Name: OECD_SIDS / SUBSTANCE : 4,4'-Bis(chloromethyl)-1,1'-biphenyl / 1667-10-3 Tue, 29 Nov 2022, 14:54:11+0900 /

Legal entity owner: National Institute of Health Sciences

Printing date: 2022-11-29T14:54:11.863+09:00

Table of Contents

DOSSIER:

UUID: 0
Dossier UUID:
Author:
Date: 2022-11-29T14:54:11.686+09:00
Remarks:

Dossier header

Dossier submission type

Name
OECD SIDS

Version
core 7.0

Name (given by user)

Dossier subject

Dossier subject
4,4'-Bis(chloromethyl)-1,1'-biphenyl / 1667-10-3

Public name

Submitting legal entity
National Institute of Health Science

Dossier creation date/time
Tue, 29 Nov 2022, 14:54:11+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'-Bis(chloromethyl)-1,1'-biphenyl

General information

Identification

Identification

SUBSTANCE: 4,4'-Bis(chloromethyl)-1,1'-biphenyl

UUID:	3ee00742-ccec-4b17-adfe-16029fd9fc15
Dossier UUID:	
Author:	
Date:	2022-11-29T14:30:05.957+09:00
Remarks:	

Substance name
4,4'-Bis(chloromethyl)-1,1'-biphenyl

Legal entity
National Institute of Health Sciences / Kawasaki / Japan

Identification of substance

Reference substance
4,4’-bis(chloromethyl)-1,1’-biphenyl / 1667-10-3

EC number	EC name
CAS number	**CAS name**
1667-10-3	
IUPAC name	

Role in the supply chain

Manufacturer
false

Importer
false

Only representative
false

Downstream user
false

Toxicological information

Repeated dose toxicity

Repeated dose toxicity: oral

ENDPOINT_STUDY_RECORD: Repeated dose toxicity: oral. 001

UUID: 2e93454b-1d43-4608-b211-5261e973773b
Dossier UUID:
Author:
Date: 2022-11-29T14:30:05.957+09:00
Remarks:

Administrative data

Endpoint
short-term repeated dose toxicity: oral

Type of information
experimental study

Adequacy of study
key study

Robust study summary
false

Used for classification
false

Used for SDS
false

Reliability
1 (reliable without restriction)

Rationale for reliability incl. deficiencies
guideline study OECD Test Guideline study under GLP condition
Reliability 1

Cross-reference

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

Related information
OECD / Toxicity to reproduction / Toxicity to reproduction. 001 / 4,4'-Bis(chloromethyl)-1,1'-biphenyl / 1667-10-3

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
4,4'-bis(chloromethyl)-1,1'-biphenyl

Specific details on test material used for the study
- Name of test material (as cited in study report): 4,4'-bis(chloromethyl)-1,1'-biphenyl
- Analytical purity: 99.8%
- Storage condition of test material: Room temperature, shading, airtightness, moisture proof
- Stability under test conditions: The stability of test material was identified by analysis of the remainder.

Test animals

Species
rat
common rodent species

Strain
other: Crl:CD (SD)

Sex
male/female

Details on test animals or test system and environmental conditions
TEST ANIMALS
- Source: Charles River Japan, Inc., Hino Breeding Center.
- Age at study initiation: 10 weeks old
- Weight at study initiation:
Males (main study groups): 325-367 g, females (main study groups): 223-258 g, females (mating stu dy groups): 222-259 g
- Housing: Animals were individually housed in stainless steel suspension cage (240W × 380D × 200H mm), from gestation day 18 to lactation day 4, Dams were bred individually or with individual litte rmates in plastic cages (310W x 360D x 175H mm) and bedding.
- Diet: Solid feed (CRF-1: Oriental Yeast Co., ltd.) was given ad libitum.
- Water: Tap water was given ad libitum.
- Acclimation period: Males (main study groups): 18 days, females (main study groups): 19 days, females (mating study groups): 18 days

ENVIRONMENTAL CONDITIONS
- Temperature (°C): 20-26°C (actual temperature: 22.5-24.8°C)
- Humidity (%): 40.0-70.0% (actual humidity: 40.7-60.4%)
- Air changes (per hr): 12
- Photoperiod (hrs dark / hrs light): 12 hr dark/12 hr light (light: 6:00~18:00)

Administration / exposure

Route of administration
oral: gavage

Vehicle
methylcellulose 0.5 w/v% methylcellulose

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

Analytical verification of doses or concentrations
yes

Details on analytical verification of doses or concentrations
Test suspensions at each concentration to be used for males in main group and females mating group in day 1 of administration were analyzed by HPLC method. Results showed that the concentration of test article in each concentration was 102.7 to 106.7% of the nominal concentration and both values were within the acceptable range (concentration: percentage of nominal concentration, 100±10%)

Duration of treatment / exposure
Males: 28 days including 14 days pre-mating
Females (main study groups): 28 days
Females (mating groups): 42-46 days including 14 days pre-mating, mating and gestation periods and the days until day 4 of lactation

Frequency of treatment
Once/day, 7 days/week

Doses / concentrations

Dose / conc.	
0	mg/kg bw/day (actual dose received)
Dose / conc.	
62.5	mg/kg bw/day (actual dose received)
Dose / conc.	
250	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 study groups:
Control- and high-dose groups: 12 males and 10 females per group (half of both sexes assigned as t he treatment groups, and the remaining half assigned as the recovery groups)
Low- and middle-dose groups: 12 males and 5 females per group (half of males assigned as the treatment groups, and the remaining half assigned as the recovery groups)

- Mating groups:
12 females per dose

Control animals
yes, concurrent vehicle

Details on study design
- Dose selection rationale: Based on the results of a 14-day preliminary study, the high dose was set to 1000 mg/kg bw/day, which is the upper limit in OECD TG422, and the intermediate dose and low dose were set to 250 mg/kg bw/day and 62.5 mg/kg bw/day, respectively.

[14-day preliminary study]
A 14-day repeated dose oral toxicity test (Crl:CD(SD) rats, doses: 0, 200, 500 or 1000 mg/kg bw/day). In males at 1000 mg/kg bw/day, decrease tendencies in body weight and decrease in food cons umption were observed. In females at 1000 mg/kg bw/day, increase in A/G and relative liver weights 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:
Males and females (main study groups): 2 times/day (before administration, 54-137 minutes after administration) during the administration period. Once a day during the recovery period.
Females (mating groups): 2 times/day (before administration, 60-138 minutes after administration) d uring the administration period.

DETAILED CLINICAL OBSERVATIONS: Yes
- Time schedule:
Males and females (main study groups): on day of grouping, on days 7, 14, 21 and 27 of admin istration period.
Females (mating groups): on day of grouping, on days 7 and 14 of administration period, on days 1, 8 and 15 of gestation period, on day 4 of lactation period.

BODY WEIGHT: Yes
- Time schedule for examinations:
Males and females (main study groups):
Twice a week (On days 1, 4, 8, 11, 15, 18, 22, 25, 28 and 29 of administration period, on days 1, 4, 8, 11 and 14 of recovery period).
Females (mating groups): Twice a week (On days 1, 4, 8, 11, 15 and 18 of administration period, on days 0, 7, 14 and 20 of gestation period, on days 0, 4 and 5 of lactation period).

FOOD CONSUMPTION AND COMPOUND INTAKE (if feeding study):
- Food consumption: Yes
- Time schedule for examinations:
Males and females (main study groups):
Twice a week (Males: On days 2, 5, 9 and 12 of administration period, on days 2, 5, 9 and 12 of reco very period; Females: On days 2, 5, 9, 12, 16, 19, 23 and 26 of administration period, on days 2, 5, 9 and 12 of recovery period).

Females (mating groups): Twice a week (On days 2, 5, 9 and 12 of administration period, on days 2, 9, 16 and 20 of gestation period, on days 2 of lactation period).

WATER INTAKE: Yes
- Time schedule for examinations:
Males and females (main study groups):
Twice a week (Males: On days 2, 5, 9 and 12 of administration period, on days 2, 5, 9 and 12 of recovery period; Females: On days 2, 5, 9, 12, 16, 19, 23 and 26 of administration period, on days 2, 5, 9 and 12 of recovery period).
Females (mating groups): Twice a week (On days 2, 5, 9 and 12 of administration period, on days 2, 9, 16 and 20 of gestation period, on days 2 of lactation period).

OPHTHALMOSCOPIC EXAMINATION: No

HAEMATOLOGY: Yes
- Time schedule for collection of blood:
Males and females (main study groups): At the end of administration period, or at the end of recovery period in both sexes
- Anaesthetic used for blood collection: Pentobarbital sodium
- Animals fasted: Yes
- How many animals:
At the end of administration period: 6 males/dose (0, 62.5, 250, 1000 mg/kg bw/day), 5 females/dose (0, 62.5, 250, 1000 mg/kg bw/day)
At the end of recovery period: 6 males/dose (0, 62.5, 250, 1000 mg/kg bw/day), 5 females/dose (0 and 1000 mg/kg bw/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, prothrombin time, activated partial thromboplastin time, fibrinogen.

CLINICAL CHEMISTRY: Yes
- Time schedule for collection of blood:
Males and females (main study groups): At the end of administration period, or at the end of recovery period in both sexes
- Animals fasted: Yes
- How many animals:
At the end of administration period: 6 males/dose (0, 62.5, 250, 1000 mg/kg bw/day), 5 females/dose (0, 62.5, 250, 1000 mg/kg bw/day)
At the end of recovery period: 6 males/dose (0, 62.5, 250, 1000 mg/kg bw/day), 5 females/dose (0 and 1000 mg/kg bw/day)
- Parameters checked: ALP, total cholesterol, triglyceride, total bilirubin, glucose, urea nitrogen, creatinine, sodium, potassium, chloride, calcium, inorganic phosphorus, total protein, albumin, A/G ratio, AST, ALT, γ-GT

BLOOD HORMONE: Yes
- Time schedule for collection of serum:
Males and females (main study groups): At the end of administration period in both sexes
- Animals fasted: Yes
- How many animals:
6 males/dose (0, 62.5, 250, 1000 mg/kg bw/day), 5 females/dose (0, 62.5, 250, 1000 mg/kg bw/day)
- Parameters checked: Triiodothyronine (T3), Thyroxin (T4), and thyroid stimulating hormone (TSH)

URINALYSIS: Yes
- Time schedule for collection of urine:
Males and females (main study groups): Before the end of the administration period (day 23 of administration period) and before the end of recovery (days 12 of recovery period).
- Metabolism cages used for collection of urine: Yes

A urine collector to collect fresh urine samples under fasting but ad libitum drinking conditions, followed by collection of 24-hour urine samples under ad libitum feeding and drinking conditions.
- How many animals:
At the end of administration period: 6 males/dose (0, 62.5, 250, 1000 mg/kg bw/day), 5 females/dose (0, 62.5, 250, 1000 mg/kg bw/day)
At the end of recovery period: 6 males/dose (0, 62.5, 250, 1000 mg/kg bw/day), 5 females/dose (0 and 1000 mg/kg bw/day)
- Parameters checked:
Fresh urine: Color, pH, protein, glucose, ketones, bilirubin, occult blood, urobilinogen, sediment
24-urine: Specific gravity, urine volume (24-hour volume)

NEUROBEHAVIOURAL EXAMINATION: Yes
- Time schedule for examinations:
Males and females (main study groups): Final week of administration (Manipulative test and measurement of grip strength: Day 27 of administration, measurement of motor activity: Day 26 of administration)
- Dose groups that were examined: Autopsy animals after the end of the administration period
- Battery of functions tested:
1) Manipulative Test. Pupillary reflex, approaching behavior, response to touch, auditory reflex, pain reflex
2) Measurement of Grip Strength. Following manipulative test, grip strength of forelimb and hind limb were measured by CPU gauge (San Diego Instruments Inc.).
3) Measurement of Spontaneous Motor Activity. Spontaneous motor activity (Ambulatory and vertical counts) was measured by Activity Monitor (MED Associates Inc.).
The measurements were collected at 10-minute intervals from 1 hour to 2 hours after administration.

Sacrifice and pathology
GROSS PATHOLOGY: Yes
ORGAN WEIGHT: Yes [main study groups: brain, pituitary, salivary glands, thyroids, adrenal gland, thymus, spleen, heart, liver, kidney, testes, epididymides, ventral prostate, seminal vesicles, ovaries, uterus; females in mating groups: ovary, uterus]

HISTOPATHOLOGY: Yes, [main study groups: heart, lung, trachea, liver, pancreas, sublingual gland, submandibular gland, esophagus, stomach, duodenum, jejunum, ileum (including Peyer’s patch), cecum, colon, rectum, thymus, spleen, mandibular lymph nodes, mesenteric lymph nodes, kidney, urinary bladder, testis, epididymis, ventral prostate, seminal vesicles (including coagulating gland), ovaries, uterus, vagina, pituitary, adrenal glands, thyroid (including parathyroid), cerebrum, cerebellum, pons, spinal cord, sciatic nerve, eye ball, Harderian gland, sternum and femur (including bone marrows), muscle (rectus femoris), mammary gland; females in mating groups: ovaries, uterus, vagina]

Statistics
For quantitative data, homogeneity of variance was tested using Bartlett method first. If the variance was homogenous, statistical difference between each treatment group and the control group was analyzed using Dunnett method. If not homogenous, statistical difference between each treatment group and the control group was tested using Steel method. For comparison of quantitative data between two groups in the recovery test, homogeneity of variance was analyzed by F-test. Then, if homogenous, student's t-test was applied. If not homogenous, Aspin-Welch's t-test was used.
For histopathological findings, statistical analysis was carried out in combination with Steel-test and Cochran-Armitage trend test. Regarding clinical observation (except for frequency of urination, defecation, rearing and grooming) and sensory reactivity, Steel test was applied.

Results and discussion

Results of examinations

Clinical signs
no effects observed

Mortality
no mortality observed

Body weight and weight changes
no effects observed

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

Food efficiency
not examined

Water consumption and compound intake (if drinking water study)
no effects observed

Ophthalmological findings
not examined

Haematological findings
effects observed, treatment-related

Description (incidence and severity)
[At the end of administration period]:
Prolongation of PT was 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.

Clinical biochemistry findings
effects observed, treatment-related

Description (incidence and severity)
Including blood hormones (T3, T4, TSH)
CLINICAL BIOCHEMISTRY:
[At the end of administration period]:
Increase in ALT and decrease in triglyceride were observed in males at 1000 mg/kg bw/day. Increase in A/G was observed in females of main study group at 250 mg/kg bw/day and above.
[At the end of recovery period]:
Increase in ALT was observed in males at 1000 mg/kg bw/day.

BLOOD HORMONES:
There were no changes related to the test substance in any groups at the end of administration and recovery periods.

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)
[At the end of administration period]:

Increases in absolute and relative thyroids weights, increase in relative liver weight and increase t endencies in absolute liver weight were observed in females of main study group at 1000 mg/kg bw/ day.
[At the end of recovery period]:
Increase in relative liver weight and increase tendency in absolute liver weight were observed in males at 1000 mg/kg bw/day.

Gross pathological findings
no effects observed

Neuropathological findings
not examined

Histopathological findings: non-neoplastic
no effects observed

Histopathological findings: neoplastic
not examined

Effect levels

Key result
true

Dose descriptor
NOAEL

Effect level

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

Based on
test mat.

Sex
male

Basis for effect level
clinical biochemistry
At 1000 mg/kg bw/day, increase in ALT and decrease in triglyceride were observed in males.

Key result
true

Dose descriptor
NOAEL

Effect level

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

Based on
test mat.

Sex
female

Basis for effect level
clinical biochemistry
At 250 mg/kg bw/day, increase in A/G was observed in non-mating females (main study groups)

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/PDF1667-10-3d.pdf

Applicant's summary and conclusion

Conclusions
The NOAELs for the repeated dose toxicity were 250 mg/kg bw/day in males based on increased ALT and decreased TG at 1000 mg/kg bw/day and 62.5 mg/kg bw/day in females based on increased A/G at 250 mg/kg bw/day.

Executive summary

In the combined repeated dose and reproductive/developmental screening test (OECD TG422), SD rats were treated orally with the test substance at the doses of 0, 62.5, 250 and 1000 mg/kg bw/day. Males (12 animals/dose: 6 animals were treated as a recovery group) were dosed for 28 days including a 14 day pre-mating period. Females (12 animals/dose) were dosed for 42-46 days including 14 day premating, mating, and gestation periods and days until day 4 of lactation. In addition, as the main study group of females, 5 or 10 females/group was dosed for 28 days without mating (5 females at 0 and 1000 mg/kg bw/day were treated as recovery groups).

The following findings were observed in examination at the end of administration period. In the hematological examination, prolongation of PT was observed in males at 1000 mg/kg bw/day. In the clinical chemistry, an increase in ALT and a decrease in triglyceride were observed in males at 1000 mg/kg bw/day, an increase in A/G was observed in females of main study group at 250 mg/kg bw/day and above. In the organ weights, increases in absolute and relative thyroids weights, increase in relative liver weight and increase tendency in absolute liver weight were observed in females of main study group at 1000 mg/kg bw/day.

Based on the above results, NOAELs for the repeated dose toxicity of 4,4’-bis(chloromethyl)-1,1’-biphenyl were determined to be 250 mg/kg bw/ day in male rats and 62.5 mg/kg bw/day in female rats.

Genetic toxicity

Genetic toxicity in vitro

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.001

UUID:	42637a34-e7bc-4ab4-8ac0-ed16cb012d88
Dossier UUID:	
Author:	
Date:	2021-03-15T16:13:55.000+09:00
Remarks:	

Administrative data

Endpoint
in vitro gene mutation study in bacteria

Type of information
experimental study

Adequacy of study
key study

Robust study summary
false

Used for classification
false

Used for SDS
false

Reliability
1 (reliable without restriction)

Rationale for reliability incl. deficiencies
guideline study under GLP condition
Reliability 1

Data source

Reference

Reverse Mutation Test of 4,4'-bis(chloromethyl)-1,1'-biphenyl on Bacteria. / Ministry of Health, Labour and Welfare (MHLW), Japan / study report

Data access
data published

Materials and methods

Test guideline

Qualifier
according to guideline

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

Deviations
no

Qualifier
according to guideline

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

Deviations
no

GLP compliance
yes

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

Test material

Test material information
4,4'-bis(chloromethyl)-1,1'-biphenyl

Specific details on test material used for the study
Purity: 99.8%

Method

Species / strain

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

Species / strain / cell type
E. coli WP2 uvr A
bacteria

Metabolic activation
with and without

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

Test concentrations with justification for top dose
-S9 mix:
0.05, 0.15, 0.5, 1.5, 5, 15, 50, 150, 500, 1500, 5000 µg/plate (TA 1535, TA 98 and TA 100 strains)
50, 150, 500, 1500, 5000 µg/plate (TA1537and WP2uvrA strain)
+S9 mix:
5, 15, 50, 150, 500, 1500, 5000 µg/plate (TA 98 and TA 100 strains)
15, 50, 150, 500, 1500, 5000 µg/plate (TA 1535 strain)

50, 150, 500, 1500, 5000 µg/plate (TA1537 and WP2uvrA 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 not observed for all strains with or without S9 mix.

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

Controls

Untreated negative controls
no

Negative solvent / vehicle controls
yes

True negative controls
no

Positive controls
yes

Positive control substance
9-aminoacridine
9-amimoacridine hydrochloride (9AA): -S9 mix: (TA1537)
sodium azide
NaN3: -S9 mix: (TA1535)
furylfuramide
2-(2-Furyl)-3-(5-nitro-2-furyl) acrylamide (AF-2): -S9 mix: (TA100, TA98, WP2 uvrA)
other: 2-aminoanthracene (2AA)
+S9 mix: (TA1535, TA100, TA98, TA1537 and WP2 uvrA)

Details on test system and experimental conditions
METHOD OF APPLICATION: Preincubation
DURATION- Preincubation period: 20 min at 37°C
- Exposure duration: ca.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
no

Results and discussion

Test results

Key result
true

Species / strain
S. typhimurium TA 1535
bacteria

Metabolic activation
with and without

Genotoxicity
positive

Cytotoxicity / choice of top concentrations
no cytotoxicity

Vehicle controls validity
valid

Untreated negative controls validity
not examined

True negative controls validity
not examined

Positive controls validity
valid

Key result
true

Species / strain
S. typhimurium TA 1537
bacteria

Metabolic activation
with

Genotoxicity
positive

Cytotoxicity / choice of top concentrations
no cytotoxicity

Vehicle controls validity
valid

Untreated negative controls validity
not examined

True negative controls validity
not examined

Positive controls validity
valid

Key result
false

Species / strain
S. typhimurium TA 1537
bacteria

Metabolic activation
without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
no cytotoxicity

Vehicle controls validity
valid

Untreated negative controls validity
not examined

True 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
positive

Cytotoxicity / choice of top concentrations
no cytotoxicity

Vehicle controls validity
valid

Untreated negative controls validity
not examined

True 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
positive

Cytotoxicity / choice of top concentrations
no cytotoxicity

Vehicle controls validity
valid

Untreated negative controls validity
not examined

True negative controls validity
not examined

Positive controls validity
valid

Key result
true

Species / strain
E. coli WP2 uvr A
bacteria

Metabolic activation
with and without

Genotoxicity
positive

Cytotoxicity / choice of top concentrations
no cytotoxicity

Vehicle controls validity
valid

Untreated negative controls validity
not examined

True negative controls validity
not examined

Positive controls validity
valid

Additional information on results
The maximum specific activity of mutation was 142666.7 revertants/mg/plate, which was obse rved in plates of Salmonella typhimurium TA100 treated with the test article at 1.5 µg/plate without metabolic activation.

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/PDF1667-10-3e.pdf

Applicant's summary and conclusion

Conclusions
Positive with or without metabolic activation

Executive summary

In a bacterial reverse mutation assay using Salmonella typhimurium TA100, TA1535, TA98, and TA 1537, and Escherichia coli WP2uvrA/pKM101 (OECD TG 471), 4,4’-bis(chloromethyl)-1,1’-biphenyl was positive for TA100, TA1535, TA98 and Escherichia coli WP2uvrA with or without metabolic activation, positive for TA1537 with metabolic activation. The maximum specific activity of mutation was 142666.7 revertants/mg/plate, which was observed in plates of Salmonella typhimurium TA100 treated with the test article at 1.5 µg/plate without metabolic activation.

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.002

UUID:	ce367ab8-29bb-4af3-aee0-bbd090bcba9c
Dossier UUID:	
Author:	
Date:	2021-03-15T16:14:34.000+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
guideline study under GLP condition
Reliability 1

Data source

Reference

In Vitro Chromosomal Aberration Test of on 4,4'-bis(chloromethyl)-1,1'-biphenyl Cultured Chinese Ham / 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 Chromosomal Aberration Test)
in vitro cytogenicity / chromosomal aberration study in mammalian cells (from 26 September 2014)

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
in vitro mammalian chromosome aberration test
in vitro cytogenicity / chromosome aberration study in mammalian cells

Test material

Test material information
4,4'-bis(chloromethyl)-1,1'-biphenyl

Specific details on test material used for the study
Purity: 99.8%

Method

Species / strain

Species / strain / cell type
Chinese hamster lung (CHL/IU)
mammalian cell line

Cytokinesis block (if used)
colcemid

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): 20.3, 40.6, 81.3, 162.5, 325, 650, 1300, 2600 ug/mL
+S9 mix (short-term treatment): 20.3, 40.6, 81.3, 162.5, 325, 650, 1300, 2600 ug/mL
-S9 mix (continuous treatment, 24hr): 20.3, 40.6, 81.3, 162.5, 325, 650, 1300, 2600 ug/mL
Main study
-S9 (short-term treatment): 5, 10, 20, 40 ug/mL
+S9 (short-term treatment): 12.5, 25, 50, 100 ug/mL
-S9 mix (continuous treatment, 24hr): 2.5, 5, 10, 20 ug/mL

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

Controls

Untreated negative controls
no

Negative solvent / vehicle controls
yes

True negative controls
no

Positive controls
yes

Positive control substance
N-dimethylnitrosamine
+S9
mitomycin C
-S9

Details on test system and experimental conditions
METHOD OF APPLICATION: Exposure duration: [short-term treatment]:6 hrs + 18 hr, [continuous treatment]: 24 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
Chinese hamster lung (CHL/IU)
mammalian cell line

Metabolic activation
with and without

Genotoxicity
positive structural aberration, D20: 0.0011 mg/mL, TR: 9300

Cytotoxicity / choice of top concentrations
no cytotoxicity

Vehicle controls validity
valid

Untreated negative controls validity
not examined

True 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/PDF1667-10-3e.pdf

Applicant's summary and conclusion

Conclusions
Positive with or without metabolic activation

Executive summary

In an in vitro chromosomal aberration test using CHL/IU cells (OECD TG 473), 4,4’-bis(chloromethyl)-1,1’-biphenyl induced structural chromosomal aberrations but did not induce chromosome numerical aberrations under the conditions of this study.

Toxicity to reproduction

Toxicity to reproduction

ENDPOINT_STUDY_RECORD: Toxicity to reproduction. 001

UUID: 85eab845-8249-48de-9a6b-4acc2e41e5a6
Dossier UUID:
Author:
Date: 2022-11-17T16:49:30.411+09:00
Remarks:

Administrative data

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

Type of information
experimental study

Adequacy of study
key study

Robust study summary
false

Used for classification
false

Used for SDS
false

Reliability
1 (reliable without restriction)

Rationale for reliability incl. deficiencies
guideline study OECD Test Guideline study under GLP condition
Reliability 1

Cross-reference

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

Related information
OECD / Repeated dose toxicity: oral / Repeated dose toxicity: oral. 001 / 4,4'-Bis(chloromethyl)-1,1'-biphenyl / 1667-10-3

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
4,4'-bis(chloromethyl)-1,1'-biphenyl

Specific details on test material used for the study
- Name of test material (as cited in study report): 4,4'-bis(chloromethyl)-1,1'-biphenyl
- Analytical purity: 99.8%
- Storage condition of test material: Room temperature, shading, airtightness, moisture proof
- Stability under test conditions: The stability of test material was identified by analysis of the remainder.

Test animals

Species
rat

Strain
other: Crl:CD(SD)

Sex
male/female

Details on test animals or test system and environmental conditions
TEST ANIMALS
- Source: Charles River Japan, Inc., Hino Breeding Center.
- Age at study initiation: 10 weeks old
- Weight at study initiation: Males in main group male: 325-367 g, females in main group: 223-258 g, females in mating group: 222-259 g
- Housing: Animals were individually housed in stainless steel suspension cage (240W × 380D × 200H mm), from gestation day 18 to lactation day 4, Dams were bred individually or with individual littermates in plastic cages (310W x 360D x 175H mm) and bedding.
- Diet: Solid feed (CRF-1: Oriental Yeast Co., ltd.) was given ad libitum.
- Water: Tap water was given ad libitum.
- Acclimation period: Males in main group: 18 days, females in main group: 19 days, females in mating group: 18 days

ENVIRONMENTAL CONDITIONS
- Temperature (°C): 20-26°C (actual temperature: 22.5-24.8°C)
- Humidity (%): 40.0-70.0% (actual humidity: 40.7-60.4%)
- Air changes (per hr): 12
- Photoperiod (hrs dark / hrs light): 12 hr dark/12 hr light (light: 6:00~18:00)

Administration / exposure

Route of administration
oral: gavage

Vehicle
other: 0.5 w/v% methylcellulose

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

Details on mating procedure
- M/F ratio per cage:1/1
- Length of cohabitation: up to 14 days
- Proof of pregnancy: vaginal plug / sperm in vaginal smear referred to as day 0 of pregnancy

Analytical verification of doses or concentrations
yes

Details on analytical verification of doses or concentrations
Concentrations of the test suspensions using administration on day 1 were analyzed with HPLC. Analytical concentrations of the test suspensions were all within the range of 102.7-106.7% of the nominal concentrations and both values were within the acceptable range (concentration: percentage of nominal concentration, 100±10%).

Duration of treatment / exposure
Males: 28 days including 14 days pre-mating
Females (main study groups): 28 days
Females (mating groups): 42-46 days including 14 days pre-mating, mating and gestation periods and the days until day 4 of lactation

Frequency of treatment
Once/day, 7 days/week

Doses / concentrations

Dose / conc.	
0	mg/kg bw/day (actual dose received)
Dose / conc.	
62.5	mg/kg bw/day (actual dose received)
Dose / conc.	
250	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 study groups:

Control- and high-dose groups: 12 males and 10 females per group (half of both sexes assigned as t he treatment groups, and the remaining half assigned as the recovery groups)
Low- and middle-dose groups: 12 males and 5 females per group (half of males assigned as the treatment groups, and the remaining half assigned as the recovery groups)

- Mating groups:
12 females per dose

Control animals
yes, concurrent no treatment

Details on study design
- Dose selection rationale: Based on the results of a 14-day preliminary study, the high dose was set to 1000 mg/kg bw/day, which is the upper limit in OECD TG422, and the intermediate dose and low dose were set to 250 mg/kg bw/day and 62.5 mg/kg bw/day, respectively.

[14-day preliminary study]
A 14-day repeated dose oral toxicity test (Crl:CD(SD) rats, doses: 0, 200, 500 or 1000 mg/kg bw/day).
Males in the 1000 mg/kg bw/day group tended to have lower body weights and significantly lower food intakes, females in the 1000 mg/kg bw/day group had significantly higher A/G and significantly higher relative liver weights.

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

Examinations

Parental animals: Observations and examinations
CAGE SIDE OBSERVATIONS: Yes
- Time schedule:
Males and females (main study groups): 2 times/day (before administration, 54-137 minutes after administration) during the administration period. Once a day during the recovery period.
Females (mating groups): 2 times/day (before administration, 60-138 minutes after administration) d uring the administration period.

DETAILED CLINICAL OBSERVATIONS: Yes
- Time schedule:
Males and females (main study groups): on day of grouping, on days 7, 14, 21 and 27 of admin istration period.
Females (mating groups): on day of grouping, on days 7 and 14 of administration period, on days 1, 8 and 15 of gestation period, on day 4 of lactation period.

BODY WEIGHT: Yes
- Time schedule for examinations:
Males and females (main study groups):
Twice a week (On days 1, 4, 8, 11, 15, 18, 22, 25, 28 and 29 of administration period, on days 1, 4, 8, 11 and 14 of recovery period).
Females (mating groups): Twice a week (On days 1, 4, 8, 11, 15 and 18 of administration period, on days 0, 7, 14 and 20 of gestation period, on days 0, 4 and 5 of lactation period).

FOOD CONSUMPTION AND COMPOUND INTAKE (if feeding study):
- Food consumption: Yes
- Time schedule for examinations:
Males and females (main study groups):
Twice a week (Males: On days 2, 5, 9 and 12 of administration period, on days 2, 5, 9 and 12 of reco very period; Females: On days 2, 5, 9, 12, 16, 19, 23 and 26 of administration period, on days 2, 5, 9 and 12 of recovery period).

Females (mating groups): Twice a week (On days 2, 5, 9 and 12 of administration period, on days 2, 9, 16 and 20 of gestation period, on days 2 of lactation period).

WATER INTAKE: Yes
- Time schedule for examinations:
Males and females (main study groups):
Twice a week (Males: On days 2, 5, 9 and 12 of administration period, on days 2, 5, 9 and 12 of recovery period; Females: On days 2, 5, 9, 12, 16, 19, 23 and 26 of administration period, on days 2, 5, 9 and 12 of recovery period).
Females (mating groups): Twice a week (On days 2, 5, 9 and 12 of administration period, on days 2, 9, 16 and 20 of gestation period, on days 2 of lactation period).

OPHTHALMOSCOPIC EXAMINATION: No

HAEMATOLOGY: Yes
- Time schedule for collection of blood:
Males and females (main study groups): At the end of administration period, or at the end of recovery period in both sexes
- Anaesthetic used for blood collection: Pentobarbital sodium
- Animals fasted: Yes
- How many animals:
At the end of administration period: 6 males/dose (0, 62.5, 250, 1000 mg/kg bw/day), 5 females/dose (0, 62.5, 250, 1000 mg/kg bw/day)
At the end of recovery period: 6 males/dose (0, 62.5, 250, 1000 mg/kg bw/day), 5 females/dose (0 and 1000 mg/kg bw/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, prothrombin time, activated partial thromboplastin time, fibrinogen.

CLINICAL CHEMISTRY: Yes
- Time schedule for collection of blood:
Males and females (main study groups): At the end of administration period, or at the end of recovery period in both sexes
- Animals fasted: Yes
- How many animals:
At the end of administration period: 6 males/dose (0, 62.5, 250, 1000 mg/kg bw/day), 5 females/dose (0, 62.5, 250, 1000 mg/kg bw/day)
At the end of recovery period: 6 males/dose (0, 62.5, 250, 1000 mg/kg bw/day), 5 females/dose (0 and 1000 mg/kg bw/day)
- Parameters checked: ALP, total cholesterol, triglyceride, total bilirubin, glucose, urea nitrogen, creatinine, sodium, potassium, chloride, calcium, inorganic phosphorus, total protein, albumin, A/G ratio, AST, ALT, γ-GT

BLOOD HORMONE: Yes
- Time schedule for collection of serum:
Males and females (main study groups): At the end of administration period in both sexes
- Animals fasted: Yes
- How many animals:
6 males/dose (0, 62.5, 250, 1000 mg/kg bw/day), 5 females/dose (0, 62.5, 250, 1000 mg/kg bw/day)
- Parameters checked: Triiodothyronine (T3), Thyroxin (T4), and thyroid stimulating hormone (TSH)

URINALYSIS: Yes
- Time schedule for collection of urine:
Males and females (main study groups): Before the end of the administration period (day 23 of administration period) and before the end of recovery (days 12 of recovery period).
- Metabolism cages used for collection of urine: Yes

A urine collector to collect fresh urine samples under fasting but ad libitum drinking conditions, followed by collection of 24-hour urine samples under ad libitum feeding and drinking conditions.
- How many animals:
At the end of administration period: 6 males/dose (0, 62.5, 250, 1000 mg/kg bw/day), 5 females/dose (0, 62.5, 250, 1000 mg/kg bw/day)
At the end of recovery period: 6 males/dose (0, 62.5, 250, 1000 mg/kg bw/day), 5 females/dose (0 and 1000 mg/kg bw/day)
- Parameters checked:
Fresh urine: Color, pH, protein, glucose, ketones, bilirubin, occult blood, urobilinogen, sediment
24-urine: Specific gravity, urine volume (24-hour volume)

NEUROBEHAVIOURAL EXAMINATION: Yes
- Time schedule for examinations:
Males and females (main study groups): Final week of administration (Manipulative test and measurement of grip strength: Day 27 of administration, measurement of motor activity: Day 26 of administration)
- Dose groups that were examined: Autopsy animals after the end of the administration period
- Battery of functions tested:
1) Manipulative Test. Pupillary reflex, approaching behavior, response to touch, auditory reflex, pain reflex
2) Measurement of Grip Strength. Following manipulative test, grip strength of forelimb and hind limb were measured by CPU gauge (San Diego Instruments Inc.).
3) Measurement of Spontaneous Motor Activity. Spontaneous motor activity (Ambulatory and vertical counts) was measured by Activity Monitor (MED Associates Inc.).
The measurements were collected at 10-minute intervals from 1 hour to 2 hours after administration.

Oestrous cyclicity (parental animals)
Vaginal smears were collected from all females in the mating study 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, epididymis and seminal vesicle weight, histopathological 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 pentobarbital sodium anesthesia.
SACRIFICE: Males and females (main study groups): On next day after the last administration, Maternal animals: on Day 5 of lactation, and males and females recovery group: on Day 14 of recovery .

GROSS PATHOLOGY: Yes

ORGAN WEIGHT: Yes [main study groups: brain, pituitary, salivary glands, thyroids, adrenal gland, thymus, spleen, heart, liver, kidney, testes, epididymides, ventral prostate, seminal vesicles, ovaries, uterus; females in mating group: ovary, uterus]

HISTOPATHOLOGY: Yes, [main study groups: heart, lung, trachea, liver, pancreas, sublingual gland, submandibular gland, esophagus, stomach, duodenum, jejunum, ileum (including Peyer's patch), cecum, colon, rectum, thymus, spleen, mandibular lymph nodes, mesenteric lymph nodes, kidney, urinary bladder, testis, epididymis, ventral prostate, seminal vesicles (including coagulating gland),

ovaries, uterus, vagina, pituitary, adrenal glands, thyroid (including parathyroid), cerebrum, cerebellum , pons, spinal cord, sciatic nerve, eye ball, Harderian gland, sternum and femur (including bone mar rows), muscle (rectus femoris), mammary gland; females in mating group: ovaries, uterus, vagina]

Postmortem examinations (offspring)
SACRIFICE
- The F1 offsprings were euthanized on PND4 by exsanguination under 20%Isoflurane anesthesia.
GROSS NECROPSY: Yes
- Gross necropsy consisted of external and internal examinations including the cervical, thoracic, and abdominal viscera.
HISTOPATHOLOGY / ORGAN WEIGTHS
- Not examined.

Statistics
For quantitative data, homogeneity of variance was tested using Bartlett method first. If the variance was homogenous, statistical difference between each treatment group and the control group was analyzed using Dunnett method. If not homogenous, statistical difference between each treatment group and the control group was tested using Steel method. For comparison of quantitative data be tween two groups in the recovery test, homogeneity of variance was analyzed by F-test. Then, if homo genous, student's t-test was applied. If not homogenous, Aspin-Welch's t-test was used.
For histopathological findings, statistical analysis was carried out in combination with Steel-test a nd Cochran-Armitage trend test. Regarding clinical observation (except for frequency of urination, d efecation, rearing and grooming) and sensory reactivity, Steel test was applied. Regarding implantat ion index, delivery index, birth index, live birth index, viability index, sex ratio and external abnormalitie s, Steel test was performed between administration groups and control groups. Regarding copulation, fertility index, and gestation index, Fisher's test was applied.

Reproductive indices
Each parameter was determined by the following equations:
Copulation index (%) = (No. of pairs with successful copulation / No. of pairs) × 100
Fertility index (%) = (No. of pregnant females / No. of pairs with successful copulation) × 100
Gestation index (%) = (No. of dams having live pups / No. of pregnant dams) × 100
Length of gestation (days)
Implantation index (%) = (No. of implantation scars / No. of corpora lutea) × 100
Delivery index (%) = (No. of pups born / No. of implantation scars) × 100
Birth index (%) = (No. of live pups born / No. of implantation scars) × 100
Live birth index (%) = (No. of live pups born / No. of pups born) × 100
Sex ratio on Day 4 of lactation = No. of male pups / No. of female pups
External abnormalities (%) = (No. of pups with external abnormalities / No. of live pups) × 100

Offspring viability indices
Viability index (%) = (No. of live pups on Day 4 of lactation/ No. of live pups born) × 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)
no effects observed

Ophthalmological findings
not examined

Haematological findings
effects observed, treatment-related

Description (incidence and severity)
See 7.5.1 Repeated dose toxicity. 001

Clinical biochemistry findings
effects observed, treatment-related

Description (incidence and severity)
See 7.5.1 Repeated dose toxicity. 001

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 Repeated dose toxicity. 001

Gross pathological findings
no effects observed

Neuropathological findings
not examined

Histopathological findings: non-neoplastic
no effects observed

Histopathological findings: neoplastic
not examined

Reproductive function / performance (P0)

Reproductive function: oestrous cycle
no effects observed

Reproductive function: sperm measures
no effects observed

Reproductive performance
no effects observed

Details on results (P0)

General toxicity: See 7.5.1 Repeated dose toxicity. 001
Reproductive function / performance: There were no effects on reproductive parameters up to 1000 mg/kg bw/day.

Effect levels (P0)

Key result
false

Dose descriptor
NOAEL

Effect level

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

Based on
test mat.

Sex
male/female

Remarks on result
other: There were no effects on reproductive parameters up to 1000 mg/kg bw/day.

Results: F1 generation

General toxicity (F1)

Clinical signs
no effects observed

Mortality / viability
no mortality observed

Body weight and weight changes
no effects observed

Gross pathological findings
no effects observed

Details on results (F1)

There were no effects on developmental parameters up to 1000 mg/kg bw/day.

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: There were no effects on developmental parameters up to 1000 mg/kg bw/day.

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/PDF1667-10-3d.pdf

Applicant's summary and conclusion

Conclusions
In the combined repeated oral dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) described above, there were no effects on the reproductive and dev elopmental parameters up to 1000 mg/kg bw/day. The NOAEL for the rat reproductive/developmental toxicity of 4,4’-bis(chloromethyl)-1,1’-biphenyl was regarded as 1000 mg/kg bw/day, the highest dose tested.

References

Reference Substances

REFERENCE_SUBSTANCE: 4,4’-bis(chloromethyl)-1,1’-biphenyl

UUID: 7e71486c-3f27-4c3d-93ee-5b14b41905c6
Dossier UUID:
Author:
Date: 2020-12-24T13:27:13.000+09:00
Remarks:

Reference substance name
4,4’-bis(chloromethyl)-1,1’-biphenyl

Inventory

CAS number
1667-10-3

Molecular and structural information

Molecular formula
C14H12Cl2

Molecular weight

ca. 251.15

Test Materials

TEST_MATERIAL_INFORMATION: 4,4’-bis(chloromethyl)-1,1’-biphenyl

UUID: 757212f2-5e32-4874-89c5-f2c6d7e985cd
Dossier UUID:
Author:
Date: 2020-12-24T13:28:24.000+09:00
Remarks:

Name
4,4’-bis(chloromethyl)-1,1’-biphenyl

Composition

Composition

Type
Constituent

Reference substance
4,4’-bis(chloromethyl)-1,1’-biphenyl / 1667-10-3

EC number	EC name
CAS number	CAS name
1667-10-3	

IUPAC name

Concentration

99.8	% (w/w)

Other characteristics

Test material form
solid: crystalline

Literatures

LITERATURE: Combined repeated dose toxicity study with the reproductive/developmental toxicity screening test of 4,4’-bis(chloromethyl)-1,1’-biphenyl by oral administration in rats

UUID: 41bada24-1592-4bf3-b1bd-e21062c1a849
Dossier UUID:
Author:
Date: 2020-12-24T13:15:44.000+09:00
Remarks:

General information

Reference Type
study report

Title
Combined repeated dose toxicity study with the reproductive/developmental toxicity screening test of 4,4’-bis(chloromethyl)-1,1’-biphenyl by oral administration in rats

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

Year
2011

Bibliographic source
available in the web of Japan Existing Chemical Data Base (JECDB) https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF1667-10-3d.pdf

Testing facility
Nihon Bioresearch Inc.

Report number
100630

LITERATURE: In Vitro Chromosomal Aberration Test of on 4,4’-bis(chloromethyl)-1,1’-biphenyl Cultured Chinese Hamster Cells.

UUID: fcb1e260-3f6a-4179-8167-ed926c3f7785
Dossier UUID:
Author:
Date: 2021-03-15T16:14:31.000+09:00
Remarks:

General information

Reference Type
study report

Title
In Vitro Chromosomal Aberration Test of on 4,4’-bis(chloromethyl)-1,1’-biphenyl Cultured Chinese Hamster Cells.

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

Year
2011

Bibliographic source
Japan Existing Chemical Data Base (JECDB)
https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF1667-10-3e.pdf

Testing facility
Nihon Bioresearch Inc.

Report number
971030

LITERATURE: Reverse Mutation Test of 4,4’-bis(chloromethyl)-1,1’-biphenyl on Bacteria.

UUID: 88df2882-f6cc-4ab8-8657-609ba7f82941
Dossier UUID:
Author:
Date: 2021-03-10T13:39:13.000+09:00
Remarks:

General information

Reference Type
study report

Title
Reverse Mutation Test of 4,4’-bis(chloromethyl)-1,1’-biphenyl on Bacteria.

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

Year
2011

Bibliographic source
Japan Existing Chemical Data Base (JECDB)
https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF1667-10-3e.pdf

Testing facility
Nihon Bioresearch Inc.

Report number
901430

Legal Entities

LEGAL_ENTITY: National Institute of Health Sciences

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

General information

Legal entity name
National Institute of Health Sciences

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

Address

Address 1
Tonomachi 3-25-26

Address 2
Kawasaki-ku

Postal code
210-9501

Town
Kawasaki

Region / State
Kanagawa

Country
Japan
JP

Identifiers

Other IT system identifiers

IT system LEO **ID** 10767
IT system IUCLID4

ID
16558402024DIV750