Name: COMPLETE / SUBSTANCE : 1,2-Ethanediyl ester octadecanoic acid / 627-83-8 Tue, 5 Sep 2023, 13:39:24+0900 /

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

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Author:
Date: 2023-09-05T13:39:24.666+09:00
Remarks:

Dossier header

Dossier submission type

Name
Complete table of contents

Version
core 8.0

Name (given by user)

Dossier subject

Dossier subject
1,2-Ethanediyl ester octadecanoic acid / 627-83-8

Public name

Submitting legal entity
National Institute of Health Sciences / Kawasaki / Japan

Dossier creation date/time
Tue, 5 Sep 2023, 13:39:24+0900

Used in category

LEGAL_ENTITY: National Institute of Health Sciences

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Author:
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Remarks:

General information

Legal entity name
National Institute of Health Sciences

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

Address

Address 1
Tonomachi 3-25-26

Address 2
Kawasaki-ku

Postal code
210-9501

Town
Kawasaki

Region / State
Kanagawa

Country
Japan
JP

Identifiers

Other IT system identifiers

IT system
LEO

ID
10767

IT system
IUCLID4

ID
16558402024DIV750

1,2-Ethanediyl 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-Ethanediyl 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-Ethanediyl 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-ethanediyl ester
- Analytical purity: 99.99% (Solid content as a mixture of long-chain fatty acid esters mainly oct adecanoic 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 nomi nal 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 (Crl: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 prot ein 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 admin istration, 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 admi nistration
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 pe riods.

BODY WEIGHT:
There were no changes related to the test substance in any groups at the dosing and recovery perio ds.

FOOD CONSUMPTION:
There were no changes related to the test substance in any groups at the dosing and recovery per iods.

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 period s.
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 pe riods.

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 be1000 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

UUID:	470f0cc5-44f8-4220-bd0a-fab4d69d78f0
Dossier UUID:	
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-Ethanediyl 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

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

Deviations
no

GLP compliance
yes

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

Test material

Test material information
1,2-Ethanediyl 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-ethanediyl 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 ug/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 i ncrease 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 ne gative with or without metabolic activation.

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.002

UUID: fb8b8e4b-f1d4-4958-a283-53ed461f9d90
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-Ethanediyl 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-Ethanediyl 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-ethanediyl 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(±): 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): cytot oxicity

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-Ethanediyl 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-Ethanediyl 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-ethanediyl ester
- Analytical purity: 99.99% (Solid content as a mixture of long-chain fatty acid esters mainly oc tadecanoic 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: 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: 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±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 (Crl: 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 obser ved 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 a fter 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 admi nistration, 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 ad ministration 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 adm inistration
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, histopatho logical 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 anim als: 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, ute rus, 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 WEIGTHS
- 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 be tween two groups in the recovery test, homogeneity of variance was analyzed by F-test. Then, if homo genous, 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 dev elopmental 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-Ethanediyl 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-Ethanediyl ester octadecanoic acid

Legal entity
National Institute of Health Sciences / Kawasaki / Japan

Identification of substance

Reference substance
1,2-Ethanediyl 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-Ethanediyl 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-Ethanediyl 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-Ethanediyl 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-Ethanediyl 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-Ethanediyl 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-Ethanediyl 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-Ethanediyl 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-Ethanediyl 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