



Name: benzenesulfonamide / benzenesulfonamide / 98-10-2

Legal entity owner: National Institute of Health Sciences / Kawasaki / Japan

Printing date: 2018-03-12T13:58:00.524+09:00

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benzenesulfonamide

CORE

General information

Identification

SUBSTANCE: benzenesulfonamide

UUID: f596d537-c3e7-44bf-b585-e989d5d06385

Dossier UUID:

Author: Dra

Date: 2018-03-06T14:58:59.200+09:00

Remarks:

Substance name

benzenesulfonamide

Legal entity

[National Institute of Health Sciences / Kawasaki / Japan](#)

Identification of substance

Reference substance

[benzenesulphonamide / benzenesulfonamide / 98-10-2 / 202-637-1](#)

EC number

202-637-1

EC name

EC Inventory

CAS number

98-10-2

CAS name

IUPAC name

benzenesulfonamide

Role in the supply chain

Manufacturer

false

Importer

false

Only representative

false

Downstream user

false

OECD

Health Effects

Repeated dose toxicity: oral

ENDPOINT_STUDY_RECORD: Repeated dose toxicity: oral.001

UUID: 1714385f-7fdd-41bd-b111-39e3944c99e4

Dossier UUID:

Author: Dra

Date: 2018-03-07T13:57:41.457+09:00

Remarks:

Administrative data

Endpoint

short-term repeated dose toxicity: oral

Type of information

experimental study

Adequacy of study

key study

Robust study summary

true

Used for classification

false

Used for SDS

false

Reliability

1 (reliable without restriction)

Rationale for reliability incl. deficiencies

guideline study

Reliability 1

Data source

Reference

[Twenty-eight-day Repeat Dose Oral Toxicity Test of benzenesulfonamide in Rats / MHLW, Japan / study report](#)

Data access

data published

Materials and methods

Test guideline

Qualifier
equivalent or similar to

Guideline
OECD Guideline 407 (Repeated Dose 28-Day Oral Toxicity in Rodents)

Qualifier
according to

Guideline
other: Guideline for 28-Day Repeated Dose Toxicity Test in Mammalian Species (Chemical Substances Control Law of Japan)

GLP compliance
yes

Test material

Test material information
[benzenesulfonamide](#)

Specific details on test material used for the study

- Name of test material (as cited in study report): benzenesulfonamide
- Analytical purity: 99.6%
- Lot No.: GF01
- Storage condition of test material: at a cold (temperature 2-6 °C) and dark place, with airtight stopper.
- Stability under test conditions: The stability of test material was identified by analysis of the remainder.

Test animals

Species
rat
common rodent species

Strain
other: CrI:CD(SD)

Sex
male/female

Details on test animals and environmental conditions

TEST ANIMALS

- Source: Charles River Japan, Inc.
- Age at study initiation: 5 weeks old
- Weight at study initiation: male 168 g (150-177 g), female 143 g (135-152 g)
- Housing: Animals were individually housed in a metallic cage with wire mesh bottoms
- Diet: Solid feed (MR stock: Nosan Corporation) was given ad libitum.
- Water: Tap water was given ad libitum.
- Acclimation and quarantine period: 7-8 days

ENVIRONMENTAL CONDITIONS

- Temperature (°C): 22.0-22.8 °C
- Humidity (%): 53-62%

- Air changes (per hr): 10 or more
- Photoperiod (hrs dark / hrs light): 12 hr dark/12 hr light (light: 7:00~19:00)

Administration / exposure

Route of administration

oral: gavage

Vehicle

methylcellulose

Analytical verification of doses or concentrations

yes

Duration of treatment / exposure

28 days

Frequency of treatment

once a day

Doses / concentrations

Dose / conc.	
0	mg/kg bw/day (actual dose received)
Dose / conc.	
6	mg/kg bw/day (actual dose received)
Dose / conc.	
30	mg/kg bw/day (actual dose received)
Dose / conc.	
150	mg/kg bw/day (actual dose received)

No. of animals per sex per dose

10/sex (0, 150 mg/kg bw/day)

5/sex (16, 30 mg/kg bw/day)

Control animals

yes, concurrent vehicle

Details on study design

- Dose selection rationale: Doses in this test were set based on the results of the following study: 14-day repeated dose oral toxicity test (CrI:CD(SD) rats, doses: 0 (olive oil), 2, 6, 20, 60, or 200 mg/kg bw/day). At 60 mg/kg/day and higher, increased relative liver and kidney weights and changes in blood chemistry were observed. At 200 mg/kg bw/day, changes in body weight were observed. On the basis of these effects, a dose level of 150 mg/kg was selected as the maximum dose expecting to

induce the toxic changes, while a dose level of 6 mg/kg bw/day was selected as the lowest dose expected to induce no toxicological effects. A dose level of 30 mg/kg bw/day was selected as a middle dose.

- Rationale for animal assignment (if not random): Body weight-balanced randomization
- Post-exposure recovery period in satellite groups: 14 days

Examinations

Observations and examinations performed and frequency

LINICAL OBSERVATIONS: Yes

- Time schedule: every day during the administration period (4 times a day) and the recovery period (at least once a day)

DETAILED CLINICAL OBSERVATIONS: Yes

The functional observational battery testing (FOB) was performed on all animals. Among the measures in the FOB, detailed clinical observations were made before the initiation of dosing. Thereafter, detailed clinical observations were made once a week in dosing and recovery periods.

Sensory motor reflexes, forelimb and hindlimb grip strengths, and motor activity were measured on week 4 of administration period (main/recovery group animals) and week 2 of recovery period (recovery group animals).

BODY WEIGHT: Yes

- Time schedule for examinations: Before administration (on days 1, 7, 14, 21 and 28 of the administration period, days 7 and 14 of the recovery period) and the necropsy days after completion of every period.

FOOD CONSUMPTION AND COMPOUND INTAKE (if feeding study):

- Food consumption: Yes. Once a week for 24-h (males: on days 5, 12, 19 and 26 of the administration period and days 5 and 12 of the recovery period. females: on days 4, 11, 18 and 25 of the administration period and days 4 and 11 of the recovery period)

OPHTHALMOSCOPIC EXAMINATION: No

HAEMATOLOGY: Yes

- Time schedule for collection of blood: the after completion of the administration and recovery periods
- Anaesthetic used for blood collection: ether
- Animals fasted: Yes (overnight)
- How many animals: all animals

CLINICAL CHEMISTRY: Yes

- Time schedule for collection of blood: the day after completion of the administration and recovery periods
- Anaesthetic used for blood collection: ether
- Animals fasted: Yes (overnight)
- How many animals: all animals

URINALYSIS: Yes

- Time schedule for collection of urine: on weeks 4 of the administration period and weeks 2 of the recovery period.
- Metabolism cages used for collection of urine: Yes

NEUROBEHAVIOURAL EXAMINATION: No

Sacrifice and pathology

GROSS PATHOLOGY: Yes

ORGAN WEIGHT: Yes [brain, pituitary gland, thyroid, adrenal, spleen, heart, liver, kidney, thymus, testis, epididymis, ovary]

HISTOPATHOLOGY: Yes [brain (cerebrum, cerebellum and medulla oblongata), pituitary gland, spinal cord (cervical, thoracic, lumbar), thymus, thyroid (including parathyroid), adrenal glands, spleen, heart, stomach, liver, duodenum, jejunum, ileum (including Peyer's patches), cecum, colon, rectal, mesenteric lymph nodes, submandibular lymph nodes, trachea, lung, kidney, bladder, testis, epididymis, prostate, seminal vesicles, ovary, uterus, vagina, eye, bone marrow (femur) and the sciatic nerve.

Statistics

As for parametric data (grip strength, locomotor activity, body weight, body weight gain, food consumption, hematology and clinical chemistry data, organ weights), the values of means and standard deviations were calculated per group. When more than three groups exist in the test group, Bartlett test for variance was done, and if the variance was homogenous, ANOVA was applied. If the variance was not homogenous or data was non-parametric (differential WBC percentage, urinalysis data), Kruskal-Wallis rank sum test was used. Consequently, if the result was significant, Dunnett multiple comparison or Dunnett-typed method was used for detection of statistical significance against control group. When the number of the test group was two, F-test was used as for parametric data. Then, student's t-test or Aspin-Welch's t-test was applied depending on the result of homogeneity of variance. While, as for non-parametric data, Man-Whitney's U-test was applied. Furthermore, as for categorized data (incidence of abnormal findings in clinical observation, detailed observation, sensory functional examination, necropsy and histopathology), Fischer's exact test was used. In any tests, level of significance was set at 5%.

Results and discussion

Results of examinations

Clinical signs

effects observed, treatment-related

Description (incidence and severity)

At 150 mg/kg bw/day, one male died on day 21. This animal showed decrease in locomotor activity, pale skin, prone position, and convulsion. Decreased locomotor activity was also observed in 4 out of 9 males and one out of 10 females at 150 mg/kg bw/day. Transient salivation was also observed at this dose.

Mortality

mortality observed, treatment-related

Description (incidence)

At 150 mg/kg bw/day, one male died on day 21.

Body weight and weight changes

effects observed, treatment-related

Description (incidence and severity)

Body weight and body weight gain were significantly decreased at 30 mg/kg bw/day and higher in both sexes. After the recovery period, body weight was still significantly low, but body weight gain was significantly increased.

Food consumption and compound intake (if feeding study)

effects observed, treatment-related

Description (incidence and severity)

Food consumption was significantly decreased at 6 mg/kg bw/day and higher in males and 30 mg/kg bw/day and higher in females.

Haematological findings

effects observed, treatment-related

Description (incidence and severity)

At the end of the administration period, no effects were observed. Decreased Hb and Ht were observed at the end of the recovery period. These effects were considered to be due to low food consumption and low body weight.

Clinical biochemistry findings

effects observed, treatment-related

Description (incidence and severity)

At 150 mg/kg bw/day, significantly high values of ALT, T-Cho, and T-Bil in males, and significantly high values of BUN and T-Cho in females were observed. At the end of the recovery period, there were significantly decreased Alb and Crea in both sexes, and significantly increased ALT and decreased Glu and BUN in males. These changes observed at the end of the administration period tended to recover.

Urinalysis findings

no effects observed

Organ weight findings including organ / body weight ratios

effects observed, treatment-related

Description (incidence and severity)

Absolute weights of the heart and pituitary gland in both sexes, spleen and epididymis in males, and brain in females were significantly decreased due to low body weights at 150 mg/kg bw/day. Relative weights of the brain were increased in males at 30 and 150 mg/kg bw/day and in females at 150 mg/kg bw/day. Relative weights of the heart, liver, and kidney in both sexes and adrenal gland and testis in males were also significantly increased at 150 mg/kg bw/day. These changes observed at the end of the administration period tended to recover.

Gross pathological findings

no effects observed

Histopathological findings: non-neoplastic

effects observed, treatment-related

Description (incidence and severity)

Mineralization of the lung alveolar septa and kidney papilla/pelvis was observed in both sexes at 150 mg/kg bw/day. Hypertrophy of the centrilobular hepatocytes was observed in both sexes at 150 mg/kg bw/day. Hyaline droplet of the proximal tubular epithelium in the kidney observed in male animals at 30 mg/kg bw/day and higher were considered to be male rat-specific α -2u globulin nephropathy. Hyperplasia of transitional cells in the urinary bladder was observed at 30 mg/kg bw/day and higher in both sexes. Sulfonamides are known to produce urinary bladder hyperplasia, but the effect is specific to rats due to urinary composition. At the end of the recovery period, all of the changes except mineralization in the lung had resolved or showed a tendency to resolve.

Effect levels**Key result**

false

Dose descriptor

NOAEL

Effect level

6

mg/kg bw/day (actual dose received)

Based on

act. ingr.

Sex

male/female

Basis for effect level

body weight and weight gain

Male and female rats administered 30 and 150 mg/kg bw/day showed significantly decreased body weight.

food consumption and compound intake

Male and female rats administered 30 and 150 mg/kg bw/day showed significantly decreased food consumption.

histopathology: non-neoplastic

changes in the urinary bladder were observed at 30 mg/kg bw/day

Target system / organ toxicity**Key result**

false

Critical effects observed

yes

Lowest effective dose / conc.

30 mg/kg bw/day (nominal)

Organ

bladder

Treatment related

yes

Dose response relationship

yes

Any other information on results incl. tables

Figures and Tables (in English) are available in the following full report of the study.

http://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF98-10-2b.pdf

Applicant's summary and conclusion**Executive summary**

A repeated-dose 28-day oral toxicity study was performed in accordance with the Japanese guidelines (similar to OECD TG 407). Male and female rats (5 or 10 animals/sex/dose) were administered benzenesulfonamide for 28 days at 0 (vehicle:1 w/v% methyl cellulose solution), 6, 30, and 150 mg/kg bw/day. Five out of 10 males with this administration at 0 and 150 mg/kg bw/day were used as a recovery assessment group and examined after a 14-day recovery period. At 150 mg/kg bw/day, one male died and decrease in locomotor activity was observed in both sexes during the administration period. Male and female rats administered 30 and 150 mg/kg bw/day showed significantly decreased food consumption and body weight. Upon the administration of benzenesulfonamide at 150 mg/kg bw/day, the following effects on the liver were also observed in both sexes: significantly increased relative organ weight with centrilobular hypertrophy and changes in blood chemical parameters. Mineralization was observed in the kidney and lung at 150 mg/kg bw/day in both sexes. Moreover, hyperplasia of

transitional cells in the urinary bladder was observed at 30 mg/kg bw/day and higher in both sexes. Sulfonamides are known to produce urinary bladder hyperplasia, but the effect is specific to rats due to urinary composition. At the end of the recovery period, all of the changes except mineralization in the lung had resolved or showed a tendency to resolve. Based on decreases in food consumption and body weight and histopathological changes in the urinary bladder at 30 mg/kg bw/day, the NOAEL of the repeated-dose toxicity was determined to be 6 mg/kg bw/day for male and female rats.

Genetic toxicity in vitro

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.001

UUID: e8c3ace4-eb02-488a-a13f-f7add8d8aca7

Dossier UUID:

Author: Dra

Date: 2018-03-07T10:26:07.909+09:00

Remarks:

Administrative data

Endpoint

in vitro gene mutation study in bacteria

Type of information

experimental study

Adequacy of study

key study

Robust study summary

true

Used for classification

false

Used for SDS

false

Reliability

1 (reliable without restriction)

Rationale for reliability incl. deficiencies

guideline study

Reliability 1

Data source

Reference

[Reverse mutation test of benzenesulfonamide in Bacteria / MHLW, Japan / study report](#)

Data access

data published

Materials and methods

Test guideline

Qualifier

according to

Guideline

OECD Guideline 471 (Bacterial Reverse Mutation Assay)
in vitro gene mutation study in bacteria

Qualifier

according to

Guideline

JAPAN: Guidelines for Screening Mutagenicity Testing Of Chemicals
genetic toxicity in vitro, other

GLP compliance

yes

Type of assay

bacterial reverse mutation assay
in vitro gene mutation study in bacteria

Test material

Test material information

[benzenesulfonamide](#)

Specific details on test material used for the study

- Name of test material (as cited in study report): benzenesulfonamide
- Analytical purity: 99.2%
- Lot/batch No.:EWG6537 (Wako)
- Stability under test conditions: Stable
- Storage condition of test material: dark place at room temperature (21.1-25.3 C degree)

Method

Species / strain**Species / strain**

S. typhimurium TA 1535, TA 1537, TA 98, TA 100 and E. coli WP2
bacteria

Metabolic activation

with and without

Metabolic activation system

rat liver, induced by phenobarbital and 5,6-benzoflavone

Test concentrations with justification for top dose

Dose-range finding test (-S9 mix and +S9 mix): 0 (vehicle), 1.22, 4.88, 19.5, 78.1, 313, 1250, and 5000 µg/plate

In range-finding studies, growth inhibition was not observed on all plates with concentration of up to 5000 µg/plate with/without metabolic activation.

Main bacterial reverse mutation test (-S9 mix and +S9 mix): 0 (vehicle), 313, 625, 1250, 2500, and 5000 µg/plate

Vehicle

- Vehicle(s)/solvent(s) used: DMSO
- Justification for choice of solvent/vehicle: The test substance was soluble in DMSO, but not in water.

Controls

Negative controls

yes

Solvent controls

yes

Positive controls

yes

Positive control substance

9-aminoacridine

(9-aminoacridine acid), -S9 mix, TA1537

sodium azide

-S9 mix, TA1535

other: 2-aminoanthracene (+S9 mix, all strains), 2-methoxy-6-chloro-9-[3-(2-chloroethyl)-aminopropylamino]acridine-2HCl, -S9mix TA100, WP2, TA98

Details on test system and conditions

METHOD OF APPLICATION: Preincubation

The mixtures were incubated at 37 C degree with shaking (90 times/min).

DURATION

- Preincubation period: 20 min

- Exposure duration: 48 hours

NUMBER OF REPLICATIONS: 3

DETERMINATION OF CYTOTOXICITY

- Method: Cell growth

Evaluation criteria

Criteria for determining a positive result were as follows; A 2-fold or more increase in the number of revertant colonies compared with the solvent control, a concentration-related increase in the number of revertant colonies, and a reproducible increase in the number of revertant colonies.

Statistics

No statistic method was used for judging of results.

Results and discussion

Test results

Key result

false

Species / strain

S. typhimurium TA 1535

bacteria

Metabolic activation

with and without

Genotoxicity

negative

Cytotoxicity

no, but tested up to limit concentrations

Vehicle controls valid

yes

Negative controls valid

yes

Positive controls valid

yes

Key result

false

Species / strain

S. typhimurium TA 1537
bacteria

Metabolic activation

with and without

Genotoxicity

negative

Cytotoxicity

no, but tested up to limit concentrations

Vehicle controls valid

yes

Negative controls valid

yes

Positive controls valid

yes

Key result

false

Species / strain

S. typhimurium TA 98
bacteria

Metabolic activation

with and without

Genotoxicity

negative

Cytotoxicity

no, but tested up to limit concentrations

Vehicle controls valid

yes

Negative controls valid

yes

Positive controls valid

yes

Key result

false

Species / strain

S. typhimurium TA 100
bacteria

Metabolic activation

with and without

Genotoxicity

negative

Cytotoxicity

no, but tested up to limit concentrations

Vehicle controls valid

yes

Negative controls valid

yes

Positive controls valid

yes

Key result

false

Species / strain

E. coli WP2 uvr A pKM 101
bacteria

Metabolic activation

with and without

Genotoxicity

negative

Cytotoxicity

no, but tested up to limit concentrations

Vehicle controls valid

yes

Negative controls valid

yes

Positive controls valid

yes

Additional information on results

TEST-SPECIFIC CONFOUNDING FACTORS

- Precipitation: Precipitation was not observed on any plates with/without metabolic activation.

COMPARISON WITH HISTORICAL CONTROL DATA:

In all test conditions and in all tested strains, the number of revertant colonies of solvent controls and positive controls were within the range of historical control data.

Any other information on results incl. tables _____

Figures and Tables (in Japanese) are available in the following full report of the study.http://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF98-10-2e.pdf

Applicant's summary and conclusion

Conclusions

Interpretation of results: Negative

Executive summary

In a bacterial reverse mutation assay using *S. typhimurium* TA100, TA1535, TA98, and TA1537 and *E. coli* WP2uvrA (OECD TG 471), benzenesulfonamide was negative with or without metabolic activation.

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.002

UUID: 2fde2394-2aba-4eeb-ab5a-acaf0d8feae

Dossier UUID:

Author: Dra

Date: 2018-03-07T11:08:01.507+09:00

Remarks:

Administrative data

Endpoint

in vitro cytogenicity / chromosome aberration study in mammalian cells

Type of information

experimental study

Adequacy of study

key study

Robust study summary

true

Used for classification

false

Used for SDS

false

Reliability

1 (reliable without restriction)

Rationale for reliability incl. deficiencies

guideline study

Reliability 1

Data source

Reference

[In Vitro Chromosomal Aberration Test of benzenesulfonamide on Cultured Chinese Hamster Cells. / MHLW, Japan / study report](#)

Materials and methods

Test guideline

Qualifier

according to

Guideline

OECD Guideline 473 (In Vitro Mammalian Chromosome Aberration Test)
in vitro cytogenicity / chromosome aberration study in mammalian cells

Qualifier

according to

Guideline

JAPAN: Guidelines for Screening Mutagenicity Testing Of Chemicals
genetic toxicity in vitro, other

GLP compliance

yes

Type of assay

in vitro mammalian chromosome aberration test
in vitro cytogenicity / chromosome aberration study in mammalian cells

Test material

Test material information

[benzenesulfonamide](#)

Specific details on test material used for the study

- Name of test material (as cited in study report): benzenesulfonamide
- Analytical purity: 99.2%
- Lot/batch No.:EWG6537 (Wako)
- Stability under test conditions: Stable
- Storage condition of test material: dark place at room temperature (21.1-25.3 C degree)

Method

Target gene

Chromosome

Species / strain**Species / strain**

other: Chinese hamster lung(CHL/IU) cells

Metabolic activation

with and without

Metabolic activation system

rat liver, induced by phenobarbital and 5,6-benzoflavone

Test concentrations with justification for top dose

+/-S9 mix (short-term treatment): 0, 100, 200, 400, 800, 1600 µg/mL

-S9 mix (continuous treatment): 0, 100, 200, 400, 800, 1600 µg/mL

Test concentrations were set based on the following results of a preliminary study:

short term treatment (-S9): growth inhibition was not observed at 5000 µg/mL

short term treatment (+S9): growth inhibition was not observed at 5000 µg/mL

continuous treatment (-S9): growth inhibition was not observed at 500 µg/mL, but 90% growth inhibition was observed at 5000 µg/mL

According to the Guideline, the maximum concentration was set at 10 mmol/L (1600 ug/mL).

Vehicle

- Vehicle(s)/solvent(s) used: DMSO

- Justification for choice of solvent/vehicle: The test substance was soluble in DMSO, but not in water.

Controls

Solvent controls

yes

Positive controls

yes

Positive control substance

benzo(a)pyrene
+S9 mix
mitomycin C
-S9 mix

Details on test system and conditions

METHOD OF APPLICATION: Exposure duration: [continuous treatment]: 24 hrs

[short-term treatment]: 6 hrs + 18 hr

SPINDLE INHIBITOR: Colcemid

NUMBER OF REPLICATIONS: 2

NUMBER OF CELLS EVALUATED: 500 cells / plate (1000 cells/concentration)

DETERMINATION OF CYTOTOXICITY

- Method: relative total growth

Evaluation criteria

For the evaluation of the frequencies of structural aberrations and of polyploidy induced, the following criteria were employed.

Appearance incidence of cells with chromosomal aberrations: Negative (-): < 5%; equivocal (±): 5-10%; positive (+): > 10%.

Finally, the substance is positive when the incidence is considered to be dose-related and reproducible.

Statistics

not used

Results and discussion

Test results**Key result**

false

Species / strain

other: Chinese hamster lung (CHL/IU) cells

Metabolic activation

with and without

Genotoxicity

negative

Cytotoxicity

no, but tested up to limit concentrations

Vehicle controls valid

yes

Positive controls valid

yes

Any other information on results incl. tables

Figures and Tables (in English) are available in the following full report of the study.

http://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF98-10-2f.pdf

Applicant's summary and conclusion

Conclusions

Interpretation of results: Negative

Executive summary

An in vitro chromosomal aberration test using CHL/IU cells (OECD TG 473) showed positive result with metabolic activation.

Toxicity to reproduction

ENDPOINT_STUDY_RECORD: Toxicity to reproduction.001

UUID: 05f7bda6-7b60-4623-befb-3860a7656a92

Dossier UUID:

Author: Dra

Date: 2018-03-07T16:37:35.809+09:00

Remarks:

Administrative data

Endpoint

screening for reproductive / developmental toxicity

Type of information

experimental study

Adequacy of study

key study

Robust study summary

true

Used for classification

false

Used for SDS

false

Reliability

1 (reliable without restriction)

Rationale for reliability incl. deficiencies

guideline study

Reliability 1

Data source

Reference

[A reproduction/developmental toxicity screening test in rats treated orally with benzenesulphonamide / MHLW, Japan / study report](#)

Data access

data published

Materials and methods

Test guideline

Qualifier

according to

Guideline

OECD Guideline 421 (Reproduction / Developmental Toxicity Screening Test)

GLP compliance

yes

Test material

Test material information

benzenesulfonamide

Specific details on test material used for the study

- Name of test material (as cited in study report): benzenesulfonamide
- Purity: 99.9%
- Lot/batch No.: FQ2GG
- Stability under test conditions: Stable
- Storage condition of test material: a cool (3-8 °C) and dark place (in a refrigerator), with an airtight stopper
- Dosing solution storage condition: under a cool (3-6 °C) place (in a refrigerator), in a brown glass bottle

Test animals

Species

rat

Strain

other: CrI:CD(SD)

Sex

male/female

Details on test animals and environmental conditions

TEST ANIMALS

- Source: Charles River Laboratories Japan, Inc. Atsugi
- Age at study initiation: 10 weeks old
- Weight at study initiation: Males: 374-509 (average 442) g; Females: 228-286 (average 260) g
- Housing: Steel wire-mesh cage (254 mm x 350 mm x 170 mm), pregnant rats were housed in a plastic Econ cage with bedding (340 mm x 400 mm x 185 mm) on GD17 and after.
- Diet: ad libitum
- Water: ad libitum
- Acclimation period: 20 days

ENVIRONMENTAL CONDITIONS

- Temperature (°C): 22-24
- Humidity (%): 49-61
- Air changes: 10-15 times / hr
- Photoperiod: 12 hrs dark / 12 hrs light (07:00-19:00)

Administration / exposure

Route of administration

oral: gavage

Vehicle

other: 1 w/v% methyl cellulose solution

Details on mating procedure

- M/F ratio per cage: 1:1
- Length of cohabitation: up to 14 days
- Proof of pregnancy: [vaginal plug / sperm in vaginal smear] referred to as [day 0] of pregnancy

Analytical verification of doses or concentrations

yes

Duration of treatment / exposure

Males were dosed for 28 days, including a 14-day pre-mating period and subsequent mating period. Females were dosed for 40–53 days, including 14-day pre-mating, mating, and gestation periods, and until lactation day 3.

Frequency of treatment

once a day

Doses / concentrations

Dose / conc.	
0	mg/kg bw/day (actual dose received)
Dose / conc.	
3	mg/kg bw/day (actual dose received)
Dose / conc.	
10	mg/kg bw/day (actual dose received)
Dose / conc.	
30	mg/kg bw/day (actual dose received)

No. of animals per sex per dose

12/sex/dose

Control animals

yes, concurrent vehicle

Details on study design

- Dose selection rationale: Doses in this test were set based on the 28-day repeated dose oral toxicity test (Repeated dose toxicity: oral.001). A dose level of 30 mg/kg was selected as the maximum dose expecting to induce the toxic changes, and then dose levels of 10 and 3 mg/kg bw/day were selected as a middle dose and a minimum dose levels, respectively, in accordance with a common ratio of 3.

- Rationale for animal assignment (if not random): Body weight-balanced randomization

Examinations**Parental animals: Observations and examinations**

AGE SIDE OBSERVATIONS: Yes

- Time schedule:

Males and females: 3 times/day

BODY WEIGHT: Yes

- Time schedule for examinations:

Males: Days 1, 8, 15, and 22 and the day of necropsy

Females: Days 1, 8, 15, and 22 during the precopulation period; gestation days 0, 7, 14, and 20; lactation days 0 and 4; and the day of necropsy.

FOOD CONSUMPTION: Yes

Males: Days 2, 8, 15 in dosing period

Females: Days 2, 8, 15; gestation days 1, 7, 14, and 20; lactation days 2 and 4

HAEMATOLOGY: No

CLINICAL CHEMISTRY: No

URINALYSIS: No

Estrous cyclicity (parental animals)

Vaginal smears were collected from all females in the main groups and microscopically examined every day from the day after the start of administration until the day copulation was confirmed.

During the pre-mating administration period, vaginal smear pictures were classified as proestrus, estrus, metestrus or diestrus and examined for the frequency of estrus and interval between estruses (estrous cycle). During the mating period, vaginal smears were examined for the presence of sperm.

Litter observations

PARAMETERS EXAMINED: The following parameters were examined in F1 offspring [number and sex of pups, stillbirths, live births, postnatal mortality, presence of gross anomalies, and weight].

GROSS EXAMINATION OF DEAD PUPS: Yes, for external abnormalities.

Postmortem examinations (parental animals)

SACRIFICE:

Male animals: Rats were euthanized by exsanguination under ether anesthesia on the day after the last administration.

Maternal animals: Rats were euthanized by exsanguination under ether anesthesia on day 4 of lactation.

GROSS PATHOLOGY: Yes

HISTOPATHOLOGY: Yes (epididymis, prostate, seminal vesicle, testis, ovary, uterus, vagina, and gross abnormal sites)

ORGAN WEIGHTS, Yes: Testes and epididymis

Statistics

The data were analyzed for homogeneity of variance by the Bartlett test. If variances were homogeneous, data was analyzed by the Dunnett test, whereas heterogeneous data was analyzed by the Steel test ($p < 0.05$, two-sided).

2 groups: The data were analyzed for homogeneity of variance by the F test. If variances were homogeneous, data was analyzed by the Student t test, whereas heterogeneous data was analyzed by the Aspin-Welch t test ($p < 0.05$, two-sided).

Especially,

Implantation index, Stillborn index, Liveborn index, External abnormalities, Viability index: the Steel test ($p < 0.05$ and < 0.01 , two-sided)

Copulation index, Fertility index, Insemination index, Delivery index: Fisher's exact test ($p < 0.05$ and < 0.01 , two-sided)

Reproductive indices

Each parameter was determined by the following equations:

Copulation index (%) = (No. of copulated animals/No. of co-housed animals) × 100

Fertility index (%) = (No. of pregnant females/No. of copulated females) × 100

Insemination index (%) = (No. of pregnant females/No. of copulated males) × 100

Duration of gestation (days) = day 0 of lactation – day 0 of gestation

Delivery index (%) = (No. of females delivered liveborn pups/No. of pregnant females) × 100

Implantation index (%) = (No. of implantation sites/No. of corpora lutea) × 100

Stillborn index (%) = (No. of stillborn pups/Total No. of pups born) × 100

Liveborn index (%) = (No. of liveborn pups/Total No. of pups born) × 100

External abnormalities (%) = (No. of pups with external abnormalities/No. of liveborn pups) × 100

Sex ratio = No. of liveborn male pups/(No. of liveborn male pups + No. of liveborn female pups)

Offspring viability indices

Viability index (%) = (No. of surviving pups on day 4 after birth/No. of liveborn pups on day 0 after birth) × 100

Results and discussion

Results: P0 (first parental animals)

General toxicity (P0)

Clinical signs

no effects observed

Mortality

no mortality observed

Body weight and weight changes

effects observed, treatment-related

Description (incidence and severity)

Body weights were significantly decreased at 30 mg/kg bw/day and body weight gain was significantly decreased at 100 mg/kg bw/day in males.

Food consumption and compound intake (if feeding study)

effects observed, treatment-related

Description (incidence and severity)

Food consumption was significantly low at 30 mg/kg bw/day in males.

Organ weight findings including organ / body weight ratios

effects observed, treatment-related

Description (incidence and severity)

Absolute and relative weights of the ovary were also significantly increased at 30 mg/kg bw/day.

Gross pathological findings

effects observed, non-treatment-related

Description (incidence and severity)

White focus in the epididymis was found in one males at 10 mg/kg bw/day.

Histopathological findings: non-neoplastic

effects observed, treatment-related

Description (incidence and severity)

Hyperplasia/hypertrophy of the transitional cells in the urinary bladder was observed at 10 and 30 mg/kg bw/day in males. In females, hyperplasia/hypertrophy of the transitional cells in the urinary bladder was observed upon administration of benzenesulfonamide at doses ≥ 3 mg/kg bw/day.

Reproductive function / performance (P0)

Reproductive function: estrous cycle

no effects observed

Reproductive performance

no effects observed

Effect levels (P0)

Key result

false

Dose descriptor

NOAEL

Effect level

30

mg/kg bw/day (actual dose received)

Based on

act. ingr.

Sex

male/female

Basis for effect level

reproductive performance
No effects on fertility

Key result

false

Dose descriptor

LOAEL

Effect level

3

mg/kg bw/day (actual dose received)

Based on

act. ingr.

Sex

male/female

Basis for effect level

histopathology: non-neoplastic
histopathological change in the urinary bladder

Results: F1 generation

General toxicity (F1)

Mortality / viability

no mortality observed

Body weight and weight changes

effects observed, treatment-related

Description (incidence and severity)

The body weights of pups on postnatal day (PND) 0 and/or 4 were found to be significantly decreased at 30 mg/kg bw/day in both sexes.

Effect levels (F1)

Key result

false

Dose descriptor

NOAEL

Generation

F1

Effect level

10

mg/kg bw/day (actual dose received)

Based on

act. ingr.

Sex

male/female

Basis for effect level

body weight and weight gain

the body weights of pups on postnatal day (PND) 0 and/or 4 were found to be significantly decreased at 30 mg/kg bw/day in both sexes.

Any other information on results incl. tables

Figures and Tables (in English) are available in the following full report of the study. http://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF98-10-2c.pdf

Applicant's summary and conclusion

Conclusions

The NOAEL for the rat reproductive/developmental toxicity of benzenesulfonamide was determined to be 10 mg/kg bw/day based on decreased pup body weights at 30 mg/kg bw/day

Executive summary

A reproduction/developmental toxicity screening test (OECD TG 421) was also performed using rats. In this study, benzenesulfonamide was administered via gavage to 12 animals/sex/dose at 0 (vehicle: 1 w/v % methyl cellulose solution), 3, 10, and 30 mg/kg bw/day. Males were dosed for 28 days, including a 14-day pre-mating period and subsequent mating period. Females were dosed for 40–53 days, including 14-day pre-mating, mating, and gestation periods, and until lactation day 3. Significantly decreased body weight and hyperplasia/hypertrophy of the transitional cells in the urinary bladder were observed at 10 and 30 mg/kg bw/day in males. In females, hyperplasia/hypertrophy of the transitional cells in the urinary bladder was observed upon administration of benzenesulfonamide at doses ≥ 3 mg/kg bw/day. Absolute and relative weights of the ovary were also significantly increased at 30 mg/kg bw/day. There were no effects on fertility, but the body weights of pups on postnatal day (PND) 0 and/or 4 were found to be significantly decreased at 30 mg/kg bw/day in both sexes. The NOAEL for the rat reproductive/developmental toxicity of benzenesulfonamide was determined to be 10 mg/kg bw/day based on decreased pup body weights at 30 mg/kg bw/day while the lowest-observed-adverse-effect level for parental general toxicity was 3 mg/kg bw/day, based on the histopathological change in the urinary bladder.

References

LITERATURE: A reproduction/developmental toxicity screening test in rats treated orally with benzensulphonamide

UUID: 344feefd-0a81-43ec-a80b-54f7a38428a1

Dossier UUID:

Author: Dra

Date: 2018-03-07T11:24:27.813+09:00

Remarks:

General information

Reference Type

study report

Title

A reproduction/developmental toxicity screening test in rats treated orally with benzensulphonamide

Author

MHLW, Japan

Year

2014

Bibliographic source

available in the web of Japan Existing Chemical Data Base (JECDB) at http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp

Testing facility

BoZo Research Center

Report no.

R-1131

TEST_MATERIAL_INFORMATION: b enzenesulfonamide

UUID: 5ef05df4-03fa-4af0-9669-2bfb6f6f6e3b

Dossier UUID:

Author: Dra

Date: 2018-03-06T15:00:30.670+09:00

Remarks:

Name

benzenesulfonamide

Composition

Reference substance

benzenesulphonamide / benzenesulfonamide / 98-10-2 / 202-637-1

EC number

202-637-1

EC name

EC Inventory

CAS number

98-10-2

CAS name

IUPAC name

benzenesulfonamide

REFERENCE_SUBSTANCE: benzene sulphonamide

UUID: ECB5-7ab84e8b-3c5d-4bed-bae6-4b4361df8447

Dossier UUID:

Author: SuperUser

Date: 2007-05-10T18:00:00.000+09:00

Remarks:

General information

Reference substance name
benzenesulphonamide

Inventory

Inventory name
benzenesulphonamide

Inventory
EC

Inventory number
202-637-1

CAS number
98-10-2

Molecular formula
C₆H₇NO₂S

Description

Reference substance information

IUPAC name
benzenesulfonamide

Synonyms

Identity Benzenesulfonamide

Identity Benzenesulfonamide

CAS information

CAS number
98-10-2

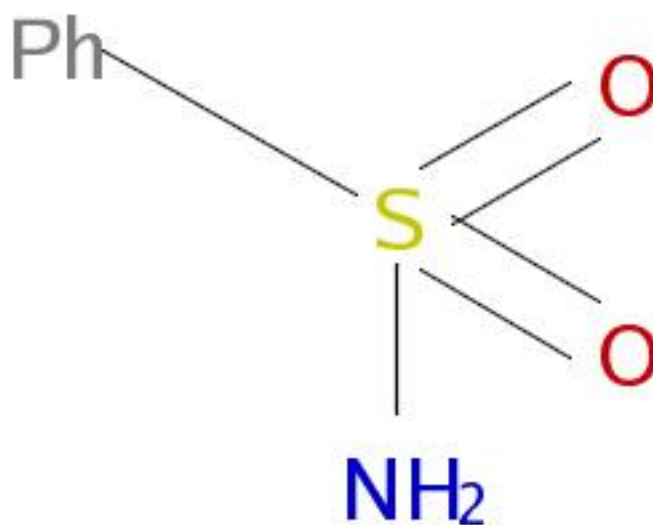
Related substances

Group / category information

DSL Category: Organics

Molecular and structural information**Molecular formula**C₆H₇NO₂S**Molecular weight**

157.1903

SMILES notationNS(=O)(=O)c1ccccc1**InChI**InChI=1/C6H7NO2S/c7-10(8,9)6-4-2-1-3-5-6/h1-5H,(H2,7,8,9)**Structural formula**

LITERATURE: In Vitro Chromosomal Aberration Test of benzenesulfonamide on Cultured Chinese Hamster Cells.

UUID: 68ce0a97-383f-4a44-b004-96474746b2c3

Dossier UUID:

Author: Dra

Date: 2018-03-07T10:16:56.538+09:00

Remarks:

General information

Reference Type

study report

Title

In Vitro Chromosomal Aberration Test of benzenesulfonamide on Cultured Chinese Hamster Cells.

Author

MHLW, Japan

Year

2007

Bibliographic source

available in the web of Japan Existing Chemical Data Base (JECDB) at http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp

Testing facility

BoZo Research Center

Report no.

B060317

LEGAL_ENTITY: National Institute of Health Sciences

UUID: IUC4-b036ff75-0f3c-323b-b200-ed5f46cf5101

Dossier UUID:

Author: Dra

Date: 2018-02-27T15:56:45.710+09:00

Remarks:

General information

Legal entity name

National Institute of Health Sciences

Identifiers

Other IT system identifiers

IT system

LEO

ID

10767

IT system

IUCLID4

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16558402024DIV750

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First name

Akihiko

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Department

Division of Risk Assessment

Title

Dr

Country

Japan

LITERATURE: Reverse mutation test of benzenesulfonamide in Bacteria

UUID: 99eda9cb-6b68-4c85-9db1-5708603fd6a8

Dossier UUID:

Author: Dra

Date: 2018-03-07T08:55:20.279+09:00

Remarks:

General information

Reference Type

study report

Title

Reverse mutation test of benzenesulfonamide in Bacteria

Author

MHLW, Japan

Year

2007

Bibliographic source

available in the web of Japan Existing Chemical Data Base (JECDB) at http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp

Testing facility

Bozo Research Center Inc.

LITERATURE: Twenty-eight-day Repeat Dose Oral Toxicity Test of benzenesulfonamide in Rats

UUID: ebf5708e-b097-4a1b-81f5-621e08563109

Dossier UUID:

Author: Dra

Date: 2018-03-06T14:53:53.013+09:00

Remarks:

General information

Reference Type

study report

Title

Twenty-eight-day Repeat Dose Oral Toxicity Test of benzenesulfonamide in Rats

Author

MHLW, Japan

Year

2011

Bibliographic source

available in the web of Japan Existing Chemical Data Base (JECDB) at http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp

Testing facility

Research institute for animal science in biochemistry and toxicology (RIAS)

Report no.

06-088