Name: COMPLETE / SUBSTANCE : 2-Nitro-p-cresol / 4-methyl-2-nitrophenol / 119-33-5 Fri, 16 Dec 2022, 14:32:16+0900 /

Legal entity owner: National Institute of Health Sciences

Printing date: 2022-12-16T14:32:16.767+09:00

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DOSSIER:

UUID: 0
Dossier UUID:
Author:
Date: 2022-12-16T14:32:16.586+09:00
Remarks:

Dossier header

Dossier submission type

Name
Complete table of contents

Version
core 7.0

Name (given by user)

Dossier subject

Dossier subject
2-Nitro-p-cresol / 4-methyl-2-nitrophenol / 119-33-5

Public name

Submitting legal entity
National Institute of Health Science

Dossier creation date/time
Fri, 16 Dec 2022, 14:32:16+0900

Used in category

LEGAL_ENTITY: National Institute of Health Science

UUID:	f51e7b54-9211-4863-90ce-fcf8a155d647
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Author:	
Date:	2022-11-07T16:24:02.822+09:00
Remarks:	

General information

Legal entity name
National Institute of Health Science

2-Nitro-p-cresol

CORE

General information

Assessment approach (assessment entities)

FIXED_RECORD: Assessment approach

UUID:	dfa5593f-0296-3e44-9e65-f8823d5a8cea
Dossier UUID:	
Author:	
Date:	2016-12-21T15:08:10.000+09:00
Remarks:	

OECD

Health Effects

Acute toxicity: oral

ENDPOINT_STUDY_RECORD: Acute toxicity: oral.001

UUID:	92069579-4fea-46b6-9947-0a4e625fdd42
Dossier UUID:	
Author:	
Date:	2022-12-15T09:10:06.134+09:00
Remarks:	

Administrative data

Endpoint
acute 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
Reliability 1

Data source

Reference

Single Dose Oral Toxicity Test of 2-nitro-p-cresol in Rats / MHLW, japan / study report

Data access
data published

Materials and methods

Test guideline

Qualifier
according to guideline

Guideline
OECD Guideline 423 (Acute Oral toxicity - Acute Toxic Class Method)

GLP compliance
yes

Test type
acute toxic class method

Limit test
yes

Test material

Test material information
2-Nitro-p-cresol

Specific details on test material used for the study
CAS; 119-33-5

Test animals

Species
rat
common species

Strain
Crj: CD(SD)
rat

Sex
female

Details on test animals or test system and environmental conditions
- Source: Charles River Japan Inc.
- Age at the time of purchase: 7 weeks old
- Weight at dosing: Females, 190 - 192 g
- Fasting period before study: Approximately 16 hrs
- Housing: One animal/cage- Diet (e.g. ad libitum): Ad libitum except fasting period for 16 hrs before administration to 3 hrs after administration
- Water (e.g. ad libitum): Ad libitum
- Acclimation period: more than one week
ENVIRONMENTAL CONDITIONS
- Temperature (°C): 21-24
- Humidity (%): 36-59
- Ventilation (per hr): Approximately > 12 times
- Photoperiod (hrs light / hrs dark): 12/12

Administration / exposure

Route of administration
oral: gavage

Vehicle
corn oil

Details on oral exposure
Test substance

-Lot no.: FBR01
-Purity: 99.8%
VEHICLE
- Lot no.: V6K0677 produced by Nacalai Tesque, INC..
MAXIMUM DOSE VOLUME APPLIED: 10 ml/kg bw

Doses
2000 mg/kg bw

No. of animals per sex per dose
First time of administration: 3 females /dose
Second time of administration: 3 females /dose

Control animals
no

Details on study design
- Duration of observation period following administration: 14 days
- Frequency of observations: Day 1 (day of administration): within 30 minutes and 1, 2, 3, 4, 5 and 6 hrs after administration. After day 2: once a day
- Frequency of weighing: on the day of administration (before administration), and 1, 3, 7, and 14 days after administration.
- Necropsy of survivors performed: Yes

The starting administration dose was set as 2000 mg/kg bw. No deaths were observed in the first administration; therefore, the second dose was also set as 2000 mg/kg bw.

Statistics
No

Results and discussion

Effect levels

Key result
true

Sex
female

Dose descriptor
LD50

Effect level

>	2000	mg/kg bw

Based on
act. ingr.

Mortality
No deaths were observed in first and second times.

Clinical signs
other: Decreased spontaneous movement was observed 30 min-4 hrs after administration in all anima ls.

Gross pathology
No changes related to the test substance were observed in first and second times.

Applicant's summary and conclusion

Conclusions
The LD50 value was considered to be more than 2000 mg/kg bw for female rats.

Repeated dose toxicity: oral

ENDPOINT_STUDY_RECORD: Repeated dose toxicity: oral.001

UUID:	IUC5-4b770d28-4eb4-4888-b89e-a27937fe34e8
Dossier UUID:	
Author:	
Date:	2022-12-16T14:25:48.717+09:00
Remarks:	

Administrative data

Endpoint
short-term repeated dose toxicity: oral

Type of information
experimental study

Adequacy of study
key study

Robust study summary
false

Used for classification
false

Used for SDS
false

Reliability
1 (reliable without restriction)

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

Cross-reference

Reason / purpose for cross-reference
reference to other study

Remarks
7.5.1 Repeated dose toxicity: oral.002

Data source

Reference

Twenty-eight-day Repeat Dose Oral Toxicity Test of 2-Nitro-p-cresol in Rats / MHLW, Japan / publication

Data access
data published

Materials and methods

Test guideline

Qualifier according to guideline **Guideline** other: other guideline: 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

Test material

Test material information
2-Nitro-p-cresol

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.
- Age at study initiation: 5 weeks old
- Weight at study initiation: male 161 g (146-173 g), female 144 g (130-154 g)
- Housing: Animals were individually housed in a metallic cage with wire mesh bottoms
- Diet: Solid feed (MR stock: Nosan Corporation) was given ad libitum.
- Water: Tap water was given ad libitum.
- Acclimation and quarantine period:7-8 days

ENVIRONMENTAL CONDITIONS
- Temperature (°C): 22±3 (actual temperature: 22.0-22.6 °C)
- Humidity (%): 55±10% (actual humidity: 55-62%)
- Air changes (per hr): 10-15
- Photoperiod (hrs dark / hrs light): 12 hr dark/12 hr light (light: 7:00~19:00)

Administration / exposure

Route of administration
oral: gavage

Vehicle
olive oil

Analytical verification of doses or concentrations
yes

Duration of treatment / exposure
28 days

Frequency of treatment
once a day

Doses / concentrations

Remarks
Doses / Concentrations:
0, 15, 60, 250, 1000 mg/kg bw/day
Basis:
actual ingested

No. of animals per sex per dose
10/sex (0, 1000 mg/kg bw/day)
5/sex (15, 60, 250 mg/kg bw/day)

Control animals
yes, concurrent vehicle

Details on study design
- Dose selection rationale: Doses in this test were set based on the results of the following study: 14-day repeated dose oral toxicity test (Crl:CD(SD) rats, doses: 0 (olive oil), 10, 30, 100, 250, 500 or 1000 mg/kg bw/day). At 500 mg/kg/day and higher, sedation and salivation, and tendency of urine oxidatio n were observed in both sexes. At 1000 mg/kg/day, anemia and changes in liver functions were observed. At 250 mg/kg/day and higher, an increasing tendency on the liver weight was observed in both sexes. On the basis of these effects, a dose level of 1000 mg/kg was selected as the maximum dose expecting to induce the toxic changes, and then dose levels of 250, 60 and 15 mg/kg bw/day were selected, in accordance with a common ratio of approximately 4.

- Rationale for animal assignment (if not random): Body weight-balanced randomization
- Post-exposure recovery period in satellite groups: 14 days

Examinations

Observations and examinations performed and frequency
CLINICAL 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
The functional observational battery testing (FOB) was performed on all animals. Among the me asures in the FOB, detailed clinical observations were made before the initiation of dosing. Thereafter, detailed clinical observations were made once a week in dosing and recovery periods.
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).

BODY WEIGHT: Yes
- Time schedule for examinations: Before administration (on days 1, 7, 14, 21 and 28 of the admi nistration period, days 7 and 14 of the recovery period) and the necropsy days after completion of e very 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 administratio n period and days 5 and 12 of the recovery period. females: on days 4, 11, 18 and 25 of the administ ration period and days 4 and 11 of the recovery period)

OPHTHALMOSCOPIC EXAMINATION: No

HAEMATOLOGY: Yes
- Time schedule for collection of blood: the after completion of the administration and recovery perio ds
- Anaesthetic used for blood collection: ether
- Animals fasted: Yes (overnight)
- How many animals: all animals

CLINICAL CHEMISTRY: 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

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
NEUROBEHAVIOURAL EXAMINATION: No

Sacrifice and pathology
GROSS PATHOLOGY: Yes

ORGAN WEIBHT: 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, thoracical, lumber), thymus, thyroid (including parathyroid), adrenal glands, spleen, he art, stomach, liver, duodenum, jejunum, ileum (including Peyer's patches), cecum, colon, rectal, mes enteric 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 consu mption, hematology and clinical chemistry data, organ weights), 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, 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 contr ol group. When the number of the test group was two, F-test was used as for parametric data. Then, s tudent'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 signi ficance was set at 5%.

Results and discussion

Results of examinations

Clinical signs
effects observed, treatment-related

Description (incidence and severity)
(see Details on results)

Mortality
mortality observed, treatment-related

Description (incidence)
(see Details on results)

Body weight and weight changes
no effects observed

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

Haematological findings
effects observed, treatment-related

Description (incidence and severity)
(see Details on results)

Clinical biochemistry findings
effects observed, treatment-related

Description (incidence and severity)
(see Details on results)

Urinalysis findings
effects observed, treatment-related

Description (incidence and severity)
(see Details on results)

Behaviour (functional findings)
no effects observed

Description (incidence and severity)
(see Details on results)

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

Description (incidence and severity)
(see Details on results)

Gross pathological findings
effects observed, treatment-related

Description (incidence and severity)
(see Details on results)

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

Description (incidence and severity)
(see Details on results)

Details on results
CLINICAL SIGNS AND MORTALITY

At 250 mg/kg bw/day and higher, sedation and ptosis were observed in both sexes.
Transient salivation was observed in both sexes at 1,000 mg/kg bw/day. Soiled fur in one female and reddish tear in one male were observed at 1,000 mg/kg bw/day.

NEUROBEHAVIOUR
Clinical signs in detailed observation: No effects.
Sensory/reflex function test: No effects.
Grip strength: In the recovery period, high value of hindlimb strength in males and low value of forelimb strength in female were observed. (These were within background date.)
Motor activity: No effects.

BODY WEIGHT AND WEIGHT GAIN: No effects.
FOOD CONSUMPTION: No toxicological effects.

HAEMATOLOGY
At 1,000 mg/kg bw/day, low values of Hb, Ht and MCHC, and high values of Ret were observed in males and females, and high value of APTT was observed in females. At the end of recovery period, high values of MCV and MCH, and low value of MCHC were observed in males.

CLINICAL CHEMISTRY
At 1,000 mg/kg bw/day, high values of Alb, A/G, T-Cho, and K in males, and high values of γ-GTP and T-Bil in females were observed. At the end of recovery period, high value of Na was observed in males.

URINALYSIS
Pale yellow color was observed at 250 mg/kg bw/day and higher in males and females. At 1,000 mg/kg bw/day, low value of pH were observed in males and females. In the recovery period, low value of specific gravity was observed in males.

ORGAN WEIGHTS
At 250 mg/kg bw/day and higher, sedation and ptosis were observed in both sexes. Increase in the liver weight was observed at 250 mg/kg bw/day and higher in females and at 1,000 mg/kg bw/day in males. Furthermore, increases in the kidney weight in males and spleen weight in both sexes were observed at 1,000 mg/kg bw/day.

GROSS PATHOLOGY
At 1,000 mg/kg bw/day, blackish color of the spleen was observed in males and females at the ends of administration and recovery periods.

HISTOPATHOLOGY: NON-NEOPLASTIC
Histopathological examinations revealed hypertrophy of hepatocytes at 250 mg/kg bw/day and higher in females. At 1,000 mg/kg bw/day, increase in the extramedullary hematopoiesis and brown pi gmentation in the spleen was observed in both sexes. Additionally in males, hypertrophy of hepatocyt es in the liver was observed at 1,000 mg/kg bw/day. Moreover, an increase in hyaline droplets contai ning α2u-globulin in the renal proximal tubular epithelium in the kidney was observed in males at the same dose. These changes, except brown pigmentation in the spleen, tended to resolve after the rec overy period.
(See tables in the full report for more details)

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
other: see 'Remark'
At 250 mg/kg bw/day and higher, sedation and ptosis were observed in both sexes. Increase in the liver weight was observed at 250 mg/kg bw/day and higher in females and at 1,000 mg/kg bw/day in males. Histopathological examinations revealed hypertrophy of hepatocytes at 250 mg/kg bw/day and higher in females.

Target system / organ toxicity

Key result
false

Critical effects observed
not specified

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/PDF119 -33 -5b.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 2-nitro-p-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 250 mg/kg bw/day and higher, sedation and ptosis were observed in both sexes. Increase in the liver weight was observed at 250 mg/kg bw/day and higher in females and at 1,000 mg/kg bw/day in males. Furthermore, increases in the kidney weight in males and spleen weight in both sexes were observed at 1,000 mg/kg bw/day. Histopathological examinations revealed hypertrophy of hepatocytes at 250 mg/kg bw/day and higher in females. At 1,000 mg/kg bw/day, increase in the extramedullary hematopoiesis and brown pigmentation in the spleen was observed in both sexes. Additionally in males, hypertrophy of hepatocytes in the liver was observed at 1,000 mg/kg bw/day. Moreover, an increase in hyaline droplets containing α2u-globulin in the renal proximal tubular epithelium in the kidney was observed in males at the same dose. These changes, except brown pigmentation in the spleen, tended to resolve after the recovery period. 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:	IUC5-c2b1b0b7-0568-4483-b21c-54cfa1d1f5a7
Dossier UUID:	
Author:	
Date:	2022-12-16T14:27:08.815+09:00
Remarks:	

Administrative data

Endpoint
repeated dose toxicity: oral combined repeated dose and reproduction / developmental screening
deactivated phrase

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: GLP guideline study

Cross-reference

Reason / purpose for cross-reference
reference to same study

Remarks
7.8.1 Toxicity to reproduction.001

Reason / purpose for cross-reference
reference to other study

Remarks
7.5.1 Repeated dose toxicity: oral.001

Data source

Reference

A reproduction/developmental toxicity screening test in rats treated orally with 2-nitro-p-cresol / MHLW, Japan / study report

Data access
data published

Materials and methods

Test guideline

Qualifier
according to guideline

Guideline
other: OECD TG 421: Reproduction/developmental toxicity screening test

Deviations
no

GLP compliance
yes

Limit test
no

Test material

Test material information
2-Nitro-p-cresol

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 Laboratories Japan, Inc. Tsukuba
- Age at study initiation: 10 weeks
- Weight at study initiation: Males: 392-474 (average 427) g; Females: 238-297 (average 270) g
- Housing: Steel wire-mesh cage (250 mm x 350 mm x 200 mm)
- Diet: ad libitum
- Water: ad libitum
- Acclimation period: 19 days

ENVIRONMENTAL CONDITIONS
- Temperature (°C): 20-24
- Humidity (%): 33-69
- Air changes: 10-15 times / hr
- Photoperiod: 12 hrs dark / 12 hrs light (07:00-19:00)

Administration / exposure

Route of administration
oral: gavage

Vehicle
olive oil

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) Femal es: 42-47 days including 14 days pre-mating, mating and gestation periods, and the days until day 4 of lactation. Infertile females: 40-53 days

Frequency of treatment
Once/day, 7days/week

Doses / concentrations

Remarks
Doses / Concentrations:
0 (vehicle), 60, 250, and 1000 mg/kg bw/day
Basis:
actual ingested

No. of animals per sex per dose
12 animals/sex/dose

Control animals
yes, concurrent vehicle

Details on study design
- Dose selection rationale: Doses in this test were set based on the results of the following study: 28-day repeated dose oral toxicity test (doses: 0, 15, 60, 250, and 1000 mg/kg bw/day). At 250 mg/kg bw/day and higher, sedation and ptosis were observed in both sexes. Increase in the liver weight was observed at 250 mg/kg bw/day and higher in females and at 1,000 mg/kg bw/day in males. Furthermore, increases in the kidney weight in males and spleen weight in both sexes were observed at 1,000 mg/kg bw/day. Histopathological examinations revealed hypertrophy of hepatocytes at 250 mg/kg bw/day and higher in females. At 1,000 mg/kg bw/day, increase in the extramedullary hema topoiesis and brown pigmentation in the spleen was observed in both sexes. Additionally in males, hy pertrophy of hepatocytes in the liver was observed at 1,000 mg/kg bw/day. Moreover, an increase in hyaline droplets containing α2u-globulin in the renal proximal tubular epithelium in the kidney was o bserved in males at the same dose. These changes, except brown pigmentation in the spleen, tended to resolve after the recovery period.
On the basis of these effects, a dose level of 1000 mg/kg was selected as the maximum dose exp ecting to induce the toxic changes, and then dose levels of 250 and 60 mg/kg bw/day were selected as a middle dose and a minimum dose levels, respectively, in accordance with a common ratio of approximately 4.
- Rationale for animal assignment (if not random): Body weight-balanced randomization

Examinations

Observations and examinations performed and frequency
CAGE SIDE OBSERVATIONS: Yes
- Time schedule:
Males and females: 3 times/day

BODY WEIGHT: Yes
- Time schedule for examinations:
Males: Days 1, 4, 8, 11, 15, 22, 25, 29, 32, 36, 39, 42, and the day of necropsy
Females: Twice a week during the precopulation period (days 1, 4, 8, 11, and 15); gestation days 0, 4, 7, 11, 14, 17, and 20; lactation days 0 and 4; and the day of necropsy. For unmating females, 18, 22 and 25 in the mating period

FOOD CONSUMPTION: Yes
Males: Days 1, 4, 8, 11, 15, 32, 36, 39, and 42 in dosing period
Females: Days 1, 4, 8, 11, and 15; gestation days 1, 4, 7, 11, 14, 17, and 20; lactation days 2 and 4

HAEMATOLOGY: No
CLINICAL CHEMISTRY: No

URINALYSIS: No

Sacrifice and pathology
GROSS PATHOLOGY: Yes (see tables)
HISTOPATHOLOGY: Yes (epididymis, prostate, seminal vesicle, testis, ovary, uterus, vagina, and gross abnormal sites)

Other examinations
Organ weight: Testes and epididymides

Statistics
3 or more groups: The data were analyzed for homogeneity of variance by the Bartlett test. If varian ces were homogeneous, data was analyzed by the Dunnett test, whereas heterogeneous data was analyzed by the steel test ($p<0.05$, two-sided).
2 groups: The data were analyzed for homogeneity of variance by the F test. If variances were homog eneous, data was analyzed by the Student t test, whereas heterogeneous data was analyzed by the Aspin-Welch t test ($p<0.05$, two-sided).

Results and discussion

Results of examinations

Clinical signs
effects observed, treatment-related

Description (incidence and severity)
At 1,000 mg/kg bw/day, ptosis and decreased locomotor activity were observed in both sexes.

Mortality
mortality observed, treatment-related

Description (incidence)
At 1,000 mg/kg bw/day, ptosis and decreased locomotor activity were observed in both sexes.

Body weight and weight changes
no effects observed

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

Food efficiency
not examined

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

Ophthalmological findings
not examined

Haematological findings
not examined

Clinical biochemistry findings
not examined

Urinalysis findings
not examined

Behaviour (functional findings)
not examined

Organ weight findings including organ / body weight ratios
no effects observed

Gross pathological findings
effects observed, treatment-related

Description (incidence and severity)
see tables in the full report.

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

Description (incidence and severity)
see tables in the full report.

Histopathological findings: neoplastic
not examined

Details on results
At 1,000 mg/kg bw/day, histopathological examinations revealed centrilobular hypertrophy of hepatocytes in the liver and increased extramedullary hematopoiesis in the spleen in both sexes.

Effect levels

Key result
false

Dose descriptor
NOAEL

Effect level

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

Based on
test mat.

Sex
male/female

Basis for effect level
other: see 'Remark'
At 1,000 mg/kg bw/day, ptosis and decreased locomotor activity were observed in both sexes. At the same dose, histopathological examinations revealed centrilobular hypertrophy of hepatocytes in the liver and increased extramedullary hematopoiesis in the spleen in both sexes.

Target system / organ toxicity

Key result
false

Critical effects observed
not specified

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/PDF119 -33 -5c.pdf

Applicant's summary and conclusion

Conclusions
In this study, NOAEL for repeated-dose toxicity was determined to be 250 mg/kg bw/day in male and female rats.

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 2-nitro-p-cresol at 0, 60, 250, and 1,000 mg/kg bw/day. Males were dosed for 42 days, including a 14 day pre-mating and mating periods. Females were dosed for 42–47 days, including a 14 day pre-mating, mating, and gestation periods, and the time until lactation day 4. At 1,000 mg/kg bw/day, ptosis and decreased locomotor activity were observed in both sexes. At the same dose, histopathological examinations revealed centrilobular hypertrophy of hepatocytes in the liver and increased extramedullary hematopoiesis in the spleen in both sexes. On the basis of these changes, NOAEL for repeated-dose toxicity was determined to be 250 mg/kg bw/day in male and female rats.

Genetic toxicity in vitro

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.001

UUID:	IUC5-052223da-12ec-41a9-9c66-24acf10465ce
Dossier UUID:	
Author:	
Date:	2022-12-16T14:28:45.851+09:00
Remarks:	

Administrative data

Endpoint
in vitro gene mutation study in bacteria Type of genotoxicity: gene mutation

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: GLP guideline study

Data source

Reference

Reverse mutation test of 2-nitro-p-cresol in Bacteria / MHLW, Japan / study report

Data access
data published

Materials and methods

Test guideline

Qualifier
according to guideline

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

GLP compliance
yes

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

Test material

Test material information
2-Nitro-p-cresol

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

Test concentrations with justification for top dose
Dose–range finding test (–S9 mix and +S9 mix): 0 (vehicle), 1.22, 4.88, 19.5, 78.1, 313, 1250, and 5000 μg/plate;
Main bacterial reverse mutation test (–S9 mix and +S9 mix): 0 (vehicle), 39.1-5000 μg/plate [1st].
0 (vehicle), 19.5-5000 μg/plate [2nd]. 0 (vehicle), 19.5-1250 μg/plate [3rd, TA98].

Vehicle / solvent
- Vehicle(s)/solvent(s) used: DMSO
- Justification for choice of solvent/vehicle: The test substance was soluble in DMSO, but not in water.

Controls

Untreated negative controls
no

Negative solvent / vehicle controls
yes

True negative controls
yes tests without all strains

Positive controls
yes

Positive control substance
sodium azide
benzo(a)pyrene
furylfuramide
other: 2-aminoanthracene, 2-methoxy-6-chloro-9-[3-(2-chloroethyl)-aminopropylamino]acridine-2HCl

Details on test system and experimental conditions
METHOD OF APPLICATION: Preincubation

DURATION
- Preincubation period: 20 min

- Exposure duration: ca. 50 hours

NUMBER OF REPLICATIONS: 3

DETERMINATION OF CYTOTOXICITY
- Method: Cell growth

Evaluation criteria
Criteria for determining a positive result were as follows; A 2–fold or more increase in the number of revertant colonies compared with the solvent control, a concentration–related increase in the nu mber of revertant colonies, and a reproducible increase in the number of revertant colonies.

Statistics
No statistic method was used for judging of results.

Results and discussion

Test results

Key result
false

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

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
cytotoxicity see tables.

Vehicle controls validity
valid

Untreated negative controls validity
not examined

Positive controls validity
valid

Key result
false

Species / strain
E. coli WP2 uvr A
bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
cytotoxicity see tables.

Vehicle controls validity
valid

Untreated negative controls validity
not examined

Positive controls validity
valid

Additional information on results
TEST-SPECIFIC CONFOUNDING FACTORS
- Precipitation: Precipitation was not observed on any plates with/without metabolic activation.
- Other effects: coloring was observed on plates with concentration of 1250 µg/plate or more with/without metabolic activation in range-finding studies.

RANGE-FINDING/SCREENING STUDIES:
In range-finding studies, growth inhibition was observed on plates with concentration of 1250 µg/plate or more in all S. typhimurium strains with/without metabolic activation and on plates with concentration of 5000 µg/plate in all E.coli strains with/without metabolic activation.
COMPARISON WITH HISTORICAL CONTROL DATA:
In all test conditions and in all tested strains, the number of revertant colonies of solvent controls and positive controls were within the range of historical control data.

Remarks on result
other: all strains/cell types tested Migrated from field 'Test system'.

Overall remarks, attachments

Overall remarks

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

http://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF119 -33 -5e.pdf

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

Attachments

Attached (sanitised) documents for publication
119-33-5_Ames Tables.xlsx / 40.077 KB (application/vnd.openxmlformats-officedocument.spreadsheetml.sheet)

Applicant's summary and conclusion

Conclusions
Interpretation of results (migrated information):
negative

Executive summary

In a bacterial reverse mutation assay using S. typhimuriumTA100, TA1535, TA98, and TA1537 and E. coli WP2uvrA (OECD TG 471), 2-nitro-p-cresol was negative with or without metabolic activation.

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.002

UUID:	IUC5-05fb6ad5-c084-4f39-96a2-3ec8deffac01
Dossier UUID:	
Author:	
Date:	2022-12-16T14:29:34.047+09:00
Remarks:	

Administrative data

Endpoint
in vitro cytogenicity / chromosome aberration study in mammalian cells Type of genotoxicity: chromosome aberration

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 2-nitro-p-cresol on Cultured Chinese Hamster Cells. / MHLW, Japan / study report

Data access
data published

Materials and methods

Test guideline

Qualifier
according to guideline

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

Deviations
no

Qualifier
according to guideline

Guideline
JAPAN: Guidelines for Screening Mutagenicity Testing Of Chemicals

Deviations
no

GLP compliance
yes

Type of assay
in vitro mammalian chromosome aberration test
chromosome aberration

Test material

Test material information
2-Nitro-p-cresol

Method

Target gene
Chromosome

Species / strain

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

Metabolic activation
with and without

Metabolic activation system
rat liver, induced by phenobarbital and 5,6-benzoflavone

Test concentrations with justification for top dose
-S9 mix (short-term treatment): 0, 25.0, 50.0, 100, 200, 400 ug/mL
+S9 mix (short-term treatment): 0, 25.0, 50.0, 100, 200, 400 ug/mL
+S9 mix (short-term treatment, confirmation test): 0, 300, 400, 500, 600, 700, 800 ug/mL
-S9 mix (continuous treatment, 24 h): 0, 25.0, 50.0, 100, 200, 400 ug/mL
-S9 mix (continuous treatment, 48 h): 0, 25.0, 50.0, 100, 200, 400 ug/mL

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

Controls

Untreated negative controls
no

Negative solvent / vehicle controls
yes

True negative controls
no

Positive controls
yes

Positive control substance
cyclophosphamide
mitomycin C

Remarks
mitomycin C (without S9 mix), cyclophosphamide (with S9 mix)

Details on test system and experimental conditions
METHOD OF APPLICATION: Exposure duration: [continuous treatment]: 24, 48 hrs [short-term t reatment]:6 hrs + 18 hr
SPINDLE INHIBITOR: Colcemid
NUMBER OF REPLICATIONS: 2
NUMBER OF CELLS EVALUATED: 200 cells / dose
DETERMINATION OF CYTOTOXICITY
- Method: relative total growth

Evaluation criteria
For the evaluation of the frequencies of structural aberrations and of polyploidy induced, the following criteria were employed.
Appearance incidence of cells with chromosomal aberrations: Negative (-): < 5%; equivocal (±): 5-10%; positive (+): > 10%.
Finally, the substance is positive when the incidence is considered to be dose-related and repro ducible.

Statistics
not used.

Results and discussion

Test results

Key result
false

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

Metabolic activation
with

Genotoxicity
positive structural aberration

Cytotoxicity / choice of top concentrations
cytotoxicity 50% cell growth inhibition: 190.0 ug/mL (short)

Vehicle controls validity
valid

Untreated negative controls validity
not examined

Positive controls validity
valid

Key result
false

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

Metabolic activation
without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
cytotoxicity 50% cell growth inhibition: 192.3 ug/mL (short), 252.6 ug/mL (24h continuous) and 200.0 ug/mL (48h continuous)

Vehicle controls validity
valid

Untreated negative controls validity
not examined

Positive controls validity
valid

Overall remarks, attachments

Overall remarks

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

http://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF119 -33 -5f.pdf

Applicant's summary and conclusion

Executive summary

An in vitro chromosomal aberration test using CHL/IU cells (OECD TG 473) showed positive result with metabolic activation.

Genetic toxicity in vivo

ENDPOINT_STUDY_RECORD: Genetic toxicity in vivo.001

UUID:	IUC5-40365d06-5dac-40cf-a914-51fc7eacba50
Dossier UUID:	
Author:	
Date:	2022-12-16T14:30:38.531+09:00
Remarks:	

Administrative data

Endpoint
in vivo mammalian somatic cell study: cytogenicity / erythrocyte micronucleus Type of genotoxicity: chromosome aberration

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 Guideline study under GLP condition

Data source

Reference

Micronucleous test of 2-nitro-p-cresol on mouse / MHLW, Japan / study report

Materials and methods

Test guideline

Qualifier
according to guideline

Guideline
OECD Guideline 474 (Mammalian Erythrocyte Micronucleus Test)
in vivo mammalian somatic cell study: cytogenicity / erythrocyte micronucleus

Deviations
not specified

Qualifier
according to guideline

Guideline
other: Testing Methods for New Chemical Substances etc.

Deviations
not specified

GLP compliance
yes (incl. QA statement)

Type of assay
micronucleus assay
chromosome aberration

Test material

Test material information
2-Nitro-p-cresol

Test animals

Species
mouse

Strain
other: Crlj: CD1(ICR)

Sex
male

Details on test animals or test system and environmental conditions
TEST ANIMALS
- Source: Charles River Laboratories Japan, Inc. Atsugi Farm Center
- Age at study initiation: 8 weeks old
- Weight at study initiation: 31.2-36.1 g
- Assigned to test groups randomly: yes
- Housing: White flake (Charles River Japan, Inc.) in plastic cage (W 155 x K 245 x H 150mm: Clea Japan, Inc.)
- Diet: ad libitum
- Water: ad libitum
- Acclimation period: 8 days

ENVIRONMENTAL CONDITIONS
- Temperature (°C):21-23
- Humidity (%):47-67
- Air changes: 10-15/h
- Photoperiod: 12 h dark/ 12 h light (light time: 7:00 to 19:00)

Administration / exposure

Route of administration
oral: gavage

Vehicle
- Vehicle(s)/solvent(s) used: olive oil
- Concentration of test material in vehicle: 0, 25, 50, and 100 mg/mL
- Amount of vehicle (if gavage or dermal): 10 mL/kg bw
- Lot/batch no. (if required): 0420, 0929

Details on exposure
PREPARATION OF DOSING SOLUTIONS:
Dosing solutions were prepared by dissolving the test substance in olive oil. They were used within 6 days.

Duration of treatment / exposure
24 h

Frequency of treatment
Twice, 24 h interval

Doses / concentrations

Remarks
Doses / Concentrations:
0 (vehicle), 250, 500, and 1000 mg/kg bw
Basis:
actual ingested

No. of animals per sex per dose
5 males/dose

Control animals
yes, concurrent vehicle

Positive control(s)
Mitomycin C (MMC)
- Justification for choice of positive control: MMC is widely used in the micronucleus test and is one of the positive control materials exemplified and recommended in the applicable guidelines.
- Route of administration: intraperitoneal injection
- Doses / concentration: 1 mg/kg bw

Examinations

Tissues and cell types examined
Polychromatic erythrocytes from the femur bone marrow

Details of tissue and slide preparation
TREATMENT AND SAMPLING TIMES (in addition to information in specific fields): Cells for specimen were collected 24 h after the administration.

DETAILS OF SLIDE PREPARATION: Cell suspensions were expanded on the slide glass and dried. The expanded cells were stained using a cover glass with a small amount of acridine orange solution (40ug/mL).

METHOD OF ANALYSIS: fluorescence microscopy, blind method

Evaluation criteria
Criterion for determining a positive result: A dose-related increase in the number of micronucleated cells.

Statistics
The number of micronucleated polychromatic erythrocytes was determined by the Kastenbaum and Bowman method, and Cochran Armitage test;
Ratio of polychromatic erythrocytes to whole erythrocytes by Bartlett's test and Dunnett's test

Results and discussion

Test results

Key result
false

Sex
male

Genotoxicity
negative

Vehicle controls validity
valid

Positive controls validity
valid

Additional information on results
RESULTS OF RANGE-FINDING STUDY
- Dose range: 250, 500, 1000, 2000 mg/kg bw for males and females
- Clinical signs of toxicity in test animals: Death was observed in one male and one female at 2000 mg/kg bw. Colored urine and lowered body weight were observed in all animals dosed.
- Harvest times: 24 h after the treatment

RESULTS OF DEFINITIVE STUDY
- Induction of micronuclei (for Micronucleus assay): Males: The number of micronucleated cells in all dosed groups was within the range of control. Females: The study was not conducted because no se x differences were found in the preliminary study.
- Ratio of PCE/NCE (for Micronucleus assay): Ratios for dose levels, 0, 250, 500, and 1000 mg/kg bw/ day: 0.13%, 0.13%, 0.16%, and 0.11%; Positive control: 2.54%

Overall remarks, attachments

Overall remarks

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

http://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF119 -33 -5g.pdf

Applicant's summary and conclusion

Conclusions
Interpretation of results (migrated information): negative
The test substance did not produce micronuclei in the immature erythrocytes of the test species.

Executive summary

The result of an in vivo micronucleus study (OECD TG 474) was negative up to the maximum tolerated dose (1,000 mg/kg bw/day for 2 days) in mice.

Toxicity to reproduction

ENDPOINT_STUDY_RECORD: Toxicity to reproduction.001

UUID:	IUC5-8f5a4886-495c-4d75-a80e-240dc9bce661
Dossier UUID:	
Author:	
Date:	2022-12-16T14:31:56.759+09:00
Remarks:	

Administrative data

Endpoint
screening for reproductive / developmental toxicity based on test type (migrated information)

Type of information
experimental study

Adequacy of study
key study

Robust study summary
false

Used for classification
false

Used for SDS
false

Reliability
1 (reliable without restriction)

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

Cross-reference

Reason / purpose for cross-reference
reference to same study

Remarks
7.5.1 Repeated dose toxicity: oral.002

Data source

Reference

A reproduction/developmental toxicity screening test in rats treated orally with 2-nitro-p-cresol / MHLW, Japan / study report

Data access
data published

Materials and methods

Test guideline

Qualifier
according to guideline

Guideline
other: OECD TG 421: Reproduction/developmental toxicity screening test

Deviations
no

GLP compliance
yes

Limit test
no

Test material

Test material information
2-Nitro-p-cresol

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 Laboratories Japan, Inc. Tsukuba
- Age at study initiation: 10 weeks
- Weight at study initiation: Males: 392-474 (average 427) g; Females: 238-297 (average 270) g
- Housing: Steel wire-mesh cage (250 mm x 350 mm x 200 mm)
- Diet: ad libitum
- Water: ad libitum
- Acclimation period: 19 days

ENVIRONMENTAL CONDITIONS
- Temperature (°C): 20-24
- Humidity (%): 33-69
- Air changes: 10-15 times / hr
- Photoperiod: 12 hrs dark / 12 hrs light (07:00-19:00)

Administration / exposure

Route of administration
oral: gavage

Vehicle
olive oil

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

Duration of treatment / exposure
(P) Males: 42 days including 14 days pre-mating and mating periods, and thereafter 14 days (P) Femal es: 42-47 days including 14 days pre-mating, mating and gestation periods, and the days until day 4 of lactation. Infertile females: 40-53 days

Frequency of treatment
Once/day, 7days/week

Doses / concentrations

Remarks
Doses / Concentrations:
0 (vehicle), 60, 250, and 1000 mg/kg bw/day
Basis:
actual ingested

No. of animals per sex per dose
12 animals/sex/dose

Control animals
yes, concurrent vehicle

Examinations

Parental animals: Observations and examinations
CAGE SIDE OBSERVATIONS: Yes
- Time schedule:
Males and females: 3 times/day

BODY WEIGHT: Yes
- Time schedule for examinations:
Males: Days 1, 4, 8, 11, 15, 22, 25, 29, 32, 36, 39, 42, and the day of necropsy
Females: Twice a week during the precopulation period (days 1, 4, 8, 11, and 15); gestation days 0, 4, 7, 11, 14, 17, and 20; lactation days 0 and 4; and the day of necropsy. For unmating females, 18, 22 and 25 in the mating period

FOOD CONSUMPTION: Yes
Males: Days 1, 4, 8, 11, 15, 32, 36, 39, and 42 in dosing period
Females: Days 1, 4, 8, 11, and 15; gestation days 1, 4, 7, 11, 14, 17, and 20; lactation days 2 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 in the main groups and microscopically examined every day from the day after the start of administration until the day copulation was confirmed. During the pre-mating administration period, vaginal smear pictures were classified as proestrus,

estrus, metestrus or diestrus and examined for the frequency of estrus and interval between estruses (estrous cycle). During the mating period, vaginal smears were examined for the presence of sperm.

Sperm parameters (parental animals)
Parameters examined in P male parental generations: testes weight, epididymides 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, and weight].
GROSS EXAMINATION OF DEAD PUPS: Yes, for external and internal abnormalities.

Postmortem examinations (parental animals)
SACRIFICE:
Male animals: Rats were euthanized by exsanguination under ether anesthesia on the day after the l ast administration.
Maternal animals: Rats were euthanized by exsanguination under ether anesthesia on day 4 of lactati on.

GROSS PATHOLOGY: Yes (see tables)
HISTOPATHOLOGY: Yes (epididymis, prostate, seminal vesicle, testis, ovary, uterus, vagina, and gross abnormal sites)
ORGAN WEIGHTS, Yes: Testes and epididymis

Postmortem examinations (offspring)
GROSS NECROPSY
- Gross necropsy consisted of external and internal examinations including the cervical, thoracic, and abdominal viscera.

Statistics
The data were analyzed for homogeneity of variance by the Bartlett test. If variances were homogeneous, data was analyzed by the Dunnett test, whereas heterogeneous data was analyzed by the Steel test ($p<0.05$, two-sided).
2 groups: The data were analyzed for homogeneity of variance by the F test. If variances were hom ogeneous, data was analyzed by the Student t test, whereas heterogeneous data was analyzed by the Aspin-Welch t test ($p<0.05$, two-sided).
Especially,
Implantation index, Stillborn index, Liveborn index, External abnormalities, Viability index: the Steel test ($p<0.05$ and <0.01, two-sided)
Copulation index, Fertility index, Insemination index, Delivery index: Fisher's exact test ($p<0.05$ and <0.01, two-sided)

Reproductive indices
Each parameter was determined by the following equations:
Copulation index (%) = (No. of copulated animals/No. of co-housed animals) × 100
Fertility index (%) = (No. of pregnant females/No. of copulated females) × 100
Insemination index (%) = (No. of pregnant females/No. of copulated males) × 100
Duration of gestation (days) = day 0 of lactation – day 0 of gestation
Delivery index (%) = (No. of females delivered liveborn pups/No. of pregnant females) × 100
Implantation index (%) = (No. of implantation sites/No. of corpora lutea) × 100
Stillborn index (%) = (No. of stillborn pups/Total No. of pups born) × 100
Liveborn index (%) = (No. of liveborn pups/Total No. of pups born) × 100
External abnormalities (%) = (No. of pups with external abnormalities/No. of liveborn pups) × 100
Sex ratio = No. of liveborn male pups/(No. of liveborn male pups + No. of liveborn female pups)

Offspring viability indices
Viability index (%) = (No. of surviving pus on day 4 after birth/No. of liveborn pups on day 0 after 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: oral.002

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

Organ weight findings including organ / body weight ratios
no effects observed

Description (incidence and severity)
on reproductive organs

Gross pathological findings
no effects observed

Description (incidence and severity)
on reproductive organs

Histopathological findings: non-neoplastic
no effects observed

Description (incidence and severity)
on reproductive organs

Reproductive function / performance (P0)

Reproductive function: oestrous cycle
no effects observed

Reproductive function: sperm measures
not examined

Reproductive performance
no effects observed

Description (incidence and severity)
on reproductive organs

Effect levels (P0)

Key result
false

Dose descriptor
NOAEL

Effect level

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

Sex
male/female

Results: F1 generation

General toxicity (F1)

Clinical signs
no effects observed

Mortality / viability
no mortality observed

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
false

Dose descriptor
NOAEL

Generation
F1

Effect level

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

Sex
male/female

Basis for effect level
other: the highest dose tested

Overall reproductive toxicity

Key result
false

Reproductive effects observed
not specified

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/PDF119 -33 -5c.pdf

Applicant's summary and conclusion

Conclusions
NOAEL for the rat reproductive/developmental toxicity of 4-chlorobenzaldehyde was determined to be 200 mg/kg bw/day.

Executive summary

In the reproduction/developmental toxicity screening test (0, 60, 250, and 1,000 mg/kg bw/day) (OECD TG 421), no effects of this substance on reproductive and developmental parameters were observed at 1,000 mg/kg bw/day. NOAEL for the rat reproductive/developmental toxicity of 2-nitro-p-cresol was determined to be 1,000 mg/kg bw/day, the highest dose tested.

DOMAIN

Substance

SUBSTANCE: 2-Nitro-p-cresol

UUID:	IUC5-b0a94a30-717c-4d02-af0c-412c12b4d472
Dossier UUID:	
Author:	
Date:	2022-12-16T14:32:04.949+09:00
Remarks:	

Substance name
2-Nitro-p-cresol

Legal entity
National Institute of Health Sciences / Kawasaki / Japan

Identification of substance

Reference substance
2-nitro-p-cresol / 4-methyl-2-nitrophenol / 119-33-5 / 204-315-6

EC number	**EC name**
204-315-6	EC Inventory
CAS number	**CAS name**
119-33-5	
IUPAC name	
4-methyl-2-nitrophenol	

Role in the supply chain

Manufacturer
false

Importer
false

Only representative
false

Downstream user
false

References

Reference Substances

REFERENCE_SUBSTANCE: 2-nitro-p-cresol

UUID:	ECB5-4c8b7908-3640-47d4-b274-fae78201d6fd
Dossier UUID:	
Author:	
Date:	2018-08-27T10:55:22.000+09:00
Remarks:	

Reference substance name
2-nitro-p-cresol

IUPAC name
4-methyl-2-nitrophenol

Inventory

Inventory number

Inventory name
2-nitro-p-cresol

Inventory
EC Inventory

Inventory number
204-315-6

CAS number
119-33-5

Molecular formula
C7H7NO3

Description

CAS number
119-33-5

Synonyms

Synonyms

Identity
2-nitro-p-cresol

Identity
Phenol, 4-methyl-2-nitro-

Molecular and structural information

Molecular formula
C7H7NO3

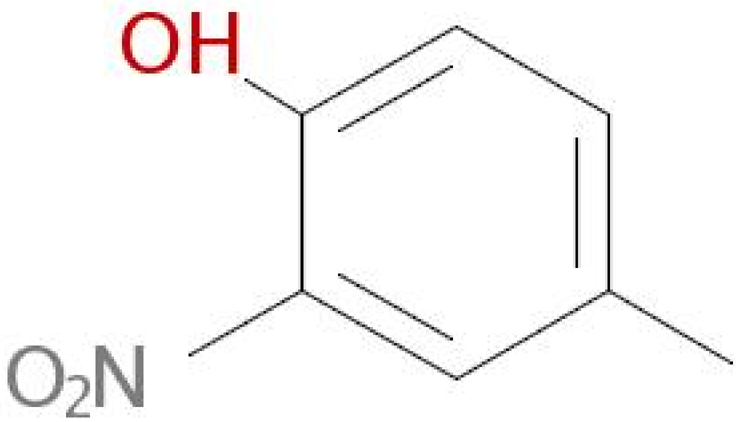
Molecular weight

153.1354

SMILES notation
Cc1ccc(O)c(c1)[N+](=O)[O-]

InChI
InChI=1/C7H7NO3/c1-5-2-3-7(9)6(4-5)8(10)11/h2-4,9H,1H3

Structural formula



Related substances

Group / category information
OECD Category: m,p - Cresols
USEPA Category: Phenols

Test Materials

TEST_MATERIAL_INFORMATION: 2-Nitro-p-cresol

UUID:	122b9bdd-68e3-3539-adbb-7378661ed03e
Dossier UUID:	
Author:	
Date:	2022-12-15T09:17:52.446+09:00
Remarks:	

Name
2-Nitro-p-cresol

Composition

Composition

Type
Constituent

Reference substance
2-nitro-p-cresol / 4-methyl-2-nitrophenol / 119-33-5 / 204-315-6

EC number	**EC name**
204-315-6	EC Inventory
CAS number	**CAS name**
119-33-5	
IUPAC name	
4-methyl-2-nitrophenol	

Other characteristics

Details on test material
- Name of test material (as cited in study report): 2-nitro-p-cresol
- Purity: 99.6%
- Lot/batch No.: FHD01
- Stability under test conditions: Stable
- Storage condition of test material: a cool (3-6 °C) and dark place (in a refrigerator), with an airtight stopper
- Dosing solution storage condition: under a cool (3-6 °C) place (in a refrigerator), in a brown glass bo ttle
- Other: The dosing solution was used within 7 days of preparation.

TEST_MATERIAL_INFORMATION: 2-Nitro-p-cresol

UUID:	5bf89a9f-610d-3117-9884-daae68efa128
Dossier UUID:	
Author:	
Date:	2022-12-15T09:16:41.786+09:00
Remarks:	

Name
2-Nitro-p-cresol

Composition

Composition

Type
Constituent

Reference substance
2-nitro-p-cresol / 4-methyl-2-nitrophenol / 119-33-5 / 204-315-6

EC number	**EC name**
204-315-6	EC Inventory
CAS number	**CAS name**
119-33-5	
IUPAC name	
4-methyl-2-nitrophenol	

Other characteristics

Details on test material
- Name of test material (as cited in study report): 2-Nitro-p-cresol
- Analytical purity: 99.8%
- Lot No.: FBR01
- Storage condition of test material: at a cold (temperature 2-6 °C) and dark place, with airtight stopper.
- Stability under test conditions: The stability of test material was identified by analysis of the remainder.

Literatures

LITERATURE: A reproduction/developmental toxicity screening test in rats treated orally with 2-nitro-p-cresol

UUID:	cdbb7871-31c4-3a0d-8a4b-bf954b375559
Dossier UUID:	
Author:	
Date:	2017-02-15T15:43:40.000+09:00
Remarks:	

General information

Reference Type
study report

Title
A reproduction/developmental toxicity screening test in rats treated orally with 2-nitro-p-cresol

Author
MHLW, Japan

Year
2012

Bibliographic source
available in the web of Japan Existing Chemical Data Base (JECDB) at http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp

Testing facility
BoZo Research Center

LITERATURE: In Vitro Chromosomal Aberration Test of 2-nitro-p-cresol on Cultured Chinese Hamster Cells.

UUID:	8a48dba7-f670-3547-8ad5-6a6f48a27e32
Dossier UUID:	
Author:	
Date:	2017-02-15T15:41:24.000+09:00
Remarks:	

General information

Reference Type
study report

Title
In Vitro Chromosomal Aberration Test of 2-nitro-p-cresol on Cultured Chinese Hamster Cells.

Author
MHLW, Japan

Year
2007

Bibliographic source
available in the web of Japan Existing Chemical Data Base (JECDB) at http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp

Testing facility
BoZo Research Center

LITERATURE: Micronucleous test of 2-nitro-p-cresol on mouse

UUID:	322a5a3a-eb01-3870-ada3-90cdba50efff
Dossier UUID:	
Author:	
Date:	2017-02-15T15:42:10.000+09:00
Remarks:	

General information

Reference Type
study report

Title
Micronucleous test of 2-nitro-p-cresol on mouse

Author
MHLW, Japan

Year
2011

Bibliographic source
available in the web of Japan Existing Chemical Data Base (JECDB) at http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp

Testing facility
Bozo Research Center

LITERATURE: Reverse mutation test of 2-nitro-p-cresol in Bacteria

UUID:	99e619c7-c952-31c2-9687-ca7d8c11d691
Dossier UUID:	
Author:	
Date:	2022-12-15T09:31:25.733+09:00
Remarks:	

General information

Reference Type
study report

Title
Reverse mutation test of 2-nitro-p-cresol in Bacteria

Author
MHLW, Japan

Year
2007

Bibliographic source
available in the web of Japan Existing Chemical Data Base (JECDB) at http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp

Testing facility
Bozo Research Center Inc.

LITERATURE: Single Dose Oral Toxicity Test of 2-nitro-p-cresol in Rats

UUID: c35179d9-e9d1-4f83-8fea-4e8e3cfe7be7
Dossier UUID:
Author:
Date: 2018-08-24T16:59:16.000+09:00
Remarks:

General information

Reference Type
study report

Title
Single Dose Oral Toxicity Test of 2-nitro-p-cresol in Rats

Author
MHLW, japan

Bibliographic source
Single Dose Oral Toxicity Test of 2-nitro-p-cresol in Rats

LITERATURE: Twenty-eight-day Repeat Dose Oral Toxicity Test of 2-Nitro-p-cresol in Rats

UUID:	498a7463-633b-3f3e-93d5-83ac8e71b5bd
Dossier UUID:	
Author:	
Date:	2022-12-15T09:31:07.197+09:00
Remarks:	

General information

Reference Type
publication

Title
Twenty-eight-day Repeat Dose Oral Toxicity Test of 2-Nitro-p-cresol in Rats

Author
MHLW, Japan

Year
2011

Bibliographic source
available in the web of Japan Existing Chemical Data Base (JECDB) at http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp

Testing facility
Research institute for animal science in biochemistry and toxicology (RIAS)

Legal Entities

LEGAL_ENTITY: National Institute of Health Sciences

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

General information

Legal entity name
National Institute of Health Sciences

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

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Kanagawa

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Identifiers

Other IT system identifiers

IT system
LEO

ID
10767

IT system
IUCLID4

ID
16558402024DIV750