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Legal entity owner: National Institute of Health Science

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Remarks:

Dossier header

Dossier submission type

Name

OECD SIDS

Version

core 7.0

Name (given by user)

Dossier subject

Dossier subject

[4-Methylpyridine / 108-89-4](#)

Public name

Submitting legal entity

[National Institute of Health Science](#)

Dossier creation date/time

Tue, 29 Nov 2022, 15:17:51+0900

Used in category

LEGAL_ENTITY: National Institute of Health Science

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Remarks:

General information

Legal entity name

National Institute of Health Science

4-Methylpyridine

General information

Identification

Identification

SUBSTANCE: 4-Methylpyridine

UUID: 5e52401d-334f-4369-b96f-5a7a4e21889e

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Author:

Date: 2022-11-29T15:05:44.985+09:00

Remarks:

Substance name

4-Methylpyridine

Legal entity

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

Identification of substance

Reference substance

[4-methylpyridine / 108-89-4](#)

EC number

EC name

CAS number

CAS name

108-89-4

IUPAC name

Role in the supply chain

Manufacturer

false

Importer

false

Only representative

false

Downstream user

false

Toxicological information

Repeated dose toxicity

Repeated dose toxicity: oral

ENDPOINT_STUDY_RECORD: Repeated dose toxicity: oral. 001

UUID: 6d6b9026-81c7-4531-a1e0-4a7a3c78c430

Dossier UUID:

Author:

Date: 2022-11-29T15:05:44.985+09:00

Remarks:

Administrative data

Endpoint

short-term repeated dose toxicity: oral

Type of information

experimental study

Adequacy of study

key study

Robust study summary

false

Used for classification

false

Used for SDS

false

Reliability

1 (reliable without restriction)

Rationale for reliability incl. deficiencies

guideline study OECD Test Guideline study under GLP condition

Reliability 1

Cross-reference

Reason / purpose for cross-reference

reference to same study 7.8.1 Toxicity to reproduction: Toxicity to reproduction. 001

Related information

[OECD / Toxicity to reproduction / Toxicity to reproduction. 001 / 4-Methylpyridine / 108-89-4](#)

Data source

Reference

[Combined repeated dose toxicity study with the reproductive/developmental toxicity screening test of / Ministry of Health, Labour and Welfare \(MHLW\), Japan / study report](#)

Data access

data published https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF108-89-4d.pdf

Materials and methods

GLP compliance

yes

Limit test

no

Test material

Test material information

4-methylpyridine

Specific details on test material used for the study

- Name of test material (as cited in study report): 4-methylpyridine
- Analytical purity: 99.0%
- Storage condition of test material: Room temperature, shading, airtightness (filled with argon gas)
- Stability under test conditions: The stability of test material was identified by analysis of the remainder.

Test animals

Species

rat

common rodent species

Strain

other: CrI:CD(SD)

Sex

male/female

Details on test animals or test system and environmental conditions

TEST ANIMALS

- Source: Charles River Japan, Inc., Hino Breeding Center.
- Age at study initiation: 10 weeks old
- Weight at study initiation:
Males (main study groups): 375-421 g, females (main study groups): 185-234 g, females in (mating groups): 207-254 g
- Housing: Animals were individually housed in stainless steel suspension cage (240W × 380D × 200H mm), from gestation day 18 to lactation day 4, Dams were bred individually or with individual littermates in plastic cages (310W x 360D x 175H mm) and bedding.
- Diet: Solid feed (CRF-1: Oriental Yeast Co., Ltd.) was given ad libitum.
- Water: Tap water was given ad libitum.
- Acclimation period: Males (main study groups): 18 days, females (main study groups): 19 days, females (mating groups): 18 days

ENVIRONMENTAL CONDITIONS

- Temperature (°C): 20-26°C (actual temperature: 22.2-24.3°C)
- Humidity (%): 40.0-70.0% (actual humidity: 41.1-66.8%)
- Air changes (per hr): 12
- Photoperiod (hrs dark / hrs light): 12 hr dark/12 hr light (light: 6:00~18:00)

Administration / exposure

Route of administration

oral: gavage

Vehicle

water for injection

Details on oral exposure

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

Analytical verification of doses or concentrations

yes

Details on analytical verification of doses or concentrations

Concentrations of the test solutions using administration on day 1 were analyzed with GC. Analytical concentrations of the test solutions were all within the range of 99.5-100.5% of the nominal concentrations and both values were within the acceptable range (concentration: percentage of nominal concentration, 100±10%).

Duration of treatment / exposure

Males: 28 days including 14 days pre-mating

Females (main study groups): 28 days

Females (mating groups): 42-46 days including 14 days pre-mating, mating and gestation periods and the days until day 4 of lactation

Frequency of treatment

Once/day, 7 days/week

Doses / concentrations

Dose / conc.	
0	mg/kg bw/day (actual dose received)
Dose / conc.	
5	mg/kg bw/day (actual dose received)
Dose / conc.	
20	mg/kg bw/day (actual dose received)
Dose / conc.	
80	mg/kg bw/day (actual dose received)

No. of animals per sex per dose

- Main study groups:

Control- and high-dose groups: 12 males and 10 females per group (half of both sexes assigned as the treatment groups, and the remaining half assigned as the recovery groups)

Low- and middle-dose groups: 12 males and 5 females per group (half of males assigned as the treatment groups, and the remaining half assigned as the recovery groups)

- Mating groups:

12 females per dose

Control animals

yes, concurrent vehicle

Details on study design

- Dose selection rationale: Based on the results of a 14-day preliminary study, the high dose was set to 80 mg/kg bw/day, and the intermediate dose and low dose were set to 20 mg/kg bw/day and 5 mg/kg bw/day, respectively.

[14-day preliminary study]

A 14-day repeated dose oral toxicity test (CrI:CD(SD) rats, doses: 0, 50, 100 or 200 mg/kg bw/day).

All males and females at 200 mg/kg bw/day died or were moribund, and one male at 100 mg/kg bw/day was moribund. Decreased body weight and food consumption were observed in males at 100 mg/kg bw/day and above and females at 200 mg/kg bw/day. Decreased platelet counts were observed in females at 50 mg/kg bw/day and above. Increased in adrenal glands weight was observed in females at 100 mg/kg bw/day.

- 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 (main study groups): 2 times/day (before administration, 6-197 minutes after administration) during the administration period. Once a day during the recovery period.

Females (mating groups): 2 times/day (before administration, 8-160 minutes after administration) during the administration period.

DETAILED CLINICAL OBSERVATIONS: Yes

- Time schedule:

Males and females (main study groups): on day of grouping, on days 7, 14, 21 and 27 of administration period.

Females (mating groups): on day of grouping, on days 7 and 14 of administration period, on days 1, 8 and 15 of gestation period, on day 4 of lactation period.

BODY WEIGHT: Yes

- Time schedule for examinations:

Males and females (main study groups):

Twice a week (On days 1, 4, 8, 11, 15, 18, 22, 25, 28 and 29 of administration period, on days 1, 4, 8, 11, 14 and 15 of recovery period).

Females (mating groups): Twice a week (On days 1, 4, 8, 11, 15, 18, 22, 25, 29, 32, 36, 39, 43, 46, 50 and 53 of administration period, on days 0, 7, 14 and 20 of gestation period, on days 0, 4 and 5 of lactation period).

FOOD CONSUMPTION AND COMPOUND INTAKE (if feeding study):

- Food consumption: Yes

- Time schedule for examinations:

Males and females (main study groups):

Twice a week (Males: On days 2, 5, 9 and 12 of administration period, on days 2, 5, 9 and 12 of recovery period; Females: On days 2, 5, 9, 12, 16, 19, 23 and 26 of administration period, on days 2, 5, 9 and 12 of recovery period).

Females (mating groups): Twice a week (On days 2, 5, 9 and 12 of administration period, on days 2, 9, 16 and 20 of gestation period, on days 2 of lactation period).

WATER INTAKE

- Time schedule for examinations:

Males and females (main study groups):

Twice a week (Males: On days 2, 5, 9 and 12 of administration period, on days 2, 5, 9 and 12 of recovery period; Females: On days 2, 5, 9, 12, 16, 19, 23 and 26 of administration period, on days 2, 5, 9 and 12 of recovery period).

Females (mating groups): Twice a week (On days 2, 5, 9 and 12 of administration period, on days 2, 9, 16 and 20 of gestation period, on days 2 of lactation period).

OPHTHALMOSCOPIC EXAMINATION: No

HAEMATOLOGY: Yes

- Time schedule for collection of blood:

Males and females (main study groups): At the end of administration period, or at the end of recovery period in both sexes

- Anaesthetic used for blood collection: Pentobarbital sodium

- Animals fasted: Yes

- How many animals:

At the end of administration period: 6 males/dose (0, 5, 20, 80 mg/kg bw/day), 5 females/dose (0, 5, 20, 80 mg/kg bw/day)

At the end of recovery period: 6 males/dose (0, 5, 20, 80 mg/kg bw/day), 5 females/dose (0 and 80 mg/kg bw/day)

- Parameters examined: red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, reticulocyte percentage, platelet count, white blood cell count, differential white blood cell count, prothrombin time, activated partial thromboplastin time, fibrinogen.

CLINICAL BIOCHEMISTRY: Yes

- Time schedule for collection of blood:

Males and females (main study groups): At the end of administration period, or at the end of recovery period in both sexes

- Animals fasted: Yes

- How many animals:

At the end of administration period: 6 males/dose (0, 5, 20, 80 mg/kg bw/day), 5 females/dose (0, 5, 20, 80 mg/kg bw/day)

At the end of recovery period: 6 males/dose (0, 5, 20, 80 mg/kg bw/day), 5 females/dose (0 and 80 mg/kg bw/day)

- Parameters checked: ALP, total cholesterol, triglyceride, total bilirubin, glucose, urea nitrogen, creatinine, sodium, potassium, chloride, calcium, inorganic phosphorus, total protein, albumin, A/G ratio, AST, ALT, γ -GT

BLOOD HORMONE: Yes

- Time schedule for collection of serum:

Males and females (main study groups): At the end of administration period in both sexes

- Animals fasted: Yes

- How many animals:

6 males/dose (0, 5, 20, 80 mg/kg bw/day), 5 females/dose (0, 5, 20, 80 mg/kg bw/day)

- Parameters checked: Triiodothyronine (T3), Thyroxin (T4), and thyroid stimulating hormone (TSH)

URINALYSIS: Yes

- Time schedule for collection of urine:

Males and females (main study groups): Before the end of the administration period (day 23 of administration period) and before the end of recovery (day 12 of recovery period).

- Metabolism cages used for collection of urine: Yes

A urine collector to collect fresh urine samples under fasting but ad libitum drinking conditions, followed by collection of 24-hour urine samples under ad libitum feeding and drinking conditions.

- How many animals:

At the end of administration period: 6 males/dose (0, 5, 20, 80 mg/kg bw/day), 5 females/dose (0, 5, 20, 80 mg/kg bw/day)

At the end of recovery period: 6 males/dose (0, 5, 20, 80 mg/kg bw/day), 5 females/dose (0 and 80 mg/kg bw/day)

- Parameters checked:

Fresh urine: Color, pH, protein, glucose, ketones, bilirubin, occult blood, urobilinogen, sediment

24-urine: Specific gravity, urine volume (24-hour volume)

NEUROBEHAVIOURAL EXAMINATION: Yes

- Time schedule for examinations:

Males and females (main study groups): Final week of administration (Manipulative test and measurement of grip strength: Day 27 of administration, measurement of motor activity: Day 26 of administration), Day 10 of recovery period (measurement of motor activity: males of main study groups)
- Dose groups that were examined: Autopsy animals after the end of the administration period
- Battery of functions tested:

- 1) Manipulative Test. Pupillary reflex, approaching behavior, response to touch, auditory reflex, pain reflex
 - 2) Measurement of Grip Strength. Following manipulative test, grip strength of forelimb and hind limb were measured by CPU gauge (San Diego Instruments Inc.).
 - 3) Measurement of Spontaneous Motor Activity. Spontaneous motor activity (Ambulatory and vertical counts) was measured by Activity Monitor (MED Associates Inc.).
- The measurements were collected at 10-minute intervals from 1 hour to 2 hours after administration. Since effects were observed in males of the main test group, males of the main test group were measured before the end of the recovery period (10 days of recovery) at 10 minute intervals for 1 hour.

Sacrifice and pathology

GROSS PATHOLOGY: Yes

ORGAN WEIGHT: Yes [main study groups: brain, pituitary, salivary glands, thyroids, adrenal gland, thymus, spleen, heart, liver, kidney, testes, epididymides, ventral prostate, seminal vesicles, ovaries, uterus; females in mating group: ovary, uterus]

HISTOPATHOLOGY: Yes, [main study groups: heart, lung, trachea, liver, pancreas, sublingual gland, submandibular gland, esophagus, stomach, duodenum, jejunum, ileum (including Peyer's patch), cecum, colon, rectum, thymus, spleen, mandibular lymph nodes, mesenteric lymph nodes, kidney, urinary bladder, testis, epididymis, ventral prostate, seminal vesicles (including coagulating gland), ovaries, uterus, vagina, pituitary, adrenal glands, thyroid (including parathyroid), cerebrum, cerebellum, pons, spinal cord, sciatic nerve, eye ball, Harderian gland, sternum and femur (including bone marrows), muscle (rectus femoris), mammary gland; females in mating group: ovaries, uterus, and vagina]

Statistics

For quantitative data, homogeneity of variance was tested using Bartlett method first. If the variance was homogenous, statistical difference between each treatment group and the control group was analyzed using Dunnett method. If not homogenous, statistical difference between each treatment group and the control group was tested using Steel method. For comparison of quantitative data between two groups in the recovery test, homogeneity of variance was analyzed by F-test. Then, if homogenous, student's t-test was applied. If not homogenous, Aspin-Welch's t-test was used. For histopathological findings, statistical analysis was carried out in combination with Steel-test and Cochran-Armitage trend test. Regarding clinical observation (except for frequency of urination, defecation, rearing and grooming) and sensory reactivity, Steel test was applied.

Results and discussion

Results of examinations

Clinical signs

effects observed, non-treatment-related

Description (incidence and severity)

CLINICAL SIGNS:

[At the administration period]:

Transient salivation was observed in males and females at 80 mg/kg bw/day. This was considered to be due to the irritant properties of the test substance.

[At the recovery period]:

There were no changes related to the test substance in any groups.

DETAILED CLINICAL OBSERVATIONS:

[At the administration period]:

Transient salivation was observed in males and females at 80 mg/kg bw/day. This was considered to be due to the irritant properties of the test substance.

Mortality

mortality observed, treatment-related

Description (incidence)

At 80 mg/kg bw/day, two pregnant females died on GD 23 and 24.

Body weight and weight changes

effects observed, treatment-related

Description (incidence and severity)

[At the administration period]:

Decreased tendency in body weights were observed in late of the administration period (day 18, 22, 25 and 28) in males at 80 mg/kg bw/day. Reduced body weight gain was observed in females (mating group) at 20 mg/kg bw/day during the lactation period.

[At the recovery period]:

There were no changes related to the test substance in any groups.

Food consumption and compound intake (if feeding study)

effects observed, treatment-related

Description (incidence and severity)

[At the administration period]:

Reduced food consumption was observed in females (mating group) at 20 mg/kg bw/day during the lactation period.

[At the recovery period]:

There were no changes related to the test substance in any groups.

Food efficiency

not examined

Water consumption and compound intake (if drinking water study)

effects observed, treatment-related

Description (incidence and severity)

[At the administration period]:

Increased water consumption was observed in females (mating groups) at 80 mg/kg bw/day on days 16 and 21 of gestation.

[At the recovery period]:

There were no changes related to the test substance in any groups.

Ophthalmological findings

not examined

Haematological findings

no effects observed

Clinical biochemistry findings

effects observed, treatment-related

Description (incidence and severity)

Including blood hormones (T3, T4, TSH)

CLINICAL BIOCHEMISTRY:

[At the end of administration period]:

Decrease in chloride was observed in males at 80 mg/kg bw/day. Decrease in potassium was observed in females (main study groups) at 80 mg/kg bw/day.

[At the end of recovery period]:

There were no changes related to the test substance in any groups.

BLOOD HORMONES:

There were no changes related to the test substance in any groups at the end of administration and recovery periods.

Urinalysis findings

no effects observed

Behaviour (functional findings)

effects observed, treatment-related

Description (incidence and severity)

[At the administration period]:

Spontaneous motor activity: Decreased total ambulatory counts were observed in males at 20 mg/kg bw/day and above, decreased total vertical counts were observed in males of 80 mg/kg bw/day.

[At the recovery period]:

There were no changes related to the test substance in any groups.

Immunological findings

not examined

Organ weight findings including organ / body weight ratios

effects observed, treatment-related

Description (incidence and severity)

[At the end of administration period]:

Increase in the relative liver weight was observed in females (main study groups) at 80 mg/kg bw/day. Increases in absolute and relative uterus weights were observed in females (mating groups) at 80 mg/kg bw/day.

[At the end of recovery period]:

There were no changes related to the test substance in any groups.

Gross pathological findings

effects observed, treatment-related

Description (incidence and severity)

[At the end of administration period]:

Stomach: Dark red spots on the mucous membrane of the glandular stomach were observed in females (main study groups) at 80 mg/kg bw/day.

[At the end of recovery period]:

There were no changes related to the test substance in any groups.

Neuropathological findings

not examined

Histopathological findings: non-neoplastic

effects observed, treatment-related

Description (incidence and severity)

[At the end of administration period]:

Liver: Centrilobular cellular infiltrations were observed in males at 20 mg/kg bw/day and above.

Stomach: Erosion of glandular stomach was observed in males and females (main study groups) at 80 mg/kg bw/day.

[At the end of recovery period]:

There were no changes related to the test substance in any groups.

[Dead animals]:

Lung: Cellular infiltration of inflammatory cells was observed in dead parental females (mating groups) at 80 mg/kg bw/day.

Liver: Centrilobular necrosis of hepatocyte was observed in dead parental females (mating groups) at 80 mg/kg bw/day.

Thymus: Increased apoptosis in the cortex was observed in dead parental females (mating groups) at 80 mg/kg bw/day.

Spleen: Decreased density of lymphocytes in the periarterial lymph sheath (PALS), lymphoid follicle, marginal zone, decreased area in the PALS, and lymphoid follicle were observed in dead parental females (mating groups) at 80 mg/kg bw/day.

Mandibular lymph node: Decreased density of lymphocytes in the lymphoid follicle, increased starry sky macrophages in paracortex were observed in dead parental females (mating groups) at 80 mg/kg bw/day.

Mesenteric lymph node: Decreased density of lymphocytes in the lymphoid follicle, increased starry sky macrophages in paracortex were observed in dead parental females (mating groups) at 80 mg/kg bw/day.

Histopathological findings: neoplastic

not examined

Effect levels

Key result true	
Dose descriptor NOAEL	
Effect level	
5	mg/kg bw/day (actual dose received)
Based on test mat.	
Sex male	
Basis for effect level histopathology: non-neoplastic At 20 mg/kg bw/day, centrilobular cellular infiltrations of liver were observed in males. other: Neurobehavioural examination: At 20 mg/kg bw/day, decreased total ambulatory counts were observed in males.	
Key result true	
Dose descriptor NOAEL (non-mating females)	
Effect level	
20	mg/kg bw/day (actual dose received)

Based on
test mat.

Sex
female

Basis for effect level

clinical biochemistry

At 80 mg/kg bw/day, decrease in potassium was observed in non-mating females (main study groups).

histopathology: non-neoplastic

At 80 mg/kg bw/day, erosion of glandular stomach was observed in non-mating females (main study groups).

organ weights and organ / body weight ratios

At 80 mg/kg bw/day, increase in the relative liver weight was observed in non-mating females (main study groups).

Key result

true

Dose descriptor

NOAEL (maternal toxicity)

Effect level

5

mg/kg bw/day (actual dose received)

Based on

test mat.

Sex

female

Basis for effect level

body weight and weight gain

At 20 mg/kg bw/day, decrease in body weight gain was observed in females (mating group) during the lactation period.

food consumption and compound intake

At 20 mg/kg bw/day, decrease in food consumption was observed in females (mating group) during the lactation period.

Any other information on results incl. tables

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

https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF108-89-4d.pdf

Applicant's summary and conclusion

Conclusions

The NOAELs for repeated-dose toxicity were determined to be 5 mg/kg bw/day for males and 20 mg/kg bw/day for females (non-mating groups), and the NOAEL for maternal toxicity was determined to be 5 mg/kg bw/day.

Executive summary

In the combined repeated dose and reproductive/developmental screening test (OECD TG422), SD rats were treated orally with the test substance at the doses of 0, 5, 20 and 80 mg/kg bw/day. Males (12 animals/dose: 6 animals were treated as a recovery group) were dosed for 28 days including a 14 day pre-mating period. Females (12 animals/dose) were dosed for 42-46 days including 14 day pre-mating, mating, and gestation periods and days until day 4 of lactation. In addition, as the main study group of females, 5 or 10 females/group was dosed for 28 days without mating (5 females at 0 and 80 mg/kg bw/day were treated as recovery groups).

Two pregnant females died at 80 mg/kg bw/day on GD 23 and 24. Transient salivation was observed in males and females at 80 mg/kg bw/day. This finding was considered to be caused by irritancy unrelated to the toxicity of the test substance. Decreased tendency in body weights were observed in late of the dosing period (day 18, 22, 25 and 28) in males at 80 mg/kg bw/day. Reduced body weight gain and food consumption were observed in dams at 20 mg/kg bw/day during the lactation period. Increased water consumption was observed in females of mating group at 80 mg/kg bw/day on days 16 and 21 of gestation. Decreased total ambulatory counts were observed in males at 20 mg/kg bw/day and above, decreased total vertical counts were observed in males of 80 mg/kg bw/day. The following findings were observed in examination at the end of administration period. Decreased in chloride was observed in males at 80 mg/kg bw/day. Decrease in potassium was observed in females of main study group at 80 mg/kg bw/day. Increase in the relative liver weight was observed in females of main study group at 80 mg/kg bw/day. Increases in absolute and relative uterus weights were observed in females of mating group at 80 mg/kg bw/day. Centrilobular cellular infiltrations of liver were observed in males at 20 mg/kg bw/day and above. Erosion of glandular stomach was observed in males and females of main study group at 80 mg/kg bw/day. Histopathological examination of dead females of mating groups at 80 mg/kg bw/day revealed the following lesions. Cellular infiltration of inflammatory cells of the lungs, centrilobular necrosis of hepatocyte, increased apoptosis in the cortex of thymus, decreased density of lymphocytes in the periarterial lymph sheath (PALS), lymphoid follicle, marginal zone, decreased area in the PALS, and lymphoid follicle of the spleen, decreased density of lymphocytes in the lymphoid follicle, and increased starry sky macrophages in paracortex of the mandibular lymph node and the mesenteric lymph node.

Based on the above results, the NOAELs for the repeated dose toxicity of 4-methylpyridine were determined to be 5 mg/kg bw/day for males and 20 mg/kg bw/day for females (non-mating groups), and the NOAEL for maternal toxicity was determined to be 5 mg/kg bw/day.

Genetic toxicity

Genetic toxicity in vitro

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.001

UUID: fe5dbe02-c084-4557-bed1-c7895036cdad

Dossier UUID:

Author:

Date: 2021-03-15T16:33:05.000+09:00

Remarks:

Administrative data

Endpoint

in vitro gene mutation study in bacteria

Type of information

experimental study

Adequacy of study

key study

Robust study summary

false

Used for classification

false

Used for SDS

false

Reliability

1 (reliable without restriction)

Rationale for reliability incl. deficiencies

guideline study under GLP condition

Reliability 1

Data source

Reference

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

Data access

data published

Materials and methods

Test guideline

Qualifier

according to guideline

Guideline

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

Deviations

no

Qualifier

according to guideline

Guideline

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

Deviations

no

GLP compliance

yes

Type of assay

bacterial reverse mutation assay
in vitro gene mutation study in bacteria

Test material**Test material information**

[4-methylpyridine](#)

Specific details on test material used for the study

Purity 99.0%

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

S. typhimurium TA 1535, TA 1537, TA 98 and TA 100
bacteria

Species / strain / cell type

E. coli WP2 uvr A
bacteria

Metabolic activation

with and without

Metabolic activation system

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

Test concentrations with justification for top dose

-S9 mix:

312.5, 625, 1250, 2500, 5000 µg/plate (TA 1535, TA 1537, TA 98 and TA 100 strains)

312.5, 625, 1250, 2500, 5000 µg/plate (WP2uvrA strain)

+S9 mix:

312.5, 625, 1250, 2500, 5000 µg/plate (TA 1535, TA 1537, TA 98 and TA 100 strains)

312.5, 625, 1250, 2500, 5000 µg/plate (WP2uvrA strain)

Maximum concentration was established based on the result of the preliminary test at concentration up to 5000 ug/plate. In this test, the growth inhibition was not observed for all strains with or without S9 mix.

Vehicle / solvent

- Vehicle(s)/solvent(s) used: water for injection

Controls

Untreated negative controls

no

Negative solvent / vehicle controls

yes

True negative controls

no

Positive controls

yes

Positive control substance

9-aminoacridine

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

sodium azide

NaN₃: -S9 mix: (TA1535)

furylfuramide

2-(2-Furyl)-3-(5-nitro-2-furyl) acrylamide (AF-2): -S9 mix: (TA100, TA98, WP2 uvrA)

other: 2-aminoanthracene (2AA)

+S9 mix: (TA1535, TA100, TA98, TA1537 and WP2 uvrA)

Details on test system and experimental conditions

METHOD OF APPLICATION: Preincubation

DURATION- Preincubation period: 20 min at 37°C

- Exposure duration: ca.48 hrs

NUMBER OF PLATES: 3

NUMBER OF REPLICATIONS: 2

DETERMINATION OF CYTOTOXICITY

- Method: other: growth inhibition

Evaluation criteria

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

Statistics

no

Results and discussion

Test results

Key result

true

Species / strain

S. typhimurium TA 1535

bacteria

Metabolic activation

with and without

Genotoxicity

negative

Cytotoxicity / choice of top concentrations

no cytotoxicity

Vehicle controls validity

valid

Untreated negative controls validity

not examined

True negative controls validity

not examined

Positive controls validity

valid

Key result

true

Species / strain

S. typhimurium TA 1537
bacteria

Metabolic activation

with and without

Genotoxicity

negative

Cytotoxicity / choice of top concentrations

no cytotoxicity

Vehicle controls validity

valid

Untreated negative controls validity

not examined

True negative controls validity

not examined

Positive controls validity

valid

Key result

true

Species / strain

S. typhimurium TA 98
bacteria

Metabolic activation

with and without

Genotoxicity

negative

Cytotoxicity / choice of top concentrations

no cytotoxicity

Vehicle controls validity

valid

Untreated negative controls validity

not examined

True negative controls validity

not examined

Positive controls validity

valid

Key result

true

Species / strain

S. typhimurium TA 100
bacteria

Metabolic activation

with and without

Genotoxicity

negative

Cytotoxicity / choice of top concentrations

no cytotoxicity

Vehicle controls validity

valid

Untreated negative controls validity

not examined

True negative controls validity

not examined

Positive controls validity

valid

Key result

true

Species / strain

E. coli WP2 uvr A
bacteria

Metabolic activation

with and without

Genotoxicity

negative

Cytotoxicity / choice of top concentrations

no cytotoxicity

Vehicle controls validity

valid

Untreated negative controls validity

not examined

True negative controls validity

not examined

Positive controls validity

valid

Any other information on results incl. tables

Figures and Tables (in English) are available in the following full report of the study.
https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF108-89-4e.pdf

Applicant's summary and conclusion**Conclusions**

Negative with or without metabolic activation

Executive summary

In a bacterial reverse mutation assay using *Salmonella typhimurium* TA100, TA1535, TA98, and TA 1537, and *Escherichia coli* WP2uvrA (OECD TG 471), 4-methylpyridine was negative with or without metabolic activation.

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.002

UUID: 0301b1d6-460c-4c68-80e6-be9e94161134

Dossier UUID:

Author:

Date: 2021-03-15T16:35:22.000+09:00

Remarks:

Administrative data

Endpoint

in vitro cytogenicity / chromosome aberration study in mammalian cells

Type of information

experimental study

Adequacy of study

key study

Robust study summary

false

Used for classification

false

Used for SDS

false

Reliability

1 (reliable without restriction)

Rationale for reliability incl. deficiencies

guideline study under GLP condition

Reliability 1

Data source

Reference

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

Data access

data published

Materials and methods

Test guideline

Qualifier

according to guideline

Guideline

OECD Guideline 473 (In Vitro Mammalian Chromosomal Aberration Test)

in vitro cytogenicity / chromosomal aberration study in mammalian cells (from 26 September 2014)

Deviations

no

Qualifier

according to guideline

GuidelineJAPAN: Guidelines for Screening Mutagenicity Testing Of Chemicals
genetic toxicity in vitro, other**Deviations**

no

GLP compliance

yes

Type of assay

in vitro mammalian chromosome aberration test

in vitro cytogenicity / chromosome aberration study in mammalian cells

Test material**Test material information**[4-methylpyridine](#)**Specific details on test material used for the study**

Purity: 99.0%

Method**Species / strain****Species / strain / cell type**Chinese hamster lung (CHL/IU)
mammalian cell line**Cytokinesis block (if used)**

colcemid

Metabolic activation

with and without

Metabolic activation system

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

Test concentrations with justification for top dose

Cell growth inhibition study

-S9 mix (short-term treatment): 7.81, 15.6, 31.3, 62.5, 125, 250, 500, 1000 ug/mL

+S9 mix (short-term treatment): 7.81, 15.6, 31.3, 62.5, 125, 250, 500, 1000 ug/mL

-S9 mix (continuous treatment, 24hr): 7.81, 15.6, 31.3, 62.5, 125, 250, 500, 1000 ug/mL

Main study

-S9 (short-term treatment): 250, 500, 1000 ug/mL

+S9 (short-term treatment): 250, 500, 1000 ug/mL

-S9 mix (continuous treatment, 24hr): 250, 500, 1000 ug/mL

Vehicle / solvent

- Vehicle(s)/solvent(s) used: water for injection

Controls

Untreated negative controls

no

Negative solvent / vehicle controls

yes

True negative controls

no

Positive controls

yes

Positive control substance

N-dimethylnitrosamine

+S9

mitomycin C

-S9

Details on test system and experimental conditions

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

SPINDLE INHIBITOR: Colcemid

STAIN: Giemsa stain (2 v/v%) for 15 min.

NUMBER OF REPLICATIONS: 2

NUMBER OF CELLS EVALUATED: 100 + 100 cells /concentration

DETERMINATION OF CYTOTOXICITY

- Method: relative total growth

Evaluation criteria

For the evaluation of the frequencies of structural aberrations and of polyploidy induced, the following criteria were employed. Appearance incidence of cell with chromosomal aberrations: Negative (-): less than 5%, Equivocal(±): 5% or more and less than 10%, Positive(+): 10% or more

Statistics

no

Results and discussion

Test results**Key result**

true

Species / strain

Chinese hamster lung (CHL/IU)

mammalian cell line

Metabolic activation

with and without

Genotoxicity

negative

Cytotoxicity / choice of top concentrations

no cytotoxicity

Vehicle controls validity

valid

Untreated negative controls validity

not examined

True negative controls validity

not examined

Positive controls validity

valid

Any other information on results incl. tables

Figures and Tables (in English) are available in the following full report of the study.
https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF108-89-4f.pdf

Applicant's summary and conclusion**Conclusions**

Negative with or without metabolic activation

Executive summary

In an in vitro chromosomal aberration test using CHL/IU cells (OECD TG 473), 4-methylpyridine was negative with or without metabolic activation.

Toxicity to reproduction

Toxicity to reproduction

ENDPOINT_STUDY_RECORD: Toxicity to reproduction. 001

UUID: 55509078-56a9-4ba4-94d1-ea3ee3767720

Dossier UUID:

Author:

Date: 2022-11-29T14:26:06.844+09:00

Remarks:

Administrative data

Endpoint

reproductive toxicity, other A combined repeated dose/reproductive developmental toxicity study

Type of information

experimental study

Adequacy of study

key study

Robust study summary

false

Used for classification

false

Used for SDS

false

Reliability

1 (reliable without restriction)

Rationale for reliability incl. deficiencies

guideline study OECD Test Guideline study under GLP condition

Reliability 1

Cross-reference

Reason / purpose for cross-reference

reference to same study

Related information

[OECD / Repeated dose toxicity: oral / Repeated dose toxicity: oral. 001 / 4-Methylpyridine / 108-89-4](#)

Data source

Reference

[Combined repeated dose toxicity study with the reproductive/developmental toxicity screening test of / Ministry of Health, Labour and Welfare \(MHLW\), Japan / study report](#)

Data access

data published https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF108-89-4d.pdf

Materials and methods

Test guideline

Qualifier

according to guideline

Guideline

OECD Guideline 422 (Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test)

Deviations

no

GLP compliance

yes

Limit test

no

Test material

Test material information

[4-methylpyridine](#)

Specific details on test material used for the study

- Name of test material (as cited in study report): 4-methylpyridine
- Analytical purity: 99.0%
- Storage condition of test material: Room temperature, shading, airtightness (filled with argon gas)
- Stability under test conditions: The stability of test material was identified by analysis of the remainder.

Test animals

Species

rat

Strain

other: Crl:CD(SD)

Sex

male/female

Details on test animals or test system and environmental conditions**TEST ANIMALS**

- Source: Charles River Japan, Inc., Hino Breeding Center.
- Age at study initiation: 10 weeks old
- Weight at study initiation:
Males (main study groups): 375-421 g, females (main study groups): 185-234 g, females in (mating study groups): 207-254 g
- Housing: Animals were individually housed in stainless steel suspension cage (240W × 380D × 200H mm), from gestation day 18 to lactation day 4, Dams were bred individually or with individual littermates in plastic cages (310W x 360D x 175H mm) and bedding.
- Diet: Solid feed (CRF-1: Oriental Yeast Co., Ltd.) was given ad libitum.
- Water: Tap water was given ad libitum.
- Acclimation period: Males (main study groups): 18 days, females (main study groups): 19 days, females (mating study groups): 18 days

ENVIRONMENTAL CONDITIONS

- Temperature (°C): 20-26°C (actual temperature: 22.2-24.3°C)
- Humidity (%): 40.0-70.0% (actual humidity: 41.1-66.8%)
- Air changes (per hr): 12

- Photoperiod (hrs dark / hrs light): 12 hr dark/12 hr light (light: 6:00~18:00)

Administration / exposure

Route of administration

oral: gavage

Vehicle

water for injection

Details on exposure

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

Details on mating procedure

- M/F ratio per cage:1/1
- Length of cohabitation: up to 14 days
- Proof of pregnancy: vaginal plug / sperm in vaginal smear referred to as day 0 of pregnancy

Analytical verification of doses or concentrations

yes

Details on analytical verification of doses or concentrations

Concentrations of the test solutions using administration on day 1 were analyzed with GC. Analytical concentrations of the test solutions were all within the range of 99.5-100.5% of the nominal concentrations and both values were within the acceptable range (concentration: percentage of nominal concentration, $100\pm 10\%$).

Duration of treatment / exposure

Males: 28 days including 14 days pre-mating

Females (main study groups): 28 days

Females (mating groups): 42-46 days including 14 days pre-mating, mating and gestation periods and the days until day 4 of lactation

Frequency of treatment

Once/day, 7 days/week

Doses / concentrations

Dose / conc.	
0	mg/kg bw/day (actual dose received)
Dose / conc.	
5	mg/kg bw/day (actual dose received)
Dose / conc.	
20	mg/kg bw/day (actual dose received)
Dose / conc.	
80	mg/kg bw/day (actual dose received)

No. of animals per sex per dose

- Main study groups:

Control- and high-dose groups: 12 males and 10 females per group (half of both sexes assigned as the treatment groups, and the remaining half assigned as the recovery groups)

Low- and middle-dose groups: 12 males and 5 females per group (half of males assigned as the treatment groups, and the remaining half assigned as the recovery groups)

- Mating groups:

12 females per dose

Control animals

yes, concurrent vehicle

Details on study design

- Dose selection rationale: Based on the results of a 14-day preliminary study, the high dose was set to 80 mg/kg bw/day, and the intermediate dose and low dose were set to 20 mg/kg bw/day and 5 mg/kg bw/day, respectively.

[14-day preliminary study]

A 14-day repeated dose oral toxicity test (CrI:CD(SD) rats, doses: 0, 50, 100 or 200 mg/kg bw/day).

All males and females at 200 mg/kg bw/day died or were moribund, and one male at 100 mg/kg bw/day was moribund. Decreased body weight and food consumption were observed in males at 100 mg/kg bw/day and above and females at 200 mg/kg bw/day. Decreased platelet counts were observed in females at 50 mg/kg bw/day and above. Increased in adrenal glands weight was observed in females at 100 mg/kg bw/day.

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

Examinations

Parental animals: Observations and examinations

CAGE SIDE OBSERVATIONS: Yes

- Time schedule:

Males and females (main study groups): 2 times/day (before administration, 6-197 minutes after administration) during the administration period. Once a day during the recovery period.

Females (mating groups): 2 times/day (before administration, 8-160 minutes after administration) during the administration period.

DETAILED CLINICAL OBSERVATIONS: Yes

- Time schedule:

Males and females (main study groups): on day of grouping, on days 7, 14, 21 and 27 of administration period.

Females (mating groups): on day of grouping, on days 7 and 14 of administration period, on days 1, 8 and 15 of gestation period, on day 4 of lactation period.

BODY WEIGHT: Yes

- Time schedule for examinations:

Males and females (main study groups):

Twice a week (On days 1, 4, 8, 11, 15, 18, 22, 25, 28 and 29 of administration period, on days 1, 4, 8, 11, 14 and 15 of recovery period).

Females (mating groups): Twice a week (On days 1, 4, 8, 11, 15, 18, 22, 25, 29, 32, 36, 39, 43, 46, 50 and 53 of administration period, on days 0, 7, 14 and 20 of gestation period, on days 0, 4 and 5 of lactation period).

FOOD CONSUMPTION AND COMPOUND INTAKE (if feeding study):

- Food consumption: Yes

- Time schedule for examinations:

Males and females (main study groups):

Twice a week (Males: On days 2, 5, 9 and 12 of administration period, on days 2, 5, 9 and 12 of recovery period; Females: On days 2, 5, 9, 12, 16, 19, 23 and 26 of administration period, on days 2, 5, 9 and 12 of recovery period).

Females (mating groups): Twice a week (On days 2, 5, 9 and 12 of administration period, on days 2, 9, 16 and 20 of gestation period, on days 2 of lactation period).

WATER INTAKE

- Time schedule for examinations:

Males and females (main study groups):

Twice a week (Males: On days 2, 5, 9 and 12 of administration period, on days 2, 5, 9 and 12 of recovery period; Females: On days 2, 5, 9, 12, 16, 19, 23 and 26 of administration period, on days 2, 5, 9 and 12 of recovery period).

Females (mating groups): Twice a week (On days 2, 5, 9 and 12 of administration period, on days 2, 9, 16 and 20 of gestation period, on days 2 of lactation period).

OPHTHALMOSCOPIC EXAMINATION: No

HAEMATOLOGY: Yes

- Time schedule for collection of blood:

Males and females (main study groups): At the end of administration period, or at the end of recovery period in both sexes

- Anaesthetic used for blood collection: Pentobarbital sodium

- Animals fasted: Yes

- How many animals:

At the end of administration period: 6 males/dose (0, 5, 20, 80 mg/kg bw/day), 5 females/dose (0, 5, 20, 80 mg/kg bw/day)

At the end of recovery period: 6 males/dose (0, 5, 20, 80 mg/kg bw/day), 5 females/dose (0 and 80 mg/kg bw/day)

- Parameters examined: red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, reticulocyte percentage, platelet count, white blood cell count, differential white blood cell count, prothrombin time, activated partial thromboplastin time, fibrinogen.

CLINICAL BIOCHEMISTRY: Yes

- Time schedule for collection of blood:

Males and females (main study groups): At the end of administration period, or at the end of recovery period in both sexes

- Animals fasted: Yes

- How many animals:

At the end of administration period: 6 males/dose (0, 5, 20, 80 mg/kg bw/day), 5 females/dose (0, 5, 20, 80 mg/kg bw/day)

At the end of recovery period: 6 males/dose (0, 5, 20, 80 mg/kg bw/day), 5 females/dose (0 and 80 mg/kg bw/day)

- Parameters checked: ALP, total cholesterol, triglyceride, total bilirubin, glucose, urea nitrogen, creatinine, sodium, potassium, chloride, calcium, inorganic phosphorus, total protein, albumin, A/G ratio, AST, ALT, γ -GT

BLOOD HORMONE: Yes

- Time schedule for collection of serum:

Males and females (main study groups): At the end of administration period in both sexes

- Animals fasted: Yes

- How many animals:

6 males/dose (0, 5, 20, 80 mg/kg bw/day), 5 females/dose (0, 5, 20, 80 mg/kg bw/day)

- Parameters checked: Triiodothyronine (T3), Thyroxin (T4), and thyroid stimulating hormone (TSH)

URINALYSIS: Yes

- Time schedule for collection of urine:

Males and females (main study groups): Before the end of the administration period (day 23 of administration period) and before the end of recovery (day 12 of recovery period).

- Metabolism cages used for collection of urine: Yes

A urine collector to collect fresh urine samples under fasting but ad libitum drinking conditions, followed by collection of 24-hour urine samples under ad libitum feeding and drinking conditions.

- How many animals:

At the end of administration period: 6 males/dose (0, 5, 20, 80 mg/kg bw/day), 5 females/dose (0, 5, 20, 80 mg/kg bw/day)

At the end of recovery period: 6 males/dose (0, 5, 20, 80 mg/kg bw/day), 5 females/dose (0 and 80 mg/kg bw/day)

- Parameters checked:

Fresh urine: Color, pH, protein, glucose, ketones, bilirubin, occult blood, urobilinogen, sediment

24-urine: Specific gravity, urine volume (24-hour volume)

NEUROBEHAVIOURAL EXAMINATION: Yes

- Time schedule for examinations:

Males and females (main study groups): Final week of administration (Manipulative test and measurement of grip strength: Day 27 of administration, measurement of motor activity: Day 26 of administration), Day 10 of recovery period (measurement of motor activity: males of main study groups)

- Dose groups that were examined: Autopsy animals after the end of the administration period

- Battery of functions tested:

1) Manipulative Test. Pupillary reflex, approaching behavior, response to touch, auditory reflex, pain reflex

2) Measurement of Grip Strength. Following manipulative test, grip strength of forelimb and hind limb were measured by CPU gauge (San Diego Instruments Inc.).

3) Measurement of Spontaneous Motor Activity. Spontaneous motor activity (Ambulatory and vertical counts) was measured by Activity Monitor (MED Associates Inc.).

The measurements were collected at 10-minute intervals from 1 hour to 2 hours after administration.

Since effects were observed in males of the main test group, males of the main test group were measured before the end of the recovery period (10 days of recovery) at 10 minute intervals for 1 hour.

Oestrous cyclicity (parental animals)

Vaginal smears were collected from all females in the mating groups and microscopically examined every day from the day after the start of administration until the day copulation was confirmed.

Sperm parameters (parental animals)

Parameters examined in all P male parental generations: testis, epididymis and seminal vesicle weight, histopathological examinations for testes, epididymides, seminal vesicle and ventral prostate.

Litter observations

PARAMETERS EXAMINED: The following parameters were examined in F1 offspring: Number and sex of pups, stillbirths, live births, postnatal mortality, presence of gross anomalies, and weight gain.

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

Postmortem examinations (parental animals)

METHOD OF SACRIFICED: All animals were sacrificed by exsanguination under pentobarbital sodium anesthesia.

SACRIFICE: Males and females (main study groups): On next day after the last administration,

Maternal animals: on Day 5 of lactation, and males and females recovery group: on Day 14 of recovery

GROSS PATHOLOGY: Yes

ORGAN WEIGHT: Yes [main study groups: brain, pituitary, salivary glands, thyroids, adrenal gland, thymus, spleen, heart, liver, kidney, testes, epididymides, ventral prostate, seminal vesicles, ovaries, uterus; females in mating groups: ovary, uterus]

HISTOPATHOLOGY: Yes, [main study groups: heart, lung, trachea, liver, pancreas, sublingual gland, submandibular gland, esophagus, stomach, duodenum, jejunum, ileum (including Peyer's patch), cecum, colon, rectum, thymus, spleen, mandibular lymph nodes, mesenteric lymph nodes, kidney, urinary bladder, testis, epididymis, ventral prostate, seminal vesicles (including coagulating gland), ovaries, uterus, vagina, pituitary, adrenal glands, thyroid (including parathyroid), cerebrum, cerebellum, pons,

spinal cord, sciatic nerve, eye ball, Harderian gland, sternum and femur (including bone marrows), muscle (rectus femoris), mammary gland; females in mating groups: ovaries, uterus, vagina]

Postmortem examinations (offspring)

SACRIFICE

- The F1 offsprings were euthanized on PND4 by exsanguination under 20% Isoflurane anesthesia.

GROSS NECROPSY: Yes

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

HISTOPATHOLOGY / ORGAN WEIGHTS

- Not examined.

Statistics

For quantitative data, homogeneity of variance was tested using Bartlett method first. If the variance was homogenous, statistical difference between each treatment group and the control group was analyzed using Dunnett method. If not homogenous, statistical difference between each treatment group and the control group was tested using Steel method. For comparison of quantitative data between two groups in the recovery test, homogeneity of variance was analyzed by F-test. Then, if homogenous, student's t-test was applied. If not homogenous, Aspin-Welch's t-test was used.

For histopathological findings, statistical analysis was carried out in combination with Steel-test and Cochran-Armitage trend test. Regarding clinical observation (except for frequency of urination, defecation, rearing and grooming) and sensory reactivity, Steel test was applied. Regarding implantation index, delivery index, birth index, live birth index, viability index, sex ratio and external abnormalities, Steel test was performed between administration groups and control groups. Regarding copulation, fertility index, and gestation index, Fisher's test was applied.

Reproductive indices

Each parameter was determined by the following equations:

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

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

Gestation index (%) = (No. of dams having live pups / No. of pregnant dams) × 100

Length of gestation (days)

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

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

Birth index (%) = (No. of live pups born / No. of implantation scars) × 100

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

Sex ratio on Day 4 of lactation = No. of male pups / No. of female pups

External abnormalities (%) = (No. of pups with external abnormalities / No. of live pups) × 100

Offspring viability indices

Viability index (%) = (No. of live pups on Day 4 of lactation / No. of live pups born) × 100

Results and discussion

Results: P0 (first parental generation)

General toxicity (P0)

Clinical signs

effects observed, non-treatment-related

Description (incidence and severity)

See 7.5.1 Repeated dose toxicity. 001

Mortality

mortality observed, treatment-related

Description (incidence)

See 7.5.1 Repeated dose toxicity. 001

Body weight and weight changes

effects observed, treatment-related

Description (incidence and severity)

See 7.5.1 Repeated dose toxicity. 001

Food consumption and compound intake (if feeding study)

effects observed, treatment-related

Description (incidence and severity)

See 7.5.1 Repeated dose toxicity. 001

Food efficiency

not examined

Water consumption and compound intake (if drinking water study)

effects observed, treatment-related

Description (incidence and severity)

See 7.5.1 Repeated dose toxicity. 001

Ophthalmological findings

not examined

Haematological findings

no effects observed

Clinical biochemistry findings

effects observed, treatment-related

Description (incidence and severity)

See 7.5.1 Repeated dose toxicity. 001

Urinalysis findings

no effects observed

Behaviour (functional findings)

effects observed, treatment-related

Description (incidence and severity)

See 7.5.1 Repeated dose toxicity. 001

Immunological findings

not examined

Organ weight findings including organ / body weight ratios

effects observed, treatment-related

Description (incidence and severity)

See 7.5.1 Repeated dose toxicity. 001

Gross pathological findings

effects observed, treatment-related

Description (incidence and severity)

See 7.5.1 Repeated dose toxicity. 001

Neuropathological findings

not examined

Histopathological findings: non-neoplastic

effects observed, treatment-related

Description (incidence and severity)

See 7.5.1 Repeated dose toxicity. 001

Histopathological findings: neoplastic

not examined

Reproductive function / performance (P0)**Reproductive function: oestrous cycle**

effects observed, treatment-related

Reproductive function: sperm measures

no effects observed

Reproductive performance

effects observed, treatment-related

Details on results (P0)

General toxicity: See 7.5.1 Repeated dose toxicity. 001

Reproductive function / performance: Decrease in number of estrous cases before pairing was observed in females at 80 mg/kg bw/day. Prolonged gestation length, decreased tendency in the gestation index, prolonged delivery period, cannibalism and faulty nest-building were observed at 80 mg/kg bw/day.

There were no significant differences in the fertility index, number of corpora lutea, implantation scars and implantation index between the control group and any treatment groups.

Effect levels (P0)**Key result**

false

Dose descriptor

NOAEL

Effect level

80

mg/kg bw/day (actual dose received)

Based on

test mat.

Sex

male

Basis for effect level

other: No effects observed on reproduction.

Key result

false

Dose descriptor

NOAEL

Effect level

20

mg/kg bw/day (actual dose received)

Based on

test mat.

Sex

female

Basis for effect level

reproductive function (oestrous cycle)

Decrease in number of estrous cases before pairing was observed in females at 80 mg/kg bw/day.

reproductive performance

Prolonged gestation length, decreased tendency in the gestation index, prolonged delivery period, cannibalism and faulty nest-building were observed at 80 mg/kg bw/day.

Results: F1 generation**General toxicity (F1)****Clinical signs**

no effects observed

Mortality / viability

mortality observed, treatment-related

Body weight and weight changes

no effects observed

Gross pathological findings

no effects observed

Details on results (F1)

At 20 mg/kg bw/day and above, decreases in numbers of live pups and viability index on lactation day 4 were observed. At 80 mg/kg bw/day, an increase in the number of stillbirths, decreases in the number of live pups, the birth index and the live birth index were observed on lactation day 0.

Effect levels (F1)**Key result**

true

Dose descriptor

NOAEL

Generation

F1

Effect level

5

mg/kg bw/day (actual dose received)

Based on
test mat.

Sex
male/female

Basis for effect level
viability

At 20 mg/kg bw/day, decrease tendencies in the number of live pups and the viability index on lactation day 4 were observed.

Any other information on results incl. tables

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

https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF108-89-4d.pdf

Applicant's summary and conclusion

Conclusions

In the combined repeated oral dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) described above, there were no reproductive effects in the male parent at 80 mg/kg bw/day, decreased number of estrus cases before pairing, prolonged gestation period, decreased tendency in the gestation index, prolonged delivery period, cannibalism and faulty nest-building, increased absolute and relative weights of uterus were observed in the female parent at 80 mg/kg bw/day and decreased number of live pups and viability on day 4 of nursing in the offspring at 20 mg/kg bw/day and above.

The NOAEL for reproductive/developmental toxicity of 4-methylpyridine was determined to be 5 mg/kg bw/day based on the reduced number of live pups and survival index observed on day 4 of lactation at 20 mg/kg bw/day, a dose at which reduced body weight gain and food consumption were observed in dams.

References

Reference Substances

REFERENCE_SUBSTANCE: 4-methylpyridine

UUID: 6be2f443-a8d8-4751-a63f-96736060d0a1

Dossier UUID:

Author:

Date: 2020-12-29T17:25:24.000+09:00

Remarks:

Reference substance name

4-methylpyridine

Inventory

CAS number

108-89-4

Molecular and structural information

Molecular formula

C₆H₇N

Molecular weight

93.13

Test Materials

TEST_MATERIAL_INFORMATION: 4-methylpyridine

UUID: 7f8ae6a5-1b8c-45fb-a373-c4eab3e7f09e

Dossier UUID:

Author:

Date: 2020-12-29T17:26:15.000+09:00

Remarks:

Name

4-methylpyridine

Composition

Composition

Reference substance

4-methylpyridine / 108-89-4

EC number

EC name

CAS number

CAS name

108-89-4

IUPAC name

Concentration

99

% (w/w)

Literatures

LITERATURE: Combined repeated dose toxicity study with the reproductive/developmental toxicity screening test of 4-methylpyridine by oral administration in rats

UUID: 01eaeffa-6516-4bb9-965f-7c1e7a7a32d9

Dossier UUID:

Author:

Date: 2020-12-29T17:20:25.000+09:00

Remarks:

General information

Reference Type

study report

Title

Combined repeated dose toxicity study with the reproductive/developmental toxicity screening test of 4-methylpyridine by oral administration in rats

Author

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

Year

2013

Bibliographic source

available in the web of Japan Existing Chemical Data Base (JECDB) https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF108-89-4d.pdf

Testing facility

Nihon Bioresearch Inc.

Report number

100530

LITERATURE: In Vitro Chromosomal Aberration Test of on 4-methylpyridine Cultured Chinese Hamster Cells.

UUID: 8cc333b3-8235-4004-9818-ddc9ad0f8046

Dossier UUID:

Author:

Date: 2021-03-10T11:14:30.000+09:00

Remarks:

General information

Reference Type

study report

Title

In Vitro Chromosomal Aberration Test of on 4-methylpyridine Cultured Chinese Hamster Cells.

Author

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

Year

2011

Bibliographic source

Japan Existing Chemical Data Base (JECDB)

https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF108-89-4f.pdf

Testing facility

Nihon Bioresearch Inc.

Report number

970930

LITERATURE: Reverse Mutation Test of 4-methylpyridine on Bacteria.

UUID: a47009b2-5e3c-49de-816c-e6b376899e3f

Dossier UUID:

Author:

Date: 2021-03-10T09:57:50.000+09:00

Remarks:

General information

Reference Type

study report

Title

Reverse Mutation Test of 4-methylpyridine on Bacteria.

Author

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

Year

2011

Bibliographic source

Japan Existing Chemical Data Base (JECDB)

https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF108-89-4e.pdf

Testing facility

Nihon Bioresearch Inc.

Report number

901330

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 official MHLW opinions or any other regulatory policies.

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Identifiers

Other IT system identifiers

IT system

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IT system

IUCLID4

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16558402024DIV750