



Name: perfluoro-1,2-dimethylcyclohexane / 1,1,2,2,3,3,4,4,5,6-decafluoro-5,6-bis(trifluoromethyl)cyclohexane / 306-98-9

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

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Table of Contents

perfluoro-1,2-dimethylcyclohexane	1
CORE	1
1 General information	1
1.1 Identification	1
Identification	1
OECD	2
D Health Effects	2
67 Repeated dose toxicity: oral	2
Repeated dose toxicity: oral.001	2
70 Genetic toxicity in vitro	10
Genetic toxicity in vitro.001	10
Genetic toxicity in vitro.002	15
73 Toxicity to reproduction	18
Toxicity to reproduction.001	18
References	27
1,1,2,2,3,3,4,4,5,6-decafluoro-5,6-bis(trifluoromethyl)cyclohexane	27
A combined repeated dose/reproductive developmental toxicity study of 1, 1, 2, 2, 3, 3, 4, 4, 5, 6-decafluoro-5, 6-bis (trifluoromethyl) cyclohexane by oral administration in rats.	29
In Vitro Chromosomal Aberration Test of on perfluoro-1,2-dimethylcyclohexane Cultured Chinese Hamster Cells	30
National Institute of Health Sciences	31
Reverse Mutation Test of perfluoro-1,2-dimethylcyclohexane	33

perfluoro-1,2-dimethylcyclohexane

CORE

General information

Identification

SUBSTANCE: perfluoro-1,2-dimethylcyclohexane

UUID: ae31cb58-6a0d-42e4-b092-1d1cb9ec9989

Dossier UUID:

Author: SuperUser

Date: 2019-03-27T09:47:42.877+09:00

Remarks:

Substance name

perfluoro-1,2-dimethylcyclohexane

Legal entity

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

Identification of substance

Reference substance

[1,1,2,2,3,3,4,4,5,6-decafluoro-5,6-bis\(trifluoromethyl\)cyclohexane](#) / [1,1,2,2,3,3,4,4,5,6-decafluoro-5,6-bis\(trifluoromethyl\)cyclohexane](#) / [306-98-9](#) / [206-195-0](#)

EC number

206-195-0

EC name

EC Inventory

CAS number

306-98-9

CAS name

IUPAC name

1,1,2,2,3,3,4,4,5,6-decafluoro-5,6-bis(trifluoromethyl)cyclohexane

Role in the supply chain

Manufacturer

false

Importer

false

Only representative

false

Downstream user

false

OECD

Health Effects

Repeated dose toxicity: oral

ENDPOINT_STUDY_RECORD: Repeated dose toxicity: oral.001

UUID: 8978d9e2-7ec0-4817-be88-3d30ea58bcb8

Dossier UUID:

Author: SuperUser

Date: 2019-03-27T09:23:17.477+09:00

Remarks:

Administrative data

Endpoint

repeated dose toxicity: oral, other

Type of information

experimental study

Adequacy of study

key study

Robust study summary

false

Used for classification

false

Used for SDS

false

Reliability

1 (reliable without restriction)

Rationale for reliability incl. deficiencies

guideline study

Reliability 1

Cross-reference

Reason / purpose

reference to same study

Related information

[OECD / Toxicity to reproduction / Toxicity to reproduction.001 / perfluoro-1,2-dimethylcyclohexane / 1,1,2,2,3,3,4,4,5,6-decafluoro-5,6-bis\(trifluoromethyl\)cyclohexa...](#)

Data source

Reference

[A combined repeated dose/reproductive developmental toxicity study of 1, 1, 2, 2, 3, 3, 4, 4, 5, 6-d... / Ministry of Health, Labor and Welfare, Japan / study report](#)

Data access

data published

Materials and methods

Test guideline

Qualifier

according to

Guideline

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

Deviations

no

GLP compliance

yes

Limit test

no

Test material

Specific details on test material used for the study

- Name of test material (as cited in study report): Perfluoro-1, 2-dimethylcyclohexane
- Analytical purity: 97%
- Storage condition of test material: at a room temperature (15-23°C), protected from light
- Stability under test conditions: The stability of test material was identified by analysis of the remainder.

Test animals

Species

rat

common rodent species

Strain

other: CrI:CD(SD)

Sex

male/female

Details on test animals and environmental conditions

TEST ANIMALS

- Source: Charles River Japan, Inc., Atsugi Breeding Center.
- Age at study initiation: 11 weeks old
- Weight at study initiation: Male: 397 g (364 -442 g), Female: 244 g (226-268 g)
- Housing: Animals were individually housed in bracket-type metallic wire-mesh cages (254W × 350D × 170H mm), from gestation day 17 to lactation day 4, Dams were bred individually or with individual littermates in plastic cages (340W x 400D x 185H mm) and bedding.
- Diet: Solid feed (NMF: Oriental Yeast Co., Ltd.) was given ad libitum.
- Water: Tap water was given ad libitum.
- Acclimation period: 20 days

ENVIRONMENTAL CONDITIONS

- Temperature (°C): 23±3 (actual temperature: 21-28°C)
- Humidity (%): 50±20% (actual humidity: 33-47%)
- Air changes (per hr): 10-15
- Photoperiod (hrs dark / hrs light): 12 hr dark/12 hr light (light: 7:00~19:00)

Administration / exposure**Route of administration**

oral: gavage

Vehicle

other: 0.5 w/v% CMC-Na solution mixed containing 0.1 v/v% Tween 80

Details on oral exposure

- Amount of vehicle (if gavage): 5 mL/kg
- Dosing volume: 5 mL/kg

Analytical verification of doses or concentrations

yes

Duration of treatment / exposure

(P) Males: 42 days including 14 days pre-mating

(P) Females: 41-45 days including 14 days pre-mating, mating and gestation periods and the days until day 4 of lactation

Female (no mating, satellite group): 42 days

Frequency of treatment

Once/day, 7 days/week

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

Main group: 12 animals/sex/dose

Satellite (Recovery) group: 5 males/dose and 5 females/dose (0 and 1000 mg/kg bw/day)

Control animals

yes, concurrent vehicle

Details on study design

- Dose selection rationale: Based on the results of a 14-day preliminary study, the highest dose of 1000 mg/kg bw/day was selected as an expected obvious toxic dose, and the lowest dose of 100 mg/kg bw/day was selected as an expected no toxic dose. The middle dose levels of 300 mg/kg bw/day were selected.
- Rationale for animal assignment (if not random): Body weight-balanced randomization

[14-day preliminary study]

A 14-day repeated dose oral toxicity test (CrI:CD(SD) rats, doses: 0, 100, 300 or 1000 mg/kg bw/day). No death was observed even at 1000 mg/kg bw/day, and no effects were observed in any group s except for a slightly decreased in MCH in males at 300 and 1000 mg/kg bw/day.

Examinations

Observations and examinations performed and frequency

CAGE SIDE OBSERVATIONS: Yes

- Time schedule: 3 times/day (before administration, immediately after administration and 2 hours after administration) during the administration period. Once a day during the recovery period.

DETAILED CLINICAL OBSERVATIONS: Yes

- Time schedule:

Male main group: once before the start of administration, once every weekly during the administration and recovery periods.

Female main group: once before the start of administration, days 1, 7, 14 and 20 of gestation, and day 4 of lactation.

Male and female recovery group: once before the start of administration, once every weekly during the administration and recovery periods.

BODY WEIGHT: Yes

- Time schedule for examinations:

Males in the main groups were weighed on days 1, 4, 8, 11, 15, 18, 22, 25, 29, 32, 36, 39 and 42 of administration and on the day of necropsy, and 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 in addition to the measurement days for males in the main groups.

Females in the main groups were weighed on days 1, 4, 8, 11 and 15 of administration (uncopulated animals were weighed on day 18 of administration as well), days 0, 4, 7, 11, 14, 17 and 20 of gestation, days 0 and 4 of lactation and the day of necropsy.

FOOD CONSUMPTION AND COMPOUND INTAKE (if feeding study):

- Food consumption: Yes

Measurement of food consumption was conducted on all animals at the following frequencies:

males in the main groups on days 1, 4, 8, 11, 15, 32, 36, 39 and 42 of administration; males and females in the recovery groups on days 1, 4, 8, 11 and 14 of recovery in addition to the measurement days for males in the main groups; and females in the main groups 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.

OPHTHALMOSCOPIC EXAMINATION: No

HAEMATOLOGY: Yes

- Time schedule for collection of blood: At the end of administration period, or at the end of recovery period in both sexes
- Anaesthetic used for blood collection: ether
- Animals fasted: Yes
- How many animals: 5 animals/sex/group
- Parameters examined: red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, reticulocyte percentage, platelet count, white blood cell count, differential white blood cell count, absolute number of each white blood cell, prothrombin time, activated partial thromboplastin time, fibrinogen.

CLINICAL CHEMISTRY: Yes

- Time schedule for collection of blood: At the end of administration period, or at the end of recovery period in both sexes
- Animals fasted: Yes
- How many animals: 5 animals/sex/group
- Parameters checked: ALP, total cholesterol, triglyceride, phospholipids, total bilirubin, glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, calcium, inorganic phosphorus, total protein, albumin, A/G ratio, AST (GOT), ALT (GPT), LDH, γ -GTP

URINALYSIS OF MALES: Yes

- Time schedule for collection of urine: final week of administration (days 39 to 40 of administration) and in the final week of recovery (days 11 to 12 of recovery)
 - Metabolism cages used for collection of urine: Yes
- A urine collector to collect four-hour urine samples under fasting but ad libitum drinking conditions, followed by collection of 20-hour urine samples under ad libitum feeding and drinking conditions.
- How many animals: 5 animals/group
 - Parameters checked: pH, protein, ketones, glucose, occult blood, bilirubin, urobilinogen, color, sediment, urine volume (4-hour volume), osmotic pressure, urine volume (20-hour volume), water intake (24-hour volume)

NEUROBEHAVIOURAL EXAMINATION: Yes

- Time schedule for examinations: Manipulative test and measurements of grip strength and motor activity were conducted on 5 animals per group with the following frequencies: males in the main groups were examined in the final week of administration (day 37 of administration), females in the main groups on day 4 of lactation (day 41 to day 44 of administration) after necropsy of F1 pups, and males and females in the recovery groups in the final week of administration (day 37 of administration) and in the final week of recovery (day 9 of recovery).
- Battery of functions tested:
 - 1) Open field observation. Arousal, gait, posture, tremor, convulsion, rearing count, defecation (defecation count, urination), stereotypy (grooming, circling, etc.), abnormal behavior (self-biting, backward walking, etc.)
 - 2) Manipulative Test. Auditory response, approach response, touch response, tail pinch response, pupillary reflex, aerial righting reflex, landing foot splay
 - 3) Measurement of Grip Strength. Following manipulative test, grip strength of forelimb and hind limb was measured by CPU gauge MODEL-9502A (AIKOH Engineering Co., Ltd.).
 - 4) Measurement of Motor Activity. Following measurement of grip strength, motor activity was measured by a motor activity sensor for experimental animals NS-AS01 (Neuro Science, Inc). The measurement was conducted for 1 hour, and measured values at 10-minute intervals and from 0 to 60 minutes were collected.

Sacrifice and pathology

GROSS PATHOLOGY: Yes

ORGAN WEIGHT: Yes [brain, thyroids including parathyroids), adrenal gland, thymus, spleen, heart, liver, kidney, testis, epididymis]

HISTOPATHOLOGY: Yes, [cerebrum, cerebellum, pituitary, spinal cord (thoracic), sciatic nerve, thyroid, parathyroid, adrenal glands, thymus, spleen, submandibular lymph nodes, mesenteric lymph nodes, heart, lung (including bronchial), stomach, duodenum, jejunum, ileum, cecum, colon, rectum, liver, kidney, bladder, testis, epididymis, ovary, uterus, prostate, seminal vesicles, sternum and femur (including bone marrows), macroscopic lesions, and parts for identification (auricles)]

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 Dunnett type mean rank test ($p < 0.05$, two-sided).

In the recovery test, these values of two groups were analyzed by F test. If variances were homogeneous, data was analyzed by the Student t-test, whereas heterogeneous data was analyzed by the Aspin-Welch t-test ($p < 0.05$, two-sided).

Results and discussion

Results of examinations

Clinical signs

no effects observed

Mortality

no mortality observed

Body weight and weight changes

no effects observed

Food consumption and compound intake (if feeding study)

no effects observed

Food efficiency

not examined

Water consumption and compound intake (if drinking water study)

not examined

Ophthalmological findings

not examined

Haematological findings

effects observed, treatment-related

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

Histopathological findings: neoplastic

not examined

Details on results

CLINICAL SIGNS AND MORTALITY:

Mortality: There was no death.

Clinical signs: There were no effects related to the test substance.

DETAILED CLINICAL OBSERVATIONS, MANIPULATIVE TEST, GRIP STRENGTH TEST AND L OCOMOTOR ACTIVITY MEASUREMENT: There were no changes related to the test substance.

BODY WEIGHT:

There were no changes related to the test substance in any groups at the dosing and recovery period s.

FOOD CONSUMPTION:

There were no changes related to the test substance in any groups at the dosing and recovery periods.

URINALYSIS:

There were no changes related to the test substance in any groups at the dosing and recovery periods.

HAEMATOLOGY:

[At the end of dosing period]: At 1000 mg/kg bw/day, decrease in hemoglobin and hematocrit were observed in males.

[At the end of recovery period]: There were no changes related to the test substance in any groups.

CLINICAL CHEMISTRY:

There were no changes related to the test substance in any groups at the dosing and recovery periods.

ORGAN WEIGHTS:

There were no changes related to the test substance in any groups at the dosing and recovery periods.

GROSS PATHOLOGY:

There were no changes related to the test substance in any groups at the dosing and recovery periods.

HISTOPATHOLOGY: NON-NEOPLASTIC:

[At the end of dosing period]: At 1000 mg/kg bw/day, minimal hypertrophy of centrilobular hepatocytes were observed in males.

[At the end of recovery period]: There were no changes related to the test substance in any groups.

Effect levels

Key result true
Dose descriptor NOAEL
Effect level 300 mg/kg bw/day (actual dose received)
Based on test mat.
Sex male/female
Basis for effect level haematology At 1000 mg/kg bw/day, decrease in hemoglobin and hematocrit were observed in males. histopathology: non-neoplastic At 1000 mg/kg bw/day, minimal hypertrophy of centrilobular hepatocytes were observed in males.

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/PDF595-90-4d.pdf

Applicant's summary and conclusion

Executive summary

A combined repeated-dose toxicity study with a reproduction/developmental toxicity screening test (OECD TG422) was conducted to specify the general toxic effects of repeated administration of 1, 1, 2, 2, 3, 3, 4, 4, 5, 6-decafluoro-5, 6-bis (trifluoromethyl) cyclohexane and its effects on reproduction and development. The test substance was administered to male rats (12 males/dose) for 14 days before mating and throughout the mating period until the day before necropsy (42 days) and to female rats (12 females/dose) for 14 days before mating and throughout the mating and gestation periods until day 4 of lactation (41 to 45 days) at doses of 0 (vehicle: 0.5w/v% carboxymethylcellulose sodium solution containing 0.1v/v% Tween 80), 100, 300, and 1,000 mg/kg bw/day. Furthermore, a 14-day recovery period was set for each five males from the control and the 1,000 mg/kg bw/day groups. Five additional females at 0 and 1,000 mg/kg bw/day were dosed with the test substance for 42 days without mating and were examined after a 14-day recovery period.

No effects were observed from the administration of the test article in clinical signs, the functional observation battery (FOB: detailed clinical signs, manipulative test, grip strength, motor activity), body weight, food consumption, urinalysis, blood chemistry, or organ weight. At the end of the administration period, in hematological examination, low values of hemoglobin and hematocrit were found in males in the 1,000 mg/kg bw/day group. Histopathological examination showed minimal hypertrophy of centrilobular hepatocytes in males in the 1,000 mg/kg bw/day group. At the end of the recovery period, the changes observed were no longer observed. The changes in the hematological and histopathological examinations at 1,000 mg/kg bw/day indicated that the NOAEL of repeated-dose toxicity is 300 mg/kg bw/day in rats.

Genetic toxicity in vitro

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.001

UUID: f51293f9-962e-4846-87f0-9e54ad3514ea

Dossier UUID:

Author: SuperUser

Date: 2019-02-15T11:32:07.664+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)

Data source

Reference

[Reverse Mutation Test of perfluoro-1,2-dimethylcyclohexane / Ministry of Health, Labour and Welfare \(MHLW\), Japan / study report](#)

Data access

data published

Materials and methods

Test guideline

Qualifier

according to

Guideline

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

GLP compliance

yes

Type of assay

bacterial reverse mutation assay
in vitro gene mutation study in bacteria

Test material

Specific details on test material used for the study

- Lot No.: 11821MD (Sigma-Aldrich corporation)
- Purity: >97.7%
- Solubility: soluble in water, slightly soluble in 0.5% carboxymethyl cellulose, and insoluble in dimethyl sulfoxide and acetone.
- Physical state: Colorless liquid
- Storage condition of test material: in cool (1-8 degree C)

Method

Species / strain

Species / strain

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

Metabolic activation

with and without

Metabolic activation system

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, 250, 5000 µg /plate

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 not observed at 5000 µg/plate (highest concentration) for all strains with and without S9 mix.

Vehicle

water

Controls

Negative controls

no

Solvent controls

yes

True negative controls

no

Positive controls

yes

Positive control substance

other: without S9 mix: sodium azide (TA 1535) without S9 mix:2-(2-Furyl)-3-(5-nitro -2-furyl)acrylamide (TA100, TA98, WP2uvrA), without S9 mix: 9-Aminoacridine (TA1537) with S9 mix: 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide (all strains)

Details on test system and 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

true

Species / strain

S. typhimurium TA 100
bacteria

Metabolic activation

with and without

Genotoxicity

negative

Cytotoxicity

no, but tested up to limit concentrations

Vehicle controls valid

yes

Positive controls valid

yes

Key result

true

Species / strain

S. typhimurium TA 1535
bacteria

Metabolic activation

with and without

Genotoxicity

negative

Cytotoxicity

no, but tested up to limit concentrations

Vehicle controls valid

yes

Positive controls valid

yes

Key result

true

Species / strain

S. typhimurium TA 1537
bacteria

Metabolic activation

with and without

Genotoxicity

negative

Cytotoxicity

no, but tested up to limit concentrations

Vehicle controls valid

yes

Positive controls valid

yes

Key result

true

Species / strain

S. typhimurium TA 98
bacteria

Metabolic activation

with and without

Genotoxicity

negative

Cytotoxicity

no, but tested up to limit concentrations

Vehicle controls valid

yes

Positive controls valid

yes

Key result

true

Species / strain

E. coli WP2 uvr A pKM 101
bacteria

Metabolic activation

with and without

Genotoxicity

negative

Cytotoxicity

no, but tested up to limit concentrations

Vehicle controls valid

yes

Positive controls valid

yes

Any other information on results incl. tables

Figures and Tables (in English) are available in the following full report of the study. http://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF306-98-9e.pdf

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 perfluoro-1,2-dimethylcyclohexane with or without metabolic activation.

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.002

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Dossier UUID:

Author: SuperUser

Date: 2019-02-15T14:27:58.093+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 perfluoro-1,2-dimethylcyclohexane Cultured Chinese Hamste... / Ministry of Health, Labour and Welfare \(MHLW\), Japan / study report](#)

Data access

data published

Materials and methods

Test guideline

Qualifier

according to

Guideline

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

Test material

Specific details on test material used for the study

- Lot No.: 11821MD (Sigma-Aldrich corporation)
- Purity: >97.7%
- Solubility: soluble in water, slightly soluble in 0.5% carboxymethyl cellulose, and insoluble in dimethyl sulfoxide and acetone.
- Physical state: Colorless liquid
- Storage condition of test material: in cool (2-8 degree C)

Method

Species / strain

Species / strain

other:

Details on mammalian cell lines (if applicable)

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

0, 1000, 2000, 4000 µg/mL

Cell-growth inhibition test was conducted up to the limited concentration of 4000 µg/mL (10 mM)

Cell growth inhibition was not observed for the short-term (+/-S9 mix) and continuous treatment

Vehicle

water

Controls

Negative controls

no

Solvent controls

yes

True negative controls

no

Positive controls

yes

Positive control substance

benzo(a)pyrene

(with S9 mix)

mitomycin C

(without S9 mix)

Details on test system and conditions

METHOD OF APPLICATION: Exposure duration: [short-term treatment]:6 hrs + 18 hr, [continuous treatment]: 24h

NUMBER OF CELLS EVALUATED: 200 cells /concentration (100 cells/plate x 2)

Plates/test: 4

Evaluation criteria

The followings were judged as positive: 1) total chromosomal aberrations increased >10% and concentration dependent increase was observed, 2) total chromosomal aberrations increased >5% and reproducible.

Statistics

not used

Results and discussion

Test results

Key result

true

Species / strain

other: Chinese hamster lung(CHL/IU) cells

Metabolic activation

with and without

Genotoxicity

negative

Cytotoxicity

no, but tested up to precipitating concentrations

Vehicle controls valid

yes

Positive controls valid

yes

Any other information on results incl. tables

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

http://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF306-98-9f.pdf

Applicant's summary and conclusion

Conclusions

without S9 mix: negative

with S9 mix: negative

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: 16b6ebf8-e3bd-4d69-9a8b-de5c461b349d

Dossier UUID:

Author: SuperUser

Date: 2019-03-27T09:23:17.523+09:00

Remarks:

Administrative data

Endpoint

reproductive toxicity, other A combined repeated dose/reproductive developmental toxicity study

Type of information

experimental study

Adequacy of study

key study

Robust study summary

false

Used for classification

false

Used for SDS

false

Reliability

1 (reliable without restriction)

Rationale for reliability incl. deficiencies

guideline study

Reliability 1

Cross-reference

Reason / purpose

reference to same study

Related information

[OECD / Repeated dose toxicity: oral / Repeated dose toxicity: oral.001 / perfluoro-1,2-dimethylcyclohexane / 1,1,2,2,3,3,4,4,5,6-decafluoro-5,6-bis\(trifluoromethyl\)cyclohexa...](#)

Data source

Reference

[A combined repeated dose/reproductive developmental toxicity study of 1, 1, 2, 2, 3, 3, 4, 4, 5, 6-d... / Ministry of Health, Labor and Welfare, Japan / study report](#)

Data access

data published

Materials and methods

Test guideline

Qualifier

according to

Guideline

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

Deviations

no

GLP compliance

yes

Limit test

no

Test material

Specific details on test material used for the study

- Name of test material (as cited in study report): Perfluoro-1, 2-dimethylcyclohexane
- Analytical purity: 97%
- Storage condition of test material: at a room temperature (15-23°C) , protected from light
- Stability under test conditions: The stability of test material was identified by analysis of the remainder.

Test animals

Species

rat

Strain

other: Crl:CD(SD)

Sex

male/female

Details on test animals and environmental conditions**TEST ANIMALS**

- Source: Charles River Japan, Inc., Atsugi Breeding Center.
- Age at study initiation: 11 weeks old
- Weight at study initiation: Male: 397 g (364 -442 g), Female: 244 g (226-268 g)
- Housing: Animals were individually housed in bracket-type metallic wire-mesh cages (254W × 350D × 170H mm), from gestation day 17 to lactation day 4, Dams were bred individually or with individual littermates in plastic cages (340W x 400D x 185H mm) and bedding.
- Diet: Solid feed (NMF: Oriental Yeast Co., Ltd.) was given ad libitum.
- Water: Tap water was given ad libitum.
- Acclimation period: 20 days

ENVIRONMENTAL CONDITIONS

- Temperature (°C): 23±3 (actual temperature: 21-28°C)
- Humidity (%): 50±20% (actual humidity: 33-47%)

- Air changes (per hr): 10-15
- Photoperiod (hrs dark / hrs light): 12 hr dark/12 hr light (light: 7:00~19:00)

Administration / exposure

Route of administration

oral: gavage

Vehicle

other: 0.5 w/v% CMC-Na solution mixed containing 0.1 v/v% Tween 80

Details on exposure

- Amount of vehicle (if gavage): 5 mL/kg
- Dosing volume: 5 mL/kg

Analytical verification of doses or concentrations

yes

Duration of treatment / exposure

(P) Males: 42 days including 14 days pre-mating

(P) Females: 41-45 days including 14 days pre-mating, mating and gestation periods and the days until day 4 of lactation

Female (no mating, satellite group): 42 days

Frequency of treatment

Once/day, 7 days/week

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

Main group: 12 animals/sex/dose

Satellite (Recovery) group: 5 males/dose and 5 females/dose (0 and 1000 mg/kg bw/day)

Control animals

yes, concurrent vehicle

Details on study design

- Dose selection rationale: Based on the results of a 14-day preliminary study, the highest dose of 1000 mg/kg bw/day was selected as an expected obvious toxic dose, and the lowest dose of 100 mg/kg bw/day was selected as an expected no toxic dose. The middle dose levels of 300 mg/kg bw/day were selected.
- Rationale for animal assignment (if not random): Body weight-balanced randomization

[14-day preliminary study]

A 14-day repeated dose oral toxicity test (CrI:CD(SD) rats, doses: 0, 100, 300 or 1000 mg/kg bw/day). No death was observed even at 1000 mg/kg bw/day, and no effects were observed in any groups except for a slightly decreased in MCH in males at 300 and 1000 mg/kg bw/day.

Examinations

Parental animals: Observations and examinations

CAGE SIDE OBSERVATIONS: Yes

- Time schedule: 3 times/day (before administration, immediately after administration and 2 hours after administration) during the administration period. Once a day during the recovery period.

DETAILED CLINICAL OBSERVATIONS: Yes

- Time schedule:

Male main group: once before the start of administration, once every weekly during the administration and recovery periods.

Female main group: once before the start of administration, days 1, 7, 14 and 20 of gestation, and day 4 of lactation.

Male and female recovery group: once before the start of administration, once every weekly during the administration and recovery periods.

BODY WEIGHT: Yes

- Time schedule for examinations:

Males in the main groups were weighed on days 1, 4, 8, 11, 15, 18, 22, 25, 29, 32, 36, 39 and 42 of administration and on the day of necropsy, and 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 in addition to the measurement days for males in the main groups.

Females in the main groups were weighed on days 1, 4, 8, 11 and 15 of administration (uncopulated animals were weighed on day 18 of administration as well), days 0, 4, 7, 11, 14, 17 and 20 of gestation, days 0 and 4 of lactation and the day of necropsy.

FOOD CONSUMPTION AND COMPOUND INTAKE (if feeding study):

- Food consumption: Yes

Measurement of food consumption was conducted on all animals at the following frequencies:

males in the main groups on days 1, 4, 8, 11, 15, 32, 36, 39 and 42 of administration; males and females in the recovery groups on days 1, 4, 8, 11 and 14 of recovery in addition to the measurement days for males in the main groups; and females in the main groups 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.

OPHTHALMOSCOPIC EXAMINATION: No

HAEMATOLOGY: Yes

- Time schedule for collection of blood: At the end of administration period, or at the end of recovery period in both sexes

- Anaesthetic used for blood collection: ether

- Animals fasted: Yes

- How many animals: 5 animals/sex/group

- Parameters examined: red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, reticulocyte percentage, platelet count, white blood cell count, differential white blood cell count, absolute number of each white blood cell, prothrombin time, activated partial thromboplastin time, fibrinogen.

CLINICAL CHEMISTRY: Yes

- Time schedule for collection of blood: At the end of administration period, or at the end of recovery period in both sexes
- Animals fasted: Yes
- How many animals: 5 animals/sex/group
- Parameters checked: ALP, total cholesterol, triglyceride, phospholipids, total bilirubin, glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, calcium, inorganic phosphorus, total protein, albumin, A/G ratio, AST (GOT), ALT (GPT), LDH, γ -GTP

URINALYSIS OF MALES: Yes

- Time schedule for collection of urine: final week of administration (days 39 to 40 of administration) and in the final week of recovery (days 11 to 12 of recovery)
- Metabolism cages used for collection of urine: Yes

A urine collector to collect four-hour urine samples under fasting but ad libitum drinking conditions, followed by collection of 20-hour urine samples under ad libitum feeding and drinking conditions.

- How many animals: 5 animals/group
- Parameters checked: pH, protein, ketones, glucose, occult blood, bilirubin, urobilinogen, color, sediment, urine volume (4-hour volume), osmotic pressure, urine volume (20-hour volume), water intake (24-hour volume)
- Time schedule for examinations: Manipulative test and measurements of grip strength and motor activity were conducted on 5 animals per group with the following frequencies: males in the main groups were examined in the final week of administration (day 37 of administration), females in the main groups on day 4 of lactation (day 41 to day 44 of administration) after necropsy of F1 pups, and males and females in the recovery groups in the final week of administration (day 37 of administration) and in the final week of recovery (day 9 of recovery).

- Battery of functions tested:

- 1) Open field observation. Arousal, gait, posture, tremor, convulsion, rearing count, defecation (defecation count, urination), stereotypy (grooming, circling, etc.), abnormal behavior (self-biting, backward walking, etc.)
- 2) Manipulative Test. Auditory response, approach response, touch response, tail pinch response, pupillary reflex, aerial righting reflex, landing foot splay
- 3) Measurement of Grip Strength. Following manipulative test, grip strength of forelimb and hind limb was measured by CPU gauge MODEL-9502A (AIKOH Engineering Co., Ltd.).
- 4) Measurement of Motor Activity. Following measurement of grip strength, motor activity was measured by a motor activity sensor for experimental animals NS-AS01 (Neuro Science, Inc). The measurement was conducted for 1 hour, and measured values at 10-minute intervals and from 0 to 60 minutes were collected.

Estrous cyclicity (parental animals)

Vaginal smears were collected from all females in the main groups and microscopically examined every day from the day after the start of administration until the day copulation was confirmed. During the pre-mating administration period, vaginal smear pictures were classified as proestrus, estrus, metestrus or diestrus and examined for the frequency of estrus and interval between estruses (estrous cycle). During the mating period, vaginal smears were examined for the presence of sperm.

Sperm parameters (parental animals)

Parameters examined in all P male parental generations: testis weight, epididymis weight, histopathological examinations for testes, epididymides, seminal vesicle and ventral prostate.

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 gain.

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

Postmortem examinations (parental animals)

METHOD OF SACRIFICED: All animals were sacrificed by exsanguination under ether anesthesia.

SACRIFICE: Male animals: On next day after the last administration (Day 43), Maternal animals: on Day 4 of lactation, and Male recovery and female satellite animals: on Day 14 of recovery.

GROSS PATHOLOGY: Yes

ORGAN WEIBHT: Yes [brain, thyroids including parathyroids), adrenal gland, thymus, spleen, heart, liver, kidney, testis, epididymis]

HISTOPATHOLOGY: Yes, [cerebrum, cerebellum, pituitary, spinal cord (thoracic), sciatic nerve, thyroid, parathyroid, adrenal glands, thymus, spleen, submandibular lymph nodes, mesenteric lymph nodes, heart, lung (including bronchial), stomach, duodenum, jejunum, ileum, cecum, colon, rectum, liver, kidney, bladder, testis, epididymis, ovary, uterus, prostate, seminal vesicles, sternum and femur (including bone marrows), macroscopic lesions, and parts for identification (auricles)]

Postmortem examinations (offspring)

SACRIFICE

- The F1 offspring were sacrificed at 4 days of age.

GROSS NECROPSY

- Gross necropsy consisted of external and internal examinations including the cervical, thoracic, and abdominal viscera.

HISTOPATHOLOGY / ORGAN WEIGHTS

- Not examined.

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 Dunnett type mean rank test ($p < 0.05$, two-sided).

In the recovery test, these values of two groups were analyzed by F test. If variances were homogeneous, data was analyzed by the Student t-test, whereas heterogeneous data was analyzed by the Aspin-Welch t-test ($p < 0.05$, two-sided).

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 live pups on day 4/No. of live pups on day 0) × 100

Results and discussion

Results: P0 (first parental animals)

General toxicity (P0)

Clinical signs

no effects observed

Mortality

no mortality observed

Body weight and weight changes

no effects observed

Food consumption and compound intake (if feeding study)

no effects observed

Food efficiency

not examined

Water consumption and compound intake (if drinking water study)

not examined

Ophthalmological findings

not examined

Haematological findings

effects observed, treatment-related

Description (incidence and severity)

See 7.5.1

Clinical biochemistry findings

no effects observed

Urinalysis findings

no effects observed

Behaviour (functional findings)

no effects observed

Immunological findings

not examined

Organ weight findings including organ / body weight ratios

no effects observed

Gross pathological findings

no effects observed

Neuropathological findings

not examined

Histopathological findings: non-neoplastic

effects observed, treatment-related

Description (incidence and severity)

See 7.5.1

Histopathological findings: neoplastic

not examined

Reproductive function / performance (P0)

Reproductive function: estrous cycle

no effects observed

Reproductive function: sperm measures

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

test mat.

Sex

male/female

Basis for effect level

other:

No effects on reproduction

Results: F1 generation

General toxicity (F1)

Clinical signs

no effects observed

Mortality / viability

no mortality observed

Body weight and weight changes

no effects observed

Gross pathological findings

no effects observed

Effect levels (F1)

Key result

true

Dose descriptor

NOAEL

Generation

F1

Effect level

1000

mg/kg bw/day (actual dose received)

Based on
test mat.

Sex
male/female

Basis for effect level
other: No effects on development

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/PDF306-98-9d.pdf

Applicant's summary and conclusion _____

Executive summary

In the above-described OECD TG 422 study, no effects were observed for reproduction or development. The NOAEL for rat reproduction/developmental toxicity of 1, 1, 2, 2, 3, 3, 4, 4, 5, 6-decafluoro-5, 6-bis (trifluoromethyl) cyclohexane was estimated to be 1, 000 mg/kg bw/day (the highest dose tested).

References

REFERENCE_SUBSTANCE: 1,1,2,2,3,3,4,4,5,6-decafluoro-5,6-bis(trifluoromethyl)cyclohexane

UUID: ECB5-21f79ee5-31d6-493a-bdef-04069e6c5f5b

Dossier UUID:

Author: SuperUser

Date: 2019-02-15T14:29:53.866+09:00

Remarks:

General information

Reference substance name

1,1,2,2,3,3,4,4,5,6-decafluoro-5,6-bis(trifluoromethyl)cyclohexane

Inventory

Inventory name

1,1,2,2,3,3,4,4,5,6-decafluoro-5,6-bis(trifluoromethyl)cyclohexane

Inventory

EC

Inventory number

206-195-0

CAS number

306-98-9

Molecular formula

C₈F₁₆

Description

Reference substance information

IUPAC name

1,1,2,2,3,3,4,4,5,6-decafluoro-5,6-bis(trifluoromethyl)cyclohexane

Synonyms

Identity

1,1,2,2,3,3,4,4,5,6-decafluoro-5,6-bis(trifluoromethyl)cyclohexane
--

CAS information

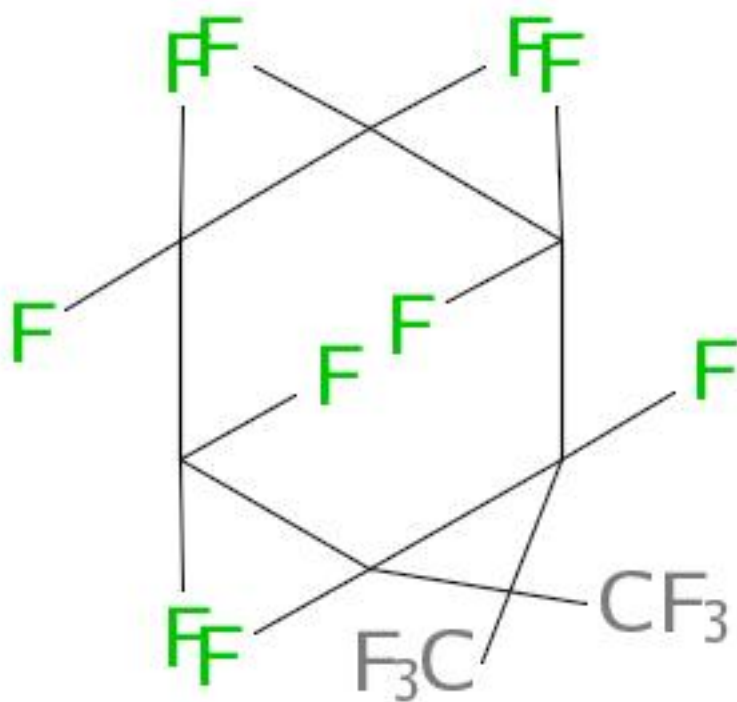
CAS number

306-98-9

Molecular and structural information

Molecular formulaC₈F₁₆**Molecular weight**

400.0601

SMILES notationFC(F)(F)C1(F)C(F)(F)C(F)(F)C(F)(F)C1(F)C(F)(F)F**InChI**InChI=1/C8F16/c9-1(7(19,20)21)2(10,8(22,23)24)4(13,14)6(17,18)5(15,16)3(1,11)12**Structural formula**

LITERATURE: A combined repeated dose/ reproductive developmental toxicity study of 1, 1, 2, 2, 3, 3, 4, 4, 5, 6-decafluoro-5, 6- bis (trifluoromethyl) cyclohexane by oral adm inistration in rats.

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Author: SuperUser

Date: 2019-03-22T10:15:50.000+09:00

Remarks:

General information

Reference Type

study report

Title

A combined repeated dose/reproductive developmental toxicity study of 1, 1, 2, 2, 3, 3, 4, 4, 5, 6-decafluoro-5, 6-bis (trifluoromethyl) cyclohexane by oral administration in rats.

Author

Ministry of Health, Labor and Welfare, Japan

Bibliographic source

Japan Existing Chemical Data Base (JCDB)

Testing facility

Bozo Research Center Inc.

Report no.

R-967

LITERATURE: In Vitro Chromosomal Aberration Test of on perfluoro-1,2-dimethylcyclohexane Cultured Chinese Hamster Cells

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Dossier UUID:

Author: SuperUser

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Remarks:

General information

Reference Type

study report

Title

In Vitro Chromosomal Aberration Test of on perfluoro-1,2-dimethylcyclohexane Cultured Chinese Hamster Cells

Author

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

Bibliographic source

http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp

LEGAL_ENTITY: National Institute of Health Sciences

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General information

Legal entity name

National Institute of Health Sciences

Remarks

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Identifiers

Other IT system identifiers

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10767

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LITERATURE: Reverse Mutation Test of perfluoro-1,2-dimethylcyclohexane

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Dossier UUID:

Author: SuperUser

Date: 2019-02-15T10:58:20.573+09:00

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General information

Reference Type

study report

Title

Reverse Mutation Test of perfluoro-1,2-dimethylcyclohexane

Author

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

Bibliographic source

http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp

Testing facility

Research Institute for Animal Science in Biochemistry and Toxicology (RIAS)