Name: OECD_SIDS / SUBSTANCE : perfluorooctane / 307-34-6 / octadecafluorooctane / 307-34-6 Fri, 16 Dec 2022, 16:36:02+0900 /

Legal entity owner: National Institute of Health Sciences

Printing date: 2022-12-16T16:36:02.199+09:00

Table of Contents

DOSSIER:

UUID: 0
Dossier UUID:
Author:
Date: 2022-12-16T16:36:02.026+09:00
Remarks:

Dossier header

Dossier submission type

Name
OECD SIDS

Version
core 7.0

Name (given by user)

Dossier subject

Dossier subject
perfluorooctane / 307-34-6 / octadecafluorooctane / 307-34-6

Public name

Submitting legal entity
National Institute of Health Science

Dossier creation date/time
Fri, 16 Dec 2022, 16:36:02+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

perfluorooctane / 307-34-6

General information

Identification

Identification

SUBSTANCE: perfluorooctane / 307-34-6

UUID:	63c139c1-694c-4136-8d94-120893d5a9a7
Dossier UUID:	
Author:	
Date:	2022-12-16T16:35:49.753+09:00
Remarks:	

Substance name
perfluorooctane / 307-34-6

Legal entity
National Institute of Health Sciences / Kawasaki / Japan

Identification of substance

Reference substance
perfluorooctane / octadecafluorooctane / 307-34-6 / 206-199-2

EC number	EC name
206-199-2	EC Inventory
CAS number	**CAS name**
307-34-6	
IUPAC name	
octadecafluorooctane	

Role in the supply chain

Manufacturer
false

Importer
false

Only representative
false

Downstream user
false

Toxicological information

Repeated dose toxicity

Repeated dose toxicity: oral

ENDPOINT_STUDY_RECORD: Repeated dose toxicity: oral.001

UUID: 58cd4087-d5eb-4503-87d4-0510528d5c98
Dossier UUID:
Author:
Date: 2022-12-16T16:34:39.463+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
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 / perfluorooctane / 307-34-6 / octadecafluorooctane / 307-34-6

Remarks
Toxicity to reproduction.001

Data source

Reference

A combined repeated-dose/reproductive-developmental toxicity study of perfluorooctane / Ministry of Health, Labour and Welfare(MHLW), Japan / publication

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 Housing humidity temporarily exceeded the prescribed range (50 ± 20%) due to power failure due to lightning. However, the degree was only 3%, which rapidly returned to the normal range. No abnormalities were observed.

GLP compliance
yes

Test material

Specific details on test material used for the study
perfluorooctane / 307-34-6

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
- Source: Charles River Laboratories Japan, Inc. Atsugi
- Age at study initiation: 10 weeks
- Weight at study initiation: Males: 348-405 g; Females: 204-257 g
- Housing: bracket-type metallic wire-mesh cages (W 250×D 350×H 200 mm)
- Diet: ad libitum
- Water: ad libitum
- Acclimation period: 15 days

ENVIRONMENTAL CONDITIONS
- Temperature (°C): 21-26
- Humidity (%): 45-73
- Air changes: 10-15 times / hr
- Photoperiod: 12 hrs dark / 12 hrs light

Administration / exposure

Route of administration
oral: gavage

Vehicle
CMC (carboxymethyl cellulose)

Details on oral exposure
Vehicle: 1 w/v% CMC (carboxymethyl cellulose) solution with 1v/v% Tween 80
Lot/batch no. (if required): 7627 produced by Maruishi Pharmaceutical Co., Ltd.

- Dosing volume: 5 mL/kg bw
- Stability (test solutions): At least 7 days
- Storage condition of test solution: 3 - 8 ℃

Analytical verification of doses or concentrations
yes

Details on analytical verification of doses or concentrations
Test suspensions at each concentration to be used for males in week 1 and final preparations were analyzed by the GC method. Results showed that the concentration of the test article in each concentration was 100.0 to 110.0% of the nominal concentration and both values were within the acceptable range (concentration: percentage of the nominal concentration, 100 ± 10%, C.V.: <= 10%)

Duration of treatment / exposure
males: 42 days, females: 41-53 days from 14 days before mating to day 4 of lactation.

Frequency of treatment
once a day

Doses / concentrations

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

No. of animals per sex per dose
12/sex/dose (0, 100, 300, 1000 mg/kg/day)
5/12 animals/sex were treated as recovery group

5 additional females were treated as satellite group

Control animals
yes, concurrent vehicle

Details on study design
- Dose selection rationale: Doses in this test were set based on the results of the following study: 14-day repeated dose oral toxicity test (Crl:CD(SD) rats).
At 1000 mg/kg/day , tendency on elevated urea nitrogen level.
On the basis of these effects, a dose level of 1000 mg/kg bw/day was selected as the maximum dose, and then dose levels of 1000, 300 and 100 mg/kg bw/day were selected, in accordance with a common ratio of approximately 3.
- Rationale for animal assignment (if not random): Body weight-balanced randomization
- Post-exposure recovery period in satellite groups: 14 days

Examinations

Observations and examinations performed and frequency
CAGE SIDE OBSERVATIONS: Yes
time Schedule：Males and females: 3 times a day during the administration period, once a day during the recovery period

DETAILED CLINICAL OBSERVATIONS: Yes
All animals were subjected to detailed clinical observations once before the start of administration Thereafter, detailed clinical observations were made once a week in dosing and recovery periods. The functional observational battery testing (FOB) , grip strengths, and motor activity were measured on week of administration period (main/recovery group animals) and week of recovery period (recovery group animals). The functional observational battery testing (FOB) , grip strengths, and motor activity were measured on day 4 of lactation (female).

BODY WEIGHT: Yes
- Time schedule for examinations:
Males in the main and recovery groups were weighed on days 1, 4, 8, 11, 15, 18, 22, 25, 29, 32, 36, 39, 42 of administration, and on the day of necropsy.
In addition, males and females in the recovery groups were weighed on days 1, 4, 8, 11 and 14 of re covery, and on the day of necropsy. Females in the main groups were weighed on days 1, 4, 8, 11 and 15 of administration and copulated females were weighed on days 0, 7, 14 and 20 of gestation, and da ys 0 and 4 of lactation.

FOOD CONSUMPTION AND COMPOUND INTAKE (if feeding study):
- Food consumption: Yes, same days of the measuring of body weight
Food consumption was determined on days 1, 4, 8, 11, 15, 32, 36, 39 and 42 of administration for mal es. In addition, it was determined on days 1, 4, 8, 11 and 14 of recovery for males and females in the recovery groups. Food consumption was determined on days 1, 4, 8, 11, and 15 of administration, d ays 1, 4, 7, 11, 14, 17 and 20 of gestation, and days 2 and 4 of lactation for females.

HAEMATOLOGY: Yes

CLINICAL CHEMISTRY: Yes

URINALYSIS: Yes
- Time schedule for collection of urine: on week 6 of administration period (main/recovery group anim als) and week 2 of recovery period (recovery group animals).
- Metabolism cages used for collection of urine: Yes
- Animals fasted: fasting (4h-urine)
no fasting (20h-urine)

Sacrifice and pathology
GROSS PATHOLOGY: Yes
ORGAN WEIGHT: Yes [brain, thyroid, parathyroid, thymus, heart, liver, spleen, kidney, adrenal gland, testis, epididymis]

HISTOPATHOLOGY: Yes
Necropsy
Gross necropsy consisted of external and internal examinations including cerebrum, cerebellum and pituitary, spinal cord, sciatic nerve, thyroid gland, parathyroid, adrenal glands, thymus, spleen, submandibular lymph nodes, mesenteric lymph nodes, heart, lung((including bronchus), stomach, duodenum, jejunum, ileum, cecum, colon, rectum, liver, kidney, bladder, testis, epididymis, ovary, uterus, seminal vesicles, breast bone(including bone marrow), femur (including bone marrow), and gross abnormal site.

Statistics
As for parametric data (body weight, food consumption, amount of water ingested hematology and clinical chemistry data, organ weights), the values of means and standard deviations were calculated per group.

When more than three groups exist in the test group, Bartlett test for variance was done, and if the variance was homogenous, ANOVA was applied. If the variance was not homogenous or data was non-parametric.
Consequently, if the result was significant, Dunnett multiple comparison or Dunnett-typed method was used for detection of statistical significance against control group.
When the number of the test group was two, F-test was used as for parametric data. Then, student's t-test or Aspin-Welch's t-test was applied depending on the result of homogeneity of variance.

Results and discussion

Results of examinations

Clinical signs
no effects observed

Description (incidence and severity)
see Details on results

Mortality
no mortality observed

Body weight and weight changes
no effects observed

Description (incidence and severity)
At 1000 mg/kg/day, female rats (main group) was showed a significant decrease in body weight gain during the pre-mating period.
Significantly higher body weight gain was observed in female rats (recovery group) during the recovery period.
These changes were only slight changes and not considered to be toxicological effects.
No significant differences in body weight and body weight gain were observed in female rats (main group) during pregnancy and lactation periods.
At 1000 mg/kg/day, female rats (recovered group) did not differ significantly from controls in body weight or body weight gain during the study.

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

Description (incidence and severity)
At 1000 mg/kg/day, female rats had significantly higher food consumption on day 4 of lactation. But it is considered to be spontaneous, because no effect was found on food consumption-related body weight changes.

Food efficiency
no effects observed

Water consumption and compound intake (if drinking water study)
no effects observed

Haematological findings
no effects observed

Clinical biochemistry findings
no effects observed

Urinalysis findings
no effects observed

Description (incidence and severity)
Significantly lower urine volumes were observed in male rats at 1000 mg/kg/day on week 6 of administration. However, there were no changes in water consuption and urine osmolality, and this effect was considered to be spontaneous.

Behaviour (functional findings)
no effects observed

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

Description (incidence and severity)
At 300 mg/kg bw/day, relative liver weights were significantly lower in males.
At 100 mg/kg bw/day and 300 mg/kg bw/day absolute heart weights were significantly lower in females.
These changes were considered to be spontaneous because histopathological changes were not observed and changes were not dose dependent.

At 1000 mg/kg bw/day, significantly lower absolute and relative thyroid weights were observed in males (recovered group).
At 1000 mg/kg bw/day, lower relative adrenal weights were significantly observed in females (recove red group).

Gross pathological findings
no effects observed

Description (incidence and severity)
At the end of the administration period, white foci of the epididymis was observed one rat at 300 mg/kg bw/day.
At 1000 mg/kg bw/day, dark red foci in the lungs (including the bronchi) was observed in one males.
At 300 mg/kg bw/day, a atrophy of seminal vesicle was observed in one male.
In control group, hypertrophy of the spleen was observed in one male.
In control group, dark red foci of glandular stomachs were observed in one female. Dark red foci of gl andular stomachs were observed in one female, two females, and three females at each 100 mg/kg bw/day, 300 mg/kg bw/day, and 1000 mg/kg bw/day.

At 100 mg/kg bw/day, atrophy of testes was observed in one male.
At the end of the recovery period, at 1000 mg/kg bw/day, dark red nests of glandular stomach were observed in one female.
At the end of the recovery period, testicular miniaturization was observed in one male in the control group.
These changes were considered to be spontaneous because these changes were not observed and changes were not dose dependent.

Histopathological findings: non-neoplastic
no effects observed

Description (incidence and severity)
At the end of the administration period
Epididymis : At 300 mg/kg bw/day, mild spermatic granulomas were observed in one male (observed with white foci at necropsy). Minor intraluminal cellular debris was observed in two males in the control group and one male at 300 mg/kg bw/day.

Heart : Minor myocarditis was observed in one male in the control group and in two males at 1000 mg/kg bw/day.

Kidney : Minor tubular regeneration was observed in three males in the control group and in two males and one female at 1000 mg/kg bw/day.

Liver : Minor microgranulomas were observed in five males and two females in the control group and in three females at 1000 mg/kg bw/day.
Mild histiocytic cell infiltration was observed in one male in the control group.

Lungs (including bronchi): Minor collection of foam cells was observed in one male in the control group. Minor foci of pneumonitis were 1000 mg/kg bw/day and one male (observed dark red foci at necropsy)
Pituitary : Cysts were observed at 1000 mg/kg bw/day in one male.

Seminal vesicle : At 300 mg/kg bw/day, no changes were observed in one rat with atrophy at n ecropsy.

Spleen: Mild foci of necrosis were observed in one male in the control group (males with hypertrophy at necropsy) and slight or mild extramedullary hematopoiesis was observed in five rats both sex in the control group and at 1000 mg/kg bw/day. Mild histiocytic cell infiltration was observed in one male in the control group.

Gastric : Slight or mild glandular stomach erosion was observed in one female in the control group and in 1, 2, and 3 females (with dark red foci at necropsy) at 100, 300, and 1000 mg/kg bw/day.
Minor forestomach erosions were observed in one female at 100 mg/kg bw/day.

Testis : Severe atrophy of seminiferous tubule was observed in one male (with atrophy at necropsy) at 100 mg/kg bw/day.
In addition, slight atrophy of the seminiferous tubules was observed in one rat each at 1000 mg/kg bw/day and control group.

Bladder: Minor submucosal cellular infiltration was observed in one male at 1000 mg/kg bw/day.

End of the recovery period:
Stomach: Minor erosions of the glandular stomach were observed in one female (with dark red nests at necropsy) at 1000 mg/kg bw/day.
Testis : Slight atrophy of the seminiferous tubules was observed in one control animal (with atrophy at necropsy).

These changes were considered to be spontaneous because changes were not dose dependent.

Effect levels

Key result
true

Dose descriptor
NOAEL

Effect level

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

Based on
test mat.

Sex
male/female

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/PDF307-34-6d.pdf

Applicant's summary and conclusion

Conclusions
The NOAEL for the repeated-dose toxicity of perfluorooctane was determined to be 1,000 mg/kg bw/day (the highest dose tested) in rats.

Executive summary

A combined repeated-dose toxicity study with a reproduction/developmental toxicity screening test was performed in accordance with OECD test guideline (TG) 422. Male and female rats (12 animals/sex/dose) received perfluorooctane via oral gavage at doses of 0 [vehicle: 1% (w/v) sodium carboxymethylcellulose solution and 1% (v/v) Tween 80], 100, 300, and 1,000 mg/kg body weight (bw)/day. Males were treated with perfluorooctane for 42 days in males, including a 14-day premating period and a subsequent mating period, while females were treated for 41–53 days, including 14-day premating, mating, and gestation periods, until lactation day 4. Of the 12 males treated with 0 and 1,000 mg/kg bw/day, five were assigned as a recovery group. Five additional females treated with 0 and 1,000 mg/kg bw/day were assigned as a satellite group and treated with perfluorooctane for 42 days, without mating, and examined after a 14-day recovery period.

There were no deaths and no changes in clinical signs, manipulative test, grip strength, motor activity, body weight, food consumption, urinalysis, hematology, blood chemistry, organ weight, or gross and histopathological findings as a result of treatment in any of the dose groups for both sexes at the end of the treatment and recovery periods. The NOAEL for the repeated-dose toxicity of perfluorooctane was determined to be 1,000 mg/kg bw/day (the highest dose tested) in rats.

Genetic toxicity

Genetic toxicity in vitro

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.001

UUID:	2e6b0625-72e8-47dd-b5c2-87ee86491767
Dossier UUID:	
Author:	
Date:	2022-12-12T15:53:12.407+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
false

Used for classification
false

Used for SDS
false

Reliability
1 (reliable without restriction)

Rationale for reliability incl. deficiencies
guideline study
Reliability 1

Data source

Reference

A reverse mutation test of perfluorooctane on bacteria / Ministry of Health, Labour and Welfare(MHLW), Japan / publication

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
perfluorooctane / 307-34-6

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

Test concentrations with justification for top dose
S9 mix; SD male rat liver, induced by phenobarbital and 5,6-benzoflavone.
-S9 mix: 0(Vehicle), 1.22, 4.88, 19.5, 78.1, 313, 1250 and 5000 μg/plate plate (all strains)
+S9 mix: 0(Vehicle), 1.22, 4.88, 19.5, 78.1, 313, 1250 and 5000 μg/plate plate (all strains)
As the results of the preliminary test, growth inhibition by the test substance was not observed irr espective of the presence or absence of metabolic activation. In observation for precipitation of the test substance on the plate, oily precipitation was observed at 5000 μg/plate in the system without metabolic activation.
Maximum concentration was established based on the result of the preliminary test at concentration up to 5000 μg/plate and diluted 4 times using a common ratio of 2 and a total of 5 dose levels were set.

Vehicle / solvent
DMF
Manufacturer Wako Pure Chemical Industries, Ltd.
Lot Number SDL2300
Specification JIS special grade, not lower than 99%
Storage Conditions Room temperature
Storage The test substance preparation and storage room at Tokyo Laboratory

Controls

Untreated negative controls
no

Negative solvent / vehicle controls
yes

True negative controls
no

Positive controls
yes

Positive control substance
sodium azide
benzo(a)pyrene
other: 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide 2-Methoxy-6-chloro-9-[3-(2-chloroethyl)-aminopro pylamino]acridine·2HCl 2-Aminoanthracene

Details on test system and experimental conditions
METHOD OF APPLICATION: Preincubation
DURATION- Preincubation period: 20 min at 37°C
- Exposure duration: 48 hours and above
NUMBER OF PLATES: 3
NUMBER OF REPLICATIONS: 2

DETERMINATION OF CYTOTOXICITY- Method: other: growth inhibition

Evaluation criteria
If over a two-fold increase in the number of revertant colonies on the test plates was observed in c omparison with the number of natural revertant colonies (the negative control) and dose response and reproducibility were noted, or if no clear dose response was observed but there was at least two-fold increase in comparison with the number of natural revertant colonies and reproducibility was observed in the two main tests, the test substance was judged to be positive. For the results of the measurement in this study, mean with standard deviation was also described.

Statistics
not used

Results and discussion

Test results

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
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
E. coli WP2 uvr A
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

Tables in English are attached.

Applicant's summary and conclusion

Conclusions
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, TA1537 and E. coli WP2 uvrA (OECD TG 471), negative results were obtained for perfluorooctane with or without metabolic activation.

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.002

UUID: ad079d1a-2f8f-46ba-80bd-458a457a25d5
Dossier UUID:
Author:
Date: 2019-05-23T13:33:00.000+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
false

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

Chromosomal aberration test in cultured chinese hamster cells treated with perfluorooctane / Ministry of Health, Labour and Welfare(MHLW), Japan / publication

Data access
data published

Materials and methods

Test guideline

Qualifier
according to guideline

Guideline
OECD Guideline 473 (In Vitro Mammalian Chromosomal Aberration Test)
in vitro cytogenicity / chromosomal aberration study in mammalian cells (from 26 September 2014)

GLP compliance
yes (incl. QA statement)

Type of assay
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
perfluorooctane / 307-34-6

Method

Species / strain

Species / strain / cell type
Chinese hamster lung (CHL/IU)
mammalian cell line

Metabolic activation
with and without

Metabolic activation system
S9 mix; SD male rat liver, induced by phenobarbital and 5,6-benzoflavone

Test concentrations with justification for top dose
Highest concentration was set as 4500 µg/mL (10 mM).
Cell growth inhibition study + S9 mix and - S9 mix
4500, 2250, 1125, 562.5, 281.3, 140.6 and 70.31 µg/mL
Chromosome Aberration Test + S9 mix and - S9 mix
4500, 2250, 1125 and 562.5 µg/mL
Cell growth inhibition was not observed up to 4500µg/mL

Vehicle / solvent
no

Controls

Untreated negative controls
no a non-treatment group was provided

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: [continuous treatment]: 24, 48 hrs [short-term t reatment]:6 hrs + 18 hr

SPINDLE INHIBITOR: Colcemid
NUMBER OF REPLICATIONS: 2
NUMBER OF CELLS EVALUATED: 200 cells / dose
DETERMINATION OF CYTOTOXICITY
- Method: relative total growth

Evaluation criteria
For the evaluation of the frequencies of structural aberrations and of polyploidy induced, the following criteria were employed.
Appearance incidence of cells with chromosomal aberrations: Negative (-): < 5%; equivocal (±): 5 -10%; positive (+): > 10%.
The total incidence of cells with structural aberrations was calculated in 2 ways, one including gaps (TAG) and another excluding gaps (TA), and the latter was used for the final evaluation.
Finally, the substance is positive when the incidence is considered to be dose-related and reproducible.

Statistics
no

Results and discussion

Test results

Key result
true

Species / strain
Chinese hamster lung (CHL/IU)
mammalian cell line

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
not examined

Untreated negative controls validity
valid

True negative controls validity
not examined

Positive controls validity
not 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/PDF307-34-6f.pdf

Applicant's summary and conclusion

Conclusions
Perfluorooctane had neither potential to induce structural chromosome aberration nor potential to in duce polyploidy under the conditions of this study.

A chromosome aberration test was conducted using cultured Chinese hamster lung fibroblast (CHL/ IU) cells to examine whether perfluorooctane has the potential to induce chromosome aberrations.

Firstly, a cell-growth inhibition test was conducted at the highest concentration of 4500 µg/mL, which is equivalent to 10 mM that is specified in the toxicity study guidelines. As the result, cell-growt h inhibition of 50% or that exceeded 50% was not observed even at 4500 µg/mL in the short-term treatment methods or continuous treatment methods, and thus the 50% cell-growth inhibition conc entration (approximate value) of the test article was calculated to be at least 4500.0 µg/mL for both the short-term treatment methods and continuous treatment methods. Based on the results of the cell growth inhibition test, the highest dose concentration was set at 4500 µg/mL and a total of 4 dose concentrations were provided using a common ratio of 2 for both the short-term treatment and continuous treatment in the chromosome aberration test to examine for the presence or absence of chromosome aberration inducibility of the test article.
In the chromosome aberration test, neither increase in chromosome structural aberration nor increase in the incidence of the occurrence of polyploidy was observed in the short-term treatment with or wit hout metabolic activation. In the 24-hour and 48-hour continuous treatments, neither increase in ch romosome structural aberration nor increase in the incidence of the occurrence of polyploidy was obs erved. In the positive control group, remarkable induction of chromosome structural aberrations was observed. The incidence of the occurrence of chromosome structural aberration and polyploidy in th e non-treatment group in each treatment method was within the judging criteria of negative results a nd similar to the historical background data of the test facility. Therefore the study was thought to be conducted appropriately.

Executive summary

Perfluorooctane had neither potential to induce structural chromosome aberration nor potential to induce polyploidy under the conditions of this study.

Toxicity to reproduction

Toxicity to reproduction

ENDPOINT_STUDY_RECORD: Toxicity to reproduction.001

UUID: 8a0a07e7-aaa7-42d1-a434-066c721423cf
Dossier UUID:
Author:
Date: 2022-12-16T16:35:41.016+09:00
Remarks:

Administrative data

Endpoint
screening for reproductive / developmental toxicity

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 / perfluorooctane / 307-34-6 / octadecafluorooctane / 307-34-6

Remarks
Repeated dose toxicity: oral.001

Data source

Reference

A combined repeated-dose/reproductive-developmental toxicity study of perfluorooctane / Ministry of Health, Labour and Welfare(MHLW), Japan / publication

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
yes Housing humidity temporarily exceeded the prescribed range (50 ± 20%) . Rapidly returned to the normal range and no abnormalities were observed in the general condition of the animals. There was no effect on the reliability of the test.

GLP compliance
yes

Test material

Specific details on test material used for the study
perfluorooctane / 307-34-6

Test animals

Species
rat

Strain
other: Crl: CD(SD)

Sex
male/female

Details on test animals or test system and environmental conditions
- Source: Charles River Laboratories Japan, Inc. Atsugi
- Age at study initiation: 10 weeks
- Weight at study initiation: Males: 348-405 g; Females: 204-257 g
- Housing: bracket-type metallic wire-mesh cages (W 250×D 350×H 200 mm)
- Diet: ad libitum
- Water: ad libitum
- Acclimation period: 15 days

ENVIRONMENTAL CONDITIONS
- Temperature (°C): 21-26
- Humidity (%): 45-73
- Air changes: 10-15 times / hr
- Photoperiod: 12 hrs dark / 12 hrs light

Administration / exposure

Route of administration
oral: gavage

Vehicle
CMC (carboxymethyl cellulose)

Details on exposure
Vehicle: 1 w/v% CMC (carboxymethyl cellulose) with 1 v/v% Tween 80
Lot/batch no. (if required): 7627 produced by Maruishi Pharmaceutical Co., Ltd.

Analytical verification of doses or concentrations
yes

Details on analytical verification of doses or concentrations
Test suspensions at each concentration to be used for males in week 1 and final preparations were analyzed by the GC method. Results showed that the concentration of the test article in each concentration was 100.0 to 110.0% of the nominal concentration and both values were within the acceptable range (concentration: percentage of the nominal concentration, 100 ± 10%, C.V.: <= 10%)

Duration of treatment / exposure
males: 42 days, females: 41-53 days from 14 days before mating to day 4 of lactation.

Frequency of treatment
once a day

Doses / concentrations

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

No. of animals per sex per dose
12/sex/dose (0, 100, 300, 1000 mg/kg/day)

Control animals
yes, concurrent vehicle

Details on study design
- Dose selection rationale: Doses in this test were set based on the results of the following study: 14-day repeated dose oral toxicity test (Crl:CD(SD) rats.
At 1000 mg/kg/day , tendency on elevated urea nitrogen level.

On the basis of these effects, a dose level of 1000 mg/kg bw/day was selected as the maximum dose, and then dose levels of 1000, 300 and 100 mg/kg bw/day were selected, in accordance with a common ratio of approximately 3.
- Rationale for animal assignment (if not random): Body weight-balanced randomization

- Post-exposure recovery period in satellite groups: 14 days

Examinations

Parental animals: Observations and examinations
CAGE SIDE OBSERVATIONS: Yes
time Schedule：Males and females: 3 times a day during the administration period, once a day during the recovery period

BODY WEIGHT: Yes
- Time schedule for examinations:
Males in the main and recovery groups were weighed on day 1, 4, 8, 11, 15, 18, 22, 25, 29, 32, 36, 39, 42 of administration, and on the day of necropsy.
In addition, males and females in the recovery groups were weighed on days 1, 4, 8, 11 and 14 of r ecovery. and on the day of necropsy.
Females in the main groups were weighed on day 1, 4, 8, 11 and 15 of administration and copulated females were weighed on day 0, 7, 14 and 20 of gestation, and days 0 and 4 of lactation.

DETAILED CLINICAL OBSERVATIONS: Yes
All animals were subjected to detailed clinical observations once before the start of administration Thereafter, detailed clinical observations were made once a week in dosing and recovery periods.
The functional observational battery testing (FOB) , grip strengths, and motor activity were measured on week of administration period (main/recovery group animals) and week of recovery period (recovery group animals).
The functional observational battery testing (FOB) , grip strengths, and motor activity were measured to day 4 of lactation(female).

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.
Mean estrous cycle (day) and abnormal estrous cycle animals (not 4 to 6 days in estrous cycle) were examined.

Sperm parameters (parental animals)
Parameters examined in P male parental generations: testes weight, epididymides weight

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.

Postmortem examinations (parental animals)
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.

Postmortem examinations (offspring)
SACRIFICE: the F1 pups were euthanized on pnd 4 by exsanguination ether anesthesia, intrap eritoneally.
gross necropsy: yes

Statistics
As for parametric data (body weight, food consumption, amount of water ingested hematology and clinical chemistry data, organ weights,

number of times of appearance of estrus, sex cycle, number of days to mating, pregnancy period, number of corpus luteums, number of implantation, number of births), the values of means and stan dard deviations were calculated per group.

When more than three groups exist in the test group, Bartlett test for variance was done, and if the vari ance was homogenous, ANOVA was applied. If the variance was not homogenous or data was non-parametric.
Consequently, if the result was significant, Dunnett multiple comparison or Dunnett-typed method was used for detection of statistical significance against control group.
When the number of the test group was two, F-test was used as for parametric data. Then, student's t-test or Aspin-Welch's t-test was applied depending on the result of homogeneity of variance.

Reproductive indices
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 = (Number of live pups on day 4 after birth/Number of live pups born) ×100

Results and discussion

Results: P0 (first parental generation)

General toxicity (P0)

Clinical signs
no effects observed

Dermal irritation (if dermal study)
no effects observed

Mortality
no mortality observed

Body weight and weight changes
no effects observed

Description (incidence and severity)
At 1000 mg/kg/day, female rats (main group) showed observed a significant decrease in body weight gain during the pre-mating period.
Significantly higher body weight gain was observed in female rats (recovery group) during the rec overy period.
These changes are only slight changes. No significant differences in body weight and body weight gain were observed in female rats (main group) during pregnancy and grooming.

At 1000 mg/kg/day, female rats (recovered group) did not differ significantly from controls in body w eight or body weight gain during the study.

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

Description (incidence and severity)
At 1000 mg/kg/day, female rats had significantly higher food consumption on day 4 of lactation, but no effect on food consumption-related body weight changes.

Food efficiency
no effects observed

Water consumption and compound intake (if drinking water study)
no effects observed

Haematological findings
no effects observed

Clinical biochemistry findings
no effects observed

Urinalysis findings
no effects observed

Description (incidence and severity)
Significantly lower urine volumes were observed in male rats at 1000 mg/kg/day 6 weeks of administration. However, there were no changes in urine volume and urine osmolality.

Behaviour (functional findings)
no effects observed

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

Description (incidence and severity)
At 300 mg/kg bw/day, relative liver weights were significantly lower in males.
At 100 mg/kg bw/day and 300 mg/kg bw/day absolute heart weights were significantly lower in females.
At 1000 mg/kg bw/day, significantly lower absolute and relative thyroid weights were observed in mal es (recovered group).
At 1000 mg/kg bw/day, lower relative adrenal weights were significantly observed in females (recov ered group).

Gross pathological findings
no effects observed

Description (incidence and severity)
At the end of the administration period, white foci of the epididymis was observed one rat at 300 mg/ kg bw/day.
At 1000 mg/kg bw/day, dark red foci in the lungs (including the bronchi) were observed in one males.
At 300 mg/kg bw/day, a small seminal vesicle was observed in one male.
In control group, big spleen was observed in one male.
In control group, dark red foci of glandular stomachs were observed in one female. Dark red foci of g landular stomachs were observed in one female, two females, and three females at each 100 mg/kg bw/day, 300 mg/kg bw/day, and 1000 mg/kg bw/day.
At 100 mg/kg bw/day, atrophy of testes was observed in one case.
At the end of the recovery period, at 1000 mg/kg bw/day, dark red nests of glandular stomach were o bserved in one female.

At the end of the recovery period, testicular miniaturization was observed in one male in the control group.

Neuropathological findings
no effects observed

Histopathological findings: non-neoplastic
no effects observed

Description (incidence and severity)
At the end of the administration period
Epididymis : 300 mg/kg bw/day, mild spermatic granulomas were observed in one male. (observed with white foci at necropsy). Minor intraluminal cellular debris was observed in two males in the control group and one male at 300 mg/kg bw/day.
Heart : Minor myocarditis was observed in one male in the control group and in two males at 1000 mg/kg bw/day.
Kidney : Minor tubular regeneration was observed in three males in the control group and in two males and one female at 1000 mg/kg bw/day.
Liver : Minor microgranulomas were observed in five males and two females in the control group and i n three females in each at 1000 mg/kg bw/day.
Mild histiocytic cell infiltration was observed in one male in the control group.
Lungs (including bronchi): Minor collection of foam cells was observed in one male in the control group. Minor foci of pneumonitis were 1000 mg/kg bw/day and one male (observed dark red foci at necropsy)
Pituitary : Cysts were observed at 1000 mg/kg bw/day in one male.
Seminal vesicle : At 300 mg/kg bw/day, no changes were observed in one rat with atrophy at n ecropsy.
Spleen: Mild foci of necrosis were observed in one male in the control group (males with hypertrophy at necropsy) and slight or mild extramedullary hematopoiesis was observed in five rats both sex in the control group and at 1000 mg/kg bw/day. Mild histiocytic cell infiltration was observed in one male in the control group.
Gastric : Slight or mild glandular stomach erosion was observed in one female in the control group and in 1, 2, and 3 females (with dark red foci at necropsy) at 100, 300, and 1000 mg/kg bw/day.
Minor forestomach erosions were observed in one female at 100 mg/kg bw/day.
Testis : Severe atrophy of seminiferous tubule was observed in one male (with atrophy at necropsy) at 100 mg/kg bw/day.
In addition, slight atrophy of the seminiferous tubules was observed in one rat each at 1000 mg/kg bw/day and control group.
Bladder: Minor submucosal cellular infiltration was observed in one male at 1000 mg/kg bw/day.

End of the recovery period:
Stomach: Minor erosions of the glandular stomach were observed in one female (with dark red nests at necropsy) at 1000 mg/kg bw/day.
Testis : Slight atrophy of the seminiferous tubules was observed in one control animal (with atrophy a t necropsy).

Histopathological findings: neoplastic
no effects observed

Reproductive function / performance (P0)

Reproductive function: oestrous cycle
no effects observed

Reproductive function: sperm measures
not examined

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

Results: F1 generation

General toxicity (F1)

Clinical signs
no effects observed

Mortality / viability
mortality observed, non-treatment-related

Body weight and weight changes
no effects observed

Gross pathological findings
effects observed, non-treatment-related

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

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/PDF307-34-6d.pdf

Applicant's summary and conclusion

Conclusions
The NOAEL for the toxicity of perfluorooctane to rat reproduction and development was determined to be 1,000 mg/kg bw/day (the highest dose tested).

Executive summary

A combined repeated-dose toxicity study with a reproduction/developmental toxicity screening test was performed in accordance with OECD test guideline (TG) 422. Male and female rats (12 animals/sex/dose) received perfluorooctane via oral gavage at doses of 0 [vehicle: 1% (w/v) sodium carboxymethylcellulose solution and 1% (v/v) Tween 80], 100, 300, and 1,000 mg/kg body weight (bw)/day. Males were treated with perfluorooctane for 42 days in males, including a 14-day premating period and a subsequent mating period, while females were treated for 41–53 days, including 14-day premating, mating, and gestation periods, until lactation day 4. Of the 12 males treated with 0 and 1,000 mg/kg bw/day, five were assigned as a recovery group. Five additional females treated with 0 and 1,000 mg/kg bw/day were assigned as a satellite group and treated with perfluorooctane for 42 days, without mating, and examined after a 14-day recovery period. No toxicity was observed in reproduction and development up to the highest dose. The NOAEL for the toxicity of perfluorooctane to rat reproduction and development was determined to be 1,000 mg/kg bw/day (the highest dose tested).

References

Reference Substances

REFERENCE_SUBSTANCE: perfluorooctane

UUID: ECB5-6946b95b-842e-4778-a8ee-138b12a440ca
Dossier UUID:
Author:
Date: 2007-05-10T18:00:00.000+09:00
Remarks:

Reference substance name
perfluorooctane

IUPAC name
octadecafluorooctane

Inventory

Inventory number

Inventory name
perfluorooctane

Inventory
EC Inventory

Inventory number
206-199-2

CAS number
307-34-6

Molecular formula
C8F18

Description

CAS number
307-34-6

Synonyms

Synonyms

Identity
Octane, octadecafluoro-

Identity
Octane, octadecafluoro-

Molecular and structural information

Molecular formula
C8F18

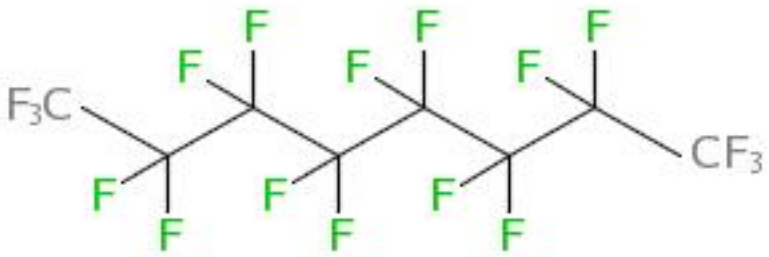
Molecular weight

438.0569

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

InChI
InChI=1/C8F18/c9-1(10,3(13,14)5(17,18)7(21,22)23)2(11,12)4(15,16)6(19,20)8(24,25)26

Structural formula



Literatures

LITERATURE: A combined repeated-dose/reproductive-developmental toxicity study of perfluorooctane

UUID: 1ade8b53-d5e9-4d63-a005-7e9144c11c32
Dossier UUID:
Author:
Date: 2019-05-21T16:55:54.000+09:00
Remarks:

General information

Reference Type
publication

Title
A combined repeated-dose/reproductive-developmental toxicity study of perfluorooctane

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

Year
2010

LITERATURE: A reverse mutation test of perfluorooctane on bacteria

UUID:	c88c8813-84fb-431a-9200-b8b45fbdb910
Dossier UUID:	
Author:	
Date:	2019-05-22T11:34:48.000+09:00
Remarks:	

General information

Reference Type
publication

Title
A reverse mutation test of perfluorooctane on bacteria

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

Year
2008

LITERATURE: Chromosomal aberration test in cultured chinese hamster cells treated with perfluorooctane

UUID:	d2331976-1be9-4863-b85f-6617e1803ace
Dossier UUID:	
Author:	
Date:	2019-05-21T16:56:07.000+09:00
Remarks:	

General information

Reference Type
publication

Title
Chromosomal aberration test in cultured chinese hamster cells treated with perfluorooctane

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

Year
2008

Legal Entities

LEGAL_ENTITY: National Institute of Health Sciences

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

General information

Legal entity name
National Institute of Health Sciences

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

Address

Address 1
Tonomachi 3-25-26

Address 2
Kawasaki-ku

Postal code
210-9501

Town
Kawasaki

Region / State
Kanagawa

Country
Japan
JP

Identifiers

Other IT system identifiers

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

ID
16558402024DIV750