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

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**Legal entity owner:** National Institute of Health Sciences

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

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# DOSSIER:

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**UUID:** 0

**Dossier UUID:**

**Author:**

**Date:** 2022-11-29T14:54:11.686+09:00

**Remarks:**

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## Dossier header

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## Dossier submission type

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**Name**

OECD SIDS

**Version**

core 7.0

**Name (given by user)**

## Dossier subject

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**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**

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# LEGAL\_ENTITY: National Institute of Health Science

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**UUID:** f51e7b54-9211-4863-90ce-fcf8a155d647

**Dossier UUID:**

**Author:**

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**Remarks:**

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## General information

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**Legal entity name**

National Institute of Health Science

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# 4,4'-Bis(chloromethyl)-1,1'-biphenyl

## General information

### Identification

#### Identification

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

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UUID: 3ee00742-ccec-4b17-adfe-16029fd9fc15

Dossier UUID:

Author:

Date: 2022-11-29T14:30:05.957+09:00

Remarks:

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#### Substance name

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

#### Legal entity

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

## Identification of substance

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#### 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

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#### Manufacturer

false

#### Importer

false

#### Only representative

false

#### Downstream user

false

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# Toxicological information

## Repeated dose toxicity

Repeated dose toxicity: oral

ENDPOINT\_STUDY\_RECORD: Repeated dose toxicity: oral. 001

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UUID: 2e93454b-1d43-4608-b211-5261e973773b

Dossier UUID:

Author:

Date: 2022-11-29T14:30:05.957+09:00

Remarks:

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## Administrative data

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### 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

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### 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

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## Materials and methods

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### 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

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## Test material

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**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.

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## Test animals

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**Species**

rat

common rodent species

**Strain**

other: CrI: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 study 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 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 (main study groups): 18 days, females (main study groups): 19 days, females (mating study groups): 18 days

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#### 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

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#### 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

<b>Dose / conc.</b>	
0	mg/kg bw/day (actual dose received)
<b>Dose / conc.</b>	
62.5	mg/kg bw/day (actual dose received)
<b>Dose / conc.</b>	
250	mg/kg bw/day (actual dose received)
<b>Dose / conc.</b>	
1000	mg/kg bw/day (actual dose received)



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**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 the 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 (CrI: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 consumption 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.

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**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) during 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 administration 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 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).

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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,  $\gamma$ -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), Thyroxine (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

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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 marrow), 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**

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### **Results of examinations**

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**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 tendencies 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)

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**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](https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF1667-10-3d.pdf)

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**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 pre-mating, 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 thyroid 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.

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## Genetic toxicity

### Genetic toxicity in vitro

ENDPOINT\_STUDY\_RECORD: Genetic toxicity in vitro.001

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UUID: 42637a34-e7bc-4ab4-8ac0-ed16cb012d88

Dossier UUID:

Author:

Date: 2021-03-15T16:13:55.000+09:00

Remarks:

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## Administrative data

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### 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

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### 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

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### 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)



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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-aminoacridine hydrochloride (9AA): -S9 mix: (TA1537)

sodium azide

NaN<sub>3</sub>: -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 increase was observed.

#### Statistics

no

## Results and discussion

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#### 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

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**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

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**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 observed 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](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-ae0-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( $\pm$ ): 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](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

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### 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

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## 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: CrI: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)

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## Administration / exposure

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### 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,  $100 \pm 10\%$ ).

### 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

<b>Dose / conc.</b>	
0	mg/kg bw/day (actual dose received)
<b>Dose / conc.</b>	
62.5	mg/kg bw/day (actual dose received)
<b>Dose / conc.</b>	
250	mg/kg bw/day (actual dose received)
<b>Dose / conc.</b>	
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 the 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 (CrI: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**

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#### **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) during 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 administration 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 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).

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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,  $\gamma$ -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), Thyroxine (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),

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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 marrow), 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 WEIGHTS**

- 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 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. Regarding implantation index, delivery index, birth index, live birth index, viability index, sex ratio and external abnormalities, 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](https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF1667-10-3d.pdf)

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**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 developmental 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

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**Molecular formula**

C<sub>14</sub>H<sub>12</sub>Cl<sub>2</sub>

**Molecular weight**

ca. 251.15

---

# Test Materials

## TEST\_MATERIAL\_INFORMATION: 4,4'-bis(chloromethyl)-1,1'-biphenyl

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**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

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### 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

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### Test material form

solid: crystalline

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## 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

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**UUID:** 41bada24-1592-4bf3-b1bd-e21062c1a849

**Dossier UUID:**

**Author:**

**Date:** 2020-12-24T13:15:44.000+09:00

**Remarks:**

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## General information

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**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](https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF1667-10-3d.pdf)

**Testing facility**  
Nihon Bioresearch Inc.

**Report number**  
100630

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

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**UUID:** fcb1e260-3f6a-4179-8167-ed926c3f7785

**Dossier UUID:**

**Author:**

**Date:** 2021-03-15T16:14:31.000+09:00

**Remarks:**

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### General information

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**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](https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF1667-10-3e.pdf)

**Testing facility**

Nihon Bioresearch Inc.

**Report number**

971030

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

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**UUID:** 88df2882-f6cc-4ab8-8657-609ba7f82941

**Dossier UUID:**

**Author:**

**Date:** 2021-03-10T13:39:13.000+09:00

**Remarks:**

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### General information

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**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](https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF1667-10-3e.pdf)

**Testing facility**

Nihon Bioresearch Inc.

**Report number**

901430



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# Legal Entities

## LEGAL\_ENTITY: National Institute of Health Sciences

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

**Dossier UUID:**

**Author:**

**Date:** 2022-11-07T15:49:29.000+09:00

**Remarks:**

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### General information

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**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](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 official MHLW opinions or any other regulatory policies.

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### Identifiers

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**Other IT system identifiers**

**IT system**

LEO

**ID**

10767

**IT system**

IUCLID4

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**ID**

16558402024DIV750