



---

**Name:** OECD\_SIDS / SUBSTANCE : 4-chloro-m-cresol / 59-50-7 Fri, 16 Dec 2022, 14:54:39+0900 /

---

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

---

**Printing date:** 2022-12-16T14:54:39.884+09:00

---

## Table of Contents

0/0 .....	1
National Institute of Health Science .....	2
4-chloro-m-cresol .....	3
1 General information .....	3
1.1 Identification .....	3
Identification .....	3
Identification .....	3
1.10 Assessment approach (assessment entities) .....	5
Assessment approach (assessment entities) .....	5
7 Toxicological information .....	6
7.5 Repeated dose toxicity .....	6
7.5.1 Repeated dose toxicity: oral .....	6
Repeated dose toxicity: oral.001 .....	6
Repeated dose toxicity: oral.002 .....	15
7.6 Genetic toxicity .....	22
7.6.1 Genetic toxicity in vitro .....	22
Genetic toxicity in vitro.001 .....	22
Genetic toxicity in vitro.002 .....	28
7.8 Toxicity to reproduction .....	32
7.8.1 Toxicity to reproduction .....	32
Toxicity to reproduction.001 .....	32
References .....	40
Reference Substances .....	40
4-chloro-m-cresol .....	40
Test Materials .....	41
4-Chloro-m-cresol .....	41
Literatures .....	42
A reproduction/developmental toxicity screening test in rats treated orally with 4-chloro-m-cresol .....	42
In Vitro Chromosomal Aberration Test of 4-chloro-m-cresol on Cultured Chinese Hamster Cells .....	43
Reverse Mutation Test of 4-chloro-m-cresol on Bacteria .....	44
Twenty-eight-day Repeat Dose Oral Toxicity Test of 4-chloro-m-cresol in Rats .....	45
Legal Entities .....	46
National Institute of Health Sciences .....	46

---

# DOSSIER:

---

**UUID:** 0

**Dossier UUID:**

**Author:**

**Date:** 2022-12-16T14:54:39.723+09:00

**Remarks:**

---

## Dossier header

---

## Dossier submission type

---

**Name**

OECD SIDS

**Version**

core 7.0

**Name (given by user)**

## Dossier subject

---

**Dossier subject**

[4-chloro-m-cresol / 59-50-7](#)

**Public name**

**Submitting legal entity**

[National Institute of Health Science](#)

**Dossier creation date/time**

Fri, 16 Dec 2022, 14:54:39+0900

**Used in category**

---

# LEGAL\_ENTITY: National Institute of Health Science

---

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

**Dossier UUID:**

**Author:**

**Date:** 2022-11-07T16:24:02.822+09:00

**Remarks:**

---

## General information

---

**Legal entity name**

National Institute of Health Science

---

# 4-chloro-m-cresol

## General information

### Identification

#### Identification

SUBSTANCE: 4-chloro-m-cresol

---

**UUID:** 053ede1d-07b6-42db-ba58-88a6a246d151

**Dossier UUID:**

**Author:**

**Date:** 2022-12-16T14:54:29.214+09:00

**Remarks:**

---

#### Substance name

4-chloro-m-cresol

#### Other substance identifiers

<b>Identifier</b>
-------------------

CAS number
------------

<b>Identity</b>
-----------------

59-50-7
---------

#### Legal entity

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

#### Contact persons

## Identification of substance

---

#### Reference substance

[4-chloro-m-cresol / 59-50-7](#)

**EC number**

**EC name**

**CAS number**

**CAS name**

59-50-7

**IUPAC name**

## Role in the supply chain

---

#### Manufacturer

false

#### Importer

false

#### Only representative

false

---

**Downstream user**  
false

---

## Assessment approach (assessment entities)

### FIXED\_RECORD: Assessment approach

---

**UUID:** 267e5bbd-91b8-3191-b372-29ce0931a40d

**Dossier UUID:**

**Author:**

**Date:** 2019-09-03T09:59:28.000+09:00

**Remarks:**

---

---

# Toxicological information

## Repeated dose toxicity

Repeated dose toxicity: oral

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

---

UUID: 71fc6c21-ce5b-44d5-acd3-ac5a76818149

Dossier UUID:

Author:

Date: 2022-12-16T14:53:11.980+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

true

### Used for classification

true

### Used for SDS

false

### Study period

28 days

### Reliability

1 (reliable without restriction)

### Rationale for reliability incl. deficiencies

guideline study

Reliability 1

## Data source

---

### Reference

[Twenty-eight-day Repeat Dose Oral Toxicity Test of 4-chloro-m-cresol in Rats / Ministry of Health, Labor and Welfare, Japan / study report](#)

### Data access

data published

## Materials and methods

---

---

## Test guideline

**Qualifier**

according to guideline

**Guideline**

other: Guideline for 28-Day Repeated Dose Toxicity Test in Mammalian Species (Chemical Substances Control Law of Japan)

**Qualifier**

equivalent or similar to guideline

**Guideline**

OECD Guideline 407 (Repeated Dose 28-Day Oral Toxicity Study in Rodents)

**GLP compliance**

yes

**Limit test**

no

---

## Test material

**Test material information**

[4-Chloro-m-cresol](#)

**Specific details on test material used for the study**

- Name of test material (as cited in study report): 4-chloro-m-cresol
- Purity: 99.9%
- Storage condition of test material: at a cold (temperature 2-6°C) and dark place, with airtight stopper.
- Stability under test conditions: stable
- Solubility and stability of the test substance in the solvent/vehicle: stable

---

## Test animals

**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 Laboratories Japan Inc., Atsugi Breeding Center.
- Age at study initiation: 5 weeks old
- Weight at study initiation: male 160g (145-171g), female 142g (130-153g)
- Housing: Animals were individually housed in stainless wire-meshed cages (260W × 380D × 180H mm).
- Diet: Solid feed (MR stock: Nosan Corporation) was given ad libitum.
- Water: irradiated tap water, ad libitum.
- Acclimation period: 7-8 days

**ENVIRONMENTAL CONDITIONS**

- Temperature (°C): 22±3°C (actual temperature: 21.5-22.1°C)

- 
- Humidity (%): 55±10% (actual humidity: 53-60%)
  - Air changes (per hr): more than ten times per hr
  - Photoperiod (hrs dark / hrs light): 12 hrs dark / 12 hrs light (light: 7:00-19:00)

## Administration / exposure

---

### Route of administration

oral: gavage

### Vehicle

olive oil

### Details on oral exposure

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

### Analytical verification of doses or concentrations

yes

### Duration of treatment / exposure

28 days

### 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>	
15	mg/kg bw/day (actual dose received)
<b>Dose / conc.</b>	
60	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

Control and high-dose group: 10 animals/sex/ (including recovery group of 5 animals/sex/each group)

---

Low- and middle-dose group: 5 animals/sex/dose

### **Control animals**

yes, concurrent vehicle

### **Details on study design**

- Dose selection rationale: Based on the results of a 14-day preliminary study, the highest dose of 1000 mg/kg bw/day was selected as an expected obvious toxic dose, and the lowest dose of 15 mg/kg bw/day was selected as an expected no toxic dose. The middle dose levels of 60 and 250mg/kg bw/day were selected.
- Rationale for animal assignment (if not random): Body weight-balanced randomization
- Rationale for selecting satellite groups: Reversibility of toxic effects by treatment was examined in recovery test with control- and high-dose groups for both sexes.
- Post-exposure recovery period in satellite groups: 14 days

[14-day preliminary study]

A 14-day repeated dose oral toxicity test (CrI:CD(SD) rats, doses: 0 (olive oil), 50, 150, 100, 500 or 1000 mg/kg bw/day). At 500 mg/kg bw/day or more or 1000 mg/kg bw/day, tremor, decrease in locomotor activity, prone position and salivation, depression body weight gain, tendency of low food consumption, decrease in platelet, total bilirubin, cholinesterase and urine protein, increase in total cholesterol and potassium were observed. At 1000 mg/kg bw/day, increase in relative brain weight, decrease in absolute spleen weight, and slight thickening of forestomach were observed.

## **Examinations**

---

### **Observations and examinations performed and frequency**

CAGE SIDE OBSERVATIONS: Yes

- Time schedule: every day during the administration (4 times a day) and recovery periods (at least once a day)

DETAILED CLINICAL OBSERVATIONS: Yes

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

BODY WEIGHT: Yes

- Time schedule for examinations: Before administration (on days 1, 7, 14, 21 and 28 of the administration period, days 7 and 14 of the recovery period) and the necropsy days after completion of every period.

FOOD CONSUMPTION AND COMPOUND INTAKE (if feeding study):

- Food consumption: Yes. Once a week for 24-h (males: on days 5, 12, 19 and 26 of the administration period and days 5 and 12 of the recovery period.  
females: on days 4, 11, 18 and 25 of the administration period and days 4 and 11 of the recovery period)

OPHTHALMOSCOPIC EXAMINATION: No

HAEMATOLOGY: Yes

- Time schedule for collection of blood: the day after completion of the administration and recovery periods
- Anaesthetic used for blood collection: ether
- Animals fasted: Yes(overnight)
- How many animals: all animals
- Parameters examined included RBC, hemoglobin, hematocrit, MCV, MCH, MCHC, platelet, reticulocyte, PT, APTT, WBC and differential WBC.

CLINICAL CHEMISTRY: Yes

- Time schedule for collection of blood: the day after completion of the administration and recovery periods

- 
- Animals fasted: Yes(overnight)
  - How many animals: all animals
  - Parameters examined included total protein, albumin, A/G ratio, total bilirubin, glucose, total cholesterol, triglyceride, phospholipid, AST, ALT, LDH, ALP, gamma-GTP, BUN, creatinine, Na, K, Cl, Ca and IP.

#### URINALYSIS: Yes

- Time schedule for collection of urine: On weeks 4 of the administration period and weeks 2 of the recovery period.
- Metabolism cages used for collection of urine: Yes
- How many animals: All animals
- Parameters examined included color, cloudy, urine volume, specific gravity, Na, K, pH, protein, glucose, ketone body, bilirubin, occult blood and urobilinogen.

#### NEUROBEHAVIOURAL EXAMINATION: Yes

- Time schedule for examinations: Sensory motor reflexes, forelimb and hindlimb grip strengths, and motor activity were measured on week 4 of administration period (main/recovery group animals) and week 2 of recovery period (recovery group animals).
- Dose groups that were examined: All animals
- Battery of functions tested: sensory activity (hearing reaction, eye sight reaction, sense of touch reaction, pain reaction, pupil reflex, righting reflex), grip strength, motor activity

#### **Sacrifice and pathology**

GROSS PATHOLOGY: Yes

ORGAN WEIGHT: Yes [brain, pituitary gland, thyroid, adrenal, spleen, heart, liver, kidney, thymus, testis, epididymis, ovary]

HISTOPATHOLOGY: Yes [brain (cerebrum, cerebellum and medulla oblongata), pituitary gland, spinal cord (cervical, thoracic, lumbar), thymus, thyroid (including parathyroid), adrenal glands, spleen, heart, stomach, liver, duodenum, jejunum, ileum (including Peyer's patches), cecum, colon, rectal, mesenteric lymph nodes, submandibular lymph nodes, trachea, lung, kidney, bladder, testis, epididymis, prostate, seminal vesicles, ovary, uterus, vagina, eye, bone marrow (femur) and the sciatic nerve. (see tables in the study report.)]

#### **Statistics**

As for parametric data (grip strength, locomotor activity, body weight, body weight gain, food consumption, hematology and clinical chemistry data, organ weights, quantitative urinalysis data), the values of means and standard deviations were calculated per group. When more than three groups exist in the test group, Bartlett test for variance was done, and if the variance was homogenous, ANOVA was applied. If the variance was not homogenous or data was non-parametric (differential WBC percentage, qualitative urinalysis data), Kruskal-Wallis rank sum test was used. Consequently, if the result was significant, Dunnett multiple comparison or Dunnett typed method was used for detection of statistical significance against control group. When the number of the test group was two, F-test was used as for parametric data.

Then, student's t-test or Aspin-Welch's t-test was applied depending on the result of homogeneity of variance. While, as for non-parametric data, Man-Whitney's U-test was applied. Furthermore, as for categorized data (incidence of abnormal findings in clinical observation, detailed observation, sensory functional examination, necropsy and histopathology), Fischer's exact test was used. In any tests, level of significance was set at 5%.

---

## **Results and discussion**

### **Results of examinations**

#### **Clinical signs**

effects observed, treatment-related

---

**Description (incidence and severity)**

[treatment-related effect]:

Tremor, decrease in locomotor activity, ptosis, prone/side position, soiled perineal region and salivation were observed in one dead female at 1000 mg/kg bw/day.

Tremor, decrease in locomotor activity, ptosis, prone position were observed in all males and females at 1000 mg/kg bw/day.

Soiled perineal region was observed in all females at 1000 mg/kg bw/day.

Transient prone position in three males and decreased locomotor activity in two males were observed at 250 mg/kg bw/day.

[non-treatment-related effect]:

Transient salivation was observed in all males and females at 250 mg/kg bw/day or more. This finding was thought to be due to the irritancy of the test substance.

**Mortality**

mortality observed, treatment-related

**Description (incidence)**

One female animal died in the 1000 mg/kg bw/day.

**Body weight and weight changes**

effects observed, treatment-related

**Description (incidence and severity)**

Decreased body weight and depression of body weight gains were observed in the males at 1000 mg/kg bw.

**Food consumption and compound intake (if feeding study)**

effects observed, treatment-related

**Description (incidence and severity)**

Significant decrease in food consumption were observed in the males at 1000 mg/kg bw/day.

**Food efficiency**

not examined

**Water consumption and compound intake (if drinking water study)**

not examined

**Ophthalmological findings**

not examined

**Haematological findings**

effects observed, non-treatment-related

**Description (incidence and severity)**

Significant decrease in monocyte ratio in differentiation of leukocyte were observed in the females at 1000 mg/kg bw/day. These variations were within ranges of historical control data. Therefore, these changes were considered to be incidental and not to be related to treatment of the test substance.

Significant lower hematocrit and significant higher reticulocytes were observed in the males, significant higher RBC were observed in the females at 1000 mg/kg bw/day. These variations were within ranges of historical control data. Therefore, these changes were considered to be incidental and not to be related to treatment of the test substance.

**Clinical biochemistry findings**

effects observed, treatment-related

**Description (incidence and severity)**

[treatment-related effect]:

---

Significant increase in ALT levels were observed in the females at 1000 mg/kg bw.

[non-treatment-related effect]:

Significant lower total bilirubin were observed in the males at 1000 mg/kg bw/day. These variations were within ranges of historical control data. Therefore, these changes were considered to be incidental and not to be related to treatment of the test substance.

Significant higher total bilirubin were observed in the females at 1000 mg/kg bw/day. These variations were within ranges of historical control data. In addition, there were no other related changes. Therefore, these changes were considered to be incidental and not to be related to treatment of the test substance.

#### **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 the dosing period, an increase in relative liver weight was observed in males and females at 1000 mg/kg bw/day.

#### **Gross pathological findings**

effects observed, treatment-related

#### **Description (incidence and severity)**

[treatment-related effect]:

At the end of the dosing period, slight thickening of forestomach mucosa was observed in all males at 1000 mg/kg bw/day.

[non-treatment-related effect]:

At the end of the recovery period, small testis (right side) was observed in one male at 1000 mg/kg bw/day. However, it was only one case, and it was known as a spontaneous lesion of rat. Therefore, this change was considered to be incidental and not to be related to treatment of the test substance.

#### **Neuropathological findings**

not examined

#### **Histopathological findings: non-neoplastic**

effects observed, treatment-related

#### **Description (incidence and severity)**

[treatment-related effect]:

Liver: Slight hypertrophy of centrilobular hepatocyte was observed in two male and three females at 1000 mg/kg bw/day.

Forestomach: Slight hyperplasia of squamous was observed in one male and two females at 250 mg/kg bw/day. Moderate hyperplasia of squamous was observed in all males at 1000 mg/kg bw/day.

Slight and Moderate hyperplasia of squamous was observed in females at 1000 mg/kg bw/day.

In one dead female at 1000 mg/kg bw/day, there were severe hyperplasia of squamous in forestomach, slight congestive edema and inflammation in lung, slight hemorrhage in thymus and slight atrophy in spleen.

[non-treatment-related effect]:

Hematoidin crystal of lung, myocardial degeneration/fibrosis of heart were observed in males at 1000 mg/kg bw/day. Atrophy cortex of thymus was observed in females at 1000 mg/kg bw/day.

---

However, these findings were only for each group, and these were known as a spontaneous lesion of rat. Therefore, these changes were considered to be incidental and not to be related to treatment of the test substance.

Atrophy seminiferous tubule of testis (unilateral) was observed in one male at 1000 mg/kg bw/day. However, it was only one case, and it was known as a spontaneous lesion of rat. Therefore, this change was considered to be incidental and not to be related to treatment of the test substance.

**Histopathological findings: neoplastic**  
not examined

## Effect levels

---

**Key result**

false

**Dose descriptor**

NOAEL

**Effect level**

60

mg/kg bw/day (actual dose received)

**Based on**

test mat.

**Sex**

male/female

**Basis for effect level**

gross pathology

At the end of the dosing period, slight thickening of forestomach mucosa was observed in all males at 1000 mg/kg bw/day.

histopathology: non-neoplastic

Liver: Slight hypertrophy of centrilobular hepatocyte was observed in two male and three females at 1000 mg/kg bw/day. Forestomach: Slight hyperplasia of squamous was observed in one male and two females at 250 mg/kg bw/day. Moderate hyperplasia of squamous was observed in all males and females at 1000 mg/kg bw/day.

organ weights and organ / body weight ratios

At the end of the dosing period, an increase in relative liver weight was observed in males and females at 1000 mg/kg bw/day.

other: In one dead female at 1000 mg/kg bw/day, there were severe hyperplasia of squamous in forestomach, slight congestive edema and inflammation in lung, slight hemorrhage in thymus and slight atrophy in spleen.

## Any other information on results incl. tables

---

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

[http://dra4.nihs.go.jp/mhlw\\_data/home/pdf/PDF59-50-7b.pdf](http://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF59-50-7b.pdf)

## Applicant's summary and conclusion

---

**Executive summary**

---

A 28-day repeated-dose toxicity test was performed according to the Japanese guideline (similar to OECD TG 407). Male and female rats (5 animals/sex/dose) were administered 4-chloro-m-cresol at 0, 15, 60, 250, and 1,000 mg/kg bw/day. In addition, both sexes (5 animals/sex/dose) were administered 0 and 1,000 mg/kg bw/day of this substance for 28 days and examined after a 14-day recovery period.

At 1000 mg/kg bw/day, one female died during the administration period. Clinical observation revealed, decrease in locomotor activity and prone position were observed in males at 250 mg/kg bw/day, tremor, decrease in locomotor activity, prone/side position in both sexes at 1000 mg/kg bw/day. Soiled perineal region were also observed in females at 1000 mg/kg bw/day. Body weights, body weight gain and food consumption were decreased in males at 1000 mg/kg bw/day. Blood chemical examination revealed a high values for ALT activity in females at 1000 mg/kg bw/day. Relative liver weights were higher in males and females at 1000 mg/kg bw/day. Gross pathology revealed slight thickening of forestomach mucosa in males at 1000 mg/kg bw/day. Histopathological examination revealed hypertrophy of centrilobular hepatocyte in the liver in male and females at 1000 mg/kg bw/day, hyperplasia of squamous in the forestomach in both sexes at 250 mg/kg bw/day or more.

On the basis of these effects, NOAEL for repeated-dose toxicity was determined to be 60 mg/kg bw/day in male and female rats.

---

**ENDPOINT\_STUDY\_RECORD: Repeated dose toxicity: oral.002**

---

**UUID:** e6fae949-411a-4c4b-96ab-8f8ac06d87f2

**Dossier UUID:**

**Author:**

**Date:** 2022-12-16T14:54:22.207+09:00

**Remarks:**

---

## Administrative data

---

### Endpoint

repeated dose toxicity: oral, other screening for reproductive / developmental toxicity

### Type of information

experimental study

### Adequacy of study

key study

### Robust study summary

false

### Used for classification

false

### Used for SDS

false

### Reliability

1 (reliable without restriction)

### Rationale for reliability incl. deficiencies

guideline study

Reliability 1

### Cross-reference

#### Reason / purpose for cross-reference

reference to same study

#### Related information

[OECD / Toxicity to reproduction / Toxicity to reproduction.001 / 4-chloro-m-cresol / 59-50-7](#)

## Data source

---

### Reference

[A reproduction/developmental toxicity screening test in rats treated orally with 4-chloro-m-cresol / Ministry of Health, Labor and Welfare, Japan / study report](#)

### Data access

data published

## Materials and methods

---

---

## Test guideline

**Qualifier**

according to guideline

**Guideline**

other: OECD Guideline 421 (Reproduction / Developmental Toxicity Screening Test)

**Deviations**

no

**GLP compliance**

yes

**Limit test**

no

---

## Test material

**Test material information**

[4-Chloro-m-cresol](#)

**Specific details on test material used for the study**

- Name of test material (as cited in study report): 4-Chloro-m-cresol
- Analytical purity: 99.9%
- Storage condition of test material: at a cold (temperature 1-8 °C) and dark place, with airtight stopper.
- 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: CrI: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: 398.6 g (366-432 g), Female: 257.2 g (235-283 g)
- Housing: Animals were housed individually, except for during the acclimation (two animals by sex), mating (one male and one female) and lactation periods (one litter), in metallic bracket-type cages with wire mesh floors (260W x 380D x 180H mm). From gestation day 17 to lactation day 4, individual dams and litters were reared on bedding.
- Diet: Solid feed (CRF-1: Oriental Yeast Co., Ltd.) was given ad libitum.
- Water: Tap water was given ad libitum.
- Acclimation period: 14 days

**ENVIRONMENTAL CONDITIONS**

- Temperature (°C): 22±3 (actual temperature: 21-25°C)
- Humidity (%): 50±20% (actual humidity: 36-62%)
- Air changes (per hr): 10-15

---

- Photoperiod (hrs dark / hrs light): 12 hr dark/12 hr light (light: 8:00~20:00)

## 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

### Details on mating procedure

- M/F ratio per cage: 1:1
- Length of cohabitation: up to 14 days
- Proof of pregnancy: vaginal plug or sperm in vaginal smear referred to as day 0 of pregnancy
- After 14 days of unsuccessful pairing replacement of first male by another male with proven fertility.

### Analytical verification of doses or concentrations

yes

### Duration of treatment / exposure

(P) Males: 42 days including 14 days pre-mating and mating periods, and thereafter 14 days

(P) Females: up to 56 days including 14 days pre-mating, mating and gestation periods, and the days until day 3 of lactation

### Frequency of treatment

Once/day, 7days/week

### Doses / concentrations

<b>Dose / conc.</b>	
0	mg/kg bw/day (actual dose received)
<b>Dose / conc.</b>	
35	mg/kg bw/day (actual dose received)
<b>Dose / conc.</b>	
150	mg/kg bw/day (actual dose received)
<b>Dose / conc.</b>	
600	mg/kg bw/day (actual dose received)

### No. of animals per sex per dose

12 animals/sex/dose

### 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 600 mg/kg bw/day was selected as an expected obvious toxic dose, and the lowest dose of 35 mg/kg bw/day was selected as an expected no toxic dose. The middle dose levels of 150 mg/kg bw/day were selected.

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

[14-day preliminary study]

A 14-day repeated dose oral toxicity test (CrI:CD(SD) rats, doses: 0 (olive oil), 35, 150, and 600 mg/kg bw/day). At 600 mg/kg bw/day, staggering gait, soiled perineal region, yellowish white mass in the cauda epididymis were observed.

---

## Examinations

### Observations and examinations performed and frequency

CAGE SIDE OBSERVATIONS: Yes

- Time schedule: Males and females: 2 times/day

DETAILED CLINICAL OBSERVATIONS: No

BODY WEIGHT: Yes

- Time schedule for examinations:

Males: Days 1, 2, 5, 7, 10, 14, 21, 28, 35, 42, and the day of necropsy

Females: Days 1, 2, 5, 7, 10, and 14; gestation days 0, 1, 3, 5, 7, 10, 14, 17, and 20; lactation days 0, 1 and 4; and the day of necropsy. For unmating females, 21 and 28 in the mating period

FOOD CONSUMPTION AND COMPOUND INTAKE (if feeding study):

- Food consumption: Yes

Males: Days 1, 2, 5, 7, 10, 14, 21, 28, 35, and 42, in dosing period

Females: Days 1, 2, 5, 7, 10, and 14; gestation days 0, 1, 3, 5, 7, 10, 14, 17, and 20; lactation days 0, 1 and 4

OTHER: Females: Numbers of corpus luteum and implantation site on the day of necropsy

### Sacrifice and pathology

SACRIFICE

- Male animals: All surviving animals were euthanized by exsanguination under ether anesthesia on the day after the last administration.

- Maternal animals: All surviving animals were euthanized by exsanguination under ether anesthesia on day 4 of lactation.

GROSS NECROPSY: Yes (gross necropsy consisted of external and internal examinations including the cervical, thoracic, and abdominal viscera.)

HISTOPATHOLOGY: Yes (Male: testis, epididymis, and gross abnormal site (ileum); Female: ovary, and gross abnormal site (pituitary gland, thymus, spleen, kidney, ileum))

### Other examinations

ORGAN WEIGHTS: Yes (brain, thymus, heart, liver, kidney, spleen, adrenal, testis, epididymis, ovary)

### Statistics

Body weights, body weight gain, food consumption, organ weights and relative organ weights, stages of spermatogenesis, length of the estrous cycle, number of corpora lutea, number of implantation sites, implantation index, delivery index, number of pups delivered, number of live pups, live birth index, sex ratio, number of live pups and viability index at lactation day 4 were analyzed for statistical significance in the following way: homogeneity of variance was evaluated first by Bartlett's test. When group variances were homogeneous, the one-way analysis of variance was used to determine if any statist

---

ical differences existed among the groups. If the analysis of variance gave a significant result, Dunnett's test was performed to detect any significant differences between the treated groups and their corresponding controls. When Bartlett's test indicated that the variances were not homogeneous, the Kruskal-Wallis test was used for detecting any statistical differences and if they were significant, the Mann-Whitney U test was performed to detect any significant differences between the treated groups and their corresponding controls. The incidences of females with abnormal estrous cyclicity, and indices of copulation, fertility and gestation, and nursing index were analyzed by the Chi-square test or Fisher's exact probability test.

## Results and discussion

---

### Results of examinations

---

#### **Clinical signs**

effects observed, treatment-related

#### **Description (incidence and severity)**

Decrease in locomotor activity was observed in one male on day 5 and 6, in one female on day 1 at 600 mg/kg bw/kg.

Crawling position, lateral position and soil of perigenital fur were observed in males and females at 600 mg/kg bw/kg.

#### **Mortality**

no mortality observed

#### **Body weight and weight changes**

effects observed, treatment-related

#### **Description (incidence and severity)**

Significantly low value of body weight was observed in both sexes at 600 mg/kg bw/day.

#### **Food consumption and compound intake (if feeding study)**

effects observed, treatment-related

#### **Description (incidence and severity)**

Significantly low value of food consumption was observed in both sexes at 600 mg/kg bw/day.

#### **Food efficiency**

not examined

#### **Water consumption and compound intake (if drinking water study)**

not examined

#### **Ophthalmological findings**

not examined

#### **Haematological findings**

not examined

#### **Clinical biochemistry findings**

not examined

#### **Urinalysis findings**

not examined

#### **Behaviour (functional findings)**

not examined

---

**Immunological findings**

not examined

**Organ weight findings including organ / body weight ratios**

effects observed, treatment-related

**Description (incidence and severity)**

[treatment-related effect]:

Increases in relative kidney weight was observed in both sexes at 600 mg/kg bw/day.

[non-treatment-related]:

Increases in relative brain weight was observed in both sexes at 600 mg/kg bw/day.

However, this change was considered due to the reduction in terminal body weights. Therefore this change was no toxicological meaning.

**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**

150

mg/kg bw/day (actual dose received)

**Based on**

test mat.

**Sex**

male/female

**Basis for effect level**

body weight and weight gain

Significantly low value of body weight was observed in both sexes at 600 mg/kg bw/day.

clinical signs

Decrease in locomotor activity was observed in one male on day 5 and 6, in one female on day 1 at 600 mg/kg bw/kg. Crawling position, lateral position and soil of perigenital fur were observed in males and females at 600 mg/kg bw/kg.

food consumption and compound intake

Significantly low value of food consumption was observed in both sexes at 600 mg/kg bw/day.

---

**Any other information on results incl. tables**

---

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

[http://dra4.nihs.go.jp/mhlw\\_data/home/pdf/PDF59-50-7c.pdf](http://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF59-50-7c.pdf)

## **Applicant's summary and conclusion**

---

### **Executive summary**

A reproduction/developmental toxicity screening test was performed according to OECD TG 421. Male and female rats (12 animals/sex/dose) were administered 4-chloro-m-cresol at 0, 35, 150, and 600 mg/kg bw/day. Males were dosed for 42 days, including a 14 day pre-mating and mating periods. Females were dosed for 56 days, including a 14 day pre-mating, mating, and gestation periods, and the time until lactation day 3. Decrease in locomotor activity was observed in both sexes at 600 mg/kg bw/kg. Crawling position, lateral position and soil of perigenital fur were observed in both sexes at 600 mg/kg bw/kg. Significantly low value of body weight was observed in both sexes at 600 mg/kg bw/day. Significantly low value of food consumption was observed in both sexes at 600 mg/kg bw/day. On the basis of these effects, NOAEL for repeated-dose toxicity was determined to be 150 mg/kg bw/day in male and female rats.

---

## Genetic toxicity

### Genetic toxicity in vitro

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

---

UUID: 764bbe55-ffa6-468b-b592-12facb8c9342

Dossier UUID:

Author:

Date: 2022-12-12T11:32:21.719+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

true

### Used for classification

false

### Used for SDS

false

### Reliability

1 (reliable without restriction)

### Rationale for reliability incl. deficiencies

guideline study

Reliability 1

## Data source

---

### Reference

[Reverse Mutation Test of 4-chloro-m-cresol on Bacteria / MHLW \(Ministry of Health, Labour and Welfare\), Japan / study report](#)

### Data access

data published

## Materials and methods

---

### Test guideline

#### Qualifier

according to guideline

---

---

**Guideline**

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

**Qualifier**

according to guideline

**Guideline**

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

**GLP compliance**

yes

**Type of assay**

bacterial reverse mutation assay  
in vitro gene mutation study in bacteria

---

**Test material****Test material information**

[4-Chloro-m-cresol](#)

**Specific details on test material used for the study**

- Name of test material (as cited in study report): 4-chloro-m-cresol
- CAS No.: 59-50-7
- Lot No.: ASL1407
- Purity: 100%
- Supplier: Wako Pure Chemical Industries, Ltd.
- Boiling point : 235°C
- Melting point/Freezing point: 65.7°C
- Vapor pressure: 0.05 mmHg (20°C)
- Solubility: 1 g/260 mL (20°C) in water.
- Physical state: white powder
- Storage condition of test material: stored at room temperature (21.1-25.3°C), light shielding

---

**Method****Species / strain****Species / strain / cell type**

S. typhimurium TA 1535, TA 1537, TA 98, TA 100 and E. coli WP2  
bacteria

**Metabolic activation**

with and without

**Metabolic activation system**

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

**Test concentrations with justification for top dose**

Preliminary study

+/-S9 mix:1.22, 4.88, 19.5, 78.1, 313, 1250, 5000 µg/plate

(growth inhibition was observed at  $\geq 313\mu\text{g/plate}$  in TA100 and TA1535 and at  $\geq 1250\mu\text{g/plate}$  in WP2uvrA/pKM101, TA98, and TA1537)

---

### Main study

+/-S9 mix: 9.77, 19.5, 39.1, 78.1, 156, 313, 625 µg/plate (TA100, TA1535 strains)

+/-S9 mix: 19.5, 39.1, 78.1, 156, 313, 625, 1250 µg/plate (WP2uvrA/pKM101, TA98, TA1537 strains)

### Vehicle / solvent

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

### Controls

#### Negative solvent / vehicle controls

yes

#### Positive controls

yes

#### Positive control substance

9-aminoacridine

9-aminoacridine hydrochloride, -S9mix: (TA1537)

sodium azide

-S9 mix: (TA1535)

other: 2-(2-Furyl)-3-(5-nitro-2-furyl) acrylamide

-S9mix: (TA 100, TA98 and WP2 uvrA/pKM101)

#### Remarks

-S9mix

#### Negative solvent / vehicle controls

yes

#### Positive controls

yes

#### Positive control substance

other: 2-aminoanthracene

(all strains)

#### Remarks

+S9 mix

### Details on test system and experimental conditions

METHOD OF APPLICATION: Preincubation

DURATION- Preincubation period: 20 min at 37°C

- Exposure duration:48 hrs

NUMBER OF PLATES: 3

NUMBER OF REPLICATIONS: 2

DETERMINATION OF CYTOTOXICITY- Method: other: growth inhibition

### Evaluation criteria

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

### Statistics

not used

## Results and discussion

---

## Test results

**Key result**

false

**Species / strain**

S. typhimurium TA 100  
bacteria

**Metabolic activation**

with and without

**Genotoxicity**

negative

**Cytotoxicity / choice of top concentrations**

cytotoxicity +/-S9: at =>313 µg/plate

**Vehicle controls validity**

valid

**Positive controls validity**

valid

**Key result**

false

**Species / strain**

S. typhimurium TA 1535  
bacteria

**Metabolic activation**

with and without

**Genotoxicity**

negative

**Cytotoxicity / choice of top concentrations**

cytotoxicity +/-S9: at =>313 µg/plate

**Vehicle controls validity**

valid

**Positive controls validity**

valid

**Key result**

false

**Species / strain**

E. coli WP2 uvr A pKM 101  
bacteria

**Metabolic activation**

with and without

**Genotoxicity**

negative

**Cytotoxicity / choice of top concentrations**

cytotoxicity -S9mix: at=>625 µg/plate, +S9mix: at 1250 µg/plate

---

**Vehicle controls validity**

valid

**Positive controls validity**

valid

**Key result**

false

**Species / strain**

S. typhimurium TA 98

bacteria

**Metabolic activation**

with and without

**Genotoxicity**

negative

**Cytotoxicity / choice of top concentrations**

cytotoxicity +/-S9mix: at =&gt;625 µg/plate

**Vehicle controls validity**

valid

**Positive controls validity**

valid

**Key result**

false

**Species / strain**

S. typhimurium TA 1537

bacteria

**Metabolic activation**

with and without

**Genotoxicity**

negative

**Cytotoxicity / choice of top concentrations**

cytotoxicity +/-S9mix: at =&gt;625 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. [http://dra4.nihs.go.jp/mhlw\\_data/home/pdf/PDF59-50-7e.pdf](http://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF59-50-7e.pdf)

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

---

## **Applicant's summary and conclusion**

---

### **Conclusions**

In a bacterial reverse mutation assay using *Salmonella typhimurium* TA100, TA1535, TA98, and TA1537, and *Escherichia coli* WP2uvrA/pKM101 (OECD TG 471), 4-chloro-m-cresol was negative with or without metabolic activation.

---

**ENDPOINT\_STUDY\_RECORD: Genetic toxicity in vitro.002**

---

**UUID:** 126966d5-1d1f-48a0-8437-c0fb2b9ac1e2

**Dossier UUID:**

**Author:**

**Date:** 2022-12-12T11:32:46.026+09:00

**Remarks:**

---

## Administrative data

---

### Endpoint

in vitro cytogenicity / chromosome aberration study in mammalian cells

### Type of information

experimental study

### Adequacy of study

key study

### Robust study summary

true

### Used for classification

false

### Used for SDS

false

### Reliability

1 (reliable without restriction)

### Rationale for reliability incl. deficiencies

guideline study

Reliability 1

## Data source

---

### Reference

[In Vitro Chromosomal Aberration Test of 4-chloro-m-cresol on Cultured Chinese Hamster Cells / MHLW \(Ministry of Health, Labour and Welfare\), Japan / study report](#)

## Materials and methods

---

### Test guideline

#### Qualifier

according to guideline

#### Guideline

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

#### Qualifier

according to guideline

---

---

**Guideline**

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

**GLP compliance**

yes

**Type of assay**

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

---

**Test material****Test material information**

4-Chloro-m-cresol

**Specific details on test material used for the study**

- Name of test material (as cited in study report): 4-chloro-m-cresol
- CAS No.: 59-50-7
- Lot No.: ASL1407
- Purity: 100%
- Supplier: Wako Pure Chemical Industries, Ltd.
- Boiling point : 235°C
- Melting point/Freezing point: 65.7°C
- Vapor pressure: 0.05 mmHg (20°C)
- Solubility: 1 g/260 mL (20°C) in water.
- Physical state: white powder
- Storage condition of test material: stored at room temperature (21.1-25.3°C), light shielding

---

**Method****Species / strain****Species / strain / cell type**

other:

**Details on mammalian cell type (if applicable)**

Chinese hamster lung(CHL/IU) cells

**Metabolic activation**

with and without

**Metabolic activation system**

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

**Test concentrations with justification for top dose**

Preliminary study

50, 500, 5000 µg/mL (100% growth inhibition was observed at 500 µg/mL and higher)

Main study

[short-term treatment (6 h)] (+/-S9 mix): 50, 100, 200, 300, 400, 500 µg/mL

[continuous treatment (24 h)]: 50, 100, 150, 200, 250, 300 µg/mL

**Vehicle / solvent**

DMSO

---

## Controls

**Untreated negative controls**

no

**Negative solvent / vehicle controls**

yes

**True negative controls**

no

**Positive controls**

yes

**Positive control substance**

benzo(a)pyrene

+S9 mix

mitomycin C

-S9 mix

**Details on test system and experimental conditions**

METHOD OF APPLICATION: Exposure duration: [short-term treatment]:6 hrs + 18 hr, [continuous treatment]: 24h

STAIN: Giemsa stain (3 v/v%) for 10 min.

NUMBER OF REPLICATIONS: 2

NUMBER OF CELLS EVALUATED: 1000 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.

For the evaluation of the frequencies of structural aberrations and of polyploidy induced, the following criteria were employed.

Appearance incidence of cell with chromosomal aberrations: Negative(-): less than 5%, Equivocal(±): 5% or more and less than 10%, Positive(+): 10% or more

**Statistics**

Not used

## Results and discussion

---

**Test results****Key result**

false

**Species / strain**

other: Chinese hamster lung(CHL/IU) cells

**Metabolic activation**

with and without

**Genotoxicity**

negative

**Cytotoxicity / choice of top concentrations**

cytotoxicity

---

**Vehicle controls validity**

valid

**Untreated negative controls validity**

not examined

**Positive controls validity**

valid

**Additional information on results**

Figures and Tables (in Japanese) are available in the following full report of the study. [http://dra4.nihs.go.jp/mhlw\\_data/home/pdf/PDF59-50-7f.pdf](http://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF59-50-7f.pdf)

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

## **Applicant's summary and conclusion**

---

**Conclusions**

Negative with and without metabolic activation

**Executive summary**

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

---

## Toxicity to reproduction

### Toxicity to reproduction

ENDPOINT\_STUDY\_RECORD: Toxicity to reproduction.001

---

UUID: 1bfb91e5-1962-41d1-b12b-a748fd549888

Dossier UUID:

Author:

Date: 2022-12-12T11:33:32.429+09:00

Remarks:

---

## Administrative data

---

### Endpoint

screening for reproductive / developmental toxicity

### Type of information

experimental study

### Adequacy of study

key study

### Robust study summary

false

### Used for classification

false

### Used for SDS

false

### Reliability

1 (reliable without restriction)

### Rationale for reliability incl. deficiencies

guideline study

Reliability 1

## Data source

---

### Reference

[A reproduction/developmental toxicity screening test in rats treated orally with 4-chloro-m-cresol / Ministry of Health, Labor and Welfare, Japan / study report](#)

### Data access

data published

## Materials and methods

---

### Test guideline

#### Qualifier

according to guideline

---

---

**Guideline**

OECD Guideline 421 (Reproduction / Developmental Toxicity Screening Test)

**Deviations**

no

**GLP compliance**

yes

---

**Test material****Test material information**

4-Chloro-m-cresol

**Specific details on test material used for the study**

- Name of test material (as cited in study report): 4-Chloro-m-cresol
- Analytical purity: 99.9%
- Storage condition of test material: at a cold (temperature 1-8 °C) and dark place, with airtight stopper.
- 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., Atsugi Breeding Center.
- Age at study initiation: 10 weeks
- Weight at study initiation: Male: 398.6 g (366-432 g), Female: 257.2 g (235-283 g)
- Housing: Animals were housed individually, except for during the acclimation (two animals by sex), mating (one male and one female) and lactation periods (one litter), in metallic bracket-type cages with wire mesh floors (260 mm x 380 mm x 180 mm). From gestation day 17 to lactation day 4, individual dams and litters were reared on bedding.
- Diet: Solid feed (CRF-1: Oriental Yeast Co., Ltd.) was given ad libitum.
- Water: Tap water was given ad libitum.
- Acclimation period: 14 days

**ENVIRONMENTAL CONDITIONS**

- Temperature (°C): 22±3 (actual temperature: 21-25°C)
- Humidity (%): 50±20% (actual humidity: 36-62%)
- Air changes (per hr): 10-15
- Photoperiod (hrs dark / hrs light): 12 hr dark/12 hr light (light: 8:00~20:00)

---

**Administration / exposure****Route of administration**

oral: gavage

---

**Vehicle**

corn oil

**Details on mating procedure**

- M/F ratio per cage: 1:1
- Length of cohabitation: up to 14 days
- Proof of pregnancy: vaginal plug or sperm in vaginal smear referred to as day 0 of pregnancy
- After 14 days of unsuccessful pairing replacement of first male by another male with proven fertility.

**Analytical verification of doses or concentrations**

yes

**Details on analytical verification of doses or concentrations**

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

**Duration of treatment / exposure**

(P) Males: 42 days including 14 days pre-mating and mating periods, and thereafter 14 days (P) Females: up to 56 days including 14 days pre-mating, mating and gestation periods, and the days until day 3 of lactation

**Frequency of treatment**

Once/day, 7days/week

**Doses / concentrations**

<b>Dose / conc.</b>	
0	mg/kg bw/day (actual dose received)
<b>Dose / conc.</b>	
35	mg/kg bw/day (actual dose received)
<b>Dose / conc.</b>	
150	mg/kg bw/day (actual dose received)
<b>Dose / conc.</b>	
600	mg/kg bw/day (actual dose received)

**No. of animals per sex per dose**

12 animals/sex/dose

**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 600 mg/kg bw/day was selected as an expected obvious toxic dose, and the lowest dose of 35 mg/kg bw/day was selected as an expected no toxic dose. The middle dose levels of 150 mg/kg bw/day were selected.
- Rationale for animal assignment (if not random): Body weight-balanced randomization

---

[14-day preliminary study]

A 14-day repeated dose oral toxicity test (CrI:CD(SD) rats, doses: 0 (olive oil), 35, 150, and 600 mg/kg bw/day). At 600 mg/kg bw/day, staggering gait, soiled perineal region, yellowish white mass in the cauda epididymis were observed.

## Examinations

---

### Parental animals: Observations and examinations

CAGE SIDE OBSERVATIONS: Yes

- Time schedule: Males and females: 2 times/day

BODY WEIGHT: Yes

- Time schedule for examinations:

Males: Days 1, 2, 5, 7, 10, 14, 21, 28, 35, 42, and the day of necropsy

Females: Days 1, 2, 5, 7, 10, and 14; gestation days 0, 1, 3, 5, 7, 10, 14, 17, and 20; lactation days 0, 1 and 4; and the day of necropsy. For unmating females, 21 and 28 in the mating period

FOOD CONSUMPTION AND COMPOUND INTAKE (if feeding study):

- Food consumption: Yes

Males: Days 1, 2, 5, 7, 10, 14, 21, 28, 35, and 42, in dosing period

Females: Days 1, 2, 5, 7, 10, and 14; gestation days 0, 1, 3, 5, 7, 10, 14, 17, and 20; lactation days 0, 1 and 4

OTHER: Females: Numbers of corpus luteum and implantation site on the day of necropsy

### Oestrous cyclicity (parental animals)

Vaginal smears were collected from all females 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 P male parental generations: testis weight, epididymis weight

### Litter observations

PARAMETERS EXAMINED

The following parameters were examined in F1 offspring:

number and sex of pups, stillbirths, live births, postnatal mortality, presence of gross anomalies, weight.

GROSS EXAMINATION OF DEAD PUPS: Yes, for external and internal abnormalities.

### Postmortem examinations (parental animals)

SACRIFICE

- Male animals: All surviving animals were euthanized by exsanguination under ether anesthesia on the day after the last administration.

- Maternal animals: All surviving animals were euthanized by exsanguination under ether anesthesia on day 4 of lactation.

GROSS NECROPSY: Yes (gross necropsy consisted of external and internal examinations including the cervical, thoracic, and abdominal viscera.)

HISTOPATHOLOGY: Yes (Male: testis, epididymis, and gross abnormal site (ileum); Female: ovary, and gross abnormal site (pituitary gland, thymus, spleen, kidney, ileum))

---

ORGAN WEIGHTS: Yes (brain, thymus, heart, liver, kidney, spleen, adrenal, testis, epididymis, ovary )

### **Postmortem examinations (offspring)**

#### **SACRIFICE**

- The F1 pups were euthanized on day 4 of lactation by using carbon dioxide.

#### **GROSS NECROPSY**

- Gross necropsy consisted of external and internal examinations including the cervical, thoracic, and abdominal viscera.

### **Statistics**

Body weights, body weight gain, food consumption, organ weights and relative organ weights, stages of spermatogenesis, length of the estrous cycle, number of corpora lutea, number of implantation sites, implantation index, delivery index, number of pups delivered, number of live pups, live birth index, sex ratio, number of live pups and viability index at lactation day 4 were analyzed for statistical significance in the following way: homogeneity of variance was evaluated first by Bartlett's test. When group variances were homogeneous, the one-way analysis of variance was used to determine if any statistical differences existed among the groups. If the analysis of variance gave a significant result, Dunnett's test was performed to detect any significant differences between the treated groups and their corresponding controls. When Bartlett's test indicated that the variances were not homogeneous, the Kruskal-Wallis test was used for detecting any statistical differences and if they were significant, the Mann-Whitney U test was performed to detect any significant differences between the treated groups and their corresponding controls. The incidences of females with abnormal estrous cyclicity, and indices of copulation, fertility and gestation, and nursing index were analyzed by the Chi-square test or Fisher's exact probability test.

### **Reproductive indices**

Each parameter was determined by the following equations:

Abnormal estrous cycle = (No. of female with abnormal estrous cycle/No. of females examined) × 100

Copulation index (%) = (No. of animals with successful copulation/No. of animals mated) × 100

Fertility index (%) = (No. of pregnant females/No. of pairs with successful copulation) × 100

Gestation index (%) = (No. of females with live pups/number of pregnant females) × 100

Nursing index (%) = (No. of females nursing live pups on lactation day 4/No. of females with live pups delivery) × 100

Implantation index (%) = (No. of implantation sites/No. of corpora lutea) × 100

Delivery index (%) = (No. of pups born/No. of implantation sites) × 100

Sex ratio = No. of live male pups/No. of live pups

Live birth index (%) = (No. of live pups on lactation day 0/No. of pups born) × 100

### **Offspring viability indices**

Viability index on lactation day 4 = (No. of live pups on lactation day 4/No. of live pups on lactation day 0) × 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: oral.002

**Mortality**

no mortality observed

**Body weight and weight changes**

effects observed, treatment-related

**Description (incidence and severity)**

see 7.5.1 Repeated dose toxicity: oral.002

**Food consumption and compound intake (if feeding study)**

effects observed, treatment-related

**Description (incidence and severity)**

see 7.5.1 Repeated dose toxicity: oral.002

**Food efficiency**

not examined

**Water consumption and compound intake (if drinking water study)**

not examined

**Ophthalmological findings**

not examined

**Haematological findings**

not examined

**Clinical biochemistry findings**

not examined

**Urinalysis findings**

not examined

**Behaviour (functional findings)**

not examined

**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: oral.002

no effects on reproductive organs

**Gross pathological findings**

no effects observed

**Description (incidence and severity)**

no effects on reproductive organs

**Neuropathological findings**

not examined

**Histopathological findings: non-neoplastic**

no effects observed

---

**Description (incidence and severity)**

no effects on reproductive organs

**Histopathological findings: neoplastic**

not examined

**Reproductive function / performance (P0)**

---

**Reproductive function: oestrous cycle**

no effects observed

**Reproductive function: sperm measures**

effects observed, non-treatment-related

**Description (incidence and severity)**

Increase number of cells on preleptotene spermatocytes at Stage VII-VIII at 600 mg/kg bw/day.

**Reproductive performance**

no effects observed

**Effect levels (P0)**

---

**Key result**

true

**Dose descriptor**

NOAEL

**Effect level**

600

mg/kg bw/day (actual dose received)

**Based on**

test mat.

**Sex**

male/female

**Results: F1 generation**

---

**General toxicity (F1)**

---

**Clinical signs**

no effects observed

**Mortality / viability**

mortality observed, non-treatment-related

**Description (incidence and severity)**

control: 2 males and 4 females died.

35 mg/kg bw/day: 2 males died.

150 mg/kg bw/day: 3 males and 2 females died.

600 mg/kg bw/day: 2 males and 1 females died.

**Body weight and weight changes**

no effects observed

---

**Sexual maturation**

not examined

**Organ weight findings including organ / body weight ratios**

not examined

**Gross pathological findings**

no effects observed

**Histopathological findings**

not examined

---

**Effect levels (F1)**

---

**Key result**

true

**Dose descriptor**

NOAEL

**Generation**

F1

**Effect level**

600

mg/kg bw/day (actual dose received)

**Based on**

test mat.

**Sex**

male/female

---

**Any other information on results incl. tables**

---

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

[http://dra4.nihs.go.jp/mhlw\\_data/home/pdf/PDF59-50-7c.pdf](http://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF59-50-7c.pdf)

---

**Applicant's summary and conclusion**

---

**Executive summary**

A reproduction/developmental toxicity screening test was performed according to OECD TG 421. Male and female rats (12 animals/sex/dose) were administered 4-chloro-m-cresol at 0, 35, 150, and 600 mg/kg bw/day. Males were dosed for 42 days, including a 14 day pre-mating and mating periods. Females were dosed for 56 days, including a 14 day pre-mating, mating, and gestation periods, and the time until lactation day 3. No effects of this substance on reproductive and developmental parameters were observed at 600 mg/kg bw/day. NOAEL for the rat reproductive/developmental toxicity of 4-chloro-m-cresol was determined to be 600 mg/kg bw/day, the highest dose tested.

---

# References

## Reference Substances

### REFERENCE\_SUBSTANCE: 4-chloro-m-cresol

---

**UUID:** fa2f9d53-ba31-416b-964a-93e8166287ef

**Dossier UUID:**

**Author:**

**Date:** 2018-02-27T14:37:55.000+09:00

**Remarks:**

---

**Reference substance name**

4-chloro-m-cresol

## Inventory

---

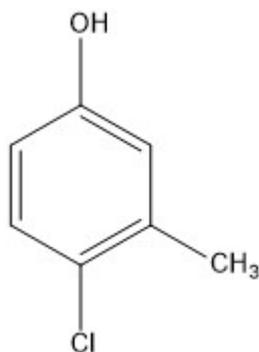
**CAS number**

59-50-7

## Molecular and structural information

---

**Structural formula**



---

# Test Materials

## TEST\_MATERIAL\_INFORMATION: 4-Chloro-m-cresol

---

**UUID:** 52e5cce7-3877-49f0-b7d7-9a7311d51401

**Dossier UUID:**

**Author:**

**Date:** 2022-12-12T11:29:11.508+09:00

**Remarks:**

---

**Name**

4-Chloro-m-cresol

---

## Literatures

### LITERATURE: A reproduction/developmental toxicity screening test in rats treated orally with 4-chloro-m-cresol

---

**UUID:** 01a49291-8a84-4bfd-80d1-76819202e03a

**Dossier UUID:**

**Author:**

**Date:** 2018-03-14T15:23:19.000+09:00

**Remarks:**

---

## General information

---

**Reference Type**

study report

**Title**

A reproduction/developmental toxicity screening test in rats treated orally with 4-chloro-m-cresol

**Author**

Ministry of Health, Labor and Welfare, Japan

**Bibliographic source**

available in the web of Japan Existing Chemical Data Bae (JCEDB) at

**Testing facility**

Safety Research Institute for Chemical Compounds Co., Ltd.

**Report number**

SR08135

---

# LITERATURE: In Vitro Chromosomal Aberration Test of 4-chloro-m-cresol on Cultured Chinese Hamster Cells

---

**UUID:** 073bdd8b-cbe0-45d4-92e8-d80334293bb1

**Dossier UUID:**

**Author:**

**Date:** 2018-02-27T16:54:46.000+09:00

**Remarks:**

---

## General information

---

### Reference Type

study report

### Title

In Vitro Chromosomal Aberration Test of 4-chloro-m-cresol on Cultured Chinese Hamster Cells

### Author

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

### Year

2007

### Bibliographic source

Japan Existing Chemical Data Base (JECDB) [http://dra4.nihs.go.jp/mhlw\\_data/jsp/SearchPageENG.jsp](http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp)

### Testing facility

Mitsubishi Safety Institute Ltd.

### Report number

B060313

---

# LITERATURE: Reverse Mutation Test of 4-chloro-m-cresol on Bacteria

---

**UUID:** 6c7ed821-3dcf-4cf8-84b3-97085910a4cb

**Dossier UUID:**

**Author:**

**Date:** 2018-02-27T16:44:27.000+09:00

**Remarks:**

---

## General information

---

**Reference Type**

study report

**Title**

Reverse Mutation Test of 4-chloro-m-cresol on Bacteria

**Author**

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

**Year**

2007

**Bibliographic source**

Japan Existing Chemical Data Base (JECDB) [http://dra4.nihs.go.jp/mhlw\\_data/jsp/SearchPageENG.jsp](http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp)

**Testing facility**

Mitsubishi Safety Institute Ltd.

**Report number**

B060312

---

# LITERATURE: Twenty-eight-day Repeat Dose Oral Toxicity Test of 4-chloro-m-cresol in Rats

---

**UUID:** 4e3fff29-f57b-43c3-a2f7-968da6f2a134

**Dossier UUID:**

**Author:**

**Date:** 2018-03-17T12:37:49.000+09:00

**Remarks:**

---

## General information

---

**Reference Type**

study report

**Title**

Twenty-eight-day Repeat Dose Oral Toxicity Test of 4-chloro-m-cresol in Rats

**Author**

Ministry of Health, Labor and Welfare, Japan

**Bibliographic source**

available in the web of Japan Existing Chemical Data Base (JCEDB) at

**Testing facility**

Research Institute for Animal Science in Biochemistry and Toxicology

**Study number**

06-087

---

# Legal Entities

## LEGAL\_ENTITY: National Institute of Health Sciences

---

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

**Dossier UUID:**

**Author:**

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

**Remarks:**

---

### General information

---

**Legal entity name**

National Institute of Health Sciences

**Remarks**

Disclaimer: The contents in this document were created based on the MHLW (Ministry of Health, Labour and Welfare) peer reviewed study reports (in Japanese) in JECDB (Japan Existing Chemical Database) at [http://dra4.nihs.go.jp/mhlw\\_data/jsp/SearchPageENG.jsp](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.

### 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**

<b>IT system</b>
LEO
<b>ID</b>
10767
<b>IT system</b>
IUCLID4

---

**ID**

16558402024DIV750