	8.4	8.4	8.3
4	Fresh	7.9	8.0	7.9	7.8	7.6	7.4	7.1
6	Old	8.3	8.3	8.3	8.3	8.3	8.2	8.2
6	Fresh	7.9	8.0	7.9	7.8	7.6	7.3	7.0
8	Old	8.2	8.0	8.0	8.0	8.0	8.0	8.1
8	Fresh	7.9	8.0	7.9	7.8	7.6	7.4	7.0
10	Old	7.9	7.9	7.9	7.8	7.8	7.8	8.0
10	Fresh	7.8	7.9	7.8	7.7	7.5	7.2	6.9
12	Old	7.9	7.8	7.8	7.8	7.8	7.8	7.9
12	Fresh	7.9	7.9	7.8	7.7	7.5	7.2	6.9
14	Old	7.9	7.8	7.7	7.6	7.6	7.7	7.7
14	Fresh	7.9	7.9	7.8	7.7	7.6	7.3	7.0
16	Old	7.8	7.7	7.7	7.6	7.6	7.6	7.6
16	Fresh	7.9	7.9	7.8	7.7	7.5	7.3	6.9
18	Old	7.9	7.9	7.8	7.6	7.6	7.7	7.8
18	Fresh	7.9	7.9	7.8	7.8	7.5	7.2	6.9
20	Old	7.9	7.9	7.8	7.6	7.5	7.6	7.7
18	Fresh	7.9	7.9	7.9	7.8	7.6	7.3	7.0
21	Old	7.9	7.9	7.8	7.8	7.8	7.7	7.7

Fesh: start of renewal period, Old: End of renewal period

- Total hardness: 87 - 88 mg/L

-Effect Data:
NOEC (21day) = 9.7 mg/L (mc)
LOEC (21day) = 22 mg/L (mc)
LC50 (21 days) >=46 mg/L (mc)
EC50 (21 days) = 15 mg/L (mc)
mc: based on measured concentration

- Cumulative Number of Died Parental Daphnids: No test organism was killed at control and all concentrations.

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

1.0	0	0	0	0	0	0	0	0	0	0
2.2	0	0	0	0	0	0	0	0	0	0
4.6	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0	0

Nominal Conc. (mg/L)	Cumulative Number of Died Parental daphnids (days)										
	11	12	13	14	15	16	17	18	19	20	21
Control	0	0	0	0	0	0	0	0	0	0	0
1.0	0	0	0	0	0	0	0	0	0	0	0
2.2	0	0	0	0	0	0	0	0	0	0	0
4.6	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0	0	0

-

-Effect Data(reproduction):

Juveniles were first produced on the 8th day in control and all concentrations. At 46 mg/L, no juvenile was produced.

Nominal Conc. (mg/L)	Measured Conc. (mg/L)	Mean Cumulative Numbers of Juveniles Produced per Adult (days) 0 --- 7	8	9	10	11	12	13
Control	---	0 --- 0	3.6	5.1	5.1	20.8	27.7	27.7
1.0	0.542	0 --- 0	3.3	5.5	5.5	21.2	29.0	29.0
2.2	1.50	0 --- 0	3.7	5.5	5.5	20.3	28.7	28.7
4.6	4.12	0 --- 0	4.3	6.1	6.1	27.7	33.0	33.0
10	9.74	0 --- 0	6.4	8.1	8.1	30.0	35.3	35.3
22	22.1	0 --- 0	3.5	4.2	4.2	4.3	4.3	4.3
46	45.9	0 --- 0	0	0	0	0	0	0

Nominal Conc. (mg/L)	Mean Cumulative Numbers of Juveniles Produced per Adult (days) 14	15	16	17	18	19	20	21
Control	42.8	59.1	59.1	75.7	90.3	90.3	95.9	114.3
1.0	50.1	60.1	60.1	77.7	85.0	85.0	89.8	106.6
2.2	50.2	60.7	60.7	75.9	87.8	87.8	96.0	107.3
4.6	54.9	65.9	65.9	83.9	90.1	90.1	98.8	111.6
10	62.0	66.6	66.6	88.9	95.3	95.3	105.7	112.4
22	4.3	4.3	4.3	4.3	4.3	4.3	4.3	4.3
46	0	0	0	0	0	0	0	0

-Cumulative

numbers of juveniles produced per adult alive for 21 days

Nominal Conc., mg/L (Measured Conc., mg/L)

Vessel No.	Cont.	1.0 (0.542)	2.2 (1.50)	4.6 (4.12)	10 (9.74)	22 (22.1)	46 (45.9)
1	121	122	117	109	122	3	0
2	103	98	100	115	103	8	0
3	110	105	118	111	117	3	0
4	110	94	103	112	110	5	0
5	114	111	100	114	98	6	0
6	129	110	106	113	115	7	0
7	116	104	120	108	120	3	0
8	116	106	102	107	113	4	0
9	106	112	96	113	119	2	0
10	118	104	108	114	107	2	0
Mean	114.3	106.6	107.0	111.6	112.4	4.3	0.0
S. D.	7.6	7.8	8.5	2.8	7.8	2.1	0.0
Inhibition rate(%)	---	6.7	6.4	2.4	1.7	96.2	100
Significant difference*1	---	*	*	NS	NS	**	---

*1: Indicates a significant difference from the control by Dunnet type multiple comparisons procedure, one-side test.
*: Significant ($p<0.05$)
**: Significant ($p<0.01$)
NS: Not significant ($p>=0.05$)

- Calculation of toxic values: Calculated based on measured concentrations, because some of the measured concentration were less than 80% of the nominal.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
16.07.2002 (19)

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

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Species	:	rat
Strain	:	Crj: CD(SD)
Sex	:	male/female
Number of animals	:	5/5
Vehicle	:	other: 1 % methylcellulose solution in water
Value	:	> 2000 mg/kg bw
Method	:	OECD Guide-line 401 "Acute Oral Toxicity"
Year	:	1999
GLP	:	yes
Test substance	:	other TS: Purity 98.79%
Remark	:	As the compound was found to be weak toxic by a preliminary test, the doses of 1000, and 2000 mg/kg were chosen for the challenge test.
Result	:	A single oral toxicity test revealed an LD50 value of above 2000 mg/kg for this chemical in both sexes. No animal died in any of the groups. No effects of the compound were found on clinical signs, body weight gain and macroscopical findings in any treated animal by autopsy.
Source	:	MHW: Japan, 1999
Test condition	:	Doses: 0 (vehicle), 1000 and 2000 mg/kg Vehicle: 1% methylcellulose solution Post dose observation: 14 days Number of animals: 5 males / 5 females per dose group
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

01.11.2002 (12)

Type	:	LD50
Species	:	rat
Strain	:	
Sex	:	male/female
Number of animals	:	10/10
Vehicle	:	other: 1 % Tween 80 water solution
Method	:	other: no data
Year	:	1974
GLP	:	no data
Test substance	:	other TS: purity : 97.2 - 97.5 %
Result	:	Value: male = 4446 mg/kg bw (3947 - 4993 mg/kg, p = 0.05) female = 4699 mg/kg bw (3837 - 5754 mg/kg, p = 0.05)

[Summary of test results]
LD50 values were determined by Probit method based on the data shown below.

<<< Numbers of animal died by dose and days >>>

Sex	Dose (mg/kg)	Days after administration Day 1	Day 2	Day 3-14	Final mortality
Males					
	2614	0	0	0	0/10
	3450	1	0	0	1/10
	4554	6	0	0	6/10

	6011	9	0	0	9/10
	7935	10	all died on day 1		10/10
	Control	0	0	0	0/10
Females					
	1136	0	0	0	0/10
	1500	0	0	0	0/10
	1980	0	0	0	0/10
	2614	1	0	0	1/10
	3450	1	0	0	1/10
	4554	3	0	0	3/10
	6011	7	1	0	8/10
	7935	10	all died on day 1		10/10
	Control	0	0	0	0/10

Source : Mitsubishi Gas Chemical Co., 1974
Test condition : Number of animals: 10 males / 10 females
Dose:
For males; vehicle, 2614, 3450, 4554, 6011 and 7935mg/kg
For females; vehicle, 1136, 1500, 1980, 2614, 3450,4554, 6011, and 7935 mg/kg
Administration:single dose
Test period:14 days
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
Flag : Material Safety Dataset
13.06.2002 (15)

Type : LD50
Species : rat
Strain :
Sex :
Number of animals :
Vehicle :
Value : = 7000 mg/kg bw
Method : other: not specified
Year : 1998
GLP : no data
Test substance : no data
Source : Mitsubishi Gas Chemical Co.,1998
Reliability : (3) invalid
01.11.2002 (13)

Type LD50
Species mouse
Strain
Sex
Number of animals
Vehicle
Value 1630
Method Other: not specified

Year		
GLP		
Test substance		
Source		NIOSH, Registory of Toxic Effects of Chemical Substances (1985 – 1986)
Reliability	:	(3) invalid
07.05.2002		(8)

5.1.2 ACUTE INHALATION TOXICITY

5.1.3 ACUTE DERMAL TOXICITY

5.1.4 ACUTE TOXICITY, OTHER ROUTES

Type	:	LC50
Species	:	mouse
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Route of admin.	:	i.p.
Exposure time	:	
Value	:	= 562 mg/kg bw
Method	:	other
Year	:	
GLP	:	
Test substance	:	
Remark	:	rigidity, muscle contraction or spasticity
Source	:	NIOSH, Registory of Toxic Effects of Chemical substances, (1985-1986)
Reliability	:	(3) invalid
13.06.2002		(20)

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	
Exposure	:	
Exposure time	:	24 hour(s)
Number of animals	:	6
PDII	:	.1
Result	:	not irritating
EC classification	:	
Method	:	Draize Test
Year	:	1992
GLP	:	no data
Test substance	:	Other TS: purity 98.87 %
Remark	:	As to skin irritation, erythema was observed at two animals out of six. At one animal, it was observed on the intact skin and the abraded skin. At the other animal, it was done on the only abraded skin. The erythema on the intact skin obseved at 24 hrs were disappeared at 48 hrs. No more abnormality was observed during 7 days observation. <<< P.I.I. of 3-Methylbenzoic Acid >>>

Items	Erythema		Edema		Rating*
observation time	24 hrs	72 hrs	24 hrs	72 hrs	
Rabbit No.					
1. int	0 a)	0 b)	0 e)	0 f)	
abr	0 c)	0 d)	0 g)	0 h)	0.00 A)
2. int	0	0	0	0	
abr	0	0	0	0	0.00 B)
3. int	0	0	0	0	
abr	1	0	0	0	0.25 C)
4. int	1	0	0	0	
abr	1	0	0	0	0.50 D)
5. int	0	0	0	0	
abr	0	0	0	0	0.00 E)
6. int	0	0	0	0	
abr	0	0	0	0	0.00 F)
P.I.I. **			0.1		

int: intact skin, abr: abraded skin
* Rating = a) + b) + c) + d) + e) + f) + g) +h) / 4
**P.I.I. = A) + B) + C) + D) + E) + F) / 6
rating: 0 No erythema, no edema
1 Light erythema, no edema
P.I.I. : < 2 Light irritation

The erythema on the intact skin observed at 24 hrs were disappeared at 48 hrs and no abnormalities were observed till the end of the observation period.

Source : Mitsubishi Gas Chemical Co., 1992
Reliability : (2) valid with restrictions
Flag : Material Safety Dataset
11.06.2002 (14)

5.2.2 EYE IRRITATION

Species :
Concentration :
Dose :
Exposure Time :
Comment :
Number of animals :
Result : irritating
EC classification :
Method :
Year : 1990
GLP : no data
Test substance : No data
Source : MSDS Service, 1990
Reliability : (3) invalid
01.11.2002 (10)

5.3 SENSITIZATION

Type : Skin sensitizing
Species : human
Number of animals : 25
Vehicle :
Result : ambiguous
Classification :
Method : other: modified Draize method
Year : 1973
GLP : no data
Test substance : other TS: > 99 %, Less than 1 % impurities are benzoic acid and acetophenone.
Remark : The sensitizing effect of m-toluic acid was not clear in this study. p-Toluic acid and o-toluic acid, however, were found to be potent allergic sensitizer when applied to human skin. Cross-sensitivity was found between all three isomers, p-toluic acid, m-toluic acid, and o-toluic acids. This cross-sensitivity is explicable in terms of carrier protein specificity rather than by the presence of a common chemical sequence in the hapten or by the conversion of the cross-reactants to an identical hapten.

Simultaneous,repeated applications of both p-toluic acid and o-toluic acid (both 50 % in polystyrene) were made on each of 10 experimental subjects. Five of the subjects became sensitized to both the p-toluic and the o-toluic acid preparations. In no case was a reaction observed to only one of the acids. In every case the reaction to p-toluic acid occurred before, and was either more severe or of the same severity as the reaction to o-toluic acid. Six weeks after the final challenge reactions were elicited, 4 of the 5 sensitized subjects (to p-toluic acid and o-toluic acid) were patch tested with p-toluic, o-toluic, and m-toluic acids (all three isomers) at concentrations of 50 % in polystyrene powder, 5 % in petrolatum, and 1 % in petrolatum. Results are shown in the table below. Reactions were observed in all 4 subjects to m-toluic acid, 50 % in polystyrene. This preparation did not produce irritation in 10 normal subjects. It was concluded that allergic sensitization to all 3 toluic acid isomers existed in the 4 experimental subjects.

<<< Patch testing with toluic acid isomers >>>

(m-Toluic Acid)

Concentration	50 % Powder		5 % Petrolatum		1 %Petrolatum	
Time (hrs)	48	96	48	96	48	96
Name of subjects #						
S.H.	++	++	+	++	-	-
R.W.	+	+	-	-	-	-
C.M.	++	++	+	++	-	-
P.C.	++	+	+	?+	-	-

(p- Toluic Acid)

Concentration	50 % Powder		5 % Petrolatum		1 %Petrolatum	
Time (hrs)	48	96	48	96	48	96
Name of subjects #						
S.H.	++	++	+++	++	++	++

R.W.	++	+	-	-	-	-
C.M.	++	+	++	++	-	-
P.C.	++	++	+++	++	++	++

(o- Toluic Acid)

Concentration	50 % Powder		5 % Petrolatum		1 %Petrolatum	
Time (hrs)	48	96	48	96	48	96
Name of subjects #						
S.H.	++	++	-	+	-	-
R.W.	++	+	-	-	-	-
C.M.	++	+	-	-	-	-
P.C.	++	+	?+	-	-	-

: Subjects (S.H., R.W., C.M., P.C.) are 4 persons who were sensitized with p-toluic acid and o-toluic acid, and reacted to p-toluic acid and o-toluic acid in the challenge test.

- : negative reaction
?+ : doubtful reaction
+ : weak (non-vesicular) reaction
++ : strong (edematous or vesicular) reaction
+++ : extreme reaction

Source : Emmett E. A. et al., 1973

Test condition : Test subjects: Human 14 males /11 females
Test substance: > 99 %. Less than 1 % impurities are benzoic acid and acetophenone (reported by the manufacturers).
Cross-contamination of one toluic acid sample with another was not analyzed, but the quantities involved must have been considerably less than 1 %. The toluic acids were pulverized before being mixed with either polystyrene or petrolatum. A small quantity of each test material was placed on the wetted (tap water) central gauze portion of a 1.5 inch sq. Band Aid.

Sensitization procedure: A modification of the method proposed by Draize. Occulsive patch on a non-hairy region of the upper back. Patches were applied to the same sites on Mondays, Wednesdays and Fridays for 3 weeks, a total of 9 applications. Patches were left in place for 24 hrs and then removed. Residual powder was removed.

Challenge applications: Challenge applications were performed on the Monday of the 6th week following the commencement of the sensitization procedure. Patches were applied to a previously untested area of the skin of the upper back. They were left in situ for 48 hr before removal. Reaction were graded a short time after removal and again at 96 and 144 hr after application.

Reliability : (2) valid with restrictions

Flag : Risk Assessment

01.11.2002 (6)

5.4 REPEATED DOSE TOXICITY

Species	:	rat
Sex	:	male/female
Strain	:	Crj: CD(SD)
Route of admin.	:	gavage
Exposure period	:	Males: 44 days from 14 days before mating Females: 41-45 days from 14 days before mating to day 3 of lactation
Frequency of treatment	:	once daily
Post obs. period	:	1 day
Doses	:	0 (vehicle), 30, 100, 300, and 1000 mg/kg/day
Control group	:	yes, concurrent vehicle
Method	:	OECD Guide-line 422, Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening test
Year	:	1999
GLP	:	yes
Test substance	:	Other TS: purity, 98.79%
Result	:	NOAEL male = 300 mg/kg/day NOAEL female = 100 mg/kg/day

The doses were decided by a preliminary test in which females of 1000mg/kg/day group showed a body weight gain suppression and a decrease of food consumption, and both of males and females showed a decrease of platelets counts at 1000mg/kg/day.

The major effects by sex and by dose are summarized below**.**

[Males]
1) Mortality, moribund sacrifice and clinical signs:
No death was observed for all animals and all doses.
At 1000 mg/kg/day, 4 males showed decreased locomotor activity after 16 days of administration.
At 300 mg/kg, the loss of fur (both arms and right arm) was observed in 2 animals. This was not considered to be related to the administration of the compound.

2) Body weight and food consumption: No changes were observed.

3) Urinalysis: No changes in all parameter were observed.

4) Hematology:
At 1000 mg/kg, a significant extension in the prothrombin time and a decrease in platelet counts were revealed.
Also at 1000 and 30 mg/kg, the increase of leucocytes were observed, but there was no dose dependency.

5) Blood chemistry:
At 1000 mg/kg, GOT value increased significantly. Sodium value, also, increased, but the increase was small.
At 300 mg/kg, alkaline phosphatase value increased significantly, but no change was observed at 1000 mg/kg.

<<< Hematological and blood biochemical findings of male rats >>>

Dose (mg/kg/day)	No. of animals	PT (Sec)	Plat (10000/uL)	GOT (IU/L)
0 (vehicle)	10	13.1 ± 0.5	134 ± 10	64 ± 5
30	10	13.1 ± 0.4	139 ± 12	64 ± 7
100	10	13.3 ± 0.6	137 ± 11	64 ± 9

300	10	13.4 ± 0.5	137 ± 17	65 ± 5
1000	10	14.3 ± 0.5**	119 ± 13*	77 ± 13**

Dose (mg/kg/day)	No. of animals	ALP (IU/L)	Na (mEq/L)	WBC (100/u)
0 (vehicle)	10	217 ± 29	144 ± 1	70 ± 24
30	10	205 ± 31	143 ± 1	94 ± 17**
100	10	223 ± 35	144 ± 1	85 ± 21
300	10	257 ± 33*	144 ± 1	81 ± 21
1000	10	248 ± 32	145 ± 1*	97 ± 24**

Each value is expressed as Mean ± S.D.
Significantly different from control: * : P<0.05, **: P<0.01

6) Necropsy: There were no findings related to the compound.

7) Organ weight:

At 1000 mg/kg/day, significant increase in the relative weight of pituitary was observed.

<<< Absolute and relative organ weights >>>

Dose mg/kg/day	No. of animal	Body weight (g)	Absolute organ weight Pituitary (mg)	Relative organ weight Pituitary (mg%)
0 (vehicle)	10	496 ± 28	13.3 ± 2.0	2.7 ± 0.4
30	10	510 ± 39	13.3 ± 1.8	2.6 ± 0.3
100	10	509 ± 35	13.5 ± 1.4	2.7 ± 0.3
300	10	508 ± 34	12.1 ± 1.6	2.4 ± 0.2
1000	10	474 ± 26	14.8 ± 2.2	3.1 ± 0.4*

Each value is expressed as Mean ± S.D.
Significantly different from control: * : P<0.05

8) Histopathology:
No findings related to the administration of the compound were observed. There were following findings those were not considered to be associated with the administration of the compound. All animals in the control group showed the PAS-stained hyaline droplet in proximal tubular epithelium, extramedullary hematopoiesis, and Berlin Blue-stained hemosidederin deposit.

At 1000 mg/kg, all animals showed the PAS-stained hyaline droplet in proximal tubular epithelium, extramedullary hematopoiesis, and Berlin Blue-stained hemosidederin deposit. The degree of changes was the same as control group.

2 animals showed the degeneration of the germ cells in testis, but it was focal and unilateral. 1 animal that failed to cause pregnancy showed the inflammation in prostate.

[Females]
1) Mortality, moribund sacrifice and clinical signs:
No death was observed for all animals at all doses.
No findings related to the administration of the compound were observed.
There were following clinical signs not associated with the administration of the compound:
At 1000 mg/kg, the loss of fur (both arms) was observed for in 1 animal.
The reddish tear was observed in 1 animal.
At 300 mg/kg, the scab formation and the loss of fur (right shoulder) were observed in 1 animal.
At 100 mg/kg, the loss of fur (both arms) was observed in 3 animals.
At 30 mg/kg, the loss of fur (both arms) was observed in 1 animal.

2) Body weight and food consumption:
Body weight: No changes associated with the administration of the compound were observed. The significant weight gain decrease was observed at 1000 mg/kg during 0 to 4th day of lactation. This, however, was due to the heavier body weight of animals than animals of the control group and the body weight at the 4th day of lactation did not show any difference from the control group.

Food consumption: No changes associated with the administration of the compound were observed.

3) Examination at necropsy. No changes associated with the administration of the compound were observed. Following symptoms not associated with the administration of the compound were observed. Redness or dark-reddish area in the lung was observed in 1 animal of control group.
Reddish spot/area in the thymus was observed in 1 animal.
At 300 mg/kg, redness or dark-reddish area in the lung was observed in one animal. Reddish spot/area in the thymus was observed in 1 animal.
At 100 mg/kg, reddish spot/area in the thymus was observed in 1 animal.
At 30 mg/kg, redness or dark-reddish area in the lung was observed in 1 animal. Prominence in the spleen was observed in 1 animal of control group. Retained placenta with hemorrhage in uterus, was observed in 1 animal who did not deliver after expected birth date.

4) Organ weight:
At 1000 mg/kg/day, significant increase in the absolute and relative weight of liver was observed.

<<< Absolute and relative organ weights >>>

Dose mg/kg/day	No. of animal	Body weight(g)	Absolute organ weight Liver (g)	Relative organ weight Liver (g%)
0 (vehicle)	9	362 ± 17	14.62 ± 1.26	4.04 ± 0.23
30	9	360 ± 22	14.45 ± 1.26	4.02 ± 0.29
100	9	356 ± 16	13.95 ± 1.21	3.92 ± 0.28
300	8	363 ± 15	15.22 ± 1.66	4.19 ± 0.45
1000	8	361 ± 20	17.55 ± 1.42**	4.85 ± 0.23**

Each value is expressed as Mean ± S.D.
Significantly different from control: **: P<0.01

5) Histopathology:
At 1000 mg/kg, 7 animals showed the periportal hepatocellular vacuolar degeneration in livers.
At 300 mg/kg, 3 animals showed the periportal hepatocellular vacuolar degeneration in livers.
These hepatocellular vacuolar degenerations were negative in sudan lll and did not show any signs of glycogen storage by PAS-stain test. The increase in numbers of animals with hepatocellular vacular degeneration at 1000 mg/kg was considered to be significant.

There were following findings which were not considered to be associated with the administration of the compound. All animals in the control group showed the PAS-stained hyaline droplet in proximal tubular epithelium, extramedullary hematopoiesis, and Berlin-Blue-Stained hemosiderin deposit.
At 1000 mg/kg, all animals showed the PAS-stained hyaline droplet in proximal tubular epithelium, extramedullary hematopoiesis, and Berlin - Blue-Stained hemosiderin deposit. The degree of changes was the same as control group. 1 animal that failed to cause pregnancy showed the endometritis.
At 30mg/kg, the hemorrhagic necrosis of placenta was obsereved in 1 animal who did not deliver after expected birth date and showed the retained placenta with hemorrhage in uterus.

<<< Histopathological findings of female rats >>>

[Liver]

Dose mg/kg/day		No of animal	Degeneration, vacuolar hepatocyte, periportal		Necrosis focal		Micrograuloma	
	Degree		-	+	-	+	-	+
0	TK	9	9	0	7	2	9	0
	NP	1	1	0	1	0	1	0
	(T)	(10)	(10)	(0)	(8)	(2)	(10)	(0)
30	TK	9	9	0	9	0	9	0
	ED	1	1	0	1	0	1	0
	(T)	(10)	(10)	(0)	(10)	(0)	(10)	(0)
100	TK	9	9	0	9	0	8	1
	NP	1	1	0	1	0	1	0
	(T)	(10)	(10)	(0)	(10)	(0)	(9)	(1)
300	TK	8	6	2	8	0	Ne	Ne
	NP	1	0	1	1	0	1	0
	UC	1	1	0	1	0	1	0
	(T)	(10)	(7)	(3)	(10)	(0)	(2)	(0)
1000	TK	8	2	6	7	1	8	0
	NP	1	0	1	1	0	1	0
	UC	1	1	0	1	0	1	0
	(T)	(10)	(3)	(7)**	(9)	(1)	(10)	(0)

** Significantly different from control. p <0.01
Degree: - : Negative, +: Slight

TK: Terminal kill
ED: Animal with embryonic death
NP: Not pregnant,
UC: Unsuccessful copulation
(T): Total, Ne: Not examined.

Note: The hematological examination and blood chemical examination were not conducted for females.

Source : MHW: Japan, 1999
Test condition : Number of animals/group: Males,10; females, 10
Preliminary test for the dose determination was conducted at the doses of 0, 80, 150, 300, 600, and 1000 mg/kg/day. At the 1000 mg/kg/day, adverse effects such as the suppression of body weight gain, the decrease in food consumption and the decrease of platelets were observed. Then the highest dose was set at 1000 mg/kg/day.

Terminal kill: Males, day 45; Females, day 4 of lactation
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
01.11.2002 (12)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Bacterial reverse mutation assay
System of testing : Salmonella typhimurium TA100, TA1535, TA98, TA1537, Escherichia coli WP2 uvr A
Concentration : -S9 mix.; 156, 313, 625, 1250, 2500, and 5000 ug/plate.
+S9 mix.: 313, 625, 1250, 2500, and 5000 ug/plate
Cycotoxic conc. : -S9: 2500 ug/plate and higher by the test for TA100, TA1535, TA1537.
5000 ug/plate by the test for TA 98 and E. Coli. WP2 uvrA.
Metabolic activation : with and without
Result : negative
Method : other: Guidelines for screening mutagenicity testing of chemicals(JAPAN) and OECD Test Guidelines 471 and 472
Year : 1999
GLP : yes
Test substance : Other TS: purity, 98.79%
Remark : The numbers of the reverse mutation colonies were within 2 times of negative control as shown below.
At 2500 and 5000 ug/plate without S9 mix, microbital toxicity was observed. At 5000 ug/plate with S9 mix, precipitates were observed.

<<< Table 1-1. 1st test results without S9 mix >>>

Test Substance Concentration (ug/plate)	Number of revertants (number of colonies/plate) Base-Pair change type		
	TA 100	TA1535	WP2urvA
0	161 ± 14	11 ± 4	31 ± 10
156	155 ± 8	11 ± 2	30 ± 4
313	140 ± 7	8 ± 2	31 ± 7
625	137 ± 14	11 ± 4	30 ± 4
1250	129 ± 10	11 ± 3	29 ± 4

2500 101* ± 5 9* ± 5 25 ± 5

5000 79* ± 7 4* ± 2 10* ± 1

Positive control without S9 mix
Name AF-2 NaN3 ENNG

Conc. 0.01 0.5 2
(ug/plate)
No of 597 ± 18 454 ± 26 552 ± 12
revertants

Test Number of revertants
Substance (number of colonies/plate)
Concentration Frameshift - type
(ug/plate) TA98 TA1537
---
0 22 ± 4 8 ± 2

156 19 ± 4 4 ± 1

313 18 ± 3 7 ± 3

625 22 ± 6 10 ± 3

1250 24 ± 4 8 ± 3

2500 19 ± 3 5* ± 3

5000 # 9* ± 1 7* ± 4

Positive control without S9 mix
Name AF-2 9-AA

Conc 0.1 80
(ug/plate)
No. of 385 ± 26 360 ± 10
revertants

Number of revertants are shown as mean of three plates ± S.D.
AF-2: 2-(2-furyl)-3-(5-nitro-2-furyl) acrylamide
NaN3: sodium azide
ENNG: N-ethyl-N'-nitro-N-nitrosoguanidine
9-AA: 9-aminoacridine
2-AA: 2-aminoanthracene

* : Microbial toxicity was observed
# : Precipitates were observed

<<< Table 1-2. 1st test results with S9 mix >>>

Test Number of revertants
Substance (number of colonies/plate)
Concentration Base-Pair change type
(ug/plate) TA 100 TA1535 WP2urvA
---
0 174 ± 27 17 ± 1 32 ± 3

313 182 ± 9 13 ± 4 39 ± 3

625	157 ± 17	15 ± 5	31 ± 8
1250	164 ± 18	12 ± 3	31 ± 4
2500	180 ± 6	14 ± 5	32 ± 4
5000 #	156 ± 2	6 ± 2	20 ± 6

Positive control with S9 mix.

Name	2-AA	2-AA	2-AA
Conc. (ug/plate)	1	2	10
No of revertants	1165 ± 42	309 ± 45	1432 ± 88

Test Substance Concentration (ug/plate)	Number of revertants (number of colonies/plate) Frameshift type TA 98	TA1537
0	32 ± 6	7 ± 1
313	33 ± 5	11 ± 2
625	26 ± 8	12 ± 1
1250	28 ± 6	12 ± 1
2500	28 ± 6	12 ± 2
5000 #	27 ± 1	12 ± 3

Positive control with S9 mix

Name	2-AA	2-AA
Conc. (ug/plate)	0.5	2
No. of revertants	349 ± 14	167 ± 42

Numbers of revertants are shown as the mean of three plates ± S.D.

2-AA: 2-aminoanthracene
: Precipitates were observed.

<<< Table 2-1. 2 nd test results without S9 mix >>>

Test Substance Concentration (ug/plate)	Number of revertants (number of colonies/plate) Base-Pair change type TA 100	TA1535	WP2urvA
0	155 ± 15	12 ± 2	25 ± 11
156	148 ± 20	13 ± 5	34 ± 7
313	146 ± 12	10 ± 2	34 ± 7
625	142 ± 10	11 ± 2	35 ± 6

1250 123 ± 15 13 (± 4) 26 ± 7

2500 86* ± 3 10* ± 1 22 ± 7

5000 80* ± 5 5* ± 1 13* ± 5

Positive control without S9 mix.
Name AF-2 NaN3 ENNG

Conc. 0.01 0.5 2
(ug/plate)
No of 607 ± 50 523 ± 73 886 ± 20
revertants

Test Number of revertants
Substance (number of colonies/plate)
Concentration Frameshift type
(ug/plate) TA 98 TA1537
---
0 26 ± 9 14 ± 5

156 24 ± 3 16 ± 5

313 21 ± 2 16 ± 3

625 22 ± 4 14 ± 3

1250 21 ± 5 14 ± 7

2500 18 ± 3 7* ± 3

5000 11* ± 5 2* ± 1

Positive control without S9 mix.
Name AF-2 9-AA

Conc. 0.1 80
(ug/plate)
No of 426 ± 26 320 ± 13
revertants

<<< Table 2-2. 2 nd test results with S9 mix >>>

Base-Pair change type

Test Number of revertants
Substance (number of colonies/plate)
Concentration Base-Pair change type
(ug/plate) TA 100 TA1535 WP2urvA
---
0 168 ± 18 17 ± 0 30 ± 3

313 156 ± 19 16 ± 2 38 ± 8

625 159 ± 8 15 ± 1 31 ± 5

1250 145 ± 4 14 ± 3 32 ± 4

2500 164 ± 7 16 ± 6 31 ± 8

5000 # 145 ± 5 11 ± 2 27 ± 3

Positive control with S9 mix

Name	2-AA	2-AA	2-AA
Conc. (ug/plate)	1	2	10
No of revertants	1003 ± 5	338 ± 46	1365 ± 73

Test Substance Concentration (ug/plate)	Number of revertants (number of colonies/plate) Frameshift type TA 98	TA1537
0	30 ± 9	21 ± 5
313	35 ± 2	18 ± 2
625	36 ± 10	22 ± 2
1250	40 ± 13	23 ± 6
2500	36 ± 14	17 ± 5
5000 #	27 ± 3	18 ± 5

Positive control with S9 mix

Name	2-AA	2-AA
Conc. (ug/plate)	0.5	2
No of revertants	395 ± 8	155 ± 17

Numbers of revertants are shown as the mean of three plates ± S.D.
2-AA: 2-aminoanthracene
: Precipitates were observed.

Source : MHW: Japan, 1999

Test condition : Procedures: Pre-incubation method
Solvent: DMSO

Positive control:
-S9 mix: AF-2(TA100, TA98), Sodium azide(TA1535),
ENNG (WP2 uvrA), and 9-Aminoacridine (TA1537)
+S9 mix: 2-Aminoanthracene (all strains)
S9 Mix: Rat liver, induced with phenobarbital and 5,6-benzoflavone
Plates/test : 3
Number of replicates: 2

Doses:
[Preliminary test to find the cytotoxic concentration]
1.22, 4.88, 19.5, 78.1, 313, 1250, and 5000 ug/plate
The cytotoxicity was observed at 5000ug/plate without S9. Then the following concentrations were decided for the tests.
[Test concentration]
-S9 mix; 156, 313, 625, 1250, 2500, and 5000 ug/plate
+S9 mix: 313, 625, 1250, 2500, and 5000 ug/plate.
At 2500 and 5000 ug/plate without S9 mix, microbital toxicity was observed. At 5000 ug/plate with S9 mix, precipitates were observed.

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint

01.11.2002 (12)

Type : Bacterial reverse mutation assay
System of testing : Salmonella typhimurium TA100, TA1535, TA98, TA1537, Escherichia coli WP2 uvr A
Concentration : [Preliminary test]
10, 50, 100, 500, 1000, and 5000 ug/plate
[Test]
156, 313, 625, 1250, 2500, 5000 ug / plate
Cycotoxic conc. :
Metabolic activation : with and without
Result : negative
Method : other: Guidelines for screening mutagenicity testing of chemicals(JAPAN) and OECD TG 471 and 472
Year : 1992
GLP : no data
Test substance : other TS: purity 98.87 wt %
Remark : The numbers of the reverse mutation colonies were within the numbers of the spontaneous reverse mutation colonies for all strains with and without S9 mix. Then this chemical was not mutagenic with or without an exogenous metabolic activation system. At 5000 ug/plate with and without S9 mix, microbital toxicity was observed.
Source : Mitsubishi Gas Chemical Co., 1992
Test condition : Procedures: Pre-incubation method
Solvent: DMSO

Positive control:
-S9 mix: AF-2 (TA100), Sodium azide (TA1535), ENNG (WP2 uvrA), 2-NF (TA98) and ICR-191 (TA1537)
+S9 mix: 2-Aminoanthracene (all strains)
S9: Rat liver, induced with phenobarbital and 5, 6-benzoflavone

Doses:
[Preliminary test to find the cytotoxic concentration]
10, 50, 100, 500, 1000, and 5000 ug/plate
[Test] 156, 313, 625, 1250, 2500, 5000 ug/plate both for with S9 and without S9 mix.
Plates/test: 3

By the preliminary test, the cytotoxicity was observed at 5000 ug/plate for all strains, but no cytotoxicity was observed at 1000 ug/plate.
The doses of the test were set at 6 levels from 0 (vehicle) up to 5000 ug/plate at the highest dose.
Reliability : (2) valid with restrictions
Flag : Material Safety Dataset

01.11.2002 (16)

Type : Chromosomal aberration test
System of testing : type of cell used: Chinese hamster CHL/IU cells
Concentration : Confirmation test:
With S9 mix: 500, 750, 1000 ug/mL
Without S9 mix: 1500, and 2000 ug/mL
Cycotoxic conc. : [24 hrs continuous treatment] 812 ug/mL
[48 hrs continuous treatment] 455 ug/mL
[Short treatment with S9] 863 ug/mL
[Short treatment without S9] 1182 ug/mL
Metabolic activation : with and without
Result : equivocal
Method : Guidelines for screening mutagenicity testing of chemicals, JAPAN
Year : 1999

GLP : yes
Test substance : Other TS: purity, 98.79%
Remark : The author of the study found increasing tendency of in the number of cells with structural aberrations in the main test. Such increase may be caused by cytotoxicity or osmotic/ionic effect. For that reason, OECD guidelines 473 clearly limit the highest dose at such that it not exceed 10 mmol/litter that is c.a. 1360 mg/litter. Consequently, all the data for more than that are not relevant.

The author may have intrigued scientific curiosity and may have tried to confirm the cause. In confirmation study in order to specify the cause, the result showed no evident dose dependency. The inference of the data is clearly not clastogenic and ambiguous result are caused from cytotoxicity judging from the degree of reproducibility.

So it is concluded that this substance is eguivocal.

In the main test, structural chromosomal aberrations including gaps, were induced at 500 and 1000 ug/mL of 48 hr treatment (5.0 and 11.0%, respectively).To confirm the repeatability and the dose dependency,a confirmation test was conducted.Structural chromosomal aberrations were induced at 1500and 2000 ug/mL without S9 mix. (8.5% and 68.6%, respectively).

Polyploidy was not induced in any treatment group. In all test conditions, some of the test substance precipitated in the medium and the color of the growth medium was changed to yellow at the beginning of the treatment for 1000 ug/mL and higher concentrations. The pH values of the growth media were more than 6.2 for the concentrations where the mutagenicity was observed. Then it was confirmed that the mutagenicity observed was due to m-toluic acid.

On the other hand, on 6 hr short-term treatment with S9 mix, the structural chromosomal aberrations, including and excluding gaps, were 1.0 % and 4.5 % at 750 ug/mL and 1000 ug/mL, respectively. 0.5 % polyploidies were determined for all doses. No mutagenicity was observed with S9 mix.

The test results were summarized below:

[Results of the main tests]

<<< Table 1-1: 24 hr continuous treatment without S9 >>>

Number of cells analyzed: 200 cells except for 2000 ug/mL.
2000 ug/mL: impossible to analyze due to toxicity.

Dose ug /mL	No. of structural aberrations							No. of cells with aberration	
	gap	ctb	cte	csb	cse	f	total	-gap(%)	+gap(%)
Solvent (DMSO)									
0	0	0	1	0	0	0	1	1(0.5)	1(0.5)
Test Substance									
250	0	2	0	1	0	0	3	3(1.5)	3(1.5)
500	0	2	1	1	0	0	4	3(1.5)	3(1.5)
1000 #	0	6	1	0	0	0	7	7(3.5)	7(3.5)
2000 #	impossible to analyze due to toxicity.								
MMC									
0.03	0	13	28	0	0	0	41	39(19.5)	39(19.5)

Note:
1) No polyploids were observed for all doses.
2) #: At 1000 and 2000 ug/mL of 24 hr continuous treatment, some of the test substance precipitated in the medium at the beginning of the treatment. Also the color of the growth medium was changed to yellow at the beginning of the treatment.

Abbreviations:
gap : chromatid gap and chromosome gap
ctb : chromatic break cte : chromatid exchange
csb : chromosome break cse : chromosome exchange (dicentric and ring)
f : fragment
- gap : total number of cells with aberrations except gap
+ gap : total number of cells with aberrations
DMSO: dimethylsulfoxide (solvent)
MMC : mitomycin C (positive control)

<<< Table 1-2: 48 hr continuous treatment without S9 >>>

Number of cells analyzed: 200 cells except for 1000 ug/mL,
for 1000 ug/mL: 100 cells

Dose ug /mL	No. of structural aberrations							No. of cells with aberration	
	gap	ctb	cte	csb	cse	f	total	-gap(%)	+gap(%)
Solvent (DMSO)									
0	0	1	3	1	0	0	5	5(2.5)	5(2.5)
Test Substance									
62.5	0	0	0	0	2	0	2	2(1.0)	2(1.0)
125	0	0	0	0	1	0	1	1(0.5)	1(0.5)
250	0	0	2	0	0	0	2	2(1.0)	2(1.0)
500	0	7	3	1	0	0	11	10(5.0)	0(5.0)
1000 #	0	5	6	0	0	0	11	11(11.0)	11(11.0)
Data at 1000 was not relevant regarded as cytotoxicity.									
MMC									
0.03	2	32	78	4	2	1	119	106(53.0)	107(53.5)

Note:
1) No polyploids were observed for all doses.
2) #: At 1000 ug/mL of 48 hr continuous treatment, some of the test substance precipitated in the medium at the beginning of the treatment. Also the color of the growth medium was changed to yellow at the beginning of the treatment.

Abbreviations:
gap : chromatid gap and chromosome gap
ctb : chromatic break cte : chromatid exchange
csb : chromosome break cse : chromosome exchange (dicentric and ring)
f : fragment
- gap : total number of cells with aberrations except gap
+ gap : total number of cells with aberrations
DMSO: dimethylsulfoxide (solvent)
MMC : mitomycin C (positive control)

<<< Table 2-1: 6 hr short treatment without S9 mix >>>

Time of exposure : 6 - 18 hrs
Number of cells analyzed: 200 cells except for 2000 ug/mL,
100 cells for 2000 ug/mL

Dose ug /mL	No. of structural aberrations							No. of cells with aberration	
	gap	ctb	cte	csb	cse	f	total	-gap(%)	+gap(%)
Solvent (DMSO)									
0	0	0	0	2	1	0	3	3(1.5)	3(1.5)
Test Substance									
250	0	0	1	0	0	0	1	1(0.5)	1(0.5)
500	2	0	0	0	2	0	4	2(1.0)	4(2.0)
1000 #	0	2	0	1	0	0	3	3(1.5)	3(1.5)
2000 #	0	4	6	0	0	0	10	7(7.0)	7(7.0)

Data at 2000 was not relevant according to OECD TG 473 (above 10mmol/L).

BP									
20	0	1	1	1	0	0	3	3(1.5)	3(1.5)

Note:
1) 0.5 % polyploid was determined at 500 ug/mL.
2) 1.5 % polyploid was determined at 1000 ug/mL.
3) #: At 1000 and 2000 ug/mL, some of the test substance precipitated in the medium at the beginning of the treatment. Also the color of the growth medium was changed to yellow at the beginning of the treatment.

Abbreviations:
gap : chromatid gap and chromosome gap
ctb : chromatic break cte : chromatid exchange
csb : chromosome break cse : chromosome exchange (dicentric and ring)
f : fragment
- gap : total number of cells with aberrations except gap
+ gap : total number of cells with aberrations
DMSO: dimethylsulfoxide (solvent)
B.P : bezo[a]pyrene (positive control)

<<< Table 2-2: 6 hr short treatment with S9 mix >>>

Time of exposure : 6 - 18 hrs
Number of cells analyzed: 200 cells except for 2000 ug/mL
For 2000 ug/mL, impossible to analyze due to toxicity.

Dose ug /mL	No. of structural aberrations							No. of cells with aberration	
	gap	ctb	cte	csb	cse	f	total	-gap(%)	+gap(%)
Solvent (DMSO)									
0	0	0	0	0	0	0	0	0(0.0)	0(0.0)

Test Substance
250 1 0 0 0 0 0 1 0(0.0) 0(0.0)

500 1 0 1 0 1 0 3 2(1.0) 3(1.5)

1000 # 0 3 10 0 0 0 13 10(5.0) 10(5.0)

2000 # Toxicity (impossible to count and analyze)

BP
20 3 17 159 2 0 0 181 164(82.0) 165(82.5)

Note:
1) 1.0% polyploid was determined at 2000 ug/mL.
2) #: At 1000 and 2000 ug/mL, some of the test substance precipitated in the medium at the beginning of the treatment. Also the color of the growth medium was changed to yellow at the beginning of the treatment.

Abbreviations:
gap : chromatid gap and chromosome gap
ctb : chromatic break cte : chromatid exchange
csb : chromosome break cse : chromosome exchange (dicentric and ring)
f : fragment
- gap : total number of cells with aberrations except gap
+ gap : total number of cells with aberrations
DMSO: dimethylsulfoxide (solvent)
BP : bezo[a]pyrene (positive control)

<<< Table 3-1: Result of the confirmation tests >>>

6 hr short treatment without S9 mix.

Time of exposure : 6 - 18 hrs
Number of cells analyzed: 200 cells except for 2000 ug/mL.
For 2000 ug/mL: 172 cells due to toxicity.

Dose ug /mL	No. of structural aberrations							No. of cells with aberration	
	gap	ctb	cte	csb	cse	f	total	-gap(%)	+gap(%)
Solvent (DMSO)									
0	1	0	0	0	1	0	2	1(0.5)	2(1.0)
Test Substance									
1000 #	0	0	0	1	0	0	1	1(0.5)	1(0.5)
1500 #	0	6	14	0	0	0	20	17(8.5)	17(8.5)
Data at 1500 was not relevant according to OECD TG 473 (above 10mmol/L).									
2000 #	6	40	102	0	1	2	151	116(67.4)	118(68.5)
Data at 2000 was not relevant according to OECD TG 473 (above 10mmol/L).									
BP									
20	0	0	0	2	0	0	2	2(1.0)	2(1.0)

Note:
1)No polyploid was determined at all doses.
2) #: At all doses of test substance, some of the test substance precipitated in the medium at the beginning of the treatment. Also the color of the growth medium was changed to yellow at the beginning of the treatment.

Abbreviations:gap : chromatid gap and chromosome gap
ctb : chromatic break cte : chromatid exchange
csb : chromosome break cse : chromosome exchange (dicentric and ring)
f : fragment
- gap : total number of cells with aberrations except gap
+ gap : total number of cells with aberrations
DMSO: dimethylsulfoxide (solvent)
BP : bezo[a]pyrene(positive control)

<<< Table 3-2: Result of the confirmation tests >>>

6 hr short treatment with S9 mix.

Time of exposure : 6 - 18 hrs
Number of cells analyzed: 200 cells for all doses

Dose ug /mL	No. of structural aberrations							No. of cells with aberration	
	gap	ctb	cte	csb	cse	f	total	-gap(%)	+gap(%)
Solvent (DMSO)									
0	0	1	0	0	0	0	1	1(0.5)	1(0.5)
Test Substance									
500	0	0	0	0	1	0	1	1(0.5)	1(0.5)
750 #1	0	1	2	0	0	0	3	2(1.0)	2(1.0)
1000 #2	1	3	7	0	1	0	12	9(4.5)	9(4.5)
BP									
20	1	22	161	0	3	0	187	167(83.5)	167(83.5)

Note:
1) 0.5 % polyploids were determined at all doses of test substance.
2) #1 at 750 ug/mL, some of the test substance precipitated in the medium at the beginning of the treatment.
3) #2 at 1000 ug/mL, some of the test substance precipitated in the medium at the beginning of the treatment. Also the color of the growth medium was changed to yellow at the beginning of the treatment.

Abbreviations:
gap : chromatid gap and chromosome gap
ctb : chromatic break cte : chromatid exchange
csb : chromosome break cse : chromosome exchange (dicentric and ring)
f : fragment
- gap : total number of cells with aberrations except gap
+ gap : total number of cells with aberrations
DMSO: dimethylsulfoxide (solvent)
BP : bezo[a]pyrene (positive control)

Source : MHW: Japan, 1999
Test condition : Solvent: DMSO
Positive control: -S9 mix, Mitomycin C
+S9 mix, Benzo[a]pyrene
S9: Rat liver, induced with phenobarbital and 5,6-benzoflavone
Plates/test: 2

[Preliminary test]
To determine the doses of the main tests, the preliminary test was

conducted. The doses causing the cytotoxicity of 50% cell growth inhibition were determined by the probit extraporation method.

These values were as follows:
(24 hrs continuous treatment) 812 ug/mL
(48 hrs continuous treatment) 455 ug/mL
(Short treatment with S9) 863 ug/mL
(Short treatment without S9) 1182 ug/mL

[Main test]
Based on the above cytotoxicity values, the doses of the main tests were set at;
-S9 Mix:
(24 hrs continuous treatment) 0, 250, 500, 1000, 2000 ug/mL
(48 hrs continuous treatment) 0, 62.5, 125, 250, 500, 1000 ug/mL
(6 hrs short-term treatment) 0, 250, 500, 1000, 2000 ug/mL
+S9 Mix:
(6 hrs short-term treatment) 0, 250, 500, 1000, 2000 ug/mL

The results of the main tests were positive in the mutagenecity as shown below:
48 hrs continuous treatment: (500 ug/mL) 5.0%, (1000 ug/mL) 11.0%
6 hrs short treatment with S9: (1000 ug/mL) 5.0%
6 hrs short treatment without S9: (2000 ug/mL) 7.0%

[Confirmation test]
The 8 hrs short treatment confirmation tests for the repeatability and the concentration dependency were conducted by the following conditions.
With S9 mix: 500, 750, 1000 ug/mL
Without S9 mix: 1500, and 2000 ug/mL

Reliability : (2) valid with restriction
Flag : Critical study for SIDS endpoint
01.11.2002 (12)

5.6 GENETIC TOXICITY 'IN VIVO'

Type : Micronucleus assay
Species : rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : gavage
Exposure period : 24 hrs after 2 nd administration
Doses : 0, 500, 1000, and 2000 mg/kg
Extended test; 0, 125, 250 and 500 mg/kg
Result : negative
Method : OECD Guide-line 474 "Genetic Toxicology: Micronucleus Test"
Year : 2002
GLP : yes
Test substance : Other TS: purity, 98.96%
Remark : Five male SDrats/group were administrated by oral gavage 2 times with 24 hr interval. The doses were set at 500, 1000, and 2000 mg/kg bw based on the oral LD50, greater than 2000 mg/kg bw. As positive control, CP(cyclophosphamide) was administrated once intraperitoneally.
At 24 hr after 2nd administration, animals were sacrificed and samples were prepared for analysis. m-Toluic acid did not induce micronuclei except that there was a separate incidence in one animal in 500 mg/kg group that showed statiscally abnormal value.

The additional test was conducted with 3 doses of 125, 250, and 500

mg/kg. As concluded from the main and the additional test combined, the chemical did not induce significant increases in the micronuclei in any treated groups of wide dose range. The reproducibility of the separate incidence was not established in the duplication of 500 mg/kg dose. The incidences of micronuclei in the negative and positive control were within the range of the test laboratory's background data.

The results of the additional test is summarized below.

<<< Results of micronucleus test (Additional test) >>>

Dosage (mg/kg)	Animal No.	No. of PCEs scored	MNPCE Number (Total)	MNPCE Incidence Mean ± SD	PCE/(PCE+NCE) % #3 Mean ± SD
Negative Control					
0	101	2000	1	0.05	57.7
	102	2000	3	0.15	50.8
	103	2000	2	0.10	53.9
	104	2000	1	0.05	58.2
	105	2000	1	0.05	52.9
			(8)	0.08 ± 0.04	54.7 ± 3.2
Test Substance (MTA)					
125	201	2000	2	0.10	46.5
	202	2000	1	0.05	49.4
	203	2000	1	0.05	52.3
	204	2000	1	0.05	48.8
	205	2000	3	0.15	55.0
			(8)	0.08 ± 0.04	50.4 ± 3.3
250	301	2000	1	0.05	51.9
	302	2000	1	0.05	52.3
	303	2000	2	0.10	48.9
	304	2000	2	0.10	40.3
	305	2000	4	0.20	51.9
			(10)	0.10 ± 0.06	49.1 ± 5.1
500	401	2000	3	0.15	47.8
	402	2000	2	0.10	50.5
	403	2000	2	0.10	54.9
	404	2000	2	0.10	48.2
	405	2000	1	0.05	51.1
			(10)	0.10 ± 0.04	50.5 ± 2.8
Positive control (CP)					
10	501	2000	50	2.50	45.6
	502	2000	28	1.40	43.1
	503	2000	31	1.55	42.6
	504	2000	44	2.20	37.3
	505	2000	33	1.65	39.2
			(186) #1	1.86 ± 0.47	41.6 ± 3.3 #2

Administration: Negative control and test substance: Two times administration by oral gavage at 24 hours interval. Positive control: One time administration by intraperitoneal injection.

#1 Significantly different from the negative control (P<0.01) by Kastenbaum and Bowman's method.
#2 Significantly different from the negative control (P<0.01) by Student's t-test.

#3 One thousand erythrocytes were scored.
PCE : polychromatic erythrocytes
MNPCE : micronucleated PCE
NCE : normochromatic erythrocytes
CP : cychrophosphamide

Result : Negative.
The test substance did not induce significant increases in the MNPCEs in any treated groups.

Source : Mitsubishi Gas Chemical Co., 2002

Test condition : Test animal: Main test ; 5 males/group x 5 groups total 25 males. The test animals were 7 weeks old and weighed 259 - 277 g.
Additional test: 5 males/group x 5 groups total 25 males.
The test animals were 7 weeks old and weighed 266 - 289 g.

Dose: As LD50 was known to be greater than 2000 mg/kg, the doses of the challenge test were set at 500, 1000, and 2000 mg/kg. Because the test substance induced a micronuclei in one animal of 500 mg/kg, the additional test was conducted with 3 dose of 125, 250, and 500 mg/kg.

Administration route and frequency: Test substance; Oral gavage twice at 24-hours intervals.
The positive control, CP was intraperitoneally administrated once.
Negative control substance: Methyl cellulose (MC) 1 w/v %
Positive control substance: Cyclophosphamide (PC) 10 mg/kg
Sampling time: Sacrificed 24 hours after the final administration.

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint

17.06.2002 (17)

5.7 CARCINOGENITY

5.8 TOXICITY TO REPRODUCTION

Type : One generation study

Species : rat

Sex : male/female

Strain : Crj: CD(SD)

Route of admin. : gavage

Exposure period : Males: 14 days before mating
Females: from 14 days before mating to day 3 of lactation

Frequency of treatment : once daily

Premating exposure period

Male : 14 days

Female : 14 days

Duration of test : Males: 44 days from 14 days before mating, Females: 41 - 45 days from 14 days before mating to day 3 of lactation

Doses : 0(vehicle), 30, 100, 300, 1000 mg/kg/day

Control group : yes, concurrent vehicle

Method : OECD Guide-line 422 'Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening test'

Year : 1999

GLP : yes

Test substance : Other TS: purity, 98.79%

Remark : The parental animals exhibited no alteration in reproductive parameters. There were no significant differences in offspring parameters, although the decreasing tendency at 1000 mg/kg/day in the number of pups born, the

live birth index, the delivery index and the body weight of live pups on day 0 of lactation was observed. This decreasing tendency was not a statistically significant difference from the control group. By the external inspection of pups, no abnormalities were found. Also no abnormalities were found in the internal organs.

The summary of the reproductive and the developmental parameters are summarized below.

<<< Table 1. Reproduction results of female rats >>>

Dose (mg/kg/day)	0	30	100	300	1000
No. of pairs with mated	10	10	10	10	10
No. of pairs with successful copulation	10	10	10	9	9
Copulation index %	100	100	100	90	90
Pairing days until copulation (day, Mean ± S.D.)	2.2 ± 1.1	2.2 ± 1.0	2.1 ± 1.1	2.4 ± 1.2	1.9 ± 1.1
No. of pregnant females	9	10	9	8	8
Fertility index %	90	100	90	89	89
No. of corpora lutea (Mean ± S.D.)	19.3 ± 2.3	17.9 ± 3.9	19.4 ± 3.8	17.5 ± 3.0	17.9 ± 2.2
No. of implantation sites (Mean ± S.D.)	17.8 ± 2.5	15.2 ± 5.4	15.9 ± 3.5	16.0 ± 4.0	16.6 ± 3.2
Implantation index(%) (Mean ± S.D.)	92.2 ± 9.5	81.9 ± 27.5	84.4 ± 23.2	90.3 ± 14.0	93.5 ± 15.7
No. of pregnant females with parturition	9	9	9	8	8
Gestation length (day)(Mean ± S.D.)	22.6 ± 0.5	22.6 ± 0.5	22.7 ± 0.5	22.8 ± 0.5	22.6 ± 0.5
No. of pregnant females with live pups	9	9	9	8	8
Gestation index (%)	100	90	100	100	100
No. of pregnant females with live pups on day 4	9	9	9	8	8

Note:
Copulation index = (No. of pairs with successful copulation/ No. of pairs mated) x 100
Fertility index = (No. of pregnant females/ No. of pairs with successful copulation) x 100

Gestation index = (No. of females with live pups/ No. of pregnant females) X 100

<<< Table 2. Litter results of female rats >>>

Dose (mg/kg/day)	0	30	100	300	1000
No. of pups born	16.4 ± 2.9	15.9 ± 2.8	15.0 ± 3.7	14.6 ± 3.4	14.3 ± 3.2
Delivery index(%)	92.1 ± 7.3	94.4 ± 5.8	94.6 ± 10.1	92.2 ± 4.8	85.4± 8.5
No. of pups alive on day 0 of lactation Total	16.2 ± 2.9	15.7 ± 2.3	14.8 ± 3.7	13.6 ± 3.6	13.3± 3.2
Male	8.2 ± 2.3	8.3 ± 2.9	7.0 ± 2.3	6.9 ± 3.2	6.8± 3.2
Female	8.0 ± 2.2	7.3 ± 2.4	7.8 ± 2.3	6.8 ± 2.1	6.5± 3.2
Live birth index (%)	98.7 ± 2.7	98.9 ± 3.2	98.6 ± 2.8	94.0 ± 14.4	92.9± 8.1
Sex ratio (Male/female)	1.03	1.17	0.90	1.02	1.00
No. of pups alive on day 4 of lactation Total	16.0 ± 3.1	15.7 ± 2.3	14.7 ± 3.6	13.6 ± 3.6	12.8± 3.0
Male	8.0 ± 2.3	8.3 ± 2.9	7.0 ± 2.3	6.9 ± 3.2	6.6± 2.9
Female	8.0 ± 2.2	7.3 ± 2.4	7.7 ± 2.3	6.8 ± 2.1	6.1± 3.2
Viability index (%)	98.5 ± 4.4	100 ± 0	99.4 ± 1.8	100 ± 0	96.7 ± 5.0
Body weight of live pups (g) on day 0 Male	7.3 ± 0.9	7.3 ± 0.6	7.5 ± 0.7	7.6 ± 0.7	6.7 ± 0.6
Female	6.9 ± 0.9	6.9 ± 0.5	7.1 ± 0.7	7.3 ± 0.8	6.2 ± 0.6
Body weight of live pups (g) on day 4 Male	11.6 ± 2.0	11.6 ± 1.2	12.3 ± 1.9	12.9 ± 2.1	11.0 ± 1.5

	Female	11.3 ± 1.9	10.8 ± 0.9	11.7 ± 1.8	12.3 ± 2.3	10.2 ± 1.3

Note:
Delivery index = (No. of pups born/No. of implantation sites) x 100
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
Viability index = (No. of live pups on day 4/No. of live pups on day 0) x 100
Each value is expressed as Mean ± S.D., except sex ratio.

Result : NOAEL reproduction/developmental = 1000 mg/kg/day
Source : MHW Japan, 1999
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
17.06.2002 (12)

5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Type : One generation study
Species : rat
Sex : male/female
Strain : Crj: CD(SD)
Route of admin. : gavage
Exposure period : Males: 14 days before mating
Females: from 14 days before mating to day 3 of lactation
Frequency of treatment : once daily
Premating exposure period
Male : 14 days
Female : 14 days
Duration of test : Males: 44 days from 14 days before mating, Females: 41 - 45 days from 14 days before mating to day 3 of lactation
Doses : 0(vehicle), 30, 100, 300, 1000 mg/kg/day
Control group : yes, concurrent vehicle
Method : OECD Guide-line 422 'Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening test'
Year : 1999
GLP : yes
Test substance : Other TS: purity, 98.79%
Remark : The parental animals exhibited no alteration in reproductive parameters. There were no significant differences in offspring parameters, although the decreasing tendency at 1000 mg/kg/day in the number of pups born, the live birth index, the delivery index and the body weight of live pups on day 0 of lactation was observed. This decreasing tendency was not a statistically significant difference from the control group. By the external inspection of pups, no abnormalities were found. Also no abnormalities were found in the internal organs.

The summary of the reproductive and the developmental parameters are summarized below.

<<< Table 1. Reproduction results of female rats >>>

Dose (mg/kg/day)	0	30	100	300	1000
No. of pairs with mated	10	10	10	10	10
No. of pairs with					

successful copulation	10	10	10	9	9
Copulation index %	100	100	100	90	90
Pairing days until copulation (day, Mean ± S.D.)	2.2 ± 1.1	2.2 ± 1.0	2.1 ± 1.1	2.4 ± 1.2	1.9 ± 1.1
No. of pregnant females	9	10	9	8	8
Fertility index %	90	100	90	89	89
No. of corpora lutea (Mean ± S.D.)	19.3 ± 2.3	17.9 ± 3.9	19.4 ± 3.8	17.5 ± 3.0	17.9 ± 2.2
No. of implantation sites (Mean ± S.D.)	17.8 ± 2.5	15.2 ± 5.4	15.9 ± 3.5	16.0 ± 4.0	16.6 ± 3.2
Implantation index(%) (Mean ± S.D.)	92.2 ± 9.5	81.9 ± 27.5	84.4 ± 23.2	90.3 ± 14.0	93.5 ± 15.7
No. of pregnant females with parturition	9	9	9	8	8
Gestation length (day)(Mean ± S.D.)	22.6 ± 0.5	22.6 ± 0.5	22.7 ± 0.5	22.8 ± 0.5	22.6 ± 0.5
No. of pregnant females with live pups	9	9	9	8	8
Gestation index (%)	100	90	100	100	100
No. of pregnant females with live pups on day 4	9	9	9	8	8

Note:
Copulation index = (No. of pairs with successful copulation/ No. of pairs mated) x 100
Fertility index = (No. of pregnant females/ No. of pairs with successful copulation) x 100
Gestation index = (No. of females with live pups/ No. of pregnant females) X 100

<<< Table 2. Litter results of female rats >>>

Dose (mg/kg/day)	0	30	100	300	1000
No. of pups born	16.4 ± 2.9	15.9 ± 2.8	15.0 ± 3.7	14.6 ± 3.4	14.3 ± 3.2
Delivery index(%)	92.1 ± 7.3	94.4 ± 5.8	94.6 ± 10.1	92.2 ± 4.8	85.4± 8.5
No. of pups alive on day 0 of					

lactation Total	16.2 ± 2.9	15.7 ± 2.3	14.8 ± 3.7	13.6 ± 3.6	13.3± 3.2
Male	8.2 ± 2.3	8.3 ± 2.9	7.0 ± 2.3	6.9 ± 3.2	6.8± 3.2
Female	8.0 ± 2.2	7.3 ± 2.4	7.8 ± 2.3	6.8 ± 2.1	6.5± 3.2
Live birth index (%)	98.7 ± 2.7	98.9 ± 3.2	98.6 ± 2.8	94.0 ± 14.4	92.9± 8.1
Sex ratio (Male/female)	1.03	1.17	0.90	1.02	1.00
No. of pups alive on day 4 of lactation					
Total	16.0 ± 3.1	15.7 ± 2.3	14.7 ± 3.6	13.6 ± 3.6	12.8± 3.0
Male	8.0 ± 2.3	8.3 ± 2.9	7.0 ± 2.3	6.9 ± 3.2	6.6± 2.9
Female	8.0 ± 2.2	7.3 ± 2.4	7.7 ± 2.3	6.8 ± 2.1	6.1± 3.2
Viability index (%)	98.5 ± 4.4	100 ± 0	99.4 ± 1.8	100 ± 0	96.7 ± 5.0
Body weight of live pups (g) on day 0					
Male	7.3 ± 0.9	7.3 ± 0.6	7.5 ± 0.7	7.6 ± 0.7	6.7 ± 0.6
Female	6.9 ± 0.9	6.9 ± 0.5	7.1 ± 0.7	7.3 ± 0.8	6.2 ± 0.6
Body weight of live pups (g) on day 4					
Male	11.6 ± 2.0	11.6 ± 1.2	12.3 ± 1.9	12.9 ± 2.1	11.0 ± 1.5
Female	11.3 ± 1.9	10.8 ± 0.9	11.7 ± 1.8	12.3 ± 2.3	10.2 ± 1.3

Note:
Delivery index = (No. of pups born/No. of implantation sites) x 100
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
Viability index = (No. of live pups on day 4/No. of live pups on day 0) x 100
Each value is expressed as Mean ± S.D., except sex ratio.

Result : NOAEL reproduction/developmental = 1000 mg/kg/day
Source : MHW Japan, 1999
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
17.06.2002 (12)

5.10 OTHER RELEVANT INFORMATION

Type : Metabolism
Remark : Urine samples from a volunteer weighing 70 kg who was exposed to separate doses of 41 micromoles of benzoic acid, an intermediate metabolite of toluene, and 33.5 micromoles of hippuric acid, a final metabolite of toluene, m-methyl benzoic acid, an intermediate metabolite of m-xylene, and m-methyl hippuric acid, a final metabolite of m-xylene, indicated total recovery of the compound through renal excretion via the kidneys. The measured urinary elimination of ingested test compound was complete in all cases of m-methylbenzoic acid and m-methylhippuric acid. The excretion of both the benzoic acid and methylbenzoic acid conjugates was rapid for some 4-5 hr after the ingestion of the acids, the excretion rate constants being on the order of 1.0 h-1. The urinary excretion rate of methylhippuric acid was halved in about 2 hr. (excretion rate constant K=0.34 h-1). The urinary excretion of intravenously injected methylhippuric acid was much more rapid than that of ingested methylhippuric acid, and the excretion rate was halved in about 30 minutes (K=1.3 h-1). Only trace of free benzoic acid and methylbenzoic acid were detected in the urine after the compounds were ingested.
The percentage of dose excreted to the dose ingested and the excretion rate constant were shown in the table below.

Dose	Percentage of dose excreted as HA	Percentage of dose excreted as MHA	Excretion rate constant b(h-1) HA	Excretion rate constant b(h-1) MHA
41 umol BA	95 a		1.0	
7.4 umol MBA		106		1.0
7.4 umol MBA+ 41 umol BA	107 a	105	1.0	1.0
33.5 umol HA	101 a		0.13	
7.8 umol MHA		107		0.34
7.8 umol MHA+ 33.5 umol HA	99 a	84	0.11	0.34

Note: a; Basal hippurate excretion (mean of two series of determination) has been subtracted.
b; Excretion 5-10 hr after ingestion

Source : Riihimaki V.et al., 1979.
Test condition : Human. One healthy male (35 years old, weighed 70 Kg).
In the single exposure: the subject orally ingested one dose one subject at a time after overnight fasting. (41 umol BA, 7.4 umol MBA, 33.5 umol HA, and 7.8 umol MHA).
In the combined exposures: the subject ingested, after overnight fasting, one subject each at a time 2 hours after the first subject administration.(7.4 umol MBA + 41 umol BA, 7.8 umol MHA + 33.5 umol HA).

Collection of samples:
After the administration of the test compounds, urine was sampled at 1hour intervals for at least the first 4 hours, thereafter at 2 hours intervals for the next 8 hours. All the urine excreted throughout the first 25-30 hours after the ingestion of the test compounds was collected, stored a few hours at +5 deg. C and then kept at -20 deg. C until analyzed.

01.11.2002 (23)

Type : Metabolism
Remark : Ethylbenzene was excreted mainly in the form of mandelic acid and phenylglyoxylic acid and m-xylene in the form of m-methylhippuric acid, respectively. All the individual metabolites of m-xylene were excreted at substantially higher rates during (and immediately after exposure) than during the following night.

Source : Riihimaki et al., 1984
Test condition : Human, four males (33-40 years old who did not smoke, use drugs or consume alcohol during the study period).
They were exposed to 150 ppm (655 mg/cubic m) ethylbenzene and 150 ppm (655 mg/cubic m) m-xylene both separately and in combination for 4 hours in a dynamic – controlled environment exposure chamber.
Urine samples were mostly obtained at 2- h intervals during the exposure, and all urine was collected throughout the following night. Benzoic acid (65850) obtained by alkaline hydrolysis of hippuric acid (495692) and m-methylbenzoic acid (99047) obtained by alkaline hydrolysis of m-methylhippuric acid (27115497) were extracted from the urine and analyzed by gas chromatography. A similar procedure was used to determine mandelic acid (90642).
Modifications of the methods were applied for determination of phenylglycoxylic acid (611734) and phenylacetic acid (103822).
01.11.2002 (21)

Type : Metabolism
Remark : It was reported that xylene was mainly oxidized to methylbenzoic acid, which in turn was conjugated with glycine to produce methylhippuric acid and excreted in the urine. The maximum urinary excretion rate of hippuric acid (final metabolite of toluene) was about 190 umol/min and was limited by the mobilization of endogenous glycine for benzoic acid conjugation. It might be presumed that the body's capacity for conjugating methylbenzoic acid with glycine was relatively similar to that of benzoic acid, i.e., that the two organic acids function rather similar as substrates and, in any event, the maximum rate of glycine mobilization limits the conjugation to a level below about 200 umol/min.
Source : Sedivec V. et al., 1976
13.06.2002 (24)

Type : Metabolism
Remark : The major route of biotransformation of benzoic acid and salicylic acid in man is conjugation with glycine, resulting in the formation of hippuric acid and salicyluric acid, respectively.
Source : Amsel L. P. et al., 1969
31.05.2002 (1)

Type : Metabolism
Remark : Sedentary volunteer subjcts were exposed to an m-xylene concentration of about 3.9 umol/cubic m over five successive days, 6 h/day. It was noted that about 60% of the inhaled xylene was retained in the lungs. The estimated daily uptake of xylene was recovered nearly quantitatively as methylhippuric acid in the urine. Other pathways of xylene excretion played a minor role.
Source : Rihimaki V. et. al.,1979.
13.06.2002 (22)

5.11 EXPERIENCE WITH HUMAN EXPOSURE

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