



---

**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

---

## Table of Contents

|  |    |
|--|----|
| 0/0 .....  | 1  |
| National Institute of Health Science .....   | 2  |
| 1,2,4,5-Benzenetetracarboxylic acid .....  | 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 .....   | 11 |
| Genetic toxicity in vitro.001 .....  | 11 |
| Genetic toxicity in vitro.002 .....  | 17 |
| 73 Toxicity to reproduction .....  | 21 |
| Toxicity to reproduction.001 .....   | 21 |
| DOMAIN .....   | 28 |
| Substance .....  | 28 |
| Substance .....  | 28 |
| References .....   | 29 |
| Reference Substances .....   | 29 |
| benzene-1,2,4,5-tetracarboxylic acid .....   | 29 |
| Test Materials .....   | 31 |
| 1,2,4,5-Benzenetetracarboxylic Acid .....  | 31 |
| Literatures .....  | 32 |
| Combined Repeated Dose Toxicity Study with the Reproduction/<br>Developmental Toxicity Screening Test of 1,2,4,5-Benzenetetracarboxylic<br>acid by Oral Administration in Rats ..... | 32 |
| In Vitro Chromosomal Aberration Test of on 1,2,4,5-benzenetetracarboxylic<br>acid Cultured Chinese Hamster Cells. ....   | 33 |
| Reverse Mutation Test of 1,2,4,5-Benzenetetracarboxylic Acid on<br>Bacteria. ....  | 34 |
| Legal Entities .....   | 35 |
| National Institute of Health Sciences .....  | 35 |

---

# 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: CrI: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

|                     |                                     |
|---------------------|-------------------------------------|
| <b>Dose / conc.</b> |                                     |
| 0                   | mg/kg bw/day (actual dose received) |
| <b>Dose / conc.</b> |                                     |
| 100                 | mg/kg bw/day (actual dose received) |
| <b>Dose / conc.</b> |                                     |
| 300                 | mg/kg bw/day (actual dose received) |
| <b>Dose / conc.</b> |                                     |
| 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, pupillary 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 weights: 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**

Dunnnett's test for continuous data, Dunnnett-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 stomach 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.

## 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 increase 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](http://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF89-05-4e.pdf)

Tables (in English) are attached 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 using S. typhimurium TA100, TA1535, TA98, and TA1537, and E. coli WP2uvrA/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**

---

**UUID:** a11081cc-e5df-404c-92c0-f44363410538

**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( $\pm$ ): 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    | [*] [] []<br><br>clastogenicity is considered to be<br>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](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**

|                     |                                     |
|---------------------|-------------------------------------|
| <b>Dose / conc.</b> |                                     |
| 0                   | mg/kg bw/day (actual dose received) |
| <b>Dose / conc.</b> |                                     |
| 100                 | mg/kg bw/day (actual dose received) |
| <b>Dose / conc.</b> |                                     |
| 300                 | mg/kg bw/day (actual dose received) |
| <b>Dose / conc.</b> |                                     |
| 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 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.

### 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 implantation 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 animals / 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](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**

201-879-5

**EC name**

EC Inventory

**CAS number**

89-05-4

**CAS name**

**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**

C<sub>10</sub>H<sub>6</sub>O<sub>8</sub>

**Description**

**CAS number**

89-05-4

## Synonyms

---

**Synonyms**

**Identity**

1,2,4,5-Benzenetetracarboxylic acid

## Molecular and structural information

---

---

**Molecular formula**

C<sub>10</sub>H<sub>6</sub>O<sub>8</sub>

**Molecular weight**

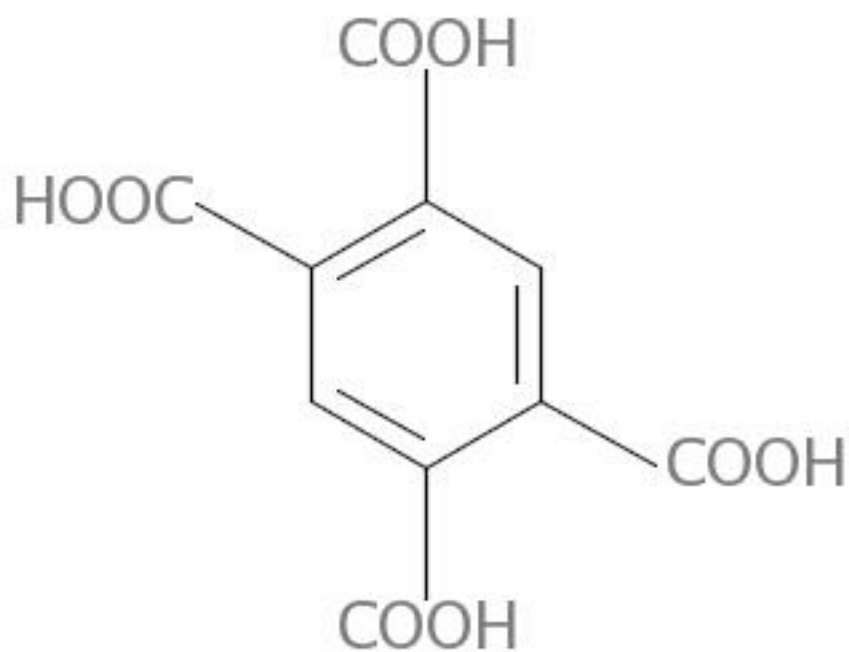
254.1498

**SMILES notation**

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

**InChI**

InChI=1/C<sub>10</sub>H<sub>6</sub>O<sub>8</sub>/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/SearchPageENG.jsp](http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.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\\_rchPageENG.jsp](http://dra4.nihs.go.jp/mhlw_data/jsp/Sea_rchPageENG.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](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](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 official 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