Name: COMPLETE / SUBSTANCE : 1,3,5-triazine-2,4,6(1H,3H,5H)-trithione / 1,3,5-triazinane-2,4,6-trithione / 638-16-4 Fri, 16 Dec 2022, 11:14:48+0900 /

Legal entity owner: National Institute of Health Sciences

Printing date: 2022-12-16T11:14:48.380+09:00

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Remarks:

Dossier header

Dossier submission type

Name
Complete table of contents

Version
core 7.0

Name (given by user)

Dossier subject

Dossier subject
1,3,5-triazine-2,4,6(1H,3H,5H)-trithione / 1,3,5-triazinane-2,4,6-trithione / 638-16-4

Public name

Submitting legal entity
National Institute of Health Science

Dossier creation date/time
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Used in category

LEGAL_ENTITY: National Institute of Health Science

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Author:	
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Remarks:	

General information

Legal entity name
National Institute of Health Science

1,3,5-triazine-2,4,6(1H,3H,5H)-trithione

CORE

General information

Assessment approach (assessment entities)

FIXED_RECORD: Assessment approach

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Author:	
Date:	2017-01-04T16:32:27.000+09:00
Remarks:	

OECD

Health Effects

Acute toxicity: oral

ENDPOINT_STUDY_RECORD: Acute toxicity: oral.001

UUID: IUC5-ee8931c1-a3d9-42f4-b95f-e4564603c53f
Dossier UUID:
Author:
Date: 2022-12-14T15:52:59.296+09:00
Remarks:

Administrative data

Endpoint
acute toxicity: oral

Type of information
experimental study

Adequacy of study
key study

Robust study summary
false

Used for classification
false

Used for SDS
false

Reliability
1 (reliable without restriction)

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

Data source

Reference

Single Dose Oral Toxicity Test of Trithiocyanuric Acid in Rats / MHW (Ministry of Health and Welfare), Japan / study report

Data access
data published

Materials and methods

Test guideline

Qualifier
according to guideline

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

Deviations
no

Qualifier
according to guideline

Guideline
other: Yakushoku-hatsu 1121003, Kanpoki-hatsu 031121004

GLP compliance
yes

Test type
acute toxic class method

Limit test
no

Test material

Test material information
1,3,5-triazinane-2,4,6-trithione / 638-16-4 / 211-322-8

Test animals

Species
rat
common species

Strain
other: Crj: CD(SD), SPF

Sex
female

Details on test animals or test system and environmental conditions
TEST ANIMALS
- Source: Charles River Japan Inc.
- Age at the time of purchase: 7 weeks old
- Weight at dosing: 186.2 – 202.4 g (1st dosing) , 204.2-219.6 g (2nd dosing), 227.2-242.2 g (3rd dosing)
– Used animal number: A total of 18 females
- Fasting period before study: Approximately 16 hrs
- Housing: One animal/cage
- Diet (e.g. ad libitum): Ad libitum except fasting period for 16 hrs before dosing to 3 hrs after dosing
- Water (e.g. ad libitum): Ad libitum
- Acclimation period: 8 days.

ENVIRONMENTAL CONDITIONS
- Temperature (°C): 23.0 – 24.5
- Humidity (%): 49.0 – 59.0
- Ventilation (per hr): Approximately 15 times
- Photoperiod (hrs light / hrs dark): 12/12

Administration / exposure

Route of administration
oral: gavage

Vehicle
other: sodium carboxymethyl cellulose

Details on oral exposure
Concentration in vehicle: 0.05, 0.5, 3, and 20% (w/v).

Doses
300 mg/kg bw (first and second dosing)
2000 mg/kg bw (third dosing)

No. of animals per sex per dose
First and second dosing (first purchase): each 3 females (animal ID No. 1 – 3 and 4 - 6)/300 mg/kg b w dose
Third dosing (second purchase): 3 females (animal ID No. 7 – 9) /2000 mg/kg bw dose

Control animals
no

Details on study design
- Duration of observation period following dosing: 14 days
- Frequency of observations: Before dosing, Day 1 (day of dosing): Continuously observed until 1 hr, thereafter, every one hour until 6 hours. After day 2: once a day
- Frequency of weighing: Just before dosing (Day 1), Day 2, 4, 8, 11, and 15. And when the dead animals found
- Necropsy of survivors performed: Yes

Statistics
No

Results and discussion

Effect levels

Key result
false

Sex
female

Dose descriptor
LD50

Effect level

>	300	2000	mg/kg bw

Based on
act. ingr.

Key result
false

Sex
female

Dose descriptor
LD50

Effect level

500 mg/kg bw

Based on
act. ingr.

Remarks on result
other: Cut off value

Mortality
No deaths were observed from first and second dosing (300 mg/kg bw). All 3 animals died in 2000 mg/kg bw group (third dosing).

Clinical signs
other: One animal received 2000 mg/kg bw of the test substance showed creeping, lid closure, lateral position and dyspnea and died at approximately 2 hours from the dosing. Smudge of perinasal area, listless and reduction o(defecation were observed in two other

Gross pathology
At necropsy, while no marked abnormalities were observed in the animals treated with 300 mg/kg bw, enlargements of the kidney and the adrenal gland, and atrophy of the spleen were observed in two animals died on Day 3 or 4 of the observation period with 2,000 mg/kg bw. White-colored liquid in the stomach was observed in two animals died at 2 hours and 3 days after dosing.

Other findings
- Organ weights: No data
- Histopathology: No lesions attributable to the test substance were observed in the 300 mg/kg bw groups. In histological examination, all the animals treated with 2000 mg/kg bw showed necrosis a nd degenerations of the proximal tubular epithelium and the glomerulus of the renal cortex, and two animals showed a decrease in the area of white pulp of the spleen.
- Potential target organs: Kidneys
- Other observations: No data

Applicant's summary and conclusion

Conclusions
The LD50 value was 300 – 2000 mg/kg bw , and the cut off LD50 value was 500 mg/kg bw for female rats.

Repeated dose toxicity: oral

ENDPOINT_STUDY_RECORD: Repeated dose toxicity: oral.001

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Date:	2022-12-16T11:10:56.374+09:00
Remarks:	

Administrative data

Endpoint
short-term repeated dose toxicity: oral combined repeated dose and reproduction / developmental screening

Type of information
experimental study

Adequacy of study
key study

Robust study summary
false

Used for classification
false

Used for SDS
false

Reliability
1 (reliable without restriction)

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

Cross-reference

Reason / purpose for cross-reference
reference to same study

Remarks
7.8.1 Toxicity to reproduction: Toxicity to reproduction.001

Data source

Reference

A combined repeated-dose/reproductive-developmental toxicity study of trithiocyanuric acid by oral a / MHW (Ministry of Health and Welfare), Japan / study report

Data access
data published

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
1,3,5-triazinane-2,4,6-trithione / 638-16-4 / 211-322-8

Test animals

Species
rat
common rodent species

Strain
other: Crj: CD(SD), SPF

Sex
male/female

Details on test animals or test system and environmental conditions
TEST ANIMALS
- Source: Atsugi Breeding Center, Charles River Laboratories Japan, Inc.
- Age at study initiation: 8 weeks of age
- Weight at study initiation: 355.5 – 405.2 g for males and 208.7 – 255.0 g for females
- Housing: bracket-type metallic wire-mesh cages (W 220 × D 270 × H 190 mm)
- Diet (e.g. ad libitum): ad libitum
- Water (e.g. ad libitum): ad libitum
- Acclimation period: 14 days
ENVIRONMENTAL CONDITIONS
- Temperature (°C): 22.5 to 26.0°C
- Humidity (%): 50.0 to 65.0%
- Air changes (per hr): 15 times per hour
- Photoperiod (hrs dark / hrs light):12-hour lighting per day

Administration / exposure

Route of administration
oral: gavage

Vehicle
other: sodium carboxymethyl cellulose

Details on oral exposure
VEHICLE
- Justification for use and choice of vehicle: No data
- Amount of vehicle (if gavage): 5 ml/kg bw
- Supplier: Maruishi pharmaceutical industry Co., Ltd.
- Lot/batch no. (if required): 4720
- Dosing volume: 5 mL/kg
- Stability (test solutions): For 8 days
- Storage condition of test solution: Stored in a dark place with room temperature

Analytical verification of doses or concentrations
yes

Details on analytical verification of doses or concentrations
Test suspensions at each concentration (20 and 0.05 w/v%) of initial and final preparations were analyzed by the HPLC method at Hatano laboratory of Food and Drug Safety Center. Results showed that the concentration of the test article in each concentration was 94.3 to 101% of the nominal concentration.

Duration of treatment / exposure
(P) Males: 42 days including 14 days pre-mating
(P)Females: Days including 14 days pre-mating, mating and gestation periods and the days until day 4 of lactation Female (no mating, satellite group): for 42 days

Frequency of treatment
Daily: 7 times / week

Doses / concentrations

Remarks
Doses / Concentrations:
0 (vehicle), 62.5, 125 and 250 mg/kg bw/day
Basis:
actual ingested

No. of animals per sex per dose
12/sex/dose (main group), and 5 females/dose at 0 and 250 mg/kg bw/day (satellite group)

Control animals
yes, concurrent vehicle

Details on study design
- Dose selection rationale: A preliminary study (study No. R-04-006) was conducted to determine the doses to be employed. Male and female rats were receiving 0, 250, 500, and 1000 mg/kg bw/day for 14 days. As a result, red colored urine was observed in more than half numbers of rats receiving 1000 mg/kg bw/day groups and all animals died in the 1000 mg/kg bw/day groups until Day 7. Black path zones of auricle and dark purple colored tail top were observed in the 500 mg/kg bw/day groups from Week 2, and moreover, one female sowing red colored urine, salivation, wasting and sedation were moribund . Body weight gains were depressed in male rats receiving 500 mg/kg bw/day at Week 2, and swelling of the spleen was observed at necropsy. No changes related to the test substance were observed in males receiving 250 mg/kg bw/day. From the results of the preliminary study, 500 mg/kg bw/day seemed to be the maximum tolerance dose for 14 days. Therefore, the high dose was set at 250 mg/kg bw/day for the main study, and the middle and low doses were set at 125 and 62.5 mg/kg bw/day using common ratio 2.

Positive control
no

Examinations

Observations and examinations performed and frequency
CAGE SIDE OBSERVATIONS: Yes
- Time schedule:
Males and females: once before the start of dosing, two times/day during the dosing period, and once during the recovery period
DETAILED CLINICAL OBSERVATIONS: Yes
- Time schedule:
Male animals: the end of acclimation period, Day 7, 14, 21, 28, 35 and 42 during the dosing and Day 7 and 14 during the recovery period. Female animals: the end of acclimation period, Day 7, 14, 21, 28, 35 and 42 during the dosing, Day 0 at delivery period and Day 0 from 4 at delivery animals, and Day 7 and 14 of satellite groups during the recovery period. Test items are following: Body position, locomotor activity, vocalization, tremor, convulsion by cage side observation, ease of removing rat from cage, reactivity to being handled, heart rate, body temperature, fur, skin color, visible mucosa color, lacrimation, exophthalmos ophthalmocele, pupillary, and salivation by terminology for removing rat from cage, and body position, walking, grooming, phonation, straub tail, gait, stereotyped, abnormal behavior, tremor, convulsion, piloerection, and ophthalmorrhexis by observation of behavior on the working table.
FANCTIONAL OBSERVATION: Yes
- Time schedule:
End of the dosing period: male, female (dam), and female (satellite group) animals. End of the dosing period: male and female (satellite group) animals.
Test items are following: Prayer's reaction, pupillary reflex, visual placing, startle reaction, withdrawal reflex, eyelid reflex, and righting reflex.
BODY WEIGHT: Yes

Males in the main and females in satellite groups were weighed on Day 1, 7, 14, 21, 28, 35 and 42 of dosing, and Day 1, 7, and 15 (necropsy day) at the end of the recovery period.
Females were weighed on Day 1, 7, 14, and 21 until successful copulation. Copulated females were weighed on Day 0, 7, 14 and 20 of gestation, days 0 and 4 of lactation, and the necropsy day.
FOOD CONSUMPTION : Yes
- Food consumption (g/day/rat) for each animal determined from the difference of the of the previous day's feeding amount: Yes
Measurement of food consumption was conducted on all animals at the following frequencies:
Males and females in the satellite groups: on Day 1-2, 7-8, 14-15, 29-30, 35-36, and 41-42 during the dosing period and Day 6-7 and 13-14 during the recovery period. Females in the main groups: on Day 1-2, 7-8, and 14-15 (before mating), on Day 0-1, 7-8, 14-15, and 20-21 (the gestation period). On Day 3-4 (the lactation period).
FOOD INTAKE: No
HAEMATOLOGY: Yes
- Time schedule for collection of blood: On Day 43 of the dosing period and Day 15 of the recovery period in males. On Day 5 of the lactation period (main group) and on Day 15 of the recovery period (satellite group) in females.
- Anaesthetic used for blood collection: Yes (pentobarbital sodium)
- Animals fasted: Yes (for 18-22 hours)
- How many animals: 5 animals/sex/group
- Parameters examined red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, reticulocyte count, platelet count, white blood cell count, differential white blood cell count, prothrombin time, activated partial thromboplastin time
CLINICAL CHEMISTRY: Yes
- Time schedule for collection of blood: Same as hematology examination.
- Animals fasted: Yes (for 18-22 hours)
- How many animals: 5 animals/sex/group

- Parameters checked: ASAT (GOT), ALAT (GPT), γ-GT, ALP, total bilirubin, blood urea nitrogen, crea tinine, glucose, total cholesterol, triglyceride, total protein, albumin, A/G ratio, calcium, inorganic phosphorus, sodium, potassium, chloride
URINALYSIS OF MALES: Yes
- Time schedule for collection of urine: Five males on Day 33 during the dosing period and all animals on Day 13 during the recovery period.
Five females on Day 34 (main group). All animals on Day 34 during the dosing period and Day 13 dur ing the recovery period (satellite group).
- Metabolism cages used for collection of urine: Yes
- Animals fasted: Yes
- Parameters checked: color, muddy, pH, occult blood, protein, glucose, ketones. bilirubin, urobilino gen, and sediments
BLOOD HORMONE: No
NEUROBEHAVIOURAL EXAMINATION: Yes
Detailed clinical observation: on Day 7, 14, 21, 28, 35, and 42 of the dosing period, on Day 7 and 14 of the recovery period,
Functions test: on Day 42 of the dosing period and on Day 14 of the recovery period (males and satell ite group females). On Day 4 of the lactation period (main group females).

Sacrifice and pathology
GROSS PATHOLOGY AND ORGAN WEIGHTS：Yes Brain, heart, liver, kidneys, adrenals, thymus, sple en, testes, and epididymis.
HISTOPATHOLOGY: Yes Brain, puitality, thymus, lymph nodes (including mesenteric and mandibul ar lymph nodes), trachea, lung (including bronchus), stomach, intestinal tract (duodenum, jejunum, i leum, cecum, colon, rectum), thyroids, heart, liver, spleen, kidneys, adrenals, urinary bladder, testes, epididymis, seminal vesicles (including the coagulating gland), prostate (ventral lobe), ovaries, uterus, vagina, bone marrow (one side femur), sciatic nerve (one side femur), spinal cord, and gross abnorm alities site.

Statistics
Changes in estrous cyclicity and conception rate were analyzed by Fisher’s test. Graded pathological data was analyzed by Mann-Whitney’s U test (significance level = 0.05) and pathological data with n umber of positive and negative animals was analyzed by one-sided Fisher’s test.
Other data, obtained values in each animal or mean of a litter was one data, and these data were co mpared among the satellite groups and other among the groups. These data were analyzed using F-test for homogeneity of distribution. The Student’s t-test and the Aspin-Welch’s t-test were conducted for homogenous and non-homogenous distribution, respectively to compare the control and indi vidual treatment groups. Three or more groups setting, these data were analyzed using Bartlett’s test for homogeneity of distribution. The Dunnett’s multiple comparison test after the ANOVA and the Du nnett’s-type mean rank sum test after Kruskal-Wallis’s H test were conducted for homogenous and non-homogenous distribution, respectively to compare the control and individual treatment groups. Significance level was set at 0.05 compared with the control group and among the groups.

Results and discussion

Results of examinations

Clinical signs
effects observed, treatment-related

Mortality
mortality observed, treatment-related

Body weight and weight changes
effects observed, treatment-related

Food consumption and compound intake (if feeding study)
effects observed, treatment-related

Haematological findings
effects observed, treatment-related

Clinical biochemistry findings
effects observed, treatment-related

Urinalysis findings
effects observed, treatment-related

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

Gross pathological findings
effects observed, treatment-related

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

Details on results
CLINICAL SIGNS AND MORTALITY: Mortality: One male and one female died in the 250 mg/kg bw/day group on Day 8 and Day 42, respectively. Clinical signs: Incomplete eyelid opening and emaciation were observed in one dead female receiving 250 mg/kg bw/day, but no clinical sign was observed in one dead male receiving 250 mg/kg bw/day. The followings were observed in the 250 mg/kg bw/day groups: black area of the pinna in one male and three females, dark purple distally of the tail in two males, nodule of the tail in four males and one female, nodule of the pinna and emaciation in one male and one female, anemic in one male, induction of the scrotum in one male, nodule of the scrotum in three males, swelling of the left forelimb in one male, and crust formation of the snout in one female. Reddish urine was observed in one male receiving 125 mg/kg bw/day and three males and one female receiving 250 mg/kg bw/day groups. Sporadically salivation just after dosing was observed in six males receiving 125 mg/kg bw/day and eight males and 10 females receiving 250 mg/kg bw/day groups. Loss of fur was observed in two males in the control group, one male and one female receiving 125 mg/kg bw/day, and one female receiving 250 mg/kg bw/day. Crust formation of the dorsal neck was observed in one female receiving 62.5 mg/kg bw/day and mass of the perineal region was observed in one female receiving 125 mg/kg bw/day. No adverse changes were observed in both sexes during the recovery period.

DETAILED CLINICAL OBSERVATIONS AND FANCTIONAL OBSERVATION: Detailed clinical observations, no changes were observed in both sexes during the recovery period. When removing rats from the cage or handling rats, vocalization and flinches were observed in both sexes sporadically, and running around in the cage was observed in one female rat receiving 250 mg/kg bw/day. When handling rats, tenseness or rigidity was observed in one female rat receiving 125 mg/kg bw/day and 250 mg/kg bw/day. Rearing of stereotypy was observed in two females receiving 250 mg/kg bw/day. Functional observation, no changes were observed in both sexes during the dosing and recovery periods.

BODY WEIGHT: Significant decreases in body weights, weight gains, and cumulative weight gains were observed in males receiving 250 mg/kg bw/day from Day 21 of the dosing period to Day 14 of the recovery period, from Day 7 to Day 35 of the dosing period, and from Day 14 to Day 42 of the dosing period. Significant decreases in body weights, weight gains, and cumulative weight gains were observed in females receiving 250 mg/kg bw/day from Day 42 of the dosing period to Day 14 of the recovery period, from Day 21 to Day 35 of the dosing period, and from Day 35 to Day 42 of the dosing period. No changes in body weights were observed in both sexes receiving 125 mg/kg bw/day and 62.5 mg/kg bw/day groups compared with the control groups during the dosing and recovery periods.
FOOD CONSUMPTION: Significant decreases in food consumption were observed in males receiving 250 mg/kg bw/day from Day 7 to Day 8 and Day 29 to Day 30 during the dosing period. Significant decreases in food consumption were observed in females receiving 250 mg/kg bw/day of the sate

llite group from Day 1 to Day 2 and Day 29 to Day 30 during the dosing period. No changes in food co nsumption were observed in both sexes receiving 125 mg/kg bw/day and 62.5 mg/kg bw/day groups compared with the control groups during the dosing and recovery periods.

URINALYSIS: Slight turbidity was observed in one male receiving 250 mg/kg bw/day during the dosing period. Occult blood was observed in each one male in the 250 mg/kg bw/day group and the control group during the dosing period. Red blood cells in sediments were observed in six males receiving 250 mg/kg bw/day and remained in one male during the recovery period.

HAEMATOLOGY: At the end of the dosing period, significant decreases in hematocrit value and In creasing tendency in reticulocyte ratio were observed in males receiving 250 mg/kg bw/day. No changes were observed in female receiving 250 mg/kg bw/day. At the end of the recovery period, s ignificant decreases in hemoglobin concentration, hematocrit value, MCV, and MCH were observed in females receiving 250 mg/kg bw/day. No significant differences in males receiving 250 mg/kg bw/ day compared with the control group.
CLINICAL CHEMISTRY: At the end of the dosing period, significant decreases in albumin value were observed in males receiving 62.5 mg/kg bw/day and 250 mg/kg bw/day. A significant decrease in creatinine value was observed in males receiving 250 mg/kg bw/day and remained after the recovery period. No changes were observed in female receiving 250 mg/kg bw/day compare with the control group after the dosing period. At the end of the recovery period, a significant decrease in a creatinine value and a significant increase in triglyceride value were observed in females receiving 250 mg/kg bw/day.

ORGAN WEIGHTS: At the end of the dosing, A significant decrease in body weight was observed in male receiving 250 mg/kg bw/day; therefore, significant increases in relative brain, heart, and adrenals weights were observed in this group. No changes in organ weight were observed in females. At the end of the recovery period, significant decreases in absolute liver and kidneys weights and significant increases in relative brain, heart, kidneys, spleen, adrenals, testes, and epididymis were observed in males receiving 250 mg/kg bw/day. Significant decreases in absolute thymus weight and significant increases in relative brain, heart, and liver weights were observed in females receiving 250 mg/kg bw/day compared with the control group.
GROSS PATHOLOGY: Edematous and subinvolution in the lungs and enlargement and dark red co lored in the kidneys were observed in the dead male. Edematous in the lungs and thymus, enlarges and pale colored kidneys, pale colored and small sized spleen, and pale colored bone marrow of femur were observed in the dead female. At the end of the dosing period, abscess, yellow zone, and adhesion with scrotum in the epididymis were observed in one or two males receiving 250 mg/kg bw/ day. Enlargement and rough surface in the kidneys, small sized spleen, nodule and dark red zone in tai l were observed in males receiving 250 mg/kg bw/day. Enlargement of the kidneys and white spot in the liver were observed in males receiving 62.5 mg/kg bw/day. Small sized spleen and thymus, black spot or recessed area in mucosa of the glandular stomach, and nodule and black spot of skin in the auricle were observed in females receiving 250 mg/kg bw/day. Cyst in the kidney, mass of around the vulva in the subcutis, black spot of mucosa in the glandular stomach, and white spot in the liver were observed in females receiving 125 mg/kg bw/day. At the end of the recovery period, abscess and adhesion with scrotum, nodule of scrotum in skin, and black spot of auricle in skin were observe d in one male receiving 250 mg/kg bw/day. Alopecia of skin in clavicular area were observed in one f emale receiving 250 mg/kg bw/day.

HISTOPATHOLOGY: NON-NEOPLASTIC: Granuloma with multinucleated giant cells and inflammatory cell infiltration was observed in subcutaneous tissues in lesion of the auricle, tail and scrotum. Necro sis or edemas of the papilla of the kidneys were observed in males receiving 62.5 mg/kg bw/day and more and females receiving 250 mg/kg bw/day groups. Deposit of pigment of proximal tubule in the kidneys was observed in both sexes receiving 62.5 mg/kg bw/day or more. Diffuse hypertrophy of fascicular cells in the adrenal glands was observed in both sexes receiving 62.5 mg/kg bw/day or mo re. Lesions in the kidneys or adrenal glands were observed in both sexes receiving 250 mg/kg bw/day at the end of the recovery period.

Effect levels

Key result
false

Dose descriptor
LOAEL

Effect level

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

Based on
test mat.

Sex
male/female

Basis for effect level
other: Effects of lesions in the deposit of pigment in proximal tubule in kidneys and diffuse hyp ertrophy in adrenals in males and females receiving 62.5 mg/kg bw/day or more groups.

Target system / organ toxicity

Key result
false

Critical effects observed
not specified

Any other information on results incl. tables

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

http://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF638-16-4d.pdf

Applicant's summary and conclusion

Conclusions
Based on the effects of dosing on the kidney and adrenal gland, the LOAEL for the male and female ra t repeated dose toxicity of 1,3,5-triazine-2,4,6(1H,3H,5H)-trithione was determined to be 62.5 mg/kg bw/day.

Executive summary

A combined repeated oral dose toxicity study with the reproduction/developmental toxicity screening test was performed according to the OECD TG 422. Male and female rats (12 animals/sex/dose) were administered 1,3,5-triazine-2,4,6(1H,3H,5H)-trithione at 0, 62.5, 125, and 250 mg/kg bw/day. Males were dosed for 48 days, including a 14 day pre-mating period and subsequent mating period. Females were dosed for up to 54 days, including 14 day pre-mating, mating, and gestation periods, and the time until lactation day 4. Five out of 12 males at 0 and 250 mg/kg bw/day were treated as a recovery group. In addition, 5 females/dose administered 0 and 250 mg/kg bw/day were dosed for 42 days without

mating and were treated as a recovery group. One male and one female died after 250 mg/kg bw/day dosing. Clinical signs of toxicity included black areas on the pinna, dark purple coloration at the distal end of the tail, reddish urine, induration of the scrotum, and nodules of the tail, pinna, and scrotum in the 250 mg/kg bw/day group. Transient salivation was observed in males at 125 mg/kg bw/day and in both sexes at 250 mg/kg bw/day. At 250 mg/kg bw/day, food consumption and body weight gain were decreased in males and non-mating females. Red blood cells were observed in the urinary sediment from 6 males in the 250 mg/kg bw/day group. In the blood, hematocrit and albumin were decreased in males at 250 mg/kg bw/day. Gross pathological changes were observed in the tail, pinna and scrotum, and the histopathological examination revealed granulation tissues with multinucleated giant cells and inflammatory cell infiltration in the subcutis of the tail, pinna, and scrotum. In the kidney, papilla necrosis and edema were observed in males at doses of 62.5 mg/kg bw/day and higher, and in females at 250 mg/kg bw/day. Deposition of brown pigment in the basophilic tubule cortex was observed in both sexes at doses of 62.5 mg/kg bw/day and higher. In the adrenal grand, diffuse hypertrophy of the fascicular cells was observed in both sexes at doses of 62.5 mg/kg bw/day and higher. The histopathological changes observed in the kidneys and adrenal grand did not resolve after the recovery period. Based on the effects of dosing on the kidney and adrenal gland, the LOAEL for the male and female rat repeated dose toxicity of 1,3,5-triazine-2,4,6(1H,3H,5H)-trithione was determined to be 62.5 mg/kg bw/day.

Genetic toxicity in vitro

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.001

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Dossier UUID:	
Author:	
Date:	2022-12-16T11:13:07.075+09:00
Remarks:	

Administrative data

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

Type of information
experimental study

Adequacy of study
key study

Robust study summary
false

Used for classification
false

Used for SDS
false

Reliability
1 (reliable without restriction)

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

Data source

Reference

Reverse Mutation Test of trithiocyanuric acid on Bacteria. / MHW (Ministry of Health and Welfare), Japan / study report

Data access
data published

Materials and methods

Test guideline

Qualifier
according to guideline

Guideline
OECD Guideline 471 (Bacterial Reverse Mutation Assay)

in vitro gene mutation study in bacteria

Deviations
no

Qualifier
according to guideline

Guideline
JAPAN: Guidelines for Screening Mutagenicity Testing Of Chemicals

Deviations
yes

GLP compliance
yes

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

Test material

Test material information
1,3,5-triazinane-2,4,6-trithione / 638-16-4 / 211-322-8

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 pKM 101
bacteria

Metabolic activation
with and without

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

Test concentrations with justification for top dose
-/+ S9 mix: 0, 313, 625, 1250, 2500, 5000 µg/plate (all test strains)

Vehicle / solvent
Dimethyl sulfoxide

Controls

Untreated negative controls
no

Negative solvent / vehicle controls
yes

True negative controls
no

Positive controls
yes

Positive control substance
other: -S9 mix: 2-(2-Furyl)-3-(5-nitro-2-furyl) acrylamide (TA 100, TA98 and WP2 uvrA/pKM101), s odium azide (TA1535) and 9-aminoacridine hydrochloride (TA1537). +S9 mix: 2-aminoanthracene (all strains)

Details on test system and experimental conditions
METHOD OF APPLICATION: Preincubation
DURATION
- Preincubation period: 20 min at 37°C
- Exposure duration:48 hrs
NUMBER OF PLATES: 3
NUMBER OF REPLICATIONS: 2
DETERMINATION OF CYTOTOXICITY
- Method: other: growth inhibition

In a cytotoxicity test, growth inhibition was not observed at 50, 150, 500, 1500, 5000 µg/plate with or without S9 mix.

Evaluation criteria
A chemical was judged to be positive when the mean number of revertant colonies per plate increased more than twice in comparison with that of the negative control and dose-responsibility and reproducibility was confirmed.

Statistics
no

Results and discussion

Test results

Key result
false

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

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
no cytotoxicity nor precipitates, but tested up to recommended limit concentrations

Vehicle controls validity
valid

Untreated negative controls validity
not examined

Positive controls validity
valid

Key result
false

Species / strain
E. coli WP2 uvr A pKM 101
bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
no cytotoxicity nor precipitates, but tested up to recommended limit concentrations

Vehicle controls validity
valid

Untreated negative controls validity
not examined

Positive controls validity
valid

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

Any other information on results incl. tables

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

http://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF638-16-4e.pdf

Applicant's summary and conclusion

Conclusions
Interpretation of results (migrated information):
negative

In a bacterial reverse mutation assay using Salmonella typhimurium TA100, TA1535, TA98, and TA1537, and Escherichia coli WP2uvrA (OECD TG 471), 1,3,5-triazine-2,4,6(1H,3H,5H)-trithione was n egative with or without metabolic activation.

Executive summary

No increase in revertant colonies was observed in the test with either the non-activation method (-S9) or activation (+S9) method. Reverse mutation assays using microorganisms (Salmonella typhimurium, Escherichia coli) were conducted to assess the potential of trithiocyanuric acid to induce gene mutations. Trithiocyanuric acid did not induce gene mutations in the bacteria under the conditions of this study. The positive control showed expected results.

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.002

UUID:	IUC5-0f48a174-5ea0-4c50-9a94-e9edcc53a764
Dossier UUID:	
Author:	
Date:	2017-01-04T16:29:49.000+09:00
Remarks:	

Administrative data

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

Type of information
experimental study

Adequacy of study
key study

Robust study summary
false

Used for classification
false

Used for SDS
false

Reliability
1 (reliable without restriction)

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

Data source

Reference

In Vitro Chromosomal Aberration Test of Trithiocyanuric acid on Cultured Chinese Hamster Cells. / MHW (Ministry of Health and Welfare), Japan / study report

Data access
data published

Materials and methods

Test guideline

Qualifier
according to guideline

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

Deviations
no

Qualifier
according to guideline

Guideline
JAPAN: Guidelines for Screening Mutagenicity Testing Of Chemicals

Deviations
no

GLP compliance
yes

Type of assay
in vitro mammalian chromosome aberration test
chromosome aberration

Test material

Test material information
1,3,5-triazinane-2,4,6-trithione / 638-16-4 / 211-322-8

Method

Species / strain

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

Metabolic activation
with and without

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

Test concentrations with justification for top dose
-S9 mix (continuous treatment): 0.14, 0.21, 0.31, 0.47, 0.70 mg/mL
-S9 mix (short-term treatment): 0.36, 0.53, 0.80, 1.2, 1.8 mg/mL
+S9 mix (short-term treatment): 0.36, 0.53, 0.80, 1.2, 1.8 mg/mL

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

Controls

Untreated negative controls
no

Negative solvent / vehicle controls
yes

True negative controls
no

Positive controls
yes

Positive control substance
other: [continuous treatment -S9]: mitomycin C; [continuous treatment +S9]: Benzo[a]pyrene

Details on test system and experimental conditions
METHOD OF APPLICATION: Exposure duration: [continuous treatment]: 24 hrs [short-term treatment]: No description
SPINDLE INHIBITOR: Colcemid
STAIN: Giemsa stain (3%)
NUMBER OF REPLICATIONS: 2
NUMBER OF CELLS EVALUATED: 200 cells / dose
DETERMINATION OF CYTOTOXICITY
- Method: statistic method and biological evaluation by the relative total growth

Evaluation criteria
Increased uumber of cells with aberations were statisticaly examined.

Statistics
Fisher's test (P < 0.01 by one-sided test) and Chochran-Armitage trend test (P < 0.01 by one-sided t est)

Results and discussion

Test results

Key result
false

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

Metabolic activation
with

Genotoxicity
positive

Cytotoxicity / choice of top concentrations
cytotoxicity

Vehicle controls validity
valid

Untreated negative controls validity
not examined

Positive controls validity
valid

Key result
false

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

Metabolic activation
without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
cytotoxicity

Vehicle controls validity
valid

Untreated negative controls validity
not valid

Positive controls validity
valid

Remarks on result
other: strain/cell type: Migrated from field 'Test system'.

Any other information on results incl. tables

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

http://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF638-16-4f.pdf

Applicant's summary and conclusion

Conclusions
Interpretation of results (migrated information):
positive with metabolic activation

An in vitro chromosomal aberration test using CHL/IU cells (OECD TG 473) was positive with met abolic activation.

Genetic toxicity in vivo

ENDPOINT_STUDY_RECORD: Genetic toxicity in vivo.001

UUID: IUC5-b741db6c-1836-485b-9a8c-d9818db114bb
Dossier UUID:
Author:
Date: 2022-12-14T15:47:04.148+09:00
Remarks:

Administrative data

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

Type of information
experimental study

Adequacy of study
key study

Robust study summary
false

Used for classification
false

Used for SDS
false

Reliability
1 (reliable without restriction)

Rationale for reliability incl. deficiencies
other: GLP guideline study

Data source

Reference

Micronucleus test of Trithiocyanuric acid on mouse / MHW (Ministry of Health and Welfare), Japan / study report

Data access
data published

Materials and methods

Test guideline

Qualifier
according to guideline

Guideline
OECD Guideline 474 (Mammalian Erythrocyte Micronucleus Test)

in vivo mammalian somatic cell study: cytogenicity / erythrocyte micronucleus

Deviations
no

Qualifier
according to guideline

Guideline
JAPAN: Guidelines for Screening Mutagenicity Testing Of Chemicals

Deviations
no

GLP compliance
yes

Type of assay
micronucleus assay
chromosome aberration

Test material

Test material information
1,3,5-triazinane-2,4,6-trithione / 638-16-4 / 211-322-8

Specific details on test material used for the study
Name of test material (cited in study report): 2,4,6-trimercapto-S-triazine

Test animals

Species
mouse

Strain
other: Crlj:CD1(ICR)

Sex
male

Details on test animals or test system and environmental conditions
TEST ANIMALS
- ICR, [CD1 (ICR), SPF
- Source: Charles River Laboratories Japan, Inc.
- Age at study initiation: 9 weeks
- Weight at study initiation: range findings, males: 33.9-38.1 g, females: 25.8-29.3 g: main study: males: 32.4-39.2 g
- Assigned to test groups randomly: yes
- Fasting period before study: no
- Housing: bracket type TPX resin cage, (143W×293D×148Hmm)
- Diet: ad libitum
- Water: ad libitum
- Acclimation period: 9 days

ENVIRONMENTAL CONDITIONS
- Temperature (°C): 21-25
- Humidity (%): 40-75
- Air changes (per hr): 10-15/h

- Photoperiod : 12 h dark/12 h light (light time: 8:00 AM to 8:00 PM)

Administration / exposure

Route of administration
oral: gavage

Vehicle
- Vehicle(s)/solvent(s) used: 0.5%CMC
- Concentration of test material in vehicle: 250, 500, 1000, and 2000 mg/mL
- Amount of vehicle: 10 mL/kg bw

Details on exposure
RESULTS OF RANGE-FINDING STUDY
- Dose range: 0, 250, 500, 1000, and 2000 mg/kg bw/day (24 h interval, twice)
- Clinical signs of toxicity in test animals: Decreases in locomotor activity and piloerection were o bserved in one male receiving 2000 mg/kg bw/day and one female receiving 1000 mg/kg bw/day. One male and one female mice died at 2000 mg/kg bw/day.

Duration of treatment / exposure
48 h

Frequency of treatment
Twice, 24 h interval

Doses / concentrations

Remarks
Doses / Concentrations:
250, 500, 1000, and 2000 mg/kg bw/day
Basis:
actual ingested

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

Control animals
yes, concurrent vehicle

Positive control(s)
Cyclophosphamide monohydrate (CP)
- Route of dosing: oral gavage
- Doses / concentrations: 50 mg/kg bw (single dose)

Examinations

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

Details of tissue and slide preparation
TREATMENT AND SAMPLING TIMES: Cells for specimen were collected 24 h after the last dosing.

DETAILS OF SLIDE PREPARATION: Cell suspensions were spread on a slide glass, dried, and fixed wi th methanol for five min. Each specimen was stained with acridine orange.

METHOD OF ANALYSIS: fluorescence microscopy, blind method

Evaluation criteria
The test substance was determined to be positive if the micronucleated cells were statistically incr eased in the dosing groups as compared with negative control group.

Statistics
Appearance frequency of micronuclei: Fisher's test (one-sided test), Test was used to correct the Bo nferroni in consideration of multiplicity. Significant level was 5 and 1% levels setting. Appearance frequency of micronuclei was used trend test of Chochran-Armitage (one-sided test).
Polychromatic erythrocytes in erythrocytes: These rates were analyzed using Bartlett's test for homogeneity of distribution excluding positive control. Result of analysis, homogenous was observ ed. Next, difference between negative control group and each treated groups wad analysed by Dunnett's multiple comparison test (one-sided test). Difference between negative and positive cont rols was analyses by F-test and Student's t-test. These analyses method, Bartlett's test and F-test were setting 5% significant levels. Dunnett's test and Student t-test were 5% and 1% levels setting.

Results and discussion

Test results

Key result
false

Sex
male

Genotoxicity
negative

Toxicity
yes

Vehicle controls validity
valid

Negative controls validity
not examined

Positive controls validity
valid

Additional information on results
- Induction of micronuclei: appearance frequency of micronucleated cells (%MNPCE) for dose levels of 0,250, 500, and 1000 mg/kg bw/day were 0.15%, 0.17%, 0.14%, and 0.13%, respectively.
- Ratio of PCE/NCE::ratio for dose levels, 0,250, 500, and 1000 mg/kg bw/day were 56.8%, 57.6%%, 59.1%, and 59.5%,, respectively.
- Body weight: not examined
- Statistical evaluation: statistically significant increases were not observed.

Any other information on results incl. tables

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

http://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF638-16-4g.pdf

Applicant's summary and conclusion

Conclusions
Interpretation of results (migrated information): negative
The in vivo micronucleus study (OECD TG 474) was negative up to the maximum tolerated dose (1000 mg/kg bw/day for 2 days) in mice.

Toxicity to reproduction

ENDPOINT_STUDY_RECORD: Toxicity to reproduction.001

UUID: IUC5-a60fe279-2ba7-4dea-9abd-4cbd6e5a6ee6
Dossier UUID:
Author:
Date: 2022-12-16T11:14:13.699+09:00
Remarks:

Administrative data

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

Type of information
experimental study

Adequacy of study
key study

Robust study summary
false

Used for classification
false

Used for SDS
false

Reliability
1 (reliable without restriction)

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

Cross-reference

Reason / purpose for cross-reference
reference to same study

Remarks
7.5.Repeated dose toxicity: oral: Repeated dose toxicity: oral.001

Data source

Reference

A combined repeated-dose/reproductive-developmental toxicity study of trithiocyanuric acid by oral a / MHW (Ministry of Health and Welfare), Japan / study report

Data access
data published

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
1,3,5-triazinane-2,4,6-trithione / 638-16-4 / 211-322-8

Test animals

Species
rat

Strain
other: Crj: CD(SD), SPF

Sex
male/female

Administration / exposure

Route of administration
oral: gavage

Vehicle
other: 0.5% sodium carboxymethyl cellulose

Details on exposure
VEHICLE
- Justification for use and choice of vehicle: No data
- Amount of vehicle (if gavage): 5 ml/kg bw
- Supplier: Maruishi pharmaceutical industry Co., Ltd.
- Lot/batch no. (if required): 4720
- Dosing volume: 5 mL/kg
- Stability (test solutions): For 8 days
- Storage condition of test solution: Stored in a dark place with room temperature

Details on mating procedure
- M/F ratio per cage:1:1
- Length of cohabitation:up to two weeks
- 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
Test suspensions at each concentration (20 and 0.05 w/v%) of initial and final preparations were analyzed by the HPLC method at Hatano laboratory of Food and Drug Safety Center. Results showed that the concentration of the test article in each concentration was 94.3 to 101% of the nominal concentration.

Duration of treatment / exposure
(P) Males: 42 days including 14 days pre-mating, mating, and thereafter 14 periods (subsequent 28 days)
(P) Females: Days including 14 days pre-mating, mating and gestation periods and the days until day 4 of lactation

Frequency of treatment
Daily: 7 times / week

Doses / concentrations

Remarks
Doses / Concentrations:
0 (vehicle), 62.5, 125 and 250 mg/kg bw/day
Basis:
actual ingested

No. of animals per sex per dose
12/sex/dose (main group), and 5 females/dose at 0 and 250 mg/kg bw/day (satellite group)

Control animals
yes, concurrent vehicle

Details on study design
- Dose selection rationale: A preliminary study (study No. R-04-006) was conducted to determine the doses to be employed. Male and female rats were receiving 0, 250, 500, and 1000 mg/kg bw/day for 14 days. As a result, red colored urine was observed in more than half numbers of rats receiving 1000 mg/kg bw/day groups and all animals died in the 1000 mg/kg bw/day groups until Day 7. Black path zones of auricle and dark purple colored tail top were observed in the 500 mg/kg bw/day groups from Week 2, and moreover, one female sowing red colored urine, salivation, wasting and sedation were moribund . Body weight gains were depressed in male rats receiving 500 mg/kg bw/day at Week 2, and swelling of the spleen was observed at necropsy. No changes related to the test substance were observed in males receiving 250 mg/kg bw/day. From the results of the preliminary study, 500 mg/kg bw/day seemed to be the maximum tolerance dose for 14 days. Therefore, the high dose was set at 250 mg/kg bw/day for the main study, and the middle and low doses were set at 125 and 62.5 mg/kg bw/day using common ratio 2..

Examinations

Parental animals: Observations and examinations
CAGE SIDE OBSERVATIONS: Yes
- Time schedule:
Males and females: once before the start of dosing, two times/day during the dosing period, and once during the recovery period
DETAILED CLINICAL OBSERVATIONS: Yes
- Time schedule:
Male animals: the end of acclimation period, Day 7, 14, 21, 28, 35 and 42 during the dosing and Day 7 and 14 during the recovery period. Female animals: the end of acclimation period, Day 7, 14, 21, 28, 35 and 42 during the dosing, Day 0 at delivery period and Day 0 from 4 at delivery animals, and Day 7 and 14 of satellite groups during the recovery period. Test items are following: Body position, locomotor activity, vocalization, tremor, convulsion by cage side observation, ease of removing rat from

cage, reactivity to being handled, heart rate, body temperature, fur, skin color, visible mucosa color, lacrimation, exophthalmos ophthalmocele, pupillary, and salivation by terminology for removing rat from cage, and body position, walking, grooming, phonation, straub tail, gait, stereotyped, abnormal behavior, tremor, convulsion, piloerection, and ophthalmorrhexis by observation of behavior on the working table.

BODY WEIGHT: Yes
Males in the main and females in satellite groups were weighed on Day 1, 7, 14, 21, 28, 35 and 42 of dosing, and Day 1, 7, and 15 (necropsy day) at the end of the recovery period.
Females were weighed on Day 1, 7, 14, and 21 until successful copulation. Copulated females were weighed on Day 0, 7, 14 and 20 of gestation, days 0 and 4 of lactation, and the necropsy day.

FOOD CONSUMPTION : Yes
- Food consumption (g/day/rat) for each animal determined from the difference of the of the previous day's feeding amount: Yes
Measurement of food consumption was conducted on all animals at the following frequencies:
Males and females in the satellite groups: on Day 1-2, 7-8, 14-15, 29-30, 35-36, and 41-42 during the dosing period and Day 6-7 and 13-14 during the recovery period. Females in the main groups: on Day 1-2, 7-8, and 14-15 (before mating), on Day 0-1, 7-8, 14-15, and 20-21 (the gestation period). On Day 3-4 (the lactation period).

FOOD INTAKE: No
COMPOUND INTAKE: No
FOOD EFFICIENCY: No
WATER CONSUMPTION: No

Oestrous cyclicity (parental animals)
Vaginal smears were collected from all females in the main groups and microscopically examined every day from the day after the start of dosing until the day copulation was confirmed. Mean estrous cycle (day) and abnormal estrous cycle animals were examined by dams.

Sperm parameters (parental animals)
testis weight, epididymis weight

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

Postmortem examinations (parental animals)
METHOD OF SACRIFICED: All animals were sacrificed by exsanguination under pentobarbital sodium anesthesia, intraperitoneally.
SACRIFICE: Male animals: On Day 42, Maternal animals: on Day 4 of lactation, and Male recovery and female satellite animals: on Day 56.
GROSS PATHOLOGY AND ORGAN WEIGHTS : Yes Brain, heart, liver, kidneys, adrenals, thymus, sp leen, testes, and epididymis.
HISTOPATHOLOGY: Yes Brain, puitality, thymus, lymph nodes (including mesenteric and mandibular lymph nodes), trachea, lung (including bronchus), stomach, intestinal tract (duodenum, jejunum, ileum, cecum, colon, rectum), thyroids, heart, liver, spleen, kidneys, adrenals, urinary bladder, testes, epididymis, seminal vesicles (including the coagulating gland), prostate (ventral lobe), ovaries, uteru s, vagina, bone marrow (one side femur), sciatic nerve (one side femur), spinal cord, and gross abno rmalities site.

Postmortem examinations (offspring)
SACRIFICE: F1 pups were euthanized on PND 4 by exsanguination pentobarbital sodium anesthesia, intraperitoneally.
GROSS NECROPSY: Yes

Statistics
Changes in estrous cyclicity and conception rate were analyzed by Fisher's test. Graded pathological data was analyzed by Mann-Whitney's U test (significance level = 0.05) and pathological data with number of positive and negative animals was analyzed by one-sided Fisher's test.
Other data, obtained values in each animal or mean of a litter was one data, and these data were compared among the satellite groups and other among the groups. These data were analyzed using F-test for homogeneity of distribution. The Student's t-test and the Aspin-Welch's t-test were conducted for homogenous and non-homogenous distribution, respectively to compare the control and individual treatment groups. Three or more groups setting, these data were analyzed using Bartlett's test for homogeneity of distribution. The Dunnett's multiple comparison test after the ANOVA and the Dunnett's-type mean rank sum test after Kruskal-Wallis's H test were conducted for homogenous and non-homogenous distribution, respectively to compare the control and individual treatment groups. Significance level was set at 0.05 compared with the control group and among the groups.

Reproductive indices
1) Each parameter was determined by the following equations:
Mean estrus cycle, incidence of females with irregular estrus cycle, mating periods,
Copulation index (%) = (No. of copulated animals/No. of co-housed animals) × 100
Fertility index (%) = (No. of pregnant females/No. of copulated females) × 100
Gestation length, number of corpora lutea, number of implantation sites, total number of offspring,
Implantation index (%) = (No. of implantation sites/No. of corpora lutea) × 100
Delivery index (%) = (No. of females delivered liveborn pups/No. of pregnant females) × 100
Gestation index (%) = (No. of pregnant animals delivered live offspring/number of pregnant animals) × 100

Offspring viability indices
Total number of offspring at birth, number of live offspring at birth,
Number of live pups on day 0 of lactationBirth index (%) = (Number of live pups on day 0/Number of implantation sites) ×100
Viability index = (Number of live pups on day 4 after birth/Number of live pups born) ×100
External examination of offspring, necropsy finding
Pups weight on day 0 of lactation
Sex ratio on day 0 of lactation
Number of live pups on day 4 of lactation
Pups weight on day 4 of lactation
Sex ratio on day 4 of lactation

Results and discussion

Results: P0 (first parental generation)

General toxicity (P0)

Clinical signs
effects observed, treatment-related

Body weight and weight changes
effects observed, treatment-related

Food consumption and compound intake (if feeding study)
effects observed, treatment-related

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

Gross pathological findings
effects observed, treatment-related

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

Reproductive function / performance (P0)

Reproductive function: oestrous cycle
no effects observed

Reproductive performance
no effects observed

Details on results (P0)

1) Estrous Cycle
A few changes in estrous cycles were observed in females receiving 125 mg/kg bw/day and 250 mg/kg bw/day, however these frequencies were not significantly different compared with the control gr oup.
2) Results of Mating
Mating was successful in all the animals, but Infertility was observed in three females receiving 250 mg/kg bw/day.
3) Delivery Data and Delivery
There were no significant differences in the gestation length, number of implantation sites, impl antation index, and delivery index between the control group and any treatment groups. Significant d ecreases in number of corpora lutea were observed in females receiving 250 mg/kg bw/day
GROSS PATHOLOGY
See 7.5.1 Repeated dose toxicity: oral
HISTOPATHOLOGY
See 7.5.1 Repeated dose toxicity: oral

Effect levels (P0)

Key result
false

Dose descriptor
NOAEL

Effect level

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

Based on
test mat.

Sex
female

Basis for effect level
other: Infertility was observed in 3 females at 250 mg/kg bw/day. The number of corpora lutea dec reased in rats given 250 mg/kg bw/day

Results: F1 generation

General toxicity (F1)

Clinical signs
no effects observed

Mortality / viability
no mortality observed

Body weight and weight changes
no effects observed

Details on results (F1)

no effects

Overall reproductive toxicity

Key result
false

Reproductive effects observed
not specified

Any other information on results incl. tables

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

http://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF638-16-4d.pdf

Applicant's summary and conclusion

Conclusions
The NOAEL for the rat reproductive/developmental toxicity of 1,3,5-triazine-2,4,6(1H,3H,5H)-trithione was determined to be 125 mg/kg bw/day based on infertility and a decrease in corpora lutea.

Executive summary

In the combined repeated oral dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422), infertility was observed in 3 females at 250 mg/kg bw/day. The number of corpora lutea decreased in rats given 250 mg/kg bw/day. No effects were observed in any pups. The NOAEL for the rat reproductive/developmental toxicity of 1,3,5-triazine-2,4,6(1H,3H,5H)-trithione was determined to be 125 mg/kg bw/day based on infertility and a decrease in corpora lutea.

DOMAIN

Substance

SUBSTANCE: 1,3,5-triazine-2,4,6(1H,3H,5H)-trithione

UUID: IUC5-80e43b49-60cb-49c6-87bc-4abf9b428515
Dossier UUID:
Author:
Date: 2022-12-16T11:14:34.696+09:00
Remarks:

Substance name
1,3,5-triazine-2,4,6(1H,3H,5H)-trithione

Legal entity
National Institute of Health Sciences / Kawasaki / Japan

Identification of substance

Reference substance
1,3,5-triazine-2,4,6(1H,3H,5H)-trithione / 1,3,5-triazinane-2,4,6-trithione / 638-16-4 / 211-322-8

EC number	EC name
211-322-8	EC Inventory

CAS number	CAS name
638-16-4	

IUPAC name
1,3,5-triazinane-2,4,6-trithione

Role in the supply chain

Manufacturer
false

Importer
false

Only representative
false

Downstream user
false

References

Reference Substances

REFERENCE_SUBSTANCE: 1,3,5-triazine-2,4,6(1H,3H,5H)-trithione

UUID: ECB5-c72a77ea-657c-4fbf-a95d-f61240e1c79d
Dossier UUID:
Author:
Date: 2007-05-10T18:00:00.000+09:00
Remarks:

Reference substance name
1,3,5-triazine-2,4,6(1H,3H,5H)-trithione

IUPAC name
1,3,5-triazinane-2,4,6-trithione

Inventory

Inventory number

Inventory name
1,3,5-triazine-2,4,6(1H,3H,5H)-trithione

Inventory
EC Inventory

Inventory number
211-322-8

CAS number
638-16-4

Molecular formula
C3H3N3S3

Description

CAS number
638-16-4

Synonyms

Synonyms

Identity
1,3,5-triazine-2,4,6(1h,3h,5h)-trithione

Identity
1,3,5-Triazine-2,4,6(1H,3H,5H)-trithione

Molecular and structural information

Molecular formula
C3H3N3S3

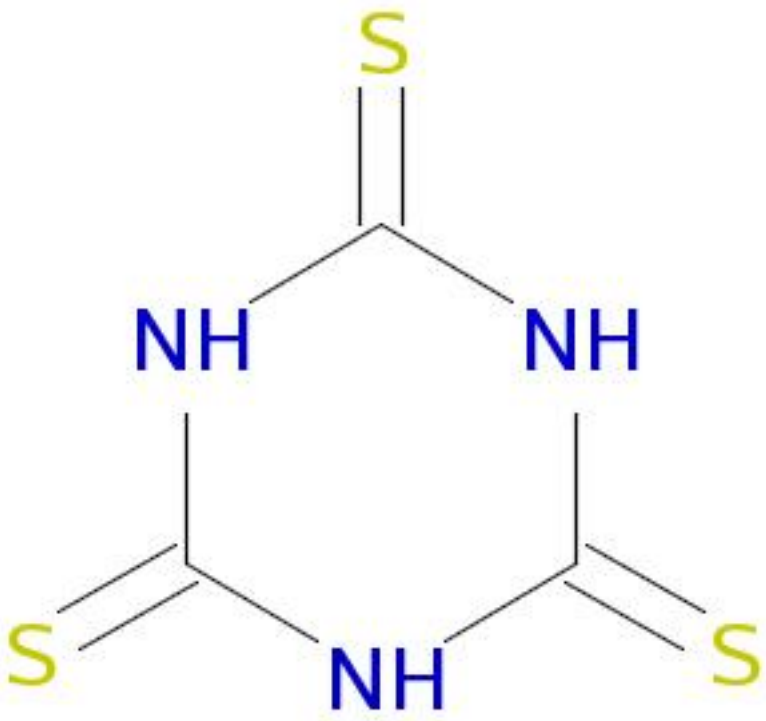
Molecular weight

177.271

SMILES notation
S=C1NC(=S)NC(=S)N1

InChI
InChI=1/C3H3N3S3/c7-1-4-2(8)6-3(9)5-1/h(H3,4,5,6,7,8,9)

Structural formula



Related substances

Group / category information
USEPA Category: Substituted Triazines;Thiols

Test Materials

TEST_MATERIAL_INFORMATION: 1,3,5-triazinane-2,4,6-trithione / 638-16-4 / 211-322-8

UUID: 1cc62be1-b4ac-3ddf-9266-ccd0243f7850
Dossier UUID:
Author:
Date: 2017-01-04T16:29:25.000+09:00
Remarks:

Name
1,3,5-triazinane-2,4,6-trithione / 638-16-4 / 211-322-8

Composition

Composition

Type
Constituent

Reference substance
1,3,5-triazine-2,4,6(1H,3H,5H)-trithione / 1,3,5-triazinane-2,4,6-trithione / 638-16-4 / 211-322-8

EC number	EC name
211-322-8	EC Inventory
CAS number	**CAS name**
638-16-4	
IUPAC name	
1,3,5-triazinane-2,4,6-trithione	

Other characteristics

Details on test material
- Name of test material (as cited in study report): Trithiocyanuric acid
- CAS No.: 638-16-4
- Molecular formula: C3H3N3S3
- Molecular weight: 177.27
- Purity: 99.8% (HPLC)
- Impurities: 0.13% sulfur
- Physical state: Slightly pale yellow powder
- Melting point: >300°C
- Boiling point, specific gravity, partition coefficient, vapor pressure: No data
- Solubility: Sparingly soluble in water, slightly soluble in methanol, acetone, and dioxane, and soluble i n cellosolve and THF
- Stability: The stable to normal handling
- Supplier: Kawaguchi Chemical Industry Co., Ltd.
- Lot No.: 407518
- Storage condition until use: Room temperature

TEST_MATERIAL_INFORMATION: 1,3,5-triazinane-2,4,6-trithione / 638-16-4 / 211-322-8

UUID: 7f161f9c-ae98-3924-aa62-73524d965804
Dossier UUID:
Author:
Date: 2017-01-04T16:30:03.000+09:00
Remarks:

Name
1,3,5-triazinane-2,4,6-trithione / 638-16-4 / 211-322-8

Composition

Composition

Type
Constituent

Reference substance
1,3,5-triazine-2,4,6(1H,3H,5H)-trithione / 1,3,5-triazinane-2,4,6-trithione / 638-16-4 / 211-322-8

EC number	EC name
211-322-8	EC Inventory
CAS number	**CAS name**
638-16-4	
IUPAC name	
1,3,5-triazinane-2,4,6-trithione	

Other characteristics

Details on test material
- Name of test material (as cited in study report): Trithiocyanuric acid
- CAS No.: 638-16-4
- Molecular formula: C3H3N3S3
- Molecular weight: 177.27
- Purity: 99.8% (HPLC)
- Impurities: 0.13% sulfur
- Physical state: Slightly pale yellow powder
- Melting point: >300°C
- Boiling point, specific gravity, partition coefficient, vapor pressure: No data
- Solubility: Sparingly soluble in water, slightly soluble in methanol, acetone, and dioxane, and soluble in cellosolve and THF
- Stability: The stable to normal handling
- Supplier: Kawaguchi Chemical Industry Co., Ltd.
- Lot No.: 407518
- Storage condition until use: Room temperature

TEST_MATERIAL_INFORMATION: 1,3,5-triazinane-2,4,6-trithione / 638-16-4 / 211-322-8

UUID: 4ddf3c8e-6843-3714-9bc2-20503be39c0b
Dossier UUID:
Author:
Date: 2017-01-04T16:29:34.000+09:00
Remarks:

Name
1,3,5-triazinane-2,4,6-trithione / 638-16-4 / 211-322-8

Composition

Composition

Type
Constituent

Reference substance
1,3,5-triazine-2,4,6(1H,3H,5H)-trithione / 1,3,5-triazinane-2,4,6-trithione / 638-16-4 / 211-322-8

EC number	EC name
211-322-8	EC Inventory
CAS number	**CAS name**
638-16-4	

IUPAC name
1,3,5-triazinane-2,4,6-trithione

Other characteristics

Details on test material
- Name of test material (as cited in study report): Trithiocyanuric acid
- CAS No.: 638-16-4
- Molecular formula: C3H3N3S3
- Molecular weight: 177.27
- Purity: 99.8% (HPLC)
- Impurities: 0.13% sulfur
- Physical state: Slightly pale yellow powder
- Melting point: ＞300°C
- Boiling point, specific gravity, partition coefficient, vapor pressure: No data
- Solubility: Sparingly soluble in water, slightly soluble in methanol, acetone, and dioxane, and soluble in cellosolve and THF
- Stability: The stable to normal handling
- Supplier: Kawaguchi Chemical Industry Co., Ltd.
- Lot No.: 407518
- Storage condition until use: Room temperature

TEST_MATERIAL_INFORMATION: 1,3,5-triazinane-2,4,6-trithione / 638-16-4 / 211-322-8

UUID: aa3065f1-b8b3-3f79-9a41-c5d6004bfc5a
Dossier UUID:
Author:
Date: 2017-01-04T16:29:49.000+09:00
Remarks:

Name
1,3,5-triazinane-2,4,6-trithione / 638-16-4 / 211-322-8

Composition

Composition

Type
Constituent

Reference substance
1,3,5-triazine-2,4,6(1H,3H,5H)-trithione / 1,3,5-triazinane-2,4,6-trithione / 638-16-4 / 211-322-8

EC number	EC name
211-322-8	EC Inventory
CAS number	**CAS name**
638-16-4	

IUPAC name
1,3,5-triazinane-2,4,6-trithione

Other characteristics

Details on test material
- Name of test material (as cited in study report): Trithiocyanuric acid
- CAS No.: 638-16-4
- Molecular formula: C3H3N3S3
- Molecular weight: 177.27
- Purity: 99.8% (HPLC)
- Impurities: 0.13% sulfur
- Physical state: Slightly pale yellow powder
- Melting point:> 300°C
- Boiling point, specific gravity, partition coefficient, vapor pressure: No data
- Solubility: Sparingly soluble in water, slightly soluble in methanol, acetone, and dioxane, and soluble i n cellosolve and THF
- Stability: The stable to normal handling
- Supplier: Kawaguchi Chemical Industry Co., Ltd.
- Lot No.: 407518
- Storage condition until use: Room temperature

TEST_MATERIAL_INFORMATION: 1,3,5-triazinane-2,4,6-trithione / 638-16-4 / 211-322-8

UUID: 112cb490-c985-347f-a67a-75b77768ba53
Dossier UUID:
Author:
Date: 2022-12-14T16:01:14.616+09:00
Remarks:

Name
1,3,5-triazinane-2,4,6-trithione / 638-16-4 / 211-322-8

Composition

Composition

Reference substance
1,3,5-triazine-2,4,6(1H,3H,5H)-trithione / 1,3,5-triazinane-2,4,6-trithione / 638-16-4 / 211-322-8

EC number	EC name
211-322-8	EC Inventory
CAS number	**CAS name**
638-16-4	
IUPAC name	
1,3,5-triazinane-2,4,6-trithione	

Other characteristics

Details on test material
- Name of test material (as cited in study report): Trithiocyanuric acid
- CAS No.: 638-16-4
- Molecular formula: C3H3N3S3
- Molecular weight: 177.27
- Purity: 99.8% (HPLC)
- Impurities: 0.13% sulfur
- Physical state: Slightly pale yellow powder
- Melting point:> 300°C
- Boiling point, specific gravity, partition coefficient, vapor pressure: No data
- Solubility: Sparingly soluble in water, slightly soluble in methanol, acetone, and dioxane, and soluble i n cellosolve and THF
- Stability: The stable to normal handling
- Supplier: Kawaguchi Chemical Industry Co., Ltd.
- Lot No.: 407518
- Storage condition until use: Room temperature

TEST_MATERIAL_INFORMATION: 1,3,5-triazinane-2,4,6-trithione / 638-16-4 / 211-322-8

UUID: c6be500f-a596-303a-a70d-da93de6e578a
Dossier UUID:
Author:
Date: 2017-01-04T16:30:18.000+09:00
Remarks:

Name
1,3,5-triazinane-2,4,6-trithione / 638-16-4 / 211-322-8

Composition

Composition

Type
Constituent

Reference substance
1,3,5-triazine-2,4,6(1H,3H,5H)-trithione / 1,3,5-triazinane-2,4,6-trithione / 638-16-4 / 211-322-8

EC number	EC name
211-322-8	EC Inventory
CAS number	**CAS name**
638-16-4	

IUPAC name
1,3,5-triazinane-2,4,6-trithione

Other characteristics

Details on test material
- Name of test material (as cited in study report): Trithiocyanuric acid
- CAS No.: 638-16-4
- Molecular formula: C3H3N3S3
- Molecular weight: 177.27
- Purity: 99.2%
- Physical state: Slightly pale yellow powder
- Supplier: Wako Pure Chemical Industries, Ltd.
- Lot No.: KWM0501
- Storage condition until use: Room temperature (17.0-23.2°C)

Literatures

LITERATURE: A combined repeated-dose/reproductive-developmental toxicity study of trithiocyanuric acid by oral administration in rats.

UUID: 6db66ae3-4239-3ec3-b05c-5b4ebfe32d4e
Dossier UUID:
Author:
Date: 2017-01-04T16:30:03.000+09:00
Remarks:

General information

Reference Type
study report

Title
A combined repeated-dose/reproductive-developmental toxicity study of trithiocyanuric acid by oral a dministration in rats.

Author
MHW (Ministry of Health and Welfare), Japan

Year
2007

Bibliographic source
Japan Existing Chemical Data Base (JECDB)

Testing facility
Food and Drug Safety Center

Study number
R-04-007

LITERATURE: In Vitro Chromosomal Aberration Test of Trithiocyanuric acid on Cultured Chinese Hamster Cells.

UUID: 01544345-7007-3fb0-a7ca-9655250d7e7c
Dossier UUID:
Author:
Date: 2017-01-04T16:29:49.000+09:00
Remarks:

General information

Reference Type
study report

Title
In Vitro Chromosomal Aberration Test of Trithiocyanuric acid on Cultured Chinese Hamster Cells.

Author
MHW (Ministry of Health and Welfare), Japan

Year
2007

Bibliographic source
Japan Existing Chemical Data Base (JECDB)

Testing facility
Food and Drug Safety Center

Study number
G-04-065

LITERATURE: Micronucleus test of Trithiocyanuric acid on mouse

UUID: f531482c-693f-3b5a-b0fd-6cf9ac151c22
Dossier UUID:
Author:
Date: 2017-01-04T16:30:18.000+09:00
Remarks:

General information

Reference Type
study report

Title
Micronucleus test of Trithiocyanuric acid on mouse

Author
MHW (Ministry of Health and Welfare), Japan

Year
2010

Bibliographic source
Japan Existing Chemical Data Base (JECDB)

Testing facility
Food and Drug Safety Center

Study number
G-09-021

LITERATURE: Reverse Mutation Test of trithiocyanuric acid on Bacteria.

UUID:	50307a75-a19c-3293-8805-666e4e4e1f9a
Dossier UUID:	
Author:	
Date:	2017-01-04T16:29:42.000+09:00
Remarks:	

General information

Reference Type
study report

Title
Reverse Mutation Test of trithiocyanuric acid on Bacteria.

Author
MHW (Ministry of Health and Welfare), Japan

Year
2007

Bibliographic source
Japan Existing Chemical Data Base (JECDB)

Testing facility
Food and Drug Safety Center

Study number
M-04-075

LITERATURE: Single Dose Oral Toxicity Test of Trithiocyanuric Acid in Rats

UUID:	9c90037a-d506-35bc-ac16-4d03353e2a2d
Dossier UUID:	
Author:	
Date:	2017-01-04T16:29:25.000+09:00
Remarks:	

General information

Reference Type
study report

Title
Single Dose Oral Toxicity Test of Trithiocyanuric Acid in Rats

Author
MHW (Ministry of Health and Welfare), Japan

Year
2007

Bibliographic source
Japan Existing Chemical Data Base (JECDB)

Testing facility
Food and Drug Safety Center

Study number
A-04-074

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.

Address

Address 1
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210-9501

Town
Kawasaki

Region / State
Kanagawa

Country
Japan
JP

Identifiers

Other IT system identifiers

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

ID
16558402024DIV750