



Name: 1-propene, tetramer / 6842-15-5

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

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Table of Contents

1-propene, tetramer	1
CORE	1
1 General information	1
1.1 Identification	1
Identification	1
OECD	2
D Health Effects	2
60 Acute toxicity: oral	2
Acute toxicity: oral.001	2
67 Repeated dose toxicity: oral	6
Repeated dose toxicity: oral.001	6
70 Genetic toxicity in vitro	14
Genetic toxicity in vitro.001	14
Genetic toxicity in vitro.002	18
73 Toxicity to reproduction	22
Reproductive/developmental toxicity.001	22
References	29
1-propene, tetramer	29
6842-15-5	30
6842-15-5	31
6842-15-5	32
6842-15-5	33
6842-15-5	34
Combined repeat dose and reproductive/developmental toxicity screening test of 1-Propene, tetramer by oral administration in rats	35
In Vitro Chromosomal Aberration Test of 1-Propene, tetramer on Cultured C hinese Hamster Cells.	36
National Institute of Health Sciences	37
Reverse Mutation Test of 1-Propene, tetramer on Bacteria.	39
Single Dose Oral Toxicity Test of 1-Propene, tetramer in Rats	40

1-propene, tetramer

CORE

General information

Identification

SUBSTANCE: 1-propene, tetramer

UUID: IUC5-e0ca2a88-57ae-44ba-bb7f-0f74fba1efe5

Dossier UUID:

Author: SuperUser

Date: 2016-12-21T14:37:12.000+09:00

Remarks:

Substance name

1-propene, tetramer

Legal entity

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

Identification of substance

Reference substance

[1-propene, tetramer / 6842-15-5](#)

EC number

EC name

CAS number

CAS name

6842-15-5

IUPAC name

Role in the supply chain

Manufacturer

false

Importer

false

Only representative

false

Downstream user

false

OECD

Health Effects

Acute toxicity: oral

ENDPOINT_STUDY_RECORD: Acute toxicity: oral.001

UUID: IUC5-42c5e945-ea8f-47a0-aa27-0890a1df8e11

Dossier UUID:

Author: SuperUser

Date: 2017-02-15T15:52:21.000+09:00

Remarks:

Administrative data

Endpoint

acute 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

other: OECD Test Guideline study under GLP condition

Data source

Reference

[Single Dose Oral Toxicity Test of 1-Propene, tetramer in Rats / MHLW, Japan / study report](#)

Data access

data published

Materials and methods

Test guideline

Qualifier

according to

Guideline

OECD Guideline 423 (Acute Oral toxicity - Acute Toxic Class Method)

Test type

acute toxic class method

Limit test

no

Test material

Test material information

[6842-15-5](#)

Test animals

Species

rat

common species

Strain

other: CrI:CD(SD)

Sex

female

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

- Source :Charles River Japan Inc.
- Age at study initiation: 9~10 weeks old
- Weight at study initiation: females, 236 (233-238) g (1st step group), 237 (234-242) g (2nd), 237 (232-241) g (3rd), 236 (233-240) g (4th)
- Fasting period before study: Approximately 16 hrs
- Housing: 3/cage
- Diet (e.g. ad libitum): Ad libitum except fasting period for 16 hrs before administration to 3 hrs after administration
- Water (e.g. ad libitum): Ad libitum
- Acclimation period: 5 days

ENVIRONMENTAL CONDITIONS

- Temperature (°C): 22±3 °C(actual temperature: 21.2-22.1°C)
- Humidity (%): 55 ± 10% (actual humidity: 58-62%)
- Air changes (per hr): > 10 times/hr
- Photoperiod (hrs dark / hrs light): 12 hrs light / 12 hrs dark

Administration / exposure

Route of administration

oral: gavage

Vehicle

olive oil

Details on oral exposure

- Amount of vehicle (if gavage): 5 ml/kg bw

Doses

300 mg/kg bw (1st and 2nd steps), 2000 mg/kg bw (3rd and 4th steps)

No. of animals per sex per dose

3 (each step)

Control animals

no

Details on study design

- Duration of observation period following administration: 14 days
- Frequency of observations: nearly successive observation (from time just to 1 hr after administration) and observation of every 2 hr (from 2 hr – 6 hr after administration) (day 0); twice a day (day 1); once a day (from day 2-day14)
- Frequency of weighing: just before administration (day 0), and 3,7 and 14 day after administration
- Necropsy of survivors performed: yes

Results and discussion

Effect levels

Key result false	
Sex female	
Dose descriptor LD50	
Effect level ca. 5000	mg/kg bw

Mortality

No deaths were observed in any group.

Clinical signs

Diarrhea was observed at 300 mg/kg bw. Decreased locomotor activity, diarrhea and soiled perineal region were observed at 2000 mg/kg bw.

Body weight

No changes related to the test substance were observed in any group.

Gross pathology

No changes related to the test substance were observed in any group.

Any other information on results incl. tables

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

http://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF6842-15-5a.pdf

Applicant's summary and conclusion

Interpretation of results

Category 5 based on GHS criteria Migrated information

Conclusions

No deaths were observed at 300 and 2000 mg/kg bw. The LD50 was considered to be approximately 5000 mg/kg bw (GHS: 5).

Executive summary

The acute oral LD50 of 1-propene, tetramer was > 2,000 mg/kg bw in female rats based on a study conducted according to OECD TG 423. No deaths were observed at 2,000 mg/kg bw. This substance at 300 mg/kg bw caused diarrhea and at 2,000 mg/kg bw caused decreased locomotor activity, diarrhea, and soiled perineal region.

Repeated dose toxicity: oral

ENDPOINT_STUDY_RECORD: Repeated dose toxicity: oral.001

UUID: IUC5-8ed0c66e-401a-4010-aec3-de2e382eddd0

Dossier UUID:

Author: SuperUser

Date: 2017-02-15T15:56:31.000+09:00

Remarks:

Administrative data

Endpoint

short-term repeated dose toxicity: oral combined repeated dose and reproduction / developmental screening

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: The study was conducted in accordance with Test Guidelines and under GLP.

Cross-reference

Reason / purpose

reference to same study

Remarks

7.8.1 Reproductive/developmental toxicity.001

Data source

Reference

[Combined repeat dose and reproductive/developmental toxicity screening test of 1-Propene, tetramer b... / MHLW, Japan / study report](#)

Data access

data published

Materials and methods

Test guideline

Qualifier

equivalent or similar to

Guideline

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

GLP compliance

yes

Limit test

no

Test material

Test material information

[6842-15-5](#)

Test animals

Species

rat

common rodent species

Strain

other: Crl: CD(SD)

Sex

male/female

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

- Source: Charles River Laboratories Japan, Inc. Atsugi
- Age at study initiation: 8 weeks
- Weight at study initiation: Males: 264-308 g; Females: 178-225 g
- Housing: bracket-type metallic wire-mesh cages (W 260 × D 380 × H 180 mm)
- Diet: ad libitum
- Water: ad libitum
- Acclimation period: 12 days

ENVIRONMENTAL CONDITIONS

- Temperature (°C): 20-24
- Humidity (%): 41-58
- Air changes: 10-15 times / hr
- Photoperiod: 12 hrs dark / 12 hrs light

Administration / exposure

Route of administration

oral: gavage

Vehicle

corn oil

Details on oral exposure

PREPARATION OF DOSING SOLUTIONS: Test substance was dissolved in corn oil for injection.

VEHICLE

- Lot/batch no. (if required): VIR7200 produced by Nacalai Tesque, INC.
- Dosing volume: 5 mL/kg bw
- Stability (test solutions): At least 9 days
- Storage condition of test solution: Room temperature

Analytical verification of doses or concentrations

yes

Details on analytical verification of doses or concentrations

Test suspensions at each concentration to be used for males in week 1 and six week of administration were analyzed by the HPLC method at Nisso chemical analysis service Co., Ltd. Results showed that the concentration of the test article in each suspension was 99.7 to 108.2% of the nominal concentration and both values were within the acceptable range (concentration: percentage of the nominal concentration, 100 ± 10%; C.V.: 10% or below)

Duration of treatment / exposure

- (P) Males: 42 days including 14 days pre-mating, mating, and thereafter 14 days
- (P) Females: 42–51 days including 14 days pre-mating, mating and gestation periods and the days until day 4 of lactation. 42 days for satellite females (without mating).

Frequency of treatment

Once/day, 7 days/week

Doses / concentrations

Remarks

Doses / Concentrations:
0 (vehicle), 40, 150, and 600 mg/kg bw/day
Basis:
actual ingested

No. of animals per sex per dose

- 12 animals/sex/dose as a main dose group,
- 5* males and 5 females at 0 and 600 mg/kg bw/day as a satellite group (without mating)
- * From corresponding main dose groups

Control animals

yes, concurrent vehicle

Details on study design

- Dose selection rationale: Doses in this test were set based on the results of the following dose-setting study: a 14-day repeated dose oral toxicity test (doses: 0, 30, 100, 300, and 1000 mg/kg bw/day). In the dose-setting study, increased liver and kidney weights were observed at 300 mg/kg bw/day and above, and diarrhea, mucous stool, low values of body weight and food consumption, high values of urine volume, ALT, urea nitrogen, creatinine and total cholesterol were observed at 1000 mg/kg bw/day. On the basis of these effects, a dose level of 600 mg/kg was selected as the maximum dose expecting to induce the toxic changes, and then dose levels of 150 and 40 mg/kg bw/day were selected as a middle dose and a minimum dose levels, respectively, in accordance with a common ratio of approximately 4.
- Rationale for animal assignment (if not random): Body weight-balanced randomization
- Post-exposure recovery period in satellite groups: 14 days

Examinations

Observations and examinations performed and frequency

- CAGE SIDE OBSERVATIONS: Yes
- Time schedule:

Males and females: 2 times/day during the administration period (before and after dosing) and the recovery period (am and pm)

DETAILED CLINICAL OBSERVATIONS: Yes

The functional observational battery testing (FOB) was performed on all animals. Among the measures in the FOB, detailed clinical observations were made before the initiation of dosing. Thereafter, in males of the main groups, detailed clinical observations were made once a week. Also in females of the main groups, detailed clinical observations were made once a week in pre-mating and mating periods thereafter, and then those were made on days 1, 7, 14 and 20 of gestation, and on day 4 of lactation. For the satellite group, detailed clinical observations were made once a week in dosing and recovery periods.

Sensory motor reflexes, forelimb and hindlimb grip strengths, and motor activity were measured on week 6 of administration period (main/recovery group animals) and week 2 of recovery period (recovery group animals).

BODY WEIGHT: Yes

- Time schedule for examinations: Males (main/recovery group): Days 1, 3, 5, 7, 10, 14, 21, 28, 35, 42, and the day of necropsy (after ca. 16h-fasting) in dosing period

Males and females (recovery group): Days 1, 7, 14, and the day of necropsy (after ca. 16h-fasting) in recovery period

Females (main group): Twice a week during the precopulation period (days 1, 3, 5, 7, 10, and 14); gestation days 0, 1, 3, 5, 7, 10, 14, 17, and 20; lactation days 0, 1, and 4; and the day of necropsy (after ca. 16 h-fasting)

FOOD CONSUMPTION AND COMPOUND INTAKE (if feeding study):

- Food consumption: Yes, same days of the measuring of body weight

OPHTHALMOSCOPIC EXAMINATION: No

HAEMATOLOGY: Yes

- Time schedule for collection of blood: Blood was collected on the day of necropsy

- Anaesthetic used for blood collection: Yes (pentobarbital sodium)

- Animals fasted: Yes, 16-22h

- How many animals: 5 sex/dose/group

- Parameters checked in table were examined.

- Measurement of thyroid hormone: Yes (T3, T4, TSH)

CLINICAL CHEMISTRY: Yes

- Time schedule for collection of blood: Same as hematology

- Animals fasted: Same as hematology

- How many animals: Same as hematology

- Parameters checked in table were examined.

URINALYSIS: Yes

- Time schedule for collection of urine: on week 6 of administration period (main/recovery group animals) and week 2 of recovery period (recovery group animals).

- Metabolism cages used for collection of urine: Yes

- Animals fasted: no fasting (3h- and 21h-urine)

Sacrifice and pathology

GROSS NECROPSY

- Gross necropsy consisted of external and internal examinations including the brain (cerebrum, cerebellum and pons), spinal cord, pituitary, thymus, thyroid gland (including parathyroid), adrenal glands, spleen, heart, esophagus, stomach, liver, pancreas, submandibular gland, duodenum, jejunum, ileum (including Peyer's patches), cecum, colon, rectum, trachea, lung, kidney, bladder, testis, epididymis, prostate, seminal vesicles (including coagulating gland), ovary, uterus (the corners and neck), vagina, eye and Harder gland, mammary gland (right abdomen), femur (including the

bone marrow, right), mesenteric lymph nodes, submandibular lymph nodes, skeletal muscle (gastrocnemius), sciatic nerve and gross abnormal site (including the boundary areas between the normal and abnormal sites)

HISTOPATHOLOGY: Organs and tissues (same as gross necropsy)

Other examinations

Organ weight: Brain, pituitary gland, thyroids (including parathyroids), thymus, heart, liver, kidneys, spleen, adrenal gland, thymus, testis, epididymis, prostate (ventral), seminal vesicles (including coagulating gland and secretions), ovary, uterus

Statistics

The data were analyzed for homogeneity of variance by the Bartlett test. If variances were homogeneous, data was analyzed by one-way ANOVA and the Dunnett test, whereas heterogeneous data was analyzed by Kruskal-Wallis test and the Steel test.

For findings two or more grades was observed, data was analyzed by Kruskal-Wallis test and the Steel test. For findings one grade was observed, data was analyzed by a multi-sample chi-square test and a two-sample chi-square test. For the comparison tests with the control group, the significance level was 5%.

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)

effects observed, treatment-related

Food efficiency

not examined

Water consumption and compound intake (if drinking water study)

not examined

Ophthalmological findings

not examined

Haematological findings

effects observed, treatment-related

Clinical biochemistry findings

effects observed, treatment-related

Description (incidence and severity)

including thyroid hormones (T3, T4, and TSH)

Urinalysis findings

effects observed, treatment-related

Behaviour (functional findings)

no effects observed

Description (incidence and severity)

see clinical signs.

Organ weight findings including organ / body weight ratios

effects observed, treatment-related

Gross pathological findings

effects observed, treatment-related

Histopathological findings: non-neoplastic

effects observed, treatment-related

Histopathological findings: neoplastic

not examined

Details on results

FOOD CONSUMPTION

Low values were observed in females of main group at 600 mg/kg bw/day on 3-5 day of dosing and on 1-3 and 3-5 days of gestation.

HAEMATOLOGY

In males, at the end of dosing period, low values of red blood cell count, hemoglobin level, and hematocrit were observed at 150 mg/kg bw/day and higher.

At the end of recovery period, low values of red blood cell count, hemoglobin level, and hematocrit, and high value of reticulocyte count were observed at 600 mg/kg bw/day.

In females, at the end of dosing period, low value of reticulocyte count was observed at 600 mg/kg bw/day (main group), and low value of red blood cell count and prolonged activated partial thromboplastin time were observed at 600 mg/kg bw/day (satellite group). No effects were observed at the end of recovery period.

CLINICAL CHEMISTRY

In males, at 600 mg/kg bw/day: High values of α 2-globulin fraction, gamma-GTP, total cholesterol, and urea nitrogen, and low value of glucose were observed at the end of dosing period, and high values of gamma-GTP, urea nitrogen, and inorganic phosphorus were observed at the end of recovery period.

In females, at 600 mg/kg bw/day: High values of gamma-GTP and low value of inorganic phosphorus were observed at the end of dosing period (main group), and high values of α 2-globulin fraction, total cholesterol, and potassium, and low value of total bilirubin and sodium were observed at the end of dosing period (satellite group). Low value of A/G ration and albumin was observed at the end of recovery period.

On the thyroid hormone, high value of T4 was observed in females at the end of the recovery period.

URINALYSIS

Circular epithelial cells appeared in the urinary sediment of males at 600 mg/kg bw/day.

ORGAN WEIGHTS

In males, high value of kidney weight at 40 mg/kg bw/day and higher, high value of liver weight at 150 mg/kg bw/day and higher were observed at the end of the dosing period. High value of a kidney weight was observed at 600 mg/kg bw/day at the end of the recovery end.

In females, high values of liver weight at 150 mg/kg bw/day and higher, thyroid weight at 600 mg/kg bw/day, and kidney weight at 40 and 600 mg/kg bw/day were observed at the end of the dosing period (main group), and liver, kidney, and thyroid weights at 600 mg/kg bw/day were observed at the end of the dosing period (satellite group). Kidney and thyroid weights at 600 mg/kg bw/day were observed at the end of the recovery period.

GROSS PATHOLOGY: See tables in the full report.

HISTOPATHOLOGY: See tables in the full report.

Main lesions were observed in the kidney and the liver in males, and were observed in the liver and the thyroid in females.

Effect levels

Dose descriptor

NOAEL

Effect level

40

mg/kg bw/day (actual dose received)

Based on

test mat.

Sex

male

Basis for effect level

other: anemia and increased liver weight

Dose descriptor

NOAEL

Effect level

40

mg/kg bw/day (actual dose received)

Based on

test mat.

Sex

female

Basis for effect level

other: increased liver weight

Target system / organ toxicity

Key result

false

Critical effects observed

not specified

Any other information on results incl. tables

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

http://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF6842-15-5d.pdf

Applicant's summary and conclusion

Executive summary

A combined repeated oral dose toxicity study with the reproduction/developmental toxicity screening test was performed according to a Japanese guideline (similar to OECD TG 422). Male and female rats (12 animals/sex/dose) were administered 1-propene, tetramer at 0, 40, 150, and 600 mg/kg bw/day. Males were dosed for 42 days, including a 14-day pre-mating and mating periods. Females were dosed for 40–45 days, including a 14-day pre-mating, mating, and gestation periods and the time until day 4 of lactation. Five out of 12 males with administered doses of 0 and 600 mg/kg bw/day were evaluated as a 14-day recovery group. In addition, 10 females/dose were administered 0 and 600 mg/kg bw/day for 42 days without mating; they were examined after the administration period or after a 14-day recovery period. Regarding hematology parameters, anemia was observed at 150 mg/kg bw/day and higher in males, with decreased red blood cell counts at 600 mg/kg bw/day in females without mating. In the kidney, in males, α 2u-globulin nephropathy was observed at 40 mg/kg bw/day and higher, with increased kidney weight at 40 mg/kg bw/day and higher and basophilic changes in the tubular epithelium at 150 mg/kg bw/day and higher. Furthermore, necrosis of the tubular epithelium, increased blood urea nitrogen level, and round epithelial cells in urinary sediments were observed in males at 600 mg/kg bw/day. These effects were considered to be caused by α 2u-globulin accumulation in the kidney as male rat specific disease, and were not relevant in human health. In the liver, in both sexes, increased liver weight was observed at 150 mg/kg bw/day and higher, with centrilobular hepatocytes hypertrophy at 600 mg/kg bw/day. Furthermore, increases in the α 2-globulin fraction, γ -glutamyl transpeptidase, and total cholesterol levels and a decrease in glucose level were observed at 600 mg/kg bw/day in both sexes. In the thyroid, in females, increased thyroid weight and hypertrophy of follicular cells were observed at 600 mg/kg bw/day, with thyroxin level increasing after the recovery period at this dose. Hematology, kidney, and liver, but not thyroid, changes tended to resolve after the recovery period. On the basis of anemia in males and increased liver weight in both sexes, NOAEL for repeated-dose toxicity was determined to be 40 mg/kg bw/day in male and female rats.

Genetic toxicity in vitro

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.001

UUID: IUC5-e1c75adb-a8dd-43ee-864e-bfc1af110861

Dossier UUID:

Author: SuperUser

Date: 2017-02-15T15:58:12.000+09:00

Remarks:

Administrative data

Endpoint

in vitro gene mutation study in bacteria Type of genotoxicity: gene mutation

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-Propene, tetramer on Bacteria. / MHLW, Japan / study report](#)

Data access

data published

Materials and methods

Test guideline

Qualifier

according to

Guideline

JAPAN: Guidelines for Screening Mutagenicity Testing Of Chemicals

Deviations

no

GLP compliance

yes

Type of assay

bacterial reverse mutation assay
in vitro gene mutation study in bacteria

Test material

Test material information

[6842-15-5](#)

Method

Species / strain

Species / strain

S. typhimurium TA 1535, TA 1537, TA 98 and TA 100
bacteria

Metabolic activation

with and without

Metabolic activation system

rat liver, induced by phenobarbital and 5,6-benzoflavone

Species / strain

E. coli WP2 uvr A
bacteria

Metabolic activation

with and without

Metabolic activation system

rat liver, induced by phenobarbital and 5,6-benzoflavone

Test concentrations with justification for top dose

-S9 mix and + S9 mix: 156, 313, 625, 1250, 2500, 5000 µg/plate (all strains)

Vehicle

- Vehicle(s)/solvent(s) used: Acetone

Controls

Negative controls

no

Solvent controls

yes

True negative controls

other: tests without all strains, and with vehicle, S9 mix or the highest dose

Positive controls

yes

Positive control substance

other: -S9 mix: 2-(2-Furyl)-3-(5-nitro-2-furyl) acrylamide (AF2:TA 100, TA98 & WP2 uvrA), sodium azide (SA:TA1535) and 9-aminoacridine hydrochloride (9AA:TA1537). +S9 mix: 2-aminoanthracene (2AA:all strains).

Remarks

AF2 & 2AA were dissolved with DMSO, and SA & 9AA were dissolved with distilled water.

Details on test system and conditions

RANGE-FINDING/SCREENING STUDIES:Concentration: 20-5000 µg/plate

Cytotoxic conc.: [-S9mix] No, [+S9mix] No.

Precipitate: Yes, >1000 µg/plate

METHOD OF APPLICATION: Preincubation

DURATION

- Preincubation period: 20 min at 37 °C

- Exposure duration:48 hrs

NUMBER OF PLATES: 3

NUMBER OF REPLICATIONS: 2

DETERMINATION OF CYTOTOXICITY

- Method: other: growth inhibition

Evaluation criteria

In any strain(s) tested with or without S9 mix, when the mean number of revertant colonies per plate increased twice more than that of the negative control and when the increase was shown to be dose-related and reproducible, the chemical was judged mutagenic.

Statistics

No.

Results and discussion

Test results

Key result

false

Species / strain

S. typhimurium TA 1535, TA 1537, TA 98 and TA 100
bacteria

Metabolic activation

with and without

Genotoxicity

negative

Cytotoxicity

no, but tested up to limit concentrations

Vehicle controls valid

yes

Positive controls valid

yes

Remarks on result

other: all strains/cell types tested Migrated from field 'Test system'.

Key result

false

Species / strain

E. coli WP2 uvr A
bacteria

Metabolic activation

with and without

Genotoxicity

negative

Cytotoxicity

no, but tested up to limit concentrations

Vehicle controls valid

yes

Positive controls valid

yes

Remarks on result

other: all strains/cell types tested Migrated from field 'Test system'.

Additional information on results

Contamination with any other bacterias was not found.

Any other information on results incl. tables

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

http://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF6842-15-5e.pdf

Applicant's summary and conclusion

Conclusions

Interpretation of results (migrated information):
negative

Executive summary

In a bacterial reverse mutation assay using *Salmonella typhimurium* TA100, TA1535, TA98, and TA1537 and *Escherichia coli* WP2uvrA (similar to OECD TG 471), 2,3,4,4'-tetrahydroxybenzophenone was negative with or without metabolic activation.

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.002

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Dossier UUID:

Author: SuperUser

Date: 2017-02-15T15:59:26.000+09:00

Remarks:

Administrative data

Endpoint

in vitro cytogenicity / chromosome aberration study in mammalian cells Type of genotoxicity: chromosome aberration

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-Propene, tetramer on Cultured Chinese Hamster Cells. / MHLW, Japan / study report](#)

Data access

data published

Materials and methods

Test guideline

Qualifier

according to

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

JAPAN: Guidelines for Screening Mutagenicity Testing Of Chemicals

Deviations

no

GLP compliance

yes

Type of assay

in vitro mammalian chromosome aberration test
chromosome aberration

Test material

Test material information

[6842-15-5](#)

Method

Target gene

Chromosome

Species / strain

Species / strain

other: Chinese hamster lung(CHL/IU) cells

Metabolic activation

with and without

Metabolic activation system

rat liver, induced by phenobarbital and 5,6-benzoflavone

Test concentrations with justification for top dose

-S9 mix (short-term treatment): 0, 53.1, 106, 213, 425 ug/mL

+S9 mix (short-term treatment): 0, 213, 425, 850, 1700 ug/mL

-S9 mix (continuous treatment, 24 h): 0, 53.1, 106, 213, 425 ug/mL

-S9 mix (continuous treatment, 48 h): 0, 53.1, 106, 213, 425 ug/mL

Vehicle

- Vehicle(s)/solvent(s) used:Acetone

Controls

Negative controls

no

Solvent controls

yes

True negative controls

no

Positive controls

yes

Positive control substance

cyclophosphamide
mitomycin C

Remarks

mitomycin C (without S9 mix), cyclophosphamide (with S9 mix)

Details on test system and conditions

METHOD OF APPLICATION: Exposure duration: [continuous treatment]: 24, 48 hrs [short-term treatment]: 6 hrs + 18 hr

SPINDLE INHIBITOR: Colcemid

NUMBER OF REPLICATIONS: 2

NUMBER OF CELLS EVALUATED: 200 cells / dose

DETERMINATION OF CYTOTOXICITY

- Method: relative total growth

Evaluation criteria

For the evaluation of the frequencies of structural aberrations and of polyploidy induced, the following criteria were employed.

Appearance incidence of cells with chromosomal aberrations: Negative (-): < 5%; equivocal (±): 5-10%; positive (+): > 10%.

Finally, the substance is positive when the incidence is considered to be dose-related and reproducible.

Statistics

not used.

Results and discussion

Test results

Key result

false

Species / strain

other: Chinese hamster lung (CHL/IU) cells

Metabolic activation

with

Genotoxicity

negative

Cytotoxicity

no

Vehicle controls valid

yes

Negative controls valid

not examined

Positive controls valid

yes

Key result

false

Species / strain

other: Chinese hamster lung (CHL/IU) cells

Metabolic activation

without

Genotoxicity

negative

Cytotoxicity

yes 50% cell growth inhibition: 315.3 ug/mL (short), 336.7 ug/mL (24h continuous) and 219.2 ug/mL (48h continuous)

Vehicle controls valid

yes

Negative controls valid

not examined

Positive controls valid

yes

Any other information on results incl. tables _____

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

http://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF6842-15-5f.pdf

Applicant's summary and conclusion _____

Executive summary

An in vitro chromosomal aberration test using CHL/IU cells (OECD TG 473) showed positive.

Toxicity to reproduction

ENDPOINT_STUDY_RECORD: Reproductive/developmental toxicity.001

UUID: IUC5-e522e89f-3b32-4842-a874-9ca34277d649

Dossier UUID:

Author: SuperUser

Date: 2017-02-15T16:01:46.000+09:00

Remarks:

Administrative data

Endpoint

screening for reproductive / developmental toxicity based on test type (migrated information)

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: The study was conducted in accordance with Test Guidelines and under GLP.

Cross-reference

Reason / purpose

reference to same study

Remarks

7.5.1 Repeated dose toxicity: oral.001

Data source

Reference

[Combined repeat dose and reproductive/developmental toxicity screening test of 1-Propene, tetramer b... / MHLW, Japan / study report](#)

Data access

data published

Materials and methods

Test guideline

Qualifier

equivalent or similar to

Guideline

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

GLP compliance

yes

Test material

Test material information

[6842-15-5](#)

Test animals

Species

rat

Strain

other: Crl: CD(SD)

Sex

male/female

Details on test animals and environmental conditions

TEST ANIMALS

- Source: Charles River Laboratories Japan, Inc. Atsugi
- Age at study initiation: 8 weeks
- Weight at study initiation: Males: 264-308 g; Females: 178-225 g
- Housing: bracket-type metallic wire-mesh cages (W 260 × D 380 × H 180 mm)
- Diet: ad libitum
- Water: ad libitum
- Acclimation period: 12 days

ENVIRONMENTAL CONDITIONS

- Temperature (°C): 20-24
- Humidity (%): 41-58
- Air changes: 10-15 times / hr
- Photoperiod: 12 hrs dark / 12 hrs light

Administration / exposure

Route of administration

oral: gavage

Vehicle

corn oil

Details on exposure

PREPARATION OF DOSING SOLUTIONS: Test substance was dissolved in corn oil for injection.

VEHICLE

- Lot/batch no. (if required): VIR7200 produced by Nacalai Tesque, INC.
- Dosing volume: 5 mL/kg bw

- Stability (test solutions): At least 9 days
- Storage condition of test solution: Room temperature

Details on mating procedure

- M/F ratio per cage: 1:1
- Length of cohabitation: up to 14 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

Test suspensions at each concentration to be used for males in week 1 and six week of administration were analyzed by the HPLC method at Nisso chemical analysis service Co., Ltd. Results showed that the concentration of the test article in each suspension was 99.7 to 108.2% of the nominal concentration and both values were within the acceptable range (concentration: percentage of the nominal concentration, $100 \pm 10\%$; C.V.: 10% or below)

Duration of treatment / exposure

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

(P) Females: 42–51 days including 14 days pre-mating, mating and gestation periods and the days until day 4 of lactation. 42 days for satellite females (without mating).

Frequency of treatment

Once/day, 7 days/week

Doses / concentrations

Remarks

Doses / Concentrations:

0 (vehicle), 40, 150, and 600 mg/kg bw/day

Basis:

actual ingested

No. of animals per sex per dose

12 animals/sex/dose as a main dose group,

5* males and 5 females at 0 and 600 mg/kg bw/day as a satellite group (without mating)

* From corresponding main dose groups

Control animals

yes, concurrent vehicle

Examinations

Parental animals: Observations and examinations

see 7.5.1 repeated dose toxicity: oral.001

Estrous cyclicity (parental animals)

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

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

Sperm parameters (parental animals)

Parameters examined in P male parental generations: testes weight, epididymides weight

Litter observations

PARAMETERS EXAMINED: The following parameters were examined in F1 offspring:

Number and sex of pups, stillbirths, live births, postnatal mortality, presence of gross anomalies, and weight gain.

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

Postmortem examinations (parental animals)

SACRIFICE

- Male animals: Rats were euthanized by exsanguination under ether anesthesia on the day after the last administration.

- Maternal animals: Rats were euthanized by exsanguination under ether anesthesia on day 4 of lactation.

GROSS NECROPSY

- Gross necropsy consisted of external and internal examinations including the brain (cerebrum, cerebellum and pons), spinal cord, pituitary, thymus, thyroid gland (including parathyroid), adrenal glands, spleen, heart, esophagus, stomach, liver, pancreas, submandibular gland, duodenum, jejunum, ileum (including Peyer's patches), cecum, colon, rectum, trachea, lung, kidney, bladder, testis, epididymis, prostate, seminal vesicles (including coagulating gland), ovary, uterus (the corners and neck), vagina, eye and Harder gland, mammary gland (right abdomen), femur (including the bone marrow, right), mesenteric lymph nodes, submandibular lymph nodes, skeletal muscle (gastrocnemius), sciatic nerve and gross abnormal site (including the boundary areas between the normal and abnormal sites)

ORGAN WEIGHT: Brain, pituitary gland, thyroids (including parathyroids), thymus, heart, liver, kidneys, spleen, adrenal gland, thymus, testis, epididymis, prostate (ventral), seminal vesicles (including coagulating gland and secretions), ovary, uterus

HISTOPATHOLOGY: See "Gross necropsy."

Postmortem examinations (offspring)

SACRIFICE

- The F1 pups were sacrificed at PND 4 by exsanguination under ether anesthesia.

GROSS NECROPSY

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

Statistics

The data were analyzed for homogeneity of variance by the Bartlett test. If variances were homogeneous, data was analyzed by one-way ANOVA and the Dunnett test, whereas heterogeneous data was analyzed by Kruskal-Wallis test and the Steel test.

For findings two or more grades was observed, data was analyzed by Kruskal-Wallis test and the Steel test. For findings one grade was observed, data was analyzed by a multi-sample chi-square test and a two-sample chi-square test. For the comparison tests with the control group, the significance level was 5%.

Reproductive indices

Each parameter was determined by the following equations:

Duration of gestation (days) = day 0 of lactation – day 0 of gestation

Abnormal estrous cycle = (No. of female with abnormal estrous cycle / No. of females examined) × 100

Copulation index (males or females, %) = (No. of copulated males or females / No. of co-housed males or females) × 100

Fertility index (%) = (No. of pregnant females / No. of copulated females) × 100

Gestation index (%) = (No. of females delivered liveborn pups / No. of pregnant females) × 100

Nursing index (%) = (No. of females nursing live pups on lactation day 4 / No. of females with live pups delivery) × 100

Implantation index (per litter, %) = (No. of implantation sites/No. of corpora lutea) × 100

Delivery index (per litter, %) = (No. of pups born/No. of implantation sites) × 100

Sex ratio on Lactation day 0 = (No. of male pups born / No. of pups born) and (No. of live male pups / No. of live pups)

Sex ratio on Lactation day 4 = No. of live male pups/No. of live pups

Live birth index (%) = (No. of liveborn pups/Total No. of pups born) × 100

Offspring viability indices

Viability index (%) = (No. of surviving pus on day 4 after birth/No. of liveborn pups on day 0 after birth) × 100

Results and discussion

Results: P0 (first parental animals)

General toxicity (P0)

Organ weight findings including organ / body weight ratios

no effects observed

Description (incidence and severity)

(on reproductive organs)

Gross pathological findings

no effects observed

Description (incidence and severity)

(on reproductive organs)

Histopathological findings: non-neoplastic

no effects observed

Description (incidence and severity)

(on reproductive organs)

Reproductive function / performance (P0)

Reproductive function: estrous cycle

no effects observed

Reproductive performance

no effects observed

Effect levels (P0)

Dose descriptor

NOAEL

Effect level

600

mg/kg bw/day (actual dose received)

Sex

male/female

Basis for effect level

other: No effects on reproduction

Results: F1 generation

General toxicity (F1)

Clinical signs

no effects observed

Mortality / viability

no mortality observed

Body weight and weight changes

no effects observed

Sexual maturation

not examined

Organ weight findings including organ / body weight ratios

not examined

Gross pathological findings

no effects observed

Histopathological findings

no effects observed

Effect levels (F1)

Dose descriptor

NOAEL

Generation

F1

Effect level

600

mg/kg bw/day (actual dose received)

Sex

male/female

Basis for effect level

other: No effects on development

Overall reproductive toxicity

Key result

false

Reproductive effects observed

not specified

Any other information on results incl. tables

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

http://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF6842-15-5d.pdf

Applicant's summary and conclusion

Conclusions

NOAEL for the rat reproductive/developmental toxicity of 1-propene, tetramer was determined to be 600 mg/kg bw/day, the highest dose tested.

Executive summary

In the combined repeated oral dose toxicity study (0, 40, 150, and 600 mg/kg bw/day) with the reproduction/developmental toxicity screening test (OECD TG 422), no effects of this substance on reproductive and developmental parameters were observed at 600 mg/kg bw/day. NOAEL for the rat reproductive/developmental toxicity of 1-propene, tetramer was determined to be 600 mg/kg bw/day, the highest dose tested.

References

REFERENCE_SUBSTANCE: 1-propene, tetramer

UUID: IUC5-67a7f2be-af23-4a38-8ea7-67a5ffccffba

Dossier UUID:

Author: SuperUser

Date: 2017-10-30T11:27:04.000+09:00

Remarks:

General information

Reference substance name

1-propene, tetramer

Reference substance information

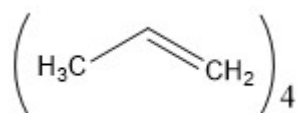
CAS information

CAS number

6842-15-5

Molecular and structural information

Structural formula



TEST_MATERIAL_INFORMATION: 6842-15-5

UUID: e334fdc6-f78b-3025-a4d2-f4c305496a6f

Dossier UUID:

Author: SuperUser

Date: 2017-02-15T15:52:21.000+09:00

Remarks:

Name

6842-15-5

Composition

Type

Constituent

Reference substance

1-propene, tetramer / 6842-15-5

EC number

EC name

CAS number

CAS name

6842-15-5

IUPAC name

Other characteristics

Details on test material

Name of test material (as cited in study report): 1-Propene, tetramer

- Analytical purity: 99.9%

- Lot/batch No.: MZ5G05-2

- Storage condition of test material: at a cold place (temperature 2~6°C) in a light resistant container

- Stability under test conditions: The stability of test material was identified by analysis of the remainder.

TEST_MATERIAL_INFORMATION: 6842-15-5

UUID: a7b2c6cb-5090-36bb-abb7-b59599e70713

Dossier UUID:

Author: SuperUser

Date: 2017-02-15T15:56:31.000+09:00

Remarks:

Name

6842-15-5

Composition

Type

Constituent

Reference substance

1-propene, tetramer / 6842-15-5

EC number

EC name

CAS number

CAS name

6842-15-5

IUPAC name

Other characteristics

Details on test material

Name of test material (as cited in study report): 1-Propene, tetramer

- Analytical purity: 99.9%

- Lot/batch No.: C6UE654

- Storage condition of test material: at a cold place (temperature 2~10 °C) in a light resistant container

- Stability under test conditions: The stability of test material was identified by analysis of the remainder.

TEST_MATERIAL_INFORMATION: 6842-15-5

UUID: d25d1671-4d65-3bad-8e32-fbb280dac1a4

Dossier UUID:

Author: SuperUser

Date: 2017-02-15T15:58:12.000+09:00

Remarks:

Name

6842-15-5

Composition

Type

Constituent

Reference substance

1-propene, tetramer / 6842-15-5

EC number

EC name

CAS number

CAS name

6842-15-5

IUPAC name

Other characteristics

Details on test material

- Name of test material (as cited in study report): 1-Propene, tetramer
- Purity: 99.9%
- Lot/batch No.: MZ5G05-2
- Storage condition of test material: Refrigeration
- Stability under test conditions: The stability of test material was identified by analysis of the remainder.

TEST_MATERIAL_INFORMATION: 6842-15-5

UUID: e1d877e3-561a-33ec-8363-d285fa00151a

Dossier UUID:

Author: SuperUser

Date: 2017-02-15T15:59:26.000+09:00

Remarks:

Name

6842-15-5

Composition

Type

Constituent

Reference substance

1-propene, tetramer / 6842-15-5

EC number

EC name

CAS number

CAS name

6842-15-5

IUPAC name

Other characteristics

Details on test material

- Name of test material (as cited in study report): 1-Propene, tetramer
- Analytical purity: 71.2% for (C₃H₆)₄
- Supplier: Nippon Oil Corporation
- Lot/batch No.: MZ5A01
- Storage condition of test material: under room temperature, closed container

TEST_MATERIAL_INFORMATION: 6842-15-5

UUID: f9331651-2bbd-3ea8-90d5-24c83253a4ac

Dossier UUID:

Author: SuperUser

Date: 2017-02-15T16:01:46.000+09:00

Remarks:

Name

6842-15-5

Composition

Type

Constituent

Reference substance

1-propene, tetramer / 6842-15-5

EC number

EC name

CAS number

CAS name

6842-15-5

IUPAC name

Other characteristics

Details on test material

Name of test material (as cited in study report): 1-Propene, tetramer

- Analytical purity: 99.9%

- Lot/batch No.: C6UE654

- Storage condition of test material: at a cold place (temperature 2~10 °C) in a light resistant container

- Stability under test conditions: The stability of test material was identified by analysis of the remainder.

LITERATURE: Combined repeat dose and reproductive/developmental toxicity screening test of 1-Propene, tetramer by oral administration in rats

UUID: 660d1cf9-7876-3bf6-9119-c6d011cadd7

Dossier UUID:

Author: SuperUser

Date: 2017-02-15T15:56:31.000+09:00

Remarks:

General information

Reference Type

study report

Title

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Propene, tetramer by oral administration in rats

Author

MHLW, Japan

Year

2013

Bibliographic source

available in the web of Japan Existing Chemical Data Base (JECDB) at http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp

Testing facility

Safety Research Institute for Chemical Compounds Co., Ltd.

LITERATURE: In Vitro Chromosomal Aberration Test of 1-Propene, tetramer on Cultured Chinese Hamster Cells.

UUID: 17074494-e98d-3b6c-b658-4c47fbe425cd

Dossier UUID:

Author: SuperUser

Date: 2017-02-15T15:59:26.000+09:00

Remarks:

General information

Reference Type

study report

Title

In Vitro Chromosomal Aberration Test of 1-Propene, tetramer on Cultured Chinese Hamster Cells.

Author

MHLW, Japan

Year

2006

Bibliographic source

Japan Existing Chemical Data Base (JECDB)

Testing facility

BoZo Research Center

LEGAL_ENTITY: National Institute of Health Sciences

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

Dossier UUID:

Author: SuperUser

Date: 2011-06-23T11:55:01.000+09:00

Remarks:

General information

Legal entity name

National Institute of Health Sciences

Identifiers

Other IT system identifiers

IT system

LEO

ID

10767

IT system

IUCLID4

ID

16558402024DIV750

Contact information

Contact address

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Country

Japan

Contact persons

Person

Hirose, Akihiko; National Institute of Health Sciences

Last name

Hirose

First name

Akihiko

Organisation

National Institute of Health Sciences

Department

Division of Risk Assessment

Title

Dr.

Address 1

1-18-1 Kamiyoga

Address 2

Setagaya-ku

Postal code

158-8501

Town

Tokyo

Country

Japan

LITERATURE: Reverse Mutation Test of 1-Propene, tetramer on Bacteria.

UUID: 9cab12b7-5381-3ef6-9a60-ca82a090a84a

Dossier UUID:

Author: SuperUser

Date: 2017-02-15T15:58:12.000+09:00

Remarks:

General information

Reference Type

study report

Title

Reverse Mutation Test of 1-Propene, tetramer on Bacteria.

Author

MHLW, Japan

Year

2006

Bibliographic source

Japan Existing Chemical Data Base (JECDB)

Testing facility

Research Institute for Animal Science in Biochemistry & Toxicology (RIAS)

LITERATURE: Single Dose Oral Toxicity Test of 1-Propene, tetramer in Rats

UUID: 5da23c5a-577c-376b-9ef5-ad3683ba9b5a

Dossier UUID:

Author: SuperUser

Date: 2017-02-15T15:52:21.000+09:00

Remarks:

General information

Reference Type

study report

Title

Single Dose Oral Toxicity Test of 1-Propene, tetramer in Rats

Author

MHLW, Japan

Year

2006

Bibliographic source

available in the web of Japan Existing Chemical Data Base (JECDB) at http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp

Testing facility

Research Institute for Animal Science in Biochemistry and Toxicology.