Name: COMPLETE / SUBSTANCE : perfluoro-1,2-dimethylcyclohexane / 1,1,2,2,3,3,4,4,5,6-decafluoro-5,6-bis(trifluoromethyl)cyclohexane / 306-98-9 Fri, 16 Dec 2022, 16:31:01+0900 /

Legal entity owner: National Institute of Health Science

Printing date: 2022-12-16T16:31:01.918+09:00

Table of Contents

DOSSIER:

UUID: 0
Dossier UUID:
Author:
Date: 2022-12-16T16:31:01.802+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
perfluoro-1,2-dimethylcyclohexane / 1,1,2,2,3,3,4,4,5,6-decafluoro-5,6-bis(trifluoromethyl)cyclohexane / 306-98-9

Public name

Submitting legal entity
National Institute of Health Science

Dossier creation date/time
Fri, 16 Dec 2022, 16:31:01+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

perfluoro-1,2-dimethylcyclohexane

CORE

General information

Assessment approach (assessment entities)

FIXED_RECORD: Assessment approach

UUID:	a165ff3b-4bd5-3920-8cc2-87bd649de09e
Dossier UUID:	
Author:	
Date:	2019-03-27T09:47:42.000+09:00
Remarks:	

OECD

Health Effects

Repeated dose toxicity: oral

ENDPOINT_STUDY_RECORD: Repeated dose toxicity: oral.001

UUID: 8978d9e2-7ec0-4817-be88-3d30ea58bcb8
Dossier UUID:
Author:
Date: 2022-12-16T16:28:05.305+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 for cross-reference
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 perfluoro-1,2-dimethylcyclohex / Ministry of Health, Labor 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)

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 remai nder.

Test animals

Species
rat
common rodent species

Strain
other: Crl:CD(SD)

Sex
male/female

Details on test animals or test system and environmental conditions
TEST ANIMALS
- Source: Charles River Japan, Inc., 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 (Crl: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

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 p eriod 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, sedim ent, 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 th e 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 administ ration) 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 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 no des, heart, lung (including bronchial), stomach, duodenum, jejunum, ileum, cecum, colon, rectum, liv er, 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 homogeneo us, 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 LOC OMOTOR 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 periods.

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 pe riods.

HAEMATOLOGY:
[At the end of dosing period]: At 1000 mg/kg bw/day, decrease in hemoglobin and hematocrit were ob served 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 hepat ocytes 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 perfluoro-1,2-dimethylcyclohexane 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

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Dossier UUID:	
Author:	
Date:	2022-12-15T11:20:22.622+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

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
- Name of test material (as cited in study report): Perfluoro-1, 2-dimethylcyclohexane
- 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 / 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, 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 / solvent
water

Controls

Untreated negative controls
no

Negative solvent / vehicle 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)acry lamide (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 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
true

Species / strain
S. typhimurium TA 100
bacteria

Metabolic activation
with and without

Genotoxicity
negative

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

Vehicle controls validity
valid

Positive controls validity
valid

Key result
true

Species / strain
S. typhimurium TA 1535
bacteria

Metabolic activation
with and without

Genotoxicity
negative

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

Vehicle controls validity
valid

Positive controls validity
valid

Key result
true

Species / strain
S. typhimurium TA 1537
bacteria

Metabolic activation
with and without

Genotoxicity
negative

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

Vehicle controls validity
valid

Positive controls validity
valid

Key result
true

Species / strain
S. typhimurium TA 98
bacteria

Metabolic activation
with and without

Genotoxicity
negative

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

Vehicle controls validity
valid

Positive controls validity
valid

Key result
true

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

Positive controls validity
valid

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. typhimuriumTA100, 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:
Date: 2022-12-15T11:21:11.797+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

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
- Name of test material (as cited in study report): Perfluoro-1, 2-dimethylcyclohexane
- 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 / cell type
other:

Details on mammalian cell type (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 / solvent
water

Controls

Untreated negative controls
no

Negative solvent / vehicle 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 experimental 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 / choice of top concentrations
no cytotoxicity, but tested up to precipitating concentrations

Vehicle controls validity
valid

Positive controls validity
valid

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:	
Date:	2022-12-16T16:30:34.204+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 for cross-reference
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 perfluoro-1,2-dimethylcyclohex / Ministry of Health, Labor 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)

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 rema inder.

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 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 (Crl: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 meas urement 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 gesta tion, 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 fem ales in the recovery groups on days 1, 4, 8, 11 and 14 of recovery in addition to the measurement da ys for males in the main groups; and females in the main groups on days 1, 4, 8, 11 and 15 of admini stration, 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 volu me, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, reticulocyte p ercentage, 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.

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

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 WEIGTHS
- 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 generation)

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: oestrous 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 perfluoro-1, 2-dimethylcyclohexane was estimated to be 1, 000 mg/kg bw/day (the highest dose tested).

DOMAIN

Substance

SUBSTANCE: perfluoro-1,2-dimethylcyclohexane

UUID: ae31cb58-6a0d-42e4-b092-1d1cb9ec9989
Dossier UUID:
Author:
Date: 2022-12-16T16:30:50.963+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	EC name
206-195-0	EC Inventory

CAS number	CAS name
306-98-9	

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

References

Reference Substances

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:
Date: 2019-02-15T14:29:53.000+09:00
Remarks:

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

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

Inventory

Inventory number

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

Inventory
EC Inventory

Inventory number
206-195-0

CAS number
306-98-9

Molecular formula
C8F16

Description

CAS number
306-98-9

Synonyms

Synonyms

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

Molecular and structural information

Molecular formula
C8F16

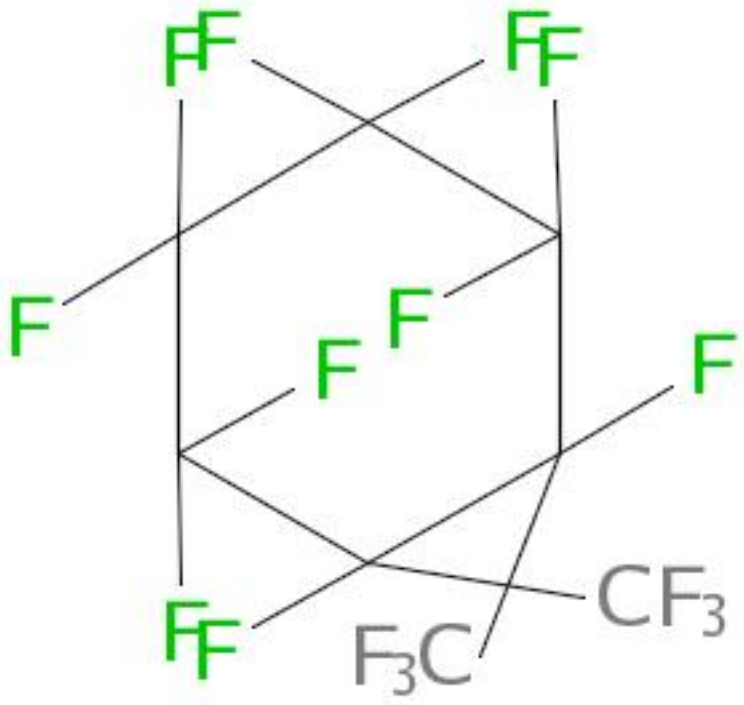
Molecular weight

400.0601

SMILES notation
FC(F)(F)C1(F)C(F)(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



Literatures

LITERATURE: A combined repeated dose/reproductive developmental toxicity study of perfluoro-1,2-dimethylcyclohexane cyclohexane by oral administration in rats.

UUID: b50cc229-f562-4295-b872-8794524835ce
Dossier UUID:
Author:
Date: 2022-12-15T11:14:48.001+09:00
Remarks:

General information

Reference Type
study report

Title
A combined repeated dose/reproductive developmental toxicity study of perfluoro-1,2-dimeth ylcyclohexane 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 number
R-967

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

UUID: 8ae74eb1-b9e0-40a3-9deb-604b590b5be4
Dossier UUID:
Author:
Date: 2019-02-15T14:16:35.000+09:00
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

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

UUID:	5ae4c893-1e85-46a7-ab87-7a22f378cfe1
Dossier UUID:	
Author:	
Date:	2019-02-15T10:58:20.000+09:00
Remarks:	

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)

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.

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Region / State
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Country
Japan
JP

Identifiers

Other IT system identifiers

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

ID
16558402024DIV750