Name: COMPLETE / SUBSTANCE : benzenesulfonamide / benzenesulfonamide / 98-10-2 Fri, 16 Dec 2022, 16:24:13+0900 /

Legal entity owner: National Institute of Health Sciences

Printing date: 2022-12-16T16:24:13.265+09:00

Table of Contents

0/0 1
National Institute of Health Science 2
benzenesulfonamide 3
CORE 3
1 General information 3
1.10 Assessment approach (assessment entities) 3
Assessment approach (assessment entities) 3
OECD 4
D Health Effects 4
67 Repeated dose toxicity: oral 4
Repeated dose toxicity: oral.001 4
70 Genetic toxicity in vitro 12
Genetic toxicity in vitro.001 12
Genetic toxicity in vitro.002 18
73 Toxicity to reproduction 22
Toxicity to reproduction.001 22
DOMAIN 30
Substance 30
Substance 30
References 31
Reference Substances 31
benzenesulphonamide 31
Test Materials 33
benzenesulfonamide 33
Literatures 34
A reproduction/developmental toxicity screening test in rats treated orally with benzensulphonamide 34
In Vitro Chromosomal Aberration Test of benzenesulfonamide on Cultured Chinese Hamster Cells. 35
Reverse mutation test of benzenesulfonamide in Bacteria 36
Twenty-eight-day Repeat Dose Oral Toxicity Test of benzenesulfonamide in Rats 37
Legal Entities 38
National Institute of Health Sciences 38

DOSSIER:

UUID: 0
Dossier UUID:
Author:
Date: 2022-12-16T16:24:13.088+09:00
Remarks:

Dossier header

Dossier submission type

Name
Complete table of contents

Version
core 7.0

Name (given by user)

Dossier subject

Dossier subject
benzenesulfonamide / benzenesulfonamide / 98-10-2

Public name

Submitting legal entity
National Institute of Health Science

Dossier creation date/time
Fri, 16 Dec 2022, 16:24:13+0900

Used in category

LEGAL_ENTITY: National Institute of Health Science

UUID:	f51e7b54-9211-4863-90ce-fcf8a155d647
Dossier UUID:	
Author:	
Date:	2022-11-07T16:24:02.822+09:00
Remarks:	

General information

Legal entity name
National Institute of Health Science

benzenesulfonamide

CORE

General information

Assessment approach (assessment entities)

FIXED_RECORD: Assessment approach

UUID:	2555ffdf-66f9-392b-bc0b-202a7dab8391
Dossier UUID:	
Author:	
Date:	2018-03-06T14:58:59.000+09:00
Remarks:	

OECD

Health Effects

Repeated dose toxicity: oral

ENDPOINT_STUDY_RECORD: Repeated dose toxicity: oral.001

UUID:	1714385f-7fdd-41bd-b111-39e3944c99e4
Dossier UUID:	
Author:	
Date:	2022-12-16T16:20:14.131+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

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

Qualifier
according to guideline

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 ℃) 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: Crl:CD(SD)

Sex
male/female

Details on test animals or test system 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 ℃
- 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 (Crl: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 expecting 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 WEIBHT: 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, thoracical, lumber), thymus, thyroid (including parathyroid), adrenal glands, spleen, he art, stomach, liver, duodenum, jejunum, ileum (including Peyer's patches), cecum, colon, rectal, mes enteric 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 consu mption, 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 contr ol group. When the number of the test group was two, F-test was used as for parametric data. Then, s tudent'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 signi ficance 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 dented 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 dented to recover.

Gross pathological findings
no effects observed

Histopathological findings: non-neoplastic
effects observed, treatment-related

Description (incidence and severity)
Mineralization of the lung alvenolar 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 b
ody 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:
Date: 2022-12-16T16:21:23.677+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

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

Qualifier
according to guideline

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

Controls

Untreated negative controls
yes

Negative solvent / vehicle 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)-aminopro pylamino]acridine-2HCl, -S9mix TA100, WP2, TA98

Details on test system and experimental 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 / choice of top concentrations
no cytotoxicity nor precipitates, but tested up to recommended limit concentrations

Vehicle controls validity
valid

Untreated negative controls validity
valid

Positive controls validity
valid

Key result
false

Species / strain
S. typhimurium TA 1537
bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
no cytotoxicity nor precipitates, but tested up to recommended limit concentrations

Vehicle controls validity
valid

Untreated negative controls validity
valid

Positive controls validity
valid

Key result
false

Species / strain
S. typhimurium TA 98
bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
no cytotoxicity nor precipitates, but tested up to recommended limit concentrations

Vehicle controls validity
valid

Untreated negative controls validity
valid

Positive controls validity
valid

Key result
false

Species / strain
S. typhimurium TA 100
bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
no cytotoxicity nor precipitates, but tested up to recommended limit concentrations

Vehicle controls validity
valid

Untreated negative controls validity
valid

Positive controls validity
valid

Key result
false

Species / strain
E. coli WP2 uvr A pKM 101
bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
no cytotoxicity nor precipitates, but tested up to recommended limit concentrations

Vehicle controls validity
valid

Untreated negative controls validity
valid

Positive controls validity
valid

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

Tables (in English) are attachted to this document. Please download the export file to see the Tables.

Overall remarks, attachments

Attachments

Attached (sanitised) documents for publication
98-10-2_Ames.xlsx / 26.894 KB (application/vnd.openxmlformats-officedocument.spreadsheetml.sheet)

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), benzenesulfonamidewas negative with or without metabolic activation.

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.002

UUID:	2fde2394-2aba-4eeb-ab5a-acaf0d8feaee
Dossier UUID:	
Author:	
Date:	2022-12-16T16:22:01.200+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

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

Qualifier
according to guideline

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 / cell type
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 inhib
ition was observed at 5000 µg/mL
According to the Guideline, the maximum concentration was set at 10 mmol/L (1600 ug/mL).

Vehicle / solvent
- 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 solvent / vehicle controls
yes

Positive controls
yes

Positive control substance
benzo(a)pyrene
+S9 mix
mitomycin C
-S9 mix

Details on test system and experimental 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 repro ducible.

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 / choice of top concentrations
no cytotoxicity nor precipitates, but tested up to recommended limit concentrations

Vehicle controls validity
valid

Positive controls validity
valid

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/PDF98-10-2f.pdf

Tables (in English) are attachted to this document. Please download the export file to see the Tables.

Overall remarks, attachments

Attachments

Attached (sanitised) documents for publication
98-10-2_CA Tables.xlsx / 25.046 KB (application/vnd.openxmlformats-officedocument.spreadsheetml.sheet)

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:
Date: 2022-12-16T16:23:53.886+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 benzensulphonamide / MHLW, Japan / study report

Data access
data published

Materials and methods

Test guideline

Qualifier
according to guideline

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 s topper
- 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: Crl:CD(SD)

Sex
male/female

Details on test animals or test system 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 pla stic 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; l actation 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

Oestrous 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 l ast administration.
Maternal animals: Rats were euthanized by exsanguination under ether anesthesia on day 4 of lactati on.

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 hom ogeneous, 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 pus on day 4 after birth/No. of liveborn pups on day 0 after birth) × 100

Results and discussion

Results: P0 (first parental generation)

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 sign ificantly 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: oestrous 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.

DOMAIN

Substance

SUBSTANCE: benzenesulfonamide

UUID: f596d537-c3e7-44bf-b585-e989d5d06385
Dossier UUID:
Author:
Date: 2022-12-16T16:23:53.886+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	EC name
202-637-1	EC Inventory
CAS number	**CAS name**
98-10-2	
IUPAC name	
benzenesulfonamide	

Role in the supply chain

Manufacturer
false

Importer
false

Only representative
false

Downstream user
false

References

Reference Substances

REFERENCE_SUBSTANCE: benzenesulphonamide

UUID: ECB5-7ab84e8b-3c5d-4bed-bae6-4b4361df8447
Dossier UUID:
Author:
Date: 2007-05-10T18:00:00.000+09:00
Remarks:

Reference substance name
benzenesulphonamide

IUPAC name
benzenesulfonamide

Inventory

Inventory number

Inventory name
benzenesulphonamide

Inventory
EC Inventory

Inventory number
202-637-1

CAS number
98-10-2

Molecular formula
C6H7NO2S

Description

CAS number
98-10-2

Synonyms

Synonyms

Identity
Benzenesulfonamide

Identity
Benzenesulfonamide

Molecular and structural information

Molecular formula
C6H7NO2S

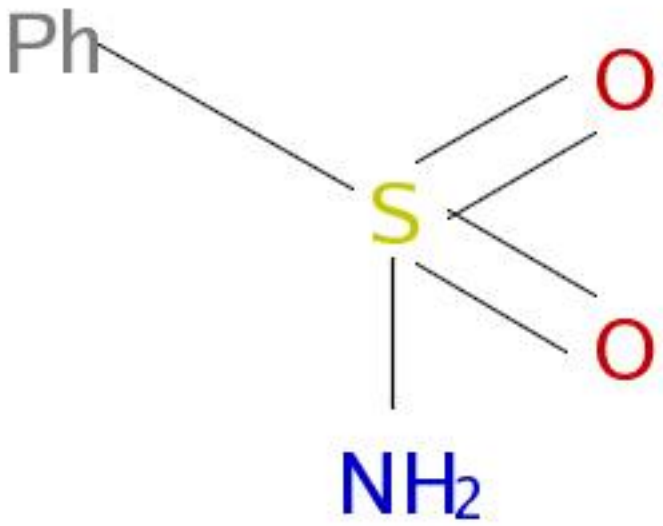
Molecular weight

157.1903

SMILES notation
NS(=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



Related substances

Group / category information
DSL Category: Organics

Test Materials

TEST_MATERIAL_INFORMATION: benzenesulfonamide

UUID: 5ef05df4-03fa-4af0-9669-2bfb6f6f6e3b
Dossier UUID:
Author:
Date: 2018-03-06T15:00:30.000+09:00
Remarks:

Name
benzenesulfonamide

Composition

Composition

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

EC number	**EC name**
202-637-1	EC Inventory
CAS number	**CAS name**
98-10-2	
IUPAC name	
benzenesulfonamide	

Literatures

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

UUID: 344feefd-0a81-43ec-a80b-54f7a38428a1
Dossier UUID:
Author:
Date: 2018-03-07T11:24:27.000+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 number
R-1131

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

UUID: 68ce0a97-383f-4a44-b004-96474746b2c3
Dossier UUID:
Author:
Date: 2018-03-07T10:16:56.000+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 number
B060317

LITERATURE: Reverse mutation test of benzenesulfonamide in Bacteria

UUID:	99eda9cb-6b68-4c85-9db1-5708603fd6a8
Dossier UUID:	
Author:	
Date:	2018-03-07T08:55:20.000+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:
Date: 2018-03-06T14:53:53.000+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 number
06-088

Legal Entities

LEGAL_ENTITY: National Institute of Health Sciences

UUID: IUC4-b036ff75-0f3c-323b-b200-ed5f46cf5101
Dossier UUID:
Author:
Date: 2022-11-07T15:49:29.000+09:00
Remarks:

General information

Legal entity name
National Institute of Health Sciences

Remarks
Disclaimer: The contents in this document were created based on the MHLW (Ministry of Health, Labour and Welfare) peer reviewed study reports (in Japanese) in JECDB (Japan Existing Chemical Database) at http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp. Authorship is in the Division of Risk Assessment, the National Institute of Health Sciences, and the contents do not reflect any o fficial MHLW opinions or any other regulatory policies.

Address

Address 1
Tonomachi 3-25-26

Address 2
Kawasaki-ku

Postal code
210-9501

Town
Kawasaki

Region / State
Kanagawa

Country
Japan
JP

Identifiers

Other IT system identifiers

IT system LEO **ID** 10767
IT system IUCLID4

ID
16558402024DIV750