FOREWORD INTRODUCTION

4-Methylbenzenesulfonyl chloride

CAS N°: 98-59-9

SIDS Initial Assessment Report

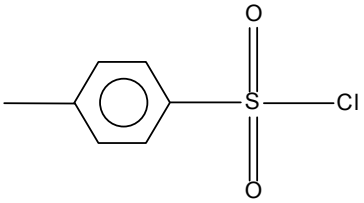
For

SIAM 17

Arona, Italy, 11-14 November 2003

1. Chemical Name:	4-Methylbenzenesulfonyl chloride
2. CAS Number:	98-59-9
3. Sponsor Country:	Republic of Korea Contact Point: Hyun-Mi KIM, Ph. D. National Institute of Environmental Research. Gyeongseo-dong, Seo-gu, Incheon, 404-708, Korea Tel: +82-(0)32-560-7124 FAX: +82-(0)32-560-7161 E-mail: hmikim@me.go.kr
4. Shared Partnership with:	
5. Roles/Responsibilities of the Partners:	
• Name of industry sponsor /consortium	
• Process used	
6. Sponsorship History	
• How was the chemical or category brought into the OECD HPV Chemicals Programme ?	This substance is sponsored by Korea. The assessment process was started in 1999. Korea National Institute of Environmental Research conducted a literature search, reviewed of submitted data and prepared document for SIAM 17.
7. Review Process Prior to the SIAM:	Korea National Institute of Environmental Research peer-reviewed the document and checked the quality.
8. Quality check process:	Korea National Institute of Environmental Research peer-reviewed selected endpoints and compared original studies with data in SIDS dossier.
9. Date of Submission:	August 2004
10. Date of last Update:	
11. Comments:	

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	98-59-9
Chemical Name	4-Methylbenzenesulfonyl chloride
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

There is no information on toxicokinetics, metabolism and distribution.

The acute oral toxicity study [OECD TG 423] of 4-methylbenzenesulfonyl chloride in rats showed that this chemical did not cause any significant changes in terms of LD_{50} at 2,000 mg/kg b.w for 1st and 2nd steps, and 5,000 mg/kg bw for limit test. Therefore, the oral LD_{50} value in female rats was greater than the highest tested dose (5,000 mg/kg bw). However, in a dose-finding study for an *in vivo* micronucleus test, at 200 mg/kg bw, all three female mice died.

Investigation was performed to observe effects of 4-methylbenzenesulfonyl chloride such as erythema and oedema on the abraded and intact backs of New Zealand White rabbits [OECD TG 404]. According to the results, the test substance induced irritation on the skins of rabbits. regarding eye irritation, a test was performed according to the FHSA protocol, in which the eyes were exposed for 24 hours then scored at 24, 48 and 72 hours after the exposure. Accordingly, 4-methylbenzenesulfonyl chloride induced corrosion and irritation on the eyes of New Zealand Albino Rabbits.

In the Combined Repeated Dose and Reproduction/Developmental Toxicity Screening Test in rats [OECD TG 422], 4-methylbenzenesulfonyl chloride was administrated by gavage at the dose levels of 0, 150, 350 and 750 mg/kg bw/day for 35 days and 36 ~ 51 days for male and female rats, respectively. Some clinical signs were observed at the dose level of 150 mg/kg bw/day in males such as intermittent (blood-like) salivation and staining around mouth; and in females such as intermittent (blood-like) salivation, staining around mouth, difficult delivery, poor nursing, irregular respiration. Based on these results, the LOAEL and NOAEL were determined to be 150 mg/kg/day and below the lowest tested dose (150 mg/kg/day) for both sexes, respectively.

In vitro bacterial gene reverse mutation tests [OECD TG 471 and 472] gave negative results in *Salmonella typhimurium* (strains TA98, TA100, TA1535 and TA1537) and *Escherichia coli* WP2 *uvr*A with and without metabolic activation. *Salmonella tryphimurium* (TA100 strain) showed positive mutagenic effects at concentrations of 1,250, 2,500 and 5,000 μg/plate without metabolic activation and the same strain (TA100) showed negative results with metabolic activation. Furthermore, an *in vivo* mutagenicity test, mammalian erythrocyte micronucleus assay (OECD TG 474) was negative. No firm conclusion can be reached from the available mutagenicity results.

In a reproduction/developmental toxicity screening test [OECD TG 422] with male and female rats, there were no significant treatment-related changes in terms of pregnancy, fertility, examination of pups etc. Therefore, LOAEL and NOAEL for reproduction and development are considered to be greater than 750 mg/kg bw/day.

Environment

4-Methylbenzenesulfonyl chloride is a colorless to light yellow crystalline solid which is hygroscopic and highly reactive. It has a melting point of 71 °C, a boiling point of 145 - 146 °C at 15 mmHg, a density of 1.33 g/cm^3, a vapour pressure of 0.16 Pa at 25 °C and a Henry's law constant of 9.67×10^{-6} $atm \cdot m^3/mole$ at 25 °C. Due to the rapid hydrolysis of 4-methylbenzenesulfonyl chloride, water solubility and partition coefficient n-octanol/water cannot be measured. Hence a partition coefficient n-octanol/water (log P_{ow}) of 3.49 at 25 °C and a water solubility of 51.18 mg/L at 25 °C were estimated.

4-Methylbenzenesulfonyl chloride is hydrolysed to 4-methylsulfonic acid and half-lives ($t_{1/2}$) at 25 °C in water are 2.2 min at pH 4, 2.2 min at pH 7 and 2.6 min at pH 9. The substance is not readily biodegradable. The calculated half-life for photochemical-oxidative degradation in the atmosphere by OH radicals is 8.7 days. According to a level III fugacity modeling (EQC model) if 4-methylbenzenesulfonyl chloride is emitted to air, it will mainly partition to soil (97.6 %) and if it is released to water, it will mainly remain in water (79.2 %). If it is released to soil, it will mainly remain in soil (100 %). Based on rapid hydrolysis of the substance, bioconcentration of 4-methylbenzenesulfonyl chloride is not expected. 4-Methylbenzenesulfonic acid is a strong acid (pK = -1.34) and is completely dissociated at the environmental pH. According to a level III fugacity modeling (EQC model) if 4-methylbenzenesulfonic acid is emitted to air, it will mainly partition to soil (78.4 %) and if it is released to water, it will mainly remain in water (99.8 %). If it is released to soil, it will mainly remain in soil (80.6 %). The calculated BCF value of 4-methylbenzenesulfonic acid was 3.16. Both the substance and its hydrolysis product have a low potential for bioaccumulation.

The following toxicity data for aquatic organisms are available for 4-methylbenzenesulfonyl chloride:
Green algae (*Selenastrum capricornutum)*: EC_{g50} (72 h) > 100 mg/L (growth rate)
Invertebrates (*Daphnia magna):* EC_{50} (48 h) = 70 mg/L.
Fish (*Oryzias latipes*): LC_{50} (96 h) = 55 mg/L.

In preliminary tests with adjustment of pH with fish and daphnia, at 100 mg/L of 4-methylbenzenesulfonyl chloride, no effects were seen in fish and daphnia after 48 hours of exposure.

The following toxicity data for aquatic organisms are available for 4-methylbenzenesulfonic acid:
Green algae (*Chlorella vulgaris*): EC_{50}(24h) = 245 mg/L (unspecified)
Invertebrates (*Daphnia magna*) : EC_0(24h) > 2500 mg/L.
Fish (*Leuciscus idus melanotus*): LC_{50} (96h) > 500 mg/L
Microorganisms (anaerobic bact. from a domestic water treatment plant): SG(24h) > 5000 mg/L

No data are available on terrestrial organisms.

Exposure

In the Sponsor country, the production amount for 4-methylbenzenesulfonyl chloride was estimated to be about 542.7 tonnes in 2001. Around 689.8 tonnes were imported into Korea from China in 2001.
In the Sponsor country 4-methylbenzenesulfonyl chloride is produced as a by-product from the reaction of HSO_3Cl and toluene in the food additives industry and this chemical is used as a raw material for the production of foaming agents for the plastic and rubber industry, of riboflavin and antithrombotic drug in the pharmaceutical industry and of a condensing agent in the dye industry.
Environmental releases are unlikely to occur during industrial production and processing of 4-methylbenzenesulfonyl chloride as these processes take place in closed systems. If environmental releases occur during these operations, they will be in the form of the hydrolysis product 4-methylbenzenesulfonic acid.
There is a potential of exposure for workers via dust inhalation and dermal routes at the packaging process. Based on physico-chemical properties and the hygroscopic nature of this chemical, if workers are exposed, they are likely to be exposed to the acid. Although 4-methylbenzenesulfonyl chloride is used as a raw material in several industries, there is no direct use or consumer products containing the substance. Therefore, consumer exposure to the substance is not expected.

RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

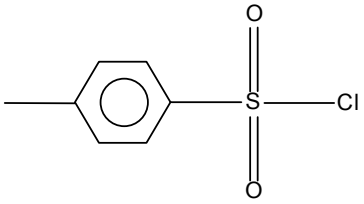
The chemical possesses properties indicating a hazard for human health (e.g. irritation, uncertainty for genotoxicity). Based on data presented by the Sponsor country, exposure to humans is anticipated to be low, and therefore this chemical is currently of low priority for further work. Countries may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

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 98-59-9
IUPAC Name: 4-Methylbenzenesulfonyl chloride
Molecular Formula: $C_7H_7ClO_2S$
Structural Formula:



Molecular Weight: 190.65
Synonyms: *p*-Toluenesulfonyl chloride

p-Methylbenzene sulfonyl chloride

p-Toluene sulfonic acid chloride

Tosyl chloride

1.2 Purity/Impurities/Additives

Purity : > 99 %
Impurities: ≤ 0.3 % *o*-Toluenesulfonyl chloride
Additives:

1.3 Physico-Chemical properties

Table 1 Summary of physico-chemical properties

Property	Value	References
Physical state	Solid	(1)
Melting point	71 °C	(1), (2)
Boiling point	145 ~ 146 °C at 15 mmHg	(1), (2)
Density	1.33 g/cm^3	(3)
Vapour pressure	0.16 Pa at 25 °C	(4)
Water solubility	51.18 mg/L at 25 °C	(4)
Partition coefficient n-octanol/water (log value)	3.49 at 25 °C	(4)
Henry's law constant	9.67 x 10^{-6} atm•m^3/mole at 25 °C	(4)

4-Methylbenzenesulfonyl chloride is a colorless to light yellow, highly reactive, hygroscopic crystalline solid (3).

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

The estimated amount of production for 4-methylbenzenesulfonyl chloride was 542.7 tonnes in Korea in 2001. 4-Methylbenzenesulfonyl chloride was produced in only one industry in Korea and the substance was not exported to other countries. Around 689.8 tonnes of the substance was imported into Korea from China in 2001.

In Nordic countries (Norway, Sweden, Denmark and Finland) and EU, 4-methylbenzenesulfonyl chloride was not listed in product registers in 2003.

4-Methylbenzenesulfonyl chloride is manufactured as a by-product to produce toluenesulfonyl amide ($C_7H_9O_2NS$) from chlorosulfonic acid (HSO_3) and toluene in the food additive industry.

4-Methylbenzenesulfonyl chloride is used as a raw material for the production of foaming agent used in plastic and rubber industry, of riboflavin and antithrombotic drugs in the pharmaceutical industry and of condensing agents in the dye industry in Korea (5).

2.2 Environmental Exposure and Fate

2.2.1 Sources of Environmental Exposure

Environmental releases are unlikely to occur during industrial production and processing of 4-methylbenzenesulfonyl chloride as these processes take place in closed systems. If environmental releases occur during these operations, they will be in the form of the hydrolysis product 4-methylbenzenesulfonic acid due to the short half-life of the parent substance. Wastewater of 4-methylbenzenesulfonyl chloride is discharged to wastewater treatment plants so significant releases are not expected. (5), (6).

2.2.2 Photodegradation

Photodegradation of 4-methylbenzenesulfonyl chloride was estimated by AOPWIN modelling. The calculated half-life of photochemical-oxidative degradation in the atmosphere by OH radicals is 8.7 days at 12 hour daily exposure and the rate constant is 0.0000000000012 cm^3/molecule*sec (4).

2.2.3 Stability in Water

4-Methylbenzenesulfonyl chloride hydrolyses rapidly in water, with a half-life (at 25 °C) of 2.2 min (pH 4.0 and 7.0) or 2.6 min (pH 9.0). Analysis was conducted using an HPLC column (Waters, µ-Bondapak C-18, 300 x 3.9 mm). Degradation of the test substance was in all cases accompanied by an equivalent production of hydrolysis products. The hydrolysis rates at pH 4.0 and 9.0 (around 70 % hydrolysis after 4 mins, and 90 % hydrolysis after 8 mins) were similar to the rate at pH 7.0 (74 % hydrolysis after 4 mins, and 93 % hydrolysis after 8 mins). However, the pattern of degradation at pH 7.0 differed from that at pH 4.0 and pH 9.0, as follows: HPLC analysis showed a single peak at pH 4.0 and pH 9.0. This was considered to be the hydrolysis product 4-methylbenzenesulfonic acid. At pH 7.0, an additional hydrolysis product was found, which could not be determined. This additional product degraded to 4-methylbenzenesulfonic acid over a period of 8 days (6).

2.2.4 Transport between Environmental Compartments

The environmental fate of 4-methybenzenesulfonyl chloride was estimated by the EQC model. 4-Methylbenzenesulfonyl chloride distributed in environmental compartments according to a fugacity level III model as follows: 4-methylbenzenesulfonyl chloride is mainly distributed to soil (99.9 %). If the substance is emitted to air, it will mainly partition in soil (97.6 %) and if it is released to water, it will mainly remain in water (79.2 %). If it is released to soil, it will mainly remain in soil (100 %).

Table 2-1. Environmental Distribution of 4-Methylbenzenesulfonyl chloride using the EQC Model Fugacity Level III

Compartment	Release 100 % to air	Release 100 % to water	Release 100 % to soil	All three (%)
Air	2.4	0.3	0.01	0.7
Water	0.0001	79.2	0.00004	0.0001
Soil	97.6	10.9	100	99.9
Sediment	0.00001	9.6	0.000005	0.00001

Environmental distribution for 4-methylbenzenesulfonic acid was also calculated. In the result of the fugacity level III model, 4-methylbenzenesulfonic acid distributed in environmental compartment as follows: 4-methylbenzenesulfonic acid is mainly distributed to soil (71.8 %) and water (27.8 %). If the substance is emitted to air, it will mainly partition in soil (78.4 %) and if it is released to water, it will mainly remain in water (99.8 %). If it is released to soil, it will mainly remain in soil (80.6 %).

Table 2-2. Environmental Distribution of 4-Methylbenzenesulfonic acid using the EQC Model Fugacity Level III

Compartment	Release 100 % to air	Release 100 % to water	Release 100 % to soil	All three (%)
Air	0.6	0.0002	0.03	0.3
Water	20.9	99.8	19.3	27.8
Soil	78.4	0.03	80.6	71.8
Sediment	0.044	0.2	0.041	0.06

(4).

2.2.5 Biodegradation

The percent of biodegradation was estimated by using a BOD meter and the medium was water with activated sludge in a modified MITI test (I) (OECD TG 301C). Aniline (100 mg/L) with 30 mg/L activated sludge was used as a positive control and an inoculum blank with activated sludge only was used as a negative control for the test substance. 4-Methylbenzenesulfonyl chloride achieved a biodegradation rate of 15.4 % after 7 days, 17.7 % after 14 days and 17.7 % after 28 days. The test substance, 4-methylbenzenesulfonyl chloride, was not readily biodegradable by micro organisms in aquatic environment (7). Because 4-methylbenzenesulfonyl chloride is readily hydrolysed to 4-methylbenzenesulfonic acid, the test result also reflects the biodegradability of 4-methylbenzenesulfonic acid.

2.2.6 Bioaccumulation

Bioaccumulation of 4-methylbenzenesulfonyl chloride was estimated by BCFWIN modelling. The calculated BCF value of the substance was 96.9. Based on rapid hydrolysis of the substance,

bioconcentration of 4-methylbenzenesulfonyl chloride is not expected. A bioaccumulation value of 3.16 is calculated for 4-methylbenzenesulfonic acid using BCFWIN. According to the result, both the substance and its hydrolysis product 4-methylbenzenesulfonyl chloride are expected to have a low potential for bioaccumulation (4).

2.3 Human Exposure

2.3.1 Occupational Exposure

4-Methylbenzenesulfonyl chloride is produced and processed in a closed system in Korea. Workers could be exposed to the substance via dust inhalation and dermal routes at the packaging or handling of the raw material process. In these operations, occupational exposure is controlled with personal protective equipment like goggles and mask and with ventilation facilities. Based on physico-chemical properties and hydroscopic nature of this chemical, if workers are exposed, they are likely to be exposed to the acid. The substance is not a hazardous chemical which is monitored for workplace exposure in Korea annually so monitoring data for occupational exposure is not available (5).

2.3.2 Consumer Exposure

Although 4-methylbenzenesulfonyl chloride is used as a raw material for the production of foaming agents used in plastic and rubber industry, of riboflavin and antithrombotic drug in pharmaceutical industry and of condensing agents used in the dye industry, there is no direct use or consumer products containing the substance. Consumer exposure to the substance is not expected in Korea (5).

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

There is no information in terms of Toxicokinetics, Metabolism and Distribution.

3.1.2 Acute Toxicity

Oral

The oral LD_{50} value was greater than 5,000 mg/kg bw. After single oral administration of 2,000, 2,000 and 5,000 mg/kg for 1st step, 2nd step, and limit test, respectively, of the test substance to 3 female rats for each test by gavage, the LD_{50} was determined in accordance with OECD TG 423, Acute Oral Toxicity. Test animals were observed for 14 days after the administration. The observation items were clinical signs, mortality, body weight, necropsy, and histopathological test. No dead animals were observed at all doses. Body weights of some animals were decreased but were recovered and increased during the test period. According to the necropsy, all animals had thickening of cutaneous membrane in the nongranular stomach because cutaneous membrane was stimulated. Two animals from each test group had a slight spontaneous alopecia. Histopathological findings include several cases of ulceration and mild to severe inflammation with hyperkeratosis of nongranular stomach in all the test groups and mild thickening of epithelial layer in all treated animals. Some clinical symptoms were observed as follows; 0.5 hours after the administration,

mucous diarrhea and diarrhea were observed for 1st and 2nd step, respectively. Contamination of the perineal region was observed from 1 hour after the administration in all 3 tests until the administration of the test substance was stopped. Depilation at the perineal region was observed on day 9 and 11 for two animals in the 1st test. In the limited test, depilation of the anal and perineal region including, haematological scab around the anal region were observed from day 9 in 2 animals and not recovered by day 14(11).

Another study in rats resulted in an LD_{50} of 10,200 mg/kg. In addition, rats had symptoms such as salivation, diarrhea, tremors leading to convulsions. Necropsy showed kidney and liver hyperemia with some discoloration in the latter organ (15, 17).

However, in a dose-finding study for an *in vivo* micronucleus test, at 200 mg/kg bw, all three female mice died (21).

Dermal

The test substance was applied as a 40 % solution-suspension in corn oil on New Zealand Albino Rabbit. There were some signs of intoxication, for instance, reduced appetite and activity (2 - 3 days in survivors), increased weakness, collapes, and death. At necropsy, lung hyperomia, liver & kidney discolouration, enlarged gall bladder, and gastrointestinal inflammation were observed. The LD_{50} was greater than 5,010 mg/kg (15).

3.1.3 Irritation

Skin Irritation

One test was carried out in accordance with OECD TG 404, Acute Dermal Irritation/Corrosion. 500 mg of the test material with about 0.1 mL of sterile distilled water was applied to the abraded and intact sites on the shaved backs of rabbits for 4 hours. The skin of animals was examined in accordance with an OECD scoring method for signs of erythema and oedema at 1, 24, 48 and 72 hours after removal of the patches. Erythema, oedema, and scab were observed and their scores ranged from 2 to 3, and 1 to 3 for erythema and oedema, respectively. In addition, mortality, clinical signs, and body weight were investigated as well. A case of weight loss was observed 24 hours after the administration, but it recovered within 48 hours. No clinical signs in relation to the spread of 4-methylbenzenesulfonyl chloride were observed (12). Two out of three other limited studies with rabbits showed that the test substance induced irritation on the skins of rabbits but one using powder form showed no irritation (15, 16, 17).

Eye Irritation

Regarding eye irritation, a test was performed according to the FHSA protocol. The eyes were exposed 24 hours then scored at 24, 48 and 72 hours after the exposure. Effects were seen immediately with severe discomfort with eyes tightly closed, pawing, squealing observed. Signs of recovery started from 24 hours after administration and full recovery occurred by 72 hours. In conclusion, 4-methylbenzenesulfonyl chloride is corrosive to the eyes of New Zealand Albino Rabbit. Another study also showed that the test substance was irritating and corrosive to eyes of rabbits and their symptoms were similar to the key study (15).

3.1.4 Sensitisation

There is no information on sensitization.

3.1.5 Repeated Dose Toxicity

In a gavage study with Sprague-Dawley rats in accordance with OECD TG 422, Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Screening Test, the rats were exposed to 4-methylbenzenesulfonyl chloride at levels of 0, 150, 350 and 750 mg/kg/day for 35 days and 36 - 51 days for male and female rats, respectively. Some clinical signs were observed at the dose level of 150 mg/kg/day for males animals such as intermittent (blood-like) salivation and staining around mouth; and for female animals such as intermittent (blood-like) salivation, staining around mouth, difficulty delivery, poor nursing, and irregular respiration. Moreover, at the dose level of 150 mg/kg/day, the digestive system and nongranular stomach were also affected. Therefore, the NOAEL and LOAEL for both sexes were determined as below the lowest tested dose (150 mg/kg bw/day) and 150 mg/kg bw/day, respectively (13).

3.1.6 Mutagenicity

In vitro Studies

Bacterial test – Bacterial Reverse Mutation Assay: This test was carried out in accordance with OECD TG 471 and 472. A preliminary test was carried out to decide the appropriate starting dose level of the main test at the concentrations of 0, 313, 625, 1,250, 2,500, and 5,000 μg/plate. The number of revertant colonies in the plate was counted after 2 days incubation at 37 °C. In the main study, 4-methylbenzenesulfonyl chloride was positive in the bacterial reverse mutation assay with *Salmonella typhimurium* (strain TA100) without metabolic activation at concentrations of 1,250, 2,500 and 5,000 μg/plate because the number of revertant colonies in the plate was increased significantly as compared with that of the negative control group. However, other assays with and without metabolic activation showed negative results for *Salmonella typhimurium* (strains TA98, TA1535, and TA1537) and *Escherichia coli* WP2 *uvr*A. Therefore, this test showed that mutation could be induced by 4-methylbenzenesulfonyl chloride without metabolic activation (14). Results of *Salmonella typhimurium* (strain TA100) with metabolic activation at various concentration of the test substance were negative. To clarify the mutagenicity study, an *in vivo* genetic study (mammalian erythrocyte micronucleus test) was done.

In vivo Studies

Mammalian erythrocyte micronucleus test: An *in vivo* mammalian erythrocyte micronucleus test with 6 mice had yielded negative response up to the test concentration of 80 mg/kg bw in accordance with OECD TG 474, Genetic toxicity: Micronucleus Test. The route of administration was I.P for the test substance and the positive control. This test indicated that 4-methylbenzenesulfonyl chloride did not induce gene mutation up to the test concentration since MNPCE frequency in the treatment groups was in the normal range in contrast with that of the control group (21).

3.1.7 Carcinogenicity

There is no information regarding carcinogenicity.

3.1.8 Toxicity for Reproduction

A gavage study was conducted with Sprague-Dawley rats in accordance with OECD TG 422, Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Screening Test. The rats were exposed to 4-methylbenzenesulfonyl chloride at levels of 0, 150, 350 and 750 mg/kg/day for 35 days and 36 - 51 days for male and female animals, respectively.

All pregnant female rats delivered pups not exceeding three days after the expected date and there was no significant difference between the treatment groups and the control group. There was also no significant difference between the treatment groups and the control group in terms of the number of corpus luteum and implantation. In addition, there were no significant differences between the control and treatment group in terms of copulation, fertility and gestation index. For instance, according to the result of copulation index, both 150 mg/kg/day and 350 mg/kg/day treatment groups had 100 %, and 750 mg/kg/day treatment group had 90.9 %. There were no runt and congenital malformation under the influence of the test substance. Therefore, NOAEL for both reproduction and development was determined to be greater than the highest tested dose (750 mg/kg/day)(13).

3.2 Initial Assessment for Human Health

There is no information on toxicokinetics, metabolism and distribution.

The acute oral toxicity study [OECD TG 423] of 4-methylbenzenesulfonyl chloride in rats showed that this chemical did not cause any significant changes in terms of LD_{50} at 2,000 mg/kg b.w for 1st and 2nd steps, and 5,000 mg/kg bw for limit test. Therefore, the oral LD_{50} value in female rats was greater than the highest tested dose (5,000 mg/kg bw). However, in a dose-finding study for an *in vivo* micronucleus test, at 200 mg/kg bw, all three female mice died.

Investigation was performed to observe effects of 4-methylbenzenesulfonyl chloride such as erythema and oedema on the abraded and intact backs of New Zealand White rabbits [OECD TG 404]. According to the results, the test substance induced irritation on the skins of rabbits. Regarding eye irritation, a test was performed according to the FHSA protocol, in which the eyes were exposed for 24 hours then scored at 24, 48 and 72 hours after the exposure. Accordingly, 4-methylbenzenesulfonyl chloride induced corrosion and irritation on the eyes of New Zealand Albino Rabbits.

In the Combined Repeated Dose and Reproduction/Developmental Toxicity Screening Test in rats [OECD TG 422], 4-methylbenzenesulfonyl chloride was administrated by gavage at the dose levels of 0, 150, 350 and 750 mg/kg bw/day for 35 days and 36 ~ 51 days for male and female rats, respectively. Some clinical signs were observed at the dose level of 150 mg/kg bw/day in males such as intermittent (blood-like) salivation and staining around mouth; and in females such as intermittent (blood-like) salivation, staining around mouth, difficult delivery, poor nursing, irregular respiration. Based on these results, the LOAEL and NOAEL were determined to be 150 mg/kg bw/day and below the lowest tested dose (150 mg/kg bw/day) for both sexes, respectively.

In vitro bacterial gene reverse mutation tests [OECD TG 471 and 472] gave negative results in *Salmonella typhimurium* (strains TA98, TA1535 and TA1537) and *Escherichia coli* WP2 *uvr*A with and without metabolic activation. *Salmonella tryphimurium* (TA100 strain) showed positive mutagenic effects at concentrations of 1,250, 2,500 and 5,000 μg/plate without metabolic activation and the same strain (TA100) showed negative results with metabolic activation. Furthermore, an *in vivo* mutagenicity test, mammalian erythrocyte micronucleus assay (OECD TG 474) was negative. No firm conclusion can be reached from the available mutagenicity results.

In a reproduction/developmental toxicity screening test [OECD TG 422] with male and female rats, there were no significant treatment-related changes in terms of pregnancy, fertility, examination of

pups etc. Therefore, LOAEL and NOAEL for reproduction and development are considered to be greater than 750-mg/kg bw/day.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

The results of hydrolysis study showed that the test substance, 4-methylbenzenesulfonyl chloride is hydrolysed rapidly to 4-methylbenzenesulfonic acid which is a strong acid (pKa = -1.34) and is completely dissociated at environmental pH. 4-Methylbenzenesulfonic acid was analyzed in place of 4-methylbenzenesulfonyl chloride in the acute toxicity tests with fish, daphnia and algae using ion pair HPLC. A preliminary screening test was conducted to identify the stability of the hydrolysis product, 4-methylbenzenesulfonic acid, of 4-methylbenzenesulfonyl chloride in the aquatic environment. 100 mg/L of 4-methylbenzenesulfonyl chloride was dissolved in culture media of fish, daphnia and algae under stirring and the concentration of 4-methylbenzenesulfonic acid in the aqueous solution was analysed. The results of the stability test of 4-methylbenzenesulfonic acid are summarised in table 4.1.

Table 4-1 The results of stability test of 4-methylbenznesulfinic acid in aqueous solution which is prepared with 100mg/L concentration of 4-methylbenzenesulfonyl chloride

Time	4 hrs	7 hrs	24 hrs	30 hrs	48 hrs	72 hrs	96 hrs	120 hrs
Measured concentrations of 4-methylbenzene sulfonic acid (mg/L) in water for fish toxicity test	32.0±0.6	40.7±1.9	67.5±1.8	85.6±1.4	86.5±0.6	87.3±0.3	86.3±0.4	87.7±2.0
Measured concentrations of 4-methylbenzene sulfonic acid (mg/L) in culture media for daphnia toxicity test	34.4±0.1	68.9±4.1	82.9±0.4	87.6±3.6	88.6±1.0	87.8±0.6	-	-
Measured concentrations of 4-methylbenzene sulfonic acid (mg/L) in culture media for algae toxicity test	38.0±0.1	57.2±2.7	100.9±0.3	-	103.3±1.4	104.5±0.5	103.4±1.6	-

From the results of the stability test it could be concluded that 4-methylbenzenesulfonyl chloride was hydrolysed to 4-methylbenzenesulfonic acid and that 4-methylbenzenesulfonic acid was stable (> 80 % recovery) in aqueous solution after 24 hours in daphnia and algae medium and after 30 hours in fish medium. So in the aquatic toxicity test, solutions of 4-methylbenzenesulfonyl chloride were stirred during 24 hours for the daphnia and algae test and during 48 hours for the fish test to saturate to 4-methylbenzenesulfonic acid. These stability test results are somewhat different from those in the hydrolysis study of 4-methylbenzenesulfonyl chloride. The concentration of the substance in the stability test was 5 times higher (100 ppm) than in the hydrolysis study. And in the hydrolysis study, 4-methylbenzenesulfonyl chloride was dissolved in distilled water with buffer medium added to it. Test substance was not soluble in water, so less than 1 per cent of acetonitrile was used as a solvent. In the hydrolysis test, the degradation of 4-methylbenzenesulfonyl chloride occurred quickly. On the other hand, in the stability test, 4-methylbenzenesulfonyl chloride was

dissolved in tap water or OECD M4 medium and stirred more than 24 hr to saturate completely. So the hydrolysis rate of the substance in the stability tests was slower than in the hydrolysis study.

The following results of acute toxicity tests with aquatic organisms are available:

Table 4-2 Effect of 4-methylbenzenesulfonyl chloride on aquatic organisms

Organisms	Species	Protocol	Result	Reference
Fish	*Oryzias latipes*	OECD TG 203, Static	LC_{50} (96 hrs) = 55 mg/L	(19)
Invertebrates	*Daphnia magna*	OECD TG 202, Static	EC_{50} (48 hrs) = 70 mg/L	(20)
Algae	*Selenastrum capricornutum*	OECD TG 201	EC_{50} (72 hrs) > 100 mg/L, (growth rate)	(21)

All of the aquatic acute tests were performed in accordance with the principles of GLP. In the acute toxicity tests with fish and daphnia, the test solutions became acidic due to hydrolysis of the parent compound. At the start of the toxicity tests, the pH of the test solution had decreased to 3.33 at 90 mg/L of 4-methylbenzenesulfonyl chloride for fish and 3.27 at 141 mg/L of 4-methylbenzenesulfonyl chloride for daphnia. The preliminary tests of acute toxicity with adjustment of pH were studied for fish and daphnia during 48 hours. At the nominal concentration of 100 mg/L with adjustment of 1 N-NaOH in the fish test, none of tested fish were dead after 48 hours. In the daphnia test nominal concentrations with adjustment of 1/10 N-NaOH at 40, 68, 116, 197 and 334 mg/L were used and no immobilization and mortality were observed during 48 hours in this study. In the growth inhibition test for algae, pH in test solution was adjusted with 1N-NaOH according to the EPA method because in the preliminary test at 100 mg/L of 4-methylbenzenesulfonyl chloride without control of pH, all cells were affected. From the aquatic toxicity tests, 4-methylbenzenesulfonyl chloride has effects to aquatic organisms due to acidity of the hydrolysis product, 4- methylbenzenesulfonic acid. (18), (19), (20).

4-Methylbenzenesulfonyl chloride is hydrolysed rapidly to 4-methylbenzenesulfonic acid.

Results of the aquatic toxicity of 4-methylbenzenesulfonic acid presented below:

Fish : *Leuciscus idus melanotus*, Static, LC_{50} (96 hrs) > 500 mg/L

Invertebrates : *Daphnia magna,* EC_0 (24 hrs) > 2,500 mg/L

Green algae : *Chlorella vulgaris,* EC_{50} (24 hrs) = 245 mg/L (unspecified)

Microorganisms : anaerobic bact. from a domestic water treatment plant,

SG (24 hrs) > 5,000 mg/L (8)

4.2 Terrestrial Effects

No data are available for terrestrial effects.

4.3 Other Environmental Effects

No data are available.

4.4 Initial Assessment for the Environment

4-Methylbenzenesulfonyl chloride is a colorless to light yellow crystalline solid which is hygroscopic and highly reactive. It has a melting point of 71 °C, a boiling point of 145 - 146 °C at 15 mmHg, a density of 1.33 g/cm^3, a vapour pressure of 0.16 Pa at 25 °C and a Henry's law constant of 9.67 x 10^{-6} atm•m^3/mole at 25 °C. Due to the rapid hydrolysis of 4-methylbenzenesulfonyl chloride, water solubility and partition coefficient n-octanol/water cannot be measured. Hence a partition coefficient n-octanol/water (log P_{ow}) of 3.49 at 25 °C and a water solubility of 51.18 mg/L at 25 °C were estimated.

4-Methylbenzenesulfonyl chloride is hydrolysed to 4-methylsulfonic acid and half-lives ($t_{1/2}$) at 25 °C in water are 2.2 min at pH 4, 2.2 min at pH 7 and 2.6 min at pH 9. The substance is not readily biodegradable. The calculated half-life for photochemical-oxidative degradation in the atmosphere by OH radicals is 8.7 days. According to a level III fugacity modeling (EQC model) if 4-methylbenzenesulfonyl chloride is emitted to air, it will mainly partition to soil (97.6 %) and if it is released to water, it will mainly remain in water (79.2 %). If it is released to soil, it will mainly remain in soil (100 %). Based on rapid hydrolysis of the substance, bioconcentration of 4-methylbenzenesulfonyl chloride is not expected. 4-Methylbenzenesulfonic acid is a strong acid (pK = -1.34) and is completely dissociated at the environmental pH. According to a level III fugacity modeling (EQC model) if 4-methylbenzenesulfonic acid is emitted to air, it will mainly partition to soil (78.4 %) and if it is released to water, it will mainly remain in water (99.8 %). If it is released to soil, it will mainly remain in soil (80.6 %). The calculated BCF value of 4-methylbenzenesulfonic acid was 3.16. Both the substance and its hydrolysis product have a low potential for bioaccumulation.

The following toxicity data for aquatic organisms are available for 4-methylbenzenesulfonyl chloride:

Green algae (*Selenastrum capricornutum)*: EC_{g50} (72 h) > 100 mg/L (growth rate)

Invertebrates (*Daphnia magna):* EC_{50} (48 h) = 70 mg/L.

Fish (*Oryzias latipes*): LC_{50} (96 h) = 55 mg/L.

In preliminary tests with adjustment of pH with fish and daphnia, at 100 mg/L of 4-methylbenzenesulfonyl chloride, no effects were seen in fish and daphnia after 48 hours of exposure.

The following toxicity data for aquatic organisms are available for 4-methylbenzenesulfonic acid:

Green algae (*Chlorella vulgaris*): EC_{50}(24h) = 245 mg/L (unspecified)

Invertebrates (*Daphnia magna*) : EC_0(24h) > 2500 mg/L.

Fish (*Leuciscus idus melanotus*): LC_{50} (96h) > 500 mg/L

Microorganisms (anaerobic bact. from a domestic water treatment plant): SG(24h) > 5000 mg/L

No data are available on terrestrial organisms.

5 RECOMMENDATIONS

The chemical possesses properties indicating a hazard for human health (e.g. irritation, uncertainty for genotoxicity). Based on data presented by the Sponsor country, exposure to humans is anticipated to be low, and therefore this chemical is currently low priority for further work.

Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

6 REFERENCES

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SIDS DOSSIER ON THE HPV CHEMICAL

4-Methylbenzenesulfonyl chloride

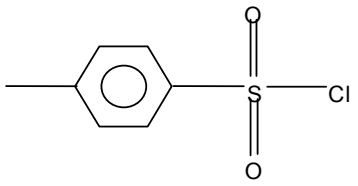
CAS No. : 98-59-9

Sponsor Country: Republic of Korea

Date of submission to OECD: December 2003

1.01 SUBSTANCE INFORMATION

***A. CAS number** : 98-59-9
B. Name (Primary name) : 4-Methylbenzenesulfonyl chloride
***C. Name (OECD name)** : 4-Methylbenzenesulfonyl chloride
†D. CAS Descriptor :
E. EINECS-Number : 202-684-8
F. Molecular Formula : $C_7H_7ClO_2S$
***G. Structural Formula** :



H. Substance Group :

I. Substance Remark (Indicate the substance remark as prescribed in the EINECS Inventory, if possible)

J. Molecular Weight : 190.65

1.02 OECD INFORMATION

A. Sponsor Country : Republic of Korea

B. Lead Organisation : Name of Lead Organisation: National Institute of Environmental Research
Contact person : Hyun-Mi KIM, Ph. D.
Address : Environmental Risk Assessment Division
Street : Environmental Research Complex, Gyeongseo-dong, Seo-gu
Postal code : 404-170
Town : Incheon
Country : Republic of Korea
Tel : +82-(0)32-560-7124
Fax : +82-(0)32-568-2037
E-mail : hmikim@me.go.kr

C. Name of responder (Information on a responder should be provided when companies respond to Lead Organisation or SIDS Contact Points.)
Name : Same as above
Address : Same as above

1.1 GENERAL SUBSTANCE INFORMATION

A. Type of Substance : Organic
B. Physical State (at 20 °C and 1.013 hPa)
: Solid
C. Purity : > 99 %

Source : JMC Corporation, Korea

1.2 SYNONYMS

p-Toluenesulfonyl chloride

p-Toluene sulfonic acid chloride
p-Methylbenzene sulfonyl chloride
Tosyl chloride

1.3 IMPURITIES

CAS No	:	133-59-5
EINECS No	:	
Name	:	*o*-Toluenesulfonyl chloride
Value	:	≤ 0.3 %
Source	:	JMC Corporation, Korea

1.4 ADDITIVES

1.5 QUANTITY

Estimated production	:	4-Methylbenzenesulfonyl chloride of 542.7 tonnes was produced in 2001 in Korea. 689.8 tonnes imported into Korea from China in 2001.
Remarks	:	
Reference	:	(1)

1.6.1 LABELLING

Labelling	:	As in Directive 67/548/EEC
Specific limits	:	
Symbols	:	C
Nota	:	
R-phrases	:	R 42 Causes burns
		R 20 Harmful by inhalation
S-phrases	:	S 7/8 Keep container tightly closed and dry
		S 26 In case of contact with eyes, rinse immediately with plenty of water and seek medical advice
Remarks	:	

1.6.2 CLASSIFICATION

Classified	:	Listed on the TSCA Inventory
Reason for regulation	:	Chemical in commerce
Remarks	:	
Classified	:	Listed on the CAA 111
Reason for regulation	:	Volatility
Remarks	:	

1.7 USE PATTERN

Type	:	Type
Category	:	Non dispersive use
Type	:	Type
Category	:	Used in closed system
Type	:	Industrial
Category	:	Plastic and rubber industry; Source of foarming agent
Type	:	Industrial
Category	:	Parmaceutical industry; source of riboflavin tetrabutyrate
Type	:	Industrial
Category	:	Parmaceutical industry; source of antithrombotic drug
Type	:	Industrial
Category	:	Dye industry; Source of condensing agent
Type	:	Industrial
Category	:	Organic synthesis

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUE

Exposure limit value

Type	:	TLV - 15 minute TWA
Value	:	5 mg/m^3 (AIHA-WEEL)
Reference	:	(2)

1.9 SOURCES OF EXPOSURE

Source	:	Production and processing
Remarks	:	Environmental releases are unlikely to occur during industrial production and processing of 4-methylbenzenesulfonyl chloride as these processes take place in closed systems. If environmental releases occur during these operations, they will be in the form of the hydrolysis product 4-methylbenzenesulfonic acid due to the short half-life of the parent substance. Wastewater of 4-methylbenzenesulfonyl chloride is discharged to wastewater treatment plant so significant releases are not expected.
Reference	:	(1)

1.10 ADDITIONAL REMARKS

2.1 MELTING POINT

Value	:	71 °C	
Remarks	:		
Reliability	:	(2) Reliable with restrictions	
Flag	:	Critical study for SIDS endpoint	
Reference	:		(3), (4)
Value	:	69 °C	
Reliability	:	(2) Reliable with restrictions	
Reference	:		(2)
Value	:	69 - 71 °C	
Reliability	:	(2) Reliable with restrictions	
Reference	:		(5)
Value	:	104 - 105 °C	
Decomposition	:	No	
Sublimation	:	No	
Method	:	Directive 84/449/EEC, A.1 “Melting point /melting range”	
GLP	:	No data	
Source	:	Hickson-Manro Ltd Stalybridge	
Test substance	:	4-methylbenzenesulfonic acid (CAS No. 104-15-4)	
Reliability	:	(2) Reliable with restrictions	
Reference	:		(6)

2.2 BOILING POINT

Value	:	145 - 146 °C at 15 mmHg	
Decomposition	:		
Reliability	:	(2) Reliable with restrictions	
Flag	:	Critical study for SIDS endpoint	
Reference	:		(3), (4)
Value	:	152 °C at 20 mmHg	
Decomposition	:		
Reliability	:	(2) Reliable with restrictions	
Reference	:		(2)
Value	:	146 °C at 15 mmHg	
Decomposition	:		
Reliability	:	(2) Reliable with restrictions	
Reference	:		(5)
Value	:	290.16 °C	
Decomposition	:		
Method	:	Estimated by MPVPWIN v.1.40	
Remarks	:	Input parameter O=S(=O)(c(ccc(c1)C)c1)Cl	
Reliability	:	(2) Reliable with restrictions	
Reference	:		(8)
Value	:	> 400 °C at 1013 hPa	
Decomposition	:	No	
Method	:	Other: Reagenzglastest	
Remark	:	Gefaehrliche Zersetaungsprodukte: Schwefeldioxid	
Source	:	Hoechst AG Frankurt 80 Hoechst AG Frankurt/Main	

Test substance	:	4-methylbenzenesulfonic acid (CAS No. 104-15-4)	
Reliability	:	(2) Reliable with restrictions	
Reference	:		(6)

2.3 DENSITY (RELATIVE DENSITY)

Type	:	Density	
Value	:	1.33 g/cm^3	
Temperature	:		
Reliability	:	(2) Reliable with restrictions	
Flag	:	Critical study for SIDS endpoint	
Reference	:		(2)

2.4 VAPOUR PRESSURE

Value	:	0.16 Pa	
Temperature	:	25 °C	
Method	:	Estimated by MPVPWIN v.1.40	
Remarks	:	Input parameter O=S(=O)(c(ccc(c1)C)c1)Cl	
Reliability	:	(2) Reliable with restrictions	
Flag	:	Critical study for SIDS endpoint	
Reference	:		(8)
Value	:	1 mmHg	
Temperature	:	88 °C	
Method	:		
Remarks	:		
Reliability	:	(2) Reliable with restrictions	
Flag	:		
Reference	:		(2)
Value	:	0.1 hPa	
Temperature	:	20 °C	
Method	:		
Source	:	Hoechst AG Frankurt 80 Hoechst AG Frankurt/Main	
Test substance	:	4-methylbenzenesulfonic acid (CAS No. 104-15-4)	
Reliability	:	(2) Reliable with restrictions	
Reference	:		(6)

2.5 PARTITION COEFFICIENT $LOG_{10}\ P_{OW}$

Log P_{OW}	:	3.49	
Method	:	Estimated by KOWWIN v.1.66	
Remarks	:	Input parameter O=S(=O)(c(ccc(c1)C)c1)Cl	
Reliability	:	(2) Reliable with restrictions	
Reference	:		(7)
Log P_{OW}	:	0.784 at 20 °C	
Source	:	Hoechst AG Frankurt 80 Hoechst AG Frankurt/Main	
Test substance	:	4-methylbenzenesulfonic acid (CAS No. 104-15-4)	

Reliability : (2) Reliable with restrictions
Reference : (6)

2.6 WATER SOLUBILITY

Value : 51.18 mg/L
Temperature : 25 °C
Remark : Estimated by WSKOWWIN v.1.40 from estimated log Kow value of 3.49
Reliability : (2) Reliable with restrictions
Reference : (7)

Value : 700 g/L at 20 °C
pH : < 1 at 650 g/L and 20 °C
Source : Hoechst AG Frankurt 80
Hoechst AG Frankurt/Main
Test substance : 4-methylbenzenesulfonic acid (CAS No. 104-15-4)
Reliability : (2) Reliable with restrictions
Reference : (6)

2.7 FLASH POINT

Value : 110 °C
Method : Cleveland open cup
Reliability : (2) Reliable with restrictions
Reference : (2)

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

Results : Combustible
Reliability : (2) Reliable with restrictions
Reference : (4)

Results : Combustible when exposed to heat or flame. When heated to decompose, it emits very toxic fumes of SO_x and Cl^-.
Reliability : (2) Reliable with restrictions
Reference : (2)

2.11 OXIDIZING PROPERTIES

2.12 OXIDATION: REDUCTION POTENTIAL

2.13 ADDITIONAL DATA

Value : Decomposition
Result : 220 °C
Remarks :
Reliability : (2) Reliable with restrictions

Reference	:		(2)
Value	:	Henry's law constant	
Result	:	9.67 x 10^{-6} atm•m^3/mole	
Temperature	:	25 °C	
Method	:	Estimated by HENRYWIN v.3.10	
Remarks	:	Input parameter O=S(=O)(c(ccc(c1)C)c1)Cl	
Reliability	:	(2) Reliable with restrictions	
Flag	:	Critical study for SIDS endpoint	
Reference	:		(8)

3.1 STABILITY

3.1.1 PHOTODEGRADATION

Type	:	Air	
Indirect Photolysis	:		
Type of sensitizer	:	OH radical	
Concentration of sensitizer	:	1500000 molecule/cm^3	
Rate constant (radical)	:	0.0000000000012 cm^3/molecule*sec	
Degradation	:	50 % after 8.7 days at 12 hour exposure	
Method	:	Estimated by AOPWIN v.1.90	
Reliability	:	(2) Reliable with restrictions	
Flag	:	Critical study for SIDS endpoint	
Reference	:		(8)

Type	:	Air	
Indirect Photolysis	:		
Type of sensitizer	:	OH radical	
Concentration of sensitizer	:	1500000 molecule/cm^3	
Rate constant (radical)	:	0.00000000000136 cm^3/molecule*sec	
Degradation	:	50 % after 7.8 days at 12 hour exposure	
Method	:	Estimated by AOPWIN v.1.90	
Test substance	:	4-methylbenzenesulfonic acid (CAS No. 104-15-4)	
Reliability	:	(2) Reliable with restrictions	
Flag	:	Critical study for SIDS endpoint	
Reference	:		(8)

3.1.2 STABILITY IN WATER

Type	:	Abiotic (hydrolysis)
Half-life at 25 °C	:	$t_{1/2}$ at pH 4 = 2.2 minutes (Rate Constant, k_{obs} = 0.30 1/s x 10^5) $t_{1/2}$ at pH 7 = 2.2 minutes (Rate Constant, k_{obs} = 0.32 1/s x 10^5) $t_{1/2}$ at pH 9 = 2.6 minutes (Rate Constant, k_{obs} = 0.27 1/s x 10^5)
Degradation %	:	57 % at pH 4.0 at 25 ºC after 3 min 82 % at pH 4.0 at 25 ºC after 6 min 92 % at pH 4.0 at 25 ºC after 8 min 63 % at pH 7.0 at 25 ºC after 3 min 87 % at pH 7.0 at 25 ºC after 6 min 93 % at pH 7.0 at 25 ºC after 8 min 61 % at pH 9.0 at 25 ºC after 3 min 85 % at pH 9.0 at 25 ºC after 6 min 91 % at pH 9.0 at 25 ºC after 8 min The hydrolysis rates of the substrate were very similar among three pH conditions. However, the hydrolysis pattern at pH 7.0 was somewhat different to those at the other pHs (pH 4.0 and pH 9.0). The hydrolysed product from HPLC chromatography showed single peak, which was identified as 4-methylbenzenesulfonic acid at pH 4.0 and pH 9.0. But a couple of the hydrolysed products could be seen from HPLC chromatography at pH 7.0. Major product was determined to be 4-methylbenzene-sulfonic acid and the minor peak could not be determined. The undetermined one has turned into 4-methylbenzene-sulfonic acid eight days after hydrolysis.
Method	:	OECD TG111, “Hydrolysis as a Function of pH”
Year	:	2003
GLP	:	Yes

Test substance : 4-Methylbenzenesulfonylchloride, source – Fluka Co.(Lot no. 426207/1), purity = 100.1 %
Remarks: Concentration of test substance was 20 mg/L. The test substance, 4-methylbenzenesulfonyl-chloride, was analyzed by using HPLC column, Phenomenex, Luna 5 µ C-18(2), 250 x 4.6 mm. The mobile phase was acetonitrile/water (80/20, v/v) and the wavelength for detection was 246 nm. The hydrolysed product, 4-methylbenzenesulfonic acid, was analysed by HPLC column. (Waters, µ-Bondapak C-18, 300 x 3.9 mm) and the detection wavelength was 220 nm. The hydrolysis rate of the test substance and the formation rate of the hydrolysis product were coincident at pH 4.0 and pH 9.0, respectively. At pH 4.0 and pH 9.0, around 70 percent of the substrates (4-methylbenzenesulfonyl chloride) were hydrolyzed and the same amounts of the hydrolysed products (4-methylbenzene-sulfonic acid) were produced after 4 min of hydrolysis. At the same pH (pH 4.0 and pH 9.0), 90 percent of the substrates (4-methylbenzene-ulfonyl chloride) was hydrolyzed and the same amounts of the hydrolysed products (4-methylbenzene-sulfonic acid) were produced after 8 minutes of hydrolysis.
Reliabilities : (1) Reliable without restrictions
Flag : Critical study for SIDS endpoint
References : (7)

Type : Abiotic (hydrolysis)
Rate constant :

Table. Measured rate constant for the hydrolysis of the 4-methylbenzene sulfonyl chloride in 1 % dioxan

T/K (ºC)	278.96 (5.81)	282.96 (9.81)	289.16 (16.01)	293.48 (20.33)	296.46 (23.31)
10^3 κ/s^{--1}	0.484	0.680	1.39	2.10	2.82
T/K (ºC)	297.96 (24.81)	302.36 (29.21)	304.15 (31)	308.96 (35.81)	
10^3 κ/s^{--1}	3.42	4.28	5.28	9.34	

Degradation % : No data are available
Half-life at 25 °C : No data are available
Method : 4-Methylbenzenesulfonyl chloride in 1 % dioxan was followed spectrophotometrically by the change in absorbance at 245 nm as before on a Perkin-Elmer 139 spectrohpotometer with a Honeywell VT 100 digital reactant. For this compound which gave no change in absorbance in the reation (and also little-change on ionization of the sulphonic acid), conductance measurements were done as before using a Wayne-Kerr B641 autobalance univerdal bridge.
Year : 1975
GLP : No data are available
Test substance : Other TS: 4-methylbenzenesulfonyl chloride
Reliabilities : (2) Reliable with restrictions
References : (9)

3.1.3 STABILITY IN SOIL

3.2 MONITORING DATA (ENVIRONMENT)

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

3.3.1 TRANSPORT

3.3.2 THEORETICAL DISTRIBUTION (FUGACITY CALCULATION)

Type : Fugacity level III
Media : Calculation
Method : Estimated by EQC model (Mackay, D.)
Results :

Table. Environmental Distribution of 4-methylbenzenesulfonyl chloride Using EQC model (Mackay, D.), Fugacity model level III

Compartment	Release 100% to air (%)	Release 100% to water (%)	Release 100% to soil (%)	All three (%)
Air	2.4	0.3	0.01	0.7
Water	0.0001	79.2	0.00004	0.0001
Soil	97.6	10.9	100	99.9
Sediment	0.00001	9.6	0.000005	0.00001

Remarks : Input parameter:
Molecular weight: 190.65
Temperature: 25 ℃
Melting point: 71 ℃
Water solubility: 51.18 g/m^3
Vapor pressure: 0.16 Pa
Log Kow: 3.49
Half life in air: 104.8 hr (estimated by AOPWIN)
Half life in water: 0.04 hr (measured data)
Half life in soil: default value (10^{11})
Half life in sediment: default value (10^{11})
Reliabilities : (2) Reliable with restrictions
References : (8)

Type : Fugacity level III
Media : Calculation
Method : Estimated by EQC model (Mackay, D.)
Test substance : 4-methylbenzenesulfonic acid (CAS No. 104-15-4)
Results :

Table. Environmental Distribution of 4-methylbenzenesulfonic acid Using EQC model (Mackay, D.), Fugacity model level III

Compartment	Release 100% to air (%)	Release 100% to water (%)	Release 100% to soil (%)	All three (%)
Air	0.6	0.0002	0.03	0.3
Water	20.9	99.8	19.3	27.8
Soil	78.4	0.03	80.6	71.8
Sediment	0.044	0.2	0.41	0.06

Remarks : Input parameter:
Molecular weight: 172.2
Temperature: 20 ° C
Melting point: 104.5 ° C
Water solubility: 700000 g/m^3
Vapor pressure: 10 Pa
Log Kow: 0.78
Half life in air: 94 hr (estimated by AOPWIN)
Half life in water: 360 hr (estimated by EPIWIN)
Half life in soil: default value (10^{11})
Half life in sediment: default value (10^{11})

Reliabilities : (2) Reliable with restrictions

References : (8)

3.4 IDENTIFICATION OF MAIN MODE OF DEGRADABILITY IN ACTUAL USE

3.5 BIODEGRADATION

Type : Aerobic
Inoculum : Activated sludge, 30 mg/L as suspended solid
Concentration : 100 mg/L related to test substance without pre-acclimation
Contact time : 28 days
Medium : Water/activated sludge
Degradation : 17.7 % after 28 days (based on BOD)
Results : Not readily biodegradable

Kinetic : 15.4 % after 7 days (based on BOD)
17.7 % after 14 days (based on BOD)
17.7 % after 28 days (based on BOD)

Method : OECD TG 301C, “Ready Biodegradability; Modified MITI Test (I)”
Year : 2003

GLP : Yes
Test substance : 4-Methylbenzenesulfonylchloride, source – Fluka Co.(Lot no. 426207/1), purity = 100.1 %
Remarks : Temperature of incubation: 25 ± 1 ºC
500 mL of test solution was made up of 15 mg/L test substance in mineral medium with 30 mg/L activated sludge. Activity control (aniline in mineral medium at 100 mg/L with 30 mg/L activated sludge) and inoculum blank (mineral medium with 30 mg/L activated sludge) were used. BOD was analyzed continuously using automatic electrolytic biochemical oxygen demand meter.
Reliabilities : (1) Reliable without restrictions

Flag : Critical study for SIDS endpoint
References : (10)

Type	:	Aerobic
Inoculum	:	Activated sludge, industrial, adapted
Degradation	:	> 90 % after 10 day
Kinetic	:	5 day = 51 %
Method	:	OECD TG 302 B, "Inherent biodegradability: Modified Zahn-Wellens Test"
Year	:	1981
GLP	:	No
Test substance	:	4-methylbenzenesulfonic acid (CAS No. 104-15-4), 65% solution
Source	:	Hoechst AG Frankurt 80 Hoechst AG Frankurt/Main
Reliabilities	:	(2) Reliable with restrictions
Flag	:	Critical study for SIDS endpoint
References	:	(6)

3.6 BOD5, COD OR RATIO BOD5/COD

3.7 BIOACCUMULATION

BCF	:	Based on rapid hydrolysis of the substance, bioconcentration of 4-methylbenzenesulfonyl chloride is not expected.
Method	:	
Reliabilities	:	(2) Reliable with restrictions
Flag	:	Critical study for SIDS endpoint
Reference	:	

BCF	:	3.16
Method	:	Estimated by BCFWIN v.2.14 from estimated logK_{ow} value of 3.49
Test substance	:	4-methylbenzenesulfonic acid (CAS No. 104-15-4)
Reliabilities	:	(2) Reliable with restrictions
Flag	:	Critical study for SIDS endpoint
Reference	:	(8)

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	Static
Species	:	*Oryzias latipes*
Exposure period	:	96 hours
Unit	:	mg/L
Analytical monitoring	:	Yes
LC_{50}	:	55
NOEC	:	35
Method	:	OECD TG 203, “Fish, Acute Toxicity Test”
Year	:	2003
GLP	:	Yes
Test substance	:	Other TS; 4-Methylbenzenesulfonyl chloride, purity = 100.1 % Fluka (Sigma –Aldrich Corporation), Lot.No.-426707/1
Test Conditions	:	- Test Organisms Age: 4 months Length: 2.7 ± 0.1 cm Weight: 0.15 ± 0.02 g Loading: 8.7 L aquarium per 7 fish Pretreatment: 55 fish were acclimated for 7 days before test. No food was fed before 1 day and during test. - Test Conditions Dilution water source: Tap water passed through activated carbon and membrane filter (1 μm), hardness: 47 mg/L as $CaCO_3$, alkalinity: 27 mg/L as $CaCO_3$, Water chemistry: DO: 69 - 100 %, pH: 3.33 - 7.68 Temperature: 24.4 ± 0.4 °C Light: 1,160 - 1,200 Lux, Light periocity: 16/8 (light/dark) A group of 7 fish was used and no replicate.
Remark	:	The results of hydrolysis study (see chapter 3.1.2) showed that the test substance, 4-methylbenzenesulfonyl chloride is hydrolyzed rapidly to 4-methylbenzene sulfonic acid. 4-Methylbenzenesulfonic acid was analyzed in place of 4-methylbenzenesulfonyl chloride in this study using ion pair HPLC. In a preliminary screening test on stability of the hydrolysis product in water without control of pH, 4-methylbenzene-sulfonic acid remained stable in water over a 120 hours periods (87.7 % recovery after 120 hours, Table). From the results of stability test, the measured concentration of the hydrolysis product, 4-methylbenzene sulfonic acid was remained constantly after 30 hours. So test solutions of each concentration were stirred for 48 hours because the substance would have fully hydrolysed to form the degradation products prior to initiating the tests.
Result	:	Nominal concentrations at 9, 14, 22, 35, 56 and 90 mg/L (measured concentrations = 8, 12, 20, 31, 49 and 84 mg/L) were studied. Due to hydrolysis of 4-methylbenzenesulfonyl chloride to 4-methylbenzenesulfonic acid, test condition was changed to acid. Nominal concentration was used to determine toxicity end point for 4-methylbenzenesulfonyl chloride. LC_{50}, and NOECs were calculated by Moving-Average Angle program(EPA/600/4-85/013,1985). 95 % confidence limit of LC_{50} (96 hr) was 45 - 65 mg/L.

Table. The results of stability test of 4-methylbenznesulfinic acid in aqueous solution which is prepared with 100 mg/L concentration of 4-methylbenzenesulfonyl chloride.

Time	4 hr	7 hr	24 hr	30 hr	48 hr	72 hr	96 hr	120 hr
Measured concentrations of 4-methylbenzene sulfonic acid (mg/L)	320±06	407±19	675±18	856±14	865±06	873±03	863±04	877±20

Table. Cumulative mortality of *Oryzias latipes*

Nominal concentrations (mg/L)	Number of organisms tested	Cumulative number of dead fish			
		24 hr	48 hr	72 hr	96 hr
Control	7	0	0	0	0
9	7	0	0	0	0
14	7	0	0	0	0
22	7	0	0	0	0
35	7	0	0	0	0
56	7	0	0	4	4
90	7	7	0	7	7
			2		
			7		

Table. pH of test condition.

Nominal concentrations (mg/L)	0 hr	24 hr	48 hr	72 hr	96 hr
Control	7.59	7.43	7.16	7.64	7.68
9	7.62	7.27	7.09	7.61	7.63
14	7.57	7.16	7.05	7.57	7.58
22	7.47	7.06	6.95	7.43	7.44
35	7.12	6.69	6.60	7.19	7.20
59	4.01	4.04	4.23	4.19	4.21
90	3.33	-	-	-	-

Table. The results of acute toxicity test with adjustment of pH

Nominal concentration (mg/L)	Number of organisms tested	0 hr			24 hr			48 hr		
		No. of dead fish	pH	DO (mg/L)	No. of dead fish	pH	DO (mg/L)	No. of dead fish	pH	DO (mg/L)
100	5	0	7.8	8.5	0	7.1	7.3	0	7.0	7.1

A preliminary test was conducted to see the effect of pH in fish, acute toxicity test of 4-methylbenzenesulfonyl chloride. 100 mg/L of 4-methylbenzenesulfonyl chloride was dissolved completely with stirring for 24 hours. pH in test solution was adjusted with 1N-NaOH. 5 fish were used and no replicate. None of tested fish were dead.

Reliabilities : (1) Reliable without restrictions
Flag : Critical study for SIDS endpoint
References : (13)

Type : Static
Species : *Leuciscus idus melanotus* (Fish, fresh water)
Exposure period : 96 hours

Unit	:	mg/L
Analytical monitoring	:	No data
LC_{50}	:	> 500
Method	:	Other : DIN 38412, Teil 15
Year	:	1981
GLP	:	No data
Source	:	Hoechst AG Frankurt 80 Hoechst AG Frankurt/Main
Test substance	:	4-methylbenzenesulfonic acid (CAS No. 104-15-4), 65 % solution
Reliabilities	:	(2) Reliable with restrictions
Flag	:	Critical study for SIDS endpoint
References	:	(6)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

A. Daphnia

Type	:	Static
Species	:	*Daphnia magna*
Exposure period	:	48 hours
Unit	:	mg/L
EC_{50}	:	70
Analytical monitoring	:	Yes
Method	:	OECD TG 202, "*Daphnia sp.*, Acute Immobilisation Test and Reproduction Test"
Year	:	2003
GLP	:	Yes
Test substance	:	Other TS; 4-Methylbenzenesulfonyl chloride, purity = 100.1 % Fluka (Sigma –Aldrich Corporation), Lot.No.-426707/1
Test condition	:	- Test Organisms Age: juveniles within 24 hrs old. Supplier: GSF Institute of Ecological Chemistry, Germany - Test Conditions Dilution water source: OECD M4 medium, hardness: 249 mg/L as $CaCO_3$, alkalinity: 42 mg/L as $CaCO_3$ Water chemistry: DO 88 - 91 %, pH 3.21 - 7.82 Temperature: 20 $\pm$ 0.2 °C Light: 998 - 1,177 Lux, Light periodity: 16/8 (light/dark) 3 replicates per 10 organisms were used.
Remark	:	4-Methylbenzenesulfonyl chloride is hydrolyzed rapidly to 4-methylbenzene sulfonic acid. 4-Methylbenzenesulfonic acid was analyzed in place of 4-methylbenzenesulfonyl chloride in this study using ion pair HPLC. In a preliminary screening test on stability of the hydrolysis product in OECD M4 medium without control of pH, 4-methylbenzenesulfonic acid remained stable over a 72 hours periods (87.8 % recovery after 72 hours, Table). From the results of stability test, the measured concentration of the hydrolysis product, 4-methylbenzene sulfonic acid was remained constantly after 30 hours. So test solutions of each concentration were stirred for 24 hours because the substance would have fully hydrolysed to form the degradation products prior to initiating the tests.
Result	:	Nominal concentration at 68, 82, 98, 118 and 141 mg/L (measured concentrations = 64, 78, 92, 113 and 135 mg/L) were used. Nominal concentration was used to determine toxicity end point for 4-methylbenzenesulfonyl chloride. EC_{50}, and NOECs were calculated by Moving-Average Angle program(EPA/600/4-85/013,1985). 95 % confidence limit of EC_{50} (48 hr) was 68 - 71 mg/L.

Table. The results of stability test of 4-methylbenznesulfinic acid in aqueous solution which is prepared with 100 mg/L concentration of 4-methylbenzenesulfonyl chloride.

Time	4 hr	7 hr	24 hr	30 hr	48 hr	72 hr
Measured concentrations of 4-methyl benzene sulfonic acid (mg/L)	34.4 ±0.1	68.9 ±4.1	82.9 ±0.4	87.6 ±3.6	88.6 ±1.0	87.8 ±0.6

Table. The results of cumulative immobilization data for *Daphnia magna*

Nominal concentrations (mg/L)	Number of organisms tested	Cumulative number of organisms immobilized	
		24 hr	48 hr
Control	30	0	0
68	30	0	0
82	30	26	30
98	30	30	30
118	30	30	30
141	30	30	30

Table. pH of test condition

Nominal concentrations (mg/L)	0 hr	48 hr
Control	7.82	7.77
68	6.60	7.11
82	4.69	-
98	3.88	-
118	3.49	-
141	3.21	-

Table. The results of cumulative immobilization data for *Daphnia magna* with adjustment of pH

Nominal concentrations (mg/L)	Number of organisms tested	Cumulative number of organisms immobilized	pH			DO (mg/L)	
			0 hr		48 hr	0 hr	48 hr
			Before	After			
Control	30	0	8.7	-	7.8	8.3	8.8
40	30	0	7.1	8.6	7.5	8.3	8.6
68	30	0	6.4	8.6	7.4	8.0	8.8
116	30	0	3.4	8.7	7.3	8.2	8.7
197	30	0	2.9	8.6	7.3	8.0	8.8
334	30	0	2.6	8.6	7.5	8.2	8.8

A preliminary test was conducted to see the effect of pH in *Daphnia magna*, acute immobilisation test of 4-methylbenzenesulfonyl chloride. The condition of test solution was changed to acid because 4-methylbenzenesulfonyl chloride was hydrolyzed rapidly to 4-methylbenzene sulfonic acid. So toxicity test with adjustment of pH was studied. Each concentrations of 4-methylbenzenesulfonyl chloride were dissolved completely with stirring for 24 hours. pH in test solution was adjusted with 1/10N-NaOH. No immobilization and mortality were observed in this study of condition with control of pH.

Reliabilities : (1) Reliable without restrictions
Flag : Critical study for SIDS endpoint
Reference : (14)

Species : *Daphnia magna*
Exposure period : 24 hours
Unit : mg/L
EC_0 : > 2500
Analytical monitoring : No data

Method	:	Other: DIN 38412, Teil 11
Year	:	1983
GLP	:	No data
Source	:	Hoechst AG Frankurt 80 Hoechst AG Frankurt/Main
Test substance	:	4-methylbenzenesulfonic acid (CAS No. 104-15-4), 65 % solution
Reliabilities	:	(2) Reliable with restrictions
Flag	:	Critical study for SIDS endpoint
References	:	(6)

4.3 TOXICITY TO AQUATIC PLANTS

ALGAE

Species	:	*Selenastrum capricornutum*
Endpoint	:	Growth rate
Exposure period	:	72 hours
Unit	:	mg/L
EC_{50}	:	> 100
NOEC	:	2.6
LOEC	:	6.4
Analytical monitoring	:	Yes
Method	:	OECD TG 201, “Alga, Growth Inhibition Test”, US EPA Ecological Effects Test Guidelines, OPPTS 850, 5400 “Algal toxicity Tiers I and II”
Year	:	2003
GLP	:	Yes
Test substance	:	Other TS; 4-Methylbenzenesulfonyl chloride, purity = 100.1 % Fluka (Sigma –Aldrich Corporation), Lot.No.-426707/1
Test condition	:	- Test organisms Laboratory culture: ATCC culture medium 625 Gorham’s medium Strain No.: ATCC 22662 Method of cultivation: sterilization - Test conditions Temperature: 22 - 23 °C Dilution water source: OECD medium Water chemistry: pH 7.8 - 8.1 at start and pH 7.3 - 7.9 at end with adjustment of 1N NaOH. Light level: 8,148 - 8,232 Lux Initial cell density: 1 x 10^4 cells/mL Test design: 3 replicates
Remark	:	4-Methylbenzenesulfonyl chloride is hydrolyzed rapidly to 4-methyl-benzene sulfonic acid. The acid condition of test solution was able to effect in growth of algae. 4-Methylbenzenesulfonic acid was analyzed in place of 4-methylbenzenesulfonyl chloride in this study using ion pair HPLC. In a preliminary screening test on stability of the hydrolysis product in OECD medium with control of pH, 4-methylbenzenesulfonic acid remained stable over a 96 hours periods (100% recovery after 24 hours, Table). From the results of stability test, the measured concentration of the hydrolysis product, 4-methylbenzene sulfonic acid was remained constantly after 24 hours. So test solutions of each concentration were stirred for 24 hours because the substance would have fully hydrolysed to form the degradation products prior to initiating the tests.
Result	:	Nominal concentrations at 2.6, 6.4, 16, 40 and 100 mg/L L (measured concentrations = 2.5, 6.0, 15, 36 and 90 mg/L) were used. Nominal concentration was used to determine toxicity end point for 4-methylbenzene-sulfonyl chloride. EC_{50}, and NOECs were calculated by Program TOXCALC Version 5.0.12(Tidepool scientific Software, USA).

In the following experiment the pH of the test solutions was adjusted.

Table. The results of stability test of 4-methylbenznesulfinic acid in aqueous solution which is prepared with 100 mg/L concentration of 4-methylbenzenesulfonyl chloride.

Time	4hr	7hr	24hr	48hr	72hr	96hr
Measured concentrations of 4-methyl benzene sulfonic acid (mg/L)	38.0 ± 0.1	57.2 ± 2.7	100.9 ± 0.3	103.3 ± 1.4	104.5 ± 0.5	103.4 ± 1.6

Table. Cell density of *Selenastrum capricornutum* (ATCC 22662) during the test

Nominal Concentrations (mg/L)	Cell density (x104 cell/mL)			
	0 hr	24 hr	48 hr	72 hr
Control	0.79	6.6	16	73
2.6	0.84	5.0	14	68
6.4	0.88	4.0	7.3	33
16	0.9	3.7	6.5	36
40	0.83	3.8	7	41
100	0.83	1.6	5.2	34

Table. Percent growth inhibition rates per concentration.

Nominal Concentrations (mg/L)	Growth rates		
	Growth rate	Relative growth rates (%)	Relative inhibition (%)
Control	0.063	-	-
2.6	0.061	96.6	3.4
6.4	0.050	80.2	19.8
16	0.052	82.3	17.7
40	0.053	84.4	15.6
100	0.052	82.6	17.4

Nominal Concentrations (mg/L)	Areas under the curve		
	Areas under the curve	Relative growth rates (%)	Relative inhibition (%)
Control	13,836,000	-	-
2.6	12,206,000	88.2	11.8
6.4	6,150,000	44.5	55.5
16	6,212,000	44.9	55.1
40	7,052,000	51.0	49.0
100	5,244,000	37.9	62.1

Table. pH of test condition

Nominal Concentrations (mg/L)	0 hr	72 hr
Control	8.00	7.93
2.6	7.55	7.88
6.4	7.69	7.79
16	8.12	7.89
40	7.82	7.66
100	7.69	7.26

Table. Percent growth inhibition rates per concentration without adjustment of pH (0 hr)

Nominal concentrations (mg/L)	pH	Growth rate (%) with adjustment of 1N NaOH	pH	Growth rate (%)
Control	7.51	0.052	8.0	0.055
0.1	7.96	0.056	7.6	0.060
1	7.86	0.047	7.6	0.055
10	7.76	0.048	7.4	0.054
100	7.64	0.040	3.5	No cell was existed

A preliminary test was conducted to see the effect of pH in algae, growth inhibition test of 4-methylbenzenesulfonyl chloride. The condition of test solution of 100 mg/L concentration of 4-methylbenzenesulfonyl chloride was changed to acid. In the 100 mg/L concentration of 4-methylbenzenesulfonyl chloride without control of pH, no cell was existed. The acid condition of test solution was affected to growth of algae seriously.

Reliabilities : (1) Reliable without restrictions
Flag : Critical study for SIDS endpoint
Reference : (15)

Species : *Chlorella vulgaris* (Algae)
Endpoint : Other : unspecified
Exposure period : 24 hours
Unit : mg/L
EC_{50} : 245000
Analytical monitoring : No data
Method : Other : keine Daten
Year : No data
GLP : No data
Source : Hoechst AG Frankurt 80
Hoechst AG Frankurt/Main
Test substance : 4-methylbenzenesulfonic acid (CAS No. 104-15-4)
Reliabilities : (2) Reliable with restrictions
Flag : Critical study for SIDS endpoint
References : (6)

4.4 TOXICITY TO MICROORGANISMS

Type : Aquatic
Species : Anaerobic bacteria. From a domestic water treatment plant
Exposure period : 24 hours
Unit : mg/L
SG : > 5000
Analytical monitoring : No data
Method : ETAD Fermentation tube method “Determination of damage to effluent bacteria by the Fermentation Tube Method”
Year : 1972
GLP : No data
Source : Hoechst AG Frankurt 80
Hoechst AG Frankurt/Main
Test substance : 4-methylbenzenesulfonic acid (CAS No. 104-15-4)
Remark : SG = Schaedlichkeitsgrenze
Reliabilities : (2) Reliable with restrictions
Flag : Critical study for SIDS endpoint
References : (6)

4.5 CHRONIC TOXICITY TO AQUATIC ORGANISMS

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6 TERRESTRIAL ORGANISMS

4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

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

4.7 BIOLOGICAL EFFECTS MONITORING (INCLUDING BIOMAGNIFICATION)

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.1 ACUTE TOXICITY

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD_{50}
Species/strain	:	Rat (Sprague-Dawley)
Sex	:	Female
Number of animals	:	9 animals
Vehicle	:	Not used
Value	:	2,000 mg/kg for 1st and 2nd steps, and 5,000 mg/kg for limit test
Route of administration	:	Oral (gavage)
Method	:	OECD Test Guideline 423 annex 2d (Acute Oral Toxicity – acute toxic class method)
Method remarks		- *Preparation of test substance* The test substance was warming up in a double boiler and using a sonicator to dissolve them in solvent (corn oil: Lot No.-70K0127) as much as possible - *1st step* 2000 mg/kg of test substance were administered to three rats - *2nd step* 2000 mg/kg of test substance were administered to three rats - *limit test* 5000 mg/kg of test substance were administered to three rats - *Observation* *General symptoms*: These were observed 0.5 and every hour till 8 hours after the treatment on the day of administration, after that were observed once a day till 14 days. *Mortality*: It was observed once a day for dead and dying animals. *Body weight*: It was weighed just before the treatment; after the treatment on the day 1, 3, 7 and the day of necropsy. *Necropsy*: This was observed on the day of death for dead animals and after the observation period for survived animals with unaided eyes. *Histopathological test*: According to the scheduled necropsy for all survived animals, some abnormal organs and tissues were extracted to fix with 10 % neutral formalin. Then they were trimmed in 3 mm thickness and mounted to make 4 ㎛ section. After that they were stained using Hematotoxylin & Erosin stain method to carry out histopathological test with a microscope (Olympus B X 50).
Year	:	2003
GLP	:	Yes
Test substance	:	Other TS: 4-Methylbenzenesulfonyl chloride, purity = 99.7 %, Fluka, Lot No. - 422308/1
Test condition	:	Age: 9 ~ 10 weeks old Body weight at study acute oral toxicity: 188.8 ~ 199.4 g Doses per time period: single treatment Volume administered: 10 mL/kg for 1st and 2nd steps, 20 mL/kg for the limit test Post dose observation period: 14 days

Results : - *Mortality*: no death was observed during observation period.

- *Clinical signs*:
1st step: 0.5 hours after the administration, mucous diarrhea was observed, and from 1 hour, contamination of the perineal region including the anal region and abdominal region for all animals was observed because of mucous diarrhea. However, this symptom was not observed on the day 2. Depilation at the perineal region was observed on the day 9 and 11 for some animals.

2nd step: 0.5 hours after the administration, diarrhea was observed for an animal, and from 2 hours mucous diarrhrea was observed for all animals. Contamination of the perineal region was observed 1 hour after the administration for an animal and from 3 hours it was observed for all animals. This symptom was observed till 1 day after the treatment.

Limit test: From 1 hour to 2 days after the administration, mucous diarrhea and contamination of the perineal region including the anal region and abdominal region were observed for all animals. From 8 days, depilation of the anal region and perineal region including both insides of hind legs, and haematological scab around the anal region were observed.

- *Body weight*: Body weights of some animals for each test group were decreased because stomach was stimulated by test substance but were recovered and increased during test period.

- *Necropy opinions*: All animals in each test group had a symptom such as thickening of cutaneous membrane in the nongrandular stomach because inflammation and vegetion of the epithelium which was caused by stimulating cutaneous membrane. Two animals from each test group had a symptom of slight alopecia but it was occurred spontaneously.

- *Histopathological opinions*: In the 1st step, there were two cases of ulceration and mild inflammation with mild hyperkeratosis, a case of mild inflammation with mild hyperkeratosis and three case of mild thickening of epithelial layer within nongrandular stomach at the treatment group.

In the 2nd step, a case of slight inflammation with mild hyperkeratosis, two case of severe inflammation with mild hyperkeratosis and three cases of mild thickening of epithelial layer within nongrandular stomach in the treatment group.
In the limit test, a case of ulceration and mild inflammation with mild hyperkeratosis, a case of slight inflammation with mild hyperkeratosis, two cases of severe inflammation with mild hyperkeratosis, three cases of mild thickening of epithelial layer in the nongrandular stomach, and a case of slight focal submucosal inflammation of grandular stomach were observed.

Table. Necropsy findings

Organs	Findings	Sex	Female		
		Step Dose (mg/kg)	1st 2,000	2nd 2,000	Limit test 5,000
		No. of animals	3	3	3
Nongrandular stomach	Thickening of cutaneous mucous membrane		3	3	3
Skin, perinal area	Alopecia, slight		2	—	2

Table. Histopathological findings

Organs	Findings		Sex	Female		
			Step Dose (mg/kg)	1st 2,000	2nd 2,000	Limit test 5,000
			No. of animals	3	3	3
Nongrandular stomach	Ulceration and inflammation, mild, with mild hyperkeratosis			2		1
	Inflammation	- Mild with mild hyperkeratosis		1	1	1
		- Severe with mild hyperkeratosis			2	2
	Thickening of epithelial layer, mild			3	3	3
Glandular stomach	Submucosal inflammation, focal, slight			—	—	1

Table. Change of body weight (Sex: Female)

Step/Dose (mg/kg)	Animal ID	Day after treatment				
		0	1	3	7	14
1st 2000	F01	199.39	191.85	214.50	223.42	247.04
	F02	196.55	196.04	206.20	201.09	229.23
	F03	196.79	193.85	208.32	207.97	246.52
	Mean	197.58	193.91	209.67	210.83	240.93
	S.D.	1.57	2.10	4.31	11.44	10.14
	N	3	3	3	3	3
2nd 2000	F07	188.79	188.88	210.51	228.08	231.40
	F08	190.97	192.85	212.73	224.56	249.09
	F09	192.72	188.18	201.07	216.58	225.71
	Mean	190.8	190.0	208.1	223.1	235.4
	S.D.	2.0	2.5	6.2	5.9	12.2
	N	3	3	3	3	3
Limit test 5000	F04	195.03	186.52	190.59	206.96	241.81
	F05	195.82	199.46	205.88	222.71	242.08
	F06	188.91	180.09	188.87	210.74	225.39
	Mean	193.03	188.7	195.1	213.5	236.4
	S.D.	3.8	9.9	9.4	8.2	9.6
	N	3	3	3	3	3

N: Number of animals

Table. Clinical signs (Sex: Female)

Step		1st			2nd			Limit test		
Dose (mg/kg)		2000			2000			5000		
Animal ID		F01	F02	F03	F07	F08	F09	F04	F05	F06
<Time after	0.5	MD	MD	MD	NAD	D	NAD	NAD	NAD	NAD
treatment>	1	SP	SP	SP/MD	NAD	SP	NAD	MD/SP	MD/SP	MP/SP
	2	MD/SP	MD/SP	SP	MD/SP	MD/SP	MD	MD/SP	MD/SP	MD/SP
	3	MD/SP	MD/ SP	MD/SP	MD/SP	MD/SP	MD/SP	MD/SP	MD/SP	MD/SP
Day 0	4	MD/SP	SP	SP	MD/SP	SP	MD/SP	SP	MD/SP	SP
	5	MD/SP	MD/SP	SP/SN	MD/SP	MD/SP	MD/SP	MD/SP	MD/SP	MD/SP
(Hour)	6	SP	SP	SP/MD/SN	SP	SP	MD/SP	SP	MD/SP	SP
	7	SP	SP	SP	SP	SP	SP	MD/SP	SP	SP
	8	MD/SP	MD/SP	MD/SP	SP	SP	SP	MD/SP	SP	SP/MD
Day 1 ~14	1	SP	SP	SP	SP	SP	SP	MD/SP	SP	SP
	2	NAD	NAD	NAD	NAD	NAD	NAD	SP	NAD	SP
	3	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD
	4	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD
	5	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD
	6	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD
	7	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD
	8	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD
	9	NAD	NAD	AP	NAD	NAD	NAD	AP	NAD	AP/BP
	10	NAD	NAD	AP	NAD	NAD	NAD	AP	NAD	AP/BP
	11	NAD	AP	AP	NAD	NAD	NAD	AP	NAD	AP/ScP
	12	NAD	AP	AP	NAD	NAD	NAD	AP	NAD	AP
	13	NAD	AP	AP	NAD	NAD	NAD	AP	NAD	AP
	14	NAD	AP	AP	NAD	NAD	NAD	AP	NAD	AP

NAD: No Abnormalities Detected
SP: Soiled Perineal region Dy: Dyspnea AP: Alopecia of Perineal region (with hind leg)
SM: Soiled perineal Mouth MD: Mucous diarrhea BP: Bloody crust of Perineal region
SN: Soiled peripheral Nose D: Diarrhea ScP: Scar of Perineal region

Conclusion : Oral LD_{50} value was presumed to be above the highest test dose 5,000 mg/kg b.w. The test substance, 4-Methylbenzenesulfonyl chloride, was classified into category 5 or unclassified, in accordance with Harmonized Classification System, and LD_{50} cut-off was also unclassified (∞).
Reliability : (1) Reliable without restrictions
Flag : Critical study for SIDS endpoint
Reference :

(16)

Type : LD_{50}
Species : New Zealand Albino rabbit
Number of animals : 20
Value : 3,980, 5,010, 6,310 and 7,940 mg/kg
Route of administration Oral (20 % solution suspension in corn oil)
Method : Other: no data
Year : 1976
GLP : No
Test substance : Other TS: 4-Methylbenzenesulfonyl chloride, Lot No. – QH-5095, no further data
Test condition :
Result : *Sign of intoxication*: reduce appetite & activity (1 to 3 day in survivors), increased weakness
Necropsy: lung and liver problem; hyperemia, acute gastrointestinal inflammation

Table. Mortality

Animal No.	Dose	Weight (Ave)		Mortality			Time of Mortality
		M	F	M	F	Combined	
1	3,98	210	230	0/2	0/3	0/5	1 - 4 days
2	5,01	215	225	0/3	2/2	2/5	
3	6,31	205	210	2/2	2/3	4/5	
4	7,94	220	210	3/3	2/2	5/5	

Conclusion : 5,300 mg/kg
Reliability : (3) not reliable
Reference : (21)

Type : LD_{50}
Species/strain : Rat (Sprague-Dawley)
Sex : Male/Female
No. of animals : 21
Value : 8,320, 9,550, 10,900 and 12,600 mg/kg
Route of administration : Oral (gavage)
Method : Other: no data
Year : 1976
GLP : No
Test substance : Other TS: 4-Methylbenzenesulfonyl chloride, no further data
Test condition :
Results : The oral LD_{50} for rat was 10,200 mg/kg with lower and upper limits of 9,100 to 11,000 mg/kg.
Survival time was overnight to 4 days with most deaths in 2 days
Toxic symptoms: disrrhea, tremors leading to the conversive stage in some animals.
Necropsy: kidney and lung hyperomia with some discolouration of the latter organ.

Table. Mortality

Animal No.	Sex	Weight (g)	Dose (mg/kg)	Fate
1	M	230	8,320	Survived
2	F	220	8,320	Survived
3	F	195	8,320	Died
4	M	215	8,320	Survived
5	M	240	8,320	Survived
6	F	210	9,550	Died
7	M	225	9,550	Survived
8	M	205	9,550	Died
9	F	200	9,550	Survived
10	F	215	9,550	Survived
11	M	230	9,550	Survived
12	M	200	10,900	Died
13	M	195	10,900	Died
14	F	190	10,900	Survived
15	F	215	10,900	Died
16	M	230	10,900	Died
17	M	210	12,600	Died
18	F	200	12,600	Died
19	M	220	12,600	Survived
20	M	230	12,600	Died
21	F	205	12,600	Died

Conclusion : LD_{50} was placed at 10,200 mg/kg
Reliability : (2) Reliable with restrictions
Flag : Critical study for SIDS endpoint

Reference : (23)

Type : LD_{50}
Species/strain : Rat
Sex :
Number of animals :
Vehicle :
Value :
Route of administration : Oral
Method : Other: no data
Year : 1982
GLP : No
Test substance : Other TS: 4-Methylbenzenesulfonyl chloride, no further data
Test condition :
Results :

Conclusion : LD_{50} was 5.30 g/kg
Reliability : (3) Not reliable
Flag : Critical study for SIDS endpoint
Reference : (20)

5.1.2 ACUTE INHALATION TOXICITY

5.1.3. ACUTE DERMAL TOXICITY

Type : LD_{50}
Species/strain : New Zealand Albino Rabbit
No of animals : 3

Route of Administration	:	Test substance was applied as a 40 % solution-suspension in corn oil
Exposure time	:	24 hours
Value	:	3,160, 5,010 and 7,940 mg/kg
Method	:	Other: No data
GLP	:	No
Test substance	:	Other TS: 4-Methylbenzenesulfonyl chloride, Lot No. – QH-5095, no further data
Results	:	*Sign of intoxication*: reduced appetite and activity (2 - 3 days in survivors) Increased weakness, collapse, death *Necropsy*: lung hyperomia, liver & kidney discolouration, enlarged gall bladder, gastrointestinal inflammation

Table. Mortality

Animal No.	Dose	Weight (Ave)		Mortality			Time of Mortality
		M	F	M	F	Combined	
1	3,160	220	-	0/1	-	0/1	
2	5,010	-	180	-	0/1	0/1	9 days
3	7,940	210	-	1/1	-	1/1	

Conclusion	:	LD_{50} > 5,010 mg/kg
Remarks	:	
Reliability	:	(2) Reliable with restrictions
Flag	:	Critical study for SIDS endpoint
Reference	:	(21)
Type	:	LD_{50}
Species/strain	:	Rabbit
Route of Administration	:	
Exposure time	:	24 hours
Value	:	
Method	:	Other: No data
GLP	:	No data
Test substance	:	Other TS: 4-Methylbenzenesulfonyl chloride, no further data
Results	:	
Cinclusion	:	LD_{50} > 5.01 g/kg
Reliability	:	(3) Not reliable
Flag	:	Critical study for SIDS endpoint
Reference	:	(20)

5.1.4 ACUTE TOXICITY, OTHER ROUTES OF ADMINISTRATION

5.2 CORROSIVENESS/IRRITATION

5.2.1 SKIN IRRITATION

Test type	:	*In vivo*
Species/strain	:	Rabbit (New Zealand White)

Results	:	Moderately irritating The skin on the backs of three rabbits appeared affected.
Method	:	OECD TG 404 (1991) “Acute Dermal Irritation/Corrosion”
Method remark		500 mg of test material with about 0.1 mL of sterile distilled water for humidity was applied to the abraded and intact sites on the shaved backs (2.5 x 2.5 cm) of rabbits. It was held in place for 4 hours with three fold gauze patches, which was applied in place with elasticity bandage then was fixed with non-irritating tape (3M paper-tape) to prevent leakage. After 4 hours, three fold gauze patches were removed and the exposed areas washed using warm water without altering the existing response or the integrity of the epidermis. The skin of animals was examined in accordance with an OECD scoring method for signs of erythema and oedema and the responses scored at 1, 24, 48 and 72 hours after the patches removal. Mortality, clinical signs and body weight were also investigated.
Year	:	2003
GLP	:	Yes
Test substance	:	Other TS: 4-Methylbenzenesulfonyl chloride, purity = 99.7 %, Sigma-Aldrich Corporation, Lot No. – 422308/1
Test condition	:	**Test organism** - Age: 3 to 4 months old - Number of animals: 3 animals - Sex: Male animals - Weight: 2.1 - 2.3 kg Total dose: 500 mg/site/rabbit of 4-Methylbenzenesulfonyl chloride Vehicle: Not used Route of administration: With an occluded patch Exposure time period: 4 hours Scoring method: Used (OECD method – Grading of skin reaction)
Result	:	- Irritating: erythema, scab and oedema were observed at the abraded and intact skins on the backs of three rabbits. - There were no clinical signs in relation to spread of 4-Methylbenzenesulfonyl chloride. - A case of weight loss was observed in 24 hours after the administration but it was almost recovered after 48 hours.

Table. Evaluation of skin irritation

Left site: Control

Change	Erythema & Eschar							
Applicated area	Intact				Abraded			
Phase (hrs)	1	24	48	72	1	24	48	72
Animal ID								
M01	0	0	0	0	0	0	0	0
M02	0	0	0	0	0	0	0	0
M03	0	0	0	0	0	0	0	0
Total	0	0	0	0	0	0	0	0

Mean	0	0	0	0	0	0	0	0
Total of mean	0							

Left site: Control

Change	Edema							
Applicated area	Intact				Abraded			
Phase (hrs)	1	24	48	72	1	24	48	72
Animal ID								
M01	0	0	0	0	0	0	0	0
M02	0	0	0	0	0	0	0	0
M03	0	0	0	0	0	0	0	0
Total	0	0	0	0	0	0	0	0
Mean	0	0	0	0	0	0	0	0
Total of mean	0							

Right site: 4-Methylbenzenesulfonyl chloride

Change	Erythema & Eschar							
Applicated area	Intact				Abraded			
Phase (hrs)	1	24	48	72	1	24	48	72
Animal ID								
M01	2	3	3	3	2	3	3	3
M02	2	3	3	3	2	3	3	3
M03	2	3	3	3	2	3	3	3
Total	6	9	9	9	6	9	9	9
Mean	2.0	3.0	3.0	3.0	2.0	3.0	3.0	3.0
Total of mean	22.0							

Right site: 4-Methylbenzenesulfonyl chloride

Change	Edema							
Applicated area	Intact				Abraded			
Phase (hrs)	1	24	48	72	1	24	48	72
Animal ID								
M01	1	2	2	2	2	2	2	2
M02	1	3	2	2	2	3	2	2

M03	1	2	2	1	2	2	2	1
Total	3	7	6	5	6	7	6	5
Mean	1.0	2.3	2.0	1.7	2.0	2.3	2.0	1.7
Total of mean	15.0							

- Erythema and Eschar formation

0 – No erythema

1 – Very slight erythema (barely perceptible)

2 – Well defined erythema

3 – Moderate to severe erythema

4–Severe erythema (beef redness) to eschar formation preventing grading of erythema

- Oedema formation

0 – No oedema

1 – Very slight oedema (barely perceptible)

2 – Slight oedema (edges of area well defined by definite raising)

3 – Moderate oedema (raised approximately 1 mm)

4 – Severe oedema (raised more than 1 mm and extending beyond area of exposure)

Conclusion : 4-Methylbenzenesulfonyl chloride did make skin irritation/corrosion at the test concentration
Reliability : (1) Reliable without restrictions
Flag : Critical study for SIDS endpoint
Reference : (17)

Test type : *In vivo*
Species/strain : New Zealand Albino Rabbit
Results : Moderately irritating
Method : FHSA protocol; 0.5 mg applied as finely ground powder moistened with water in contact with both intact and abraded skin. After 24 hours, application was removed and the exposed areas washed using soap and warm water without altering the existing response or the integrity of the epidermis.
Year : 1976
GLP : No
Test substance : Other TS: 4-Methylbenzenesulfonyl chloride, Lot No. – QH5095, no further data
Test condition : 24 hours exposure

Results : Defatting effect- skin sloughted off in 10 to 15 days
No injury in depth

Table. Evaluation of skin irritation

Change	Erythema									
Applicated area	Intact					Abraded				
Phase (hrs)	1	24	48	72	168	1	24	48	72	168

Animal ID										
1	0	2	2	2	0	0	2	2	2	0
2	0	1	1	1	0	0	2	2	2	0
3	0	2	2	2	0	0	2	2	2	0
4	0	2	2	2	0	0	2	2	2	0
5	0	1	1	1	0	0	2	2	2	0
6	0	2	2	2	0	0	2	2	2	0

Change	Edema									
Applicated area	Intact					Abraded				
Phase (hrs)	1	24	48	72	168	1	24	48	72	168
Animal ID										
1	0	2	2	1	0	0	2	2	2	0
2	0	1	1	1	0	0	2	2	1	0
3	0	1	1	1	0	0	1	1	1	0
4	0	2	2	1	0	0	2	2	1	0
5	0	1	1	1	0	0	1	1	1	0
6	0	2	1	1	0	0	2	1	1	0

Conclusion : Moderately irritating
Reliability : (2) Reliable with restrictions
Flag : Critical study for SIDS endpoint

Reference : (21)

Test type : *In vivo*
Species/strain : New Zealand Albino Rabbit
Results : The powder was non-irritating when left on the intact skin for 24 hours. 0.5 mg in corn oil produced barely perceptible redness in one of the three rabbits in 4 hours. Very slight erythema was present on all of the animals overnight. No oedema developed.

Table. Evaluation of skin irritation

Applied as a powder form (hour)					
Animal No.	1 h	4 h	24 h	48 h	72 h
1	0	0	0	0	0
2	0	0	0	0	0
3	0	0	0	0	0
Applied as a 25 % solution in corn oil(hour)					
Animal No.	1 h	4 h	24 h	48 h	72 h
1	0	0	1	0	0
2	0	1	1	0	0
3	0	0	1	0	0

Method	:	Finely ground powder and 25 % solution in corn oil in contact with intact skin of rabbits. After 24 hours, application was removed and the exposed areas washed using soap and warm water without altering the existing response or the integrity of the epidermis. The skin of animals was examined in accordance with a method of Drains, Woodard and Calvary and the responses scored at 1, 4, 24, 48 and 72 hours after the application removal.
Year	:	1976
GLP	:	No
Test substance	:	Other TS: 4-Methylbenzenesulfonyl chloride, no further data
Conclusion	:	Non-irritating in powder form Very mild irritating in a 25 % corn oil solution
Reliability	:	(2) Reliable with restrictions
Flag	:	Critical study for SIDS endpoint
Reference	:	(22)

Test type	:	*In vivo*
Species/strain	:	New Zealand Albino Rabbit
Method	:	0.5 mg of finely ground powder was moistened with water, which was applied on the intact skin of rabbits. After 24 hours, application was removed and the exposed areas washed using soap and warm water without altering the existing response or the integrity of the epidermis. The skin of animals was examined and the responses scored at 4, 24, 48, 72 and 168 hours after the application removal.
Year	:	1976
GLP	:	No
Test substance	:	Other TS: 4-Methylbenzenesulfonyl chloride, no further data
Results	:	Defatting effect: skin slought off in 10 to 14 days. No injury in depth

Table. Evaluation of skin irritation

Change	Erythema									
Applicated area	Intact					Abraded				
Phase (hrs)	4	24	48	72	168	4	24	48	72	168
Animal ID										
1	0	2	2	2	0					
2	0	2	2	2	0					
3	0	2	1	1	0					

Change	Edema									
Applicated area	Intact					Abraded				
Phase (hrs)	4	24	48	72	168	4	24	48	72	168
Animal ID										

	0	2	2	1	0					
	0	1	1	1	0					
	0	1	1	1	0					

Conclusion : Moderately irritating
Reliability : (2) Reliable with restrictions
Flag : Critical study for SIDS endpoint

Reference : (23)

Test type : *In vivo*
Species/strain : Rabbit
Results : Moderately irritating
Method : FHSA protocol; finely ground powder in contact with both intact and abraded skin.
Year : 1982
GLP : No data
Test substance : Other TS: 4-Methylbenzenesulfonyl chloride, no further data
Test condition : 24 hours exposure

Results :
Conclusion : Moderately irritating
Reliability : (3) Not reliable
Flag : Critical study for SIDS endpoint
Reference : (20)

5.2.2 EYE IRRITATION/CORROSION

Test type : *In vivo*
Species/strain : New Zealand Albino Rabbit
Method : Other: FHSA protocol
Year : 1976
GLP : No
Test substance : Other TS: 4-Methylbenzenesulfonyl chloride, Lot No. – QH5095, no further data
Test condition : Test substance was applied as fine ground sample.
Exposure period: 24 hours for corrosion, 1 min for Irritation
Irritation was scored at 24, 48 and 72 hours
Dose: 0.1 mL/vol for both Irritation and corrosion

Results : Comments for corrosion:
1. Immediate: discomfort was severe with pawing, squealing, thrashing about stocks, eye tightly closed
2. 10 min: moderate erythema, very slight edema, copious discharge
3. 1 hour: severe erythema, very slight edema, copious discharge
4. 24 hours: areas of corneal clodness, iris congestion, severe erythema, slight to moderate edema, copious discharge
5. 48 hours: increasing corneal cloudness
6. 72 hours: corrosive

Comments for Irritation:
1. Immediate: discomfort was severe with pawing, squealing, thrashing about stocks, eye tightly closed.
2. 10 min: moderate erythema, mederate discharge
3. 1 hour: moderate erythema, copious discharge
4. 24 hours: slight erythema, slight to moderate discharge
5. 48 hours: gradual improvement
6. 72 hours: all scored 0

Table. Evaluation of eye irritation

Animal No.	Hour	1	24	48	72
	structure	Conjunctiva	Conjunctiva	Conjunctiva	Conjunctiva
1		10	4	2	0
2		10	6	2	0
3		10	4	2	0

Conclude : 4-Methylbenzenesulfonyl chloride induced corrosion and irritation on the eyes of New Zealand Albino Rabbit.
This substance was classified as corrosive by F.H.S.A
Reliability : (2) Reliable with restrictions
Flag : Critical study for SIDS endpoint

Reference : (21)

Test type : *In vivo*
Species/strain : New Zealand Albino Rabbit
Method : 100 mg of finely ground powder was applied on the eyes of the rabbits. After 24 hours of exposure, the eyes of animals were examined at immediately, 10 minutes, 1, 24, and 48 hours.
Year : 1976
GLP : No
Test substance : Other TS: 4-Methylbenzenesulfonyl chloride, no further data
Test condition :
Results : Responses
1. Immediate: discomfort was moderate with eyes tightly closed.
2. 10 min: moderate to severe erythema, copious discharge
3. 1 hour: severe erythema, very slight to slight edema, copious discharge
4. 24 hours; slight to moderate corneal cloudness, Iris congestion, severe erythema, mederate edema, copious discharge
5. Corrosive

Conclude : Test substance was corrosive for eyes of the rabbit at test concentration.
Reliability : (2) Reliable with restrictions
Flag : Critical study for SIDS endpoint

Reference : (23)

Test type : *In vivo*
Species/strain : Rabbit

Method	:	Other: FHSA protocol
Year	:	1982
GLP	:	No data
Test substance	:	Other TS: 4-Methylbenzenesulfonyl chloride, no further data
Test condition	:	24 hours exposure
Result	:	Irritating
Result remarks		24 hours in conjunctiva sac corrosive, irreversible damage
Reliability	:	(3) Not reliable
Flag	:	Critical study for SIDS endpoint
Reference	:	(20)

5.3 SKIN SENSITIZATION

5.4 REPEATED DOSE TOXICITY

Species/strains	:	Rat (Sprague-Dawley)
Sex	:	Male/Female
Route of administration	:	Oral (Gavage)
Method	:	OECD TG No. 422 “Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test”
Year	:	2003
GLP	:	Yes
Test substance	:	Other TS: 4-Methylbenzenesulfonyl chloride, purity = 99.7 %, Fluka, Lot No. - 422308/1
Dose level	:	According to the preliminary test (Report No. P104), dose level was determined as 0, 150, 350 and 750 mg/kg/day.
Exposure period	:	34, 36 - 45, and 51 days for male, copulated female and not copulated female animals, respectively.
Frequency of treatment	:	Daily
Control group	:	Yes (concurrent no treatment)
Post exposure observation period	:	
Statistical methods	:	Statistical decision tree, but in case of recovery group, either two-side Student’s t-test or two-side Aspin-Welch t-test was used. In case of categorical data, two-sided Fisher’s exact test was used.

Test condition : Test organism
- Sex: male/female
- Age of animals at study: 9 weeks old for males and females
- Weight at study repeated dose toxicity: 325.8 - 363.1 g for males and 198.5 - 229.3 g for females
- Number of test animals: 60 animals for each sex

Observation of F0
- *Clinical observations performed and frequency*: Clinical symptoms were observed once a day but were observed once a week in detail; a death rate was observed twice a day and in case of animals with dying condition, they were allowed euthanasia to necropsy, if it is not possible immediately, they were refrigerated; body weight was observed once a week and just before the necropsy, but in case of pregnant females, it was measured on the day 0, 7, 14, 20 of the gestation period, date of delivery, and 4 days of the lactation day; and consumption rate of fodder was observed once a week except mating period.
- *Tests for sensory organ and reflex action*: 5 animals were randomly selected from each test group. Both prayer reflex test and corneal reflex test were performed before necropsy and during lactation for males and females, respectively.
- *Behaviour test*: 5 animals were randomly selected from each test group to do grip strength test in terms of behaviour test. This test was performed before necropsy and during lactation for males and females, respectively.
- *Haematological and biochemical test of blood*: randomly selected 5 male and female rats from each test group were fasted a day before necropsy for both tests. Animals were anesthetized using ether and cut the abdomen open to collect blood. In case of the haematological test, blood coagulation preventative chemicals for the test of blood coagulation and the calculation of blood-corpuscles were 3.2 % sodium citrate and EDTA-2K, respectively. On the other hand, blood coagulation preventative chemical was not used for the biochemical test, but gathered blood was left itself in the room temperature then the sera were separated using a centrifuge. For haematological test, 6 following items were measured; Haematocrit, hemoglobin concentration, erythrocyte count, total and different leucocyte count, platelet count, prothrombin time, and active partial thromboplastin time. For biochemical test of blood, twelve following items were measured; sodium, potassium, chloride, glucose, total cholesterol, blood urea nitrogen, creatinine, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, and total bilirubin.

Organs examined at necropsy:
Organ weight: testes, epididymider (all males) liver, kidney, adrenals, thymus, spleen, brain and heart (5 male and female rats from each test group).
Fixation: 22 kinds of tissues were fixed to do histopathologic tests such as testes, epididymides, ovaries, accessory sex organs for all animals, brain (including cerebrum, cerebellum and pons), spinal cord, stomach, small and large intestines (including peyer's patches), liver, kidneys, adrenals, spleen, heart, thymus, thyroid, trachea, lungs, uterus, urinary bladder, lymph nodes (cervical mesenteric), peripheral nerve (sciatic or tibial), and bone marrow.

NOAEL : Less than 150 mg/kg/day for both sexes
LOAEL : 150 mg/kg/day mg/kg/day for both sexes

Results : Results for F0

- *Mortality*: No death was observed for male animals. In case of female rats, a moribund and humane sacrifice, and a found dead were observed on the day 37 (GD 20) and 41 (LD 1), respectively, for the 350 mg/kg/day treatment group. In 750 mg/kg/day treatment group, each case of moribund and humane sacrifice was observed at day 6 and 29 (GD13), respectively; and each case of found dead was observed at day 8 and 38, respectively. Therefore, 4-Methylbenzenesulfonyl chloride has relationship with increase of mortality in female rats.

- *Body weight*: In male group, body weight of treatment groups was decreased in relation to dose-dependent as compared with that of the control groups during test period. In the 750 mg/kg/day treatment group, their weights were decreased on the day 8, 22, 29 ($p < 0.001$) and 15 ($p < 0.01$) in contrast with those of the control groups. In addition, the amounts of body weight change for all animals in the treatment groups were decreased in contrast with those of the control groups on the day 1 - 8 and 15 - 22 in relation to dose-dependent but in 750 mg/kg/day treatment group, the amount of body weight change was decreased significantly in contrast with that of the control groups. The body weight for the recovery group (1 week) was decreased significantly in contrast to that of the control group but no difference was found for the recovery group (2 week).
In female group, body weight and the amount of body weight change were not changed significantly in contrast to those of the control groups. However, the amount of body weight change for the 750 mg/kg/day recovery group was decreased significantly on the day 22 - 29 as compare with that of the control groups.
Therefore, 4-Methylbenzenesulfonyl chloride has a relationship with reduction of the amount of body weight change but its effect was specific for sex since male rats were more sensitive for the amount of body weight change.

- *Clinical signs*: In male rats, intermittent (blood-like) salivation and 3 cases of staining around mouth were observed on the day 27 for the 150 mg/kg/day treatment group. In the 350 mg/kg/day treatment group, (blood-like) salivation and staining around mouth were observed after the day 20 of administration; and 7 cases of (blood-like) staining around nose were observed after the day 21 of administration. After the day 3 of administration, intermittent soft stool and staining around anorectal region were observed for the most animals. In the 750 mg/kg/day treatment group, soft stool and staining around anorectal region for most animals; and 5 cases of loss of hair around tail region were observed after the day 3 and 14 of administration, respectively. After the day 7 and 21 of administration, (blood-like) salivation and 9 cases of staining around mouth and 9 cases of (blood-like) staining around nose for most animals were observed, respectively. In the control groups, there were no specific clinical symptoms during test period.
In the 750 mg/kg/day recovery group, salivation, staining around mouth, soft stool and staining around anorectal region were not observed during the recovery period. In female rats, after the day 15 of administration, intermittent (blood-like) salivation and 6 cases of staining around mouth; and from the day of delivery, difficult delivery, poor nursing, irregular respiration, uterus introsusception and piloerection were observed for the 150 mg/kg/day treatment group. In the 350 mg/kg/day treatment group, (blood-like) salivation and staining around mouth were observed for all animals after the day 15 of administration; and 4 cases of intermittent (blood-like) staining around nose were observed after the day 28 of administration.

In addition, 2 cases of soft stool and staining around anorectal region; and a case of difficult delivery, lacrimation, and irregular respiration were found after the day 4 of administration and from the delivery to death, respectively. In the 750 mg/kg/day treatment group, (blood-like) salivation and staining around mouth for all animals; soft stool and staining around anorectal region for all animals; and 3 cases of intermittent diarrhea were observed after the day 5, 3 and 38 of administration, respectively. Some animals with found dead and in dying condition had symptoms such as irregular respiration, crawing position, hypoactivity, and abdominal swelling. In the control group, no specific clinical signs were observed during test period. In the recovery group, any other symptoms were not observed.

- *Amount of fodder consumption*: No crucial difference between the treatment groups (150 mg/kg/day and 350 mg/kg/day) and the control group for male rats. In the 750 mg/kg/day treatment group, the amount of fodder consumption was decreased as compared with that of the control group (1 week) but after that no more significant difference was found between the two. In the female rats, no critical difference was found. Therefore, 4-Methylbenzenesulfonyl chloride led specific reduction of fodder consumption rate for male rats.

- *Test of reflex action*: normal responses were observed from selected animals.

- *Grip strength test*: For male rats, 5 animals were left out from the treatment group but no significant difference was found between the treatment and control group. For female rats, no animals were left out. All things being considered, there was no illness at the related organs such as the cerebellum and muscle in relation to the test substance.

- *Organ weight*: According to the results of organ weight for male rats, absolute and relative weight of genital organs including testicles and epididymis for treatment group were not different significantly from those of the control groups. However, both absolute and relative weights of the spleen for treatment groups were increased as compared with that of the control groups in relation to dose-correlation. In addition, the absolute and relative weights of spleen for both treatment groups with 350 and 750 mg/kg/day were increased significantly as compared to those of the control groups. In the 750 mg/kg/day treatment group, although absolute weight of heart was decreased significantly in contrast to that of the control group, relative weight was not.
In case of the recovery group with 750 mg/kg/day, weights of genital organs including testicles and epididymis, and both absolute and relative weight of other organs were not critically different from those of the control groups. According to the results of organ weight for female animals, in the 350 mg/kg/day treatment group, absolute weight of the spleen was increased significantly as compared to that of the control group, but relative weight was not. In the 750 mg/kg/day treatment group, both absolute and relative weights were the same pattern as the spleen. In case of the recovery group with 750 mg/kg/day, absolute and relative weights for adrenal and the brain were increased significantly, respectively, as compared with that of the control group.

- *Analysis of haematological test of blood*: According to the analysis of male animals, the concentration of RBC was decreased as compared to that of the control group in relation to dose-correlation, and it was also significantly decreased as compared to that of the control group for the treatment group with 350 and 750 mg/kg/day. The concentration of PLT was increased in contrast to that of the control group in relation to dose-correlation, and it was also significantly increased for the treatment group with 350 and 750 mg/kg/day. The concentration of HCT was decreased significantly in contrast to that of the control

group. In case of 750 mg/kg/day recovery group, no significant difference for all test items as compared with that of the control group. According to the analysis of female animals, no significant difference was found between the treatment and the control group including the 750 mg/kg/day recovery group for all test items.

- *Analysis of biochemical test of blood*: According to the analysis of male animals, the thickness of BUN is decreased as compared with that of the control group in relation to dose-correlation and its concentration for the 750 mg/kg/day treatment group was significantly decreased in contrast to that of the control group. The concentration of CREA and TCHO were critically decreased in contrast to those of the control group for the recovery group with 750 mg/kg/day. According to the analysis of female animals, the concentration of ALB and TBIL were increased significantly for the 350 and 750 mg/kg/day treatment group, respectively as compared with that of the control group. In case of 750 mg/kg/day recovery group, the concentration of Cl was decreased significantly as compared with that of the control group.

- *Histopathological findings*: These findings were summarised in the Tables.

Table. Mortalities and fates of females (group)

Group:	C	T1	T2	T3
Test article:	------	4-Methylbenzenesulfonyl chloride		-------
Dose level (mg/kg/day):	0	150	350	750

Group	Day	Description	No. of animals
C	42-46	Terminal sacrifice	12
	57	Terminal sacrifice-Recovery	6
T1	43-46	Terminal sacrifice	12
T2	43-46	Terminal sacrifice	10
	37	Humane sacrifice	1
	41	Found dead	1
T3	43-52	Terminal sacrifice	9
	57	Terminal sacrifice-Recovery	5
	6, 29	Humane sacrifice	3
	8, 38	Found dead	2

Table. Body weights of males(group)

Group:		C	T1		T2			T3
Test article:		------	4-Methylbenzenesulfonyl chloride					-------
Dose level (mg/kg/day):		0	150		350			750
Unit:			g					
Group		Day						
		1	8	15	22	29	36	43
C	Mean	346.2	380.2	399.5	418.8	438.6	460.9	484.3
	SD	15.1	20.8	21.3	22.4	24.0	24.3	25.6
	N	18	18	18	18	18	6	6
T1	Mean	348.0	381.7	401.0	417.3	434.0		
	SD	10.3	20.8	27.4	30.3	32.5		
	N	12	12	12	12	12		
T2	Mean	343.0	371.0	388.1	401.9	418.0		
	SD	11.5	14.4	12.2	15.7	16.2		
	N	12	12	12	12	12		
T3	Mean	346.7	360.6	378.1	387.5	405.9	424.0	455.4
	SD	8.6	11.1	14.8	16.5	17.6	23.5	28.3
	N	18	18	18	18	18	6	6

Table. Body weights gains of males (group)

Group:		C	T1		T2			T3
Test article:		------	4-Methylbenzenesulfonyl chloride					-------
Dose level (mg/kg/day):		0	150		350			750
Unit:			g					
Group		Day						
		1 - 8	8 - 15	15 - 22	22 - 29	29 - 36	36 - 43	
C	Mean	34.0	19.3	19.3	19.8	16.7	23.4	
	SD	9.0	5.9	5.5	8.9	8.0	8.0	
	N	18	18	18	18	6	6	
T1	Mean	33.7	19.2	16.3	16.7			
	SD	13.8	8.1	5.4	5.5			
	N	12	12	12	12			
T2	Mean	27.9	17.1	13.8	16.1			
	SD	7.7	4.9	5.5	5.6			
	N	12	12	12	12			
T3	Mean	14.0	17.4	9.4	18.4	17.0	31.4	
	SD	6.1	7.2	7.2	5.2	9.9	7.6	
	N	18	18	18	18	6	6	

Table. Body weights of females during pre-mating period

Group:		C	T1		T2			T3
Test article:		------	4-Methylbenzenesulfonyl chloride					------
Dose level (mg/kg/day):		0	150		350			750
Unit:		g						
Group		Day						
		1	8	15	22	29	36	43	50
C	Mean	211.2	230.8	239.4	244.0	256.3	262.9	272.4	273.1
	SD	8.9	6.6	10.1	14.3	12.3	14.5	15.2	12.4
	N	18	18	18	6	6	6	6	6
T1	Mean	209.8	230.6	239.9					
	SD	9.0	9.7	8.1					
	N	12	12	12					
T2	Mean	211.1	231.2	240.2					
	SD	11.7	11.8	13.9					
	N	12	12	12					
T3	Mean	211.8	222.2	235.7	238.9	244.7	251.0	257.9	263.3
	SD	6.3	14.3	7.0	7.7	6.3	9.2	12.5	12.3
	N	18	17	16	5	5	5	5	5

Table. Body weights gains of females during pre-mating period (group)

Group:		C	T1		T2			T3
Test article:		------	4-Methylbenzenesulfonyl chloride					-------
Dose level (mg/kg/day):		0	150		350			750
Unit:		g						
Group		Day						
		1-8	8-15	15-22	22-29	29-36	36-43	43-50
C	Mean	19.7	8.5	4.5	12.3	6.6	9.5	0.7
	SD	6.4	5.6	6.3	4.7	4.8	5.8	5.6
	N	18	18	6	6	6	6	6
T1	Mean	20.8	9.3					
	SD	5.4	2.9					
	N	12	12					
T2	Mean	20.1	9.1					
	SD	6.2	4.4					
	N	12	12					
T3	Mean	11.1	10.4	7.7	5.8	6.3	6.9	5.4
	SD	13.0	4.5	3.8	4.2	5.5	4.0	2.9
	N	17	16	5	5	5	5	5

Table. Body weights of females during pregnancy and lactation (group)

Group:	C	T1	T2	T3
Test article:	------	4-Methylbenzenesulfonyl chloride		-------
Dose level (mg/kg/day):	0	150	350	750
Unit:		g		

Group		Gestation day (0-20)			Lactation day		
		0	7	14	20	At birth	4
C	Mean	237.7	272.9	302.6	357.7	263.6	275.2
	SD	9.1	8.9	10.2	12.4	19.1	14.1
	N	11	11	11	11	11	11
T1	Mean	236.8	270.7	299.3	350.6	259.4	265.3
	SD	10.5	15.8	17.3	24.9	18.6	20.8
	N	12	12	12	12	11	11
T2	Mean	236.4	269.4	301.3	359.3	273.7	274.0
	SD	12.5	12.4	11.3	9.5	24.6	16.8
	N	11	11	10	10	10	10
T3	Mean	232.8	264.5	288.9	337.6	253.9	268.2
	SD	6.7	8.5	12.8	29.3	20.4	14.8
	N	9	9	8	8	8	8

Table. Body weight gains of females during pregnancy and lactation

Group:	C	T1	T2	T3
Test article:	------	4-Methylbenzenesulfonyl chloride		-------
Dose level (mg/kg/day):	0	150	350	750
Unit:		g		

Group		Gestation day (0-20)		Lactation day	
		0 - 7	7 - 14	14 - 20	At birth- 4
C	Mean	35.2	29.6	55.1	11.6
	SD	5.5	3.2	6.1	8.8
	N	11	11	11	11
T1	Mean	33.9	28.6	51.3	5.9
	SD	7.2	4.2	15.6	13.3
	N	12	12	12	11
T2	Mean	33.0	30.0	58.0	0.3
	SD	6.0	2.8	6.8	20.4
	N	11	10	10	10
T3	Mean	31.7	24.4	48.7	14.3
	SD	6.1	12.8	19.5	11.9
	N	9	8	8	8

Table. Food consumption of males (group)

Group:	C	T1	T2	T3
Test article:	------	4-Methylbenzenesulfonyl chloride		-------
Dose level (mg/kg/day):	0	150	350	750
Unit:	g			

Group		Week					
		1	2	4	5	6	7
C	Mean	25.9	24.5	18.7	20.2	24.7	25.9
	SD	2.2	2.3	2.1	2.9	3.7	4.1
	N	18	18	18	18	6	6
T1	Mean	26.5	25.9	17.5	20.3		
	SD	2.1	3.4	2.1	1.9		
	N	12	12	12	12		
T2	Mean	24.5	22.7	18.5	19.6		
	SD	2.3	1.9	2.2	2.7		
	N	12	12	11	12		
T3	Mean	22.8	26.2	19.8	21.7	24.3	29.3
	SD	3.0	3.2	2.3	2.6	2.7	2.5
	N	18	18	16	18	6	6

Table. Food consumption of females during pregnancy and lactation (group)

Group:	C	T1	T2	T3
Test article:	------	4-Methylbenzenesulfonyl chloride		-------
Dose level (mg/kg/day):	0	150	350	750
Unit:	g			

Group		Gestation (w1-w4)		Lactation		
		Week1	Week2	Week3	Week4	Week1
C	Mean	14.3	18.1	15.4	14.9	23.6
	SD	1.7	1.6	3.3	3.0	6.2
	N	11	11	11	11	11
T1	Mean	13.7	17.1	16.7	15.1	23.5
	SD	2.8	3.4	3.3	4.0	9.0
	N	12	12	12	12	11
T2	Mean	15.2	17.1	15.3	17.0	25.8
	SD	1.4	2.9	5.6	6.4	7.5
	N	11	11	11	11	10
T3	Mean	16.5	17.6	15.3	16.7	29.0
	SD	2.1	2.9	4.1	3.4	5.1
	N	9	9	8	8	8

Table. Food consumption of females during pre-mating period (group)

Group:	C	T1	T2	T3
Test article:	------	4-Methylbenzenesulfonyl chloride		-------
Dose level (mg/kg/day):	0	150	350	750
Unit:	g			

Group		Week						
		1	2	4	5	6	7	8
C	Mean	17.1	16.9	15.9	12.3	16.4	18.0	17.8
	SD	2.2	3.4	1.8	1.9	2.0	2.3	2.1
	N	18	18	6	6	6	6	6
T1	Mean	16.8	16.8					
	SD	2.0	3.3					
	N	12	12					
T2	Mean	18.2	17.5					
	SD	2.0	2.7					
	N	12	12					
T3	Mean	16.1	17.7	15.5	13.7	15.2	19.4	17.8
	SD	2.4	3.0	1.2	2.1	3.1	1.8	2.0
	N	18	16	5	5	5	5	5

Table. Clinical Biochemistry of males (group mean)

Treatment (mg/kg/day)	TP g/dL	ALB g/dL	AST IU/L	ALT IU/L	BUN mg/dL	CREA mg/dL	TCHO mg/dL	GLU mg/dL	Na mmol/L	K mmol/L	Cl mmol/L
0	6.0	2.3	148.3	46.5	11.3	0.6	98.8	69.0	147.2	4.6	104.0
150	5.8	2.2	132.5	28.6	10.7	0.5	114.2	64.4	143.8	4.6	102.0
350	5.8	2.3	122.8	31.3	9.6	0.5	102.8	66.0	145.4	4.9	102.4
750	5.6	2.2	127.2	41.3	7.8	0.5	102.8	58.6	145.6	4.4	102.6

Table. Clinical Biochemistry of males - Recovery (group mean)

Treatment (mg/kg/day)	TP g/dL	ALB g/dL	AST IU/L	ALT IU/L	BUN mg/dL	CREA mg/dL	TCHO mg/dL	GLU mg/dL	Na mmol/L	K mmol/L	Cl mmol/L
0	5.8	2.3	103.9	32.7	11.7	0.6	116.0	67.2	143.2	4.7	104.8
750	5.0	1.9	93.0	31.4	12.8	0.5	105.2	46.4	128.8	4.1	94.2

Table. Clinical Biochemistry of females (group mean)

Treatment (mg/kg/day)	TP g/dL	ALB g/dL	AST IU/L	ALT IU/L	BUN mg/dL	CREA mg/dL	TCHO mg/dL	GLU mg/dL	Na mmol/L	K mmol/L	Cl mmol/L
0	5.0	2.0	102.5	59.9	14.1	0.7	105.6	85.0	140.4	4.1	100.4
150	5.1	2.1	101.6	54.1	13.6	0.7	112.2	70.6	144.0	4.5	102.6
350	5.4	2.2	94.3	61.1	13.3	0.7	102.8	73.0	139.4	4.6	100.8
750	5.2	2.1	107.2	63.4	11.4	0.6	121.4	79.6	142.2	4.9	99.6

Table. Clinical Biochemistry of females - Recovery (group mean)

Treatment (mg/kg/day)	TP g/dL	ALB g/dL	AST IU/L	ALT IU/L	BUN mg/dL	CREA mg/dL	TCHO mg/dL	GLU mg/dL	Na mmol/L	K mmol/L	Cl mmol/L
0	6.7	3.1	125.4	38.8	12.1	0.6	140.6	96.8	145.0	4.3	107.2
750	6.6	2.9	103.9	30.6	15.3	0.6	128.0	86.6	144.4	4.2	103.6

Table. Absolute (sex) organ weight of males

Dose (mg/kg)	0	150	350	750	(+)	satellite	
						0	750
Testes(g)	3.040	3.285	3.332	3.203		3.337	3.208
Epididymis(g)	1.258	1.290	1.370	1.300		1.388	1.335
Liver (g)	10.698	11.142	10.698	10.010		11.139	10.736
Thymus(g)	0.355	0.307	0.356	0.320		0.310	0.297
Kidneys(g)	2.364	2.272	2.502	2.385		2.397	2.474
Adrenals(g)	0.061	0.064	0.062	0.068		0.053	0.055
Spleen(g)	0.632	0.725	0.783	0.794		0.844	0.716
Brain(g)	1.985	1.947	2.022	1.910		2.064	2.018
Heart(g)	1.325	1.244	1.282	1.182		1.411	1.382

Table. Absolute organ weight of females

Dose (mg/kg)	0	150	350	750	(+)	satellite	
						0	750
Liver(g)	6.947	6.886	7.298	7.431		6.855	6.621
kidneys(g)	1.460	1.451	1.433	1.500		1.523	1.509
adrenals(g)	0.071	0.073	0.073	0.072		0.057	0.066
Thymus (g)	0.106	0.140	0.161	0.096		0.298	0.291
Brain (g)	1.884	1.885	1.883	1.855		1.742	1.870
Spleen (g)	0.397	0.419	0.494	0.476		0.477	0.472
Heart (g)	0.818	0.809	0.853	0.767		0.876	0.829

Table. Hematology of males (group mean)

Group	WBC (10^3/mm^3)	RBC (10^6/mm^3)	HGB (g/dl)	HCT (%)	PLT (10^3/mm^3)
C	11.2	8.0	15.4	43.2	910.6
T1	13.6	7.7	15.3	41.7	999.2
T2	13.7	7.3	14.7	40.3	1,092.0
T3	13.1	7.3	14.7	41.0	1,100.0

Table. Hematology of males - Recovery (group mean)

Group	WBC (10^3/mm^3)	RBC (10^6/mm^3)	HGB (g/dl)	HCT (%)	PLT (10^3/mm^3)
C	13.2	7.8	15.1	41.4	917.0
T3	13.7	7.8	15.4	42.9	915.2

Table. Histopathological findings of males (Group)

Group	C	T1	T2	T3
Test article	-- 4-Methylbenzenesulfonyl Chloride --			
Dose level (mg/kg/day)	0	150	350	700
No. of animals examined	5	0	0	0
Observation(s)	No. of animals observed			
No significant findings	2	4	4	3
Liver: focal necrosis, minimal	0	0	0	1
Nongrandular stomach: epithelial proliferation and vacuolation				
Minimal	0	2	0	0
Moderate	0	3	0	0
Marked	0	0	5	5
Nongrandular stomach: hyperkeratosis				
Minimal	0	3	0	0
Slight	0	2	5	5
Nongrandular stomach: submucosal edema				
Minimal	0	0	0	1

Slight	0	0	4	4
Moderate	0	3	1	0
Nongrandular stomach: inflammation				
Slight	0	3	5	5
No. of animals examined (reproductive organs)	12	12	12	12
Observation(s)	No. of animals observed			
No significant findings	10	12	12	10
Testes: atrophy and degeneration of seminiferous tubules				
Minimal	0	0	0	1
Moderate	2	0	0	0
Marked	0	0	0	1
Epididymides: oligospermia				
Minimal	1	0	0	0
Marked	1	0	0	1

Table. Histopathological findings of females (Group)

Group	C	T1	T2	T3
Test article	-- 4-Methylbenzenesulfonyl Chloride --			
Dose level (mg/kg/day)	0	100	300	1,000
No. of animals examined	5	5	5	5
Observation(s)	No. of animals observed			
No significant findings	5	1	0	0
Liver: focal necrosis				
Minimal	0	0	0	0
Heart: inflammatorycell foci				
Minimal	1	0	0	0
Nongrandular stomach: epithelial proliferation and vacuolation				
Minimal	0	1	1	1
Slight	0	2	3	3
Moderate	0	0	1	1
Nongrandular stomach: hyperkeratosis				
Minimal	0	1	3	1
Slight	0	0	2	3
Moderate	0	0	0	1
Nongrandular stomach: submucosal edema				
Slight	0	1	1	1
Nongrandular stomach: inflammation				
Minimal	0	1	2	3
No. of animals examined (reproductive organ)	12	12	10	9
Observation(s)	No. of animals observed			
No significant findings	12	12	10	9

Conclusion	:	There were several specific opinions about test items such as clinical symptoms, body weight change, food consumption, reflex action, and etc. under the influence of the test substance. In case of male animals, the test substance did affect the some clinical signs such as intermittent (blood-like) salivation and staining around mouth. at dose level 150 mg/kg/day. In case of female animals, some clinical signs were also observed at the dose level of 150 mg/kg/day since there such as intermittent (blood-like) salivation, staining around mouth, difficulty delivery, poor nursing, and irregular respiration. Moreover, at the dose level of 150 mg/kg/day, the digestive system and nongrandular stomach were also affected for both sexes. Therefore, the LOAEL was determined as 150 mg/kg/day for both sexes. In addition, the NOAEL for both sexes were considered to be below the lowest tested dose 150 mg/kg/day because up to the lowest tested dose level (150 mg/kg/day), the NOAEL was not established .
Reliability	:	(1) Reliable without restrictions
Flag	:	Critical study for SIDS endpoint
Reference	:	(18)

5. 5 GENETIC TOXICITY *IN VITRO*

A. BACTERIAL TEST

Type	:	Bacterial reverse mutation assay
Species/Strain	:	*Salmonella typhimurium* (strains TA 98, TA 100, TA 1535, and TA 1537), and *Escherichia coli* WP2 *uvr*A
Method	:	OECD TG 471, 472
System of testing	:	Bacterial
Year	:	2003
GLP	:	Yes
Metabolic activation	:	- Species and cell type: Rat (Sprague-Dawley strain), liverhomogenate - Quantity: 10 % v/v S-9 in the S-9 mix - Induced: Aroclor-1254 induced
Concentrations tested	:	With 10 % S9 mix: 79, 157, 313, 625, and 1250 μg/ Plate Without 10 % S9 mix: 313, 625, 1,250, 2,500 and 5,000 μg/ Plate
Statistical Methods	:	Student t-test
Test substance	:	Other TS: 4-Methylbenzenesulfonyl chloride, purity = 99.7 %, Sigma-Aldrich Corporation, LOT No. – 422308/1
Test condition	:	Number of replicates: one Frequency of dosing: 3 plates/dose Positive and negative control groups and treatment: Negative control-solvent control (0.1 % Dimethyl sulfoxide (DMSO)), positive control: 2-aminoanthracene (2-AA) with S9, 2-nitrofluorene (2-NF), Sodium azide (SA), Sodium azide (SA), 9-aminoacridine (9AA), 4-Nitroquinone N-oxide (4-NQO) Number of metaphases analyzed: Not analyzed Solvent: Dimethyl sulfoxide, and sterile distilled water *Description of follow up repeated study*: Preliminary test had carried out to decide the appropriate starting dose level of the main study at the concentrations of 0, 313, 625, 1,250, 2,500 and 5,000 μg/plate using TA100 with/without S9 mix. *Criteria for evaluating results*: The number of revertant colonies in the plate was counted after 2 day-incubation at 37 °C.

Results :

Cytotoxicity conc
With metabolic activation: not observed
Without metabolic activation: not observed

Genotoxic effects
With metabolic activation: showed negative at the nominal concentrations with *Salmonella tryphimurium* (strains TA 98, TA 100, TA 1535, and TA 1537), and *Escherichia coli* WP2 *uvr*A.
Without metabolic activation: showed negative at the nominal concentrations with *Salmonella tryphimurium* (strains TA 98, TA 1535, and TA 1537), and *Escherichia coli* WP2 *uvr*A. However, there was a positive result in TA100 with serial concentrations of 1,250, 2,500 and 5,000 μg/plate because the number of revertant colonies in the plate was increased significantly as compared with that of the negative control group.

Table. In vitro reverse mutation study of 4-Methylbenzenesulfonyl chloride using Salmonella tryphimurium, and Escherichia coli without S9 mix (Group summary)

Dose (μg/plate)	Number of revertants/plate (mean±S.D., n=3)				
	Bsae-pair substitution type			Frame-shift type	
	TA100	TA1535	WP2 *uvr*A(pKM101)	TA98	TA1537
0	173 ± 6	19 ± 2	136 ± 8	37 ± 6	19 ± 2
313	171 ± 9	19 ± 3	131 ± 2	40 ± 3	17 ± 1
625	175 ± 8	21 ± 2	126 ± 6	41 ± 8	19 ± 2
1,250	247 ± 23	20 ± 1	127 ± 5	41 ± 4	19 ± 3
2,500	353 ± 7	20 ± 2	133 ± 11	41 ± 6	21 ± 1
5,000	442 ± 25	19 ± 2	127 ± 10	42 ± 6	20 ± 1
Positive control	582 ± 29	702 ± 18	615 ± 18	484 ± 14	514 ± 25

Strain	: Positive control	Concentration
TA100	: Sodium azide (SA)	1.5 (μg/plate)
TA1535	: Sodium azide (SA)	1.5 (μg/plate)
WP2 *uvr*A (pKM101)	: 4-nitroquinoline N-oxide (4NQO)	5.0 (μg/plate)
TA98	: 2-nitrofluorene (2NF)	5.0 (μg/plate)
TA1537	: 9-amino acridine (9-AA)	80 (μg/plate)

Table. In vitro reverse mutation study of 4-Methylbenzenesulfonyl chloride using Salmonella tryphimurium, and Escherichia coli with S9 mix (Group summary)

Dose (μg/plate)	Number of revertants/plate (mean±S.D., n=3)				
	Bsae-pair substitution type			Frame-shift type	
	TA100	TA1535	WP2 *uvr*A(pKM101)	TA98	TA1537
0	220 ± 7	19 ± 1	126 ± 5	44 ± 6	21 ± 1
79	225 ± 8	19 ± 2	135 ± 8	41 ± 3	19 ± 2
157	224 ± 9	19 ± 3	131 ± 6	41 ± 3	18 ± 2
313	224 ± 6	17 ± 1	127 ± 8	42 ± 1	20 ± 1
625	223 ± 7	19 ± 1	129 ± 1	40 ± 3	19 ± 0
1,250	182 ± 8	16 ± 1	115 ± 3	29 ± 6	16 ± 1
Positive control	591 ± 14	177 ± 15	589 ± 7	476 ± 21	182 ± 7

Strain	: Positive control	Concentration
TA100	: 2-aminoanthracene (2-AA)	1.0 (μg/plate)
TA1535	: 2-aminoanthracene (2-AA)	2.0 (μg/plate)
WP2 *uvr*A (pKM101)	: 2-aminoanthracene (2-AA)	2.0 (μg/plate)
TA98	: 2-aminoanthracene (2-AA)	1.0 (μg/plate)
TA1537	: 2-aminoanthracene (2-AA)	2.0 (μg/plate)

Conclusion	:	As a result, 4-Methylbenzenesulfonyl chloride could induce mutagenic effects in TA100 strain (Base-change type) without metabolic activation.
Reliability	:	(1) Reliable without restrictions
Flag	:	Critical study for SIDS endpoint
Reference	:	(19)

B. NON-BACTERIAL TEST

5. 6 GENETIC TOXICITY *IN VIVO*

Type	:	Mammalian erythrocyte micronucleus test
Species/Strains	:	Mouse/ICR
Sex	:	Male
Method	:	OECD TG No.474 “Genetic Toxicity: Micronucleus Test” - 4-Methylbenzenesulfonyl chloride was dissolved in corn oil. - To observe the cell multiplication of bone mallow, a specimen was fixed with methanol for 10 minutes. Giemsa solution (5 %) and 0.004 % citric acid were used for dyeing and washing, respectively, to observe the ratio of polychromatic erythrocytes.
Year	:	2003
GLP	:	Yes
Route of administration	:	I.P
Dose	:	20, 40, 80 mg/kg b.w
Exposure period	:	24 hours per dose
Statistical methods	:	Chi-squire test
Exposure period	:	24 hours
Test substance	:	Other TS: 4-Methylbenzenesulfonyl chloride, purity = 99.7 %, Sigma-Aldrich Corporation, LOT No. – 422308/1
Test condition	:	- Age at study initiation: 8 weeks - No. of animals per dose: 6 - Vehicle: Corn oil - Duration of test: 3 days - Frequency of treatment: single treatment per day - Sampling times and number of samples: 24 hours after the administration - Control groups and treatment: Negative control (Corn oil), Positive control (2 mg/kg of Mitomycin C); negative control was administered once a day for 3 days but positive control was administered once on the day 3 of administration. - Clinical observations performed: It was observed for 4 hours after the administration then once a day from day 1 for 4 days. - Organs examined at necropsy: not examined - Criteria for evaluating results: at least 2,000 polychromatic erythrocytes per animals were scored for the incidence of micronuclei. - Criteria for selection of maximum tolerated dose (M.T.D): preliminary test had conducted with 100, 200, 500, 1,000, and 2,000 mg/kg b.w. to determine appropriate starting dose level.

Results	:	No death was observed in relation to the treatments. In the 80 mg/kg treatment group, some clinical symptoms such as pioerection and soft stool were observed on the day 3 and 4. On the day 4, body weights were decreased significantly in the both 40 and 80 mg/kg treatment groups as compared with those of the control group. MNPCE frequence in the treatment groups was in the normal range in contrast with that of the control group and vice verse for the positive control groups. In addition, PCE/(PCE+NCE) ratio was greater than 0.2, so it did not have cytotoxicity.

Table. Effect on mitotic index or PCE/NCE ratio by dose level

Dose (mg/kg)	Group mean (PCE/(PCE+NCE)) (%)	Group mean frequency of MNPCE
Vehicle	0.70	2.8 (1.3
20	0.69	2.3 (1.0
40	0.65	4.0 (2.3
80	0.53	2.2 (1.2
Positive control (2 mg/kg)	0.53	143.0 (14.8

Genotoxic effects	:	Negative - Statistical results: only positive control group showed statistically increased frequency of micronucleated cells.
Conclusion	:	All things being considered, 4-Methylbenzenesulfonyl chloride showed negative result in the micronucleus test *in vivo* up to the test concentration of 80 mg/kg.
Reliability	:	(1) Reliable without restrictions
Flag	:	Critical study for SIDS endpoint
Reference	:	(24)

5. 7 CARCINOGENICITY

5. 8 TOXICITY TO REPRODUCTION

Species/strains	:	Rat (Sprague-Dawley)
Sex	:	Male/Female
Method	:	OECD TG No. 422 “Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test”
Year	:	2003
GLP	:	Yes
Route of administration	:	Gavage
Dose level	:	According to the preliminary test (Report No. P104), dose level was determined as 0, 150, 350 and 750 mg/kg/day.
Exposure period	:	34, 36 - 45, and 51 days for male, copulated female and not copulated female rats, respectively.
Frequency of treatment	:	Daily
Control group	:	Yes (concurrent no treatment)
Post exposure observation period	:	
Premating exposure period	:	2 weeks

Statistical methods	:	Statistical decision tree, but in case of recovery group, either two-side Student's t-test or two-side Aspin-Welch t-test was used. In case of categorical data, two-sided Fisher's exact test was used.
Test substance	:	Other TS: 4-Methylbenzenesulfonyl chloride, purity = 99.7 %, Fluka, Lot No. - 422308/1
Test condition	:	**Test organism** - Sex: male/female - Age of animals at study: 9 weeks old for males and females - Weight at study repeated dose toxicity: 325.8 - 363.1 g for males and 198.5 - 229.3 g for females - Number of test animals: 60 animals for each sex **Observation of F0** - *A number of implantation and corpus luteum*: While female rats were necropsied, the number of corpus leteum and implantation were counted; and the former was measured in the ovary and the latter was measured in the uterus. - *Mating*: Each male and female rat was selected from the same test group in order to copulate. It spent 14 days in terms of mating. The day after the copulating, mating would be determined through the observation of sperm in a vaginal rinse. - *Pregnancy and delivery*: A period of pregnancy was calculated from mating date (day 0). - *Clinical observations performed and frequency*: Clinical symptoms were observed once a day but were observed once a week in detail; a death rate was observed twice a day and in case of animals with dying condition, they were allowed euthanasia to necropsy, if it is not possible immediately, they were refrigerated; body weight was observed once a week and just before the necropsy, but in case of pregnant females, it was measured on the day 0, 7, 14, 20 of gestation period, date of delivery, and 4 days of the lactation day; and consumption rate of fodder was observed once a week except mating period. **Observation of F1** - The number of survivors and deaths during delivery - Body weight and Survival rate: measured on the day of delivery and on the day 4 of lactation. - Sex ratio: It is determined by anogenital distance, for more than 2 mm and less than 1 mm were male and female, respectively. **Organs examined at necropsy:** - *Organ weight*: testes, epididymider (all males) liver, kidney, adrenals, thymus, spleen, brain, and heart (5 male and female rats from each test group). - *Fixation*: 22 kinds of tissues were fixed to do histopathologic tests such as testes, epididymides, ovaries, accessory sex organs for all animals, brain (including cerebrum, cerebellum and pons), spinal cord, stomach, small and large intestines (including peyer's patches), liver, kidneys, adrenals, spleen, heart, thymus, thyroid, trachea, lungs, uterus, urinary bladder, lymph nodes (cervical mesenteric), peripheral nerve (sciatic or tibial), bone marrow.
NOAEL parental	:	Above the highest tested dose (750 mg/kg/day)
NOAEL F1 Offspring	:	
NOAEL F2 Offspring	:	

Results : **Results for F0**
- *Pregnancy and delivery*: All pregnant female rats were delivered pups not exceeding three day of the expected date and no significant difference between the treatment groups and the control group. There was no significant difference between the treatment groups and the control group in terms of the number of corpus luteum and implantation. In case of the percent of pre-implantation loss, total 4 cases were discovered at the 150 mg/kg/day and 350 mg/kg/day treatment group, but no significant difference between the treatment groups and the control group. In case of the percent of post-implantation loss, 6 cases were discovered at the 150 mg/kg/day, 350 mg/kg/day, and 750 mg/kg/day treatment group, but no significant difference between the treatment groups and the control group. In conclusion, although pre and post-implantation loss were quite high, these were spontaneous for SD rats.

- *Index of copulation, fertility and gestation*: According to the result of copulation index, both 150 mg/kg/day and 350 mg/kg/day treatment groups had 100 %, and 750 mg/kg/day treatment group had 90.9 %. In case of the fertility index, the control and every treatment group had 91.7 % and 100 %, respectively. Finally, gestation index for the control group, 150 mg/kg/day, 350 mg/kg/day and 750 mg/kg/day treatment group had 100 %, 91.7 %, 83.3 % and 90.0 %, respectively. There was no significant difference between the control and treatment group in terms of copulation, fertility and gestation index. The sex mis-confirmation for new born pups in this test did not have relationship with test substance since its frequency was low and no dose-correlation.
- *Clinical signs*: In male rats, intermittent (blood-like) salivation and 3 cases of staining around mouth were observed on the day 27 for the 150 mg/kg/day treatment group. In the 350 mg/kg/day treatment group, (blood-like) salivation and staining around mouth were observed after the day 20 of administration; and 7 cases of (blood-like) staining around nose were observed after the day 21 of administration. After the day 3 of administration, intermittent soft stool and staining around anorectal region were observed for the most animals. In the 750 mg/kg/day treatment group, soft stool and staining around anorectal region for most animals; and 5 cases of loss of hair around tail region were observed after the day 3 and 14 of administration, respectively. After the day 7 and 21 of administration, (blood-like) salivation and 9 cases of staining around mouth and 9 cases of (blood-like) staining around nose for most animals were observed, respectively. In the control groups, there were no specific clinical symptoms during test period. In the 750 mg/kg/day recovery group, salivation, staining around mouth, soft stool and staining around anorectal region were not observed during the recovery period.
In female rats, after the day 15 of administration, intermittent (blood-like) salivation and 6 cases of staining around mouth; and from the day of delivery, difficult delivery, poor nursing, irregular respiration, uterus introsusception and piloerection were observed for the 150 mg/kg/day treatment group. In the 350 mg/kg/day treatment group, (blood-like) salivation and staining around mouth were observed for all animals after the day 15 of administration; and 4 cases of intermittent (blood-like) staining around nose were observed after the day 28 of administration. In addition, 2 cases of soft stool and staining around anorectal region; and a case of difficult delivery, lacrimation, and irregular respiration were found after the day 4 of administration and from the delivery to death, respectively.
In the 750 mg/kg/day treatment group, (blood-like) salivation and staining around mouth for all animals; soft stool and staining around anorectal region for all animals; and 3 cases of intermittent diarrhea were observed after the day 5, 3 and 38 of administration, respectively.
Some animals with found dead and in dying condition had symptoms such as irregular respiration, crawling position, hypoactivity, and abdominal swelling. In the control group, no specific clinical signs were observed during test period. In the recovery group, any other symptoms were not observed.

Results for F1
- *Number of pups born, viability and sex ratio*: No significant difference was observed between the treatment group and the control group at the time of the delivery and on the day 4 of the lactation. There were re-confirmed of sex ratio at the day 4 of the lactation since total 3 cases of sex were decided again.

Table. mating, fertility, gestation and viability data

DOSE: (mg/kg)	0	150	350	750
No. of mated males	12	12	12	11
Copulation index (%)	100.0	100.0	100.0	90.9
Fertility index (%)	91.7	100.0	100.0	100.0
No. of mated females	12	12	12	11
Copulation index (%)	100.0	100.0	100.0	90.9
Fertility index (%)	91.7	100.0	100.0	100.0
Gestation index (%)	100.0	91.7	83.3	90.0
No. of corpora lutea	14.9	14.5	15.1	14.1
Mean±S.D	1.1	2.5	1.7	0.9
No. of implantations	14.4	12.7	12.7	13.3
Mean±S.D	1.0	4.2	2.8	1.0
Mean % preimplantation loss	3.5	15.5	14.3	5.4
No. of embryo/fetal death	2.0	1.7	2.0	2.3
No. of live pups born	12.4	12.0	10.7	11.0
Mean±S.D	0.9	2.5	3.3	3.2
Mean pregnancy period (day)	21.7	21.8	21.8	21.9
Viability at birth pp	95.4	92.1	93.9	92.3
Viability at LD 4	99.2	97.8	88.3	99.0
Body weights of pups (g)				
Male (at birth)	6.25	5.99	6.37	5.98
LD 4	8.57	8.56	9.71	8.70
Female (at birth)	5.75	5.62	5.73	5.59
LD 4	8.03	7.98	8.59	8.21

Conclusion : There were no runt and congenital malformation under the influence of the test substance with test concentrations, so NOAEL was determined as greater than the highest tested dose (750 mg/kg/day).
Reliability : (1) Reliable without restrictions
Flag : Critical study for SIDS endpoint
Reference :

(18)

5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species/strains : Rat (Sprague-Dawley)
Sex : Male/Female
Route of administration : Oral (Gavage)
Method : OECD TG No. 422 “Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test”
Year : 2003
GLP : Yes
Dose level : According to the preliminary test (Report No. P104), dose level was determined as 0, 150, 350 and 750 mg/kg/day.
Exposure period : 34, 36 - 45, and 51 days for male, copulated female and not copulated female animals, respectively.
Frequency of treatment : Daily
Control group : Yes
Concurrent no treatment

Post exposure observation period	:	
Statistical methods	:	Statistical decision tree, but in case of recovery group, either two-side Student's t-test or two-side Aspin-Welch t-test was used. In case of categorical data, two-sided Fisher's exact test was used.
NOAEL for developmental	:	Above the highest tested dose (750 mg/kg/day)
Test condition	:	**Test organism** - Sex: male/female - Age of animals at study: 9 weeks old for males and females - Weight at study repeated dose toxicity: 325.8 - 363.1 g for males and 198.5 - 229.3 g for females - Number of test animals: 60 animals for each sex **Observation of F0** - *Mating procedure*: each male and female rat was selected from the same test group in order to copulate. It spent 14 days in terms of mating. The day after the copulating, mating would be determined through the observation of sperm in a vaginal rinse. - *Clinical observations performed and frequency*: Clinical symptoms were observed once a day but were observed once a week in detail; a death rate was observed twice a day and in case of animals with dying condition, they were allowed euthanasia to necropsy, if it is not possible immediately, they were refrigerated; body weight was observed once a week and just before the necropsy, but in case of pregnant females, it was measured on the day 0, 7, 14, 20 of gestation period, date of delivery, and 4 days of the lactation day; and consumption rate of fodder was observed once a week except mating period. **Observation of F1** - *Examination of the external surface of pups:* It was observed on the day of delivery and on the day 4 of lactation to determine abnormalities. **Organs examined at necropsy:** - *Organ weight*: testes, epididymider (all males) liver, kidney, adrenals, thymus, spleen, brain, and heart (5 male and female animals from each test group). - *Fixation*: 22 kinds of tissues were fixed to do histopathologic tests such as testes, epididymides, ovaries, accessory sex organs for all animals, brain (including cerebrum, cerebellum and pons), spinal cord, stomach, small and large intestines (including peyer's patches), liver, kidneys, adrenals, spleen, heart, thymus, thyroid, trachea, lungs, uterus, urinary bladder, lymph nodes (cervical mesenteric), peripheral nerve (sciatic or tibial), bone marrow.
Test substance	:	Other TS: 4-Methylbenzenesulfonyl chloride, purity = 99.7 %, Fluka, Lot No. - 422308/1
Results	:	**Results for F0** - *Pregnancy and delivery*: All pregnant rats were delivered not exceeding three day of the expected date and no significant difference between the treatment groups and the control group. There was no significant difference between the treatment groups and the control group in terms of the number of corpus luteum and implantation. In case of the percent of pre-implantation loss, total 4 cases were discovered at the 150 mg/kg/day and 350 mg/kg/day treatment group, but no significant difference between the treatment groups and the control group. In case of the percent of post-implantation loss, 6 cases were discovered at the 150 mg/kg/day, 350 mg/kg/day, and 750 mg/kg/day treatment group, but no significant difference between the treatment groups and the control group. In conclusion, although pre and post-implantation loss were quite high, these were spontaneous for SD rats.

- *Clinical signs*: In male rats, intermittent (blood-like) salivation and 3 cases of staining around mouth were observed on the day 27 for the 150 mg/kg/day treatment group. In the 350 mg/kg/day treatment group, (blood-like) salivation and staining around mouth were observed after the day 20 of administration; and 7 cases of (blood-like) staining around nose were observed after the day 21 of administration. After the day 3 of administration, intermittent soft stool and staining around anorectal region were observed for the most animals. In the 750 mg/kg/day treatment group, soft stool and staining around anorectal region for most animals; and 5 cases of loss of hair around tail region were observed after the day 3 and 14 of administration, respectively. After the day 7 and 21 of administration, (blood-like) salivation and 9 cases of staining around mouth and 9 cases of (blood-like) staining around nose for most animals were observed, respectively. In the control groups, there were no specific clinical symptoms during test period. In the 750 mg/kg/day recovery group, salivation, staining around mouth, soft stool and staining around anorectal region were not observed during the recovery period.
In female rats, after the day 15 of administration, intermittent (blood-like) salivation and 6 cases of staining around mouth; and from the day of delivery, difficult delivery, poor nursing, irregular respiration, uterus introsusception and piloerection were observed for the 150 mg/kg/day treatment group. In the 350 mg/kg/day treatment group, (blood-like) salivation and staining around mouth were observed for all animals after the day 15 of administration; and 4 cases of intermittent (blood-like) staining around nose were observed after the day 28 of administration. In addition, 2 cases of soft stool and staining around anorectal region; and a case of difficult delivery, lacrimation, and irregular respiration were found after the day 4 of administration and from the delivery to death, respectively.
In the 750 mg/kg/day treatment group, (blood-like) salivation and staining around mouth for all animals; soft stool and staining around anorectal region for all animals; and 3 cases of intermittent diarrhea were observed after the day 5, 3 and 38 of administration, respectively. Some animals with found dead and in dying condition had symptoms such as irregular respiration, crawling position, hypoactivity, and abdominal swelling. In the control group, no specific clinical signs were observed during test period. In the recovery group, any other symptoms were not observed.

Results for F1
- *Examination of the external surface of pups*: There were no abnormalities in the treatment groups but in the control groups, a case of runt and 2 cases of blunt-tipped tail were observed. On the day 4 of lactation, 2 cases of blunt-tipped tail were observed but no abnormalities in the treatment groups.
- *Body weight of pups*: At the time of delivery for new born male pups, no significant difference was observed for bodyweights between the control and treatment groups. On the day 4 of lactation, in the 350 mg/kg/day treatment group, bodyweights of pups increased as compared with that of the control group. However, there was no finding for female pups on the day delivery and on the day 4 of lactation in terms of bodyweight.

Table. Body weights of pups (group)

Group:	C	T1	T2	T3
Test article:	------	4-Methylbenzenesulfonyl chloride		-------
Dose level (mg/kg/day):	0	150	350	750
Unit:		g		

Group	Pup bodyweights at birth			At lactation day 4	
	Sex	Male	Female	Male	Female
C	Mean	6.25	5.75	8.57	8.03
	SD	0.60	0.66	1.26	1.18
	N	67	69	66	69
T1	Mean	5.99	5.62	8.56	7.98
	SD	0.56	0.46	1.34	1.27
	N	62	70	63	66
T2	Mean	6.37	5.73	9.71	8.59
	SD	0.90	0.80	2.17	1.57
	N	59	48	55	44
T3	Mean	5.98	5.59	8.70	8.21
	SD	0.60	0.51	0.87	0.74
	N	48	51	46	49

Table. External examination of pups (group)

Group:	C	T1	T2	T3
Test article:	------	4-Methylbenzenesulfonyl chloride		-------
Dose level (mg/kg/day):	0	150	350	750
Unit:		g		

Group	No. of animals	At birth			No. of animals	Lactation day 4		
		No. of pups examined	No. of pups	Observations		No. of pups examined	No. of pups	Observations
C	11	143	140	NGF	11	136	134	NGF
			2	BT			2	BT
			1	Runt				
T1	11	143	144	NGF	11	129	129	NGF
T2	10	116	116	NGF	9	100	100	NGF
T3	9	105	105	NGF	8	95	95	NGF

NGF: No Gross findings
BT: Blunt-tipped Tail

Reliability : (1) Reliable without restrictions

Flag : Critical study for SIDS endpoint

Reference : (18)

5.10 OTHER RELEVANT INFORMATION

A. Specific toxicities

B. Toxicodynamics, toxicokinetics

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