Name: COMPLETE / SUBSTANCE : 4,4'-Isopropylidenediphenol, ethoxylated / 32492-61-8 Fri, 16 Dec 2022, 13:07:30+0900 /

Legal entity owner: National Institute of Health Sciences

Printing date: 2022-12-16T13:07:31.040+09:00

Table of Contents

DOSSIER:

UUID: 0
Dossier UUID:
Author:
Date: 2022-12-16T13:07:30.808+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
4,4'-Isopropylidenediphenol, ethoxylated / 32492-61-8

Public name

Submitting legal entity
National Institute of Health Science

Dossier creation date/time
Fri, 16 Dec 2022, 13:07:30+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

4,4'-Isopropylidenediphenol, ethoxylated

CORE

General information

Assessment approach (assessment entities)

FIXED_RECORD: Assessment approach

UUID:	4b885d0f-df0a-3978-9241-ebeceb037719
Dossier UUID:	
Author:	
Date:	2019-03-27T10:07:28.000+09:00
Remarks:	

OECD

Health Effects

Acute toxicity: oral

ENDPOINT_STUDY_RECORD: Acute toxicity: oral.001

UUID: f2830c60-32a8-46fb-b925-046b067f65fc
Dossier UUID:
Author:
Date: 2022-12-16T12:27:00.856+09:00
Remarks:

Administrative data

Endpoint
acute toxicity: oral

Robust study summary
false

Used for classification
false

Used for SDS
false

Reliability
1 (reliable without restriction)

Rationale for reliability incl. deficiencies
guideline study
Reliability 1

Materials and methods

Test guideline

Qualifier
according to guideline

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

GLP compliance
yes

Test type
acute toxic class method

Limit test
yes

Test material

Test material information
4,4'-Isopropylidenediphenol, ethoxylated

Specific details on test material used for the study
- Name of test material (as cited in study report): 4,4'-Isopropylidenediphenol, ethoxylated
- Lot No.: L3-6S004-A (Sanyo Chemical Industries, Ltd.)
- Purity: >99%
- Solubility: insoluble in water
- Physical state: Colorless liquid
- Storage condition of test material: in cool (2-6 ℃) and dark place

Test animals

Species
rat
common species

Strain
Crj: CD(SD)
rat

Sex
female

Administration / exposure

Route of administration
oral: gavage

Vehicle
water

Details on oral exposure
MAXIMUM DOSE VOLUME APPLIED: 10 ml/kg b.w.

Doses
2000 mg/kg bw (1st and 2nd steps)

No. of animals per sex per dose
3 females/dose

Control animals
no

Details on study design
- Duration of observation period following administration: 14 days
- Frequency of observations: for one hour after dosing, and 2h, 4h, and 6h after dosing. Twice a day on the next day of dosing. Thereafter once a day.
- Frequency of weighing: Days 1 (before administration), 4, 8 and 15
- Necropsy of survivors performed: Yes

Statistics
Not used

Results and discussion

Effect levels

Sex
female

Dose descriptor
approximate LD50

Effect level

5000	mg/kg bw

Mortality
No mortality observed.

Clinical signs
other:
Restlessness and decreased locomotor activity were observed on on the day of administration. Soiled fur was observed the day after administration.

Body weight
other body weight observations No effects observed/

Gross pathology
No abnormarities were observed.

Repeated dose toxicity: oral

ENDPOINT_STUDY_RECORD: Repeated dose toxicity: oral.001

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Author:	
Date:	2022-12-16T11:55:45.687+09:00
Remarks:	

Administrative data

Endpoint
repeated dose toxicity: oral, other

Type of information
experimental study

Adequacy of study
key study

Robust study summary
false

Used for classification
false

Used for SDS
false

Reliability
1 (reliable without restriction)

Rationale for reliability incl. deficiencies
guideline study
Reliability 1

Cross-reference

Reason / purpose for cross-reference
reference to same study

Related information
OECD / Toxicity to reproduction / Toxicity to reproduction.001 / 4,4'-Isopropylidenediphenol, ethoxylated / 32492-61-8

Data source

Reference

A combined repeated dose/reproductive developmental toxicity study of 4,4'-Isopropylidenediphenol, e / Ministry of Health, Labor and Welfare, Japan / study report

Data access
data published

Materials and methods

Test guideline

Qualifier
according to guideline

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

Deviations
no

GLP compliance
yes

Limit test
no

Test material

Test material information
4,4'-Isopropylidenediphenol, ethoxylated

Specific details on test material used for the study
- Name of test material (as cited in study report): 4,4'-Isopropylidenediphenol, ethoxylated
- Analytical purity: > 99%
- Storage condition of test material: at a cold (temperature 2-6°C) and dark place, with airtight stopper.
- Stability under test conditions: The stability of test material was identified by analysis of the rem ainder.

Test animals

Species
rat
common rodent species

Strain
other: Crl:CD(SD)

Sex
male/female

Details on test animals or test system and environmental conditions
TEST ANIMALS
- Source: Charles River Japan, Inc., Atsugi Breeding Center.
- Age at study initiation: 10 weeks old
- Weight at study initiation: male 361 g (334-396 g), female 235 g (216-260 g)
- Housing: Animals were individually housed in bracket-type metallic wire-mesh cages (265W × 426D × 200H mm), Dams were bred individually or with individual littermates in polycarbonate cages with flat floors (265W x 426D x 200H mm) and standard bedding.
- Diet: Solid feed (MR stock: Nosan Corporation) was given ad libitum.
- Water: Tap water was given ad libitum.
- Acclimation period: 12 days
ENVIRONMENTAL CONDITIONS
- Temperature (°C): 22±3 (actual temperature: 22.1-25.0°C)
- Humidity (%): 55±10% (actual humidity: 46-60%)
- Air changes (per hr): >10

- Photoperiod (hrs dark / hrs light): 12 hr dark/12 hr light (light: 7:00~19:00)

Administration / exposure

Route of administration
oral: gavage

Vehicle
olive oil

Details on oral exposure
- Amount of vehicle (if gavage): 5 mL/kg
- Dosing volume: 5 mL/kg

Analytical verification of doses or concentrations
yes

Duration of treatment / exposure
(P) Males: 42 days including 14 days pre-mating
(P)Females: 42-47 days including 14 days pre-mating, mating and gestation periods and the days until day 4 of lactation
Female (no mating, satellite group): 42 days

Frequency of treatment
Once/day, 7 days/week

Doses / concentrations

Dose / conc.	
0	mg/kg bw/day (actual dose received)
Dose / conc.	
30	mg/kg bw/day (actual dose received)
Dose / conc.	
120	mg/kg bw/day (actual dose received)
Dose / conc.	
500	mg/kg bw/day (actual dose received)
Dose / conc.	
1000	mg/kg bw/day (actual dose received)

No. of animals per sex per dose
Main group:12 animals/sex/dose
Satellite (Recovery) group: 5 males/dose and 5 females/dose (0 and 1000 mg/kg bw/day)

Control animals
yes, concurrent vehicle

Details on study design
- Dose selection rationale: Based on the results of a 14-day preliminary study, the highest dose of 1000 mg/kg bw/day was selected as an expected obvious toxic dose, and the lowest dose of 30 mg/kg bw/day was selected as an expected no toxic dose. The middle dose levels of 120 and 500 mg/kg bw/day were selected.
- Rationale for animal assignment (if not random): Body weight-balanced randomization
[14-day preliminary study]
A 14-day repeated dose oral toxicity test (Crl:CD(SD) rats, doses: 0 (olive oil), 50, 100, 200, 500 or 1000 mg/kg bw/day). At 500 mg/kg bw/day or more, salivation, low value trend of urinary ketone bodies, high value trend of total cholesterol and liver weight were observed. At 1000 mg/kg bw/day, high value trend of blood calcium, and reduced prothrombin time were observed.

Examinations

Observations and examinations performed and frequency
CAGE SIDE OBSERVATIONS: Yes
- Time schedule: 3 times/day (am: before and after administration; pm) during the administration period. 2 times/day (am and pm) during the recovery period.

DETAILED CLINICAL OBSERVATIONS: Yes
- Time schedule: Once before the start of administration, and once every week by the end of the study period.

BODY WEIGHT: Yes
- Time schedule for examinations:
Males were weighed on Day 1, 7, 14, 21, 28, 35, and 42 of administration, and weighed on Day 7 and 14 of recovery.
Female satellite groups were weighted same frequencies to male recovery groups.
Females in the main groups were weighed on Day 1, 7 and 14 of administration and copulated females were weighed on Day 0, 7, 14 and 20 of gestation, and days 0 and 4 of lactation.

FOOD CONSUMPTION AND COMPOUND INTAKE (if feeding study):
- Food consumption: Yes
Measurement of food consumption was conducted on all animals at the following frequencies:
Males in the main and recovery groups; on Day 1, 7, 14, 21, 28, 35, and 41 of administration, and on Day 7 and 13 of recovery.
Female satellite groups were weighted same frequencies to male recovery groups.
Females in the main group; on Day 1, 7 and 14 of administration and copulated females were weighed on Day 0, 7, 14 and 20 of gestation, and days 0 and 3 of lactation.

OPHTHALMOSCOPIC EXAMINATION: No

HAEMATOLOGY: Yes
- Time schedule for collection of blood: At the end of administration period, or at the end of recovery period in both sexes
- Anaesthetic used for blood collection: ether
- Animals fasted: Yes
- How many animals: 5 animals/sex/group
- Parameters examined included RBC, hemoglobin, hematocrit, MCV, MCH, MCHC, platelet, reticulocyte, PT, APTT, WBC and differential WBC.

CLINICAL CHEMISTRY: Yes

- Time schedule for collection of blood: At the end of administration period, or at the end of recovery period in both sexes
- Animals fasted: Yes
- How many animals: 5 animals/sex/group
- Parameters examined included total protein, albumin, A/G ratio, total bilirubin, glucose, total cholesterol, triglyceride, phospholipid, AST, ALT, LDH, ChE, ALP, gamma-GTP, BUN, creatinine, Na, K, Cl, Ca and IP.

URINALYSIS OF MALES: Yes
- Time schedule for collection of urine (male only): On Day 37 of administration, and on Day 9 of recovery.
- Metabolism cages used for collection of urine: Yes
- How many animals: 5 animals/group
- Parameters examined included color, cloudy, urine volume, specific gravity, pH, protein, glucose, ketone body, bilirubin, occult blood and urobilinogen.

NEUROBEHAVIOURAL EXAMINATION: Yes
- Time schedule for examinations: On week 6 of the administration period, and on week 2 of the recovery period
- Dose groups that were examined: All dose groups (5 animals/sex/group)
- Battery of functions tested: sensory activity (hearing reaction, eye sight reaction, sense of touch reaction, pain reaction, pupil reflex, righting reflex), grip strength, motor activity

Sacrifice and pathology
GROSS PATHOLOGY: Yes

ORGAN WEIBHT: Yes [brain, thymus, heart, liver, kidney, adrenal gland, spleen, seminal vesicle, testis, epididymis, pituitary, thyroid]

HISTOPATHOLOGY: Yes, [brain, pituitary, spinal cord, thyroid, parathyroid, heart, thymus, trachea, lung, liver, kidney, adrenal, spleen, stomach, small intestine, large intestine, sciatic nerve, bone, bone marrow, lymph nodes (mesenteric and cervical lymph nodes), urinary bladder, testis, seminal vesicle, prostate, epididymis, mammary gland, ovary and uterus.]

Statistics
As for parametric data (grip strength, locomotor activity, body weight, body weight gain, food consumption, hematology and clinical chemistry data, organ weights, quantitative urinalysis data, number of corpora lutea, number of implantation sites, number of pups born, number of pups alive, number of stillborn), the values of means and standard deviations were calculated per group. When more than three groups exist in the test group, Bartlett test for variance was done, and if the variance was homogenous, ANOVA was applied. If the variance was not homogenous or data was non-parametric (differential WBC percentage, qualitative urinalysis data, stages of spermatogenesis, length of the estrous cycle, implantation index, delivery index, live birth index, viability index,), Kruskal-Wallis rank sum test was used. Consequently, if the result was significant, Dunnett multiple comparison or Dunnett typed method was used for detection of statistical significance against control group. When the number of the test group was two, F-test was used as for parametric data.
Then, student's t-test or Aspin-Welch's t-test was applied depending on the result of homogeneity of variance. While, as for non-parametric data, Man-Whitney's U-test was applied. Furthermore, as for categorized data (incidence of abnormal findings in clinical observation, detailed observation, sensory functional examination, necropsy and histopathology, copulation index, fertility index, gestation index), Fischer's exact test was used. In any tests, level of significance was set at 5%.

Results and discussion

Results of examinations

Clinical signs
effects observed, non-treatment-related

Description (incidence and severity)
Transient salivation was observed in all males and females at 500 and 1000 mg/kg bw/day.

Mortality
no mortality observed

Body weight and weight changes
effects observed, treatment-related

Food consumption and compound intake (if feeding study)
no effects observed

Food efficiency
not examined

Water consumption and compound intake (if drinking water study)
not examined

Ophthalmological findings
not examined

Haematological findings
effects observed, treatment-related

Clinical biochemistry findings
effects observed, treatment-related

Urinalysis findings
no effects observed

Behaviour (functional findings)
no effects observed

Organ weight findings including organ / body weight ratios
effects observed, treatment-related

Gross pathological findings
no effects observed

Histopathological findings: non-neoplastic
effects observed, treatment-related

Histopathological findings: neoplastic
not examined

Details on results
CLINICAL SIGNS AND MORTALITY:
Mortality: There was no death.
Clinical signs: Transient salivation was observed in all males and females at 500 and 1000 mg/kg bw/day.

DETAILED CLINICAL OBSERVATIONS, MANIPULATIVE TEST, GRIP STRENGTH TEST AND LOCOMOTOR ACTIVITY MEASUREMENT: There were no changes related to the test substance.

BODY WEIGHT:

[At the dosing period]
Depression of body weight gains were observed in males at 1000 mg/kg bw/day.

[At the recovery period]
There were no changes related to the test substance in any groups.

FOOD CONSUMPTION: There were no changes related to the test substance in any groups at the do sing and recovery periods.

HAEMATOLOGY:
[At the end of dosing period]: Decrease in RBC, hemoglobin concentration and hematocrit value, and increases in reticulocyte count were observed in females at 1000 mg/kg bw/day.

[At the end of recovery period]: There were no changes related to the test substance in any groups.

CLINICAL CHEMISTRY:
[At the end of dosing period]: Increases in total cholesterol and Ca were observed in males at 500 mg/kg bw/day. Increase in total cholesterol were observed in males and females at 1000 mg/kg bw/day. Increase in ALT and Ca were observed in females at 1000 mg/kg bw/day.

[At the end of recovery period]: There were no changes related to the test substance in any groups.

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

ORGAN WEIGHTS:
[At the end of dosing period]
Increase in absolute and relative liver weights were observed in females at 500 and 1000 mg/kg bw/day. Increase in relative liver weights were observed in males at 500 and 1000 mg/kg bw/day groups. Increase in absolute and relative kidney weights were observed in males at 500 mg/kg bw/day. Inc rease in relative kidney weights were observed in males at 1000 mg/kg bw/day.

[At the end of recovery period]: There were no changes related to the test substance in any groups.
GROSS PATHOLOGY: There were no changes related to the test substance in any groups at the end of dosing and recovery periods.

HISTOPATHOLOGY: NON-NEOPLASTIC:
[At the end of dosing period]
Liver: Slightly centrilobular hypertrophy hepatocyte was observed in two males and three females at 500 mg/kg bw/day and three males and five females at 1000 mg/kg bw/day.
Kidney: Moderately basophilic change in the proximal tubule was observed in one male at 500 mg/kg bw/day and two males at 1000 mg/kg bw/day.

[At the end of recovery period]: There were no changes related to the test substance in any groups.

Effect levels

Key result
true

Dose descriptor
NOAEL

Effect level

120 mg/kg bw/day (actual dose received)

Based on
test mat.

Sex
male/female

Basis for effect level
histopathology: non-neoplastic
Liver: Centrilobular hypertrophy hepatocyte was observed in males and females at 500 mg/kg bw/day or more.
organ weights and organ / body weight ratios
Increase in liver weight was observed in males and females at 500 mg/kg bw/day.

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/PDF32492-61-8d.pdf

Applicant's summary and conclusion

Executive summary

A combined repeated-dose toxicity study with a reproduction/developmental toxicity screening test was performed in accordance with OECD TG422. Male and female rats (12 animals/sex/dose) were administered 4,4'-isopropylidenediphenol, ethoxylated at 0 (vehicle: olive oil), 30, 120, 500, and 1000 mg/kg bw/day. Including a 14-day pre-mating period and a subsequent mating period, males were dosed for 42 days. Females were dosed for 42–47 days, including 14-day premating, mating, and gestation periods, until lactation day 4. Of the 12 males dosed at 0 and 1000 mg/kg bw/day, 5 were treated as a recovery group. Five additional females receiving 0 and 1000 mg/kg bw/day were treated as a satellite group. These females were dosed with 4,4'-isopropylidenediphenol, ethoxylated for 42 days, without mating, and examined after a 14-day recovery.

Decreased body weight was observed in males in the 1000 mg/kg bw/day group. Decreases in RBC, hemoglobin and hematocrit and increases in the reticulocyte of females in the 1000 mg/kg bw/day group were observed toward the end of the administration period. The total cholesterol and Ca levels were increased in males receiving 500 and 1000 mg/kg bw/day and in females at 1000 mg/kg bw/day. Increases in ALT were observed in females at 1000 mg/kg bw/day. In both sexes, the absolute and/or relative liver weights were increased at 500 mg/kg bw/day and greater. Relative kidney weight were also greater in males at 500 mg/kg bw/day and greater. Histopathological analysis also revealed a hypertrophy of centrilobular hepatocytes for both sexes as well as a basophilic tubule of the kidney in males at 500 and 1000 mg/kg bw/day. Such changes were no longer observed after the recovery period. Judging from the effects on the liver and kidney of the 4,4'-Isopropylidenediphenol, ethoxylated at 500 mg/kg bw/day, it was concluded that the NOAEL for the repeated-dose toxicity in rats was 120 mg/kg bw/day.

Genetic toxicity in vitro

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.001

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Author:
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Remarks:

Administrative data

Type of information
experimental study

Adequacy of study
key study

Robust study summary
true

Used for classification
false

Used for SDS
false

Reliability
1 (reliable without restriction)

Rationale for reliability incl. deficiencies
guideline study
Reliability 1

Data source

Reference

Reverse Mutation Test of poly(oxy-1,2-ethanediyl),alpha,alpha'- [(1-methylethylidene)di-4,1-phenylen / Ministry of Health, Labour and Welfare (MHLW), Japan / study report

Data access
data published

Materials and methods

Test guideline

Qualifier
according to guideline

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

GLP compliance
yes

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

Test material

Test material information
4,4'-Isopropylidenediphenol, ethoxylated

Method

Species / strain

Species / strain / cell type
S. typhimurium TA 1535, TA 1537, TA 98, TA 100 and E. coli WP2
bacteria

Metabolic activation
with and without

Metabolic activation system
S9 mix: Rat liver, induced with phenobarbital and 5,6-benzoflavone

Test concentrations with justification for top dose
Dosage of each strain with or without S9 mix
-S9 mix: 0, 62.5, 125, 250, 500, 1000 and 2000 µg /plate (TA strains) and 156, 313, 625, 1250, 2500, and 5000 µg/plate (E. coli WP2)
+S9 mix: 0, 156, 313, 625, 1250, 2500, 5000 µg /plate (All strains)

Maximum concentration was established based on the result of the preliminary test at concentration up to 5000 ug/plate. In this test, the growth inhibition was observed at 2000 µg/plate and higher for S. typhimurium TA100, TA1535, TA98 and TA1537 without S9 mix.

Vehicle / solvent
DMSO

Controls

Untreated negative controls
no

Negative solvent / vehicle controls
yes

True negative controls
no

Positive controls
yes

Positive control substance
9-aminoacridine
without S9 mix (TA1537)
sodium azide
without S9 mix (TA1535)
other: 2-(2-Furyl)-3-(5-nitro -2-furyl)acrylamide (without S9 mix TA100, TA98, WP2uvrA), 2-Aminoanthracene (with S9 mix all strains)

Details on test system and experimental conditions
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
A chemical was judged to be mutagenic when the mean number of revertant colonies per plate increased more than twice that of the negative control and when the dose-related and reproducible i ncrease was observed.

Statistics
not used

Results and discussion

Test results

Key result
false

Species / strain
S. typhimurium TA 1535
bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
cytotoxicity at 1000 µg/plate (-S9mix), 2500 and 5000 µg/plate (+S9 mix)

Vehicle controls validity
valid

Positive controls validity
valid

Key result
false

Species / strain
S. typhimurium TA 1537
bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
cytotoxicity at 2000 µg/plate (-S9 mix), 2500 and 5000 µg/plate (+S9 mix)

Vehicle controls validity
valid

Positive controls validity
valid

Key result
false

Species / strain
S. typhimurium TA 98
bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
cytotoxicity at 2000 µg/plate (-S9 mix), 2500 and 5000 µg/plate (+S9 mix)

Vehicle controls validity
valid

Positive controls validity
valid

Key result
false

Species / strain
S. typhimurium TA 100
bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
cytotoxicity at 2000 µg/plate (-S9 mix), 2500 and 5000 µg/plate (+S9 mix)

Vehicle controls validity
valid

Positive controls validity
valid

Key result
false

Species / strain
E. coli WP2 uvr A pKM 101
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
There were no precipitation in any test concentration.

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/PDF32492-61-8e.pdf

Tables (in English) are attachted to this document. Please download the export file to see the Tables.

Overall remarks, attachments

Attachments

Remarks
Tables for Ames test

Applicant's summary and conclusion

Conclusions
In a bacterial reverse mutation assay using S. typhimurium TA100, TA1535, TA98, and TA1537, and E. coli WP2uvrA/pKM101 (OECD TG 471), negative results were obtained for 4,4'-isopropylidenedi phenol, ethoxylated with or without metabolic activation.

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.002

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Dossier UUID:	
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Date:	2022-12-16T11:47:38.574+09:00
Remarks:	

Administrative data

Endpoint
in vitro cytogenicity / chromosome aberration study in mammalian cells

Type of information
experimental study

Adequacy of study
key study

Robust study summary
true

Used for classification
false

Used for SDS
false

Reliability
1 (reliable without restriction)

Rationale for reliability incl. deficiencies
guideline study
Reliability 1

Data source

Reference

In Vitro Chromosomal Aberration Test of poly(oxy-1,2-ethanediyl),alpha,alpha'- [(1-methylethylidene) / 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

Qualifier
according to guideline

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

GLP compliance
yes

Test material

Test material information
4,4'-Isopropylidenediphenol, ethoxylated

Specific details on test material used for the study
- Lot No.: L3-6S004-A (Sanyo Chemical Industries, Ltd.)
- Purity: >99%
- Solubility: insoluble in water
- Physical state: Colorless liquid
- Storage condition of test material: in cool (2-6 degree C) and dark place

Method

Species / strain

Species / strain / cell type
other:

Details on mammalian cell type (if applicable)
Chinese hamster lung(CHL/IU) cell

Metabolic activation
with and without

Metabolic activation system
S9 mix: Rat liver, induced with phenobarbital and 5,6- benzoflavone

Test concentrations with justification for top dose
Cell-growth inhibition test was conducted up to the limited concentration of 3000 µg/mL (maximum concentration to be prepared)
-Short term treatment, +/-S9 mix: concentration of 50% cell-growth inhibition was determined as 375-750 µg/mL
-Continuous treatment (24 h): concentration of 50% cell-growth inhibition was determined as 1 87.5-375 µg/mL
-Continuous treatment (48 h): concentration of 50% cell-growth inhibition was determined as 187.5 µg/mL

Vehicle / solvent
DMSO

Controls

Untreated negative controls
no

Negative solvent / vehicle controls
yes

True negative controls
no

Positive controls
yes

Positive control substance
other: 1-Methyl-3nitro-1-nitrosoguanidine (without S9 mix) 3,4-Benzo[a]pyrene (with S9 mix)

Details on test system and experimental conditions
METHOD OF APPLICATION: Exposure duration: [short-term treatment]:6 hrs + 18 hr, [continuous treatment]: 24h
NUMBER OF CELLS EVALUATED: 200 cells /concentration (100 cells/plate x 2)
Plates/test: 4

Evaluation criteria
For the evaluation of the frequencies of structural aberrations and of polyploidy induced, statistical analysis was employed. When significant deference (<5%) was obtained by the multiple chi-square test, Fisher's exact test was employed to compare the vehicle control group and each concentration group. When frequencies of chromosomal aberrations were significantly increased in >=2 concentration groups, and when concentration dependent increase was observed, it was judged to be positive.

Results and discussion

Test results

Key result
true

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

Metabolic activation
with and without

Genotoxicity
positive

Cytotoxicity / choice of top concentrations
cytotoxicity

Vehicle controls validity
valid

Positive controls validity
valid

Any other information on results incl. tables

Figures and Tables (in Japanese) are available in the following full report of the study. http://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF32492-61-8f.pdf

Tables (in English) are attachted to this document. Please download the export file to see the Tables.

Overall remarks, attachments

Attachments

Remarks
Tables for chromosome aberration tests

Applicant's summary and conclusion

Conclusions
4,4'-Isopropylidenediphenol, ethoxylated induced structural aberrations for the short-term study with and without S9 mix. Positive and vehicle control groups were valid.

Executive summary

In an in vitro chromosomal aberration test using CHL/IU cells (OECD TG 473), positive results were obtained with or without metabolic activation.

Toxicity to reproduction

ENDPOINT_STUDY_RECORD: Toxicity to reproduction.001

UUID:	127203f9-63e8-4583-90a4-8ce936e9259b
Dossier UUID:	
Author:	
Date:	2022-12-16T11:58:59.455+09:00
Remarks:	

Administrative data

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

Type of information
experimental study

Adequacy of study
key study

Robust study summary
false

Used for classification
false

Used for SDS
false

Reliability
1 (reliable without restriction)

Rationale for reliability incl. deficiencies
guideline study
Reliability 1

Cross-reference

Reason / purpose for cross-reference
reference to same study

Related information
OECD / Repeated dose toxicity: oral / Repeated dose toxicity: oral.001 / 4,4'-Isopropylidenediphenol, ethoxylated / 32492-61-8

Data source

Reference

A combined repeated dose/reproductive developmental toxicity study of 4,4'-Isopropylidenediphenol, e / Ministry of Health, Labor and Welfare, Japan / study report

Data access
data published

Materials and methods

Test guideline

Qualifier
according to guideline

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

Deviations
no

GLP compliance
yes

Limit test
no

Test material

Test material information
4,4'-Isopropylidenediphenol, ethoxylated

Specific details on test material used for the study
- Name of test material (as cited in study report): 4,4'-isopropylidenediphenol, ethoxylated
- Analytical purity: > 99%
- Storage condition of test material: at a cold (temperature 2-6°C) and dark place, with airtight stopper.
- Stability under test conditions: The stability of test material was identified by analysis of the rem ainder.

Test animals

Species
rat

Strain
other: Crl:CD(SD)

Sex
male/female

Details on test animals or test system and environmental conditions
TEST ANIMALS
- Source: Charles River Japan, Inc., Atsugi Breeding Center.
- Age at study initiation: 10 weeks old
- Weight at study initiation: male 361 g (334-396 g), female 235 g (216-260 g)
- Housing: Animals were individually housed in bracket-type metallic wire-mesh cages (265W × 426D × 200H mm) , Dams were bred individually or with individual littermates in polycarbonate cages with flat floors (265W x 426D x 200H mm) and standard bedding.
- Diet: Solid feed (MR stock: Nosan Corporation) was given ad libitum.
- Water: Tap water was given ad libitum.
- Acclimation period: 12 days

ENVIRONMENTAL CONDITIONS
- Temperature (°C): 22±3 (actual temperature: 22.1-25.0°C)
- Humidity (%): 55±10% (actual humidity: 46-60%)
- Air changes (per hr): >10
- Photoperiod (hrs dark / hrs light): 12 hr dark/12 hr light (light: 7:00~19:00)

Administration / exposure

Route of administration
oral: gavage

Vehicle
olive oil

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

Analytical verification of doses or concentrations
yes

Duration of treatment / exposure
(P) Males: 42 days including 14 days pre-mating
(P)Females: 42-47 days including 14 days premating, mating and gestation periods and the days until day 4 of lactation
Female (no mating, satellite group): 42 days

Frequency of treatment
Once/day, 7 days/week

Doses / concentrations

Dose / conc.	
0	mg/kg bw/day (actual dose received)
Dose / conc.	
30	mg/kg bw/day (actual dose received)
Dose / conc.	
120	mg/kg bw/day (actual dose received)
Dose / conc.	
500	mg/kg bw/day (actual dose received)
Dose / conc.	
1000	mg/kg bw/day (actual dose received)

No. of animals per sex per dose
Main group:12 animals/sex/dose
Satellite (Recovery) group: 5 males/dose and 5 females/dose (0 and 1000 mg/kg bw/day)

Control animals
yes, concurrent vehicle

Details on study design
- Dose selection rationale: Based on the results of a 14-day preliminary study, the highest dose of 1000 mg/kg bw/day was selected as an expected obvious toxic dose, and the lowest dose of 30 mg/kg bw/day was selected as an expected no toxic dose. The middle dose levels of 120 and 500 mg/kg bw/day were selected.
- Rationale for animal assignment (if not random): Body weight-balanced randomization
[14-day preliminary study]
A 14-day repeated dose oral toxicity test (Crl:CD(SD) rats, doses: 0 (olive oil), 50, 100, 200, 500 or 1000 mg/kg bw/day). At 500 mg/kg bw/day or more, salivation, low value trend of urinary ketone bodies, high value trend of total cholesterol and liver weight were observed. At 1000 mg/kg bw/day, high value trend of blood calcium, and reduced prothrombin time were observed.

Examinations

Parental animals: Observations and examinations
CAGE SIDE OBSERVATIONS: Yes
- Time schedule: 3 times/day (am: before and after administration; pm) during the administration period. 2 rimes/day (am and pm) during the recovery period.

DETAILED CLINICAL OBSERVATIONS: Yes
- Time schedule: Once before the start of administration, and once every week by the end of the study period.

BODY WEIGHT: Yes
- Time schedule for examinations:
Males were weighed on Day 1, 7, 14, 21, 28, 35, and 42 of administration, and weighed on Day 7 and 14 of recovery.
Female satellite groups were weighted same frequencies to male recovery groups.
Females in the main groups were weighed on Day 1, 7 and 14 of administration and copulated females were weighed on Day 0, 7, 14 and 20 of gestation, and days 0 and 4 of lactation.

FOOD CONSUMPTION AND COMPOUND INTAKE (if feeding study):
- Food consumption: Yes
Measurement of food consumption was conducted on all animals at the following frequencies:
Males in the main and recovery groups; on Day 1, 7, 14, 21, 28, 35, and 41 of administration, and on Day 7 and 13 of recovery.
Female satellite groups were weighted same frequencies to male recovery groups.
Females in the main group; on Day 1, 7 and 14 of administration and copulated females were weighed on Day 0, 7, 14 and 20 of gestation, and days 0 and 3 of lactation.

OPHTHALMOSCOPIC EXAMINATION: No

HAEMATOLOGY: Yes
- Time schedule for collection of blood: At the end of administration period, or at the end of recovery period in both sexes
- Anaesthetic used for blood collection: ether
- Animals fasted: Yes
- How many animals: 5 animals/sex/group
- Parameters examined included RBC, hemoglobin, hematocrit, MCV, MCH, MCHC, platelet, reticulocyte, PT, APTT, WBC and differential WBC.

CLINICAL CHEMISTRY: Yes
- Time schedule for collection of blood: At the end of administration period, or at the end of recovery period in both sexes
- Animals fasted: Yes
- How many animals: 5 animals/sex/group

- Parameters examined included total protein, albumin, A/G ratio, total bilirubin, glucose, total cho lesterol, triglyceride, phospholipid, AST, ALT, LDH, ChE, ALP, gamma-GTP, BUN, creatinine, Na, K, Cl, Ca and IP.

URINALYSIS OF MALES: Yes
- Time schedule for collection of urine (male only): On Day 37 of administration, and on Day 9 of rec overy.
- Metabolism cages used for collection of urine: Yes
- How many animals: 5 animals/group
- Parameters examined included color, cloudy, urine volume, specific gravity, pH, protein, glucose, keto ne body, bilirubin, occult blood and urobilinogen.

NEUROBEHAVIOURAL EXAMINATION: Yes
- Time schedule for examinations: On week 6 of the administration period, and on week 2 of the recovery period
- Dose groups that were examined: All dose groups (5 animals/sex/group)
- Battery of functions tested: sensory activity (hearing reaction, eye sight reaction, sense of touch reaction, pain reaction, pupil reflex, righting reflex), grip strength, motor activity

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.

Sperm parameters (parental animals)
Parameters examined in all P male parental generations: testis weight, epididymis weight, histopatho logical examinations for testes, epididymides, seminal vesicle including coagulating gland and ventral prostate.

Litter observations
PARAMETERS EXAMINED: The following parameters were examined in F1 offspring: number and sex of pups, stillbirths, live births, postnatal mortality, presence of gross anomalies, weight gain, physical or behavioral abnormalities.

Postmortem examinations (parental animals)
METHOD OF SACRIFICED: All animals were sacrificed by exsanguination under ether anesthesia.

SACRIFICE: Male animals: On Day 42, Maternal animals: on Day 5 of lactation, and Male recovery and female satellite animals: on next Day 14 of recovery.

GROSS PATHOLOGY: Yes

ORGAN WEIBHT: Yes [brain, thymus, heart, liver, kidney, adrenal gland, spleen, seminal vesicle, testis, epididymis, pituitary, thyroid]

HISTOPATHOLOGY: Yes, [brain, pituitary, spinal cord, thyroid, parathyroid, heart, thymus, trachea, lung, liver, kidney, adrenal, spleen, stomach, small intestine, large intestine, sciatic nerve, bone, bone marrow, lymph nodes (mesenteric and cervical lymph nodes), urinary bladder, testis, seminal vesicle, prostate, epididymis, mammary gland, ovary and uterus.]

Postmortem examinations (offspring)
SACRIFICE
- The F1 offspring were sacrificed at 4 days of age.
GROSS NECROPSY
- Gross necropsy consisted of external and internal examinations including the cervical, thoracic, and abdominal viscera.
HISTOPATHOLOGY / ORGAN WEIGTHS
- Not examined.

Statistics
As for parametric data (grip strength, locomotor activity, body weight, body weight gain, food consu mption, hematology and clinical chemistry data, organ weights, quantitative urinalysis data, number of corpora lutea, number of implantation sites, number of pups born, number of pups alive, number of stillborn), the values of means and standard deviations were calculated per group. When more than three groups exist in the test group, Bartlett test for variance was done, and if the variance was ho mogenous, ANOVA was applied. If the variance was not homogenous or data was non-parametric (differential WBC percentage, qualitative urinalysis data, stages of spermatogenesis, length of the estrous cycle, implantation index, delivery index, live birth index, viability index,), Kruskal-Wallis rank s um test was used. Consequently, if the result was significant, Dunnett multiple comparison or Dunnet t typed method was used for detection of statistical significance against control group. When the nu mber of the test group was two, F-test was used as for parametric data.
Then, student's t-test or Aspin-Welch's t-test was applied depending on the result of homogeneity of variance. While, as for non-parametric data, Man-Whitney's U-test was applied. Furthermore, as fo r categorized data (incidence of abnormal findings in clinical observation, detailed observation, se nsory functional examination, necropsy and histopathology, copulation index, fertility index, gestation index), Fischer's exact test was used. In any tests, level of significance was set at 5%.

Reproductive indices
Estrous cycle: Mean days from metaeatrus I (III) to next III.
Copulation index (%) = (No. of pairs with successful copulation/No. of pairs mated) × 100
Fertility index (%) = (No. of pregnant females/No. of pairs with successful copulation) × 100
Gestation index (%) = (No. of females with live pups/No. of pregnant females) × 100
Implantation index (%) = (No. of implantation sites/No. of corpora lutea) × 100
Delivery index (%) = (No. of pups born/No. of implantation sites) × 100
Live birth index (%) = (No. of live pups on day 0/No. of pups born) × 100
Sex ratio =Total number of male pups/Total number of female pups

Offspring viability indices
Viability index (%) = (No. of live pups on day 4/No. of live pups on day 0) × 100

Results and discussion

Results: P0 (first parental generation)

General toxicity (P0)

Clinical signs
effects observed, non-treatment-related

Description (incidence and severity)
See 7.5.1

Mortality
no mortality observed

Body weight and weight changes
effects observed, treatment-related

Description (incidence and severity)
See 7.5.1

Food consumption and compound intake (if feeding study)
no effects observed

Food efficiency
not examined

Water consumption and compound intake (if drinking water study)
not examined

Ophthalmological findings
not examined

Haematological findings
effects observed, treatment-related

Description (incidence and severity)
See 7.5.1

Clinical biochemistry findings
effects observed, treatment-related

Description (incidence and severity)
See 7.5.1

Urinalysis findings
no effects observed

Behaviour (functional findings)
no effects observed

Immunological findings
not examined

Organ weight findings including organ / body weight ratios
effects observed, treatment-related

Description (incidence and severity)
See 7.5.1

Gross pathological findings
no effects observed

Neuropathological findings
not examined

Histopathological findings: non-neoplastic
effects observed, treatment-related

Description (incidence and severity)
See 7.5.1

Histopathological findings: neoplastic
not examined

Reproductive function / performance (P0)

Reproductive function: oestrous cycle
no effects observed

Reproductive function: sperm measures
no effects observed

Reproductive performance
no effects observed

Effect levels (P0)

Key result
true

Dose descriptor
NOAEL

Effect level

1000 mg/kg bw/day (actual dose received)

Based on
test mat.

Sex
male/female

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

Gross pathological findings
no effects observed

Effect levels (F1)

Key result
true

Dose descriptor
NOAEL

Generation
F1

Effect level

1000 mg/kg bw/day (actual dose received)

Based on
test mat.

Sex
male/female

Basis for effect level
other: No effects on development

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/PDF32492-61-8d.pdf

Applicant's summary and conclusion

Executive summary

In the combined repeated-dose toxicity study together with a toxicity screening test of reproduction and development (OECD TG422) described above, reproduction and development were not observed to be affected. The NOAEL for the toxicity of 4,4'-isopropylidenediphenol, ethoxylated to rat reproduction and development was estimated to be 1000 mg/kg bw/day (the highest dose tested).

DOMAIN

Substance

SUBSTANCE: 4,4'-Isopropylidenediphenol, ethoxylated

UUID: 3361b877-d877-4ef7-9b93-95cba0844f45
Dossier UUID:
Author:
Date: 2022-12-16T12:27:12.767+09:00
Remarks:

Substance name
4,4'-Isopropylidenediphenol, ethoxylated

Other substance identifiers

Identifier
CAS number

Identity
32492-61-8

Legal entity
National Institute of Health Sciences / Kawasaki / Japan

Identification of substance

Reference substance
4,4'-Isopropylidenediphenol, ethoxylated / 32492-61-8

EC number	EC name	
CAS number	**CAS name**	
32492-61-8	poly(oxy-1,2-ethanediyl),alpha,alpha'-phenylene]bis[omega-hydroxy-	[(1-methylethylidene)di-4,1-

IUPAC name

Type of substance

Type of substance
polymer

Role in the supply chain

Manufacturer
false

Importer
false

Only representative
false

Downstream user
false

References

Reference Substances

REFERENCE_SUBSTANCE: 4,4'-Isopropylidenediphenol, ethoxylated

UUID: 2a195910-823f-4f39-9d75-df85cfc04647
Dossier UUID:
Author:
Date: 2022-12-16T11:40:03.381+09:00
Remarks:

Reference substance name
4,4'-Isopropylidenediphenol, ethoxylated

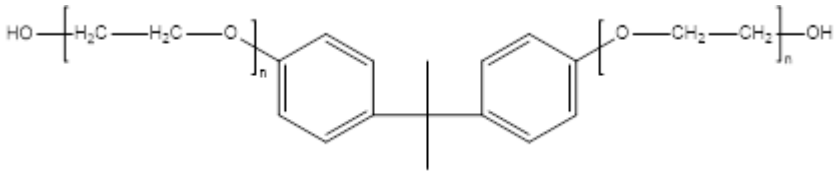
Inventory

CAS number
32492-61-8

CAS name
poly(oxy-1,2-ethanediyl),alpha,alpha'- [(1-methylethylidene)di-4,1-phenylene]bis[omega-hydroxy-

Molecular and structural information

Structural formula



Remarks
[Molar ratio] 1 mole:0.0%, 2 moles: 5.6%, 3 moles: 16.9%, 4 moles:23.3%, 5 moles: 21.1%, 6 moles: 15 .8%, 7 moles: 8.2%, 8 moles: 4.0%, >= 9 moles: 5.1%

Test Materials

TEST_MATERIAL_INFORMATION: 4,4'-Isopropylidenediphenol, ethoxylated

UUID: 58a72914-84d0-48e3-986e-f8e6d37e3d07
Dossier UUID:
Author:
Date: 2022-12-16T11:44:12.638+09:00
Remarks:

Name
4,4'-Isopropylidenediphenol, ethoxylated

Composition

Composition

Reference substance
4,4'-Isopropylidenediphenol, ethoxylated / 32492-61-8

EC number	EC name	
CAS number	**CAS name**	
32492-61-8	poly(oxy-1,2-ethanediyl),alpha,alpha'-phenylene]bis[omega-hydroxy-	[(1-methylethylidene)di-4,1-

IUPAC name

Literatures

LITERATURE: A combined repeated dose/ reproductive developmental toxicity study of 4,4'-Isopropylidenediphenol, ethoxylated by oral administration in rats.

UUID: c3bab17e-0137-47ed-b811-e57f1f580c8c
Dossier UUID:
Author:
Date: 2019-03-22T10:30:43.000+09:00
Remarks:

General information

Reference Type
study report

Title
A combined repeated dose/reproductive developmental toxicity study of 4,4'-Isopropylidenediphenol, ethoxylated by oral administration in rats.

Author
Ministry of Health, Labor and Welfare, Japan

Bibliographic source
Japan Existing Chemical Data Base (JCDB)

Testing facility
Research institute for animal science in biochemistry and toxicology (RIAS)

Report number
06-123

LITERATURE: In Vitro Chromosomal Aberration Test of poly(oxy-1,2-ethanediyl),alpha,alpha'- [(1-methylethylidene)di-4,1-phenylene]bis[omega-hydroxy- on Cultured Chinese Hamster Cells

UUID: 73366170-1230-469e-8ac5-4388a11e323c
Dossier UUID:
Author:
Date: 2019-02-15T09:57:10.000+09:00
Remarks:

General information

Reference Type
study report

Title
In Vitro Chromosomal Aberration Test of poly(oxy-1,2-ethanediyl),alpha,alpha'- [(1-methylethylidene) di-4,1-phenylene]bis[omega-hydroxy- on Cultured Chinese Hamster Cells

Author
MHLW, Japan

Bibliographic source
http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp

Testing facility
Research Institute for Animal Science in Biochemistry and Toxicology (RIAS)

LITERATURE: Reverse Mutation Test of poly(oxy-1,2-ethanediyl),alpha,alpha'- [(1-methylethylidene)di-4,1-phenylene]bis[omega-hydroxy-

UUID: b4cfffab-f224-43b9-89b6-ad7d9aa6328c
Dossier UUID:
Author:
Date: 2019-02-13T16:02:43.000+09:00
Remarks:

General information

Reference Type
study report

Title
Reverse Mutation Test of poly(oxy-1,2-ethanediyl),alpha,alpha'- [(1-methylethylidene)di-4,1-phenylene]bis[omega-hydroxy-

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

Bibliographic source
JECDB(http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp)

Testing facility
Research Institute for Animal Science in Biochemistry and Toxicology (RIAS)

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.

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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