Name: OECD_SIDS / SUBSTANCE : 4-Methylpyridine / 108-89-4 Tue, 29 Nov 2022, 15:17:51+0900 /

Legal entity owner: National Institute of Health Sciences

Printing date: 2022-11-29T15:17:51.897+09:00

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DOSSIER:

UUID: 0
Dossier UUID:
Author:
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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

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

General information

Legal entity name
National Institute of Health Science

4-Methylpyridine

General information

Identification

Identification

SUBSTANCE: 4-Methylpyridine

UUID:	5e52401d-334f-4369-b96f-5a7a4e21889e
Dossier UUID:	
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 r emainder.

Test animals

Species
rat
common rodent species

Strain
other: Crl:CD(SD)

Sex
male/female

Details on test animals or test system and environmental conditions
TEST ANIMALS
- Source: Charles River Japan, Inc., 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 litterma tes 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 (Crl: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) dur ing 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, 4and 5 of lacta tion 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 recov ery 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 re covery 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, cr eatinine, 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 ad ministration 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 g roup) 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 re covery 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 m g/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 fe males (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 g roups).
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) du ring 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-amimoacridine 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 i ncrease was observed.

Statistics
no

Results and discussion

Test results

Key result
true

Species / strain
S. typhimurium TA 1535

bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
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

Guideline
JAPAN: 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 re mainder.

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 × 2 00H mm), from gestation day 18 to lactation day 4, Dams were bred individually or with individual li ttermates 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, fema les (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±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 t he 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 (Crl: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) dur ing 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, 4and 5 of lacta tion 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 recov ery 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 re covery 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, cr eatinine, 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 ad ministration 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 WEIGTHS
- 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 be tween two groups in the recovery test, homogeneity of variance was analyzed by F-test. Then, if homo genous, 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 a nd Cochran-Armitage trend test. Regarding clinical observation (except for frequency of urination, d efecation, rearing and grooming) and sensory reactivity, Steel test was applied. Regarding implantat ion index, delivery index, birth index, live birth index, viability index, sex ratio and external abnormalitie s, 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 o fficial MHLW opinions or any other regulatory policies.

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Identifiers

Other IT system identifiers

IT system LEO **ID** 10767
IT system IUCLID4

ID
16558402024DIV750