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

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Remarks:

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Dossier subject

[1,2-Ethanediy l ester octadecanoic acid / 627-83-8](#)

Public name

Submitting legal entity

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

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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.

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Town

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Identifiers

Other IT system identifiers

IT system

LEO

ID

10767

IT system

IUCLID4

ID

16558402024DIV750

1,2-Ethanediy l ester octadecanoic acid

OECD

Health Effects

Repeated dose toxicity: oral

ENDPOINT_STUDY_RECORD: RepeatedDoseToxicityOral.

UUID: 4855e70e-3f38-4a31-9a97-e0233b88fa0c

Dossier UUID:

Author:

Date: 2022-03-25T11:28:58.000+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 OECD Test Guideline study under GLP condition

Reliability 1

Cross-reference

Reason / purpose for cross-reference

reference to same study

Related information

[OECD / Toxicity to reproduction / ToxicityReproduction. / 1,2-Ethanediy l ester octadecanoic acid / 627-83-8](#)

Data source

Reference

[Combined repeated dose toxicity study with the reproductive/developmental toxicity screening test of / Ministry of Health, Labour and Welfare \(MHLW\), Japan / study report](#)

Data access

data published https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF627-83-8d.pdf

Materials and methods**Test guideline****Qualifier**

according to guideline

Guideline

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

Deviations

no

GLP compliance

yes

Limit test

no

Test material**Test material information**

[1,2-Ethanediy l ester octadecanoic acid](#)

Specific details on test material used for the study

- Name of test material (as cited in study report): Octadecanoic acid, 1,2-ethanediy l ester
- Analytical purity: 99.99% (Solid content as a mixture of long-chain fatty acid esters mainly octadecanoic acid)
- Storage condition of test material: sealed, cool and dark place (2-8°C)
- Stability under test conditions: The stability of test material was identified by analysis of the remainder.

Test animals**Species**

rat

common rodent species

Strain

other: Crl: CD (SD)

Sex

male/female

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

- Source: Charles River Japan, Inc., Atsugi Breeding Center.
- Age at study initiation: 10 weeks old
- Weight at study initiation: Male: 405 g (380-446 g), Female: 250 g (222-285 g)
- Housing: Animals were individually housed in bracket-type metallic wire-mesh cages (254W × 350D × 170H mm), from gestation day 17 to lactation day 4, Dams were bred individually or with individual littermates in plastic cages (340W x 400D x 185H mm) and bedding.
- Diet: Solid feed (NMF: Oriental Yeast Co., Ltd.) was given ad libitum.

- Water: Tap water was given ad libitum.
 - Acclimation period: 17 days
- ENVIRONMENTAL CONDITIONS**
- Temperature (°C): 23±3 (actual temperature: 22-25°C)
 - Humidity (%): 50±20% (actual humidity: 40-55%)
 - Air changes (per hr): 10-15
 - Photoperiod (hrs dark / hrs light): 12 hr dark/12 hr light (light: 7:00~19:00)

Administration / exposure

Route of administration

oral: gavage

Vehicle

methylcellulose 0.5w/v%

Details on oral exposure

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

Analytical verification of doses or concentrations

yes

Details on analytical verification of doses or concentrations

The concentration of each suspensions used in weeks 1 and 6 of administration were analyzed by GC. Results showed that the concentrations of each suspensions were 96.0 to 110.0% of the nominal concentration and both values were within the acceptable range (concentration: percentage of nominal concentration, 100±10%)

Duration of treatment / exposure

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

(P) Females: 41-46 days including 14 days pre-mating, mating and gestation periods and the days until day 4 of lactation

Female (no mating, satellite group): 42 days

Frequency of treatment

Once/day, 7 days/week

Doses / concentrations

Dose / conc.	
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

Mating group: 12 animals/sex/dose (0, 100, 300 and 1000 mg/kg bw/day)

Non-mating group: 10 females/dose (0 and 1000 mg/kg bw/day)

Recovery group: 5 males/dose in the mating group and 5 females/dose in the non-mating groups (0 and 1000 mg/kg bw/day)

Control animals

yes, concurrent vehicle

Details on study design

- Dose selection rationale: Based on the results of a 14-day preliminary study, the high dose was set to 1000 mg/kg bw/day, which is the upper limit in OECD TG422, and the intermediate dose and low dose were set to 300 mg/kg bw/day and 100 mg/kg bw/day, respectively.

[14-day preliminary study]

A 14-day repeated dose oral toxicity test (CrI:CD(SD) rats, doses: 0, 250, 500 or 1000 mg/kg bw/day). There were no deaths in the high-dose 1000 mg/kg bw/day group. However, decreased total protein was observed in males at 250 mg/kg bw/day and above, increased relative heart weight was observed in males at 1000 mg/kg bw/day, and increased hematocrit and total protein were observed in females at 1000 mg/kg bw/day.

- Rationale for animal assignment (if not random): Body weight-balanced randomization.

Examinations

Observations and examinations performed and frequency

CAGE SIDE OBSERVATIONS: Yes

- Time schedule: 3 times/day (before administration, immediately after administration and 1-3 hours after administration) during the administration period. Once a day during the recovery period.

DETAILED CLINICAL OBSERVATIONS: Yes

- Time schedule:

Males in the main groups and females in the non-mating groups: once before the start of administration, once every weekly during the administration.

Females in the mating groups: once before the start of administration, days specified during mating, gestation, and lactation (mated animals: gestation days 1, 7, 14 and 20, parturient animals: lactation day 4)

Males and females in the recovery groups: once before the start of administration, once every weekly during the administration and recovery periods.

BODY WEIGHT: Yes

- Time schedule for examinations:

Males in the main groups and females in the non-mating groups: days 1, 8, 15, 22, 29, 36 and 42 of administration and on the day of necropsy

Males and females in the recovery groups: days 1, 8, 15, 22, 29, 36 and 42 of administration, and days 1, 8 and 14 of recovery and on the day of necropsy.

Females in the mating groups: days 1, 8 and 15 of administration, days 0, 7, 14, and 20 of gestation, days 0, 4 of lactation, and on the day of necropsy

Food consumption: Yes

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

Males in the main groups and females in the non-mating groups: days 1, 8, 15, 30, 36 and 42 of administration

Males and females in the recovery groups: days 1, 8, 15, 30, 36 and 42 of administration, and days 1, 8 and 14 of recovery

Females in the mating groups: days 1, 8 and 15 of administration, days 1, 7, 14, and 20 of gestation, days 2 and 4 of lactation

OPHTHALMOSCOPIC EXAMINATION: No

HAEMATOLOGY: Yes

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

CLINICAL CHEMISTRY: Yes

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

URINALYSIS OF MALES: Yes

- Time schedule for collection of urine: final week of administration (days 36 to 37 of administration) and in the final week of recovery (days 8 to 9 of recovery)
- Metabolism cages used for collection of urine: Yes
A urine collector to collect four-hour urine samples under fasting but ad libitum drinking conditions, followed by collection of 20-hour urine samples under ad libitum feeding and drinking conditions.
- How many animals: 5 animals/group
- Parameters checked: pH, protein, ketones, glucose, occult blood, bilirubin, urobilinogen, color, sediment, urine volume (4-hour volume), osmotic pressure, sodium, potassium, chloride, urine volume (20-hour volume), water intake (24-hour volume)

BLOOD HORMONE: No

NEUROBEHAVIOURAL EXAMINATION: Yes

- Time schedule for examinations:
Males in the main groups and females in the non-mating groups: final week of administration (day 41 of administration)
Females in the mating groups: lactation day 4 (day 41 to day 43 of administration) after necropsy of F1 pups
Males and females in the recovery groups: final week of administration (day 41 of administration) and in the final week of recovery (day 13 of recovery).
- Dose groups that were examined: All dose groups (5 animals/sex/group)
- Battery of functions tested:
 - 1) Manipulative Test. Auditory response, approach response, touch response, tail pinch response, pupillary reflex, aerial righting reflex, landing foot splay
 - 2) Measurement of Grip Strength. Following manipulative test, grip strength of forelimb and hind limb were measured by CPU gauge MODEL-RX-5 (AIKOH Engineering Co., Ltd.).
 - 3) Measurement of Motor Activity. Following measurement of grip strength, motor activity was measured by a motor activity sensor for experimental animals NS-AS01 (Neuro Science, Inc.). The measurement was conducted for 1 hour, and measured values at 10-minute intervals and from 0 to 60 minutes were collected.

Sacrifice and pathology

GROSS PATHOLOGY: Yes

ORGAN WEIGHT: Yes [brain, pituitary, thyroids (including parathyroids), adrenal gland, thymus, spleen, heart, liver, kidney, testis, epididymis, prostate, seminal vesicles, ovary, uterus]

HISTOPATHOLOGY: Yes, [cerebrum, cerebellum (including pons), sciatic nerve, spinal cord (thoracic), eye ball, optic nerve, Harderian gland, pituitary, thyroid, parathyroid, adrenal glands, thymus, spleen, submandibular lymph nodes, mesenteric lymph nodes, heart, thoracic aorta, trachea, lung (including bronchial), tongue, larynx, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, submandibular gland, sublingual gland, liver, pancreas, kidney, bladder, testis, ovary, epididymis, uterus, vagina, prostate, seminal vesicles, skin (inguinal), mammary gland (inguinal), sternum and femur (including bone marrows), skeletal muscle of femur, and individual identification site (pinna with ear tag)]

Statistics

For quantitative data, homogeneity of variance was tested using Bartlett method first. If the variance was homogenous, statistical difference between each treatment group and the control group was analyzed using Dunnett method. If not homogenous, statistical difference between each treatment group and the control group was tested using Steel method. For comparison of quantitative data between two groups in the recovery test, homogeneity of variance was analyzed by F-test. Then, if homogenous, student's t-test was applied. If not homogenous, Aspin-Welch's t-test was used. Regarding clinical observation (except for frequency of urination, defecation, rearing and grooming) and sensory reactivity, Steel test was applied. Regarding auditory response, approach response, touch response, tail pinch response, pupillary reflex, aerial righting reflex, Fisher's test was applied.

Results and discussion

Results of examinations

Clinical signs

no effects observed

Mortality

no mortality observed

Body weight and weight changes

no effects observed

Food consumption and compound intake (if feeding study)

no effects observed

Food efficiency

not examined

Water consumption and compound intake (if drinking water study)

not examined

Ophthalmological findings

not examined

Haematological findings

no effects observed

Clinical biochemistry findings

no effects observed

Urinalysis findings

no effects observed

Behaviour (functional findings)

no effects observed

Immunological findings

not examined

Organ weight findings including organ / body weight ratios

no effects observed

Gross pathological findings

no effects observed

Neuropathological findings

not examined

Histopathological findings: non-neoplastic

no effects observed

Histopathological findings: neoplastic

not examined

Details on results**CLINICAL SIGNS AND MORTALITY:**

Mortality: There was no death.

Clinical signs:

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

DETAILED CLINICAL OBSERVATIONS:

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

BODY WEIGHT:

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

FOOD CONSUMPTION:

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

URINALYSIS:

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

HAEMATOLOGY:

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

CLINICAL CHEMISTRY:

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

NEUROBEHAVIOURAL EXAMINATION:**1) MANIPULATIVE TEST:**

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

2) GRIP STRENGTH TEST:

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

3) LOCOMOTOR ACTIVITY MEASUREMENT:

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

ORGAN WEIGHTS:

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

GROSS PATHOLOGY:

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

HISTOPATHOLOGY: NON-NEOPLASTIC:

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

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.

https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF627-83-8d.pdf

Applicant's summary and conclusion**Conclusions**

The NOAEL for repeated dose toxicity in this study was determined to be 1000 mg/kg bw/day for males and females.

Executive summary

In the combined repeated dose and reproductive/developmental screening test (OECD TG422), SD rats were treated orally with 1,2-ethanediyl ester octadecanoic acid at the doses of 0, 100, 300 and 1000 mg/kg bw/day. Males (12 males/dose: 5 males were treated as a recovery group) were dosed for 42 days including a 14 day pre-mating period and mating periods. Mating females (12 females/dose) were dosed for 41-46 days including 14 day premating, mating, and gestation periods and days until day 4 of lactation. Non-mating female (10 females/dose: 5 females were treated as a recovery group) were dosed for 42 days.

As a result, no deaths were observed, and no effects of the test substance administration were observed in any of the examination. Based on the above results, NOAEL for the repeated dose toxicity of 1,2-

ethanediyl ester octadecanoic acid was determined to be 1000 mg/kg bw/day for males and female rats.

Genetic toxicity in vitro

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.001

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Author:

Date: 2022-03-10T13:26:23.000+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

other: OECD Test Guideline study under GLP condition

Data source

Reference

[Reverse Mutation Test of 1,2-Ethanedioyl ester octadecanoic acid on Bacteria. / Ministry of Health, Labour and Welfare \(MHLW\), Japan / study report](#)

Data access

data published

Materials and methods

Test guideline

Qualifier

according to guideline

Guideline

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

Deviations

no

Qualifier

according to guideline

GuidelineJAPAN: Guidelines for Screening Mutagenicity Testing Of Chemicals
genetic toxicity in vitro, other**Deviations**

no

GLP compliance

yes

Type of assaybacterial reverse mutation assay
in vitro gene mutation study in bacteria

Test material**Test material information**[1,2-Ethanediy ester octadecanoic acid](#)**Specific details on test material used for the study**

- Name of test material (as cited in study report): Octadecanoic acid, 1,2-ethanediy ester

Method**Species / strain****Species / strain / cell type**S. typhimurium TA 1535, TA 1537, TA 98 and TA 100
bacteria**Species / strain / cell type**E. coli WP2 uvr A
bacteria**Metabolic activation**

with and without

Metabolic activation system

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

Justification for deviation from the high dose level

-S9 mix:

4.88, 9.77, 19.5, 39.1, 78.1 µg/plate (All strains)

+S9 mix:

19.5, 39.1, 78.1, 156, 313 µg/plate (All strains)

Maximum concentration was established based on the result of the preliminary test at concentration up to 5000 µg/plate. In this test, In this study, no growth inhibition was observed in either strain with or without metabolic activation, so the lowest dose at which the test substance precipitated was used as the highest dose, with 5 doses in the range of 4.88 - 78.1 µg/plate for no metabolic activation and 5 doses in the range of 19.5 - 313 µg/plate for metabolic activation.

Vehicle / solvent

- Vehicle(s)/solvent(s) used: Tetrahydrofuran (THF)

Controls**Untreated negative controls**

no

Negative solvent / vehicle controls

yes

True negative controls

no

Positive controls

yes

Positive control substance

other: -S9 mix: 2-(2-furyl)-3-(5-nitro-2-furyl) acrylamide (AF-2), sodium azide (SAZ) and 2-methoxy-6-chloro-9-[3-(2-chloroethyl)-aminopropylamino]acridine 2HCl (ICR-191) ;
+S9 mix: 2-aminoanthracene (2AA), benzo[a]pyrene (B[a]P)

Details on test system and experimental conditions

METHOD OF APPLICATION: plate incorporation

DURATION- Preincubation period: 9 hrs at 37°C

- Exposure duration: 48 or 50 hrs

NUMBER OF PLATES: 3

NUMBER OF REPLICATIONS: 2

DETERMINATION OF CYTOTOXICITY

- Method: other: growth inhibition

Evaluation criteria

A chemical was judged to be mutagenic when the mean number of revertant colonies per plate increased more than twice that of the negative control and when the dose-related and reproducible increase was observed.

Statistics

no

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, but tested up to precipitating 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, but tested up to precipitating 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, but tested up to precipitating 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, but tested up to precipitating 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, but tested up to precipitating concentrations

Vehicle controls validity

valid

Positive controls validity

valid

Any other information on results incl. tables

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

https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF627-83-8e.pdf

Please also see the attached files (Tables in English)

Applicant's summary and conclusion**Conclusions**

Interpretation of results (migrated information): negative

In a bacterial reverse mutation assay using *Salmonella typhimurium* TA100, TA1535, TA98, and TA 1537, and *Escherichia coli* WP2uvrA (OECD TG 471), 1,2-ethanediyl ester octadecanoic acid was negative with or without metabolic activation.

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.002

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Dossier UUID:

Author:

Date: 2022-03-25T11:11:57.000+09:00

Remarks:

Administrative data

Endpoint

in vitro 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

other: OECD Test Guideline study under GLP condition

Data source

Reference

[In Vitro Chromosomal Aberration Test of 1,2-EthanediyI ester octadecanoic acid on Cultured Chinese H / Ministry of Health, Labour and Welfare \(MHLW\), Japan / study report](#)

Data access

data published

Materials and methods

Test guideline

Qualifier

according to guideline

Guideline

OECD Guideline 473 (In Vitro Mammalian Chromosome Aberration Test)

in vitro cytogenicity / chromosome aberration study in mammalian cells

Deviations

no

Qualifier

according to guideline

Guideline

JAPAN: Guidelines for Screening Mutagenicity Testing Of Chemicals
genetic toxicity in vitro, other

Deviations

no

GLP compliance

yes

Type of assay

other: in vitro mammalian chromosome aberration test

Test material

Test material information

[1,2-Ethanediy ester octadecanoic acid](#)

Specific details on test material used for the study

- Name of test material (as cited in study report): Octadecanoic acid, 1,2-ethanediy ester

Method

Species / strain

Species / strain / cell type

other: Chinese hamster lung (CHL/IU) cells

Metabolic activation

with and without

Metabolic activation system

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

Justification for deviation from the high dose level

Cell growth inhibition study

-S9 mix (short-term treatment): 9.77, 19.5, 39.1, 78.1, 156, 313, 625, 1250, 2500, 5000 ug/mL

+S9 mix (short-term treatment): 9.77, 19.5, 39.1, 78.1, 156, 313, 625, 1250, 2500, 5000 ug/mL

-S9 mix (continuous treatment, 24hr): 9.77, 19.5, 39.1, 78.1, 156, 313, 625, 1250, 2500, 5000 ug/mL

-S9 mix (continuous treatment, 48hr): 9.77, 19.5, 39.1, 78.1, 156, 313, 625, 1250, 2500, 5000 ug/mL

Main study

-S9 (short-term treatment): 1250, 2500, 5000 ug/mL

+S9 (short-term treatment): 1250, 2500, 5000 ug/mL

-S9 (continuous treatment, 24hr): 1480, 2220, 3330, 5000 ug/mL

-S9 (continuous treatment, 48hr): 1480, 2220, 3330, 5000 ug/mL

Vehicle / solvent

- Vehicle(s)/solvent(s) used: 0.5%CMC Na

Controls

Untreated negative controls

no

Negative solvent / vehicle controls

yes

True negative controls

no

Positive controls

yes

Positive control substance

other: [-S9]: mitomycin C; [+S9]: cyclophosphamide

Details on test system and experimental conditions

METHOD OF APPLICATION:

Exposure duration:

- [short-term treatment]: 6 hrs + 18 hrs

- [continuous treatment]: 24, 48 hrs

SPINDLE INHIBITOR: Colcemid

STAIN: Giemsa stain (2 v/v%) for 15 min.

NUMBER OF REPLICATIONS: 2

NUMBER OF CELLS EVALUATED: 100 + 100 cells /concentration

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 cell with chromosomal aberrations: Negative (-): less than 5%, Equivocal(\pm): more than 5% and less than 10%, Positive(+): 10% and above

Statistics

no

Results and discussion

Test results

Key result

true

Species / strain

other: Chinese hamster lung (CHL/IU) cells

Metabolic activation

with and without

Genotoxicity

negative

Cytotoxicity / choice of top concentrations

other: Short-term treatment (+/-S9 mix): no cytotoxicity; Continuous treatment (24hr/48hr): cytotoxicity

Vehicle controls validity

valid

Positive controls validity

valid

Additional information on results

RANGE-FINDING/SCREENING STUDIES (if applicable):

50% cell growth inhibition (IC50): 3372 ug/mL (continuous treatment, 48hr)

Any other information on results incl. tables

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

https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF627-83-8f.pdf

Applicant's summary and conclusion

Conclusions

Interpretation of results (migrated information): negative with or without metabolic activation

In an in vitro chromosomal aberration test using CHL/IU cells (OECD TG 473), 1,2-ethanediyl ester octadecanoic acid was negative with or without metabolic activation.

Toxicity to reproduction

ENDPOINT_STUDY_RECORD: ToxicityReproduction.

UUID: 9de6b42d-f271-400e-9da1-ac629fa13a40

Dossier UUID:

Author:

Date: 2022-03-25T11:30:17.000+09:00

Remarks:

Administrative data

Endpoint

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

Type of information

experimental study

Adequacy of study

key study

Robust study summary

false

Used for classification

false

Used for SDS

false

Reliability

1 (reliable without restriction)

Rationale for reliability incl. deficiencies

guideline study OECD Test Guideline study under GLP condition

Reliability 1

Cross-reference

Reason / purpose for cross-reference

reference to same study

Related information

[OECD / Repeated dose toxicity: oral / RepeatedDoseToxicityOral. / 1,2-Ethanediy l ester octadecanoic acid / 627-83-8](#)

Data source

Reference

[Combined repeated dose toxicity study with the reproductive/developmental toxicity screening test of / Ministry of Health, Labour and Welfare \(MHLW\), Japan / study report](#)

Data access

data published https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF627-83-8d.pdf

Materials and methods

Test guideline

Qualifier

according to guideline

Guideline

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

Deviations

no

GLP compliance

yes

Limit test

no

Test material

Test material information

[1,2-Ethanediy l ester octadecanoic acid](#)

Specific details on test material used for the study

- Name of test material (as cited in study report): Octadecanoic acid, 1,2-ethanediy l ester
- Analytical purity: 99.99% (Solid content as a mixture of long-chain fatty acid esters mainly octadecanoic acid)
- Storage condition of test material: sealed, cool and dark place (2-8°C)
- Stability under test conditions: The stability of test material was identified by analysis of the remainder.

Test animals

Species

rat

Strain

other: CrI:CD(SD)

Sex

male/female

Details on test animals or test system and environmental conditions

TEST ANIMALS

- Source: Charles River Japan, Inc., Atsugi Breeding Center.
- Age at study initiation: 10 weeks old
- Weight at study initiation: Male: 405 g (380-446 g), Female: 250 g (222-285 g)
- Housing: Animals were individually housed in bracket-type metallic wire-mesh cages (254W × 350D × 170H mm), from gestation day 17 to lactation day 4, Dams were bred individually or with individual littermates in plastic cages (340W x 400D x 185H mm) and bedding.
- Diet: Solid feed (NMF: Oriental Yeast Co., Ltd.) was given ad libitum.
- Water: Tap water was given ad libitum.
- Acclimation period: 16 days

ENVIRONMENTAL CONDITIONS

- Temperature (°C): 23±3 (actual temperature: 22-25°C)
- Humidity (%): 50±20% (actual humidity: 40-55%)
- Air changes (per hr): 10-15
- Photoperiod (hrs dark / hrs light): 12 hr dark/12 hr light (light: 7:00~19:00)

Administration / exposure

Route of administration

oral: gavage

Vehicle

other: 0.5w/v% methylcellulose

Details on exposure

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

Details on mating procedure

- M/F ratio per cage: 1/1
- Length of cohabitation: up to 5 days
- Proof of pregnancy: vaginal plug / sperm in vaginal smear referred to as day 0 of pregnancy

Analytical verification of doses or concentrations

yes

Details on analytical verification of doses or concentrations

The concentration of each suspensions used in weeks 1 and 6 of administration were analyzed by GC. Results showed that the concentrations of each suspensions were 96.0 to 110.0% of the nominal concentration and both values were within the acceptable range (concentration: percentage of nominal concentration, $100 \pm 10\%$)

Duration of treatment / exposure

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

(P) Females: 41-46 days including 14 days pre-mating, mating and gestation periods and the days until day 4 of lactation

Female (no mating, satellite group): 42 days

Frequency of treatment

Once/day, 7 days/week

Doses / concentrations

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

No. of animals per sex per dose

Mating group: 12 animals/sex/dose (0, 100, 300, and 1000 mg/kg bw/day)

Non-mating group: 10 females/dose (0 and 1000 mg/kg bw/day)
Recovery group: 5 males/dose in the mating group and 5 females/dose in the non-mating groups (0 and 1000 mg/kg bw/day)

Control animals

yes, concurrent vehicle

Details on study design

- Dose selection rationale: Based on the results of a 14-day preliminary study, the high dose was set to 1000 mg/kg bw/day, which is the upper limit in OECD TG422, and the intermediate dose and low dose were set to 300 mg/kg bw/day and 100 mg/kg bw/day, respectively.

[14-day preliminary study]

A 14-day repeated dose oral toxicity test (CrI: CD (SD) rats, doses: 0, 250, 500 or 1000 mg/kg bw/day). There were no deaths in the high-dose 1000 mg/kg bw/day group. However, decreased total protein was observed in males at 250 mg/kg bw/day and above, increased relative heart weight was observed in males at 1000 mg/kg bw/day, and increased hematocrit and total protein were observed in females at 1000 mg/kg bw/day.

- Rationale for animal assignment (if not random): Body weight-balanced randomization.

Examinations

Parental animals: Observations and examinations

CAGE SIDE OBSERVATIONS: Yes

- Time schedule: 3 times/day (before administration, immediately after administration and 1-3 hours after administration) during the administration period. Once a day during the recovery period.

DETAILED CLINICAL OBSERVATIONS: Yes

- Time schedule:

Males in the main groups and females in the non-mating groups: once before the start of administration, once every weekly during the administration.

Females in the mating groups: once before the start of administration, days specified during mating, gestation, and lactation (mated animals: gestation days 1, 7, 14 and 20, parturient animals: lactation day 4)

Males and females in the recovery groups: once before the start of administration, once every weekly during the administration and recovery periods.

BODY WEIGHT: Yes

- Time schedule for examinations:

Males in the main groups and females in the non-mating groups: days 1, 8, 15, 22, 29, 36 and 42 of administration and on the day of necropsy

Males and females in the recovery groups: days 1, 8, 15, 22, 29, 36 and 42 of administration, and days 1, 8 and 14 of recovery and on the day of necropsy.

Females in the mating groups: days 1, 8 and 15 of administration, days 0, 7, 14, and 20 of gestation, days 0, 4 of lactation, and on the day of necropsy

Food consumption: Yes

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

Males in the main groups and females in the non-mating groups: days 1, 8, 15, 30, 36 and 42 of administration

Males and females in the recovery groups: days 1, 8, 15, 30, 36 and 42 of administration, and days 1, 8 and 14 of recovery

Females in the mating groups: days 1, 8 and 15 of administration, days 1, 7, 14, and 20 of gestation, days 2 and 4 of lactation

OPHTHALMOSCOPIC EXAMINATION: No

HAEMATOLOGY: Yes

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

CLINICAL CHEMISTRY: Yes

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

URINALYSIS OF MALES: Yes

- Time schedule for collection of urine: final week of administration (days 36 to 37 of administration) and in the final week of recovery (days 8 to 9 of recovery)
- Metabolism cages used for collection of urine: Yes
A urine collector to collect four-hour urine samples under fasting but ad libitum drinking conditions, followed by collection of 20-hour urine samples under ad libitum feeding and drinking conditions.
- How many animals: 5 animals/group
- Parameters checked: pH, protein, ketones, glucose, occult blood, bilirubin, urobilinogen, color, sediment, urine volume (4-hour volume), osmotic pressure, sodium, potassium, chloride, urine volume (20-hour volume), water intake (24-hour volume)

BLOOD HORMONE: No

NEUROBEHAVIOURAL EXAMINATION: Yes

- Time schedule for examinations:
Males in the main groups and females in the non-mating groups: final week of administration (day 41 of administration)
Females in the mating groups: lactation day 4 (day 41 to day 43 of administration) after necropsy of F1 pups
Males and females in the recovery groups: final week of administration (day 41 of administration) and in the final week of recovery (day 13 of recovery).
- Dose groups that were examined: All dose groups (5 animals/sex/group)
- Battery of functions tested:
 - 1) Manipulative Test. Auditory response, approach response, touch response, tail pinch response, pupillary reflex, aerial righting reflex, landing foot splay
 - 2) Measurement of Grip Strength. Following manipulative test, grip strength of forelimb and hind limb were measured by CPU gauge MODEL-RX-5 (AIKOH Engineering Co., Ltd.).
 - 3) Measurement of Motor Activity. Following measurement of grip strength, motor activity was measured by a motor activity sensor for experimental animals NS-AS01 (Neuro Science, Inc.). The measurement was conducted for 1 hour, and measured values at 10-minute intervals and from 0 to 60 minutes were collected.

Oestrous cyclicity (parental animals)

Vaginal smears were collected from all females in the mating groups and microscopically examined every day from the day after the start of administration until the day copulation was confirmed.

During the pre-mating administration period, vaginal smear pictures were classified as proestrus, estrus, metestrus or diestrus and examined for the frequency of estrus and interval between estruses (estrous cycle). During the mating period, vaginal smears were examined for the presence of sperm.

Sperm parameters (parental animals)

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

Litter observations

PARAMETERS EXAMINED: The following parameters were examined in F1 offspring: Number and sex of pups, stillbirths, live births, postnatal mortality, presence of gross anomalies, and weight gain.

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

Postmortem examinations (parental animals)

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

SACRIFICE: Males in main groups and females in non-mating groups: On next day after the last administration (Day 43), Maternal animals: on Day 4 of lactation, and Male and females recovery animals: on Day 14 of recovery.

ORGAN WEIGHT: Yes [brain, pituitary, thyroids (including parathyroids), adrenal gland, thymus, spleen, heart, liver, kidney, testis, epididymis, prostate, seminal vesicles, ovary, uterus]

HISTOPATHOLOGY: Yes, [cerebrum, cerebellum (including pons), sciatic nerve, spinal cord (thoracic), eye ball, optic nerve, Harderian gland, pituitary, thyroid, parathyroid, adrenal glands, thymus, spleen, submandibular lymph nodes, mesenteric lymph nodes, heart, thoracic aorta, trachea, lung (including bronchial), tongue, larynx, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, submandibular gland, sublingual gland, liver, pancreas, kidney, bladder, testis, ovary, epididymis, uterus, vagina, prostate, seminal vesicles, skin (inguinal), mammary gland (inguinal), sternum and femur (including bone marrows), skeletal muscle of femur, and individual identification site (pinna with ear tag)]

Postmortem examinations (offspring)

SACRIFICE

- The F1 offsprings were euthanized on PND4 by exsanguination under isoflurane anesthesia.

GROSS NECROPSY : Yes

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

HISTOPATHOLOGY / ORGAN WEIGHTS

- Not examined.

Statistics

For quantitative data, homogeneity of variance was tested using Bartlett method first. If the variance was homogenous, statistical difference between each treatment group and the control group was analyzed using Dunnett method. If not homogenous, statistical difference between each treatment group and the control group was tested using Steel method. For comparison of quantitative data between two groups in the recovery test, homogeneity of variance was analyzed by F-test. Then, if homogenous, student's t-test was applied. If not homogenous, Aspin-Welch's t-test was used.

Regarding clinical observation (except for frequency of urination, defecation, rearing and grooming) and sensory reactivity, Steel test was applied. Regarding implantation index, stillborn index, live birth index, viability index and external abnormalities, Steel test was applied. Regarding copulation index, insemination index, fertility index, and delivery index, auditory response, approach response, touch response, tail pinch response, pupillary reflex, aerial righting reflex, Fisher's test was applied.

Reproductive indices

Each parameter was determined by the following equations:

Copulation index (%) = (No. of copulated animals / No. of mated animals) × 100

Fertility index (%) = (No. of pregnant females / No. of copulated females) × 100
Insemination index (%) = (No. of males which impregnated females / No. of copulated males) × 100
Gestation length (days) = No. of days from pregnancy day 0 to parturition day
Delivery index (%) = (No. of females which delivered liveborns / No. of pregnant females) × 100
Implantation index (%) = (No. of implantation sites / No. of corpora lutea) × 100
Stillborn index (%) = (No. of stillborn / No of liveborns and stillborns) × 100
Live birth index (%) = (No. of liveborn / No. of implantation sites) × 100
External abnormalities (%) = (No. of pups with external abnormalities / No. of liveborns) × 100
Sex ratio = No. of liveborns males / No. of liveborns
Sex ratio of live pups on day 4 = No. of live males on day 4 / No. of live pups on day 4

Offspring viability indices

Viability index on postnatal day 4 (%) = (No. of live pups on day 4 / No. of liveborns on day 0) × 100

Results and discussion

Results: P0 (first parental generation)

General toxicity (P0)

Clinical signs

no effects observed

Mortality

no mortality observed

Body weight and weight changes

no effects observed

Food consumption and compound intake (if feeding study)

no effects observed

Food efficiency

not examined

Water consumption and compound intake (if drinking water study)

not examined

Ophthalmological findings

not examined

Haematological findings

no effects observed

Clinical biochemistry findings

no effects observed

Urinalysis findings

no effects observed

Behaviour (functional findings)

no effects observed

Immunological findings

not examined

Organ weight findings including organ / body weight ratios

no effects observed

Gross pathological findings

no effects observed

Neuropathological findings

not examined

Histopathological findings: non-neoplastic

no effects observed

Histopathological findings: neoplastic

not examined

Reproductive function / performance (P0)**Reproductive function: oestrous cycle**

no effects observed

Reproductive function: sperm measures

no effects observed

Reproductive performance

no effects observed

Details on results (P0)

General toxicity: See 7.5.1 Repeated dose toxicity.001

Reproductive function / 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

Key result

true

Dose descriptor

NOAEL

Effect level

1000

mg/kg bw/day (actual dose received)

Based on

test mat.

Sex

male/female

Basis for effect level

reproductive performance

No reproductive effects were observed in both males and females up to 1000 mg/kg bw/day.

Results: F1 generation**General toxicity (F1)****Clinical signs**

no effects observed

Mortality / viability

no mortality observed

Body weight and weight changes

no effects observed

Gross pathological findings

no effects observed

Details on results (F1)

No effects observed.

Effect levels (F1)**Key result**

false

Dose descriptor

NOAEL

Generation

F1

Effect level

1000

mg/kg bw/day (actual dose received)

Based on

test mat.

Sex

male/female

Basis for effect level

other:

There were no effects on developmental parameters up to 1000 mg/kg bw/day.

Overall reproductive toxicity

Key result

false

Reproductive effects observed

no

Any other information on results incl. tables

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

https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF627-83-8d.pdf

Applicant's summary and conclusion**Conclusions**

In the combined repeated oral dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) described above, there were no effects on the reproductive and developmental parameters up to 1000 mg/kg bw/day. The NOAEL for the rat reproductive/developmental toxicity of 1,2-ethanediyl ester octadecanoic acid was regarded as 1000 mg/kg bw/day, the highest dose tested.

DOMAIN

SUBSTANCE: 1,2-Ethanediy l ester octadecanoic acid

UUID: 7f7fd0af-2d67-4d26-80c1-6102ca1c431e

Dossier UUID:

Author:

Date: 2022-03-25T11:11:57.000+09:00

Remarks:

Substance name

1,2-Ethanediy l ester octadecanoic acid

Legal entity

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

Identification of substance

Reference substance

[1,2-Ethanediy l ester octadecanoic acid / 627-83-8](#)

EC number

EC name

CAS number

CAS name

627-83-8

IUPAC name

Role in the supply chain

Manufacturer

false

Importer

false

Only representative

false

Downstream user

false

References

Reference Substances

REFERENCE_SUBSTANCE: 1,2-Ethanediy l ester octadecanoic acid

UUID: e628f22e-848c-4dd6-802b-a13991de8ef8

Dossier UUID:

Author:

Date: 2022-03-10T13:44:24.000+09:00

Remarks:

Reference substance name

1,2-Ethanediy l ester octadecanoic acid

Inventory

CAS number

627-83-8

Molecular and structural information

Molecular formula

C₃₈H₇₄O₄

Molecular weight

594.99

Test Materials

TEST_MATERIAL_INFORMATION: 1,2-Ethanediy l ester octadecanoic acid

UUID: 97be9601-509d-4cbc-880d-e76da4f04a9a

Dossier UUID:

Author:

Date: 2022-03-10T13:23:12.000+09:00

Remarks:

Name

1,2-Ethanediy l ester octadecanoic acid

Literatures

LITERATURE: Combined repeated dose toxicity study with the reproductive/developmental toxicity screening test of 1,2-ethanediyl ester octadecanoic acid by oral administration in rats

UUID: 6747ce6c-b9cc-4ce2-bcdc-58ffba213f9a

Dossier UUID:

Author:

Date: 2022-03-10T13:29:55.000+09:00

Remarks:

General information

Reference Type
study report

Title
Combined repeated dose toxicity study with the reproductive/developmental toxicity screening test of 1,2-ethanediyl ester octadecanoic acid by oral administration in rats

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

Year
2013

Bibliographic source
available in the web of Japan Existing Chemical Data Base (JECDB) https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF627-83-8d.pdf

Testing facility
BoZo Research Center

Report date
2013-08-23

Report number
R-1089

LITERATURE: In Vitro Chromosomal Aberration Test of 1,2-Ethanedithiol ester octadecanoic acid on Cultured Chinese Hamster Cells.

UUID: b227c8e2-451b-4d7f-ac60-6d2204c7be47

Dossier UUID:

Author:

Date: 2022-03-10T13:27:42.000+09:00

Remarks:

General information

Reference Type

study report

Title

In Vitro Chromosomal Aberration Test of 1,2-Ethanedithiol ester octadecanoic acid on Cultured Chinese Hamster Cells.

Author

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

Year

2012

Bibliographic source

Japan Existing Chemical Data Base (JECDB) https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF627-83-8f.pdf

Testing facility

Bozo Research Center Inc.

Report date

2012-03-23

Report number

T-G024

LITERATURE: Reverse Mutation Test of 1,2-EthanediyI ester octadecanoic acid on Bacteria.

UUID: b0a5cd3f-57a8-4505-8907-9224f31b3971

Dossier UUID:

Author:

Date: 2022-03-10T13:29:17.000+09:00

Remarks:

General information

Reference Type

study report

Title

Reverse Mutation Test of 1,2-EthanediyI ester octadecanoic acid on Bacteria.

Author

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

Year

2012

Bibliographic source

Japan Existing Chemical Data Base (JECDB) https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF627-83-8e.pdf

Testing facility

Bozo Research Center Inc.

Report date

2012-03-22

Report number

T-0880