Name: COMPLETE / SUBSTANCE : 2,4-Di-tert-pentylphenol / 120-95-6 Tue, 5 Sep 2023, 13:10:56+0900 /

Legal entity owner: National Institute of Health Sciences / Kawasaki / Japan

Printing date: 2023-09-05T13:10:57.157+09:00

Table of Contents

DOSSIER:

UUID: 0
Dossier UUID:
Author:
Date: 2023-09-05T13:10:56.913+09:00
Remarks:

Dossier header

Dossier submission type

Name
Complete table of contents

Version
core 8.0

Name (given by user)

Dossier subject

Dossier subject
2,4-Di-tert-pentylphenol / 120-95-6

Public name

Submitting legal entity
National Institute of Health Sciences / Kawasaki / Japan

Dossier creation date/time
Tue, 5 Sep 2023, 13:10:56+0900

Used in category

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

2,4-Di-tert-pentylphenol

OECD

Health Effects

Repeated dose toxicity: oral

ENDPOINT_STUDY_RECORD: RepeatedDoseToxicityOral. 001

UUID: 8bc3d564-c633-4a54-a2f3-db51859887ff
Dossier UUID:
Author:
Date: 2022-03-25T11:50:41.000+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

Related information
OECD / Toxicity to reproduction / ToxicityReproduction. 001 / 2,4-Di-tert-pentylphenol / 120-95-6

Data source

Reference

Combined repeat dose and reproductive/developmental toxicity screening test of 2,4-di-tert-pentylphe / Ministry of Health, Labour and Welfare (MHLW), Japan / study report

Data access
data published https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF120-95-6d.pdf

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
2,4-Di-tert-pentylphenol

Specific details on test material used for the study
- Name of test material (as cited in study report): Phenol, 2,4-bis (1,1-dimethylpropyl)
- Analytical purity: 99.7%
- Storage condition of test material: Cold and dark place (3-6°C)
- 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., Atsugi Breeding Center.
- Age at study initiation: 10 weeks old
- Weight at study initiation: Male: 330.1-413.5 g), Female: 228.9-300.4 g
- Housing: Animals were individually housed in bracket-type metallic wire-mesh cages (220W × 270D × 190H mm), from gestation day 18 to lactation day 4, Dams were bred individually or with individual lit termates in plastic cages (350W x 400D x 180H mm) and bedding.

- Diet: Solid feed (CE-2: CLEA Japan Inc.) was given ad libitum.
- Water: Tap water was given ad libitum.

- Acclimation period: 18 days
ENVIRONMENTAL CONDITIONS
- Temperature (°C): 21.0-25.0 (actual temperature: 23.0-25.5°C)
- Humidity (%): 40.0-75.0% (actual humidity: 42.5-70.5%)
- Air changes (per hr): 15
- Photoperiod (hrs dark / hrs light): 12 hr dark/12 hr light (light: 7:00~19:00)

Administration / exposure

Route of administration
oral: gavage

Vehicle
corn oil

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

Analytical verification of doses or concentrations
yes

Details on analytical verification of doses or concentrations
The concentrations of each test suspensions used in day1 of administration were analyzed by HPLC. Results showed that the concentrations of each test suspensions were 93.8 to 97.7% of the nominal concentration.

Duration of treatment / exposure
(P) Males: 42 days including 14 days pre-mating
(P)Females: 41-44 days including 14 days pre-mating, mating and gestation periods and the days until day 4 of lactation
Female (no mating, satellite group): 42 days

Frequency of treatment
Once/day, 7 days/week

Doses / concentrations

Dose / conc.	
10	mg/kg bw/day (actual dose received)
Dose / conc.	
50	mg/kg bw/day (actual dose received)
Dose / conc.	
100	mg/kg bw/day (actual dose received)

Remarks
At the start of administration: 250 mg/kg bw/day

No. of animals per sex per dose
Mating group: 13 animals/sex/dose (0, 10, 50, and 100 mg/kg bw/day)

Non-mating group: 10 females/dose (0 and 100 mg/kg bw/day)
Recovery group: 5 males/dose in the mating group (0 and 50 mg/kg bw/day) and 5 females/dose in the non-mating groups (0 and 100 mg/kg bw/day)

Control animals
yes, concurrent vehicle

Details on study design
- Dose selection rationale: Based on the results of a 14-day preliminary study, the highest dose of 250 mg/kg bw/day was selected as an expected obvious toxic dose, and the lowest dose of 10 mg/kg bw/day was selected as an expected no toxic dose. The middle dose levels of 50 mg/kg bw/day were selected.

[14-day preliminary study]
A 14-day repeated dose oral toxicity test (Crl:CD(SD) rats, doses: 0, 250, 500 or 1,000 mg/kg bw/day. At 500 mg/kg bw/day and above, all animals died or were moribund, and necropsy showed lesions i n the stomach, lung and kidney. At 250 mg/kg bew/day, soft stool, salivation, decrease in body weigh t, decreased body weight, pale spots on the kidneys, increased liver and kidney weights, decreases in RBC, Ht, Hb and total cholesterol, increases in triglyceride, γ-GTP, ALP, BUN, and LDH 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: 2 times/day (before administration, after administration) during the administration p eriod. Once a day during the recovery period.
DETAILED CLINICAL OBSERVATIONS: Yes
- Time schedule:
Males in the main groups and females in the non-mating groups: the end of acclimation period, day 7, 14, 21, 28, 35, and 42 during the administration.
Females in the mating groups: the end of acclimation period, day 7, 14, 21, 28, 35, and 42 during the administration period, and once during lactation period (lactation day 0from day 4)
Males and females in the recovery groups: the end of acclimation period, day 7, 14, 21, 28, 35, and 42 during the administration period and day 7 and 14 during recovery period.

BODY WEIGHT: Yes
- Time schedule for examinations:
Males in the main groups and females in the non-mating groups: days 1, 7, 10, 12, 14, 17, 21, 24, 28, 31, 35, 38 and 42 of administration period and on the day of necropsy.
Males and females in the recovery groups: days1, 7, 10, 12, 14, 17, 21, 24, 28, 31, 35, 38 and 42 of administration period, and days 1, 7 and 14 of recovery period and on the day of necropsy.
Females in the mating groups: days 1, 7, 10, 12, 14 and 17 of administration period (uncopulated an imals : day 26), days 0, 3, 7, 10, 14, 17 and 20 of gestation, days 0, 4 of lactation, and on the day of necropsy.

Food consumption: Yes
Measurement of food consumption was conducted on all animals at the following frequencies:
Males in the main groups and females in the non-mating groups: days 1-2, 7-8, 14-15, 29-30, 35-36 and 41-42 of administration period.
Males and females in the recovery groups: days 1-2, 7-8, 14-15, 29-30, 35-36 and 41-42 of admin istration, period and days 6-7 and 12-13 of recovery period.
Females in the mating groups: days 1-2, 7-8 and 14-15 of administration period, days 0-1, 7-8, 14-15, and 20-21 of gestation period, days 3-4 of lactation period.

OPHTHALMOSCOPIC EXAMINATION: No

HAEMATOLOGY: Yes
- Time schedule for collection of blood: At the end of administration period, or at the end of recovery period in both sexes
- Anaesthetic used for blood collection: Pentbarbital sodium
- Animals fasted: Yes
- How many animals:
5 animals/sex/group
- 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.

CLINICAL CHEMISTRY: Yes
- Time schedule for collection of blood: At the end of administration period, or at the end of recovery period in both sexes
- Animals fasted: Yes
- How many animals:
5 animals/sex/group
- Parameters checked: ALP, total cholesterol, triglyceride, phospholipids, total bilirubin, glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, calcium, inorganic phosphorus, total protein, albumin, A/G ratio, AST, ALT, LDH, γ-GTP, bile acid.

URINALYSIS OF MALES: Yes
- Time schedule for collection of urine: final week of administration (days 37 of administration) and in the final week of recovery (days 13 of recovery)
- Metabolism cages used for collection of urine: Yes
A urine collector to collect four-hour urine samples under fasting but ad libitum drinking conditions, followed by collection of 20-hour urine samples under ad libitum feeding and drinking conditions.
- How many animals: 5 animals/group
- Parameters checked: pH, protein, ketones, glucose, occult blood, bilirubin, urobilinogen, color, sediment, osmotic pressure, sodium, potassium, chloride, urine volume (24-hour volume)

BLOOD HORMONE: No

NEUROBEHAVIOURAL EXAMINATION: Yes
- Time schedule for examinations:
Males in the main groups and females in the non-mating groups: final week of administration (Manipulative Test: day 42, Measurement of Grip Strength and Motor Activity: day 39 for males, day 41 for females)
Females in the mating groups: lactation day 5
Males and females in the recovery groups: final week of administration (Manipulative Test: day 42, Measurement of Grip Strength and Motor Activity: day 39 for males, day 41 for females) and in the final week of recovery (day 14 of recovery).
- Dose groups that were examined: All dose groups (5 animals/sex/group)
- Battery of functions tested:
1) Manipulative Test. Prayer's reaction, pupillary reflex, visual placing, startle reaction, withdrawal reflex, eyelid reflex, and righting reflex
2) Measurement of Grip Strength. Grip strength of forelimb and hind limb were measured by grip strength meter.
3) Measurement of Motor Activity. Motor activity was measured by a motor activity sensor for experimental animals SUPER-MEX (Muromachi Kikai. C0., Ltd.). The measurement was conducted for 20 min.

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

HISTOPATHOLOGY: Yes, [brain, spinal cord, pituitary, eye ball (Harderian gland), submandibular gland, sublingual gland, trachea, thyroid, parathyroid, thymus, heart, lung (including bronchial), liver, kidney, spleen, pancreas, adrenal gland, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, submandibular lymph node, mesenteric lymph node, testis, epididymis, prostate, seminal vesicles, ovary, uterus, vagina, bladder, femur (including bone marrows), skeletal muscle, sciatic nerve, mammary gland, and gross abnormalities site.

Statistics

Changes in estrous cyclicity and conception rate were analyzed by Fisher's test. Graded pathological data was analyzed by Mann-Whitney's U test (significance level = 0.05) and pathological data with number of positive and negative animals was analyzed by one-sided Fisher's test. Other data, obtained values in each animal or mean of a litter was one data, and these data were compared among the satellite groups and other among the groups. These data were analyzed using F-test for homogeneity of distribution. The Student's t-test and the Aspin-Welch's t-test were conducted for homogenous and non-homogenous distribution, respectively to compare the control and individual treatment groups. Three or more groups setting, these data were analyzed using Bartlett's test for homogeneity of distribution. The Dunnett's multiple comparison test after the ANOVA and the Dunnett's-type mean rank sum test after Kruskal-Wallis's H test were conducted for homogenous and non-homogenous distribution, respectively to compare the control and individual treatment groups. Significance level was set at 0.05 compared with the control group and among the groups.

Results and discussion

Results of examinations

Clinical signs
effects observed, treatment-related

Mortality
mortality observed, treatment-related

Body weight and weight changes
effects observed, treatment-related

Food consumption and compound intake (if feeding study)
effects observed, treatment-related

Food efficiency
not examined

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

Ophthalmological findings
not examined

Haematological findings
effects observed, treatment-related

Clinical biochemistry findings
effects observed, treatment-related

Urinalysis findings
effects observed, treatment-related

Behaviour (functional findings)
effects observed, treatment-related

Immunological findings
not examined

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

Gross pathological findings
effects observed, treatment-related

Neuropathological findings
not examined

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

Histopathological findings: neoplastic
not examined

Details on results
CLINICAL SIGNS AND MORTALITY:
Mortality:
[At the dosing period]: In the 100 (250) mg/kg bw/day group, death or moribund animals were obser ved in 9 of 13 males from day 6 to day 13 of administration and in 12 of 23 females from day 6 to day 9 of administration.
In the 50 mg/kg bw/day group, maternal death or moribund death occurred in 1 animal each on the d ay of parturition.
[At the recovery period]: No mortality observed.

Clinical signs:
[At the dosing period]: Salivation, soiled perineal region, emaciation, hypothermia, piloerection, pale skin were observed in males and females at 50 mg/kg bw/day and above. Loose stool, decrease in amount feces, decrease in locomotor activity, mucous feces, lacrimation, reddish tear, smudge of perinasal area, reddish urine, moribundity were observed in males and females, and blackish feces, no-feces, loss of locomotor activity, bradypnea, lateral position were observed in males at 100 (250) mg/kg bw/day.
[At the recovery period]: There were no changes related to the test substance in any groups.
DETAILED CLINICAL OBSERVATIONS:
[At the dosing period]: Decrease in locomotor activity, and soiled fur were observed in males and females at 100 mg/kg bw/day. Crouching position, bradycardia, decrease in temperature, pale skin, anemic skin, hypopnea, reddish tear, tip toe gait, no resistance, piloerection were observed in femal es at 100 (250) mg/kg bw/day. loss of locomotor activity, soiled fur, reddish tear, crouching position, bradycardia, decrease in temperature, hypopnea, anemic skin, tip toe gait were observed in satellite females at 100 mg/kg bw/day.
[At the recovery period]: There were no changes related to the test substance in any groups.

BODY WEIGHT:
[At the dosing period]:
A decrease in body weight gain was observed in males at 50 mg/kg bw/day and above.
[At the recovery period]:
There were no changes related to the test substance in any groups.

FOOD CONSUMPTION:
[At the dosing period]:
A decrease in food consumption was observed in males and females at 100 mg/kg bw/day.
[At the recovery period]:
There were no changes related to the test substance in any groups.

URINALYSIS:
[At the dosing period]: An increase tendency in urine volume was observed in males, an increase in ur ine volume was observed in females at 100 mg/kg bw/day.

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

HAEMATOLOGY:
[At the end of dosing period]: Decreases in hemoglobin and hematocrit, an increase tendency in RBC, an increase in prothrombin time, and an increase tendency in activated partial thromboplastin time were observed in males at 100 mg/kg bw/day. Decreases in RBC, hemoglobin and hematocrit were observed in non -mating females at 100 mg/kg bw/day. A decrease in mean corpuscular hemoglobin concentration (MCHC), an increase in reticulocyte (%) were observed in mating-females at 50 mg/kg bw/day.
[At the end of recovery period]: There were no changes related to the test substance in any groups.

CLINICAL CHEMISTRY:
[At the end of dosing period]: An increase tendency in ALP was observed in males at 100 mg/kg bw/day.
[At the end of recovery period]: There were no changes related to the test substance in any groups.
NEUROBEHAVIOURAL EXAMINATION:
1) MANIPULATIVE TEST:
There were no changes related to the test substance in any groups at the dosing and recovery per iods.
2) GRIP STRENGTH TEST:
There were no changes related to the test substance in any groups at the dosing and recovery periods .
3) LOCOMOTOR ACTIVITY MEASUREMENT:
[At the dosing period]: A decrease in locomotor activity was observed in non-mating females at 100 mg/kg bw/day.
[At the recovery period]: There were no changes related to the test substance in any groups.

ORGAN WEIGHTS:
[At the end of dosing period]:
An increase in relative liver weight was observed in males at 50 mg/kg bw/day. Increases in absolute and relative liver weights were observed in males and non-mating females at 100 mg/kg bw/day and in mating-females at 50 mg/kg bw/day. An increase in spleen weight was observed in non-mating females at 100 mg/kg bw/day
[At the end of recovery period]: An increase in spleen weight was observed in non-mating females at 100 mg/kg bw/day

GROSS PATHOLOGY:
[At the end of dosing period]:
Enlargement of liver was observed in males at 50 mg/kg bw/day and above. Enlargement of kidney was observed in males at 100 mg/kg bw/day.
[At the end of recovery period]:
There were no changes related to the test substance in any groups.

HISTOPATHOLOGY: NON-NEOPLASTIC:
[At the end of dosing period]:
Kidney: Basophilic tuble, hyalin cast in cortex/medulla were observed in males at 100 mg/kg bw/day. Basophilic tuble in cortex were observed in non-mating females at 100 mg/kg bw/day.
[At the end of recovery period]:
Kidney: Basophilic tuble in cortex were observed in non-mating females at 100 mg/kg bw/day.

Effect levels

Key result
false

Dose descriptor
NOAEL

Effect level

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

Based on
test mat.

Sex
male/female

Basis for effect level
clinical signs
Salivation, soiled perineal region, emaciation, hypothermia, piloerection, pale skin were observed in males and females at 50 mg/kg bw/day and above.
gross pathology
Enlargement of liver was observed in males at 50 mg/kg bw/day and above.
haematology
A decrease in mean corpuscular hemoglobin concentration (MCHC), an increase in reticulocyte (%) were observed in mating-females at 50 mg/kg bw/day.
mortality
In the 50 mg/kg bw/day group, maternal death or moribund death occurred in 1 animal each on the day of parturition.
organ weights and organ / body weight ratios
An increase in relative liver weight was observed in males at 50 mg/kg bw/day. Increases in absolute and relative liver weights were observed in males and non-mating females at 100 mg/kg bw/day and in mating-females at 50 mg/kg bw/day.

Any other information on results incl. tables

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

https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF120-95-6d.pdf

Applicant's summary and conclusion

Conclusions
The NOAEL for repeated dose toxicity in this study was determined to be 10 mg/kg bw/day both for males and females.

Executive summary

In the combined repeated dose and reproductive/developmental screening test (OECD TG422), SD rats were treated orally with 2,4-di-tert-pentylphenol at the doses of 0, 10, 50 and 100 (250) mg/kg bw/day. After the start of treatment, the dose was changed from 250 mg/kg bw/day to 100 mg/kg bw/day after day 12 of treatment because about half of the animals in the high dose group died or were moribund. No fertility study was performed in this group.

The following findings were observed in the examination during the administration period or at the end of administration period. In the 100 (250) mg/kg bw/day group, died or moribund animals were observed in 9 of 13 males from day 6 to day 13 of the administration and in 12 of 23 females from day 6 to day 9 of the administration. In the 50 mg/kg bw/day group, maternal death or moribund death occurred in 1 animal each on the day of parturition. In the clinical signs, salivation, soiled perineal region, emaciation, hypothermia, piloerection, pale skin were observed in males and females at 50 mg/kg bw/day and above. Loose stool, a decrease in amount of feces, a decrease in locomotor activity, mucous feces, lacrimation, reddish tear, smudge of perinasal area, reddish urine, moribundity were observed in males and females, and blackish feces, no-feces, loss of locomotor activity, bradypnea, lateral position

were observed in males at 100 (250) mg/kg bw/day. In the locomotor activity measurement, a decrease in locomotor activity was observed in non-mating females at 100 mg/kg bw/day. In the urinalysis, an increase tendency in urine volume was observed in males and an increase in urine volume was observed in females at 100 mg/kg bw/day. In the hematology, decreases in hemoglobin and hematocrit, an increase tendency in RBC, an increase in prothrombin time, and an increase tendency in activated partial thromboplastin time were observed in males at 100 mg/kg bw/day. Decreases in RBC, hemoglobin and hematocrit were observed in non -mating females at 100 mg/kg bw/day. A decrease in mean corpuscular hemoglobin concentration (MCHC), increase in reticulocyte (%) were observed in mating-females at 50 mg/kg bw/day. In the clinical chemistry, increase tendency in ALP was observed in males at 100 mg/kg bw/day. In the organ weights, an increase in relative liver weight was observed in males at 50 mg/kg bw/day. Increases in absolute and relative liver weights were observed in males and non-mating females at 100 mg/kg bw/day and in mating-females at 50 mg/kg bw/day. Increased spleen weight was observed in non-mating females at 100 mg/kg bw/day. In the gross pathology, enlargement of liver was observed in males at 50 mg/kg bw/day and above. In the histopathology, basophilic tuble, hyalin cast in cortex/medulla of kidney were observed in males at 100 mg/kg bw/day and basophilic tuble in cortex of kidney were observed in non-mating females at 100 mg/kg bw/day. Based on the above results, NOAEL for the repeated dose toxicity of 2,4-di-tert-pentylphenol was determined to be 10 mg/kg bw/day for both males and female rats.

Genetic toxicity in vitro

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.001

UUID:	00b89fa3-84f9-4dad-a3b7-49a2272d3b64
Dossier UUID:	
Author:	
Date:	2022-03-25T10:19:38.000+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
other: OECD Test Guideline study under GLP condition

Data source

Reference

Reverse Mutation Test of Phenol, 2,4-bis (1,1-dimethylpropyl) 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
JAPAN: Guidelines for Screening Mutagenicity Testing Of Chemicals
genetic toxicity in vitro, other

Deviations
not specified

GLP compliance
yes

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

Test material

Test material information
2,4-Di-tert-pentylphenol

Specific details on test material used for the study
- Name of test material (as cited in study report): Phenol, 2,4-bis (1,1-dimethylpropyl)
- Analytical purity: 99.7%

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

Justification for deviation from the high dose level
-S9 mix:
19.5, 39.1, 78.1, 156, 313, 625 µg/plate (TA100, TA98 strains)
4.88, 9.77, 19.5, 39.1, 78.1, 156 µg/plate (TA1535, WP2uvrA strains)
0.610, 1.22, 2.44, 4.88, 9.77, 19.5 µg/plate (TA1537 strain)
+S9 mix:
39.1, 78.1, 156, 313, 625, 1250, 2500 µg/plate (TA100, TA1535 strains)
156, 313, 625, 1250, 2500, 5000 µg/plate (WP2uvrA, TA98 strains)
19.5, 39.1, 78.1, 156, 313, 625 µg/plate (TA1537 strain)

Maximum concentration was established based on the result of the preliminary test at concentration up to 5000 ug/plate. In this test, the growth inhibition was observed at 500 µg/plate and above for S. typhimurium TA 100 and TA98, at 150 µg/plate and above for S. typhimurium TA1535 and E. coli WP2uvrA, at 15.0 µg/plate and above for S. typhimurium TA1537 strain without S9 mix and at 1500 µg/plate and above for S. typhimurium TA 100 and TA1535, at 5000 µg/plate for S. typhimurium TA98 and E. coli WP2uvrA, at 500 µg/plate and above for S. typhimurium TA 1537 with 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
other: -S9 mix: 2-(2-Furyl)-3-(5-nitro-2-furyl) acrylamide (AF-2), Sodium azide (SAZ) and 9-Amino acridine (9 AA)
+S9 mix, 2-Aminoanthracene (2AA) and Benzo[a]pyrene (B[a]P)

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

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

Statistics
no

Results and discussion

Test results

Key result
true

Species / strain
S. typhimurium TA 1535
bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
cytotoxicity -S9 mix: 78.1 µg/plate and above, +S9 mix: 2500 µg/plate

Vehicle controls validity
valid

Positive controls validity
valid

Key result
true

Species / strain
S. typhimurium TA 1537
bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
cytotoxicity -S9 mix: 9.77 µg/plate and above, +S9 mix: 625 µg/plate

Vehicle controls validity
valid

Positive controls validity
valid

Key result
true

Species / strain
S. typhimurium TA 98
bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
cytotoxicity -S9 mix: 625 µg/plate, +S9 mix: 5000 µg/plate

Vehicle controls validity
valid

Positive controls validity
valid

Key result
true

Species / strain
S. typhimurium TA 100
bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
cytotoxicity -S9 mix: 313 µg/plate and above, +S9 mix: 2500 µg/plate

Vehicle controls validity
valid

Positive controls validity
valid

Key result
true

Species / strain
E. coli WP2 uvr A
bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
cytotoxicity -S9 mix: 156 µg/plate, +S9 mix: 5000 µg/plate

Vehicle controls validity
valid

Positive controls validity
valid

Any other information on results incl. tables

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

https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF120-95-6e.pdf

Please also see the attached files (Tables in English)

Applicant's summary and conclusion

Conclusions
Interpretation of results (migrated information): negative

In a bacterial reverse mutation assay using Salmonella typhimurium TA100, TA1535, TA98, and TA 1537, and Escherichia coli WP2uvrA, phenol, 2,4-bis (1,1-dimethylpropyl) was negative with or without metabolic activation.

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.002

UUID:	d818e117-30a7-4c59-ac6f-e7fc8a0b6e4b
Dossier UUID:	
Author:	
Date:	2023-01-10T14:34:00.000+09:00
Remarks:	

Administrative data

Endpoint
in vitro chromosome aberration study in mammalian cells

Type of information
experimental study

Adequacy of study
key study

Robust study summary
false

Used for classification
false

Used for SDS
false

Reliability
1 (reliable without restriction)

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

Data source

Reference

In Vitro Chromosomal Aberration Test of Phenol, 2,4-bis (1,1-dimethylpropyl) on 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
JAPAN: Guidelines for Screening Mutagenicity Testing Of Chemicals
genetic toxicity in vitro, other

Deviations
no

GLP compliance
yes

Type of assay
other: in vitro mammalian chromosome aberration test

Test material

Test material information
2,4-Di-tert-pentylphenol

Specific details on test material used for the study
- Name of test material (as cited in study report): Phenol, 2,4-bis (1,1-dimethylpropyl)
- Analytical purity: 99.7%

Method

Species / strain

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

Metabolic activation
with and without

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

Justification for deviation from the high dose level
Cell growth inhibition study
-S9 mix (short-term treatment): 0.0091, 0.018, 0.037, 0.073, 0.15, 0.29, 0.59, 1.2, 2.3 mg/mL
+S9 mix (short-term treatment): 0.0091, 0.018, 0.037, 0.073, 0.15, 0.29, 0.59, 1.2, 2.3 mg/mL
-S9 mix (continuous treatment, 24hr): 0.0091, 0.018, 0.037, 0.073, 0.15, 0.29, 0.59, 1.2, 2.3 mg/mL

Main study
-S9 (short-term treatment): 0.0031, 0.0063, 0.013, 0.025, 0.050, 0.10 mg/mL
+S9 (short-term treatment): 0.00094, 0.0019, 0.0038, 0.0075, 0.015, 0.030 mg/mL
-S9 (continuous treatment, 24hr): 0.0019, 0.0038, 0.0075, 0.015, 0.030, 0.060 mg/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
other: [-S9]: mitomycin C; [+S9]: cyclophosphamide

Details on test system and experimental conditions
METHOD OF APPLICATION:
Exposure duration:
- [short-term treatment]: 6 hr + 18 hr
- [continuous treatment]: 24 hr
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
The frequency of cells with structural chromosomal aberrations and polyploid cells was tested for si gnificance by Fisher's exact test (one-sided test, P = 2.5%) between the negative control and test s ubstance treated groups. If a significant difference was observed, a Chochran-Armitage trend tests (one-sided test, P = 2.5%) was performed for dose dependency. The results of these tests were used as a reference for a comprehensive evaluation, taking into account biological considerations.

Statistics
yes

Results and discussion

Test results

Key result
true

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

Metabolic activation
with and without

Genotoxicity
positive +S9 mix (short-term treatment): Significant increases in cells with structural chromosomal abnormalities and polyploid cells were observed in the high concentration group (frequencies: 12% and 4.8%, respectively).

Cytotoxicity / choice of top concentrations
cytotoxicity

Vehicle controls validity
valid

Positive controls validity
valid

Additional information on results
RANGE-FINDING/SCREENING STUDIES (if applicable):
50% cell growth inhibition (IC50): 0.015 mg/mL (short-term treatment, +S9 mix), 0.049 m g/mL (short-term treatment, -S9 mix), 0.029 mg/mL (continuous treatment)

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/PDF120-95-6f.pdf

Applicant's summary and conclusion

Conclusions
Interpretation of results (migrated information): Positive with metabolic activation

In an in vitro chromosomal aberration test using CHL/IU cells, phenol, 2,4-bis (1,1-dimethylpropyl) was positive with metabolic activation.

Toxicity to reproduction

ENDPOINT_STUDY_RECORD: ToxicityReproduction. 001

UUID:	c7b88315-6407-4869-b0f8-48f79ac4e1a3
Dossier UUID:	
Author:	
Date:	2022-03-25T11:51:46.000+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

Related information
OECD / Repeated dose toxicity: oral / RepeatedDoseToxicityOral. 001 / 2,4-Di-tert-pentylphenol / 120-95-6

Data source

Reference

Combined repeat dose and reproductive/developmental toxicity screening test of 2,4-di-tert-pentylphe / Ministry of Health, Labour and Welfare (MHLW), Japan / study report

Data access
data published https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF120-95-6d.pdf

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
2,4-Di-tert-pentylphenol

Specific details on test material used for the study
- Name of test material (as cited in study report): Phenol, 2,4-bis (1,1-dimethylpropyl)
- Analytical purity: 99.7%
- Storage condition of test material: Cold and dark place (3-6°C)
- 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., Atsugi Breeding Center.
- Age at study initiation: 10 weeks old
- Weight at study initiation: Male: 330.1-413.5 g), Female: 228.9-300.4 g
- Housing: Animals were individually housed in bracket-type metallic wire-mesh cages (220W × 270D × 190H mm), from gestation day 18 to lactation day 4, Dams were bred individually or with individual lit termates in plastic cages (350W x 400D x 180H mm) and bedding.

- Diet: Solid feed (CE-2: CLEA Japan Inc.) was given ad libitum.
- Water: Tap water was given ad libitum.
- Acclimation period: 18 days
ENVIRONMENTAL CONDITIONS
- Temperature (°C): 21.0-25.0 (actual temperature: 23.0-25.5°C)
- Humidity (%): 40.0-75.0% (actual humidity: 42.5-70.5%)
- Air changes (per hr): 15
- Photoperiod (hrs dark / hrs light): 12 hr dark/12 hr light (light: 7:00~19:00)

Administration / exposure

Route of administration
oral: gavage

Vehicle
corn oil

Details on 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
The concentrations of each test suspensions used in day1 of administration were analyzed by HPLC. Results showed that the concentrations of each test suspensions were 93.8 to 97.7% of the nominal concentration.

Duration of treatment / exposure
(P) Males: 42 days including 14 days pre-mating
(P)Females: 41-44 days including 14 days pre-mating, mating and gestation periods and the days until day 4 of lactation
Female (no mating, satellite group): 42 days

Frequency of treatment
Once/day, 7 days/week

Doses / concentrations

Dose / conc.	
0	mg/kg bw/day (actual dose received)
Dose / conc.	
10	mg/kg bw/day (actual dose received)
Dose / conc.	
50	mg/kg bw/day (actual dose received)
Dose / conc.	
100	mg/kg bw/day (actual dose received)

Remarks
At the start of administration: 250 mg/kg bw/day

No. of animals per sex per dose
Mating group: 13 animals/sex/dose (0, 10, 50, and 100 mg/kg bw/day)
Non-mating group: 10 females/dose (0 and 100 mg/kg bw/day)

Recovery group: 5 males/dose in the mating group (0 and 50 mg/kg bw/day) and 5 females/dose in the non-mating groups (0 and 100 mg/kg bw/day)

Control animals
yes, concurrent vehicle

Details on study design
- Dose selection rationale: Based on the results of a 14-day preliminary study, the highest dose of 250 mg/kg bw/day was selected as an expected obvious toxic dose, and the lowest dose of 10 mg/kg bw/day was selected as an expected no toxic dose. The middle dose levels of 50 mg/kg bw/day were selected.

[14-day preliminary study]
A 14-day repeated dose oral toxicity test (Crl:CD(SD) rats, doses: 0, 250, 500 or 1,000 mg/kg bw/day. At 500 mg/kg bw/day and above, all animals died or were moribund, and necropsy showed lesions i n the stomach, lung and kidney. At 250 mg/kg bew/day, soft stool, salivation, decrease in body weigh t, decreased body weight, pale spots on the kidneys, increased liver and kidney weights, decreases in RBC, Ht, Hb and total cholesterol, increases in triglyceride, γ-GTP, ALP, BUN, and LDH were observed.

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

Examinations

Parental animals: Observations and examinations

CAGE SIDE OBSERVATIONS: Yes
- Time schedule: 2 times/day (before administration, after administration) during the administration period. Once a day during the recovery period.
DETAILED CLINICAL OBSERVATIONS: Yes
- Time schedule:
Males in the main groups and females in the non-mating groups: the end of acclimation period, day 7, 14, 21, 28, 35, and 42 during the administration.
Females in the mating groups: the end of acclimation period, day 7, 14, 21, 28, 35, and 42 during the administration period, and once during lactation period (lactation day 0from day 4)
Males and females in the recovery groups: the end of acclimation period, day 7, 14, 21, 28, 35, and 42 during the administration period and day 7 and 14 during recovery period.

BODY WEIGHT: Yes
- Time schedule for examinations:
Males in the main groups and females in the non-mating groups: days 1, 7, 10, 12, 14, 17, 21, 24, 28, 3 1, 35, 38 and 42 of administration period and on the day of necropsy.
Males and females in the recovery groups: days1, 7, 10, 12, 14, 17, 21, 24, 28, 31, 35, 38 and 42 of administration period, and days 1, 7 and 14 of recovery period and on the day of necropsy.
Females in the mating groups: days 1, 7, 10, 12, 14 and 17 of administration period (uncopulated a nimals : day 26), days 0, 3, 7, 10, 14, 17 and 20 of gestation, days 0, 4 of lactation, and on the day of necropsy.

Food consumption: Yes
Measurement of food consumption was conducted on all animals at the following frequencies:
Males in the main groups and females in the non-mating groups: days 1-2, 7-8, 14-15, 29-30, 35-36 and 41-42 of administration period.
Males and females in the recovery groups: days 1-2, 7-8, 14-15, 29-30, 35-36 and 41-42 of admi nistration, period and days 6-7 and 12-13 of recovery period.
Females in the mating groups: days 1-2, 7-8 and 14-15 of administration period, days 0-1, 7-8, 14-15, and 20-21 of gestation period, days 3-4 of lactation period.

OPHTHALMOSCOPIC EXAMINATION: No
HAEMATOLOGY: Yes

- Time schedule for collection of blood: At the end of administration period, or at the end of recovery p eriod in both sexes
- Anaesthetic used for blood collection: Pentbarbital sodium
- Animals fasted: Yes
- How many animals:
5 animals/sex/group
- Parameters examined: red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, me an 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.

CLINICAL CHEMISTRY: Yes
- Time schedule for collection of blood: At the end of administration period, or at the end of recovery period in both sexes
- Animals fasted: Yes
- How many animals:
5 animals/sex/group
- Parameters checked: ALP, total cholesterol, triglyceride, phospholipids, total bilirubin, glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, calcium, inorganic phosphorus, total protein, albumin, A/G ratio, AST, ALT, LDH, γ-GTP, bile acid.

URINALYSIS OF MALES: Yes
- Time schedule for collection of urine: final week of administration (days 37 of administration) and in the final week of recovery (days 13 of recovery)
- Metabolism cages used for collection of urine: Yes
A urine collector to collect four-hour urine samples under fasting but ad libitum drinking conditions, followed by collection of 20-hour urine samples under ad libitum feeding and drinking conditions.
- How many animals: 5 animals/group
- Parameters checked: pH, protein, ketones, glucose, occult blood, bilirubin, urobilinogen, color, sediment, osmotic pressure, sodium, potassium, chloride, urine volume (24-hour volume)
BLOOD HORMONE: No

NEUROBEHAVIOURAL EXAMINATION: Yes
- Time schedule for examinations:
Males in the main groups and females in the non-mating groups: final week of administration (Manipulative Test: day 42, Measurement of Grip Strength and Motor Activity: day 39 for males, day 41 for females)
Females in the mating groups: lactation day 5
Males and females in the recovery groups: final week of administration (Manipulative Test: day 42, Measurement of Grip Strength and Motor Activity: day 39 for males, day 41 for females) and in the final week of recovery (day 14 of recovery).
- Dose groups that were examined: All dose groups (5 animals/sex/group)
- Battery of functions tested:
1) Manipulative Test. Prayer's reaction, pupillary reflex, visual placing, startle reaction, withdrawal reflex, eyelid reflex, and righting reflex
2) Measurement of Grip Strength. Grip strength of forelimb and hind limb were measured by grip strength meter.
3) Measurement of Motor Activity. Motor activity was measured by a motor activity sensor for experimental animals SUPER-MEX (Muromachi Kikai. C0., Ltd.). The measurement was conducted for 20 min.

Oestrous cyclicity (parental animals)
Vaginal smears were collected from all females in the mating groups and microscopically examined every day from the day after the start of administration until the day copulation was confirmed.
During the pre-mating administration period, vaginal smear pictures were classified as proestrus, estrus, metestrus or diestrus and examined for the frequency of estrus and interval between estruses (estrous cycle). During the mating period, vaginal smears were examined for the presence of sperm.

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

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

Postmortem examinations (parental animals)
METHOD OF SACRIFICED: All animals were sacrificed by exsanguination under pentbarbital sodium anesthesia.
SACRIFICE: Males in main groups and females in non-mating groups: On next day after the last a dministration (Day 42), Maternal animals: on Day 4 of lactation, and Male and females recovery anima ls: on Day 14 of recovery.

ORGAN WEIGHT: Yes [brain, thyroids (including parathyroids), adrenal gland, thymus, spleen, heart, liv er, kidney, testis, epididymis, prostate, seminal vesicles, ovary, uterus]
HISTOPATHOLOGY: Yes, [brain, spinal cord, pituitary, eye ball (Harderian gland), submandibular gland, sublingual gland, trachea, thyroid, parathyroid, thymus, heart, lung (including bronchial), liver, kidney, spleen, pancreas, adrenal gland, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, submandibular lymph node, mesenteric lymph node, testis, epididymis, prostate, seminal vesicl es, ovary, uterus, vagina, bladder, femur (including bone marrows), skeletal muscle, sciatic nerve, mammary gland, and gross abnormalities site.

Postmortem examinations (offspring)
SACRIFICE
- The F1 offsprings were euthanized on PND4 by exsanguination under sevoflurane 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
Changes in estrous cyclicity and conception rate were analyzed by Fisher’s test. Graded pathological data was analyzed by Mann-Whitney’s U test (significance level = 0.05) and pathological data with n umber of positive and negative animals was analyzed by one-sided Fisher’s test. Other data, obtained values in each animal or mean of a litter was one data, and these data were compared among the satellite groups and other among the groups. These data were analyzed using F-test for homogen eity of distribution. The Student’s t-test and the Aspin-Welch’s t-test were conducted for homogenous and non-homogenous distribution, respectively to compare the control and individual treatment grou ps. Three or more groups setting, these data were analyzed using Bartlett’s test for homogeneity of distribution. The Dunnett’s multiple comparison test after the ANOVA and the Dunnett’s-type mean rank sum test after Kruskal-Wallis’s H test were conducted for homogenous and non-homogenous distribution, respectively to compare the control and individual treatment groups. Significance level was set at 0.05 compared with the control group and among the groups.

Reproductive indices
Each parameter was determined by the following equations:
Copulation index (%) = (No. of copulated pares / No. of mated pares) × 100
Fertility index (%) = (No. of fertile males / No. of copulated pares) × 100
Delivery index (dams, %) = (No. of dams with live offspring / No. of pregnant dams) × 100
Implantation index (%) = (No. of implantation scars / No. of corpora lutea) × 100
Sex ratio = No. of male offspring / (No. of male offspring + No. of female offspring)
Delivery index (offspring) = (No. of offspring at birth/ No. of implantation scars) × 100
Birth index = (No. of live offspring at birth/No. of implantation scars) × 100

Live birth index = (No. of live offspring at birth/No. of offspring at birth) × 100

Offspring viability indices
Viability index = (No. of live offspring 4days after birth / No. of live offspring at birth) × 100

Results and discussion

Results: P0 (first parental generation)

General toxicity (P0)

Clinical signs
effects observed, treatment-related

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

Mortality
mortality observed, treatment-related

Description (incidence)
See 7.5.1 Repeated dose toxicity.001

Body weight and weight changes
effects observed, treatment-related

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

Food consumption and compound intake (if feeding study)
effects observed, treatment-related

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

Food efficiency
not examined

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

Ophthalmological findings
not examined

Haematological findings
effects observed, treatment-related

Description (incidence and severity)
See 7.5.1 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
effects observed, treatment-related

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

Behaviour (functional findings)
effects observed, treatment-related

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

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
effects observed, treatment-related

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

Neuropathological findings
not examined

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

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

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: no effects observed

Effect levels (P0)

Key result
false

Dose descriptor
NOAEL

Effect level

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

Based on
test mat.

Sex
male/female

Basis for effect level
clinical signs
Salivation, soiled perineal region, emaciation, hypothermia, piloerection, pale skin were observed in males and females at 50 mg/kg bw/day and above.
mortality
In the 50 mg/kg bw/day group, maternal death or moribund death occurred in 1 animal each on the day of parturition.
haematology
A decrease in mean corpuscular hemoglobin concentration (MCHC), an increase in reticulocyte (%) were observed in mating-females at 50 mg/kg bw/day.
organ weights and organ / body weight ratios
An increase in relative liver weight was observed in males at 50 mg/kg bw/day. Increases in absolute and relative liver weights were observed in males and non-mating females at 100 mg/kg bw/day and in mating-females at 50 mg/kg bw/day.
gross pathology
Enlargement of liver was observed in males at 50 mg/kg bw/day and above.

Key result
false

Dose descriptor
NOAEL

Effect level

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

Based on
test mat.

Sex
male/female

Basis for effect level
reproductive performance
No reproductive effects were observed in both males and females up to 50 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)

No effects observed.

Effect levels (F1)

Key result
false

Dose descriptor
NOAEL

Generation
F1

Effect level

50 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 50 mg/kg bw/day.

Overall reproductive toxicity

Key result
false

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/PDF120-95-6d.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 50 mg/kg bw/day. The NOAEL for the rat reproductive/developmental toxicity of 2,4-di-tert-pentylphenol was regarded as 50 mg/kg bw/day, the highest dose tested.

DOMAIN

SUBSTANCE: 2,4-Di-tert-pentylphenol

UUID:	75638419-5081-47af-a448-15d10d68a280
Dossier UUID:	
Author:	
Date:	2023-09-05T13:10:50.154+09:00
Remarks:	

Substance name
2,4-Di-tert-pentylphenol

Legal entity
National Institute of Health Sciences / Kawasaki / Japan

Identification of substance

Reference substance
2,4-Di-tert-amylphenol / 120-95-6

EC number	EC name
CAS number	**CAS name**
120-95-6	
IUPAC name	

Role in the supply chain

Manufacturer
false

Importer
false

Only representative
false

Downstream user
false

References

Reference Substances

REFERENCE_SUBSTANCE: 2,4-Di-tert-amylphenol

UUID: 6c2e6826-0a81-4119-b2a4-3af2da131516
Dossier UUID:
Author:
Date: 2021-10-29T14:20:21.000+09:00
Remarks:

Reference substance name
2,4-Di-tert-amylphenol

Inventory

CAS number
120-95-6

Molecular and structural information

Molecular weight

234.38

Test Materials

TEST_MATERIAL_INFORMATION: 2,4-Di-tert-pentylphenol

UUID: e27c5e05-4e22-475d-b4ec-ac7dc5708bf2
Dossier UUID:
Author:
Date: 2021-10-29T14:32:39.000+09:00
Remarks:

Name
2,4-Di-tert-pentylphenol

Composition

Composition

Reference substance
2,4-Di-tert-amylphenol / 120-95-6

EC number	EC name
CAS number	CAS name
120-95-6	
IUPAC name	

Other characteristics

Test material form
solid: crystalline

Literatures

LITERATURE: Combined repeat dose and reproductive/ developmental toxicity screening test of 2,4-di-tert-pentylphenol by oral administration in rats

UUID: ab7756b4-037b-4784-b5cd-379d3d2326a7
Dossier UUID:
Author:
Date: 2021-11-01T14:51:20.000+09:00
Remarks:

General information

Reference Type
study report

Title
Combined repeat dose and reproductive/developmental toxicity screening test of 2,4-di-tert-pentylphenol by oral administration in rats

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

Year
2013

Bibliographic source
available in the web of Japan Existing Chemical Data Base (JECDB) at https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF120-95-6d.pdf

Testing facility
Food and drug safety center

Report number
R-11-003

LITERATURE: In Vitro Chromosomal Aberration Test of Phenol, 2,4-bis (1,1-dimethylpropyl) on Cultured Chinese Hamster Cells.

UUID: 56577b83-5a18-456d-a9fa-6d79becbe16f
Dossier UUID:
Author:
Date: 2022-03-03T17:30:33.000+09:00
Remarks:

General information

Reference Type
study report

Title
In Vitro Chromosomal Aberration Test of Phenol, 2,4-bis (1,1-dimethylpropyl) on Cultured Chinese Hamster Cells.

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

Year
2012

Bibliographic source
Japan Existing Chemical Data Base (JECDB) https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF120-95-6f.pdf

Testing facility
the Hatano Research Institute, Food and Drug Safety Center

Report date
2012-03-15

Report number
G-11-031

LITERATURE: Reverse Mutation Test of Phenol, 2,4-bis (1,1-dimethylpropyl) on Bacteria.

UUID: 76cf0669-ff0a-487e-a31c-90ee8a106701
Dossier UUID:
Author:
Date: 2022-03-08T10:55:52.000+09:00
Remarks:

General information

Reference Type
study report

Title
Reverse Mutation Test of Phenol, 2,4-bis (1,1-dimethylpropyl) on Bacteria.

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

Year
2012

Bibliographic source
Japan Existing Chemical Data Base (JECDB) https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF120-95-6e.pdf

Testing facility
the Hatano Research Institute, Food and Drug Safety Center

Report date
2012-03-09

Report number
M-11-042