Name: COMPLETE / SUBSTANCE : 1,2,4,5-Benzenetetracarboxylic acid / benzene-1,2,4,5-tetracarboxylic acid / 89-05-4 Mon, 12 Dec 2022, 09:41:47+0900 /

Legal entity owner: National Institute of Health Sciences

Printing date: 2022-12-12T09:41:47.355+09:00

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DOSSIER:

UUID: 0
Dossier UUID:
Author:
Date: 2022-12-12T09:41:47.074+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
1,2,4,5-Benzenetetracarboxylic acid / benzene-1,2,4,5-tetracarboxylic acid / 89-05-4

Public name

Submitting legal entity
National Institute of Health Science

Dossier creation date/time
Mon, 12 Dec 2022, 09:41:47+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

1,2,4,5-Benzenetetracarboxylic acid

CORE

General information

Assessment approach (assessment entities)

FIXED_RECORD: Assessment approach

UUID:	0653abb0-b7f5-3515-923e-7fe80ae066aa
Dossier UUID:	
Author:	
Date:	2018-02-27T15:49:57.000+09:00
Remarks:	

OECD

Health Effects

Repeated dose toxicity: oral

ENDPOINT_STUDY_RECORD: Repeated dose toxicity: oral.001

UUID:	5d2623ad-aba5-430b-867e-16a36feba0ab
Dossier UUID:	
Author:	
Date:	2022-12-12T09:31:30.164+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

Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test of / MHLW (Ministry of Health, Labour and Welfare), Japan / study report

Data access
data published

Materials and methods

Test guideline

Qualifier
according to guideline

Guideline
OECD Guideline 422 (Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test)

GLP compliance
yes

Limit test
no

Test material

Test material information
1,2,4,5-Benzenetetracarboxylic Acid

Specific details on test material used for the study
1,2,4,5-Benzenetetracarboxylic Acid;Purity 99.9% (CAS:89-05-4)

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 (Atsugi)
- Age at study initiation:
10 weeks old
- Weight at study initiation:
342 g -400 g (male); 213 g - 260 g (female)
- Fasting period before study:
- Housing:
metal cage (W250 x D350 x H200 mm), (W340 x D400 x H185 mm for pregnant animals on GD17 to PND 5)
- Diet:
ad libitum
- Water:
ad libitum
- Acclimation period:
14 days

DETAILS OF FOOD AND WATER QUALITY:

ENVIRONMENTAL CONDITIONS
- Temperature (°C):

20-26
- Humidity (%):
30-60
- Air changes (per hr):
12
- Photoperiod (hrs dark / hrs light):
19:00-7:00/7:00-19:00

Administration / exposure

Route of administration
oral: gavage

Vehicle
methylcellulose

Details on oral exposure
Vehicle: 0.5 w/v% methylcellulose solution

Analytical verification of doses or concentrations
yes

Duration of treatment / exposure
males: 42 days, females: 41-46 days from 14 days before mating to day 4 of lactation

Frequency of treatment
once a day

Doses / concentrations

Dose / conc.	
0	mg/kg bw/day (actual dose received)
Dose / conc.	
100	mg/kg bw/day (actual dose received)
Dose / conc.	
300	mg/kg bw/day (actual dose received)
Dose / conc.	
1000	mg/kg bw/day (actual dose received)

No. of animals per sex per dose
17(12 animals as an administration group and 5 animals as a recovery group) /sex/dose (0 and 1000 mg/kg bw/day)
12/sex/dose (100 and 300 mg/kg/day)

Control animals
yes, concurrent vehicle

Details on study design
- Dose selection rationale:
Dose finding study: Rats were dosed the test substance for 14 days at 0, 100, 300 and 1000 mg/kg bw/day. Soft feces were observed at 1000 mg/kg bw/day in both sexes, but no effects were observed on body weight. The highest dose was set at 1000 mg/kg bw/day for the main study.
- Post-exposure recovery period in satellite groups: 14 days

Examinations

Observations and examinations performed and frequency
Clinical observation performed and frequency: General condition was observed 3 times a day during the administration period (before dosing, and immediately after and approximately 2 hours after dosing) and once a day (in the morning) during the recovery period.

Detailed clinical observation was done for all animals. It was done once a week during the administration period and recovery period for males and non-mated females, and once a week during the pre-mating administration period and on the designated days during the mating, gestation and lactation periods for females in the mating group (on days 1, 7, 14 and 20 of gestation for the copulated females and on day 4 of lactation for the females that delivered). As detailed clinical observations, the animals were observed for the following items: posture, convulsion and abnormal behavior in the home cage observation; ease of removal from cage, reactivity to handling (ease of handling, vocalization, etc.) condition of fur and skin (staining of fur, unkempt fur, injury, color of skin, etc.), eyeball (exophthalmos, palpebral closure), secretions from eyes and nose, mucosal membranes, autonomic nervous function (lacrimation, salivation, piloerection, pupil size and respiration) to handling at in-the-hand observation; and arousal, gait, posture, tremor, convulsion, rearing count, defecation (defecation count, urination), stereotypy (grooming, circling, etc.), abnormal behavior (self-biting, backward walking, etc.) in the open field observation.

Manipulative test and measurement of grip strength and motor activity were done for 5 animals in each group: males in the main groups were examined in the final week of administration, females in the main groups on day 4 of lactation, and males and females in the recovery groups in the final week of administration and in the final week of recovery. Animals were examined for auditory response, approach response, touch response, tail pinch response, pulillary reflex, aerial righting reflex and landing foot splay. The grip strength of the forelimbs and hind limbs was measured. The motor activity was measured for 1 hour and measured values of 10-minute intervals and 0-60 minute value were recorded.

Body weights were determined on days 1, 4, 8, 11, 15, 18, 22, 25, 29, 32, 36, 39 and 42 of administration for males and on days 1, 4, 8, 11 and 15 of administration, days 0, 4, 7, 11, 14, 17 and 20 of gestation and days 0 and 4 of lactation for females, and the day of necropsy in males and females. In addition, males and females in the recovery groups were weighed on days 1, 4, 8, 11 and 14 of recovery and on the day of necropsy.

Food consumption was determined on days 1, 4, 8, 11, 15, 32, 36, 39 and 42 of administration for males and on days 1, 4, 8, 11 and 15 of administration, days 1, 4, 7, 11, 14, 17 and 20 of gestation and days 2 and 4 of lactation in females, but it was not determined during the mating period for males and females. In addition, it was determined on days 1, 4, 8, 11 and 14 of recovery for males and females in the recovery groups

Urinalysis was done for 5 males in each group and 5 non-mated group females in the final week of administration and in the final week of recovery.
In all animals in the control group and the high dose group and 5 males and 5 females in the low and middle dose groups, hematological examination and blood chemistry examination were carried out at time of necropsy after the end of administration or recovery period.

Sacrifice and pathology
Necropsy: Detailed macroscopic examination was conducted on the organs/tissues throughout the body of each animal, including the external appearance, head, thorax and abdomen.
Measurement of organ weighs: The brain, thyroids (including parathyroids), adrenals, thymus, spleen, heart, liver, kidneys, testes, epididymides were determined.
Histopathological examination: The stomach in males and females of all groups, the cerebrum, cerebellum, pituitary, spinal cord (thoracic), sciatic nerve, thyroids, parathyroids, adrenals, thymus, spleen, submandibular lymph node, mesenteric lymph node, heart, lung (including bronchus), stomach, duodenum, jejunum, ileum, cecum, colon, rectum, liver, kidneys, urinary bladder, testes, epididymides, ovaries, uterus, seminal vesicles, sternum (including bone marrow), femur (including bone marrow) in males and females at 0 and 1000 mg/kg bw/day.

Statistics
Dunnett's test for continuous data, Dunnett-type mean rank test for quantal data and chi-square test with Yates' continuity correction or chi-square test with Yates' continuity correction for other data were used.

Results and discussion

Results of examinations

Clinical signs
effects observed, treatment-related

Description (incidence and severity)
soft feces were observed in males and females in the 1000 mg/kg bw/day group.

Mortality
no mortality observed

Body weight and weight changes
no effects observed

Food consumption and compound intake (if feeding study)
no effects observed

Haematological findings
no effects observed

Clinical biochemistry findings
no effects observed

Urinalysis findings
no effects observed

Behaviour (functional findings)
no effects observed

Organ weight findings including organ / body weight ratios
no effects observed

Gross pathological findings
no effects observed

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

Description (incidence and severity)
At the end of the administration period, squamous hyperplasia at the limiting was observed in stomac h of males in the 1000 mg/kg group. However, reversibility was observed for this lesion at the end of the recovery period.

Effect levels

Key result
false

Dose descriptor
NOAEL

Effect level

300 mg/kg bw/day (actual dose received)

Based on
act. ingr.

Sex
male/female

Basis for effect level
histopathology: non-neoplastic

Target system / organ toxicity

Key result
false

Critical effects observed
yes

Lowest effective dose / conc.

1000 mg/kg bw/day (nominal)

System
gastrointestinal tract

Organ
intestine
stomach

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/PDF89-05-4b.pdf

Applicant's summary and conclusion

Conclusions
Based on the effects in the gastrointestinal tract, the NOAEL for local effects on rat regarding the repeated-dose toxicity of 1,2,4,5-benzenetetracarboxylic acid was determined to be 300 mg/kg bw/day.

Executive summary

A combined repeated oral dose toxicity study with the reproduction/developmental toxicity screening test was performed as described in OECD TG 422. Male and female rats (12 animals/sex/dose) were administered 1,2,4,5-benzenetetracarboxylic acid at 0 (vehicle:0.5 w/v% methyl cellulose solution), 100, 300, and 1,000 mg/kg bw/day. Males were dosed for 42 days, including a 14-day pre-mating period and subsequent mating period, whereas females were dosed for 41–46 days, including 14-day pre-mating, mating, and gestation periods, and until lactation day 4. Five out of 12 males administered 1,2,4,5-benzenetetracarboxylic acid at 0 and 1,000 mg/kg bw/day were treated as a recovery group and examined after a 14-day recovery period. Regarding the findings of clinical observation, soft feces were observed in males and females of the 1,000 mg/kg bw/day group. Upon histopathological examination, hyperplasia of the squamous epithelium at the limiting ridge, considered to be due to irritation by the test substance, was found in the stomach of males of the 1,000 mg/kg bw/day group at the end of the administration period. Reversibility was observed for this lesion at the end of the recovery period. Based on the effects in the gastrointestinal tract, the NOAEL for local effects on rat regarding the repeated-dose toxicity of 1,2,4,5-benzenetetracarboxylic acid was determined to be 300 mg/kg bw/day.

Genetic toxicity in vitro

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.001

UUID:	40c20b28-8c31-4ea3-8153-d63404543a5b
Dossier UUID:	
Author:	
Date:	2022-12-12T09:36:49.556+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 1,2,4,5-Benzenetetracarboxylic Acid on Bacteria. / Ministry of Health, Labour and Welfare (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

GLP compliance
yes

Type of assay
bacterial reverse mutation assay
in vitro gene mutation study in bacteria

Test material

Test material information
1,2,4,5-Benzenetetracarboxylic Acid

Specific details on test material used for the study
1,2,4,5-Benzenetetracarboxylic Acid;Purity 99.9% (CAS:89-05-4)

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
S9 mix: Rat liver, induced with phenobarbital and 5,6-benzoflavone

Test concentrations with justification for top dose
Dosage of each strain with or without S9
-S9 mix: 0, 313, 625, 1250, 2500, 5000 ug/plate(all strains)
+S9 mix: 0, 156, 313, 625, 1250, 2500, 5000 ug/plate(TA strains)
0, 313, 625, 1250, 2500, 5000 ug/plate (WP2 uvrA)

Maximum concentration was established based on the result of the preliminary test at concentration up to 5000 ug/plate. In this test, the growth inhibition was observed at 5000 µg/plate for S. typhimurium TA100, TA1535, TA98 and TA1537 with S9 mix.

Vehicle / solvent
Dimethylsulfoxide

Controls

Untreated negative controls
no

Negative solvent / vehicle controls
yes

True negative controls
no

Positive controls
yes

Positive control substance
sodium azide

without S9 mix:(TA 1535)
benzo(a)pyrene
with S9 mix: (TA100, TA98, TA1537)
other:
without S9 mix:2-(2-Furyl)-3-(5-nitro -2-furyl)acrylamide (TA100, TA98, WP2uvrA), ICR-191 (TA1537) with S9 mix: 2-Aminoanthracene (TA1535, WP2 uvrA)

Details on test system and experimental conditions
METHOD OF APPLICATION: Preincubation
DURATION- Preincubation period: 20 min at 37°C
- Exposure duration:48 hrs
NUMBER OF PLATES: 3
NUMBER OF REPLICATIONS: 2
DETERMINATION OF CYTOTOXICITY- Method: other: growth inhibition

Evaluation criteria
A chemical was judged to be mutagenic when the mean number of revertant colonies per plate increased more than twice that of the negative control and when the dose-related and reproducible i ncrease was observed.

Statistics
not used

Results and discussion

Test results

Key result
false

Species / strain
S. typhimurium TA 100
bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
cytotoxicity at 5000 µg/plate (+S9 mix)

Vehicle controls validity
valid

Untreated negative controls validity
not examined

Positive controls validity
valid

Key result
false

Species / strain
S. typhimurium TA 1535

bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
cytotoxicity at 5000 µg/plate (+S9 mix)

Vehicle controls validity
valid

Untreated negative controls validity
not examined

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
not examined

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
cytotoxicity at 5000 µg/plate (+/- S9 mix)

Vehicle controls validity
valid

Untreated negative controls validity
not examined

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
cytotoxicity at 5000 µg/plate (+S9 mix)

Vehicle controls validity
valid

Untreated negative controls validity
not examined

Positive controls validity
valid

Additional information on results
There were no precipitation in any test concentration.

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/PDF89-05-4e.pdf

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

Applicant's summary and conclusion

Conclusions
Genotoxic effects:
With metabolic activation: Negative
Without metabolic activation: Negative

Executive summary

In a bacterial reverse mutation assay usingS. typhimuriumTA100, TA1535, TA98, and TA1537, andE. coliWP2uvrA/pKM101 (OECD TG 471), negative results were obtained for 1,2,4,5-benzenetetracarboxylic acid with or without metabolic activation.

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.002

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Dossier UUID:
Author:
Date: 2019-09-03T11:22:59.000+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 on 1,2,4,5-benzenetetracarboxylic acid Cultured Chinese Ham / MHLW, Japan / study report

Data access
data published

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
1,2,4,5-Benzenetetracarboxylic Acid

Specific details on test material used for the study
1,2,4,5-Benzenetetracarboxylic Acid;Purity 99.9% (CAS:89-05-4)

Method

Species / strain

Species / strain / cell type
other: Chinese hamster lung(CHL/IU) cell

Metabolic activation
with and without

Metabolic activation system
S9 mix: Rat liver, induced with phenobarbital and 5,6- benzoflavone

Test concentrations with justification for top dose
-S9 mix(short-term treatment): 0, 676.8, 947.5, 1327, 1857, 2600 µg/mL
+S9 mix(short-term treatment): 0, 750, 900, 1050, 1200, 1500, 1650 µg/mL
-S9 mix(24hr-continuous treatment): 0, 900, 1050, 1200, 1500, 1650, 1800 µg/mL
-S9 mix(48hr-continuous treatment): 0, 1000, 1100, 1200, 1300, 1400 µg/m

Cell-growth inhibition test was conducted up to the limited concentration of 2600 µg/mL (10 mM)
-Short term treatment, +S9 mix: concentration of 50% cell-groth inhibition was determined as 2523.5 µg/mL
-Short term treatment, -S9 mix: concentration of 50% cell-groth inhibition was determined as 2321.4 µg/mL
-Continous treatment (24 h): concentration of 50% cell-groth inhibition was determined as 2600.0 µg/mL
-Continous treatment (48 h): concentration of 50% cell-groth inhibition was determined as 1246.9 µg/mL

Vehicle / solvent
DMSO

Controls

Untreated negative controls
no

Negative solvent / vehicle controls
yes

True negative controls
no

Positive controls
yes

Positive control substance
cyclophosphamide
(with S9)
mitomycin C
(without S9)

Details on test system and experimental conditions
METHOD OF APPLICATION: Exposure duration: [short-term treatment]:6 hrs + 18 hr, [continuous treatment]: 24h, 48 h
Plates/test: 2

Evaluation criteria
For the evaluation of the frequencies of structural aberrations and of polyploidy induced, the following criteria were employed. Appearance incidence of cell with chromosomal aberrations: Negative(-): less than 5%, Equivocal(±): 5% or more and less than 10%, Positive(+): 10% or more

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
cytotoxicity

Vehicle controls validity
valid

Untreated negative controls validity
not examined

Positive controls validity
valid

Any other information on results incl. tables

1,2,4,5-Benzenetetracarboxylic acid did not induce polyploidy under the conditions of this study, but a positive result in the incidence of the occurrence of chromosome structural aberrations was reproduced, though it was not dose-dependent. Since remarkable lowering in the pH of the culture was observed , it was judged that the structural aberrations induced by the test article were caused by the cultural environment and thus non-specific.

Genetic effects:	Clastogenicity + ? -	Polyploidy + ? -
Without metabolic activation	[ ] [ ] [*]	[ ] [ ] [*]
With metabolic activation	[ ] [ ] [*]	[ ] [ ] [*]
24hr-continuous treatment	[*] [ ] [ ] clastogenicity is considered to be due to low pH condition	[ ] [ ] [*]

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

http://dra 4.nihs.go.jp/mhlw_data/home/pdf/PDF89-05-4f.pdf

Applicant's summary and conclusion

Executive summary

*In an*in vitro*chromosomal aberration test using CHL/IU cells (OECD TG 473), negative results were obtained with or without metabolic activation.*

Toxicity to reproduction

ENDPOINT_STUDY_RECORD: Toxicity to reproduction.001

UUID: ec21741c-15da-4df3-865b-f757841e8f8a
Dossier UUID:
Author:
Date: 2022-12-12T09:35:30.729+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

Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test of / MHLW (Ministry of Health, Labour and Welfare), Japan / study report

Data access
data published

Materials and methods

Test guideline

Qualifier
according to guideline

Guideline
OECD Guideline 422 (Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test)

GLP compliance
yes

Test material

Test material information
1,2,4,5-Benzenetetracarboxylic Acid

Specific details on test material used for the study
1,2,4,5-Benzenetetracarboxylic Acid;Purity 99.9% (CAS:89-05-4)

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 (Atsugi)
- Age at study initiation:
10 weeks old
- Weight at study initiation:
342 g -400 g (male); 213 g - 260 g (female)
- Fasting period before study:
- Housing:
metal cage (W250 x D350 x H200 mm), (W340 x D400 x H185 mm for pregnant animals on GD17 to PND 5)
- Diet:
ad libitum
- Water:
ad libitum
- Acclimation period:
14 days

DETAILS OF FOOD AND WATER QUALITY:

ENVIRONMENTAL CONDITIONS
- Temperature (°C):
20-26
- Humidity (%):
30-60
- Air changes (per hr):
12
- Photoperiod (hrs dark / hrs light):
19:00-7:00/7:00-19:00

Administration / exposure

Route of administration
oral: gavage

Vehicle
other: 0.5 w/v% methylcellulose solution

Details on mating procedure
Method of mating: Males and females in the same dose group of the main groups were co-housed overnight on a one-to-one basis after the end of the pre-mating administration period. Copulation was considered successful if the formation of vaginal plugs or presence of sperm in vaginal smears was confirmed the following morning. The length of the mating period for the same male and female was 5 days at maximum.

Analytical verification of doses or concentrations
yes

Duration of treatment / exposure
males: 42 days, females: 41-46 days from 14 days before mating to day 4 of lactation

Frequency of treatment
once a day

Doses / concentrations

Dose / conc.	
0	mg/kg bw/day (actual dose received)
Dose / conc.	
100	mg/kg bw/day (actual dose received)
Dose / conc.	
300	mg/kg bw/day (actual dose received)
Dose / conc.	
1000	mg/kg bw/day (actual dose received)

No. of animals per sex per dose
17(12 animals as an administration group and 5 animals as a recovery group) /sex/dose (0 and 1000 mg/kg bw/day)
12/sex/dose (100 and 300 mg/kg/day)

Control animals
yes, concurrent vehicle

Details on study design
- Dose selection rationale:

Dose finding study: Rats were dosed the test substance for 14 days at 0, 100, 300 and 1000 mg/kg bw/day. Soft feces were observed at 1000 mg/kg bw/day in both sexes, but no effects were observed on body weight. The highest dose was set at 1000 mg/kg bw/day for the main study.
- Post-exposure recovery period in satellite groups: 14 days

Examinations

Parental animals: Observations and examinations
Clinical observation performed and frequency: General condition was observed 3 times a day during the administration period (before dosing, and immediately after and approximately 2 hours after dosing) and once a day (in the morning) during the recovery period.
Body weights were determined on days 1, 4, 8, 11, 15, 18, 22, 25, 29, 32, 36, 39 and 42 of adminis tration for males and on days 1, 4, 8, 11 and 15 of administration, days 0, 4, 7, 11, 14, 17 and 20 of gestation and days 0 and 4 of lactation for females, and the day of necropsy in males and females . In addition, males and females in the recovery groups were weighed on days 1, 4, 8, 11 and 14 of recovery and on the day of necropsy.
Food consumption was determined on days 1, 4, 8, 11, 15, 32, 36, 39 and 42 of administration for male s and on days 1, 4, 8, 11 and 15 of administration, days 1, 4, 7, 11, 14, 17 and 20 of gestation and days 2 and 4 of lactation in females, but it was not determined during the mating period for males and females. In addition, it was determined on days 1, 4, 8, 11 and 14 of recovery for males and females in the recovery groups.

Oestrous cyclicity (parental animals)
Vaginal smears were collected from all females in the main groups and microscopically examined every day (in the morning) from the day after the start of administration until the day copulation was confirmed. Vaginal smear pictures were classified as proestrus, estrus, metestrus and diestrus and examined for the frequency of estrus and interval between estruses (estrous cycle).

Litter observations
Examination of liveborn pups: The numbers of liveborn pups and stillborn pups were counted on the day of birth. After liveborn pups were examined for any external abnormality, sexed and weighed, dams were allowed to nurse their pups. Liveborn pups were observed for mortality once daily until day 4 after birth. All liveborn pups were exsanguinated after measurement of body weight on day 4 after birth, necropsied and examined for any abnormality in organs/tissues, including those in the head, thorax and abdomen. Individual body weights of liveborn pups were recorded, and the average body weight per litter was calculated by sex.
Pathological examinations were performed.

Postmortem examinations (parental animals)
See 7.5.1 Repeated dose toxicity

Postmortem examinations (offspring)
GROSS NECROPSY
- Gross necropsy consisted of external examination

Statistics
Dunnett's test for continuous data, Dunnett-type mean rank test for quantal data and chi-square test with Yates' continuity correction or chi-square test with Yates' continuity correction for other data were used.

Reproductive indices
No. of copulated animals, No. of males that impregnated females, No. of pregnant females, No. of females that delivered liveborn pups, estrous cycle, gestational length, No.of corpora lutea, No. of im plantation sites, total No. of liveborn and stillborn pups

Offspring viability indices
No. of liveborn pups, sex ratio on day 0 and day 4 after birth, copulation index (No. of copulated a nimals / No. of animals housed together x 100), insemination index (No. of pregnant females / No.

of copulated males x 100), fertility index (No. of pregnant females / No. of copulated females x 100), delivery index (No. of females that delivered liveborn pups / No. of pregnant females x 100), implantation index (No. of implantation sites / No. of corpora lutea x100), stillbirth index (No. of stillborn pups / No. of pups born x 100), index of external abnormalities (No. of pups with external abnormalities / No. of pups born x 100), live birth index (No. of liveborn pups / No. of pups born x 100), and viability index on day 4 after birth (No. of live pups on day 4 after birth / No. of liveborn pups x 100)

Results and discussion

Results: P0 (first parental generation)

General toxicity (P0)

Clinical signs
effects observed, treatment-related

Mortality
no mortality observed

Body weight and weight changes
no effects observed

Food consumption and compound intake (if feeding study)
no effects observed

Haematological findings
no effects observed

Clinical biochemistry findings
no effects observed

Urinalysis findings
no effects observed

Behaviour (functional findings)
no effects observed

Organ weight findings including organ / body weight ratios
no effects observed

Gross pathological findings
no effects observed

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

Reproductive function / performance (P0)

Reproductive function: oestrous cycle
no effects observed

Reproductive performance
no effects observed

Effect levels (P0)

Key result
true

Dose descriptor
NOAEL

Effect level

1000 mg/kg bw/day (actual dose received)

Based on
act. ingr.

Sex
male/female

Basis for effect level
reproductive performance
No effects observed

Key result
false

Dose descriptor
NOAEL

Effect level

300 mg/kg bw/day (actual dose received)

Based on
act. ingr.

Sex
male/female

Basis for effect level
clinical signs
soft feces were observed in males and females in the 1000 mg/kg group
histopathology: non-neoplastic
squamous hyperplasia at the limiting was observed in stomach of males in the 1000 mg/kg bw/daygroup

Results: F1 generation

General toxicity (F1)

Mortality / viability
no mortality observed

Body weight and weight changes
no effects observed

Effect levels (F1)

Key result
false

Dose descriptor
NOAEL

Generation
F1

Effect level

1000	mg/kg bw/day (actual dose received)

Based on
act. ingr.

Sex
male/female

Basis for effect level
viability
no effects
body weight and weight gain
no effects

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/PDF89-05-4b.pdf

Applicant's summary and conclusion

Executive summary

A combined repeated oral dose toxicity study with the reproduction/developmental toxicity screening test was performed as described in OECD TG 422. Male and female rats (12 animals/sex/dose) were administered 1,2,4,5-benzenetetracarboxylic acid at 0 (vehicle:0.5 w/v% methyl cellulose solution), 100, 300, and 1,000 mg/kg bw/day. Males were dosed for 42 days, including a 14-day pre-mating period and subsequent mating period, whereas females were dosed for 41–46 days, including 14-day pre-mating, mating, and gestation periods, and until lactation day 4. Five out of 12 males administered 1,2,4,5-benzenetetracarboxylic acid at 0 and 1,000 mg/kg bw/day were treated as a recovery group and examined after a 14-day recovery period. Regarding the findings of clinical observation, soft feces were observed in males and females of the 1,000 mg/kg bw/day group. Upon histopathological examination, hyperplasia of the squamous epithelium at the limiting ridge, considered to be due to irritation by the test substance, was found in the stomach of males of the 1,000 mg/kg bw/day group at the end of the administration period. Reversibility was observed for this lesion at the end of the recovery period. There were no effects on reproductive and developmental parameters at 1,000 mg/kg bw/day. The NOAEL for the rat reproductive/developmental toxicity of 1,2,4,5-benzenetetracarboxylic acid was thus regarded as 1,000 mg/kg bw/day, the highest dose tested.

DOMAIN

Substance

SUBSTANCE: 1,2,4,5-Benzenetetracarboxylic acid

UUID: 916619f2-21b5-4bc8-8261-6a1c647257b2
Dossier UUID:
Author:
Date: 2022-12-12T09:36:49.556+09:00
Remarks:

Substance name
1,2,4,5-Benzenetetracarboxylic acid

Legal entity
National Institute of Health Sciences / Kawasaki / Japan

Identification of substance

Reference substance
benzene-1,2,4,5-tetracarboxylic acid / benzene-1,2,4,5-tetracarboxylic acid / 89-05-4 / 201-879-5

EC number	EC name
201-879-5	EC Inventory

CAS number	CAS name
89-05-4	

IUPAC name
benzene-1,2,4,5-tetracarboxylic acid

Role in the supply chain

Manufacturer
false

Importer
false

Only representative
false

Downstream user
false

References

Reference Substances

REFERENCE_SUBSTANCE: benzene-1,2,4,5-tetracarboxylic acid

UUID:	ECB5-b71b5f8a-c0f0-46d8-91ea-ab7fbd98c99d
Dossier UUID:	
Author:	
Date:	2007-05-10T18:00:00.000+09:00
Remarks:	

Reference substance name
benzene-1,2,4,5-tetracarboxylic acid

IUPAC name
benzene-1,2,4,5-tetracarboxylic acid

Inventory

Inventory number

Inventory name
benzene-1,2,4,5-tetracarboxylic acid

Inventory
EC Inventory

Inventory number
201-879-5

CAS number
89-05-4

Molecular formula
C10H6O8

Description

CAS number
89-05-4

Synonyms

Synonyms

Identity
1,2,4,5-Benzenetetracarboxylic acid

Molecular and structural information

Molecular formula
C10H6O8

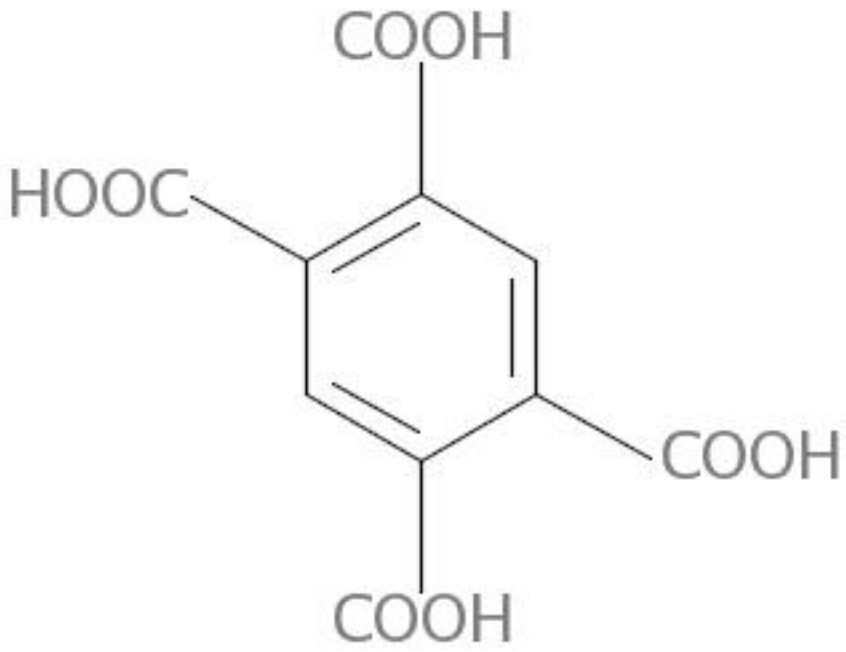
Molecular weight

254.1498

SMILES notation
OC(=O)c1cc(C(=O)O)c(cc1C(=O)O)C(=O)O

InChI
InChI=1/C10H6O8/c11-7(12)3-1-4(8(13)14)6(10(17)18)2-5(3)9(15)16/h1-2H,(H,11,12)(H,13,14)(H,15,16)(H,17,18)

Structural formula



Test Materials

TEST_MATERIAL_INFORMATION: 1,2,4,5-Benzenetetracarboxylic Acid

UUID: 7ae2f323-f6d3-4dd8-90b0-50035b807a11
Dossier UUID:
Author:
Date: 2018-03-02T16:28:06.000+09:00
Remarks:

Name
1,2,4,5-Benzenetetracarboxylic Acid

Literatures

LITERATURE: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test of 1,2,4,5-Benzenetetracarboxylic acid by Oral Administration in Rats

UUID: 89f9517b-c78d-4b09-bd20-f94f1315025c
Dossier UUID:
Author:
Date: 2018-03-06T09:17:24.000+09:00
Remarks:

General information

Reference Type
study report

Title
Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test of 1,2,4,5-Benzenetetracarboxylic acid by Oral Administration in Rats

Author
MHLW (Ministry of Health, Labour and Welfare), Japan

Year
2009

Bibliographic source
Japan Existing Chemical Data Base (JECDB) http://dra4.nihs.go.jp/mhlw_data/jsp/Sea rchPage ENG.jsp

Testing facility
Gotemba Laboratory, Bozo Research Center Inc. Gotemba Shizuoka

LITERATURE: In Vitro Chromosomal Aberration Test of on 1,2,4,5-benzenetetracarboxylic acid Cultured Chinese Hamster Cells.

UUID: 9de6c7ea-59f8-4ab2-8ba7-809fb6fed7a2
Dossier UUID:
Author:
Date: 2018-03-08T15:09:43.000+09:00
Remarks:

General information

Reference Type
study report

Title
In Vitro Chromosomal Aberration Test of on 1,2,4,5-benzenetetracarboxylic acid Cultured Chinese Hamster Cells.

Author
MHLW, Japan

Year
2008

Bibliographic source
Japan Existing Chemical Data Base (JECDB) http://dra4.nihs.go.jp/mhlw_data/jsp/Sea rchPage ENG.jsp

Testing facility
Bozo Research Center Inc.

LITERATURE: Reverse Mutation Test of 1,2,4,5-Benzenetetracarboxylic Acid on Bacteria.

UUID: 28e216ef-11ab-4f22-a9e6-05cf1412f7c8
Dossier UUID:
Author:
Date: 2018-08-27T11:46:23.000+09:00
Remarks:

General information

Reference Type
study report

Title
Reverse Mutation Test of 1,2,4,5-Benzenetetracarboxylic Acid on Bacteria.

Author
Ministry of Health, Labour and Welfare (MHLW), Japan

Year
2007

Bibliographic source
JECDB http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp

Testing facility
Bozo Research Center Inc.

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