



Name: 2-Nitro-p-cresol / 4-methyl-2-nitrophenol / 119-33-5

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

Printing date: 2018-08-27T11:02:40.456+09:00

Table of Contents

2-Nitro-p-cresol	1
CORE	1
1 General information	1
1.1 Identification	1
Identification	1
OECD	2
D Health Effects	2
60 Acute toxicity: oral	2
Acute toxicity: oral.001	2
67 Repeated dose toxicity: oral	6
Repeated dose toxicity: oral.001	6
Repeated dose toxicity: oral.002	13
70 Genetic toxicity in vitro	19
Genetic toxicity in vitro.001	19
Genetic toxicity in vitro.002	23
71 Genetic toxicity in vivo	27
Genetic toxicity in vivo.001	27
73 Toxicity to reproduction	31
Toxicity to reproduction.001	31
References	38
2-nitro-p-cresol	38
4-methyl-2-nitrophenol / 119-33-5 / 204-315-6	40
4-methyl-2-nitrophenol / 119-33-5 / 204-315-6	41
A reproduction/developmental toxicity screening test in rats treated orally with 2 -nitro-p-cresol	42
A reproduction/developmental toxicity screening test in rats treated orally with 2 -nitro-p-cresol	43
In Vitro Chromosomal Aberration Test of 2-nitro-p-cresol on Cultured Chinese Hamster Cells.	44
Micronucleous test of 2-nitro-p-cresol on mouse	45
National Institute of Health Sciences	46
Reverse mutation test of 2-nitro-p-cresol in Bacteria	48
Single Dose Oral Toxicity Test of 2-nitro-p-cresol in Rats	49
Twenty-eight-day Repeat Dose Oral Toxicity Test of 2-Nitro-p-cresol in Rats	50

2-Nitro-p-cresol

CORE

General information

Identification

SUBSTANCE: 2-Nitro-p-cresol

UUID: IUC5-b0a94a30-717c-4d02-af0c-412c12b4d472

Dossier UUID:

Author: SuperUser

Date: 2016-12-21T15:08:10.000+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

204-315-6

EC name

EC Inventory

CAS number

119-33-5

CAS name

IUPAC name

4-methyl-2-nitrophenol

Role in the supply chain

Manufacturer

false

Importer

false

Only representative

false

Downstream user

false

OECD

Health Effects

Acute toxicity: oral

ENDPOINT_STUDY_RECORD: Acute toxicity: oral.001

UUID: 92069579-4fea-46b6-9947-0a4e625fdd42

Dossier UUID:

Author: Dra

Date: 2018-08-27T10:58:39.407+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

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

[4-methyl-2-nitrophenol / 119-33-5 / 204-315-6](#)

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 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

Decreased spontaneous movement was observed 30 min-4 hrs after administration in all animals.

Body weight

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

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: Dra

Date: 2018-08-27T10:58:20.168+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

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 / publication](#)

Data access

data published

Materials and methods

Test guideline

Qualifier

according to

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

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

GLP compliance

yes

Test material

Test material information

[4-methyl-2-nitrophenol](#) / [119-33-5](#) / [204-315-6](#)

Test animals

Species

rat
common rodent species

Strain

other: Crl:CD(SD)

Sex

male/female

Details on test animals 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 (CrI: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 oxidation 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 measures 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 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 after completion of the administration and recovery periods

- 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, 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), 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 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)

(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 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 α 2u-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.

(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 α_2 -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:** Dra**Date:** 2018-08-27T10:59:28.272+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**

reference to same study

Remarks

7.8.1 Toxicity to reproduction.001

Reason / purpose

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

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

Deviations

no

GLP compliance

yes

Limit test

no

Test material

Test material information

[4-methyl-2-nitrophenol / 119-33-5 / 204-315-6](#)

Test animals

Species

rat

common rodent species

Strain

other: CrI: CD(SD)

Sex

male/female

Details on test animals 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)

Females: 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. Further more, 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 α_2 -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, 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 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 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 homogeneous, 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: Dra

Date: 2018-08-27T10:59:55.149+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

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

[4-methyl-2-nitrophenol](#) / [119-33-5](#) / [204-315-6](#)

Method

Species / strain

Species / strain

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

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

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

Controls

Negative controls

no

Solvent 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 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 number 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

yes see tables.

Vehicle controls valid

yes

Negative controls valid

not examined

Positive controls valid

yes

Remarks on result

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

Key result

false

Species / strain

E. coli WP2 uvr A
bacteria

Metabolic activation

with and without

Genotoxicity

negative

Cytotoxicity

yes see tables.

Vehicle controls valid

yes

Negative controls valid

not examined

Positive controls valid

yes

Remarks on result

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

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.

Overall remarks, attachments

Overall remarks

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

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

Applicant's summary and conclusion

Conclusions

Interpretation of results (migrated information):

negative

Executive summary

In a bacterial reverse mutation assay using *S. typhimurium* TA100, 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: Dra

Date: 2018-08-27T11:00:11.079+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

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

Deviations

no

Qualifier

according to

Guideline

JAPAN: Guidelines for Screening Mutagenicity Testing Of Chemicals

Deviations

no

GLP compliance

yes

Type of assayin vitro mammalian chromosome aberration test
chromosome aberration**Test material****Test material information**[4-methyl-2-nitrophenol / 119-33-5 / 204-315-6](#)**Method****Target gene**

Chromosome

Species / strain**Species / strain**

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

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

Controls**Negative controls**

no

Solvent controls

yes

True negative controls

no

Positive controls

yes

Positive control substancecyclophosphamide
mitomycin C**Remarks**

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

Details on test system and conditions

METHOD OF APPLICATION: Exposure duration: [continuous treatment]: 24, 48 hrs [short-term treatment]: 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 (\pm): 5-10%; positive (+): > 10%.

Finally, the substance is positive when the incidence is considered to be dose-related and reproducible.

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

yes 50% cell growth inhibition: 190.0 ug/mL (short)

Vehicle controls valid

yes

Negative controls valid

not examined

Positive controls valid

yes

Key result

false

Species / strain

other: Chinese hamster lung (CHL/IU) cells

Metabolic activation

without

Genotoxicity

negative

Cytotoxicity

yes 50% cell growth inhibition: 192.3 ug/mL (short), 252.6 ug/mL (24h continuous) and 200.0 ug/mL (48h continuous)

Vehicle controls valid

yes

Negative controls valid

not examined

Positive controls valid

yes

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-a914-51fc7eacha50

Dossier UUID:

Author: Dra

Date: 2018-08-27T11:01:25.703+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

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

Deviations

not specified

Qualifier

according to

Guideline

other: Testing Methods for New Chemical Substances etc.

Deviations

not specified

GLP compliance

yes (incl. certificate)

Type of assay

micronucleus assay

chromosome aberration

Test material

Test material information

[4-methyl-2-nitrophenol](#) / [119-33-5](#) / [204-315-6](#)

Test animals

Species

mouse

Strain

other: Crlj: CD1(ICR)

Sex

male

Details on test animals 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 valid

yes

Positive controls valid

yes

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 sex 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) were 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: Dra

Date: 2018-08-27T11:01:45.823+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

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

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

Deviations

no

GLP compliance

yes

Limit test

no

Test material

Test material information

[4-methyl-2-nitrophenol / 119-33-5 / 204-315-6](#)

Test animals

Species

rat

Strain

other: CrI:CD(SD)

Sex

male/female

Details on test animals 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)
Females: 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

Estrous 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 last administration.

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

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 homogeneous, 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) \times 100

Fertility index (%) = (No. of pregnant females/No. of copulated females) \times 100

Insemination index (%) = (No. of pregnant females/No. of copulated males) \times 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) \times 100

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

Stillborn index (%) = (No. of stillborn pups/Total No. of pups born) \times 100

Liveborn index (%) = (No. of liveborn pups/Total No. of pups born) \times 100

External abnormalities (%) = (No. of pups with external abnormalities/No. of liveborn pups) \times 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 pup on day 4 after birth/No. of liveborn pups on day 0 after birth) \times 100

Results and discussion

Results: P0 (first parental animals)

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: estrous 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.

References

REFERENCE_SUBSTANCE: 2-nitro-p-cresol

UUID: ECB5-4c8b7908-3640-47d4-b274-fae78201d6fd

Dossier UUID:

Author: Dra

Date: 2018-08-27T10:55:22.245+09:00

Remarks:

General information

Reference substance name

2-nitro-p-cresol

Inventory

Inventory name

2-nitro-p-cresol

Inventory

EC

Inventory number

204-315-6

CAS number

119-33-5

Molecular formula

C₇H₇NO₃

Description

Reference substance information

IUPAC name

4-methyl-2-nitrophenol

Synonyms

Identity
2-nitro-p-cresol
Identity
Phenol, 4-methyl-2-nitro-

CAS information

CAS number

119-33-5

Related substances

Group / category information

OECD Category: m,p - Cresols

USEPA Category: Phenols

Molecular and structural information

Molecular formula

C₇H₇NO₃

Molecular weight

153.1354

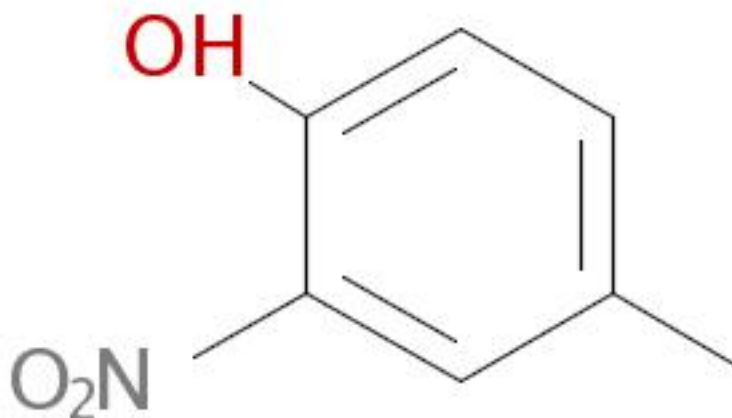
SMILES notation

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



TEST_MATERIAL_INFORMATION: 4-methyl-2-nitrophenol / 119-33-5 / 204-315-6

UUID: 122b9bdd-68e3-3539-adbb-7378661ed03e

Dossier UUID:

Author: SuperUser

Date: 2017-02-15T15:43:40.000+09:00

Remarks:

Name

4-methyl-2-nitrophenol / 119-33-5 / 204-315-6

Composition

Type

Constituent

Reference substance

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

EC number

204-315-6

EC name

EC Inventory

CAS number

119-33-5

CAS name

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 bottle
- Other: The dosing solution was used within 7 days of preparation.

TEST_MATERIAL_INFORMATION: 4-methyl-2-nitrophenol / 119-33-5 / 204-315-6

UUID: 5bf89a9f-610d-3117-9884-daae68efa128

Dossier UUID:

Author: SuperUser

Date: 2017-02-15T15:32:16.000+09:00

Remarks:

Name

4-methyl-2-nitrophenol / 119-33-5 / 204-315-6

Composition

Type

Constituent

Reference substance

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

EC number

204-315-6

EC name

EC Inventory

CAS number

119-33-5

CAS name

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 stoppered.
- Stability under test conditions: The stability of test material was identified by analysis of the remainder.

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

UUID: b4411bda-a299-3d38-b479-ab059b26ee3e

Dossier UUID:

Author: Dra

Date: 2018-08-27T10:46:46.712+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: A reproduction/developmental toxicity screening test in rats treated orally with 2-nitro-p-cresol

UUID: cdbb7871-31c4-3a0d-8a4b-bf954b375559

Dossier UUID:

Author: SuperUser

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: SuperUser

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: SuperUser

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

LEGAL_ENTITY: National Institute of Health Sciences

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

Dossier UUID:

Author: Dra

Date: 2018-02-27T15:56:45.710+09:00

Remarks:

General information

Legal entity name

National Institute of Health Sciences

Identifiers

Other IT system identifiers

IT system

LEO

ID

10767

IT system

IUCLID4

ID

16558402024DIV750

Contact information

Contact address

Address 1

Tonomachi 3-25-26

Address 2

Kawasaki-ku

Postal code

210-9501

Town

Kawasaki

Region / State

Kanagawa

Country

Japan

Contact persons

Person

Hirose, Akihiko; National Institute of Health Sciences, Japan

Last name

Hirose

First name

Akihiko

Organisation

National Institute of Health Sciences, Japan

Department

Division of Risk Assessment

Title

Dr

Country

Japan

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

UUID: 99e619c7-c952-31c2-9687-ca7d8c11d691

Dossier UUID:

Author: SuperUser

Date: 2017-02-15T15:38:25.000+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: SuperUser

Date: 2018-08-24T16:59:16.286+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: SuperUser

Date: 2017-02-15T15:32:16.000+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

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)