



Name: perfluorooctane / 307-34-6 / octadecafluorooctane / 307-34-6

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

Printing date: 2020-10-09T12:21:51.845+09:00

Table of Contents

perfluorooctane / 307-34-6	1
OECD	1
D Health Effects	1
67 Repeated dose toxicity: oral	1
Repeated dose toxicity: oral.001	1
70 Genetic toxicity in vitro	9
Genetic toxicity in vitro.001	9
Genetic toxicity in vitro.002	14
73 Toxicity to reproduction	18
Toxicity to reproduction.001	18
DOMAIN	27
Substance	27
References	28
A combined repeated-dose/reproductive-developmental toxicity study of per fluorooctane	28
A reverse mutation test of perfluorooctane on bacteria	29
Chromosomal aberration test in cultured chinese hamster cells treated with perfluorooctane	30
National Institute of Health Sciences	31
perfluorooctane	33

perfluorooctane / 307-34-6

OECD

Health Effects

Repeated dose toxicity: oral

ENDPOINT_STUDY_RECORD: Repeated dose toxicity: oral.001

UUID: 58cd4087-d5eb-4503-87d4-0510528d5c98

Dossier UUID:

Author: SuperUser

Date: 2020-10-09T09:48:26.014+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

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

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

Deviations

no Housing humidity temporarily exceeded the prescribed range ($50 \pm 20\%$) 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: CrI: CD(SD)

Sex

male/female

Details on test animals 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 °C

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, $100 \pm 10\%$, C.V.: $\leq 10\%$)

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 (CrI: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 recovery, 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 days 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 males. 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, days 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 animals) 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 consumption 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 (recovered 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 glandular 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 necropsy.

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 pre-mating period and a subsequent mating period, while females were treated for 41–53 days, including 14-day pre-mating, 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 in vitro

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.001

UUID: 2e6b0625-72e8-47dd-b5c2-87ee86491767

Dossier UUID:

Author: SuperUser

Date: 2020-10-09T12:21:24.815+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

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 irrespective 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)-aminopropyl amino]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 comparison 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: SuperUser

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

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. certificate)

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 treatment]: 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 (\pm): 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 induce 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-growth 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 concentration (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 without metabolic activation. In the 24-hour and 48-hour continuous treatments, neither increase in chromosome structural aberration nor increase in the incidence of the occurrence of polyploidy was observed. 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 the non-treatment group in each treatment method was within the judging criteria of negative results and 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

ENDPOINT_STUDY_RECORD: Toxicity to reproduction.001

UUID: 8a0a07e7-aaa7-42d1-a434-066c721423cf

Dossier UUID:

Author: SuperUser

Date: 2020-10-09T09:56:25.119+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

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

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

Deviations

yes Housing humidity temporarily exceeded the prescribed range ($50 \pm 20\%$) . 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 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, $100 \pm 10\%$, C.V.: $\leq 10\%$)

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 (CrI: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 recovery, 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, intraperitoneally.

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 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.

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 recovery 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 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 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 males (recovered group).

At 1000 mg/kg bw/day, lower relative adrenal weights were significantly observed in females (recovered 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 male.

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 glandular 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 observed 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 in 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 necropsy.

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).

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 pre-mating period and a subsequent mating period, while females were treated for 41–53 days, including 14-day pre-mating, 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).

DOMAIN

SUBSTANCE: perfluorooctane / 307-34-6

UUID: 63c139c1-694c-4136-8d94-120893d5a9a7

Dossier UUID:

Author: SuperUser

Date: 2020-10-09T12:21:24.815+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

206-199-2

EC name

EC Inventory

CAS number

307-34-6

CAS name

IUPAC name

octadecafluorooctane

Role in the supply chain

Manufacturer

false

Importer

false

Only representative

false

Downstream user

false

References

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

UUID: 1ade8b53-d5e9-4d63-a005-7e9144c11c32

Dossier UUID:

Author: SuperUser

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-b8b45fddb910

Dossier UUID:

Author: SuperUser

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: SuperUser

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_ENTITY: National Institute of Health Sciences

UUID: IUC4-b036ff75-0f3c-323b-b200-ed5f46cf5101

Dossier UUID:

Author: SuperUser

Date: 2019-09-03T10:05:28.000+09:00

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 official MHLW opinions or any other regulatory policies.

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 official MHLW opinions or any other regulatory policies.

Identifiers

Other IT system identifiers

IT system LEO
ID 10767
IT system IUCLID4
ID 16558402024DIV750

Contact information

Contact persons

Person Hirose, Akihiko; National Institute of Health Sciences, Japan
Last name Hirose

First name

Akihiko

Organisation

National Institute of Health Sciences, Japan

Department

Division of Risk Assessment

Title

Dr

Country

Japan

Contact address**Address 1**

Tonomachi 3-25-26

Address 2

Kawasaki-ku

Postal code

210-9501

Town

Kawasaki

Region / State

Kanagawa

Country

Japan

REFERENCE_SUBSTANCE: perfluorooctane

UUID: ECB5-6946b95b-842e-4778-a8ee-138b12a440ca

Dossier UUID:

Author: SuperUser

Date: 2007-05-10T18:00:00.000+09:00

Remarks:

General information

Reference substance name

perfluorooctane

Inventory

Inventory name

perfluorooctane

Inventory

EC

Inventory number

206-199-2

CAS number

307-34-6

Molecular formula

C₈F₁₈

Description

Reference substance information

IUPAC name

octadecafluorooctane

Synonyms

Identity
Octane, octadecafluoro-
Identity
Octane, octadecafluoro-

CAS information

CAS number

307-34-6

Molecular and structural information

Molecular formula

C₈F₁₈
