FOREWORD INTRODUCTION

4-AMINOTOLUENE-3-SULFONIC ACID

CAS N°: 88-44-8

SIDS Initial Assessment Report

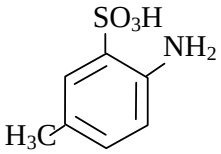
For

SIAM 16

Paris, 27-30 May 2003

1. Chemical Name:	4-Aminotoluene-3-sulfonic acid
2. CAS Number:	88-44-8
3. Sponsor Country:	Japan Mr. Yasuhisa Kawamura Director, Second International Organizations Div. Ministry of Foreign Affairs 2-2-1 Kasumigaseki, Chiyoda-ku Tokyo 100-8919
4. Shared Partnership with:	The industry consortium collected new data and prepared the updated IUCLID, and drafted versions of SIAR and SIAP.
5. Roles/Responsibilities of the Partners:	Mr. Kiminori Nagayama, Mitsuboshi Chemical Co., Ltd. e-mail: nagayama@mitsuboshi-chem.co.jp
• Name of industry sponsor /consortium	The industry contact point is Mr. K. Nagayama, Mitsuboshi Chemical Co., Ltd. acting on behalf of the 4B acid consortia (other consortium members: Han Nam Co., Ltd. (Korea), Hickson & Welch Ltd. (UK), Sun Chemical Corp. (USA)).
• 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:	The Japanese government peer-reviewed the documents and audited selected studies.
8. Quality check process:	The 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:	July 2, 2003
11. Comments:	

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	88-44-8
Chemical Name	4-Aminotoluene-3-sulfonic acid
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

From the outcome of a single dose administration reported in a preliminary examination of a 28-Day Repeat Dose Toxicity study [OECD TG407], the oral LD50 in rats is considered to be greater than 2000 mg/kg in both sexes. This substance was not corrosive or irritant to human skin.

In the 28-Day Repeated Dose Toxicity study [OECD TG407], this substance was administrated to male and female rats at 0, 100, 300, 1000 mg/kg/day dose by gavage. At 1000 mg/kg/day in males, a decrease of white blood cell count, total cholesterol and urine pH, also an enlargement of cecum were observed. At 1000 mg/kg in females, an increase of GPT and a decrease of glucose, also an enlargement of cecum were observed. All of those changes recovered within 14 days after cessation of the treatment. No other dose-dependent histopathological changes were observed in any dose groups. No changes in mortality, behavior or toxic effects on the body weight and food consumption were observed in any dose levels and in any sexes. The NOAEL for both sexes is considered to be 300 mg/kg/day.

This substance was not mutagenic in bacteria up to 5,000 ug/plate [OECD TG471, TG472] and 10,000 ug/plate. A chromosomal aberration test tested up to 1.9 mg/mL (10mM) [OECD TG473] was negative except in the 6hr short-term test in the presence of an exogenous metabolic activation system. The positive response in the 6 hr short term test was based on the low pH, because the induction of chromosomal aberration was diminished after adjustment of the pH to a neutral range. The result of an unscheduled DNA synthesis up to 187 mg/L was negative. Furthermore, an *in vivo* micronucleus test was negative. Overall, this substance can be considered to be not genotoxic *in vitro* and *in vivo*.

In a Preliminary Reproduction Toxicity Screening Test [OECD TG421], this substance was administrated to male and female rats at 0, 100, 300, 1000 mg/kg/day dose by gavage for 48 days in males and 41 – 46 days (from 14 days before mating to 3 days after parturition) in females. No compound-related dose effects were observed in the copulation index, fertility index, gestation length, number of corpora lutea or implantations, implantation index, gestation index and maternal behavior. As for pups, there were no significant differences in number of offspring or live offspring, sex ratio, the live birth index, the viability index or the body weight. No pups with malformations were found in any groups. No changes in clinical signs and necropsy findings were observed in offspring. From those results, the NOAEL for reproductive and developmental toxicity is considered to be 1000 mg/kg/day.

Environment

This substance is soluble in water (6.0 g/L at 20°C) and the vapor pressure is low (< 0.00052 Pa at 100°C) [OECD TG104]. This substance was not readily biodegradable (0% after 14 days on BOD) [OECD TG301C] and is stable to hydrolysis in water at pH 4, 7 and 9 [OECD TG111]. The bioconcentration potential is low (BCF < 4 (0.2 mg/L) and < 0.4 (2 mg/L)) [OECD TG305C]. The log Pow is –0.67 at 25°C [OECD TG107]. This substance, if released into the atmosphere, will react with photochemically produced hydroxyl radical and decrease with a half-life of 4.5 hours. The pKa value of this substance is 3.28. It is present as a zwitterion under environmental condition. The behavior of this substance in the environment is considered to be similar to a weak acid.

The fugacity model (Mackay level III) suggests that if released to water, the majority of the substance would remain in the water compartment and, if released into air or soil, ca.50% would distribute to both water and the soil compartment.

In an acute toxicity test to fish, the LC50 was greater than 10 mg/L (*Oryzias latipes*, 96hr limit test) [OECD TG203].
In an acute toxicity test to daphnia, the EC50 was greater than 10 mg/L (*Daphnia magna*, 48hr limit test) [OECD TG202].
In an acute toxicity test to algae, the EC50 was greater than 10 mg/L (*Selenastrum capricornutum*: 0 – 72 hr biomass, and 24 – 72 hr growth rate) [OECD TG201].
In a chronic toxicity test to daphnia, the NOEC was 3.2 mg/L (*Daphnia magna*, 21 days reproduction) [OECD TG211] and in a chronic toxicity test to algae, the NOEC was 10 mg/L (*Selenastrum capricornutum*: 0 – 72 hr biomass, and 24 – 72 hr growth rate) [OECD TG201].

Exposure

The production volume of this substance in 2001 is estimated to be 2,000 - 3,000 metric tonnes/year in Japan and ca.18,000 metric tonnes/year in the world. The production countries are Japan, Korea, P.R. China, United Kingdom and U.S.A. In total there are about 20 manufacturing sites and about 55 use sites in the world.

This substance is produced in closed systems, and the packing process is performed in semi-closed or open systems. The user may use it in semi-closed systems. The only recognized use is as an industrial intermediate in the synthesis of organic pigments (Pigment Red 57 and its metal salts). These pigments are utilized in ink, paint, stationery goods, cosmetic goods and for the coloring of resin, fiber, leather, paper, rubber, etc. The concentration of the non-reacted parent substance in pigments is not known, but the consumer exposure is thought to be insignificant. There are no known direct uses of this substance in any consumer product. In the case of cosmetic goods (lip stick, etc.), regulations are in place in each region, for example the content of the substance in the colouring agent must be less than 0.2 % in the USA. Therefore, the possibility of consumer exposure from cosmetic goods is considered to be low.

Because of its use limited to the pigment industry and its low vapor pressure, the release of this substance into air and soil is very low. The concentration of this substance in effluent water from waste water treatment plant of manufacturer in Japan is less than 0.009 mg/L. The total emission from manufacturer's site through water in Japan is calculated to be less than 5 kg/year.

Based on the use and the properties of the substance, only occupational exposure by inhalation and dermal routes need to be considered.

RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

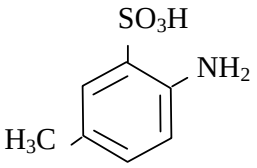
This chemical is currently of low priority for further work because of its low hazard potential.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 88-44-8
IUPAC Name: 2-Amino-5-methylbenzene sulfonic acid
Molecular Formula: C7H9NO3S
Structural Formula:



Molecular Weight: 187.22
Synonyms: 4B acid
6B acid
p-Toluidine-m-sulfonic acid
4-Aminotoluene-3-sulfonic acid
4-Methylaniline-2-sulfonic acid
Benzenesulfonic acid, 2-amino-5-methyl-

1.2 Purity/Impurities/Additives

Purity: 99 - 100 % by HPLC
Impurity: p-Toluidine (CAS 106-49-0) 0.0 – 0.1 %
Additives: none

1.3 Physico-Chemical properties

Table 1 Summary of physico-chemical properties

Property	Value	Protocol
Physical state	solid/powder	Visual inspection
Melting point	> 300 °C	JIS K4101-1993 5.1
Boiling point	> 350 °C	OECD TG103
Relative density	1.49 g/cm3 at 25 °C	JIS K7112-1980
Vapour pressure	< 0.00052 Pa at 100 °C	OECD TG104
Water solubility	6.0 g/L at 20 °C	unknown
Partition coefficient n-octanol/water (log value)	-0.67 at 25 °C -1.53 at 25 °C	OECD TG107 (flask-shaking, no buffer used) KOWWIN ver. 1.66 (calculation)
pH	3.8 at 25 °C, 6.0 g/L	unknown (pH meter)
pKa	3.28 at 25 °C	OECD TG112

Reference: CITI Japan, 1999, etc.

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

1) Manufacture

The production volume of this substance (4-Aminotoluene-3-sulfonic acid) in 2001 is estimated to be 2,000 - 3,000 metric tonnes/year in Japan and ca.18,000 metric tonnes/year in the world. The producing countries are Japan, Korea, P.R.China, United Kingdom and U.S.A. In total about 20 manufacturing sites exist in the world. Though it is produced in a closed system by a chemical reaction process, the possibility of limited leakage to the air (as dust) and the waste water at workplace (for example, at packing process) can be estimated.

The physical form of the marketed product is powder in 20 – 25 kg net paper or plastic bags, in 20 – 120 kg net drums or in 200 – 1000 kg net big bags.

2) Uses

The only recognized use is an industrial intermediate in the synthesis of Pigment Red 57 (CAS 5858-81-1) and the metal salts of the pigment. These pigments are utilized in ink, paint, stationery goods, cosmetic goods and coloring of resin, fiber, leather, paper, rubber, etc. There are no known direct uses of this substance in any consumer product.

The world consumption of this substance by region in 2001 is estimated to be as follows (unit: thousand metric tonne). Asia: 6.6, Europe: 5.9, North America: 5.4, Other: 0.1, total 18.0. In total about 55 use sites exist in the world.

The concentration of non-reacted substance in Pigment Red 57s is unknown. However; (1) no excess volume is used at chemical synthesis of the pigment (according to the pigment producers in Japan and in the USA), (2) definitely in some case human exposure from those pigments by cosmetic goods (for example, by lip stick) or stationery goods are possible, however the volume is limited (FDA requirement; less than 0.2% from the metal salts or lakes of pigment) and there are no adverse health reports from such exposure, and (3) exposure volume of ink, paint, etc. to workers in industry in its synthesis or use is limited due to good hygiene practices.

2.2 Environmental Exposure and Fate

2.2.1 Sources of Environmental Exposure

Sources of potential release to the environment are, (1) emission to the air (as dust) and waste water at producer’s chemical factories and (2) emission to the air (as dust) and waste water at user’s chemical factories.

Release to the outside of each factory through; (1) the air is very low due to very low vapour pressure (< 0.00052 Pa at 100 degrees C) [OECD TG104], (2) the soil is very low as floors are covered by concrete, etc. (3) the waste water can be considerable. However the concentration in effluent from waste water treatment plant of the production site in Japan was less than 0.009 mg/L (measured by 55 times concentrated sample) (Mitsuboshi 2002). The environmental release through effluent water at the production site in Japan is calculated to be less than 5 kg/year.

2.2.2 Photodegradation

This substance, if released to the air compartment, will react with photochemically-produced hydroxyl radical with a half-life of 4.5 hours [calculated: SRC AOP Win v.1.90] (CERI Japan 2002).

2.2.3 Stability in Water

This substance was stable to hydrolysis in water at pH 4, 7 and 9 [OECD TG111] (CITI Japan 1999).

2.2.4 Transport between Environmental Compartments

A generic Fugacity Model calculation (Mackay level III) suggests that if released to air or soil, the majority of this substance would distribute equally to soil and water. It would not distribute to air and soil from water. Those results are shown in Table 2.

Table 2 Environmental distribution using the Fugacity Model (Mackey level III)

Compartment	release: 100% to air	release: 100% to water	release: 100% to soil
Air	0.0%	0.0%	0.0%
water	50.5%	99.6%	45.0%
soil	49.3%	0.0%	54.9%
sediment	0.2%	0.4%	0.2%

2.2.5 Biodegradation

A modified MITI Test (I) [OECD TG301C] (CITI 1999) indicated that this substance is not readily biodegradable (0% based on BOD during a 14 days incubation period).

2.2.6 Bioaccumulation

The log Pow value is -0.67 [OECD TG107] (CITI 1999). This substance was tested for bioaccumulation and has shown low bioaccumulation characteristics (BCF < 4 (0.2 mg/L) and < 0.4 (2 mg/L) [OECD TG305C] (CITI 1999).

2.2.7 Other Information on Environmental Fate

As the conclusion, the preferred environmental compartment of this substance is water, and the total volume released to the environment is considered to be very low.

2.3 Human Exposure

2.3.1 Occupational Exposure

Officially assigned workplace exposure limit value was not available for this chemical.

Occupational exposure by the dust of this substance at the producer's workplace (for example during the packing process) and the user's workplace (for example during the dumping process to

the reactor or storage) may occur through the inhalation and dermal route. It should be kept in mind that the vapour pressure of this substance is very low.

At a producer's workplace in Japan, this substance is produced in a closed system by a chemical reaction process, and drying, sampling, transportation and packing are performed in semi-closed or open processes. Basically all of the semi-closed or open systems are designed with local ventilators.

The calculated Estimated Human Exposures (EHEs) are shown in Table 3.

The EASE model suggests that if all processes are operated by the same worker and if inhalation occurred at the workplace of manufacturer's site, the Estimated Human Exposure (EHE inh) would be 1.70 mg/kg/day. And the exposure by the dermal route (EHE der) through hands would be 28.5 mg/kg/day.

Table 3 Workplace exposure and EHEs (calculated)

operation	working time (hours/day)	maximum EHE (mg/kg/day)
transferring process 1	8.0	EHE inh = 5mg/m^3 x 1.25m^3/hr x 8.0hr/day /70kg = 0.71 EHE der = 1mg/cm^2/day x 840cm^2 x 8.0hr/8hr /70kg = 12.0
transferring process 2 (including sampling for process evaluation)	2.0	EHE inh = 5mg/m^3 x 1.25m^3/hr x 2.0hr/day /70kg = 0.18 EHE der = 1mg/cm^2/day x 840cm^2 x 2.0hr/8hr /70kg = 3.0
packing process and sampling	8.0	EHE inh = 5mg/m^3 x 1.25m^3/hr x 8.0hr/day /70kg = 0.71 EHE der = 1mg/cm^2/day x 840cm^2 x 8.0hr/8hr /70kg = 12.0
analysis	1.0	EHE inh = 5mg/m^3 x 1.25m^3/hr x 1.0hr/day /70kg = 0.09 EHE der = 1mg/cm^2/day x 840cm^2 x 1.0hr/8hr /70kg = 1.5
total		EHE inh = 1.70 mg/kg/day EHE der = 28.5 mg/kg/day grand total = 30.2 mg/kg/day

EHEs were calculated by following parameter.
body weight = 70 kg, respiratory volume = 1.25 m^3/hr, open hands area = 840 cm^2,
dust concentration in the air (for inhalation) = 5 mg/m^3,
dermal absorption rate = 1 mg/cm^2/day (EASE model)

Normally, workers wear protective clothing, gloves and breathing protection during the work. And, in fact each process is operated by another worker. Therefore, the actual exposure is considered to be substantially lower than the calculated value.

Occupational monitoring and working time data at user's workplace are not available. However, normally workers wear protective clothing, gloves and breathing protection during the work, and local ventilators are equipped appropriately.

2.3.2 Consumer Exposure

As mentioned in section **2.1** 2), consumer exposure by cosmetic goods or stationery goods is very limited, and there are no adverse health reports from such exposure.

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

There is no available information on Toxicokinetics, Metabolism and Distribution.

3.1.2 Acute Toxicity

There is no adequate information on humans.

Studies in Animals

Oral

In a preliminary examination of a 28-Day Repeat Dose Toxicity test in rats [OECD TG407] (MHW Japan 1996a), no death was observed at up to 2,000 mg/kg/day in both sexes.

In a preliminary examination of a Micronucleus test in mice [OECD TG474] (ETAD 1988b), no death was observed at 5,000 mg/kg in both sexes.

Conclusion

From the outcome of a single dose administration reported in a preliminary examination of a 28-Day Repeat Dose Toxicity test [OECD TG407], oral LD_{50} in rats is considered to be greater than 2,000 mg/kg in both sexes.

3.1.3 Irritation

There is no adequate information on eye irritation and respiratory tract irritation.

Skin Irritation

Studies in Humans

This substance was not corrosive to the skin of a human arm in 6hr patch test performed in accordance with IMDG Code 2002, (Mitsuboshi 2003). No irritation was observed.

Conclusion

This substance is not corrosive or irritant to human skin.

3.1.4 Sensitisation

There was no information about sensitization.

3.1.5 Repeated Dose Toxicity

There is no available information on humans.

Studies in Animals

Oral

One oral rat study was available. A 28-Day Repeat Dose Toxicity Test [OECD TG407] (MHW Japan 1996a) was conducted under well-designed protocols and detailed information were reported.

In the preliminary examination, all 4 males and 4 females survived at a dose of up to 2,000 mg/kg/day (gavage) for 14 days. In the study, no toxicological effects in the clinical signs, body weight, food consumption, urinary findings, hematological findings, blood chemical findings and weight of organs were observed in the animals of any groups up to 2,000 mg/kg/day. At necropsy, enlargement of cecum was observed in all the animal of the 2,000 mg/kg/day group.

Then, in the main test, this substance was administered to each 6 male and 6 female Sprague-Dawley rats at doses of 0, 100, 300, 1000 mg/kg/day by gavage. The dosing period was 28 days each. Increase of specific gravity and decrease of pH of urine were observed in males of the 1000mg/kg/day group. However no treatment related change was observed in other findings. Decrease of white blood cell count was observed in males of the 1000mg/kg/day group. Other dose related pathological changes were not observed in the lymphatic tissues. Increase of GPT in females, decrease of total cholesterol in males and decrease of glucose in females were observed in the 1000 mg/kg/day group. However, , no pathological change was observed in any related organs including the liver. At necropsy, enlargement of cecum was observed in one male and one female in the 1000mg/kg/day group. However no diarrhea or no growth abnormalities were observed. Decrease of thymus weight at 100 mg/kg/day and increase of spleen weight in all dose levels were observed in females. However those changes in thymus and spleen were not dose dependent. All of those changes had recovered before 14 days after cessation of treatment. No changes in mortality, behavior or toxic effects on the body weight and food consumption were observed in any dose level and in any sex.

Conclusion

Toxicological effects were decrease of white blood cell count, total cholesterol and urine pH and enlargement of cecum in males at 1000 mg/kg/day; increase of GPT, decrease of glucose and enlargement of cecum in females at 1000 mg/kg/day. The NOAEL for repeat dose toxicity to rats is 300 mg/kg/day in both sexes.

3.1.6 Mutagenicity

There is no available information on humans.

Studies in Animals

In vitro Studies

There are adequate results available from two bacterial and five non-bacterial *in vitro* studies on this substance. Also, one result from an *in vivo* test was available. The summary of those studies is shown in Table 4.

Table 4: Summary of genetic toxicity studies

type	species	protocol	dose	S9	result	reference
Bacterial test						
Ames test	*S.typh.* (TA100, TA1535, TA98, TA1537), *E.coli*	OECD TG 471 & 472	up to 5,000	-	negative	MHW Japan 1996b

	(WP2*uvr*A)		ug/plate	+	negative	
Ames test **	*S.typh.* (TA100, TA1535, TA98, TA1537, TA1538)	Maron & Ames (1983)	up to 5,000 ug/plate	-	negative	ETAD 1988a
				+	negative	
Non-bacterial *in vitro* test						
Chromosomal aberration test	CHL/IU cell	OECD TG 473	up to 1.9mg/mL	-	negative	MHW Japan 1996c
				+	negative*	
Unscheduled DNA synthesis **	Human Fibro- blasts CRL 1121	other	up to 2000mg/L		negative	CIBA 1985a
Unscheduled DNA synthesis **	hepatocytes of male Tif.RAIf rat	other	up to 2000mg/L		negative	CIBA 1985b
Unscheduled DNA synthesis	hepatocytes of male ACI rat	Williams et al.	up to 187mg/L		negative	Mutat.Res 1988
HGPRT assay **	V79 CHL cell	other	up to 1500mg/L	-	negative	CIBA 1986
				+	negative	
In vivo test						
Mouse Micro-nucleus test **	C578BL/6JfCD-1/Alpk	OECD TG 474	5000mg/kg, 3125mg/kg		negative	ETAD 1988b

* The result of +S9mix short-term Chromosomal aberration test before pH adjustment, was positive.
** Those data were obtained after SIAM-16, which was held in May 2003.

Key studies on this substance are described below. They were well conducted and reported the detailed information.

Bacterial test:

The first study (MHW Japan, 1996) was well conducted and reported according to OECD TG 471 & 472, following GLP. All results were negative up to 5,000 ug/plate in *Salmonella typhimurium* TA100, TA1535, TA98, TA1537 and *Escherichia coli* WP2*uvr*A with and without an exogenous metabolic activation system. The same result was obtained in the second study (ETAD 1988a) in *Salmonella typhimurium* TA100, TA1535, TA98, TA1537, TA1538.

Non-bacterial *in vitro* test:

The chromosomal aberration test with CHL cells (MHW Japan 1996c) was well conducted and reported according to OECD TG 473, following GLP. Except for the 6hr short-term test in the presence of S9 mix, all results were negative up to 1.9 mg/mL (10 mM). To confirm if the result is caused by low pH effect or by physiological DNA damage, the confirmation 6hr short-term test was performed before and after pH adjustment in the presence of S9mix. The summary is shown in Table 5.

Table 5: Summary of the confirmation study before and after pH adjustment of the 6hr short-term chromosomal aberration test in the presence of S9 mix(highest doses shown only).

	dose	**pH range**	**clastogenicity % (the value of control)**	**polyploid % (the value of control)**	**result**
before	1.9 mg/mL	5.84–6.26	7.0 % (1.5 %)	1.38 % (0.38 %)	positive
after	1.9 mg/mL	6.80–7.19	3.0 % (1.5 %)	0.75 % (0.13 %)	negative

As the result, this substance induced weak chromosomal aberration. However the aberration was due to acidity and not to physiological DNA damage.

The unscheduled DNA synthesis assay with hepatocytes of male ACI rats (Yoshimi et al., 1988) provided detailed information. Both “unscheduled DNA synthesis (UDS) frequency” and “% of

UDS positive cells with more than 5 grains" were within the negative range up to 187 mg/L. The results of another two unscheduled DNA synthesis assay with Human fibroblasts (CIBA 1985a) and hepatocytes of male Tif.RAIf rats (CIBA 1985B) were negative. And the result of a HGPRT assay with V79 CHL cells (CIBA 1986) was negative, too.

In vivo Studies

The *in vivo* micronucleus assay in C578BL/6JfCD-1/Alpk mice orally administered at 5000 mg/kg and 3125 mg/kg (ETAD 1988b) was well conducted and reported according to OECD TG474, following GLP. Though slight cytotoxicity was observed on polychromatic erythrocytes at 5000 mg/kg in males, it did not show a statistically significant increase on the ratio of micronucleated polychromatic erythrocytes at extended count. Therefore, the result of the micronucleus assay was negative.

Conclusion

This substance is not mutagenic in bacteria. It induces weak chromosomal aberration in CHL/IU cells with an exogenous metabolic activation system. However the aberration is due to acidity and not to physiological DNA damage. The result of unscheduled DNA synthesis tests and an HGPRT assay were negative, too. In addition, the result of a micronucleus assay was negative. Overall, this substance can be considered to be not genotoxic *in vitro* and *in vivo*.

3.1.7 Carcinogenicity

There is no adequate information on carcinogenicity.

3.1.8 Toxicity for Reproduction

There is no available information on human.

Studies in Animals

Effects on Fertility

A Preliminary Reproduction Toxicity Screening Test [OECD TG421] (MHW Japan 1999) was performed in accordance with GLP and provided detailed information.

This substance was administered to each 12 male and 12 female *Sprague-Dawley* (Crj: CD) rats at doses of 0, 100, 300, 1000 mg/kg/day by gavage. The dosing period for males was 48 days (before mating 14 days, during mating 14 days and after mating 20 days). The dosing period for pregnant females was 41 - 46 days (before mating 14 days, during mating 14 days maximum, during gestation about 21 days and after pregnancy 3 days).

No compound-related dose effects were observed in the copulation index, fertility index, gestation length, number of corpora lutea or implanations, implanation index, gestation index, parturition or maternal behavior in any groups.

Developmental Toxicity

In the above mentioned Preliminary Reproduction Toxicity Screening Test; there were no significant differences in number of offspring or live offspring, sex ratio, the live birth index, the viability index or the body weight in any groups. No pups with malformations were found in any groups. No changes in clinical signs and necropsy findings were observed in offspring.

Conclusion

NOAEL for reproductive and developmental toxicity is considered to be 1000 mg/kg/day.

3.2 Initial Assessment for Human Health

In a preliminary examination of a 28-Day Repeat Dose Toxicity test in rats [OECD TG407], no mortality was observed at up to 2,000 mg/kg/day in both sexes. This substance was not corrosive or irritant to human skin.

In the 28-Day Repeat Dose Toxicity Test, this substance was administered to male and female rats at doses of 0, 100, 300, 1000 mg/kg/day by gavage. In male of the 1000 mg/kg/day group , decreases of white blood cell count, total cholesterol and urine pH, also enlargement of cecum were observed. In females of the 1000 mg/kg group, increase of GPT and decrease of glucose, also enlargement of cecum were observed. All of those changes recovered until 14 days after cessation of the treatment. The NOAEL in both sexes is considered to be 300 mg/kg/day.

For Genetic Toxicity of this substance, there are results available from two adequate Ames tests (one was OECD TG471 & 472) and five non-bacterial *in vitro* tests (one was OECD TG473). One *in vivo* micronucleus test [OECD TG474] was available, too. This substance is not mutagenic in bacteria, but induces chromosomal aberration in CHL/IU cells with an exogenous metabolic activation system due to the acidity. The result of three unscheduled DNA synthesis was negative. Also, the result of the micronucleus test was negative. Overall, this substance can be considered to be not genotoxic *in vitro* and *in vivo*.

In a Preliminary Reproduction Toxicity Screening Test [OECD TG421], this substance was administered to male and female rats at doses of 0, 100, 300, 1000 mg/kg/day by gavage. No compound-related dose effects were observed in the copulation index, fertility index, gestation length, number of corpora lutea or implanations, implanation index, gestation index and maternal behavior in any dose groups. As for pups, there were no significant differences in number of offspring or live offspring, sex ratio, the live birth index, the viability index or body weight. No pups with malformation were found in any groups. No changes in clinical signs and necropsy findings were observed in offspring. From those results, the NOAEL for both reproduction and developmental toxicity is considered to be 1000 mg/kg/day.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

The summary of reliable studies and ECOSAR estimation is shown in Table 6.

Table 6: Aquatic toxicity

organism	test method	result (mg/L)	reference
Fish			
Medaka (*Oryzias Latipes*)	OECD TG203 96 hr (ss)	LC_{50} (96hr) > 10 (mc) LC_0 (96hr) > 10 (mc)	EA Japan 1999a
Fish	calculation (ECOSAR v0.99g)	LC_{50} (96hr) = 229000	
Daphnid			
Water flea (Daphnia magna)	OECD TG202 48 hr (s)	EC_{50} (imm, 48hr) > 10 (mc) EC_0 (imm, 48hr) > 10 (mc) NOEC (imm, 48hr) = 10 (mc)	EA Japan 1999b
Daphnia	calculation (ECOSAR v0.99g)	EC_{50} (48hr) = 116	
Water flea (Daphnia magna)	OECD TG211 21 day (ss)	EC_{50} (rep, 21day) > 10 (mc) EC_0 (rep, 21day) > 10 (mc) NOEC (rep, 21day) = 3.2*(mc) LOEC (rep, 21day) = 10 (mc)	EA Japan 1999c
Daphnia	calculation (ECOSAR v0.99g)	NOEC (chronic) = 5.0	
Algae			
Green algae (Selenastrum capricornutum)	OECD TG201 72 hr (s)	EC_{50} (bms, 0-72hr) > 10 (nc) NOEC (bms, 0-72hr) =10 (nc) EC_{50} (gr, 24-48hr) > 10 (nc) NOEC (gr, 24-48hr) = 10 (nc) EC_{50} (gr, 24-72hr) > 10 (nc) NOEC (gr, 24-72hr) = 10 (nc)	EA Japan 1999d

s: static, ss: semi-static mc: measured concentration, nc: nominal concentration (actual concentration measured and greater than 80% of the nominal) bms: biomass, gr: growth rate, imm: immobility, rep: reproduction
* No. of juveniles at Day 21 were significant few from control at the upper dose (10mg/L).
remark: Due to the author's misunderstanding, all of those OECD studies were carried out up to 10mg/L only.

In addition, though the quality of the data was not sufficient to be regarded as a key study, the following acute toxicity results to fishes was available. LC_{50} (96hr) for *Gambusia affinis* is 375 mg/L (Wallen et al., 1957). LC_{50} (48hr) for *Oryzias latipes* is 480 mg/L [JIS K0102] (METI Japan 1992).

Acute Toxicity Test Results

Regarding acute toxicity to fish, the LC_{50} was greater than 10 mg/L (*Oryzias latipes*, 96hr limit test) [OECD TG203]. In the acute toxicity test to daphnids, the EC_{50} was greater than 10 mg/L (*Daphnia magna*, 48hr limit test) [OECD TG202]. In the acute toxicity test to algae, the EC_{50} was greater than 10 mg/L (*Selenastrum capricornutum*: 0 – 72 hr biomass, and 24 – 72 hr growth rate) [OECD TG201].

Chronic Toxicity Test Results

Regarding chronic toxicity to daphnids, the NOEC was 3.2 mg/L (*Daphnia magna*, 21 days reproduction) [OECD TG211]. Regarding chronic toxicity to algae, the NOEC was 10 mg/L (*Selenastrum capricornutum*: 0 – 72 hr biomass, and 24 – 72 hr growth rate) [OECD TG201].

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

This substance is soluble in water (6.0g/L at 20°C) and its vapor pressure is low (< 0.00052 Pa at 100°C) [OECD TG104]. This substance is not readily biodegradable (0% after 14 days on BOD) [OECD TG301C] and is stable to hydrolysis in water at pH 4, 7 and 9 [OECD TG111] . The bioconcentration potential is low (BCF < 4 (0.2 mg/L), < 0.4 (2 mg/L)) [OECD TG305C]. The log Pow is –0.67 at 25°C [OECD TG107]. This substance, if released into the atmosphere, will react with photochemically-produced hydroxyl radicals and decrease with the half-life of 4.5 hours. This substance is present as a zwitterion under environmental conditions. The behavior of this substance in the environment is considered to be similar to a weak acid.

This substance could be released into the aquatic environment through waste water from the manufacturer's or user's chemical factory sites, and according to a calculation using the Fugacity Model [Mackay level III] it would remain almost entirely in the water compartment .

The concentration in the effluent water from a manufacturer's waste water treatment plant in Japan is less than 0.009 mg/L.

In an acute toxicity test to fish, the LC50 was greater than 10 mg/L (*Oryzias latipes*, 96hr limit test) [OECD TG203]. In an acute toxicity test to daphnids, the EC50 was greater than 10 mg/L (*Daphnia magna*, 48hr limit test) [OECD TG202]. In an acute toxicity test to algae, the EC50 was greater than 10 mg/L (*Selenastrum capricornutum*: 0 – 72 hr biomass, and 24 – 72 hr growth rate) [OECD TG201].

In a chronic toxicity test with daphnids, the NOEC was 3.2 mg/L (*Daphnia magna*, 21 days reproduction) [OECD TG211]. Regarding chronic toxicity to algae, the NOEC was 10 mg/L (*Selenastrum capricornutum*: 0 – 72 hr biomass, and 24 – 72 hr growth rate) [OECD TG201].

The predicted no effect concentration (PNEC) of 0.032 mg/L for aquatic organisms was calculated from the lowest NOEC (Daphnia magna, 21 days reproduction, 3.2 mg/L), using an assessment factor of 100 (as recommended by the OECD guidance), because two chronic test results (daphnids and algae) are available.

5 RECOMMENDATIONS

The chemical is currently of low priority for further work because of its low hazard potential.

6 REFERENCES

CERI Japan 2002: Calculated by Mr. Shinoda of Chemical Evaluation and Research Institute Japan in 2002

CIBA 1985a: Test No. 850213, AUTORADIOGRAPHIC DNA REPAIR TEST ON HUMAN FIBROBLASTS, CIBA-GEIGY LIMITED, unpublished report

CIBA 1985b: Test No. 850212, AUTORADIOGRAPHIC DNA REPAIR TEST ON RAT HEPATOCYTES, CIBA-GEIGY LIMITED, unpublished report

CIBA 1986: Test No. 850623, V79 CHINESE HAMSTER POINT MUTATION TEST, CIBA-BEIGY LIMITED, unpublished report

CITI Japan 1999, etc: Report No. 80157K, other, Chemical Inspection and Testing Institute, unpublished report

EA Japan 1999a: Report No. EFA98002, Environment Agency Japan, unpublished report

EA Japan 1999b: Report No. EDI98002, Environment Agency Japan, unpublished report

EA Japan 1999c: Report No. EDR98002, Environment Agency Japan, unpublished report

EA Japan 1999d: Report No. EAI98002, Environment Agency Japan, unpublished report

ETAD 1988a: Report No. CTL/P/1999, Ecological and Toxicological Association of Dyes and Organic Pigments Manufacturers, unpublished report

ETAD 1988b: Report No. CTL/P/2011, Ecological and Toxicological Association of Dyes and Organic Pigments Manufacturers, unpublished report

METI Japan 1992: BIODEGRADATION AND BIOACCUMULATION DATA OF EXISTING CHEMICALS BASED ON THE CSCL JAPAN, 1992, p3-110, Ministry of Economy, Trade and Industry Japan

MHW Japan 1996a: Twenty-eight-day Repeated Dose Oral Toxicity Test of …, Toxicity Testing Reports of Environmental Chemicals, vol.4, 1996, 99-106, Ministry of Health and Welfare Japan

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MHW Japan, 1996c: In vitro Chromosomal Aberration Test of …, Toxicity Testing Reports of Environmental Chemicals, vol.4, 1996, 111-114, Ministry of Health and Welfare Japan

MHW Japan, 1999: Preliminary Reproduction Toxicity Screening Test of …, Toxicity Testing Reports of Environmental Chemicals, vol.7, 1999, 163-171, Ministry of Health and Welfare Japan

Mitsuboshi 2002, 2003: Mitsuboshi Chemical Co., Ltd., unpublished report

Wallen, I.E. et al., 1957: TOXICITY TO *GAMBUSIA AFFINIS* OF CERTAIN PURE CHEMICALS IN TURBID WATERS, Sewage and Industrial Wastes, vol.29, No.6, 695-711

Yoshimi, N. et al., 1988: The genotoxicity of a variety of aniline derivatives in a DNA repair test with primary cultured rat hepatocytes, Mutation Research, 206, 683-691

SIDS Dossier

Existing Chemical	:	ID: 88-44-8
Memo	:	4B acid
CAS No.	:	88-44-8
EINECS Name	:	4-aminotoluene-3-sulphonic acid
EC No.	:	201-831-3
TSCA Name	:	Benzenesulfonic acid, 2-amino-5-methyl-
Molecular Formula	:	$C_7H_9NO_3S$

Producer related part

Company	:	Mitsuboshi Chemical Co., Ltd.
Creation date	:	18.04.2002

Substance related part

Company	:	Mitsuboshi Chemical Co., Ltd.
Creation date	:	18.04.2002
Status	:	
Memo	:	
Printing date	:	30.06.2003
Revision date	:	
Date of last update	:	30.06.2003
Number of pages	:	58
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

Type : lead organization
Name : Mitsuboshi Chemical Co., Ltd.
Contact person : Kiminori Nagayama
Date : 07.07.2003
Street : 1-49-4 Takashimadaira, Itabashi-ku
Town : 175-0082 Tokyo
Country : Japan
Phone : +81-3-3932-5231
Telefax : +81-3-3932-5230
Telex :
Cedex :
Email : nagayama@mitsuboshi-chem.co.jp
Homepage : http://www.mitsuboshi-chem.co.jp

Remark : 4B acid consortia
Flag : non confidential
30.06.2003

Type :
Name : BASF AG
Contact person :
Date :
Street : Karl-Bosch-Str
Town : 67056 Ludwigshafen
Country : Germany
Phone :

Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
11.02.2000

Type :
Name : BASF Italia Spa
Contact person :
Date :
Street :
Town : 20031 Cesano Maderno MI
Country : Italy
Phone :
Telefax :

Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
11.02.2000

Type :
Name : Bayer AG
Contact person :
Date :
Street :
Town : 51368 Leverkusen
Country : Germany
Phone :

Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
11.02.2000

Type :
Name : Ciba Specialty Chemicals Inc.
Contact person :
Date :
Street :
Town : 4002 Basel
Country : Switzerland
Phone :
Telefax :

Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA) 11.02.2000

Type :
Name : Francolour Pigments SA
Contact person :
Date :
Street : Plateforme De Villers-St-Paul
Town : 60870 Rieux
Country : France
Phone : 0033/4474/46-46
Telefax : -47

Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA) 11.02.2000

Type :
Name : Hickson & Welch Ltd.
Contact person :
Date :
Street : Wheldon Road
Town : WF10 2JT Castleford
Country : United Kingdom
Phone :

Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA) 11.02.2000

Type :
Name : Intermedios Orgánicos SA
Contact person :
Date :
Street : C/ carril
Town : 08110 Montcada
Country : Spain
Phone : 93 5751144
Telefax : 93 5646552

Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA) 11.02.2000

Type :
Name : SunChemical
Contact person :
Date :
Street : Gl. Lyngvej 2
Town : 4600 Køge
Country : Denmark
Phone : +45 53657585
Telefax : +45 53663019

Telex : 43589 KVK DK
Cedex : 2142007
Email :
Homepage :

Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
11.02.2000

Type :
Name : ZENECA Specialties
Contact person :
Date :
Street : PO Box 42
Town : M9 3DA Manchester
Country : United Kingdom
Phone :
Telefax :

Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
11.02.2000

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

Type : manufacturer
Name of plant : Han Nam Co., Ltd.
Street :
Town :
Country : other: Korea
Phone :
Telefax :

Country : Korea
Flag : non confidential
18.06.2003

Type : manufacturer
Name of plant : Hickson & Welch Ltd.
Street :
Town :
Country : United Kingdom
Phone :
Telefax :

Country : United Kingdom
Flag : non confidential
18.06.2003

Type : manufacturer
Name of plant : Mitsuboshi Chemical Co., Ltd. Soma Plant
Street : 280 Kabaniwamagome
Town : 979-2511 Soma-shi, Fukushima
Country : Japan
Phone : +81-244-33-5131
Telefax : +81-277-33-5130

Country : Japan
Flag : non confidential
18.06.2003

Type : manufacturer
Name of plant : Sun Chemical Corporation
Street :
Town :
Country : United States
Phone :

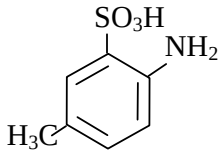
Country : U.S.A.
Reliability : (1) valid without restriction
Flag : non confidential
02.08.2002

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

IUPAC Name : 2-Amino-5-methylbenzene sulfonicacid
Smiles Code :
Molecular formula : $C_7H_9NO_3S$
Molecular weight : 187.2
Petrol class :
Structural formula :



Remark : OECD name: 4-aminotoluene-3-sulphonic acid
Flag : non confidential
18.06.2003

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type : typical for marketed substance
Substance type : organic
Physical status : solid
Purity : 99 - 99.5 % w/w
Colour : pale brown to gray
Odour : no distinct odour

Remark : Purity is the figure by diazotization titration method.
Flag : non confidential
18.06.2003 (16)

Purity type : typical for marketed substance
Substance type : organic
Physical status : solid
Purity : ca. 99 % w/w

Colour : pale brown to gray
Odour : no distinct odour

Remark : Purity is the figure by HPLC method.
Flag : non confidential
18.06.2003 (16)

Purity type :
Substance type : organic
Physical status : solid
Purity :
Colour :
Odour :

Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
11.02.2000

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

4B ACID

Flag : non confidential
18.06.2003

6B ACID

Flag : non confidential
18.06.2003

P-TOLUIDINE-M-SULFONIC ACID

Flag : non confidential
18.06.2003

2-AMINO-5-METHYLBENZENESULFONICACID

Flag : non confidential
18.06.2003

4-AMINOTOLUENE-3-SULPHONICACID

Flag : non confidential
18.06.2003

2-Amino-5-methylbenzenesulfonic acid

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
29.08.1996

2-Amino-5-methylbenzolsulfonsäure

Source : Bayer AG Leverkusen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

25.05.1998

4-Aminotoluene-3-sulfonic acid

Source **:** BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
29.08.1996

4-aminotolueno-3-sulfónico

Source **:** Intermedios Orgánicos SA Montcada
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
08.07.1998

4-Aminotoluol-3-sulfonsäure

Source **:** Bayer AG Leverkusen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
03.06.1998

4-B-Säure

Source **:** Bayer AG Leverkusen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
25.05.1998

4-Methyl-2-sulfoaniline

Source **:** BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
29.08.1996

4-Methylanilin-2-sulfonsäure

Source **:** Bayer AG Leverkusen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
25.05.1998

4-Methylaniline-2-sulfonic acid

Source **:** BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
29.08.1996

4-Toluidin-2-sulfonsäure

Source **:** Bayer AG Leverkusen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
25.05.1998

4B acid

Source **:** Hickson & Welch Ltd. Castleford
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
24.09.1993

6-Amino-m-toluenesulfonic acid

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
29.08.1996

Acide 4B

Source : Francolour Pigments SA Rieux
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
29.06.1998

Benzenesulfonic acid, 2-amino-5-methyl- (9CI)

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
29.08.1996

Benzenesulfonic acid, 2-amino-5-methyl-; Red 4B acid.

Source : SunChemical Køge
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
14.05.1998

m-Toluenesulfonic acid, 6-amino- (6CI, 7CI, 8CI)

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
29.08.1996

p-aminotoluene-m-sulphonic acid

Source : Hickson & Welch Ltd. Castleford
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
24.09.1993

p-Toluidin-m-sulfonsäure

Source : Bayer AG Leverkusen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
25.05.1998

p-Toluidine-2-sulfonic acid

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
29.08.1996

p-Toluidine-m-sulfonic acid

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
29.08.1996

p-toluidine-m-sulphonic acid

Source : ZENECA Specialties Manchester
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
07.05.1998

p-toluidine-o-sulphonic acid (NH2=1)

Source : Hickson & Welch Ltd. Castleford
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
24.09.1993

PTMS

Source : Bayer AG Leverkusen
BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
25.05.1998

PTMSA

Source : Bayer AG Leverkusen
BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
03.06.1998

1.3 IMPURITIES

Purity : typical for marketed substance
CAS-No : 106-49-0
EC-No : 203-403-1
EINECS-Name : p-toluidine
Molecular formula : C7H9N
Value : 0 - 0.1 % w/w

Source : 4B acid consortia
Flag : non confidential
18.06.2003

1.4 ADDITIVES

1.5 TOTAL QUANTITY

Quantity : ca. - 18000 tonnes produced in 2001

Remark : World consumption by region in 2001 (unit: 1000 metric tons)
Asia 6.6, Europe 5.9, N.America 5.4, Other 0.1 total 18.0
Source : estimation by 4B acid consortia
Flag : non confidential
18.06.2003

Quantity : 2000 - 3000 tonnes produced in 2001

Remark : production in Japan in 2001
18.06.2003

Quantity : 5000 - 10000 tonnes in

Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
18.06.2003

1.6.1 LABELLING

Symbols : Xi, , ,
Nota : , ,
R-Phrases : (36/37/38) Irritating to eyes, respiratory system and skin
S-Phrases : (26) In case of contact with eyes, rinse immediately with plenty of water and seek medical advice
(27) Take off immediately all contaminated clothing
(28) After contact with skin, wash immediately with plenty of ...
(36/37/39) Wear suitable protective clothing, gloves and eye/face protection

Remark : As this substance has a character like a weak acid and a powder form, some suppliers may indicate such symbol and phrases.
Flag : non confidential
30.06.2003 (2) (10)

1.6.2 CLASSIFICATION

1.6.3 PACKAGING

1.7 USE PATTERN

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

Remark : intermediate of pigment
Source : 4B acid consortia
Flag : non confidential
18.06.2003

Type of use : type
Category : Non dispersive use

Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
11.02.2000

Type of use : type
Category : Use in closed system

Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
11.02.2000

Type of use : type
Category : Use resulting in inclusion into or onto matrix

Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
11.02.2000

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

Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
11.02.2000

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

Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
11.02.2000

Type of use : use
Category : Colouring agents

Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
11.02.2000

Type of use : use
Category : Intermediates

Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
11.02.2000

Type of use : use
Category : other

Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
11.02.2000

1.7.1 DETAILED USE PATTERN

Industry category : 3 Chemical industry: chemicals used in synthesis
Use category : 33 Intermediates
Extra details on use category : Substance processed elsewhere
No extra details necessary
Emission scenario document : available
Product type/subgroup :
Tonnage for Application :
Year :
Fraction of tonnage for application :
Fraction of chemical in formulation :
Production : :
Formulation : :
Processing : :
Private use :
Recovery :

Source : 4B acid consortia
Flag : non confidential
18.06.2003

1.7.2 METHODS OF MANUFACTURE

Origin of substance : Synthesis
Type : Production

Remark : This substance can be produced by reaction of p-toluidine (C6H4CH3NH2: CAS No. 106-49-0) and sulfuric acid (H2SO4: CAS No. 7664-93-9).
In Japan, the chemical reaction is operated in closed system, and the

drying and packing are operated in semi-closed or open system.
Source : 4B acid consortia
Flag : non confidential
18.06.2003

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

Remark : kein MAK-Wert festgelegt
Source : BASF Italia Spa Cesano Maderno MI
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
14.06.1996 (30)

Remark : kein MAK-Wert festgelegt
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
17.10.1995 (31)

1.8.2 ACCEPTABLE RESIDUES LEVELS

Proposed residues level : not more than 0.2% as the content in cosmetic use Pigment Red 57 Barium lake, or the Sodium or Calcium salt
Maximum residue level : mg/kg

Remark : This substance is used for an intermediate of Pigment Red 57. One of the application of the Barium, Sodium and Calcium salt of this pigment is cosmetic product, such as lipstick, nail polish and blush. Some of them are on the positive list for cosmetic products in the USA, EU, Japan, etc.
The FDA specifications require the content to be less than 0.2% (as total excess reaction intermediate).
Source : Sun Chemical Corporation (USA)
Flag : non confidential
19.06.2003

1.8.3 WATER POLLUTION

Classified by : KBwS (DE)
Labeled by :
Class of danger : 2 (water polluting)

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
17.10.1995 (3)

Classified by : other: Bayer AG
Labeled by : other: Bayer AG
Class of danger : 2 (water polluting)

Source : BASF Italia Spa Cesano Maderno MI
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

14.06.1996 (3)

Classified by : other: Bayer AG
Labeled by :
Class of danger : 2 (water polluting)

Source : Bayer AG Leverkusen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
25.05.1998

1.8.4 MAJOR ACCIDENT HAZARDS

Legislation : Stoerfallverordnung (DE)
Substance listed : no
No. in Seveso directive :

Source : BASF Italia Spa Cesano Maderno MI
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
14.06.1996 (25)

Remark : kein Stoff der StoerfallVO
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
17.10.1995 (25)

1.8.5 AIR POLLUTION

Remark : keine Festlegung
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
17.10.1995 (3)

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

Type : TSCA
Additional information :

Flag : non confidential
18.06.2003

Type : EINECS
Additional information :

Flag : non confidential
18.06.2003

Type : ECL
Additional information :

Flag : non confidential
19.06.2003

Type : ENCS
Additional information :

Flag : non confidential
19.06.2003

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

Source of exposure : Human: exposure by production
Exposure to the : Substance

Source : 4B acid consortia
Flag : non confidential
19.06.2003

Source of exposure : Human: exposure of the operator by intended use
Exposure to the : Substance

Source : 4B acid consortia
Flag : non confidential
19.06.2003

1.11 ADDITIONAL REMARKS

1.12 LAST LITERATURE SEARCH

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

Remark : The primary source of data reference was IUCLID database ver.4.0.1. In addition, Japanese governments and the agencies provided available published and unpublished reports through JCIA. Also, members of 4B acid consortia, which were established by top four manufacturer of this substance in the world (having total about 90% of the market share), provided available in-house reports.
Supplementary literature search were conducted in on-line and CD-ROM databases - RTECS, TOXNET, IRIS, ECOTOX, etc. - in the interest of comprehensive cover page.
Flag : non confidential
19.06.2003

1.13 REVIEWS

2.1 MELTING POINT

Value	:	> 300 °C
Decomposition	:	no, at = 300 °C
Sublimation	:	no
Method	:	other: JIS K-4101-1993 5.1
Year	:	2002
GLP	:	no
Test substance	:	other TS: Mitsuboshi Chemical Co., Ltd.: purity >99%
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

19.06.2003 (16)

Value	:	= 312 °C
Decomposition	:	yes, at °C
Sublimation	:	no
Method	:	other
Year	:	
GLP	:	no
Test substance	:	
Source	:	Hickson & Welch Ltd. Castleford EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable
Flag	:	non confidential

19.06.2003

2.2 BOILING POINT

Value	:	> 350 °C at
Decomposition	:	yes
Method	:	OECD Guide-line 103 "Boiling Point/boiling Range"
Year	:	1999
GLP	:	no
Test substance	:	other TS: Tokyo Kasei Kogyo Co., Ltd.; purity 99.9%
Remark	:	The color became black at 350°C.
Source	:	METI Japan
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

19.06.2003 (7)

Remark	:	not applicable
Source	:	Hickson & Welch Ltd. Castleford EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

24.09.1993

2.3 DENSITY

Type	:	density
Value	:	= 1.49 g/cm³ at 25 °C
Method	:	other: JIS K-7112-1980

Year : 1999
GLP : no
Test substance : other TS: Tokyo Kasei Kogyo Co., Ltd.; purity 99.9%

Source : METI Japan
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
19.06.2003 (7)

Type : bulk density
Value : ca. 0.7 - 0.8 kg/ m³ at 20 °C
Method :
Year : 2001
GLP : no
Test substance : other TS: Mitsuboshi Chemical Co., Ltd.: purity >99%

Reliability : (2) valid with restrictions
Flag : non confidential
18.11.2002 (16)

2.3.1 GRANULOMETRY

Type of distribution : Volumetric Distribution
Precentile :
Method : other
Year : 2003
GLP : no
Test substance : other TS: Mitsuboshi Chemical Co., Ltd.: purity >99%

Remark : Mesh Distribution
48 mesh (0.297 mm) on 0.3 %
60 mesh (0.250 mm) on 0.3 %
80 mesh (0.177 mm) on 1.6 %
100 mesh (0.149 mm) on 5.8 %
150 mesh (0.105 mm) on 23.1 %
150 mesh (0.105 mm) pass 68.9 %
Reliability : (2) valid with restrictions
Flag : non confidential
19.06.2003 (16)

2.4 VAPOUR PRESSURE

Value : < 0.0000052 hPa at 100 °C
Decomposition : no
Method : OECD Guide-line 104 "Vapour Pressure Curve"
Year : 1999
GLP : no
Test substance : other TS: Tokyo Kasei Kogyo Co., Ltd.; purity 99.9%

Remark : The value was quantitative limit.
Source : METI Japan
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
19.06.2003 (7)

Value : = 0.000000000954 hPa at 25 °C
Decomposition :

Method : other (calculated): MPBPWIN v1.40
Year : 2003
GLP : no
Test substance :

Remark : parameters
Boiling point: 374.86 °C (estimation: Stain and Brown method)
Melting point: 306.0 °C (see Section 2.1)

The calculation has done in accordance with Modified Grain method, by which result was 7.17 x 10^{-10} mmHg (= 9.54 x 10^{-10} hPa).
Reliability : (2) valid with restrictions
Flag : non confidential
19.06.2003

2.5 PARTITION COEFFICIENT

Partition coefficient : octanol-water
Log pow : = -0.67 at 25 °C
pH value : 3.6 - 3.8
Method : OECD Guide-line 107 "Partition Coefficient (n-octanol/water), Flask-shaking Method"
Year : 1999
GLP : yes
Test substance : other TS: Tokyo Kasei Kogyo Co., Ltd.; purity 99.9%

Remark : As the Dissociation Constant (=3.28) was closed to each pH value, buffer had to be used in accordance with OECD TG107.
Result :

	A		B	
condition	pH	log Pow	pH	log Pow
1	3.8	-0.80	3.8	-0.85
2	3.7	-0.60	3.7	-0.56
3	3.6	-0.58	3.6	-0.62

remark: average of log Pow = -0.67
pH value is at water layer
Source : METI Japan
Test condition : sample weight: 1.06mg (= 5mL x 212mg/L)
component of test solution:

case	condition -1 mL	condition -2 mL	condition -3 mL
1-octanol saturated by water	5	10	20
water saturated by 1-octanol	30	25	15

temperature: 25(24-26) °C
revolution: 20/min x 5min
number of replicate: 2
analysis: HPLC
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
19.06.2003 (6)

Partition coefficient : octanol-water
Log pow : = -1.53 at °C
pH value :
Method : other (calculated): KOWWIN (version 1.66)
Year : 2003

GLP :
Test substance :

Result : NUM FRAGMENT COEFF VALUE
1 -CH3 0.5473 0.5473
6 Aromatic Carbon 0.2940 1.7640
1 -N -0.9170 -0.9170
1 -SO2-OH -3.1580 -3.1580
Equation Constant 0.2290

Log Kow = -1.5347

Reliability : (2) valid with restrictions
Flag : non confidential
19.06.2003

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in : water
Value : = 6 g/L at 20 °C
pH value : = 3.8
concentration : 6 g/L at 20 °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description : soluble (1000-10000 mg/L)
Stable : yes
Deg. product :
Method : other:
Year : 2002
GLP : no
Test substance : other TS: Mitsuboshi Chemical Co., Ltd.: purity >99%

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
01.05.2003 (16)

Solubility in :
Value : = 4.7 g/L at 25 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description : soluble (1000-10000 mg/L)
Stable :

Source : Hickson & Welch Ltd. Castleford
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable
19.06.2003

2.6.2 SURFACE TENSION

2.7 FLASH POINT

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

Result : other

Remark : Dust presents a mild explosion hazard
Source : Hickson & Welch Ltd. Castleford
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
24.09.1993

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

Acid-base constant : 3.28
Method : OECD Guide-line 112
Year : 1999
GLP : no
Test substance : other TS: Tokyo Kasei Kogyo Co., Ltd.; purity 99.9%

Remark : at 25 (24-26) °C
Source : METI Japan
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
19.06.2003 (7)

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

Memo : not corrosive material for iron, aluminum and animal; UN is not applicable.

Result : ANIMAL
patch test on human arm: After 6.0hr and after post dose 14days no change was observed compared with blank part.
METALS
iron: 0.0007mm/year
aluminum: 0.0005mm/year

Test condition : in accordance with a condition of International Maritime Dangerous Goods Code (2002)
ANIMAL
Species: human (male: age 27-48)
Number of persons: 5
Dose: ca. 50 mg/patch (direct) on an inner arm
term: 6 hrs, and post dose 14 days
METAL

material: iron and aluminum
exposure term: 9 days
number of replicate: 2

Reliability : (2) valid with restrictions
Flag : non confidential
18.11.2002 (16)

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	Sun light
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
DIRECT PHOTOLYSIS		
Halflife t1/2	:	= 0.4 day(s)
Degradation	:	% after
Quantum yield	:	
Deg. product	:	
Method	:	other (calculated): AopWin v.1.90 (Syracuse Research Corporation)
Year	:	2002
GLP	:	no
Test substance	:	other TS: based on 100% pure
Result	:	HYDROXY RADICALS Hydrogen Abstraction = 0.1360 x10^{-12} cm^3/molecule-sec Reaction with N, S and –OH = 0.1400 x10^{-12} cm^3/molecule-sec Addition to Aromatic Ring* = 28.2124 x10^{-12} cm^3/molecule-sec --- TOTAL OH Rate Constant = 28.4884 x10^{-12} cm^3/molecule-sec *Designates Estimation Using ASSUMED Value HALF-LIFE = 4.505hr = 0.375day (12hr/day; concentration of sensitizer: 1.5 x10^6 OH/ cm^3)
Source	:	calculated by Mr.Shinoda of CERI Japan (Sep.2002)
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

19.06.2003

3.1.2 STABILITY IN WATER

Type	:	abiotic
t1/2 pH4	:	> 5 day(s) at 50 °C
t1/2 pH7	:	> 5 day(s) at 50 °C
t1/2 pH9	:	> 5 day(s) at 50 °C
Deg. product	:	
Method	:	OECD Guide-line 111 "Hydrolysis as a Function of pH"
Year	:	1999
GLP	:	no
Test substance	:	other TS: Tokyo Kasei Kogyo Co., Ltd.; purity 99.9%
Result	:	According to above pre-study test, this substance has no activity of hydrolysis and stable at pH4, pH7 and pH9 .
Source	:	METI Japan
Test condition	:	pre-study test condition: concentration: about 100mg/L temperature: 50(49-51) °C pH: 4, 7 and 9 number of replicate: 2 term: 5 days
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

19.06.2003 (7)

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

3.3.2 DISTRIBUTION

Media : air - biota - sediment(s) - soil - water
Method : Calculation according Mackay, Level III
Year : 2001

Result :

compartment	amount % release 100% to air	release 100% to water	release 100% to soil
air	0.0	0.0	0.0
water	50.5	99.6	45.0
soil	49.3	0.0	54.9
sediment	0.2	0.4	0.2

Cited from Attached document (Table 1).

Source : CERI Japan
Attached document : The Fugacity Model (Mackay Level III)
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
19.06.2003 (8)

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic
Inoculum : activated sludge
Concentration : 100 mg/L related to Test substance
30 mg/L related to Test substance
Contact time : 14 day(s)
Degradation : = 0 (±) % after 14 day(s)
Result : under test conditions no biodegradation observed
Kinetic of testsubst. : 14 day(s) = 0 %
%
%
%
%
Control substance : Aniline
Kinetic : 7 day(s) > 40 %
14 day(s) > 60 %
Deg. product : no

Method : OECD Guide-line 301 C "Ready Biodegradability: Modified MITI Test (I)"
Year : 1975
GLP : no
Test substance : other TS: Dainippon Ink & Chemicals, Incorporated; purity >99%

Remark : Also, all of the results by the concurrent test detected by TOC and UV, were 0%.
Source : METI Japan
Test condition : test substance conc.: 100 mg/L, sludge conc.: 30 mg/L
Conclusion : This substance is (almost) no biodegradable.
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
19.06.2003 (5)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

Species : Cyprinus carpio (Fish, fresh water)
Exposure period : 42 day(s) at 25 °C
Concentration : 0.2 mg/L
BCF : < 4
Elimination : no
Method : OECD Guide-line 305 C "Bioaccumulation: Test for the Degree of Bioconcentration in Fish"
Year : 1978
GLP : yes
Test substance : other TS: Dainippon Ink & Chemicals, Incorporated; purity >99%

Result : high exposure concentration (2.0mg/L):

duration	14days	21days	28days	42days
concentration in water (mg/L)	1.66	1.72	1.68	1.70
BCF test 1	<0.4	<0.4	<0.4	<0.4
test 2	<0.4	<0.4	<0.4	<0.4

low exposure concentration (0.2mg/L):

duration	14days	21days	28days	42days
concentration in water (mg/L)	0.166	0.160	0.171	0.170
BCF test 1	<4	<4	<4	<4
test 2	<4	<4	<4	<4

---

analytical recovery: water; 103%, fish; 68.3%
temperature: 25(23-27) °C
quantitative limit: high concentration - 0.31mg/L
low concentration - 0.031mg/L
fish - 0.76ug/g
As all of those results were less than 0.76ug/g, BCF in high concentration is <0.4 and in low concentration is <4 .
Source : METI Japan
Test condition : TEST ORGANISMS
strain: not described
supplier: not described
size: 100mm (average)
weight: 27g (average)
number of fish used: not described
feeding: not described
DILUTION WATER
source: not described

dissolving agent: no solvent/agent was used
spec.: not described
TEST SYSTEM
pretreatment: not described
acclimation: 21days at 25°C
external disinfection: by 10ppm Chlorotetrecycline hydrochloride; 24hr
type: flow through
dosing rate: 482L/day
vessel: glass, 100L
test temperature: 25(23-27) °C

Conclusion : The results were less than quantitative limit.
BCF was < 4 (0.2 mg/L) and < 0.4 (2.0 mg/L).

Reliability : (2) valid with restrictions

Flag : Critical study for SIDS endpoint

19.06.2003 (4)

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type : semistatic
Species : *Oryzias latipes* (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/L
LC0 : > 10 measured
LC50 : > 10 measured
Limit test : yes
Analytical monitoring : yes
Method : OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year : 1999
GLP : yes
Test substance : other TS: Wako Pure Chemical Industries, Ltd.: purity >95%

Result :
CONCENTRATIONS

nominal concentration (mg/L)	measured concentration (mg/L) 0hr fresh	48hr expired
control	<0.1	<0.1
solvent control	<0.1	<0.1
10	10	10

As the result, measured concentration was equal to nominal one.
EFFECTS
No abnormal behavior, abnormal respiration nor dead one were observed in any those dose levels.
MONITORING DATA
water temperature: 23.7-23.8°C
dissolved oxygen: 6.2-8.3mg/L (Saturated concentration at 24°C is 8.25mg/L)
pH: 7.5-7.8
REMARK
This study was limit test at 10mg/L only, due to author's misunderstanding to the solubility in water (ref. section 2.6.1). Therefore it was not real limit test.

Source : EA Japan
Test condition :
TEST ORGANISMS
strain: not described
supplier: Izumimoto fish firm (Osaka, Japan)
size/weight: 22mm (20-23mm), n=10; 0.17g (0.16-0.20g), n=10
feeding: "TETRAMIN", till 24hr before test
pretreatment: acclimated for more than 12days
feeding during test: none
reference substance: Copper(II)Sulfate Pentahydrate (96hr LC_{50} = 4.0mg/L)
PREPARATION OF TEST SOLUTION
dissolving agent: DMSO
Following three solutions were prepared for test.
A. dilution water
B. 100mg/L DMSO + dilution water
C. 10mg/L test substance + 100mg/L DMSO + dilution water
DILUTION WATER
source: dechlorinated tap water
aeration: none
hardness: 55.2mg/L as $CaCO_3$
pH: 8.1
TEST SYSTEM
concentration: above A.(control), B.(solvent control), C.10mg/L

renewal of test solution: every 48hr
exposure vessel: 5.0L solution in a 7.7L glass vessel (about 21cm x 16cm x 23cm)
aeration: none
number of replicate: 1
number of fish per replicate: 10
water temperature: 23-25°C
photoperiod: 16hr-8hr light-dark cycle by room light
test parameter: mortality

Conclusion : 96hr LC_{50} (and LC_0) for *Oryzias latipes* is > 10mg/L.
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
30.06.2003 (23)

Type : other: calculation
Species :
Exposure period : 96 hour(s)
Unit : mg/L
LC50 : = 229000 calculated
Method : other: calculation, ECOSAR v0.99g
Year : 2003
GLP :
Test substance : other TS: based on 100% pure

Test condition : parameters
Log Kow: -1.53 (KOWWIN estimation)
Melting point: 306.0 °C (measured)
Water solubility: 6000 mg/L (measured)
Class: Aromatic Amines-acid
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
19.06.2003

Type : static
Species : Gambusia affinis (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/L
NOEC : = 180 nominal
LC50 : = 375 nominal
24hr LC50 : = 425 nominal
48hr LC50 : = 410 nominal
6hr LC100 : = 560 nominal
Limit test : no
Analytical monitoring : no data
Method : other: see Test Condition
Year : 1957
GLP : no data
Test substance : no data

Remark : As the water used was turbid water from farm ponds, the effect(s) to Acute Toxicity is unknown. Analytical monitoring data was not described.
Result : MORTALITY
10 fishes per dose were used.
At 180mg/L, no died fish was observed.
At 320mg/L, following numbers of fish were died.

past time	48hr	72hr	96hr	
number of dead fish	1	2	1	(total 4 at 96hr)

At 560mg/L, all fishes died within 6 hr.
MONITORING DATA
pH: 6.3-8.4

turbidity: 650(initial)-220(final), by Jackson turbid meter

Test condition : TEST ORGANISMS
strain: Western mosquitofish
supply: from stillwater creek (Oklahoma, USA)
size/weight: not described
sex: female (adult)
number of fish used: 10 for each concentration level
feeding: Various artificial foods were given. Stopped feeding during tests.
pretreatment: Acclimation data was not described. Abnormal fishes were removed. External disinfection was carried out by Terramycin, however the detail was not described.
DILUTION WATER
source: farm ponds, turbid water
dissolving agent: no solvent/agent was used
TEST SYSTEM
type: static
dosing rate: no feeding
concentration: 10, 18, 32, 56, 100, 180, 320, 560, 1000 mg/L
vessel: glass, 22.2L
water temperature: 22-24°C
aeration: yes (Oxygen content was not checked.)
test parameter: mortality

Conclusion : As the effect of dilution water, that is turbid water, is unknown, this study cannot be regarded as "key study".

Reliability : (3) invalid

Flag : non confidential

30.06.2003 (9) (11)

Type : semistatic
Species : *Oryzias latipes* (Fish, fresh water)
Exposure period : 48 hour(s)
Unit : mg/L
LC50 : = 480 calculated
Limit test : no
Analytical monitoring : no data
Method : other: JIS K 0102
Year : 1978
GLP : no
Test substance : other TS: Dainippon Ink & Chemicals, Incorporated; purity >99%

Result : The 48hr LC_{50} value was 480ppm (W/V).
Source : METI Japan
Test condition : TEST ORGANISMS
strain: not described
supplier: not described
size: not described
weight: 0.28g (average)
number of fish used: not described
feeding: not described
pretreatment: not described
DILUTION WATER
source: not described
dissolving agent: No solvent/agent was used.
TEST SYSTEM
concentrations: not described
type: static or semi-static (renewal; not described)
water temperature: 23-27°C
test parameter: mortality

Reliability : (4) not assignable

Flag : non confidential

23.06.2003 (4)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	static
Species	:	*Daphnia magna* (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/L
NOEC	:	= 10 measured
EC0	:	> 10 measured
EC50	:	> 10 measured
Limit Test	:	yes
Analytical monitoring	:	yes
Method	:	OECD Guide-line 202
Year	:	1999
GLP	:	yes
Test substance	:	other TS: Wako Pure Chemical Industries, Ltd.: purity >95%

Result :

CONCENTRATIONS

nominal concentration (mg/L)	measured concentration (mg/L) 0hr	48hr
control	<0.1	<0.1
solvent control	<0.1	<0.1
10	9.8	10

As the result, measured concentration was equivalent (99%) to nominal ones.

EFFECTS

No immobilized or abnormal movement one was observed in any those dose levels.

MONITORING DATA

water temperature: 19.6°C

dissolved oxygen: 8.3-8.7mg/L

(Saturated concentration at 20°C is 8.8mg/L.)

pH: 8.0-8.2

REMARK

This study was limit test at 10mg/L only, due to author's misunderstanding to the solubility in water (ref. section 2.6.1). Therefore it was not a real limit test.

Source	:	EA Japan
Test condition	:	TEST ORGANISMS supplier: National Institute of Environmental Studies (Japan) age: Juvenile *Daphnia magna* less than 24hr old feeding in acclimation: Chlorella vulgaris, 0.1-0.2mgC/day/one daphnia pretreatment: 2-4 weeks feeding during test: none reference substance: Potassium Dichromate (48hr EC_{50} = 0.54mg/L) PREPARATION OF TEST SOLUTION Following three solutions were prepared for test. A. dilution water B. 100mg/L DMSO (dissolving agent) + dilution water C. 10mg/L test substance + 100mg/L DMSO + dilution water DILUTION WATER source: dechlorinated tap water aeration: none hardness: 55.2mg/L as $CaCO_3$ pH: 8.1 TEST SYSTEM concentration: above A.(control), B.(solvent control), C.10mg/L

renewal of test solution: none
exposure vessel: glass beaker for 100mL
number of replicate: 4
number of daphnia per replicate: 5
water temperature: 19-21°C
photo period: 16hr-8hr light-dark cycle by room light
test parameter: immobility

Conclusion : 48hr LC_{50} (and LC_0) of Daphnia magna is > 10mg/L.
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
30.06.2003 (21)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species : *Selenastrum capricornutum* (Algae)
Endpoint : growth rate
Exposure period : 72 hour(s)
Unit : mg/L
NOEC : = 10 nominal
EC0 : > 10 nominal
EC50 : > 10 nominal
Limit test : yes
Analytical monitoring : yes
Method : OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year : 1999
GLP : yes
Test substance : other TS: Wako Pure Chemical Industries, Ltd.: purity >95%

Result : CONCENTRATIONS

nominal concentration (mg/L)	measured concentration (mg/L) 0hr (%)	72hr (%)	geometric mean 0-72hr	24-48hr	24-72hr
control	<0.1	<0.1	<0.1	<0.1	<0.1
solvent control	<0.1	<0.1	<0.1	<0.1	<0.1
10	9.6 (96)	7.9 (79)	8.5	8.5	8.5

EFFECT DATA (based on limit test)
biomass method
EbC_{50} (0-72hr) > 10mg/L
NOECb (0-72hr) = 10mg/L
growth rate method
ErC_{50} (24-48hr) > 10mg/L
NOECr (24-48hr) = 10mg/L
ErC_{50} (24-72hr) > 10mg/L
NOECr (24-72hr) = 10mg/L

AVERAGE CELL DENSITY DURING 72HR EXPOSURE

nominal concentration (mg/L)	cell density ($x10^4$ cells/mL) 0hr	24hr	48hr	72hr
control	1.00	4.68	26.3	159
solvent control	1.00	4.73	26.3	161
10	1.00	4.79	26.3	173

AVARAGE GROWTH INHIBITION

nominal concentration (mg/L)	biomass (0-72hr) %	growth rate (24-48hr) %	growth rate (24-72hr) %

control	0	0	0
solvent control	-0.7	0.7	0.1
10	-6.4	1.5	-1.6

MONITORING DATA
water temperature: 23.4-23.8°C
pH: 7.3-7.7 at start, 7.6 at end
intensity of irradiation: 4000-5000 lux

REMARK
This study was limit test at 10mg/L only, due to author's misunderstanding to the solubility in water (ref. section 2.6.1). Therefore it was not a real limit test.

Source : EA Japan

Test condition : TEST ORGANISMS
strain: ATCC22662
supplier: American Type Culture Collection
pretreatment: 3 days
initial cell concentration: $1x10^4$ cells/mL
growth/test medium: OECD medium
reference substance: Potassium Dichromate (72hr EbC_{50} = 0.44mg/L)
PREPARATION OF TEST SOLUTION
Following three solutions were prepared for test.
A. OECD medium
B. 100uL/L DMSO (dissolving agent) + OECD medium
C. 10mg/L test substance + 100uL/L DMSO + OECD medium
TEST SYSTEM
concentration: above A.(control), B.(solvent control), C.10mg/L
exposure vessel: 100mL medium in a 500mL conical flask with a cap which allows ventilation.
number of replicate: 3
water temperature: 21-25°C
pH: as it is
intensity of irradiation: 4000-5000 lux
photoperiod: continuous
shaking: 100 rpm
test parameter: cells/mL

Conclusion : No growth inhibition was observed to green algae up to 10mg/L concentration.

Reliability : (2) valid with restrictions

Flag : Critical study for SIDS endpoint

30.06.2003 (22)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

Species : *Daphnia magna* (Crustacea)

Endpoint : reproduction rate

Exposure period : 21 day(s)

Unit : mg/L

NOEC : = 3.2 measured

LOEC : = 10 measured

EC50 : > 10 measured

EC0 : > 10 measured
Analytical monitoring : yes
Method : OECD Guide-line 211
Year : 1999
GLP : yes
Test substance : other TS: Wako Pure Chemical Industries, Ltd.: purity >95%

Result : CONCENTRATIONS

nominal concentration (mg/L)	measured concentration (mg/L) (% of nominal) 2day new	5day old	9day new	12day old	16day new	19day old	21day mean
control	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	
solvent control	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	
1.0	1.0 (100)	1.0 (100)	0.90 (90)	1.1 (110)	1.0 (100)	1.1 (110)	1.0 (100)
3.2	3.1 (97)	3.3 (100)	2.9 (91)	3.5 (110)	3.2 (100)	3.5 (110)	3.2 (100)
10	9.7 (97)	10 (100)	9.1 (91)	11 (110)	10 (100)	11 (110)	10 (100)

rem. new = fresh solution
old = expired solution
mean = time-weighted mean during 21 days
As the result measured concentration was equivalent to nominal ones.
OBSERVATION
mortality: No dead parental daphnia was observed in any dose levels.
first brood day: First brood day of 1.0 (7-10 day), 3.2 (7-10 day) and 10 (7-8 day) mg/L were equivalent to control(7 day) and solvent control (7-10 day).
MEAN CUMULATIVE NUMBER OF JUVENILES PRODUCED PER ADULT

nominal concentration (mg/L)	No. of juveniles at day 21 (mean)
control	112.9
solvent control	109.1
1.0	108.6
3.2	99.1
10	74.3*

rem. * significant different (p=0.01) from solvent control

No other change was observed in any those dose levels.
MONITORING DATA
water temperature: 19.6-20.1°C
dissolved oxygen: 7.5-8.6mg/L
(Saturated concentration at 20°C is 8.8mg/L.)
pH: 7.8-8.2
hardness: 60-80mg/L as $CaCO_3$

REMARK
This study was the test up to 10mg/L, due to author's misunderstanding to the solubility in water (ref. section 2.6.1). Therefore it was not a real limit test.

Source : EA Japan
Test condition : TEST ORGANISMS
supplier: National Laboratory of Environment (Japan)
age: Juvenile *Daphnia magna* less than 24hr old
feeding in acclimation: Chlorella vulgaris, 0.1-0.2mgC/day/one daphnia
pretreatment: 2 weeks

feeding during test: same condition as acclimation
reference substance: Potassium Dichromate (48hr EC_{50} = 0.54mg/L)
PREPARATION OF TEST SOLUTION
Following three solutions were prepared for test.
A. dilution water
B. 100mg/L DMSO (dissolving agent) + dilution water
C. 1.0mg/L test substance + 100mg/L DMSO + dilution water
D. 3.2mg/L test substance + 100mg/L DMSO + dilution water
E. 10mg/L test substance + 100mg/L DMSO + dilution water
DILUTION WATER
source: dechlorinated tap water
aeration: none
hardness: 55.2mg/L as $CaCO_3$
pH: 8.1
TEST SYSTEM
concentration: above A.(control), B.(solvent control), C.1.0mg/L, D.3.2mg/L, E.10mg/L
renewal of test solution: 3 times a week
exposure vessel: 80mL of test solution in a glass beaker for 100mL
number of replicates: 10
number of daphnia per replicate: 1
water temperature: 19-21°C
photo period: 16hr-8hr light-dark cycle by room light
TEST PARAMETER
number of dead parental daphnia per day
number of juveniles produced per adult
MONITORING OF TEST SUBSTANCE CONCENTRATION
6 times each during test; by HPLC

Conclusion : 21 days EC_{50}(and EC_0) to parental *Daphnia magna* : > 10mg/L
21 days NOEC (reproduction) to *Daphnia magna* : = 3.2mg/L
21 days LOEC (reproduction) to *Daphnia magna* : = 10mg/L
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
30.06.2003 (20)

Species : Daphnia sp. (Crustacea)
Endpoint : other: chronic effects
Exposure period :
Unit : mg/L
NOEC : = 5 calculated
Method : other: calculation, ECOSAR v0.99g
Year : 2003
GLP :
Test substance : other TS: based on 100% pure

Test condition : parameters
Log Kow: -1.53 (KOWWIN estimation)
Melting point: 306.0 °C (measured)
Water solubility: 6000 mg/L (measured)
Class: Aromatic Amines-acid
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
20.06.2003

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD_{50}
Value	:	> 2000 mg/kg bw
Species	:	rat
Strain	:	*Sprague-Dawley*
Sex	:	male/female
Number of animals	:	8
Vehicle	:	other: sesame oil, 0.5mL/100g bw
Doses	:	0, 100, 250, 500, 1000, 2000 mg/kg/day
Method	:	other: preliminary examination of OECD TG407
Year	:	1996
GLP	:	yes
Test substance	:	other TS: Mitsuboshi Chemical Co., Ltd.: purity >99%
Result	:	(Following description was cited from REPEAT DOSE TIOXICITY: Please refer to section 5.4.) PRELIMINARY EXAMINATION 4 Males and 4 females were used for the 14 days Preliminary Examination. Any toxicological effects in the clinical signs, body weight, food consumption, urinary findings, hematological findings, blood chemical findings and weight of organs was not observed in all animals at upto 2000 mg/kg/day groups. At necropsy enlargement of cecum was observed in all animals at 2000 mg/kg/day group.
Source	:	MHW Japan
Test condition	:	age: 5 weeks
Conclusion	:	The LD_{50} (and LD_0) was > 2000 mg/kg. Main toxicological effect was enlargement of cecum in both sexes in 2000 mg/kg.
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

30.06.2003 (12)

Type	:	LD_{50}
Value	:	11700 mg/kg bw
Species	:	rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Method	:	
Year	:	1986
GLP	:	no data
Test substance	:	no data
Remark	:	Those are the all data available. Original report was unable to obtain.
Reliability	:	(3) invalid
Flag	:	non confidential

30.06.2003 (1)

5.1.2 ACUTE INHALATION TOXICITY

5.1.3 ACUTE DERMAL TOXICITY

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

Species	:	human
Concentration	:	50 mg
Exposure	:	Occlusive
Exposure time	:	6 hour(s)
Number of animals	:	5
Vehicle	:	other: No vehicle was used (direct).
PDII	:	
Result	:	not irritating
Classification	:	not irritating
Method	:	other: IMDG code (2002)
Year	:	2003
GLP	:	no
Test substance	:	other TS: Mitsuboshi Chemical Co., Ltd.: purity >99%
Test condition	:	Species: human (male: age 27-48) Dose: ca. 50 mg/patch (direct) on an inner arm term: 6 hrs, and post dose 14 days
Reliability	:	(2) valid with restrictions
Flag	:	non confidential

19.06.2003 (16)

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	
Dose	:	500 other: mg
Exposure time	:	24 hour(s)
Comment	:	
Number of animals	:	
Vehicle	:	
Result	:	moderately irritating
Classification	:	
Method	:	
Year	:	
GLP	:	no data
Test substance	:	no data
Remark	:	Those are the all data available. Original report was unable to obtain.
Reliability	:	(3) invalid
Flag	:	non confidential

30.06.2003 (1)

5.3 SENSITIZATION

5.4 REPEATED DOSE TOXICITY

Type	:	Sub-chronic
Species	:	rat
Sex	:	male/female
Strain	:	*Sprague-Dawley*
Route of admin.	:	gavage
Exposure period	:	28 days
Frequency of treatm.	:	once a day
Post exposure period	:	14 days for 0 mg/kg and 1000 mg/kg group
Doses	:	0, 100, 300 and 1000 mg/kg/day
Control group	:	yes, concurrent vehicle
NOAEL	:	= 300 mg/kg
Method	:	OECD Guide-line 407 "Repeated Dose Oral Toxicity - Rodent: 28-day or 14-d Study"
Year	:	1996
GLP	:	yes
Test substance	:	other TS: Mitsuboshi Chemical Co., Ltd.: purity >99%
Result	:	PRELIMINARY EXAMINATION 4 Males and 4 females were used for the 14 days Preliminary Examination. Any toxicological effects in the clinical signs, body weight, food consumption, urinary findings, hematological findings, blood chemical findings and weight of organs was not observed in the animals of any groups up to 2000 mg/kg/day. At necropsy enlargement of cecum was observed in all the animal at 2000 mg/kg/day group. HISTOLOGICAL AND STATISTICAL RESULTS general: No change in mortality and behavior were observed in any groups. body weight and food consumption: No toxic effect was observed in any groups. urinary findings: Increase of specific gravity and decrease of pH were observed in 1000mg/kg males. However no related change was observed in other findings. hematological findings: Slight decrease of white blood cell count (due lymphopenia) were observed in 1000mg/kg males. No pathological change was observed in the lymphatic tissues, such as marrowcyte, thymus, lymphknote and spleen. blood chemical finding: Slight increase of GPT in females, slight decrease of total cholesterol in males and slight decrease of glucose in females were observed in 1000mg/kg group. However, including liver, no pathological change was observed in any of related organs. According to the author, the change is within normal range, based on their other study data. necropsy finding: Slight enlargement of cecum was observed in one male and one female in 1000mg/kg group. However no diarrhea and no growth abnormalities were observed. weight of organs: Decrease of thymus weight in 100mg/kg and increase of spleen weight in all dose levels in female were observed. However those changes were no relation with dose levels. remark: All of above changes returned to normal during 14 days recovery period.
Source	:	MHW Japan
Test condition	:	TEST ORGANISMS age: 5 weeks weight at initiation: 168-183 g for males, 138-162 g for females number of animals: 6 per sex per dose for immediate histological finding

after 28 days, plus the same to 0 and 1000mg/kg/day groups for checking the change after 14 days recovery period
pellet food and water: free take
ADMINISTRATION
vehicle: sesame oil, 0.5mL/100g body weight
CLINICAL OBSERVATIONS AND FREQUENCY
clinical signs and mortality: every day
body weight: twice a week, total 9 times during the 28 days, and additional 4 times during the 14 days recovery period
food consumption: once a week (24hr consumption)
water consumption: not checked

Attached document : Hematological, Blood Chemical and Organ Weight data
Conclusion : Toxicological effects were decrease of white blood cell count, total cholesterol and urine pH and enlargement of cecum in male at 1000 mg/kg/day; increase of GPT, decrease of glucose and enlargement of cecum in female at 1000 mg/kg/day.
NOAEL for Repeat Dose Toxicity to rats is 300mg/kg/day in both sexes.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
30.06.2003 (12)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Ames test
System of testing : *Salmonella typhimurium* (TA100, TA1535, TA98, TA1537); *Escherichia coli* (WP2uvrA)
Test concentration : -S9mix and +S9mix: 0, 313, 625, 1250, 2500, 5000 ug/plate
Cycotoxic concentr. : Toxicity was not observed up to 5000ug/plate in five strains with or without S9mix.
Metabolic activation : with and without
Result : negative
Method : other: OECD Test Guidelines 471 and 472 "Genetic Toxicology (*Salmonella typhimurium* and *Escherichia coli*)
Year : 1996
GLP : yes
Test substance : other TS: Mitsuboshi Chemical Co., Ltd.: purity >99%

Result :

	Salmonella typhimurium TA100, TA1535, TA100, TA1537			*Escherichia coli* WP2 uvrA		
	+	?	-	+	?	-
-S9 mix:	[ ]	[ ]	[*]	[ ]	[ ]	[*]
+S9 mix:	[ ]	[ ]	[*]	[ ]	[ ]	[*]

In each experiment, the positive control chemicals induced the expected responses, indicating that the assay was working satisfactorily.

Source : MHW Japan
Test condition : SYSTEM OF TESTING
metabolic activation system: S9 from male rat liver, induced with phenobarbital and 5,6-benzoflavone
ADMINISTRATION
number of replicate: 2
plates per test: 3
application: pre-incubation
positive control groups and the solvent:
without S9 mix; 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide (TA98, TA100, WP2; DMSO), sodium azide (TA1535; pure water), 9-aminoacridine (TA1537; DMSO)
with S9 mix; 2-aminoanthracene (all five strains; DMSO)
test parameter: number of revertant colonies per plate

Conclusion : This substance was not mutagenic to *Salmonella typhimurium* and *Escherichia coli*.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
30.06.2003 (13)

Type : Ames test
System of testing : *Salmonella typhimurium* (TA100, TA1535, TA98, TA1537, TA1538)
Test concentration : -S9mix and +S9mix: 0, 1.6, 8.0, 40, 200, 1000, 5000 ug/plate
Cycotoxic concentr. : Toxicity was not observed up to 5000ug/plate in the five strains with or without S9mix.
Metabolic activation : with and without
Result : negative
Method : other: Maron and Ames (1983)
Year : 1988
GLP : yes
Test substance : other TS: Aldrich Chemical; purified by recrystalization; purity 99.8% (with moisture 1.03%)

Remark : This report was obtained after SIAM-16, which was held in May 2003.
Result : *Salmonella typhimurium* TA100,TA1535,TA98,TA1537,TA1538

	+	?	-
-S9 mix :	[ ]	[ ]	[*]
+S9 mix:	[ ]	[ ]	[*]

In each experiment, the positive control chemicals induced the expected responses, indicating that the assay was working satisfactorily.
Source : ETAD UK
Test condition : SYSTEM OF TESTING
metabolic activation system: S9 was prepared from male SD albino rat liver with a buffer arranged by Sucrose, Tris Base and EDTA Tetrasodium salt. Co-factor was Na2HPO4, KCl, Glucose-6-Phosphate, NADP sodium salt and MgCl2.
number of replicate: 2
plates per test: for sample 3, for neg.control 5, for pos.control 2
application: pre-incubation
negative control: DMSO 100uL/plate
positive control groups:
without S9 mix; N-Methyl-N'-nitro-N-nitrosoguanidine (TA100, TA1535), Daunomycin HCl (TA98), 4-Nitro-o-phenylene diamine (TA1538), Acridine Mutagen (TA1537)
with S9 mix; 2-aminoanthracene (all five strains; DMSO)
test parameter: number of revertant colonies per plate; If the number in any dose is more than double of negative control, or if the dose dependency is observed after statistical treatment, it will be regarded as positive.
Conclusion : This substance was not mutagenic to *Salmonella typhimurium.*
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
27.06.2003 (18)

Type : Ames test
System of testing : *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537, TA1538)
Test concentration : -S9mix and +S9mix: up to 10000 ug/plate
Cycotoxic concentr. : no data
Metabolic activation : with and without
Result : negative
Method :
Year : 1992
GLP : no data
Test substance : no data

Remark : Those are the all data available.
Original report was unable to obtain.

Result :

strain	S9	concentration (ug/plate)	result
TA98	-	667-10000	negative
TA98	+ (rat)	667-10000	negative
TA98	+ (hamster)	667-10000	negative
TA100	-	33-10000	negative
TA100	+ (rat)	667-10000	negative
TA100	+ (hamster)	667-10000	negative
TA1535	-	33-10000	negative
TA1535	+ (rat)	33-10000	negative
TA1535	+ (hamster)	33-10000	negative
TA1537	-	33-10000	negative
TA1537	+ (rat)	33-10000	negative
TA1537	+ (hamster)	33-10000	negative
TA1538	-	33-10000	negative
TA1538	+ (rat)	33-10000	negative
TA1538	+ (hamster)	33-10000	negative

Source : TOXNET, National Library of Medicine: on line data generated on Jul. 2002
Test condition : standard plate method
solvent: DMSO
Reliability : (3) invalid
Flag : non confidential
27.06.2003 (24)

Type : Chromosomal aberration test
System of testing : CHL/IU cell
Test concentration : for all tests (see Result); 0, 0.48, 0.95, 1.9 mg/mL
Cycotoxic concentr. : 1.9 mg/mL
Metabolic activation : with and without
Result : negative
Method : OECD Guide-line 473
Year : 1996
GLP : yes
Test substance : other TS: Mitsuboshi Chemical Co., Ltd.: purity >99%

Result :

	clastogenicity +	?	-	polyploid +	?	-
A. -S9 mix 24hr continuous	[ ]	[ ]	[*]	[ ]	[ ]	[*]
B. -S9 mix 48hr continuous	[ ]	[ ]	[*]	[ ]	[ ]	[*]
C. -S9 mix 6hr short term	[ ]	[ ]	[*]	[ ]	[ ]	[*]
+S9 mix 6hr short term;						
D. before pH adjustment	[*]	[ ]	[ ]	[*]	[ ]	[ ]
E. after pH adjustment	[ ]	[ ]	[*]	[ ]	[ ]	[*]

remark 1. Cytotoxicity was observed at 1.9 mg/mL on above A, B, C and D analysis, in which some aberrations and polyploid were observed.
2. On D analysis, structural aberrations (7.0% including gaps) and polyploid (1.38%) were induced at the 0.95mg/mL. While, the pH value at the beginning of D analysis was 5.84 and the after was 6.26. Therefore the E analysis had been done for confirming whether it's caused by low pH effect.
3. pH range of E analysis was 6.80 - 7.19.
4. All of the results of negative control and vehicle (0.5% carboxymethylcellulose sodium solution) were negative.

In each experiment, the positive control chemicals induced the expected responses, indicating that the assay was working satisfactorily.

Source : MHW Japan
Test condition : metabolic activation: S9 from male rat liver, induced with phenobarbital and 5,6-benzoflavone
number of replicate: 2 (plates/test)
positive control:
-S9mix 24 and 48hr continuous; Mitomycin C (0.00005mg/mL)
-S9mix, +S9mix 6hr and +S9mix confirmation; cyclophosphamide (0.005mg/mL)
number of cells analyzed:
structural aberrations; 200 (Less than 100 is regarded as cytotoxic.)
polyploid; 800 (Less than 400 is to be cytotoxic.)
test parameter: % of the cells with aberrations and/or polyploid
In case more than 5% aberrations or polyploid were observed, Cochran-Armitage's trend test should be done. If the trend is confirmed it's regarded "positive".
Conclusion : This chemical induces weak chromosomal aberration to CHL/IU cell with an exogenous metabolic activation system. However, origin of the aberration is due to the acidity, but not due to physiological DNA damage. (The low acidity effect is reported in [T.Morita et al., Mutation Res, 268, 297 1992].)
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
30.06.2003 (14)

Type : Unscheduled DNA synthesis
System of testing : Human Fibroblasts CRL 1121
Test concentration : 0, 16, 80, 400, 2000 ug/mL
Cycotoxic concentr. : > 2000 ug/mL (precipitation at 2000 ug/mL)
Metabolic activation : without
Result : negative
Method : other: see Test Condition
Year : 1985
GLP : no data
Test substance : other TS: Clayton commercial grade (probably purity > 98%)

Remark : This report was obtained after SIAM-16, which was held in May 2003.
Result :

chemical	dose ug/mL	UDS grains/nucleous mean ± sd.
test substance	2000	1.08 ± 1.03
	400	0.91 ± 0.99
	80	1.24 ± 1.07
	16	1.57 ± 1.29
positive control	5 uM	27.6 ± 13.67
negative control (medium)		1.08 ± 0.98
negative control (vehicle)		1.25 ± 1.10

remark 1. positive control = 4-nitroquinoline-N-oxide
2. negative control = medium; untreated, vehicle; Dimethylsulfoxide
3. sd. = standard deviation

Test condition : TEST ORGANISMS
cell type: Human Fibroblasts cultured in a Medium containing 10% foetal bovine serum
pre-incubation: one night on plastic coverslip (3 x 10^4 cells/compartment) in 1 mL of DULBECCO's Minimal Essential Medium
TEST CONCENTRATION
As visible precipitation was observed at 2000ug/mL, the highest concentration was set up to 2000ug/mL.
TEST SYSTEM
exposure: 5hr in the Medium with 2uCi/mL of tritiated thymidine

detection: After treatment the cells were washed and stained, then were mounted coverslip on slides. Autoradiographic grains were counted on television screen.
number of replicate: 4 coverslips/dose
number of cells observed: 50 cells/coverslip
test parameter: number of UDS grains/nucleous

Conclusion : Under the given experimental conditions, no evidence of induction of DNA damage by this substance was obtained.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
27.06.2003 (27)

Type : Unscheduled DNA synthesis
System of testing : Hepatocytes from male rat: Tif.RAIf (SPF), weight 250g
Test concentration : 1st: 0, 16, 80, 400, 2000 ug/mL
2nd: 0, 0.16, 0.8, 4, 20, 100, 500, 1000, 2000 ug/mL
Cycotoxic concentr. : > 2000 ug/mL
Metabolic activation : without
Result : negative
Method : other: see Test Condition
Year : 1985
GLP : no data
Test substance : other TS: Clayton commercial grade (probably purity > 98%)

Remark : This report was obtained after SIAM-16, which was held in May 2003.
Result :

chemical	dose ug/mL	UDS grains/nucleous mean ± sd.
1st experiment;		
test substance	2000	2.67 ± 1.57
	400	2.15 ± 1.41
	80	2.68 ± 1.62
	16	2.38 ± 1.80
positive control	100 mM	17.8 ± 7.69
negative control (medium)		1.25 ± 1.07
negative control (vehicle)		1.55 ± 1.23
2nd experiment;		
test substance	2000	2.13 ± 1.78
	1000	2.03 ± 1.34
	500	1.49 ± 1.39
	100	1.56 ± 1.38
	20	2.41 ± 1.58
	4	2.18 ± 1.31
	0.8	2.04 ± 1.42
	0.16	1.59 ± 1.24
positive control	100 mM	13.2 ± 6.20
negative control (medium)		1.90 ± 1.24
negative control (vehicle)		1.69 ± 1.30

remark 1. positive control = Dimethylnitrosamine
2. negative control = medium; untreated, vehicle; Dimethylsulfoxide
3. sd. = standard deviation
4. As the 1st experiment showed slight elevation (but not exceed double) to the mean of UDS grains/cell, 2nd experiment has executed for confirmation.

Test condition : TEST ORGANISMS
cell type: Rat Hepatocytes; prepared from male rat, Tif:RAIf (SPF), weight 250 g, cultivated in WILLIAMS' Medium E containing 10% foetal bovine serum (WME)

pre-incubation: one night on plastic coverslip (4 x 10^5 cells/compartment) in 4 mL of WME
TEST CONCENTRATION
The highest concentration was set up to 2000ug/mL.
TEST SYSTEM
exposure: 5hr in the WME with 4uCi/mL of tritiated thymidine
detection: After treatment the cells were washed and stained, then were mounted coverslip on slides. Autoradiographic grains were counted on television screen.
number of replicate: 3 coverslips/dose
number of cells observed: 50 cells/coverslip
test parameter: number of UDS grains/nucleous

Conclusion : Under the given experimental conditions, no evidence of induction of DNA damage by this substance was obtained.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
27.06.2003 (26)

Type : Unscheduled DNA synthesis
System of testing : non bacteria
Test concentration : 0.187, 1.87, 18.7, 187 mg/L
Cycotoxic concentr. : >187mg/L
Metabolic activation : with
Result : negative
Method : other: method of Williams et al.(1982)
Year : 1988
GLP : no data
Test substance : other TS: Tokyo Kasei Kogyo Co., Ltd.; purity 99.9%

Result :

chemical	dose mg/L	UDS grains/nucleous mean ± sd.	%
test substance	187	1.2 ± 1.6	2
	18.7	1.4 ± 1.4	2
	1.87	1.0 ± 1.3	0
	0.187	-0.5 ± 1.5	0
positive control	2.23	60.8 ± 8.4	100
	0.223	38.2 ± 9.4	100
solvent control		0.6 ± 1.3	0

remark 1. positive control = N-2-Fluorenylacetamide
2. solvent control = Dimethylsulfoxide
3. sd. = standard deviation
4. % = % of UDS positive cells with more than 5 grains
5. According to the author, the result of the other replicate test was "more or less identical".

Test condition : TEST ORGANISMS
cell type: hepatocytes isolated from the livers of male ACI rats weighing 200-250g
pre-incubation: 2hr on plastic coverslip (50 cells/coverslip) by Williams' Medium E The culture was washed off before test.
CONTROLS
solvent control: dimethylsulfoxide (Nakarai Chem., Tokyo Japan)
positive control: N-2-fluorenylacetamide (Nakarai Chem. Japan), with concentration 2.23mg/L and 0.223mg/L
TEST SYSTEM
exposure: 20hr by Williams' Medium E with 10uCi/mL of tritiated thymidine
detection: After treatment the cells were mounted coverslip on slides, then were stained. Autoradiographic grains were counted on television screen.
number of replicates: 3 coverslips/time, 2 times for this study

test parameter: number of UDS grains/nucleous and % of cells with more than 5 UDS grains/nucleous
REMARK
The cytotoxicity concentration was likely > 187mg/L, however the detail was unable to obtain from the original report.

Conclusion : This substance failed to induce a significant amount of DNA repair responses, compared with negative control. So, can be judged to negative.
Reliability : (2) valid with restrictions
Flag : non confidential
30.06.2003 (17) (29)

Type : HGPRT assay
System of testing : V79 Chinese Hamster cells derived from embryonic lung tissue
Test concentration : 0, 38, 75, 150, 300, 600, 900, 1200, 1500 ug/mL
Cycotoxic concentr. : > 1500 ug/mL
Metabolic activation : with and without
Result : negative
Method : other: see Test Condition
Year : 1986
GLP : no data
Test substance : other TS: Clayton commercial grade (probably purity > 98%)

Remark : This report was obtained after SIAM-16, which was held in May 2003.
Result : CYTOTOXICITY at 1500 ug/mL
viability with S9: 117.5%, viability without S9: 33.6%

MUTATION FREQUENCY

-S9mix: dose (ug/mL)	8-AG resistant: total mutant clones in 4 dishes	8-AG resistant: mutation frequency (mutants/ mil.cells)	6-TG resistant: total mutant clones in 4 dishes	6-TG resistant: mutation frequency (mutants/ mil.cells)
neg.control	1	< 4	3	7.3
38	0	< 4	2	4.3
75	2	< 4	3	5.4
150	1	< 4	1	< 4
300	2	4.4	2	4.4
600	1	< 4	3	5.1
900	0	< 4	3	6.0
1200	3	7.1	4	9.4
1500	2	4.8	5	12.0
pos.control	156	1312	278	2224

rem 1. 8-AG: 8-Azaguanine
2. 6-TG: 6-Thioguanine
3. neg.control: negative control; Ham's F10 medium with 1% DMSO
4. pos.control: positive control; neg.control + ethylmethanesulfonate (300 nL/mL)
5. cells seeded per test: 250,000/dish x 4 dishes = 1,000,000

+S9mix: dose (ug/mL)	8-AG resistant: total mutant clones in 4 dishes	8-AG resistant: mutation frequency (mutants/ mil.cells)	6-TG resistant: total mutant clones in 4 dishes	6-TG resistant: mutation frequency (mutants/ mil.cells)
neg.control	0	< 4	4	6.5

38	1	< 4	0	< 4
75	0	< 4	3	5.7
150	0	< 4	0	< 4
300	0	< 4	3	4.3
600	1	< 4	2	< 4
900	1	< 4	2	< 4
1200	1	< 4	0	< 4
1500	0	< 4	3	4.6
pos.control	35	117	66	221

rem 1. 8-AG: 8-Azaguanine
2. 6-TG: 6-Thioguanine
3. neg.control: negative control; Ham's F10 medium with 1% DMSO + S9mix
4. pos.control: positive control; neg.control + dimethylnitrosamine (1 uL/mL)
5. cells seeded per test: 250,000/dish x 4 dishes = 1,000,000

Test condition : MEDIA
growth medium: Ham's F10 tissue culture medium with 3% foetal calf serum; pH 7.2
treatment media: growth media + sample or controls
S9MIX
induced male RAI rat liver, 2% in the culture medium
co-factors: NADP, glucose-6-phosphate, Ca^{++}, Mg^{++}
PROCEDURE (In case of +S9mix, content in [ ] is to be added.)
pre-incubation: Cells were put in growth media with 3 uM Aminopterin for 3 days.
Day 1: Cells were plated at 10^6 cells in 25 mL growth medium.
Day 2: The growth media was replaced by 25 mL treatment media for 21 hrs [and by 22.5 mL treatment media + 2.5 mL S9mix for 5 hrs]. And the same for negative and positive control. The treatment was terminated by washing, then cells were replated in fresh medium into flasks.
Day 5: The medium was replaced by fresh ones.
Day 8: They were trypsinized. Then, each concentration was plated into 8 dishes each containing 250,000 cells, and 4 dishes each containing 200 cells.
The low-density cultures were used for cytotoxicity test, which was evaluated with a colony counter.
The 4 plates of high-density cultures were supplemented for 20 ug/mL 8-AG treatment, and the other 4 plates were for 8 ug/mL 6-TG treatment.
8-AG treatment: At the third day 20 ug/mL was added. At the fourth day the growth medium was replaced with fresh one and added 20 ug/mL. Terminated at seventh day.
6-TG treatment: It was kept undisturbed seven days.
After those treatment, the cells were fixed with methanol and stained with Giemsa's stain. The mutant colones were counted with naked eyes.
TEST PARAMETER
mutation frequency (number of mutants/million cells)
Not less than 2.5 times dose-dependent higher frequency than the negative control or not less than 3.0 times higher frequency would be regarded as "positive".

Conclusion : Under the given conditions with and without S9, this substance induced no mutagenic effects.

Reliability : (2) valid with restrictions

Flag : non confidential

27.06.2003 (28)

Type : Mouse lymphoma assay

System of testing : Mouse lymphoma (L5178Y TK+, L5178Y TK-)

Test concentration : -S9mix and +S9mix: 1642-3680 ug/ml

Cycotoxic concentr. : no data
Metabolic activation : with and without
Result : negative
Method :
Year : 1992
GLP : no data
Test substance : no data

Result : strain S9 concentration result

L5178Y TK+	-	1642-3680 (ug/plate)	negative
L5178Y TK-	-	1642-3680 (ug/plate)	negative
L5178Y TK+	+	1642-3680 (ug/plate)	negative
L5178Y TK-	+	1642-3680 (ug/plate)	negative

Source : TOXNET, National Library of Medicine: on line data generated on Jul. 2002
Test condition : suspension/plate method
solvent: DMSO
Reliability : (3) invalid
Flag : non confidential
27.06.2003 (24)

5.6 GENETIC TOXICITY 'IN VIVO'

Type : Micronucleus assay
Species : mouse
Sex : male/female
Strain : C57BL
Route of admin. : oral unspecified
Exposure period : single dose; Smears were prepared at 24, 48 and 72 hrs after dosing.
Doses : 3125 and 5000 mg/kg
Result : negative
Method : OECD Guide-line 474 "Genetic Toxicology: Micronucleus Test"
Year : 1988
GLP : yes
Test substance : other TS: Aldrich Chemical; purified by recrystalization; purity 99.8% (with moisture 1.03%)

Remark : This report was obtained after SIAM-16, which was held in May 2003.
Result : LETHALITY
No mortality on each 5 male and 5 female mice was observed till 4 days after 5000 mg/kg single dose.

MEAN INCIDENCE OF MICLONUCLEI/1000 CELLS
based on 5 observations:

chemical	dose	sex	24hr	48hr	72hr
negative control	20mL/kg	male	0.8	1.4	0.8
	20mL/kg	female	1.4	0.4	0.6
positive control	65mg/kg	male	17.0**		
	65mg/kg	female	13.6**		
test substance	3125mg/kg	male	2.6*		
	3125mg/kg	female	1.0		
	5000mg/kg	male	3.2*	2.8	1.4
	5000mg/kg	female	1.2	0.8	1.2

* significant increase ($p<0.05$)
** significant increase ($p<0.01$)
negative control = corn oil
positive control = Cyclophosphamide

Positive control gave the expected increase in the frequency of micronucleated polychromatic erythrocytes (MPE).
As a slight increase was observed in above (*), below confirmation experiment was executed.

based on 15 observations (confirmation experiment in male):

chemical	dose	sex	24hr
negative control	20mL/kg	male	2.5
test substance	3125mg/kg	male	2.0
	5000mg/kg	male	4.2

negative control = corn oil
No significant statistic increase was observed in male.

MEAN PERCENTAGE OF POLYCHROMATIC ERYTHROCYTES
based on 5 observations:

chemical	dose	sex	24hr	48hr	72hr
negative control	20mL/kg	male	30.0	35.4	36.2
	20mL/kg	female	32.0	36.8	39.2
positive control	65mg/kg	male	30.7		
	65mg/kg	female	30.8		
test substance	3125mg/kg	male	38.1		
	3125mg/kg	female	34.9		
	5000mg/kg	male	16.2*	28.0	34.1
	5000mg/kg	female	23.1	29.7	29.7

* significant decrease ($p<0.05$, means slight cytotoxicity)
negative control = corn oil
positive control = Cyclophosphamide

Test condition : TEST ORGANISMS and HUSBANDRY
strain: male and female C57BL/6JfCD-1/Alpk mice
age: 13-14 weeks for lethality, 8-12 weeks for micronucleus test
number of animals: each 5 for lethality, each 5 per kill-time per dose for micronucleus test
food: Porton Combined Diet
water: filtered tap water
room temperature: 17-26°C
humidity: 48-75%
lighting: 12hr light/dark cycle
air: 15 air change per hour
CONTROLS
negative control: 100% Kraft corn oil, 20mL/kg bw
positive control: Cyclophosphamide
ADMINISTRATION
single dose by oral route (probably by gavage), at 5000 and 3125 mg/kg and the controls
SMEARS
Bone marrow smears were prepared at 24, 48 and 72 hours after dosing. The preparations were stained with polychrome methylene blue and eosin. 1000 Polychromatic erythrocytes per slide were evaluated for the presence of micronuclei. Approximately 1000 erythrocytes were counted to obtain the cytotoxicity.
TEST PARAMETER
incidence of micronuclei/1000 cells

Conclusion : The data obtained indicate that this substance is not clastogenic in the mouse micronucleus test.

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint

27.06.2003 (19)

5.7 CARCINOGENICITY

Species	:	other: no data
Sex	:	no data
Strain	:	no data
Route of admin.	:	other: no data
Exposure period	:	no data
Frequency of treatm.	:	no data
Post exposure period	:	no data
Doses	:	no data
Result	:	positive
Control group	:	no data specified
Method	:	other: no data
Year	:	
GLP	:	no data
Test substance	:	no data
Remark	:	target organs: liver, blood This information did not give any data or reference information. Considering to the result of GENETIC TOXICITY 'IN VITRO' (see above section 5.5) and GENETIC TOXICITY 'IN VIVO' (see above section 5.6), the possibility of the carcinogenicity to mammal is low.
Reliability	:	(3) invalid
Flag	:	non confidential

27.06.2003 (2)

5.8.1 TOXICITY TO FERTILITY

Type	:	One generation study
Species	:	rat
Sex	:	male/female
Strain	:	*Crj: CD(SD)*
Route of admin.	:	gavage
Exposure period	:	male 48 days; female 41-48 days
Frequency of treatm.	:	once a day, every day
Premating exposure period		
Male	:	14 days
Female	:	14 days
Duration of test	:	male: 48 days, female: 41-48 days
No. of generation studies	:	1
Doses	:	0, 100, 300, 1000 mg/kg/day
Control group	:	yes, concurrent vehicle
NOAEL parental	:	= 1000 mg/kg bw
NOAEL F1 offspring	:	= 1000 mg/kg bw
Method	:	OECD Guide-line 421
Year	:	1999
GLP	:	yes
Test substance	:	other TS: Mitsuboshi Chemical Co., Ltd.: purity >99%
Remark	:	This data is a part of OECD TG421.
Result	:	STATISTICAL RESULTS (As you can see on under mentioned tables,) No effects were observed in the copulation index, fertility index, gestation

length, number of corpora lutea or implanations, implanation index, gestation index, parturition or maternal behavior. There were no significant differences in number of offspring or live offspring, sex ratio, the live birth index, the viability index and the body weight. No abnormal findings related to the test substance were noted for external features, clinical signs, or on necropsy finding for the offspring. No pups with malformation were found in any group. No change in clinical signs and necropsy finding were observed in offspring.

SUMMARY OF REPRODUCTIVE PRFORMANCE

Dose (mg/kg)	0	100	300	1000
No. of pairs mated	12	12	12	12
No. of pairs coupled	12	11	12	12
No. of pregnant females	11	10	12	12
Couplation index (%)	100.0	91.7	100.0	100.0
Fertility index (%)	91.7	90.9	100.0	100.0
Estrus cycle (days, mean±sd)	4.5±0.7	4.2±0.5	4.2±0.4	4.5±0.5

rem. Couplation index =
(No. of animals with successful couplation/No, of animals mated) x 100
Fertility index =
(No. of pregnant animals/No, of animals with successful couplation) x 100

FINDINGS OF DELIVERY IN DAMS AND OBSERVATIONS ON THEIR PUPS (F1)

Dose (mg/kg)	0	100	300	1000
No. of dams observed	11	10	12	12
No. of dams delivered live pups	11	10	12	12
Duration of gestation(mean ± sd)	22.7±0.6	22.4±0.5	22.3±0.5	22.8±0.4
No. of total corpora lutea	216	170	218	222
mean ± sd	19.6±4.5	17.0±2.1	18.2±3.7	18.5±3.2
No. of total implants	188	161	186	175
mean ± sd	17.1±1.6	16.1±2.0	15.5±3.0	14.6±3.0
No. of total pups born	172	150	178	160
mean ± sd (= litter size)	15.6±1.6	15.0±1.8	14.8±2.6	13.3±3.3
live Male	81	69	91	79
mean +- sd	7.4±1.9	6.9±2.3	7.6±2.4	6.6±1.8
live Female	87	81	87	81
mean ± sd	7.9±1.9	8.1±1.7	7.3±1.9	6.8±2.7
Sex ratio (male/female, mean ± sd)	1.00±0.41	0.93±0.51	1.13±0.43	1.21±0.81
No. of total live pops on day 4;				
Male	66	66	85	78
mean ± sd	6.0±3.2	6.6±2.2	7.1±2.5	6.5±1.7
Female	66	77	80	79
mean ± sd	6.0±3.3	7.7±1.4	6.7±1.6	6.6±2.6
No. of total dead pups born	4*	0	0	0
mean ± sd	0.4±1.2	0.0±0.0	0.0±0.0	0.0±0.0
Gestation index (%)	100.0	100.0	100.0	100.0
Implanation index(%,mean ± sd)	89.5±12.3	94.7±2.0	86.6±15.8	80.2±18.2
Delivery index (%,mean ± sd)	91.6±5.6	93.5±7.7	96.2±4.8	90.9±8.6
Livebirth index (%,mean ± sd)	97.4±8.6	100.0±0	100.0±0	100.0±0
Viability index on day 4 (%, mean ± sd);				
Male	77.8±39.1	96.0±8.4	93.1±9.7	99.1±3.2
Female	77.0±39.1	95.7±5.6	94.4±15.8	98.0±4.8

rem. Gestation index =
(No. of females with live pups/No. of pregnant females) x 100
Implanation index = (No. of implant/No. of corpora lutea) x 100
Delivery index = (No. of pups born/No. of implants) x 100
Livebirth index = (No. of live pups born/No. of pups born) x 100
Viability index on day 4 = (No. of live pups on day 4 after birth/No. of live pups born) x 100
*The reason of 4 dead pups born at 0mg/kg, was not stillbirth but cannibalism.

Source : MHW Japan

Test condition : TEST ORGANISMS
age: 10 weeks
weight at initiation: 375-414 g for males, 239-266 g for females
number of animals: 12 per sex per dose
pellet food and water: free take
ADMINISTRATION
vehicle: sesame oil, 0.5mL/100g body weight
schedule: once a day by oral gavage
male: before mating 14 days, during mating 14 days, after mating 20 days; total 48 days
pregnant female: before mating 14 days, during mating (max.) 14 days, during gestation (about 21 days), after pregnant 3 days; total 41-46 days
not pregnant female: till 25 days after gestation; total 41-43 days
not couplated female: till 20 days after mating period; total 48 days
According to the random sampling, actual dose received was between -12.5 to -0.4 % of each dose level.
MATING PROCEDURE
max. 14 days, one by one in each cage
CLINICAL OBSERVATION AND FREQUENCY
clinical signs and mortality: every day to all
male body weight: once a week, total 8 times in the 49 days
female body weight: 1st, 8th, 15th day before mating; 0th, 7th, 14th, 21st day after copulated; 0th, 4th day after pregnant
food consumption: in conformity with those body weight, except during mating for female
water consumption: not checked
Pups number, sex, weight by sex in each litter, appearance were observed on 0th and 4th day. Dead pups were checked separately.

Attached document : Organs Examined

Conclusion : NOAEL for both reproductive and developmental toxicity are considered to be 1000mg/kg/day for both parental animals and offspring.

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint

27.06.2003 (15)

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species : rat
Sex : male/female
Strain : *Crj: CD(SD)*
Route of admin. : gavage
Exposure period : male: 48 days, female: 41-48 days
Frequency of treatm. : once a day, every day
Duration of test : male: 48 days, female: 41-48 days
Doses : 0, 100, 300, 1000 mg/kg/day
Control group : yes, concurrent vehicle
NOAEL maternal tox. : = 1000 mg/kg bw
NOAEL teratogen. : = 1000 mg/kg bw
Result : of low toxicity to offspring

Method : other: OECD TG421
Year : 1999
GLP : yes
Test substance : other TS: Mitsuboshi Chemical CO., Ltd.: purity >99%

Remark : This data is a part of OECD TH421.
Result : STATISTICAL RESULTS
There were no significant differences in number of offspring or live offspring, sex ratio, the live birth index, the viability index and the body weight. No abnormal findings related to the test substance were noted for external features, clinical signs, or on necropsy finding for the offspring. No pups with malformation were found in any group. No change in clinical signs and necropsy finding were observed in offspring.

FINDINGS OF DELIVERY IN DAMS AND OBSERVATIONS ON THEIR PUPS (F1)

Dose (mg/kg)	0	100	300	1000
No. of dams observed	11	10	12	12
No. of dams delivered live pups	11	10	12	12
Duration of gestation(mean ± sd)	22.7±0.6	22.4±0.5	22.3±0.5	22.8±0.4
No. of total corpora lutea	216	170	218	222
mean ± sd	19.6±4.5	17.0±2.1	18.2±3.7	18.5±3.2
No. of total implants	188	161	186	175
mean ± sd	17.1±1.6	16.1±2.0	15.5±3.0	14.6±3.0
No. of total pups born	172	150	178	160
mean ± sd (= litter size)	15.6±1.6	15.0±1.8	14.8±2.6	13.3±3.3
live Male	81	69	91	79
mean ± sd	7.4±1.9	6.9±2.3	7.6±2.4	6.6±1.8
live Female	87	81	87	81
mean ± sd	7.9±1.9	8.1±1.7	7.3±1.9	6.8±2.7
Sex ratio (male/female, mean ± sd)	1.00±0.41	0.93±0.51	1.13±0.43	1.21±0.81
No. of total live pops on day 4;				
Male	66	66	85	78
mean ± sd	6.0±3.2	6.6±2.2	7.1±2.5	6.5±1.7
Female	66	77	80	79
mean ± sd	6.0±3.3	7.7±1.4	6.7±1.6	6.6±2.6
No. of total dead pups born	4*	0	0	0
mean ± sd	0.4±1.2	0.0±0.0	0.0±0.0	0.0±0.0
Gestation index (%)	100.0	100.0	100.0	100.0
Implanation index(%,mean ± sd)	89.5±12.3	94.7±2.0	86.6±15.8	80.2±18.2
Delivery index (%,mean±sd)	91.6±5.6	93.5±7.7	96.2±4.8	90.9±8.6
Livebirth index (%,mean±sd)	97.4±8.6	100.0±0	100.0±0	100.0±0
Viability index on day 4 (%, mean ± sd);				
Male	77.8±39.1	96.0±8.4	93.1±9.7	99.1±3.2
Female	77.0±39.1	95.7±5.6	94.4±15.8	98.0±4.8

rem. Gestation index =
(No. of females with live pups/No. of pregnant females) x 100
Implanation index = (No. of implant/No. of corpora lutea) x 100
Delivery index = (No. of pups born/No. of implants) x 100
Livebirth index = (No. of live pups born/No. of pups born) x 100
Viability index on day 4 = (No. of live pups on day 4 after birth/No. of live pups born) x 100
*The reason of 4 dead pups born at 0mg/kg, was not stillbirth but cannibalism.

Source : MHW Japan

Test condition	:	TEST ORGANISMS age: 10 weeks weight at initiation: 375-414 g for males, 239-266 g for females number of animals: 12 per sex per dose pellet food and water: free take ADMINISTRATION vehicle: sesame oil, 0.5mL/100g body weight schedule: once a day by oral gavage male: before mating 14 days, during mating 14 days, after mating 20 days; total 48 days pregnant female: before mating 14 days, during mating (max.) 14 days, during gestation (about 21 days), after pregnant 3 days; total 41-46 days not pregnant female: till 25 days after gestation; total 41-43 days not couplated female: till 20 days after mating period; total 48 days According to the random sampling, actual dose received was between -12.5 to -0.4 % of each dose level. MATING PROCEDURE max. 14 days, one by one in each cage CLINICAL OBSERVATION AND FREQUENCY clinical signs and mortality: every day to all male body weight: once a week, total 8 times in the 49 days female body weight: 1st, 8th, 15th day before mating; 0th, 7th, 14th, 21st day after copulated; 0th, 4th day after pregnant food consumption: in conformity with those body weight, except during mating for female water consumption: not checked Pups number, sex, weight by sex in each litter, appearance were observed on 0th and 4th day. Dead pups were checked separately.
Conclusion	:	NOAEL for Developmental Toxicity and Teratogenicity is considered to be 1000 mg/kg/day.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

27.06.2003 (15)

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

5.11 ADDITIONAL REMARKS

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(21) Report No. EDI98002, Environment Agency, Japan (1999b): unpublished report

(22) Report No. EDR98002, Environment Agency, Japan (1999c): unpublished report

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(25) StoerfallVO vom 20.09.1991

(26) Test No. 850212, AUTORADIOGRAPHIC DNA REPAIR TEST ON RAT HEPATOCYTES, CIBA-GEIGY LIMITED, unpublished report

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(28) Test No. 850623, V79 CHINESE HAMSTER POINT MUTATION TEST, CIBA-GEIGY LIMITED, unpublished report

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(31) TRGS 900 von 4/1995

3.3.2 Distribution

Table 1 The Fugacity Model (Mackay level III) treated with 4-Aminotoluene-3-sulphonic acid

scenario 1

	emission rate [kg/h]	conc. [g/m^3]	amount [kg]	percent [%]	transformation rate [kg/h]	
					reaction	advection
air	1,000	6.5.E-09	6.5.E+01	0.0	1.0E+01	6.5.E-01
water	0	4.9.E-02	9.8.E+05	50.5	2.8E+00	9.8.E+02
soil	0	6.0.E-01	9.6.E+05	49.3	2.8E+00	
sediment		3.9.E-02	3.9.E+03	0.2	3.8E-03	7.8.E-02
		total amount	1.9.E+06			

scenario 2

	emission rate [kg/h]	conc. [g/m^3]	amount [kg]	percent [%]	transformation rate [kg/h]	
					reaction	advection
air	0	2.1.E-14	2.1.E-04	0.0	3.3.E-05	2.1.E-06
water	1000	5.0.E-02	1.0.E+06	99.6	2.9.E+00	1.0.E+03
soil	0	2.0.E-06	3.1.E+00	0.0	9.0.E-06	
sediment		4.0.E-02	4.0.E+03	0.4	3.8.E-03	7.9.E-02
		total amount	1.0.E+06			

scenario 3

	emission rate [kg/h]	conc. [g/m^3]	amount [kg]	percent [%]	transformation rate [kg/h]	
					reaction	advection
air	0	4.2.E-12	4.2.E-02	0.0	6.5.E-03	4.2.E-04
water	0	5.0.E-02	9.9.E+05	45.0	2.9.E+00	9.9.E+02
soil	1000	7.6.E-01	1.2.E+06	54.9	3.5.E+00	
sediment		4.0.E-02	4.0.E+03	0.2	3.8.E-03	7.9.E-02
		total amount	2.2.E+06			

scenario 4

	emission rate [kg/h]	conc. [g/m^3]	amount [kg]	percent [%]	transformation rate [kg/h]	
					reaction	advection
air	600	3.9.E-09	3.9.E+01	0.0	6.0.E+00	3.9.E-01
water	300	4.9.E-02	9.9.E+05	58.5	2.9.E+00	9.9.E+02
soil	100	4.4.E-01	7.0.E+05	41.3	2.0.E+00	
sediment		3.9.E-02	3.9.E+03	0.2	3.8.E-03	7.9.E-02
		total amount	1.7.E+06			

3.3.2 Distribution (continued)

Table 2 The Fugacity Model (Mackay level III) treated with 4-Aminotoluene-3-sulphonic acid (continued)

molecular weight		187.22	Calculated
melting point [℃]		306	Measured
vapor pressure [Pa]		5.20E-04	Measured
water solubility [g/m3]		6000	Measured
log Pow		-0.67	Measured
half life [h]	in air	4.5	Calculated
	in water	240000	Estimated
	in soil	240000	Estimated
	in sediment	720000	Estimated

Temp. [°C]	25

Environmetal parameter

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

Intermedia Transport Parameters

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

Table 3 Absolute and relative organ weights of rats treated orally with 2-amino-5-methyl benzenesulfonic acid in the preliminary reproduction toxicity screening test

Dose level （mg/kg）	0	100	300	1000
Male				
No. of animals examined	12	12	12	12
Body weight (g)	542 ± 33	554 ± 45	534 ± 36	546 ± 3
Absolute organ weight				
Testes (g)	3.62 ± 0.31	3.65 ± 0.44	3.28 ± 0.59	3.70 ± 0.23
Epididymides (mg)	1313 ± 98	1295 ± 138	1168 ± 121*	1316 ± 115
Relative organ weight				
Testes (g%)	0.671 ± 0.074	0.664 ± 0.094	0.616 ± 0.119	0.680 ± 0.066
Epididymides (mg%)	243.378 ± 27.682	235.898 ± 34.456	219.293 ± 27.989	242.189 ± 27.983

Values are expressed as Mean ± S.D.
Significant difference from control group ; *: $p < 0.05$

Table 4 Summary of histological findings with statistical analysis treated orally with 2-amino-5-methylbenzenesulfonic acid in the preliminary reproduction toxicity screening test

Dose level (mg/kg)	Male animals				Female animals			
No. of animals necropsied	0	100	300	1000	0	100	300	1000
Organ Findings	11	10	12	12	9	10	12	12
HEMATOPOIETIC SYSTEM								
thymus								
atrophy	--	--	--	--	--	--	1(1)	2(2)
RESPIRATORY SYSTEM								
lung								
inflammation	1(1)	--	1(1)	--	--	--	--	1(1)
DIGESTIVE SYSTEM								
stomach								
ulcer, forestomach	--	--	--	--	--	--	--	1(1)
liver								
necrosis	--	--	1(1)	--	--	--	--	--
REPRODUCTIVE SYSTEM								
testis								
atrophy, seminiferous tubule	0	--	1(1)	0	--	--	--	--
interstitial cell hyperplasia	0	--	1(1)	0	--	--	--	--
epididymis								
decrease, sperm	0	--	1(1)	0	--	--	--	--
cellular infiltration	0	--	0(1)	1	--	--	--	--
ovary								
cyst, brusa	--	--	--	--	0	1(1)	--	0
ENDOCRINE SYSTEM								
adrenal gland								
hypertrophy	--	--	--	--	--	--	--	1(1)
INTEGUMENTARY SYSTEM								
skin								
erosion	--	--	0(1)	1(1)	--	0(1)	--	--
inflammatoly infiltration	--	--	0(1)	1(1)	--	1(1)	--	--
squamous hyperplasia	--	--	0(1)	1(1)	--	1(1)	--	--

( ) : No. of animals examined microscopically at this site. -: Not applicable

5.4 REPEATED DOSE TOXICITY

Table 5 Hematological examination of male rats treated orally with 2-amino-5-methyl benzenesulfonic acid in the 28-day repeat dose toxicity test

	After administration period				After recovery period	
Dose level (mg/kg)	0	100	300	1000	0	1000
No. of animals	6	6	6	6	6	6
Erythrocyte (10^4/mm^3)	761 ± 29	775 ± 35	755 ± 36	787 ± 35	817 ± 30	829 ± 26
Hematocrit (%)	45.0 ± 0.9	44.8 ± 1.3	44.3 ± 1.7	45.5 ± 1.9	45.6 ± 1.4	44.6 ± 1.3
Hemoglobin (g/dl)	15.4 ± 0.3	15.6 ± 0.4	15.4 ± 0.4	15.6 ± 0.6	15.5 ± 0.5	15.3 ± 0.6
Reticulocyte ($^0/_{00}$)	42 ± 15	29 ± 4	35 ± 7	29 ± 9	31 ± 5	34 ± 5
Leukocyte(10^2/mm^3)	76 ± 16	67 ± 9	73 ± 26	49 ± 11*	88 ± 28	85 ± 17
Differential count (%)						
Lymphocyte	89 ± 2	85 ± 4	84 ± 7	82 ± 3	91 ± 3	89 ± 1
Neutrophil band	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
segmented	10 ± 3	14 ± 4	14 ± 6	16 ± 4	8 ± 3	9 ± 2
Eosinophil	1 ± 1	0 ± 0	1 ± 1	1 ± 1	0 ± 1	1 ± 1
Basophil	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Monocyte	1 ± 1	1 ± 1	2 ± 1	1 ± 0	1 ± 1	1 ± 1
Platelet (10^4/mm^3)	154 ± 21	140 ± 14	158 ± 16	149 ± 12	141 ± 16	146 ± 9
PT (sec)	12.7 ± 0.4	13.1 ± 0.4	12.9 ± 0.3	13.1 ± 0.2	12.6 ± 0.3	12.6 ± 0.3
APTT (sec)	16.8 ± 0.9	17.1 ± 0.9	17.0 ± 0.9	17.8 ± 0.8	18.5 ± 1.0	18.6 ± 1.1

Values are expressed as Mean ± S.D.
Significantly different from control group (*: $p < 0.05$)

Table 6 Hematological examination of female rats treated orally with 2-amino-5-methyl benzenesulfonic acid in the 28-day repeat dose toxicity test

	After administration period				After recovery period	
Dose level (mg/kg)	0	100	300	1000	0	1000
No. of animals	6	6	6	6	6	6
Erythrocyte (10^4/mm^3)	766 ± 29	769 ± 34	775 ± 42	772 ± 25	819 ± 30	803 ± 1
Hematocrit (%)	43.1 ± 0.4	43.1 ± 1.2	43.4 ± 1.8	43.7 ± 0.9	44.7 ± 1.7	43.6 ± 0.9
Hemoglobin (g/dl)	15.0 ± 0.2	15.1 ± 0.6	15.2 ± 0.7	15.4 ± 0.3	15.4 ± 0.6	15.2 ± 0.4
Reticulocyte ($^0/_{00}$)	26 ± 7	28 ± 7	26 ± 6	24 ± 7	32 ± 7	28 ± 8
Leukocyte (10^2/mm^3)	41 ± 7	39 ± 13	49 ± 19	43 ± 7	45 ± 21	51 ± 18
Differential count (%)						
Lymphocyte	88 ± 6	88 ± 3	88 ± 5	86 ± 3	88 ± 5	86 ± 7
Neutrophil band	0 ± 0	0 ± 1	0 ± 0	0 ± 0	0 ± 0	0 ± 0
segmented	11 ± 6	11 ± 2	11 ± 5	13 ± 3	11± 5	14 ± 7
Eosinophil	1 ± 1	1 ± 1	1 ± 2	0 ± 1	0 ± 0	1 ± 1
Basophil	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Monocyte	1 ± 1	1 ± 1	0 ± 0	0 ± 1	1 ± 1	0 ± 0
Platelet (10^4/mm^3)	145 ± 17	140 ± 17	136 ± 13	138 ± 5	146 ± 12	140 ± 21
PT (sec)	12.8 ± 0.5	13.0 ± 0.4	12.9 ± 0.2	13.0 ± 0.4	13.0 ± 0.3	13.2 ± 0.3
APTT (sec)	16.0 ± 0.8	16.5 ± 0.6	16.5 ± 1.0	16.8 ± 1.0	16.5 ± 0.4	17.0 ± 0.7

Values are expressed as Mean ± S.D.

5.4 REPEATED DOSE TOXICITY (continued)

Table 7 Blood chemical examination of male rats treated orally with 2-amino-5-methyl benzenesulfonic acid in the 28-day repeat dose toxicity test

	After administration period				After recovery period	
Dose level (mg/kg)	0	100	300	1000	0	1000
No. of animals	6	6	6	6	6	6
GOT (IU/L)	61 ± 6	59 ± 6	63 ± 5	59 ± 2	58 ± 9	61 ± 6
GPT (IU/L)	32 ± 6	27 ± 3	31 ± 3	30 ± 6	26 ± 5	33 ± 6
gamma-GTP (IU/L)	0.19 ± 0.12	0.24 ± 0.15	0.35 ± 0.14	0.36 ± 0.21	0.29 ± 0.31	0.28 ± 0.19
ALP (IU/L)	428 ± 50	399 ± 70	506 ± 77	441 ± 77	270 ± 32	332 ± 57*
T.protein (g/dL)	6.03 ± 0.12	6.10 ± 0.22	6.30 ± 0.22	6.14 ± 0.09	6.34 ± 0.15	6.32 ± 0.20
Albumin (g/dL)	2.96 ± 0.16	3.05 ± 0.12	3.04 ± 0.13	2.99 ± 0.12	2.98 ± 0.09	2.95 ± 0.15
A/G ratio	0.97 ± 0.09	1.00 ± 0.04	0.93 ± 0.07	0.95 ± 0.07	0.89 ± 0.06	0.88 ± 0.09
T.cholesterol (mg/dL)	90 ± 10	77 ± 9	85 ± 9	74 ± 10*	101 ± 14	91 ± 10
Triglyceride (mg/dL)	83 ± 44	80 ± 29	87 ± 28	50 ± 15	125 ± 36	76 ± 33*
Glucose (mg/dL)	138 ± 11	145± 11	148 ± 16	137 ± 10	174 ± 19	161 ± 17
T.bilirubin (mg/dL)	0.34 ± 0.04	0.35 ± 0.04	0.34 ± 0.03	0.32 ± 0.02	0.26 ± 0.02	0.28 ± 0.02
Urea nitrogen(mg/dL)	15.1± 1.9	14.7 ± 1.8	15.9 ± 2.2	14.9 ± 1.3	17.1 ± 2.0	18.0 ± 1.4
Creatinine (mg/dL)	0.51 ± 0.02	0.52 ± 0.04	0.56 ± 0.06	0.52 ± 0.04	0.61 ± 0.03	0.61 ± 0.09
Ca (mg/dL)	10.0 ±0.5	10.1 ± 0.3	10.0 ± 0.2	9.8 ± 0.2	10.1 ± 0.3	9.9 ± 0.3
I.phosphorus (mg/dL)	7.7 ± 0.8	7.5 ± 0.7	7.5 ± 0.3	7.3 ± 0.3	8.0 ± 0.9	7.6 ± 0.3
Na (mEq/L)	141 ± 1	143 ± 0	142 ± 1	142 ± 1	141 ± 1	141 ± 1
K (mEq/L)	4.73 ± 0.13	4.39 ± 0.27	4.65 ± 0.31	4.58 ± 0.13	4.53 ± 0.35	4.41 ± 0.19
Cl (mEq/L)	103 ± 1	104 ± 1	104 ± 2	105 ± 1	104 ± 2	105 ± 1

Values are expressed as Mean ± S.D.
Significantly different from control group (*: $p < 0.05$)

Table 8 Blood chemical examination of female rats treated orally with 2-amino-5-methyl benzenesulfonic acid in the 28-day repeat dose toxicity test

	After administration period				After recovery period	
Dose level (mg/kg)	0	100	300	1000	0	1000
No. of animals	6	6	6	6	6	6
GOT (IU/L)	57 ± 7	60 ± 4	62 ± 5	66 ± 10	65 ± 9	65 ± 12
GPT (IU/L)	24 ± 4	27 ± 2	24 ± 5	32 ± 5**	25 ± 4	26 ± 6
gamma-GTP (IU/L)	0.41 ± 0.27	0.20 ± 0.14	0.25 ± 0.19	0.33 ± 0.28	0.46 ± 0.43	0.31 ± 0.28
ALP (IU/L)	237 ± 82	280 ± 50	271 ± 53	225 ± 62	202 ± 30	189 ± 36
T.protein (g/dL)	6.47 ± 0.29	6.31 ± 0.19	6.31 ± 0.20	6.51 ± 0.18	6.59 ± 0.25	6.65 ± 0.23
Albumin (g/dL)	3.27 ± 0.27	3.23 ± 0.13	3.22 ± 0.14	3.19 ± 0.11	3.39 ± 0.27	3.36 ± 0.30
A/G ratio	1.02 ± 0.10	1.05 ± 0.05	1.05 ± 0.06	0.96 ± 0.08	1.07 ± 0.15	1.03 ± 0.13
T.cholesterol (mg/dL)	101 ± 20	80 ± 9	84 ± 14	86 ± 24	111 ± 19	92 ± 18
Triglyceride (mg/dL)	51 ± 37	43 ± 11	59 ± 24	36 ± 12	51 ± 24	52 ± 15
Glucose (mg/dL)	138 ± 6	121 ± 14*	126 ± 11	116 ± 9**	137 ± 15	130 ± 11
T.bilirubin (mg/dL)	0.24 ± 0.04	0.24 ± 0.03	0.23 ± 0.03	0.23 ± 0.03	0.29 ± 0.04	0.24 ± 0.03*
Urea nitrogen(mg/dL)	17.0 ± 1.6	19.0 ± 2.7	17.3 ± 1.4	17.4 ± 2.6	20.5 ± 1.7	20.8 ± 1.4
Creatinine (mg/dL)	0.58 ± 0.05	0.57 ± 0.04	0.57 ± 0.04	0.56 ± 0.04	0.64 ± 0.06	0.62 ± 0.07
Ca (mg/dL)	10.2 ± 0.4	10.1 ± 0.2	9.9 ± 0.2	10.1 ± 0.3	10.0 ± 0.4	10.2 ± 0.1
I.phosphorus (mg/dL)	6.6 ± 0.7	6.6 ± 0.6	6.0 ± 0.4	6.3 ± 0.6	6.0 ± 0.9	5.8 ± 0.8
Na (mEq/L)	142 ± 1	142 ± 1	142 ± 1	142 ± 0	142 ± 1	142 ± 1
K (mEq/L)	4.27 ± 0.26	4.30 ± 0.23	4.38 ± 0.31	4.33 ± 0.19	4.39 ± 0.11	4.31 ± 0.25
Cl (mEq/L)	107 ± 2	107 ± 2	108 ± 1	108 ± 2	107 ± 2	107 ± 2

Values are expressed as Mean ± S.D.
Significantly different from control group (*: $p < 0.05$; **: $p < 0.01$)

5.4 REPEATED DOSE TOXICITY (continued)

Table 9 Absolute and relative organ weights of male rats treated orally with 2-amino-5-methyl benzenesulfonic acid in the 28-day repeat dose toxicity test

	After administration period				After recovery period	
Dose level (mg/kg)	0	100	300	1000	0	1000
No. of animals	6	6	6	6	6	5
Body weight (g)	340 ± 18	333 ± 14	346 ± 13	335 ± 26	399 ± 41	386 ± 22
Absolute weight						
Brain (g)	1.98 ± 0.08	2.00 ± 0.08	1.96 ± 0.07	2.02 ± 0.08	2.05 ± 0.10	2.01 ± 0.09
Liver (g)	10.44 ± 1.11	10.23 ± 0.88	10.95 ± 0.76	9.89 ± 1.51	12.01 ± 1.71	11.42 ± 1.11
Kidneys (g)	2.48 ± 0.14	2.36 ± 0.11	2.58 ± 0.25	2.51 ± 0.31	2.66 ± 0.29	2.67 ± 0.34
Spleen (g)	0.69 ± 0.09	0.65 ± 0.10	0.67 ± 0.04	0.65 ± 0.12	0.71 ± 0.08	0.76 ± 0.11
Heart (g)	1.21 ± 0.08	1.12 ± 0.11	1.21 ± 0.08	1.12 ± 0.10	1.41 ± 0.17	1.24 ± 0.09
Thymus (g)	0.61 ± 0.07	0.51 ± 0.07	0.64 ± 0.12	0.57 ± 0.14	0.49 ± 0.08	0.47 ± 0.04
Adrenals (g)	53.7 ± 7.1	53.5 ± 2.8	53.5 ± 5.8	56.8 ± 8.9	57.6 ± 6.7	51.1 ± 7.1
Testes (g)	3.03 ± 0.18	3.27 ± 0.32	3.22 ± 0.20	3.23 ± 0.21	3.22 ± 0.18	3.11 ± 0.41
Epididymides (g)	0.87 ± 0.15	0.90 ± 0.13	0.87 ± 0.14	0.87 ± 0.10	1.11 ± 0.09	1.08 ± 0.18
Relative weight						
Brain (g%)	0.58 ± 0.03	0.60 ± 0.03	0.57 ± 0.03	0.61 ± 0.05	0.52 ± 0.04	0.52 ± 0.04
Liver (g%)	3.06 ± 0.18	3.07 ± 0.15	3.17 ± 0.20	2.94 ± 0.24	3.00 ± 0.15	2.95 ± 0.18
Kidneys (g%)	0.73 ± 0.04	0.71 ± 0.01	0.75 ± 0.06	0.75 ± 0.07	0.67 ± 0.02	0.69 ± 0.07
Spleen (g%)	0.20 ± 0.02	0.20 ± 0.03	0.19 ± 0.01	0.19 ± 0.03	0.18 ± 0.01	0.20 ± 0.03
Heart (g%)	0.36 ± 0.02	0.34 ± 0.02	0.35 ± 0.02	0.33 ± 0.02	0.36 ± 0.07	0.32 ± 0.02
Thymus (g%)	0.18 ± 0.02	0.16 ± 0.03	0.19 ± 0.03	0.17 ± 0.03	0.13 ± 0.03	0.12 ± 0.02
Adrenals(mg%)	15.79 ± 1.90	16.08 ± 1.03	15.54 ± 2.07	17.03 ± 2.71	14.50 ± 1.50	13.28 ± 1.93
Testes (%g)	0.89 ± 0.08	0.98 ± 0.11	0.93 ± 0.07	0.97 ± 0.10	0.82 ± 0.10	0.81 ± 0.10
Epididymides(%g)	0.26 ± 0.05	0.27 ± 0.04	0.25 ± 0.04	0.26 ± 0.03	0.28 ± 0.04	0.28 ± 0.05

Values are expressed as Mean ± S.D.

Table 10 Absolute and relative organ weights of female rats treated orally with 2-amino-5-methyl benzenesulfonic acid in the 28-day repeat dose toxicity test

	After administration period				After recovery period	
Dose level (mg/kg)	0	100	300	1000	0	1000
No. of animals	6	6	6	6	6	5
Body weight (g)	205 ± 16	200 ± 16	192 ± 13	191 ± 15	218 ± 15	214 ± 16
Absolute weight						
Brain (g)	1.78 ± 0.08	1.84 ± 0.09	1.85 ± 0.07	1.80 ± 0.03	1.82 ± 0.10	1.86 ± 0.07
Liver (g)	6.33 ± 0.89	5.86 ± 0.50	5.75 ± 0.57	5.49 ± 0.73	5.98 ± 0.60	5.91 ± 0.55
Kidneys (g)	1.55 ± 0.12	1.49 ± 0.21	1.50 ± 0.14	1.52 ± 0.17	1.58 ± 0.13	1.51 ± 0.06
Spleen (g)	0.40 ± 0.06	0.43 ± 0.04	0.43 ± 0.03	0.43 ± 0.05	0.47 ± 0.05	0.47 ± 0.04
Heart (g)	0.80 ± 0.05	0.75 ± 0.05	0.74 ± 0.05	0.75 ± 0.10	0.80 ± 0.07	0.79 ± 0.04
Thymus (g)	0.50 ± 0.08	0.37 ± 0.05*	0.47 ± 0.09	0.43 ± 0.04	0.37 ± 0.10	0.33 ± 0.06
Adrenals (mg)	57.3 ± 7.0	60.2 ± 10.8	64.7 ± 11.5	55.2 ± 8.3	56.1 ± 5.7	58.2 ± 6.6
Ovaries (g)	78.6 ± 5.4	77.1 ± 11.1	83.8 ± 10.5	83.8 ± 20.2	78.0 ± 13.7	78.2 ± 14.6
Relative weight						
Brain (g%)	0.88 ± 0.06	0.92 ± 0.08	0.96 ± 0.05	0.95 ± 0.08	0.83 ± 0.04	0.88 ± 0.06
Liver (g%)	3.09 ± 0.25	2.94 ± 0.15	2.99 ± 0.14	2.86 ± 0.19	2.74 ± 0.25	2.77 ± 0.05
Kidneys (g%)	0.76 ± 0.04	0.74 ± 0.06	0.78 ± 0.06	0.80 ± 0.04	0.72 ± 0.06	0.71 ± 0.07
Spleen (g%)	0.19 ± 0.02	0.22 ± 0.02*	0.23 ± 0.01**	0.22 ± 0.01**	0.22 ± 0.03	0.22 ± 0.02
Heart (g%)	0.39 ± 0.01	0.38 ± 0.03	0.38 ± 0.02	0.39 ± 0.03	0.37 ± 0.03	0.37 ± 0.02
Thymus (g%)	0.24 ± 0.02	0.19 ± 0.02**	0.24 ± 0.04	0.23 ± 0.02	0.17 ± 0.04	0.16 ± 0.02
Adrenals(mg%)	28.00 ± 2.67	29.95 ± 3.39	33.70 ± 5.51	28.82 ± 3.76	25.64 ± 1.46	27.24 ± 2.32
Ovaries (g%)	38.4 ± 1.4	38.8 ± 6.2	43.6 ± 2.6	43.8 ± 9.8	35.6 ± 5.3	36.9 ± 7.9

Values are expressed as Mean ± S.D.

Significantly different from control group (*: $p < 0.05$; **: $p < 0.01$)