Name: COMPLETE / SUBSTANCE : 1-propene, tetramer / 6842-15-5 Fri, 16 Dec 2022, 16:16:07+0900 /

Legal entity owner: National Institute of Health Sciences

Printing date: 2022-12-16T16:16:08.007+09:00

Table of Contents

DOSSIER:

UUID: 0
Dossier UUID:
Author:
Date: 2022-12-16T16:16:07.825+09:00
Remarks:

Dossier header

Dossier submission type

Name
Complete table of contents

Version
core 7.0

Name (given by user)

Dossier subject

Dossier subject
1-propene, tetramer / 6842-15-5

Public name

Submitting legal entity
National Institute of Health Science

Dossier creation date/time
Fri, 16 Dec 2022, 16:16:07+0900

Used in category

LEGAL_ENTITY: National Institute of Health Science

UUID:	f51e7b54-9211-4863-90ce-fcf8a155d647
Dossier UUID:	
Author:	
Date:	2022-11-07T16:24:02.822+09:00
Remarks:	

General information

Legal entity name
National Institute of Health Science

1-propene, tetramer

CORE

General information

Assessment approach (assessment entities)

FIXED_RECORD: Assessment approach

UUID:	ce018663-1b31-3ddc-a47b-e717a1c48cd5
Dossier UUID:	
Author:	
Date:	2016-12-21T14:37:12.000+09:00
Remarks:	

OECD

Health Effects

Acute toxicity: oral

ENDPOINT_STUDY_RECORD: Acute toxicity: oral.001

UUID:	IUC5-42c5e945-ea8f-47a0-aa27-0890a1df8e11
Dossier UUID:	
Author:	
Date:	2022-12-16T16:12:07.019+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

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
1-Propene, tetramer

Test animals

Species
rat
common species

Strain
other: Crl:CD(SD)

Sex
female

Details on test animals or test system 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 a dministration
- Water (e.g. ad libitum): Ad libitum
- Acclimation period: 5 days
ENVIRONMENTAL CONDITIONS
- Temperature (°C): 22±3 ℃(actual temperature: 21.2-22.1℃)
- 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
other: Diarrhea was observed at 300 mg/kg bw. Decreased locomotor activity, diarrhea and soiled p erineal region were observed at 2000 mg/kg bw.

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

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Author:	
Date:	2022-12-16T16:13:23.471+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 for cross-reference
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

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
1-Propene, tetramer

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 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 admi nistration were analyzed by the HPLC method at Nisso chemical analysis service Co., Ltd. Results sho wed 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 unt il 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 maximu m 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 com mon 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. Ther eafter, in males of the main groups, detailed clinical observations were made once a week. Also in f emales 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 re covery 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, e pididymis, 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 (gastrocnemiu s), sciatic nerve and gross abnormal site (including the boundary areas between the normal and abnor mal sites)

HISTOPATHOLOGY: Organs and tissues (same as gross necropsy)

Other examinations
Organ weight: Brian, 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 α2-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 α2-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 per iod (main group), and liver, kidney, and thyroid weights at 600 mg/kg bw/day were observed at the e nd of the dosing period (satellite group). Kidney and thyroid weights at 600 mg/kg bw/day were obser ved 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

Key result
false

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

Key result
false

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

Field content is not in a valid XML format and thus ignored!

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, α2u-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 α2u-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 α2-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

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Author:	
Date:	2022-12-16T16:14:20.530+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

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
1-Propene, tetramer

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

Controls

Untreated negative controls
no

Negative solvent / vehicle 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 experimental 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 ℃
- 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 / choice of top concentrations
no cytotoxicity nor precipitates, but tested up to recommended limit concentrations

Vehicle controls validity
valid

Positive controls validity
valid

Key result
false

Species / strain
E. coli WP2 uvr A
bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
no cytotoxicity nor precipitates, but tested up to recommended limit concentrations

Vehicle controls validity
valid

Positive controls validity
valid

Additional information on results
Contamination with any other bacterias was not found.

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

Any other information on results incl. tables

Field content is not in a valid XML format and thus ignored!

Overall remarks, attachments

Attachments

Attached (sanitised) documents for publication
6842-15-5_Ames.xlsx / 36.463 KB (application/vnd.openxmlformats-officedocument.spreadsheetml.sheet)

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), 1-propene, tetramer was negative with or without metabolic activation.

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.002

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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

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

Deviations
no

GLP compliance
yes

Type of assay
in vitro mammalian chromosome aberration test
chromosome aberration

Test material

Test material information
1-Propene, tetramer

Method

Target gene
Chromosome

Species / strain

Species / strain / cell type
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 / solvent
- Vehicle(s)/solvent(s) used:Acetone

Controls

Untreated negative controls
no

Negative solvent / vehicle 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 experimental conditions
METHOD OF APPLICATION: Exposure duration: [continuous treatment]: 24, 48 hrs [short-term t reatment]:6 hrs + 18 hr
SPINDLE INHIBITOR: Colcemid
NUMBER OF REPLICATIONS: 2
NUMBER OF CELLS EVALUATED: 200 cells / dose
DETERMINATION OF CYTOTOXICITY
- Method: relative total growth

Evaluation criteria
For the evaluation of the frequencies of structural aberrations and of polyploidy induced, the following criteria were employed.
Appearance incidence of cells with chromosomal aberrations: Negative (-): < 5%; equivocal (±): 5-10%; positive (+): > 10%.
Finally, the substance is positive when the incidence is considered to be dose-related and repro ducible.

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 / choice of top concentrations
no cytotoxicity

Vehicle controls validity
valid

Untreated negative controls validity
not examined

Positive controls validity
valid

Key result
false

Species / strain
other: Chinese hamster lung (CHL/IU) cells

Metabolic activation
without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
cytotoxicity 50% cell growth inhibition: 315.3 ug/mL (short), 336.7 ug/mL (24h continuous) and 219.2 ug/mL (48h continuous)

Vehicle controls validity
valid

Untreated negative controls validity
not examined

Positive controls validity
valid

Any other information on results incl. tables

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

http://dra4.nihs.go.jp/mhlw_data/home/pdf/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:	
Date:	2022-12-16T16:15:45.897+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 for cross-reference
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

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

GLP compliance
yes

Test material

Test material information
1-Propene, tetramer

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 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 administrati on 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 n ominal 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

Examinations

Parental animals: Observations and examinations
see 7.5.1 repeated dose toxicity: oral.001

Oestrous cyclicity (parental animals)
Vaginal smears were collected from all females in the main groups and microscopically examined every day from the day after the start of administration until the day copulation was confirmed. 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: Brian, 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 generation)

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: oestrous cycle
no effects observed

Reproductive performance
no effects observed

Effect levels (P0)

Key result
false

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)

Key result
false

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

Field content is not in a valid XML format and thus ignored!

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.

DOMAIN

Substance

SUBSTANCE: 1-propene, tetramer

UUID: IUC5-e0ca2a88-57ae-44ba-bb7f-0f74fba1efe5
Dossier UUID:
Author:
Date: 2022-12-16T16:15:56.420+09:00
Remarks:

Substance name
1-propene, tetramer

Legal entity
National Institute of Health Sciences / Kawasaki / 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

References

Reference Substances

REFERENCE_SUBSTANCE: 1-propene, tetramer

UUID: IUC5-67a7f2be-af23-4a38-8ea7-67a5ffccffba
Dossier UUID:
Author:
Date: 2017-10-30T11:27:04.000+09:00
Remarks:

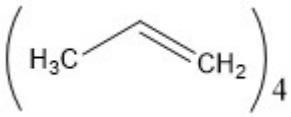
Reference substance name
1-propene, tetramer

Inventory

CAS number
6842-15-5

Molecular and structural information

Structural formula



Test Materials

TEST_MATERIAL_INFORMATION: 1-Propene, tetramer

UUID: e334fdc6-f78b-3025-a4d2-f4c305496a6f
Dossier UUID:
Author:
Date: 2022-12-15T10:52:15.792+09:00
Remarks:

Name
1-Propene, tetramer

Composition

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℃) in a light resistant container
- Stability under test conditions: The stability of test material was identified by analysis of the rem
ainder.

TEST_MATERIAL_INFORMATION: 1-Propene, tetramer

UUID: a7b2c6cb-5090-36bb-abb7-b59599e70713
Dossier UUID:
Author:
Date: 2022-12-15T10:40:41.973+09:00
Remarks:

Name
1-Propene, tetramer

Composition

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): Propylenetetramer
- Analytical purity: 99.9%
- Lot/batch No.: C6UE654
- Storage condition of test material: at a cold place (temperature 2~10 ℃) in a light resistant container
- Stability under test conditions: The stability of test material was identified by analysis of the rema inder.

TEST_MATERIAL_INFORMATION: 1-Propene, tetramer

UUID: e1d877e3-561a-33ec-8363-d285fa00151a
Dossier UUID:
Author:
Date: 2022-12-15T10:46:32.444+09:00
Remarks:

Name
1-Propene, tetramer

Composition

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: 1-Propene, tetramer

UUID: d25d1671-4d65-3bad-8e32-fbb280dac1a4
Dossier UUID:
Author:
Date: 2022-12-15T10:44:40.336+09:00
Remarks:

Name
1-Propene, tetramer

Composition

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 rema inder.

Literatures

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

UUID: 660d1cf9-7876-3bf6-9119-c6d011caddd7
Dossier UUID:
Author:
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:
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

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

UUID:	9cab12b7-5381-3ef6-9a60-ca82a090a84a
Dossier UUID:	
Author:	
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:
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.

Legal Entities

LEGAL_ENTITY: National Institute of Health Sciences

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

General information

Legal entity name
National Institute of Health Sciences

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

Address

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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