Name: COMPLETE / SUBSTANCE : Bis (2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate / 2915-49-3 Fri, 16 Dec 2022, 11:34:45+0900 /

Legal entity owner: National Institute of Health Sciences

Printing date: 2022-12-16T11:34:45.191+09:00

Table of Contents

DOSSIER:

UUID: 0
Dossier UUID:
Author:
Date: 2022-12-16T11:34:45.008+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
Bis (2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate / 2915-49-3

Public name
Bis (2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate

Submitting legal entity
National Institute of Health Science

Dossier creation date/time
Fri, 16 Dec 2022, 11:34:45+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

Bis (2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate

CORE

General information

Assessment approach (assessment entities)

FIXED_RECORD: Assessment approach

UUID:	ee8a1331-23d6-352d-a51d-ff2444168a04
Dossier UUID:	
Author:	
Date:	2020-03-24T16:07:03.000+09:00
Remarks:	

OECD

Health Effects

Repeated dose toxicity: oral

ENDPOINT_STUDY_RECORD: Repeated dose toxicity: oral.001

UUID: c5d792cc-f46f-42c1-843a-95705dc66c92
Dossier UUID:
Author:
Date: 2022-12-16T11:31:46.960+09:00
Remarks:

Administrative data

Endpoint
short-term repeated dose toxicity: oral

Type of information
experimental study

Adequacy of study
key study

Robust study summary
false

Used for classification
false

Used for SDS
false

Reliability
1 (reliable without restriction)

Rationale for reliability incl. deficiencies
other: The study was conducted in accordance with Test Guidelines and under GLP

Cross-reference

Reason / purpose for cross-reference
reference to same study 7.8.1 Toxicity to reproduction: Toxicity to reproduction. 001

Related information
OECD / Toxicity to reproduction / Toxicity to reproduction.001 / Bis (2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate / 2915-49-3

Data source

Reference

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

Data access
data published

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
Bis (2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate

Specific details on test material used for the study
- Name of test material (as cited in study report): Bis(2-ethylhexyl) 4-cyclohexene-1,2-dicarboxylate
- Analytical purity: 99.0%
- Storage condition of test material: Cold and dark place (3 - 7°C)
- 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: 382 g (356-419 g), Female: 235 g (219-268 g)
- Housing: Animals were individually housed in bracket-type metallic wire-mesh cages (254W × 350D × 170H mm), from gestation day 17 to lactation day 4, Dams were bred individually or with individual littermates in plastic cages (340W x 400D x 185H mm) and bedding.

- Diet: Solid feed (NMF: Oriental Yeast Co., ltd.) was given ad libitum.

- Water: Tap water was given ad libitum.
- Acclimation period: 19 days
ENVIRONMENTAL CONDITIONS
- Temperature (°C): 23±3 (actual temperature: 22-25°C)
- Humidity (%): 50±20% (actual humidity: 38-68%)
- Air changes (per hr): 10-15
- Photoperiod (hrs dark / hrs light): 12 hr dark/12 hr light (light: 7:00~19:00)

Administration / exposure

Route of administration
oral: gavage

Vehicle
corn 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: 41-46 days including 14 days pre-mating, mating and gestation periods and the days until day 4 of lactation
Female (no mating, satellite group): 42 days

Frequency of treatment
Once/day, 7 days/week

Doses / concentrations

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

No. of animals per sex per dose
Main group: 12 females/dose (0, 30, 100, and 300 mg/kg bw/day), 7, 12, 12, and 7 males/dose (0, 30, 100, and 300 mg/kg bw/day)
Satellite group: 5 females/dose (0 and 300 mg/kg bw/day)

Recovery group: 5 males/dose and 5 females (satellite group)/dose (0 and 300 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 300 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 100 mg/kg bw/day were selected.
[14-day preliminary study]
A 14-day repeated dose oral toxicity test (Crl:CD(SD) rats, doses: 0, 100, 300 or 1000 mg/kg bw/day). In the 300 mg/kg bw/day or more, high liver weight were observed.
- Rationale for animal assignment (if not random): Body weight-balanced randomization

Examinations

Observations and examinations performed and frequency
CAGE SIDE OBSERVATIONS: Yes
- Time schedule: 3 times/day (before administration, immediately after administration and 2 hours after administration) during the administration period. Once a day during the recovery period.
DETAILED CLINICAL OBSERVATIONS: Yes
- Time schedule:
Male main and female satellite groups: once before the start of administration, once every weekly during the administration.
Female main group: once before the start of administration, days 1, 7, 14 and 20 of gestation, and day 4 of lactation.
Male and female recovery groups: once before the start of administration, once every weekly during th e administration and recovery periods.

BODY WEIGHT: Yes
- Time schedule for examinations:
Males in the main and females satellite groups were weighed on days 1, 4, 8, 11, 15, 18, 22, 25, 29, 32, 36, 39 and 42 of administration and on the day of necropsy, and males and females in the recovery groups were weighed on days 1, 4, 8, 11 and 14 of recovery and on the day of necropsy in addition to the measurement days for males in the main groups.
Females in the main groups were weighed on days 1, 4, 8, 11 and 15 of administration (uncopulated animals were weighed on days 18 and 22 of administration as well), days 0, 4, 7, 11, 14, 17 and 20 of gestation, days 0 and 4 of lactation and the day of necropsy.

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 females satellite groups on days 1, 4, 8, 11, 15, 32, 36, 39 and 42 of admini stration; males and females in the recovery groups on days 1, 4, 8, 11 and 14 of recovery in addition to the measurement days for males in the main groups; and females in the main groups on days 1, 4, 8, 11 and 15 of administration, days 1, 4, 7, 11, 14, 17 and 20 of gestation and days 2 and 4 of lactation.

OPHTHALMOSCOPIC EXAMINATION: No

HAEMATOLOGY: Yes
- Time schedule for collection of blood: At the end of administration period, or at the end of recovery period in both sexes
- Anaesthetic used for blood collection: ether
- Animals fasted: Yes
- How many animals:
All animals/sex/group (Control and 300 mg/kg/day),

5 animals/sex/group (30 and 100 mg/kg/day)
- Parameters examined: red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, reticulocyte percentage, platelet count, white blood cell count, differential white blood cell count, absolute number of each white blood cell, prothrombin time, activated partial thromboplastin time, fibrinogen.

CLINICAL CHEMISTRY: Yes
- Time schedule for collection of blood: At the end of administration period, or at the end of recovery period in both sexes
- Animals fasted: Yes
- How many animals:
All animals/sex/group (Control and 300 mg/kg/day),
5 animals/sex/group (30 and 100 mg/kg/day)
- Parameters checked: ALP, total cholesterol, triglyceride, phospholipids, total bilirubin, glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, calcium, inorganic phosphorus, total protein, albumin, A/G ratio, AST (GOT), ALT (GPT), LDH, γ-GTP

URINALYSIS: Yes
- Time schedule for collection of urine: final week of administration (days 37 to 38 of administration) and in the final week of recovery (days 9 to 10 of recovery)
- Metabolism cages used for collection of urine: Yes
A urine collector to collect four-hour urine samples under fasting but ad libitum drinking conditions, followed by collection of 20-hour urine samples under ad libitum feeding and drinking conditions.
- How many animals: 5 animals/group
- Parameters checked: pH, protein, ketones, glucose, occult blood, bilirubin, urobilinogen, color, sediment, urine volume (4-hour volume), osmotic pressure, urine volume (20-hour volume), water intake (24-hour volume)

BLOOD HORMONE: Yes
- Time schedule for collection of serum: Same as clinical chemistry
- Animals fasted: Yes
- How many animals:
All animals/sex/group (Control and 300 mg/kg/day),
5 animals/sex/group (30 and 100 mg/kg/day)
- Parameters checked: Triiodothyronine (T3), Thyroxin (T4), and thyroid stimulating hormone (TSH)
NEUROBEHAVIOURAL EXAMINATION: Yes
- Time schedule for examinations:
Males in the main groups: final week of administration (day 40 of administration)
Females in the main groups: lactation day 4 (day 41 to day 44 of administration) after necropsy of F1 pups
Males and females in the recovery groups: final week of administration (day 40 of administration) and in the final week of recovery (day 12 of recovery).
- Dose groups that were examined: All dose groups (5 animals/sex/group)
- Battery of functions tested:
1) Manipulative Test. Auditory response, approach response, touch response, tail pinch response, pupillary reflex, aerial righting reflex, landing foot splay
2) Measurement of Grip Strength. Following manipulative test, grip strength of forelimb and hind limb was measured by CPU gauge MODEL-RX-5 (AIKOH Engineering Co., Ltd.).
3) Measurement of Motor Activity. Following measurement of grip strength, motor activity was measured by a motor activity sensor for experimental animals NS-AS01 (Neuro Science, Inc). The measurement was conducted for 1 hour, and measured values at 10-minute intervals and from 0 to 60 minutes were collected.

Sacrifice and pathology
GROSS PATHOLOGY: Yes
ORGAN WEIBHT: Yes [brain, pituitary, thyroids (including parathyroids), adrenal gland, thymus, spleen, heart, liver, kidney, testis, epididymis, ovary, uterus]

HISTOPATHOLOGY: Yes, [cerebrum, cerebellum (including pons) , pituitary, spinal cord (thoracic), sc iatic nerve, eye ball, thyroid, parathyroid, adrenal glands, thymus, spleen, submandibular lymph nod es, mesenteric lymph nodes, heart, trachea, lung (including bronchial), stomach, duodenum, jejunum, ileum, cecum, colon, rectum, liver, kidney, bladder, testis, epididymis, ovary, uterus, vagina, prostate, seminal vesicles, sternum and femur (including bone marrows),and macroscopic lesions]

Statistics
The data were analyzed for homogeneity of variance by the Bartlett test. If variances were homogeneous, data was analyzed by the Dunnett test, whereas heterogeneous data was analyzed by the Dunnett type mean rank test ($p<0.05$, two-sided).
In the recovery test, these values of two groups were analyzed by F test. If variances were homogeneo us, data was analyzed by the Student t-test, whereas heterogeneous data was analyzed by the Aspin-Welch t-test ($p<0.05$, two-sided).

Results and discussion

Results of examinations

Clinical signs
no effects observed

Mortality
no mortality observed

Body weight and weight changes
no effects observed

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

Food efficiency
not examined

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

Ophthalmological findings
not examined

Haematological findings
effects observed, treatment-related

Clinical biochemistry findings
no effects observed

Description (incidence and severity)
Including blood hormones (T3, T4, TSH)

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

Gross pathological findings
no effects observed

Neuropathological findings
not examined

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

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

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

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

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

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

HAEMATOLOGY:
[At the end of dosing period]: Decreases in white blood cell count, lymphocyte count, neutrophil count and large unstained cell count were observed in males receiving 300 mg/kg bw/day.
[At the end of recovery period]: There were no changes related to the test substance in any groups.

CLINICAL CHEMISTRY (Including blood hormones (T3, T4, TSH)):
There were no changes related to the test substance in any groups at the end of dosing and recovery periods.

ORGAN WEIGHTS:
[At the end of dosing period]: Increases in absolute and relative weights of liver were observed in mating and non-mating females receiving 300 mg/kg bw/day.
Increases in relative weights of liver and absolute and relative weights of kidney were observed in males receiving 300 mg/kg bw/day.
[At the end of recovery period]: Increases in absolute and relative weights of liver were observed in males receiving 300 mg/kg bw/day.

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: Minimal centrilobular hypertrophy of hepatocytes were observed in females receiving 100 mg/kg bw/day or more, and males receiving 300 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

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

Based on
test mat.

Sex
female

Basis for effect level
histopathology: non-neoplastic
At 100 mg/kg bw/day and above, centrilobular hypertrophy of hepatocytes were observed in females.

Any other information on results incl. tables

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

https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF2915-49-3d.pdf

Applicant's summary and conclusion

Conclusions
Based on the effects of the liver at 100 mg/kg bw/day in females, the NOAEL for repeated-dose toxicity of bis(2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate was 30 mg/kg bw/day in rats.

Executive summary

A combined repeated-dose toxicity study with the reproduction/developmental toxicity screening test was done according to OECD TG 422. Male and female rats (12 animals/sex/dose) were administered with bis(2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate via oral gavage at doses of 0 [vehicle: corn oil], 30, 100, and 300 mg/kg bw/day. Males (12/dose) were administered with bis(2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate for 42 days, which include a 14-day premating period and a subsequent mating period, while females (12/dose) were treated for 41–46 days, which include 14-day premating, mating, and gestation periods until lactation day 4. Among the 12 males administered with 0 and 300 mg/kg bw/day, 5 were assigned as the recovery group. Additionally, 10 females administered with 0 and 300 mg/kg bw/day were assigned as a satellite group and treated with bis(2-ethylhexan-1-

yl) cyclohex-4-ene-1,2-dicarboxylate for 42 days, without mating, and assessed after a 14-day recovery period.

No deaths were recorded, and there are no changes in clinical signs, manipulative test, grip strength, motor activity, body weight, food consumption, urinalysis, blood chemistry, blood hormone (T3, T4, and TSH), and gross pathological findings resulting from the treatment in any of the dose groups for both sexes at the end of the treatment and recovery periods. The level of white blood cell, lymphocyte, neutrophil, and large unstained cells was significantly decreased in males receiving 300 mg/kg bw/day at the end of the administration period. The absolute and relative weights of liver were significantly increased as well in both sexes receiving 300 mg/kg bw/day at the end of the administration period. There was also significant increase in absolute and relative weights of kidney in the males receiving 300 mg/kg bw/day at the end of the administration period. Histopathological analysis has indicated a slight hypertrophy of centrilobular hepatocytes in males receiving 300 mg/kg bw/day and in females 100 and 300 mg/kg bw/day at the end of the administration period. Since these changes lessen or disappear at the end of the recovery period, they are thought to be reversible. Based on the effects of the liver at 100 mg/kg bw/day in females, the NOAEL for repeated-dose toxicity of bis(2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylatewas 30 mg/kg bw/day in rats.

Genetic toxicity in vitro

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.001

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Dossier UUID:	
Author:	
Date:	2022-12-14T16:25:23.602+09:00
Remarks:	

Administrative data

Endpoint
in vitro gene mutation study in bacteria

Type of information
experimental study

Adequacy of study
key study

Robust study summary
false

Used for classification
false

Used for SDS
false

Reliability
1 (reliable without restriction)

Rationale for reliability incl. deficiencies
other: OECD Test Guideline study under GLP condition

Data source

Reference

Reverse Mutation Test of Bis (2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate on Bacteria. / Ministry of Health, Labour and Welfare (MHLW), Japan / study report

Data access
data published

Materials and methods

Test guideline

Qualifier
according to guideline

Guideline
OECD Guideline 471 (Bacterial Reverse Mutation Assay)

in vitro gene mutation study in bacteria

Deviations
no

GLP compliance
yes

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

Test material

Test material information
Bis (2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate

Specific details on test material used for the study
- Name of test material (cited in study report): Bis(2-ethylhexyl) 4-cyclohexene-1,2-dicarboxylate
- Purity 99.0%

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 pKM 101
bacteria

Metabolic activation
with and without

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

Test concentrations with justification for top dose
-S9 mix:
9.77, 19.5, 39.1, 78.1, 156, 313 µg/plate (TA100 strain)
2.44, 4.88, 9.77, 19.5, 39.1, 78.1µg/plate (TA1535, TA 98, TA 1537 strains),
156, 313, 625, 1250, 2500, 5000 µg/plate (WP2uvrA/pKM101 strain)
+S9 mix:
39.1, 78.1, 156, 313, 625, 1250 µg/plate (TA100, TA1535, TA98, TA1537 strains),
156, 313, 625, 1250, 2500, 5000 µg/plate (WP2uvrA/pKM101 strain)

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 78.1 µg/plate and above for S. typhimurium 1535, TA98 and 1537 without S9 mix, at 313 µg/plate and above for S. typhimurium TA100 without S9 mix, at 1250 µg/plate and above for S. typhimurium TA strains with S9 mix and at 5000 µg/plate for E. coli WP2 uvrA with or without S9 mix.

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
other: -S9 mix: 2-(2-Furyl)-3-(5-nitro-2-furyl) acrylamide, sodium azide and 2-Methoxy-6-chloro-9-[3-(2-chloroethyl)-aminopropylamino]acridine 2HCl; +S9 mix: 2-aminoanthracene, benzo(a)pyrene

Details on test system and experimental conditions
METHOD OF APPLICATION: Preincubation
DURATION- Preincubation period: 20 min at 37°C
- Exposure duration:48 or 49 hrs
NUMBER OF PLATES: 3
NUMBER OF REPLICATIONS: 2
DETERMINATION OF CYTOTOXICITY
- Method: other: growth inhibition

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

Statistics
no

Results and discussion

Test results

Key result
true

Species / strain
S. typhimurium TA 1535
bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
cytotoxicity -S9 mix: 78.1 µg/plate; +S9 mix: 1250 µg/plate

Vehicle controls validity
valid

Untreated negative controls validity
not examined

Positive controls validity
valid

Key result
true

Species / strain
S. typhimurium TA 1537
bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
cytotoxicity -S9 mix: 39.1 µg/plate or more (test 1: 78.1 µg/plate) ; +S9 mix: 625 µg/plate or more (te st 1: 1250 µg/plate)

Vehicle controls validity
valid

Untreated negative controls validity
not examined

Positive controls validity
valid

Key result
true

Species / strain
S. typhimurium TA 98
bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
cytotoxicity -S9 mix: 78.1 µg/plate; +S9 mix: 1250 µg/plate

Vehicle controls validity
valid

Untreated negative controls validity
not examined

Positive controls validity
valid

Key result
true

Species / strain
S. typhimurium TA 100
bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
cytotoxicity -S9 mix: 313 µg/plate or more; +S9 mix: 1250 µg/plate or more

Vehicle controls validity
valid

Untreated negative controls validity
not examined

Positive controls validity
valid

Key result
true

Species / strain
E. coli WP2 uvr A pKM 101
bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
cytotoxicity -S9 mix: 5000 µg/plate; +S9 mix: 2500 µg/plate or more (test 2: 5000 µg/plate)

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 Japanese) are available in the following full report of the study.

http://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF2915 -49 -3e.pdf

Please also see the attached files (Tables in English)

Overall remarks, attachments

Attachments

Attached (sanitised) documents for publication
35948-25-5_Ames.xlsx / 34.77 KB (application/vnd.openxmlformats-officedocument.spreadsheetml.sheet)

Applicant's summary and conclusion

Conclusions
Interpretation of results (migrated information): negative

In a bacterial reverse mutation assay using Salmonella typhimurium TA100, TA1535, TA98, and TA 1537, and Escherichia coli WP2uvrA/pKM101 (OECD TG 471), Bis (2-ethylhexan-1-yl) cyclohex-4-ene -1,2-dicarboxylate was negative with or without metabolic activation.

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.002

UUID: f14b50e2-3b33-4b45-b578-61865da78280
Dossier UUID:
Author:
Date: 2022-12-14T16:26:43.880+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
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 Bis (2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate on / Ministry of Health, Labour and Welfare (MHLW), Japan / study report

Data access
data published

Materials and methods

Test guideline

Qualifier
according to guideline

Guideline
OECD Guideline 473 (In Vitro Mammalian Chromosome Aberration Test)
in vitro cytogenicity / chromosome aberration study in mammalian cells

Deviations
no

Qualifier
according to guideline

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

Deviations
no

GLP compliance
yes

Type of assay
other: in vitro mammalian chromosome aberration test

Test material

Test material information
Bis (2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate

Specific details on test material used for the study
- Name of test material (cited in study report): Bis(2-ethylhexyl) 4-cyclohexene-1,2-dicarboxylate
- Purity 99.0%

Method

Species / strain

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

Metabolic activation
with and without

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

Test concentrations with justification for top dose
Cell growth inhibition study
-S9 mix (short-term treatment): 31.3, 62.5, 125, 250, 500, 1000, 2000, 4000 ug/mL
+S9 mix (short-term treatment): 31.3, 62.5, 125, 250, 500, 1000, 2000, 4000 ug/mL
-S9 mix (continuous treatment, 24hr): 31.3, 62.5, 125, 250, 500, 1000, 2000, 4000 ug/mL
-S9 mix (continuous treatment, 48hr): 31.3, 62.5, 125, 250, 500, 1000, 2000, 4000 ug/mL (IC50=52.9 ug/mL)
Main study
-S9 (short-term treatment): 1000, 2000, 4000 ug/mL
+S9 (short-term treatment): 1000, 2000, 4000 ug/mL
-S9 (continuous treatment, 24hr):1000, 2000, 4000 ug/mL
-S9 (continuous treatment, 48hr): 7.81, 15.6, 31.3, 62.5, 125 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
other: [-S9]: mitomycin C; [+S9]: cyclophosphamide

Details on test system and experimental conditions
METHOD OF APPLICATION: Exposure duration: [short-term treatment]:6 hrs + 18 hr, [continuous treatment]: 24, 48 hrs
SPINDLE INHIBITOR: Colcemid
STAIN: Giemsa stain (2 v/v%) for 15 min.
NUMBER OF REPLICATIONS: 2
NUMBER OF CELLS EVALUATED: 100 + 100 cells /concentration
DETERMINATION OF CYTOTOXICITY
- Method: relative total growth

Evaluation criteria
For the evaluation of the frequencies of structural aberrations and of polyploidy induced, the following criteria were employed. Appearance incidence of cell with chromosomal aberrations: Negative (-): less than 5%, Equivocal(±): 5% or more and less than 10%, Positive(+): 10% or more

Statistics
no

Results and discussion

Test results

Key result
true

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

Metabolic activation
without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
cytotoxicity

Vehicle controls validity
valid

Untreated negative controls validity
not examined

Positive controls validity
valid

Key result
true

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

Any other information on results incl. tables

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

https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF2915-49-3f.pdf

Applicant's summary and conclusion

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

The in vitro chromosomal aberration test using CHL/IU cells (OECD TG 473) was negative with or without metabolic activation.

Toxicity to reproduction

ENDPOINT_STUDY_RECORD: Toxicity to reproduction.001

UUID:	23453dda-38c1-4d2b-bbfe-d40fb559c6da
Dossier UUID:	
Author:	
Date:	2022-12-16T11:34:08.444+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
other: OECD Test Guideline study under GLP condition

Cross-reference

Reason / purpose for cross-reference
reference to same study 7.5.1 Repeated dose toxicity: oral: Repeated dose toxicity: oral. 001

Related information
OECD / Repeated dose toxicity: oral / Repeated dose toxicity: oral.001 / Bis (2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate / 2915-49-3

Data source

Reference

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

Data access
data published

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
Bis (2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate

Specific details on test material used for the study
- Name of test material (as cited in study report): Bis(2-ethylhexyl) 4-Cyclohexene-1,2-dicarboxylate
- Analytical purity: 99.0%
- Storage condition of test material: Cold and dark place (3 - 7°C)
- 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: 382 g (356-419 g), Female: 235 g (219-268 g)
- Housing: Animals were individually housed in bracket-type metallic wire-mesh cages (254W × 350D × 170H mm), from gestation day 17 to lactation day 4, Dams were bred individually or with individual littermates in plastic cages (340W x 400D x 185H mm) and bedding.
- Diet: Solid feed (NMF: Oriental Yeast Co., ltd.) was given ad libitum.
- Water: Tap water was given ad libitum.
- Acclimation period: 19 days
ENVIRONMENTAL CONDITIONS
- Temperature (°C): 23±3 (actual temperature: 22-25°C)
- Humidity (%): 50±20% (actual humidity: 38-68%)
- Air changes (per hr): 10-15
- Photoperiod (hrs dark / hrs light): 12 hr dark/12 hr light (light: 7:00~19:00)

Administration / exposure

Route of administration
oral: gavage

Vehicle
other: Water for injection

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

Details on mating procedure
- M/F ratio per cage:1/1
- Length of cohabitation: up to 6 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 admi nistration were analyzed by HPLC method at BoZo Research Center Inc. Results showed that the concentration of test article in each concentration was 102.2 to 106.0% of the nominal concentration and both values were within the acceptable range (concentration: percentage of nominal concentra tion, 100±10%)

Duration of treatment / exposure
(P) Males: 42 days including 14 days pre-mating
(P)Females: 41-46 days including 14 days pre-mating, mating and gestation periods and the days until day 4 of lactation
Female (no mating, satellite group): 42 days

Frequency of treatment
Once/day, 7 days/week

Doses / concentrations

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

No. of animals per sex per dose
Main group:12 females/dose (0, 30, 100, and 300 mg/kg bw/day), 7, 12, 12, and 7 males/dose (0, 30, 100, and 300 mg/kg bw/day)
Satellite group: 5 females/dose (0 and 300 mg/kg bw/day)
Recovery group: 5 males/dose and 5 females (satellite group)/dose (0 and 300 mg/kg bw/day)

Control animals
yes, concurrent no treatment

Details on study design
- Dose selection rationale: Based on the results of a 14-day preliminary study, the highest dose of 300 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 100 mg/kg bw/day were selected.
[14-day preliminary study]
A 14-day repeated dose oral toxicity test (Crl:CD(SD) rats, doses: 0, 100, 300 or 1000 mg/kg bw/day). In the 300 mg/kg bw/day or more, high liver weight was observed.

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

Examinations

Parental animals: Observations and examinations
CAGE SIDE OBSERVATIONS: Yes
- Time schedule: 3 times/day (before administration, immediately after administration and 2 hours after administration) during the administration period. Once a day during the recovery period.
DETAILED CLINICAL OBSERVATIONS: Yes
- Time schedule:
Male main and female satellite groups: once before the start of administration, once every weekly during the administration.
Female main group: once before the start of administration, days 1, 7, 14 and 20 of gestation, and day 4 of lactation.
Male and female recovery groups: once before the start of administration, once every weekly during the administration and recovery periods.

BODY WEIGHT: Yes
- Time schedule for examinations:
Males in the main and females satellite groups were weighed on days 1, 4, 8, 11, 15, 18, 22, 25, 29, 32, 36, 39 and 42 of administration and on the day of necropsy, and males and females in the recovery groups were weighed on days 1, 4, 8, 11 and 14 of recovery and on the day of necropsy in addition to the measurement days for males in the main groups.
Females in the main groups were weighed on days 1, 4, 8, 11 and 15 of administration (uncopulated animals were weighed on days 18 and 22 of administration as well), days 0, 4, 7, 11, 14, 17 and 20 of gestation, days 0 and 4 of lactation and the day of necropsy.

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 females satellite groups on days 1, 4, 8, 11, 15, 32, 36, 39 and 42 of administration; males and females in the recovery groups on days 1, 4, 8, 11 and 14 of recovery in addition to the measurement days for males in the main groups; and females in the main groups on days 1, 4, 8, 11 and 15 of administration, days 1, 4, 7, 11, 14, 17 and 20 of gestation and days 2 and 4 of lactation.

OPHTHALMOSCOPIC EXAMINATION: No

HAEMATOLOGY: Yes
- Time schedule for collection of blood: At the end of administration period, or at the end of recovery period in both sexes
- Anaesthetic used for blood collection: ether
- Animals fasted: Yes
- How many animals:
All animals/sex/group (Control and 300 mg/kg/day),
5 animals/sex/group (30 and 100 mg/kg/day)
- Parameters examined: red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, reticulocyte percentage, platelet count, white blood cell count, differential white blood cell count, absolute number of each white blood cell, prothrombin time, activated partial thromboplastin time, fibrinogen.

CLINICAL CHEMISTRY: Yes
- Time schedule for collection of blood: At the end of administration period, or at the end of recovery period in both sexes
- Animals fasted: Yes
- How many animals:
All animals/sex/group (Control and 300 mg/kg/day),
5 animals/sex/group (30 and 100 mg/kg/day)
- Parameters checked: ALP, total cholesterol, triglyceride, phospholipids, total bilirubin, glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, calcium, inorganic phosphorus, total protein, albumin, A/G ratio, AST (GOT), ALT (GPT), LDH, γ-GTP

URINALYSIS: Yes
- Time schedule for collection of urine: final week of administration (days 37 to 38 of administration) and in the final week of recovery (days 9 to 10 of recovery)
- Metabolism cages used for collection of urine: Yes
A urine collector to collect four-hour urine samples under fasting but ad libitum drinking conditions, followed by collection of 20-hour urine samples under ad libitum feeding and drinking conditions.
- How many animals: 5 animals/group
- Parameters checked: pH, protein, ketones, glucose, occult blood, bilirubin, urobilinogen, color, sediment, urine volume (4-hour volume), osmotic pressure, urine volume (20-hour volume), water intake (24-hour volume)

BLOOD HORMONE: Yes
- Time schedule for collection of serum: Same as clinical chemistry
- Animals fasted: Yes
- How many animals:
All animals/sex/group (Control and 300 mg/kg/day),
5 animals/sex/group (30 and 100 mg/kg/day)
- Parameters checked: Triiodothyronine (T3), Thyroxin (T4), and thyroid stimulating hormone (TSH)
NEUROBEHAVIOURAL EXAMINATION: Yes
- Time schedule for examinations:
Males in the main groups: final week of administration (day 40 of administration)
Females in the main groups: lactation day 4 (day 41 to day 44 of administration) after necropsy of F1 pups
Males and females in the recovery groups: final week of administration (day 40 of administration) and in the final week of recovery (day 12 of recovery).
- Dose groups that were examined: All dose groups (5 animals/sex/group)
- Battery of functions tested:
1) Manipulative Test. Auditory response, approach response, touch response, tail pinch response, pupillary reflex, aerial righting reflex, landing foot splay
2) Measurement of Grip Strength. Following manipulative test, grip strength of forelimb and hind limb was measured by CPU gauge MODEL-RX-5 (AIKOH Engineering Co., Ltd.).
3) Measurement of Motor Activity. Following measurement of grip strength, motor activity was measured by a motor activity sensor for experimental animals NS-AS01 (Neuro Science, Inc). The

measurement was conducted for 1 hour, and measured values at 10-minute intervals and from 0 to 60 minutes were collected.

Oestrous cyclicity (parental animals)
Vaginal smears were collected from all females in the 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 all P male parental generations: testis weight, epididymis weight, histopatho logical examinations for testes, epididymides, seminal vesicle and ventral prostate.

Litter observations
PARAMETERS EXAMINED: The following parameters were examined in F1 offspring: Number and sex of pups, stillbirths, live births, postnatal mortality, presence of gross anomalies, and weight gain.
GROSS EXAMINATION OF DEAD PUPS: Yes, for external and internal abnormalities.

Postmortem examinations (parental animals)
METHOD OF SACRIFICED: All animals were sacrificed by exsanguination under ether anesthesia.
SACRIFICE: Male main and female satellite animals: On next day after the last administration (Day 43), Maternal animals: on Day 4 of lactation, and male and females recovery animals: on Day 14 of re covery.
GROSS PATHOLOGY: Yes
ORGAN WEIBHT: Yes [brain, pituitary, thyroids (including parathyroids), adrenal gland, thymus, spleen, heart, liver, kidney, testis, epididymis, ovary, uterus]
HISTOPATHOLOGY: Yes, [cerebrum, cerebellum (including pons) , pituitary, spinal cord (thoracic), scia tic nerve, eye ball, thyroid, parathyroid, adrenal glands, thymus, spleen, submandibular lymph nodes , mesenteric lymph nodes, heart, trachea, lung (including bronchial), stomach, duodenum, jejunum, ileum, cecum, colon, rectum, liver, kidney, bladder, testis, epididymis, ovary, uterus, vagina, prostate, seminal vesicles, sternum and femur (including bone marrows),and macroscopic lesions]

Postmortem examinations (offspring)
SACRIFICE
- The F1 offsprings were euthanized on PND4 by exsanguination under ether anesthesia.
GROSS NECROPSY: Yes
- Gross necropsy consisted of external and internal examinations including the cervical, thoracic, and abdominal viscera.
HISTOPATHOLOGY / ORGAN WEIGTHS
- Not examined.

Statistics
The data were analyzed for homogeneity of variance by the Bartlett test. If variances were homogeneous, data was analyzed by the Dunnett test, whereas heterogeneous data was analyzed by the Dunnett type mean rank test ($p<0.05$, two-sided).
In the recovery test, these values of two groups were analyzed by F test. If variances were homogeneo us, data was analyzed by the Student t-test, whereas heterogeneous data was analyzed by the Aspin-Welch t-test ($p<0.05$, two-sided).

Reproductive indices
Each parameter was determined by the following equations:
Copulation index (%) = (No. of copulated animals / No. of mated animals) × 100
Fertility index (%) = (No. of pregnant females / No. of copulated females) × 100
Insemination index (%) = (No. of impregnated males / No. of copulated males) × 100

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

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

Results and discussion

Results: P0 (first parental generation)

General toxicity (P0)

Clinical signs
no effects observed

Mortality
no mortality observed

Body weight and weight changes
no effects observed

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

Food efficiency
not examined

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

Ophthalmological findings
not examined

Haematological findings
effects observed, treatment-related

Description (incidence and severity)
See 7.5.1

Clinical biochemistry findings
no effects observed

Description (incidence and severity)
Including blood hormones (T3, T4, TSH)

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
not examined

Reproductive performance
no effects observed

Details on results (P0)

1) Estrous Cycle
There were no animals showing abnormal estrous cycles, and there were no significant differences in the average length of the estrous cycle between the control group and any treatment groups.
2) Results of Mating
There were no significant differences in the incidence of females with irregular estrus cycle, mating period with the number of estrus and day of conceiving, copulation index, and fertility index between the control group and any treatment groups.
3) Delivery Data and Delivery
There were no significant differences in the gestation length, number of corpora lutea, number of imp lantation sites, implantation index, and delivery index between the control group and any treatment groups.

Haematological findings
See 7.5.1
Organ weight findings
See 7.5.1
HISTOPATHOLOGY
See 7.5.1

Effect levels (P0)

Key result
true

Dose descriptor
NOAEL

Effect level

300 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

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

Based on
test mat.

Sex
male/female

Basis for effect level
other: No effects on development

Overall reproductive toxicity

Key result
true

Reproductive effects observed
no

Any other information on results incl. tables

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

https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF2915-49-3d.pdf

Applicant's summary and conclusion

Conclusions
In the combined repeated oral dose toxicity study with the reproduction/developmental toxicity scree ning test (OECD TG 422) , there were no effects on reproductive and developmental parameters up to 300 mg/kg bw/day. The NOAEL for the rat reproductive/developmental toxicity of bis(2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate was regarded as 300 mg/kg bw/day, the highest dose tested.

Executive summary

A combined repeated-dose toxicity study with the reproduction/developmental toxicity screening test was done according to OECD TG 422. Male and female rats (12 animals/sex/dose) were administered with bis(2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate via oral gavage at doses of 0 [vehicle: corn oil], 30, 100, and 300 mg/kg bw/day. Males (12/dose) were administered with bis(2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate for 42 days, which include a 14-day premating period and a subsequent mating period, while females (12/dose) were treated for 41–46 days, which include 14-day premating, mating, and gestation periods until lactation day 4. Among the 12 males administered with 0 and 300 mg/kg bw/day, 5 were assigned as the recovery group. Additionally, 10 females administered with 0 and 300 mg/kg bw/day were assigned as a satellite group and treated with bis(2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate for 42 days, without mating, and assessed after a 14-day recovery period.

No mortalities were recorded with any dose during the treatment period. There were also no effects on reproductive toxicity (fertility and reproductive organs) and developmental toxicity up to the highest dose. Because there was no effect observed at 300 mg/kg bw/day administration, the NOAEL for the reproduction and development toxicity was 300 mg/kg bw/day in rats.

DOMAIN

Substance

SUBSTANCE: Bis (2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate

UUID: e7c03a78-48a6-4292-9759-dac5a84ae551
Dossier UUID:
Author:
Date: 2022-12-16T11:34:31.593+09:00
Remarks:

Substance name
Bis (2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate

Public name
Bis (2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate

Legal entity
National Institute of Health Sciences, Japan

Identification of substance

Reference substance
Bis (2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate / 2915-49-3

EC number	EC name
CAS number	**CAS name**
2915-49-3	

IUPAC name

Role in the supply chain

Manufacturer
false

Importer
false

Only representative
false

Downstream user
false

References

Reference Substances

REFERENCE_SUBSTANCE: Bis (2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate

UUID: 2d5c054f-75a7-4fd4-9f3e-4b68ed1f75a1
Dossier UUID:
Author:
Date: 2019-12-19T09:31:18.000+09:00
Remarks:

Reference substance name
Bis (2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate

Inventory

CAS number
2915-49-3

Test Materials

TEST_MATERIAL_INFORMATION: Bis (2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate

UUID:	492974ed-339a-4115-8a33-fe2da576efe4
Dossier UUID:	
Author:	
Date:	2019-12-19T09:39:02.000+09:00
Remarks:	

Name
Bis (2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate

Literatures

LITERATURE: Combined repeated dose toxicity study with the reproductive/developmental toxicity screening test of Bis(2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate by oral administration in rats

UUID: fd162373-8e99-476c-8cd6-83e09587026b
Dossier UUID:
Author:
Date: 2020-03-24T08:44:51.000+09:00
Remarks:

General information

Reference Type
study report

Title
Combined repeated dose toxicity study with the reproductive/developmental toxicity screening test of Bis(2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate by oral administration in rats

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

Bibliographic source
available in the web of Japan Existing Chemical Data Base (JECDB) https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF2915-49-3d.pdf

Testing facility
BoZo Research Center

Report number
R-1051

LITERATURE: In Vitro Chromosomal Aberration Test of Bis (2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate on Cultured Chinese Hamster Cells.

UUID: 8c0542f6-e903-4fd8-a962-902ea68b154d
Dossier UUID:
Author:
Date: 2020-03-17T15:32:41.000+09:00
Remarks:

General information

Reference Type
study report

Title
In Vitro Chromosomal Aberration Test of Bis (2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate on Cultured Chinese Hamster Cells.

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

Bibliographic source
Japan Existing Chemical Data Base (JECDB) https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF2915-49-3f.pdf

Testing facility
Bozo Research Center Inc.

Report number
M-1408

LITERATURE: Reverse Mutation Test of Bis (2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate on Bacteria.

UUID: 2b1d855f-1987-4bac-a8e1-a21083261583
Dossier UUID:
Author:
Date: 2020-03-17T15:11:21.000+09:00
Remarks:

General information

Reference Type
study report

Title
Reverse Mutation Test of Bis (2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate on Bacteria.

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

Bibliographic source
Japan Existing Chemical Data Base (JECDB) http://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF2915-49-3e.pdf

Testing facility
Bozo Research Center Inc.

Report number
T-0467

Legal Entities

LEGAL_ENTITY: National Institute of Health Sciences, Japan

UUID: 0952b3b9-2d0c-4bc8-925e-b069be7789b7
Dossier UUID:
Author:
Date: 2020-02-19T14:42:16.000+09:00
Remarks:

General information

Legal entity name
National Institute of Health Sciences, Japan