



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

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

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

CORE

General information

Identification

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

UUID: IUC5-80e43b49-60cb-49c6-87bc-4abf9b428515

Dossier UUID:

Author: SuperUser

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

Remarks:

Substance name

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

Legal entity

[National Institute of Health Sciences / Tokyo / 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

211-322-8

EC name

EC Inventory

CAS number

638-16-4

CAS name

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

OECD

Health Effects

Acute toxicity: oral

ENDPOINT_STUDY_RECORD: Acute toxicity: oral.001

UUID: IUC5-ee8931c1-a3d9-42f4-b95f-e4564603c53f

Dossier UUID:

Author: SuperUser

Date: 2017-01-04T16:29:25.000+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
OECD Guideline 423 (Acute Oral toxicity - Acute Toxic Class Method)

Deviations
no

Qualifier
according to

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 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

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

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 of defecation were observed in two other animals, and these animals died within 3 or 4 days from the dosing.

Body weight

No changes related to the test substance were observed in the 300 mg/kg bw groups. A decrease in body weight was observed in all the animals treated with 2000 mg/kg bw.

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 and 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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Dossier UUID:

Author: SuperUser

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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

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 d... / MHW \(Ministry of Health and Welfare\), Japan / study report](#)

Data access

data published

Materials and methods

Test guideline

Qualifier

according to

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-triazine-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 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

PREPARATION OF DOSING SOLUTIONS: Test substance was dissolved in corn oil for injection.
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 showing 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 ophthalmocoele, 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 ophthalmorrhaxis by observation of behavior on the working table.

FUNCTIONAL 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, creatinine, 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 during 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, urobilinogen, 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 satellite 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, spleen, testes, and epididymis.

HISTOPATHOLOGY: Yes Brain, pituitary, 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, uterus, vagina, bone marrow (one side femur), sciatic nerve (one side femur), spinal cord, and gross abnormalities 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 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.

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 FUNCTIONAL 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 satellite group from Day 1 to Day 2 and Day 29 to Day 30 during the dosing period. No changes in food consumption 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 increasing 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, significant 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 compared with the control group after the dosing period. At the end of the recovery period, a significant decrease in 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 adrenal 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 kidney weights and significant increases in relative brain, heart, kidney, spleen, adrenal, 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 colored in the kidneys were observed in the dead male. Edematous in the lungs and thymus, enlargement 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 tail 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 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 observed in one male receiving 250 mg/kg bw/day. Alopecia of skin in clavicular area were observed in one female 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. Necrosis or edema 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 more. 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

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 hypertrophy 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 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.

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 gland, 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 gland 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

UUID: IUC5-6e3a7ad5-8227-4baa-bd43-d4991de751c6

Dossier UUID:

Author: SuperUser

Date: 2017-01-04T16:29:42.000+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

OECD Guideline 471 (Bacterial Reverse Mutation Assay)

in vitro gene mutation study in bacteria

Deviations

no

Qualifier

according to

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

[638-16-4\]](#)

Method

Species / strain

Species / strain

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

bacteria

Metabolic activation

with and without

Metabolic activation system

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

Species / strain

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

Dimethyl sulfoxide

Controls

Negative controls

no

Solvent 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), sodium azide (TA1535) and 9-aminoacridine hydrochloride (TA1537). +S9 mix: 2-aminoanthracene (all strains)

Details on test system and 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

no, but tested up to limit concentrations

Vehicle controls valid

yes

Negative controls valid

not examined

Positive controls valid

yes

Remarks on result

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

Key result

false

Species / strain

E. coli WP2 uvr A pKM 101
bacteria

Metabolic activation

with and without

Genotoxicity

negative

Cytotoxicity

no, but tested up to limit concentrations

Vehicle controls valid

yes

Negative controls valid

not examined

Positive controls valid

yes

Remarks on result

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

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 negative 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: SuperUser

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

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

Deviations

no

Qualifier

according to

Guideline

JAPAN: Guidelines for Screening Mutagenicity Testing Of Chemicals

Deviations

no

GLP compliance

yes

Type of assay

in vitro mammalian chromosome aberration test
chromosome aberration

Test material

Test material information

[1,3,5-triazine-2,4,6-trithione](#) / [638-16-4](#) / [211-322-8](#)

Method

Species / strain

Species / strain

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

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

Controls

Negative controls

no

Solvent 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 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 number of cells with aberrations were statistically examined.

Statistics

Fisher's test ($P < 0.01$ by one-sided test) and Cochran-Armitage trend test ($P < 0.01$ by one-sided test)

Results and discussion

Test results

Key result

false

Species / strain

other: Chinese hamster lung(CHL/IU) cells

Metabolic activation

with

Genotoxicity

positive

Cytotoxicity

yes

Vehicle controls valid

yes

Negative controls valid

not examined

Positive controls valid

yes

Remarks on result

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

Key result

false

Species / strain

other: Chinese hamster lung(CHL/IU) cells

Metabolic activation

without

Genotoxicity

negative

Cytotoxicity

yes

Vehicle controls valid

yes

Negative controls valid

no

Positive controls valid

yes

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/PDF638-16-4f.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 metabolic activation.

Genetic toxicity in vivo

ENDPOINT_STUDY_RECORD: Genetic toxicity in vivo.001

UUID: IUC5-b741db6c-1836-485b-9a8c-d9818db114bb

Dossier UUID:

Author: SuperUser

Date: 2017-01-04T16:30:18.000+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

OECD Guideline 474 (Mammalian Erythrocyte Micronucleus Test)

in vivo mammalian somatic cell study: cytogenicity / erythrocyte micronucleus

Deviations

no

Qualifier

according to

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](#)

Test animals

Species

mouse

Strain

other: Crlj:CD1(ICR)

Sex

male

Details on test animals 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 observed 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 with 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 increased 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 Bonferroni 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 observed. Next, difference between negative control group and each treated groups was analysed by Dunnett's multiple comparison test (one-sided test). Difference between negative and positive controls was analysed 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 valid

yes

Negative controls valid

not examined

Positive controls valid

yes

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: SuperUser

Date: 2017-01-04T16:30:03.000+09:00

Remarks:

Administrative data

Endpoint

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

Type of information

experimental study

Adequacy of study

key study

Robust study summary

false

Used for classification

false

Used for SDS

false

Reliability

1 (reliable without restriction)

Rationale for reliability incl. deficiencies

other: OECD Test Guideline study under GLP condition

Cross-reference

Reason / purpose

reference to same study

Remarks

7.5.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

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-triazine-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

PREPARATION OF DOSING SOLUTIONS: Test substance was dissolved in corn oil for injection.

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 show 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 remov

ing 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

Estrous cyclicity (parental animals)

Vaginal smears were collected from all females in the main groups and microscopically examined every day from the day after the start of 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, spleen, 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, uterus, vagina, bone marrow (one side femur), sciatic nerve (one side femur), spinal cord, and gross abnormalities 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 lactation
Birth 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 animals)

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: estrous 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 group.

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, implantation index, and delivery index between the control group and any treatment groups. Significant decreases 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)

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 decreased 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.

References

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

UUID: 1cc62be1-b4ac-3ddf-9266-ccd0243f7850

Dossier UUID:

Author: SuperUser

Date: 2017-01-04T16:29:25.000+09:00

Remarks:

Name

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

Composition

Type

Constituent

Reference substance

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

EC number

211-322-8

EC name

EC Inventory

CAS number

638-16-4

CAS name

IUPAC name

1,3,5-triazine-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: SuperUser

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

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

211-322-8

EC name

EC Inventory

CAS number

638-16-4

CAS name

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: SuperUser

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

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

211-322-8

EC name

EC Inventory

CAS number

638-16-4

CAS name

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: c6be500f-a596-303a-a70d-da93de6e578a

Dossier UUID:

Author: SuperUser

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

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

211-322-8

EC name

EC Inventory

CAS number

638-16-4

CAS name

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)

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: SuperUser

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

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

211-322-8

EC name

EC Inventory

CAS number

638-16-4

CAS name

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

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

UUID: ECB5-c72a77ea-657c-4fbf-a95d-f61240e1c79d

Dossier UUID:

Author: SuperUser

Date: 2007-05-10T18:00:00.000+09:00

Remarks:

General information

Reference substance name

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

Inventory

Inventory name

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

Inventory

EC

Inventory number

211-322-8

CAS number

638-16-4

Molecular formula

C3H3N3S3

Description

Reference substance information

IUPAC name

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

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

CAS information

CAS number

638-16-4

Related substances

Group / category information

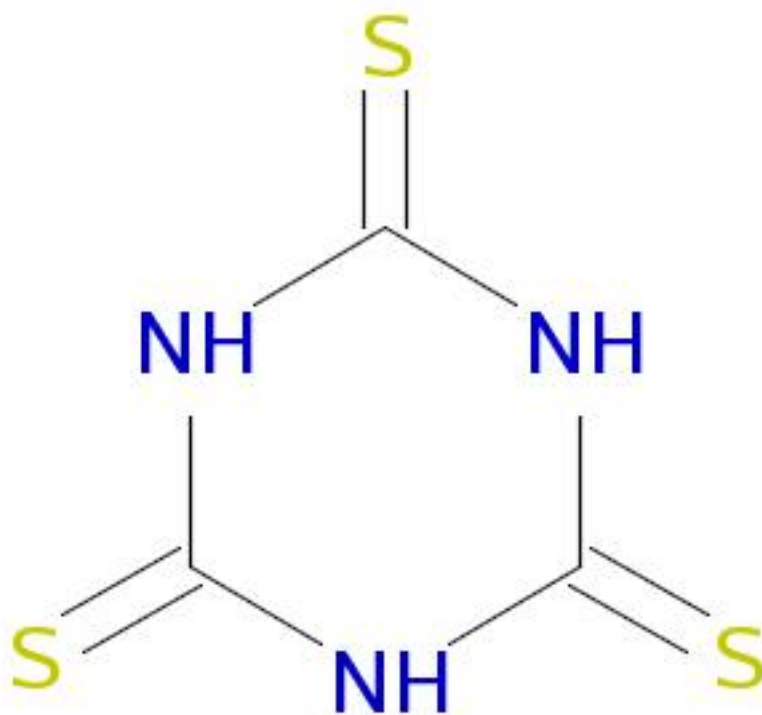
USEPA Category: Substituted Triazines;Thiols

Molecular and structural information**Molecular formula**C₃H₃N₃S₃**Molecular weight**

177.271

SMILES notationS=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

TEST_MATERIAL_INFORMATION: 638-16-4]

UUID: 112cb490-c985-347f-a67a-75b77768ba53

Dossier UUID:

Author: SuperUser

Date: 2017-01-04T16:29:42.000+09:00

Remarks:

Name

638-16-4]

Composition

Type

Constituent

Reference substance

638-16-4] / 638-16-4]

EC number

EC name

CAS number

CAS name

IUPAC name

638-16-4]

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

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: SuperUser

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 administration 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 no.

R-04-007

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

UUID: eda204aa-07f1-3daa-b811-2ecba0560d58

Dossier UUID:

Author: SuperUser

Date: 2017-01-04T16:29:34.000+09:00

Remarks:

General information

Reference Type

study report

Title

A combined repeated-dose/reproductive-developmental toxicity study of trithiocyanuric acid by oral dosing 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 no.

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: SuperUser

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 no.

G-04-065

LITERATURE: Micronucleus test of Trit hiocyanuric acid on mouse

UUID: f531482c-693f-3b5a-b0fd-6cf9ac151c22

Dossier UUID:

Author: SuperUser

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 no.

G-09-021

LEGAL_ENTITY: National Institute of Health Sciences

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

Dossier UUID:

Author: SuperUser

Date: 2011-06-23T11:55:01.000+09:00

Remarks:

General information

Legal entity name

National Institute of Health Sciences

Identifiers

Other IT system identifiers

IT system LEO

ID 10767

IT system IUCLID4

ID 16558402024DIV750

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Contact persons

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Department

Division of Risk Assessment

Title

Dr.

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Address 2

Setagaya-ku

Postal code

158-8501

Town

Tokyo

Country

Japan

LITERATURE: Reverse Mutation Test of trithiocyanuric acid on Bacteria.

UUID: 50307a75-a19c-3293-8805-666e4e4e1f9a

Dossier UUID:

Author: SuperUser

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 no.

M-04-075

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

UUID: 9c90037a-d506-35bc-ac16-4d03353e2a2d

Dossier UUID:

Author: SuperUser

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 no.

A-04-074