



Name: Diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate / diammonium hydrogen citrate / 3012-65-5

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

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Diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

CORE

General information

Identification

SUBSTANCE: Diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

UUID: IUC5-8627c376-bb47-4255-90c4-6639d07c0bb2

Dossier UUID:

Author: SuperUser

Date: 2016-12-21T15:15:08.000+09:00

Remarks:

Substance name

Diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Legal entity

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

Identification of substance

Reference substance

[diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate / diammonium hydrogen citrate / 3012-65-5 / 221-146-3](#)

EC number

221-146-3

EC name

EC Inventory

CAS number

3012-65-5

CAS name

IUPAC name

diammonium hydrogen citrate

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: IUC5-0469431d-735d-47de-8e42-89cac5c65922

Dossier UUID:

Author: SuperUser

Date: 2017-02-15T15:51:02.000+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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate in Rats / MHLW / publication](#)

Data access

data published

Materials and methods

Test guideline

Qualifier

according to

Guideline

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

Test material

Test material information

[diammonium hydrogen citrate / 3012-65-5 / 221-146-3](#)

Test animals

Species

rat

common species

Strain

other: CrI:CD(SD)

Sex

female

Details on test animals and environmental conditions

TEST ANIMALS

- Source :Charles River Japan Inc.
- Age at study initiation: 8-9 weeks old
- Weight at study initiation: Females, 207-224 g
- Fasting period before study: Approximately 16-18 hrs
- Housing:1/cage
- Diet (e.g. ad libitum): Ad libitum except fasting period for 16-18 hrs before administration to 4 hrs after administration
- Water (e.g. ad libitum):Ad libitum
- Acclimation period:6-16 days

ENVIRONMENTAL CONDITIONS

- Temperature (°C): 22±3 °C(actual temperature: 19-24°C)
- Humidity (%):50 ± 20% (actual humidity: 33-57%)
- Air changes (per hr): Approximately 10-15 times/hr
- Photoperiod (hrs dark / hrs light):12 hrs light / 12 hrs dark

Administration / exposure

Route of administration

oral: gavage

Vehicle

other: 0.5%CMC-Na

Details on oral exposure

- Amount of vehicle (if gavage):10 mL/kg bw

Doses

300, 2000 mg/kg bw

No. of animals per sex per dose

3 (1st step group), 3 (2nd step group), 3 (3rd step group) and 3 (4th step group)

Control animals

no

Details on study design

- Duration of observation period following administration: 14 days
- Frequency of observations: nearly successive observation (from time just to 1 hr after administration) and observation (at 2, 4 and 6 hr (only 3 & 4 steps) after administration) (day 0); twice a day (from day 1-day13) and once a day (day14)
- Frequency of weighing: just before administration (day 0), and 1,3,5,7,10 and 14 day after administration
- Necropsy of survivors performed: yes

Results and discussion

Effect levels

Key result

false

Sex

female

Dose descriptor

LD50

Effect level

> 2000 mg/kg bw

Mortality

No deaths were observed in any group.

Clinical signs

At 2000 mg/kg bw, mucus feces were observed.

No changes related to the test substance were observed in any group.

Body weight

No changes related to the test substance were observed in any group.

Gross pathology

No changes related to the test substance were observed in any group.

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/PDF3012-65-5a.pdf

Applicant's summary and conclusion

Executive summary

The acute oral LD50 of diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate was > 2,000 mg/kg bw in female rats based on a study conducted according to OECD TG 423. No deaths were observed at 2,000 mg/kg bw. This substance caused mucoid stools at 2,000 mg/kg bw.

Repeated dose toxicity: oral

ENDPOINT_STUDY_RECORD: Repeated dose toxicity: oral.001

UUID: IUC5-55581c53-51f6-4e2f-a181-994678536d94

Dossier UUID:

Author: SuperUser

Date: 2017-02-15T15:47:28.000+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: GLP guideline study

Cross-reference

Reason / purpose

reference to same study

Remarks

7.8.1 Reproductive/developmental toxicity.001

Data source

Reference

[Combined repeat dose and reproductive/developmental toxicity screening test of diammonium hydrogen 2... / MHLW 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

[diammonium hydrogen citrate / 3012-65-5 / 221-146-3](#)

Test animals

Species

rat

common rodent species

Strain

other: CrI: CD(SD)

Sex

male/female

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

- Source: Charles River Laboratories Japan, Inc. Atsugi
- Age at study initiation: 10 weeks
- Weight at study initiation: Males: 371-439 g; Females: 219-273 g
- Housing: Steel wire-mesh cage (250 mm x 350 mm x 200 mm)
- Diet: ad libitum
- Water: ad libitum
- Acclimation period: 15 days

ENVIRONMENTAL CONDITIONS

- Temperature (°C): 21-26
- Humidity (%): 42-64
- Air changes: 10-15 times / hr
- Photoperiod: 12 hrs dark / 12 hrs light

Administration / exposure

Route of administration

oral: gavage

Vehicle

water

Details on oral exposure

PREPARATION OF DOSING SOLUTIONS:

VEHICLE

- Amount of vehicle (if gavage): 5 mL/kg bw
- Lot/batch no. (if required): 6F74

Details on analytical verification of doses or concentrations

Test suspensions at each concentration to be used for males in week 1 and week 6 of administration were analyzed by the HPLC method at Bozo Research Center Inc. Results showed that the concentration of the test article in each suspension was 93.3 to 100.0% of the nominal concentration and both values were within the acceptable range (concentration: percentage of the nominal concentration, 100 ± 10%; C.V.: 10% or below)

Duration of treatment / exposure

(P) Males: 42 days including 14 days pre-mating and mating periods, and thereafter 14 days (P)
Females: 41-47 days including 14 days pre-mating, mating and gestation periods, and the days until day 4 of lactation; satellite animals: 42 days.

Frequency of treatment

Once/day, 7 days/week

Doses / concentrations

Remarks

Doses / Concentrations:

0 (vehicle), 100, 300, and 1000 mg/kg bw/day

Basis:

actual ingested

No. of animals per sex per dose

12 animals/sex/dose as a main dose group,
5 males and 5 females at 0 and 1000 mg/kg bw/day as a satellite group (without mating)

Control animals

yes, concurrent vehicle

Details on study design

- Dose selection rationale: Doses in this test were set based on the results of the following study: 14-day repeated dose oral toxicity test (doses: 100, 300, and 1000 mg/kg bw/day). In the 14-day repeated dose oral toxicity test, abnormalities were observed in animals in the 1000 mg/kg bw/day group, such as an increase in relative kidney weight. No effects were observed at 300 mg/kg bw/day. On the basis of these effects, a dose level of 1000 mg/kg was selected as the maximum dose expecting to induce the toxic changes, and then dose levels of 300 and 100 mg/kg bw/day were selected as a middle dose and a minimum dose levels, respectively, in accordance with a common ratio of approximately 3.
- Rationale for animal assignment (if not random): Body weight-balanced randomization
- Post-exposure recovery period in satellite groups: 14 days

Examinations

Observations and examinations performed and frequency

CAGE SIDE OBSERVATIONS: Yes

- Time schedule:

Males and females: once before the start of administration, 3 times/day during the administration period, and once during the recovery period

DETAILED CLINICAL OBSERVATIONS: Yes

The functional observational battery testing (FOB) was performed on all animals. Among the measures in the FOB, detailed clinical observations were made before the initiation of dosing. The

reafter, in males of the main groups, detailed clinical observations were made once a week. Also in females of the main groups, detailed clinical observations were made once a week in pre-mating and mating periods thereafter, and then those were made on days 1,7,14 and 20 of gestation, and on day 4 of lactation. For the satellite group, detailed clinical observations were made once a week in dosing and recovery periods.

Sensory motor reflexes, forelimb and hindlimb grip strengths, and motor activity were measured on week 6 of administration period (main/recovery group animals) and week 2 of recovery period (recovery group animals).

BODY WEIGHT: Yes

- Time schedule for examinations: Males (main) & males and females (recovery group): Days 1, 4, 8, 11, 15, 22, 25, 29, 32, 36, 39, 42, and the day of necropsy (after ca. 16h-fasting) in dosing period
Males and females (recovery group): Days 1, 4, 8, 11, 14, and the day of necropsy (after ca. 16h-fasting) in recovery period

Females (main group): Twice a week during the precopulation period (days 1, 4, 8, 11, and 15); gestation days 0, 4, 7, 11, 14, 17, and 20; lactation days 0 and 4; and the day of necropsy (after ca. 16h-fasting)

FOOD CONSUMPTION AND COMPOUND INTAKE (if feeding study):

- Food consumption: Yes

Males (main) & males and females (recovery group): Days 1, 4, 8, 11, 15, 32, 36, and 39 in dosing period

Males and females (recovery group): Days 1, 4, 8, 11, and 14 in recovery period

Females (main group): Days 1, 4, 8, 11, and 15; gestation days 1, 4, 7, 11, 14, 17, and 20; lactation days 2 and 4

OPHTHALMOSCOPIC EXAMINATION: No

HAEMATOLOGY: Yes

- Time schedule for collection of blood: Blood was collected on the day of necropsy

- Anaesthetic used for blood collection: Yes (ether)

- Animals fasted: Yes, 16-20h

- How many animals: 5 sex/dose/group

- Parameters checked in table were examined.

CLINICAL CHEMISTRY: Yes

- Time schedule for collection of blood: Same as hematology

- Animals fasted: Same as hematology

- How many animals: Same as hematology

- Parameters checked in table were examined.

URINALYSIS: Yes (males only)

- Time schedule for collection of urine: Day 37-38 in dosing period, day 11-12 in recovery period

- Metabolism cages used for collection of urine: No data

- Animals fasted: fasting and only water at libitum (4h-urine), no fasting (20h-urine)

Sacrifice and pathology

SACRIFICE:

Male animals: Rats were euthanized by exsanguination under ether anesthesia on the day after the last administration.

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

GROSS PATHOLOGY, Yes: whole organs and tissues

ORGAN WEIGHTS, Yes: Brain, thyroids(including parathyroids), thymus, heart, liver, spleen, kidneys, adrenals, testes, epididymis

HISTOPATHOLOGY, Yes: Cerebrum, cerebellum, pituitary gland, spinal cord (thoracic), sciatic nerve, thyroid, parathyroid, adrenal glands, thymus, spleen, submandibular lymph nodes, mesenteric lymph nodes, heart, lung (including the bronchi), stomach, duodenum, jejunum, ileum, cecum, colon, rectum, liver, kidney, bladder, testis, epididymis, ovary, uterus, seminal vesicles, sternum and femur (including bone marrows), macroscopic lesions.

Other examinations

Organ weight: Brian, thyroids (including parathyroids), thymus, heart, liver, spleen, kidneys, adrenals, testes, epididymis

Statistics

The data were analyzed for homogeneity of variance by the Bartlett test. If variances were homogeneous, data was analyzed by the Dunnett test, whereas heterogeneous data was analyzed by the Dunnett type mean rank test ($p < 0.05$, two-sided).

In the recovery test, these values of two groups were analyzed by F test. If variances were homogeneous, data was analyzed by the Student t-test, whereas heterogeneous data was analyzed by the Aspin-Welch t-test ($p < 0.05$, two-sided).

Results and discussion

Results of examinations

Clinical signs

no effects observed

Mortality

no mortality observed

Body weight and weight changes

no effects observed

Food consumption and compound intake (if feeding study)

no effects observed

Food efficiency

not examined

Water consumption and compound intake (if drinking water study)

not examined

Ophthalmological findings

not examined

Haematological findings

no effects observed

Clinical biochemistry findings

effects observed, treatment-related

Urinalysis findings

effects observed, treatment-related

Behaviour (functional findings)

no effects observed

Organ weight findings including organ / body weight ratios

no effects observed

Gross pathological findings

no effects observed

Histopathological findings: non-neoplastic

effects observed, treatment-related

Histopathological findings: neoplastic

not examined

Details on results

CLINICAL CHEMISTRY

High value of glucose was observed at 1000 mg/kg bw/day at the end of dosing.

URINALYSIS (male only)

At week 6 of administration in the main group, an increased trend of acidification and a decreased incidence of crystallization of phosphate were observed dose-dependently.

HISTOPATHOLOGY: NON-NEOPLASTIC

[At the end of dosing] and [At the end of recovery period]

Stomach: Minimal or mild hyperplasia of squamous cells in the limiting ridge were observed in males and females at 1000 mg/kg bw/day.

Any other changes with statistically significant in the tables were considered to be incidental due to temporary, dose-independent, or within the normal ranges of physiological variability.

Effect levels

Dose descriptor

LOAEL

Effect level

300

mg/kg bw/day (actual dose received)

Based on
test mat.

Sex
male/female

Basis for effect level
other: effects on the stomach

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/PDF3012_-65_-5d.pdf

Applicant's summary and conclusion

Conclusions

Based on the effects on the stomach in males and females at 1000 mg/kg bw/day, the NOAEL for repeated oral dosing was determined to be 300 mg/kg bw/day in male and female rats.

Executive summary

A combined repeated oral dose toxicity study with the reproduction/developmental toxicity screening test was performed according to OECD TG 422. Male and female rats (12 animals/sex/dose) were administered diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate at 0, 100, 300, and 1,000 mg/kg bw/day. Males were dosed for 42 days, including a 14-day pre-mating and mating periods. Females were dosed for 41–47 days, including a 14-day pre-mating, mating, and gestation periods and the time until day 4 of lactation. Five animals/sex/dose administered 0 and 1,000 mg/kg bw/day were treated as the recovery group and examined after a 14-day recovery period. After the administration period, squamous cell hyperplasia of the boundary edge in the stomach was observed at 1,000 mg/kg bw/day in both sexes. This change resolved after the recovery period. On the basis of the observed stomach changes, NOAEL for repeated-dose toxicity was determined to be 300 mg/kg bw/day in male and female rats.

Genetic toxicity in vitro

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.001

UUID: IUC5-253e1121-b70b-4f87-9374-6d5b549c946a

Dossier UUID:

Author: SuperUser

Date: 2019-09-03T12:13:13.832+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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate on Bacteria. / MHLW, Japan / study report](#)

Data access

data published

Materials and methods

Test guideline

Qualifier

according to

Guideline

JAPAN: Guidelines for Screening Mutagenicity Testing Of Chemicals

Qualifier

according to

Guideline

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

GLP compliance

yes

Type of assay

bacterial reverse mutation assay
in vitro gene mutation study in bacteria

Test material

Test material information

[3021-65-5](#)

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

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

Species / strain

E. coli WP2 uvr A
bacteria

Metabolic activation

with and without

Metabolic activation system

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

Test concentrations with justification for top dose

-S9 mix and + S9 mix: 313, 625, 1250, 2500, 5000 µg/plate (all strains)

Vehicle

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

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 (AF2:TA100, TA98, WP2 uvrA), sodium azide (SA:TA1535) and 9-aminoacridine hydrochloride (9AA:TA1537). +S9 mix: 2-aminoanthracene (2AA:all strains).

Details on test system and conditions

RANGE-FINDING/SCREENING STUDIES:

Concentration: 5-5000 µg/plate

Cytotoxic conc.: No.

Precipitate: No.

METHOD OF APPLICATION: Preincubation

DURATION

- Preincubation period: 20 min at 37 °C

- Exposure duration:48-49 hrs

NUMBER OF PLATES: 3

DETERMINATION OF CYTOTOXICITY

- Method: other: growth inhibition

Evaluation criteria

In any strain(s) tested with or without S9 mix, when the mean number of revertant colonies per plate increased twice more than that of the negative control and when the increase was shown to be dose-related and reproducible, the chemical was judged mutagenic.

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

Vehicle controls valid

yes

Negative controls valid

not examined

Positive controls valid

yes

Remarks on result

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

Key result

false

Species / strain

E. coli WP2 uvr A
bacteria

Metabolic activation

with and without

Genotoxicity

negative

Cytotoxicity

no

Vehicle controls valid

yes

Negative controls valid

not examined

Positive controls valid

yes

Remarks on result

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

Additional information on results

Contamination with any other bacterias was not found.

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/PDF3012-65-5e.pdf

Applicant's summary and conclusion

Conclusions

Interpretation of results (migrated information):
negative

Executive summary

In a bacterial reverse mutation assay using *S. typhimurium* TA100, TA1535, TA98, and TA1537 and *E. coli* WP2uvrA (OECD TG 471), diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate was negative with or without metabolic activation.

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.002

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Dossier UUID:

Author: SuperUser

Date: 2019-09-03T12:13:27.989+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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate on... / MHLW, Japan / study report](#)

Data access

data published

Materials and methods

Test guideline

Qualifier

according to

Guideline

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

Deviations

no

Qualifier

according to

Guideline

JAPAN: Guidelines for Screening Mutagenicity Testing Of Chemicals

Deviations

no

GLP compliance

yes

Type of assay

in vitro mammalian chromosome aberration test
chromosome aberration

Test material**Test material information**

[diammonium hydrogen citrate / 3012-65-5 / 221-146-3](#)

Method**Target gene**

Chromosome

Species / strain**Species / strain**

other: Chinese hamster lung(CHL/IU) cells

Metabolic activation

with and without

Metabolic activation system

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

Test concentrations with justification for top dose

-S9 mix (short-term treatment): 0, 565, 1130, 2260 ug/mL

+S9 mix (short-term treatment): 0, 565, 1130, 2260 ug/mL

-S9 mix (continuous treatment, 24 h): 0, 283, 656, 1130, 1695, 2260 ug/mL

Vehicle

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

Controls**Negative controls**

no

Solvent controls

yes

True negative controls

no

Positive controls

yes

Positive control substance

benzo(a)pyrene
mitomycin C

Remarks

mitomycin C (without S9 mix), benzo[a]pyrene (with S9 mix)

Details on test system and conditions

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

SPINDLE INHIBITOR: Colcemid

NUMBER OF CELLS EVALUATED: 200 cells / dose

DETERMINATION OF CYTOTOXICITY

- Method: relative total growth

Evaluation criteria

For the evaluation of the frequencies of structural aberrations and of polyploidy induced, the following criteria were employed.

Appearance incidence of cells with chromosomal aberrations: Negative (-): < 5%; equivocal (±): 5-10%; positive (+): > 10%.

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

Statistics

not used.

Results and discussion

Test results

Key result

false

Species / strain

other: Chinese hamster lung (CHL/IU) cells

Metabolic activation

with and without

Genotoxicity

negative

Cytotoxicity

no

Vehicle controls valid

yes

Negative controls valid

not examined

Positive controls valid

yes

Key result

false

Species / strain

other: Chinese hamster lung (CHL/IU) cells

Metabolic activation

without

Genotoxicity

negative

Cytotoxicity

yes 50% cell growth inhibition: 2260 ug/mL (24h continuous)

Vehicle controls valid

yes

Negative controls valid

not examined

Positive controls valid

yes

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/PDF3012-65-5f.pdf

Applicant's summary and conclusion _____

Executive summary

An in vitro chromosomal aberration test using CHL/IU cells (OECD TG 473) showed negative result with or without metabolic activation.

Toxicity to reproduction

ENDPOINT_STUDY_RECORD: Reproductive/developmental toxicity.001

UUID: IUC5-c1ff5a74-f962-4d95-a7cd-a59a30a70cb5

Dossier UUID:

Author: SuperUser

Date: 2017-02-15T15:50:34.000+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

7.5.1 Repeated dose toxicity: oral.001

Data source

Reference

[Combined repeat dose and reproductive/developmental toxicity screening test of diammonium hydrogen 2... / MHLW, 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

[diammonium hydrogen citrate / 3012-65-5 / 221-146-3](#)

Test animals

Species

rat

Strain

other: CrI:CD(SD)

Sex

male/female

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

- Source: Charles River Laboratories Japan, Inc. Atsugi
- Age at study initiation: 10 weeks
- Weight at study initiation: Males: 371-439 g; Females: 219-273 g
- Housing: Steel wire-mesh cage (250 mm x 350 mm x 200 mm)
- Diet: ad libitum
- Water: ad libitum
- Acclimation period: 15 days

ENVIRONMENTAL CONDITIONS

- Temperature (°C): 21-26
- Humidity (%): 42-64
- Air changes: 10-15 times / hr
- Photoperiod: 12 hrs dark / 12 hrs light

Administration / exposure

Route of administration

oral: gavage

Vehicle

water

Details on exposure

PREPARATION OF DOSING SOLUTIONS:

VEHICLE

- Amount of vehicle (if gavage): 5 mL/kg bw
- Lot/batch no. (if required): 6F74

Details on mating procedure

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

Analytical verification of doses or concentrations

yes

Details on analytical verification of doses or concentrations

Test suspensions at each concentration to be used for males in week 1 and week 6 of administration were analyzed by the HPLC method at Bozo Research Center Inc. Results showed that the concentration of the test article in each suspension was 93.3 to 100.0% of the nominal concentration and both values were within the acceptable range (concentration: percentage of the nominal concentration, 100 ± 10%; C.V.: 10% or below)

Duration of treatment / exposure

(P) Males: 42 days including 14 days pre-mating and mating periods, and thereafter 14 days
(P) Females: 41-47 days including 14 days pre-mating, mating and gestation periods, and the days until day 4 of lactation; satellite animals: 42 days.

Frequency of treatment

Once/day, 7days/week

Doses / concentrations

Remarks

Doses / Concentrations:
0 (vehicle), 100, 300, and 1000 mg/kg bw/day
Basis:
actual ingested

No. of animals per sex per dose

12 animals/sex/dose (main dose group), 5 males and 5 females at 0 and 1000 mg/kg bw/day as a satellite group (without mating).

Control animals

yes, concurrent vehicle

Examinations

Parental animals: Observations and examinations

CAGE SIDE OBSERVATIONS: Yes

- Time schedule:

Males and females: once before the start of administration, 3 times/day during the administration period, and once during the recovery period

DETAILED CLINICAL OBSERVATIONS: Yes

The functional observational battery testing (FOB) was performed on all animals. Among the measures in the FOB, detailed clinical observations were made before the initiation of dosing. The reafter, in males of the main groups, detailed clinical observations were made once a week. Also in

females of the main groups, detailed clinical observations were made once a week in pre-mating and mating periods thereafter, and then those were made on days 1,7,14 and 20 of gestation, and on day 4 of lactation. For the satellite group, detailed clinical observations were made once a week in dosing and recovery periods.

Sensory motor reflexes, forelimb and hindlimb grip strengths, and motor activity were measured on week 6 of administration period (main/recovery group animals) and week 2 of recovery period (recovery group animals).

BODY WEIGHT: Yes

- Time schedule for examinations: Males (main) & males and females (recovery group): Days 1, 4, 8, 11, 15, 22, 25, 29, 32, 36, 39, 42, and the day of necropsy (after ca. 16h-fasting) in dosing period
Males and females (recovery group): Days 1, 4, 8, 11, 14, and the day of necropsy (after ca. 16h-fasting) in recovery period

Females (main group): Twice a week during the precopulation period (days 1, 4, 8, 11, and 15); gestation days 0, 4, 7, 11, 14, 17, and 20; lactation days 0 and 4; and the day of necropsy (after ca. 16 h-fasting)

FOOD CONSUMPTION AND COMPOUND INTAKE (if feeding study):

- Food consumption: Yes

Males (main) & males and females (recovery group): Days 1, 4, 8, 11, 15, 32, 36, and 39 in dosing period

Males and females (recovery group): Days 1, 4, 8, 11, and 14 in recovery period

Females (main group): Days 1, 4, 8, 11, and 15; gestation days 1, 4, 7, 11, 14, 17, and 20; lactation days 2 and 4

OPHTHALMOSCOPIC EXAMINATION: No

HAEMATOLOGY: Yes

- Time schedule for collection of blood: Blood was collected on the day of necropsy

- Anaesthetic used for blood collection: Yes (ether)

- Animals fasted: Yes, 16-20h

- How many animals: 5 sex/dose/group

- Parameters checked in table were examined.

CLINICAL CHEMISTRY: Yes

- Time schedule for collection of blood: Same as hematology

- Animals fasted: Same as hematology

- How many animals: Same as hematology

- Parameters checked in table were examined.

URINALYSIS: Yes (males only)

- Time schedule for collection of urine: Day 37-38 in dosing period, day 11-12 in recovery period

- Metabolism cages used for collection of urine: No data

- Animals fasted: fasting and only water at libitum (4h-urine), no fasting (20h-urine)

Estrous cyclicity (parental animals)

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

During the pre-mating administration period, vaginal smear pictures were classified as proestrus, estrus, metestrus or diestrus and examined for the frequency of estrus and interval between estruses (estrous cycle). During the mating period, vaginal smears were examined for the presence of sperm.

Sperm parameters (parental animals)

Parameters examined in P male parental generations: testes weight, epididymides weight

Litter observations

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

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

Postmortem examinations (parental animals)

SACRIFICE:

Male animals: Rats were euthanized by exsanguination under ether anesthesia on the day after the last administration.

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

GROSS PATHOLOGY, Yes: whole organs and tissues

ORGAN WEIGHTS, Yes: Brain, thyroids(including parathyroids), thymus, heart, liver, spleen, kidneys, adrenals, testes, epididymis

HISTOPATHOLOGY, Yes: Cerebrum, cerebellum, pituitary gland, spinal cord (thoracic), sciatic nerve, thyroid, parathyroid, adrenal glands, thymus, spleen, submandibular lymph nodes, mesenteric lymph nodes, heart, lung (including the bronchi), stomach, duodenum, jejunum, ileum, cecum, colon, rectum, liver, kidney, bladder, testis, epididymis, ovary, uterus, seminal vesicles, sternum and femur (including bone marrows), macroscopic lesions.

Postmortem examinations (offspring)

GROSS NECROPSY

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

Statistics

The data were analyzed for homogeneity of variance by the Bartlett test. If variances were homogeneous, data was analyzed by the Dunnett test, whereas heterogeneous data was analyzed by the Dunnett type mean rank test ($p < 0.05$, two-sided).

In the recovery test, these values of two groups were analyzed by F test. If variances were homogeneous, data was analyzed by the Student t-test, whereas heterogeneous data was analyzed by the Aspin-Welch t-test ($p < 0.05$, two-sided).

Reproductive indices

Each parameter was determined by the following equations:

Copulation index (%) = (No. of copulated animals/No. of co-housed animals) × 100

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

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

Duration of gestation (days) = day 0 of lactation – day 0 of gestation

Delivery index (%) = (No. of females delivered liveborn pups/No. of pregnant females) × 100

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

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

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

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

Sex ratio = No. of liveborn male pups/(No. of liveborn male pups + No. of liveborn female pups)

Offspring viability indices

Viability index (%) = (No. of surviving pup on day 4 after birth/No. of liveborn pups on day 0 after birth) × 100

Results and discussion _____

Results: P0 (first parental animals) _____

General toxicity (P0) _____

Clinical signs

no effects observed

Body weight and weight changes

no effects observed

Food consumption and compound intake (if feeding study)

no effects observed

Organ weight findings including organ / body weight ratios

no effects observed

Description (incidence and severity)

on reproductive organs

Gross pathological findings

no effects observed

Description (incidence and severity)

on reproductive organs

Histopathological findings: non-neoplastic

no effects observed

Description (incidence and severity)

on reproductive organs

Reproductive function / performance (P0) _____

Reproductive function: estrous cycle

no effects observed

Reproductive function: sperm measures

not examined

Reproductive performance

no effects observed

Description (incidence and severity)

on reproductive organs

Effect levels (P0) _____

Dose descriptor

NOAEL

Effect level

300

mg/kg bw/day (actual dose received)

Sex

male/female

Basis for effect level

other: Effects of stomach (see repeated dose toxicity)

Dose descriptor

NOAEL

Effect level

1000

mg/kg bw/day (actual dose received)

Sex

male/female

Basis for effect level

other: no effects on reproduction

Results: F1 generation

General toxicity (F1)

Clinical signs

no effects observed

Mortality / viability

no mortality observed

Body weight and weight changes

no effects observed

Sexual maturation

not examined

Organ weight findings including organ / body weight ratios

not examined

Gross pathological findings

no effects observed

Histopathological findings

not examined

Effect levels (F1)

Dose descriptor

NOAEL

Generation

F1

Effect level

1000

mg/kg bw/day (actual dose received)

Sex

male/female

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/PDF3012-65-5d.pdf

Applicant's summary and conclusion

Conclusions

NOAEL for rat reproductive/developmental toxicity was determined to be 1000 mg/kg bw/day.

Executive summary

In the combined repeated oral dose toxicity study with the reproduction/developmental toxicity screening test (0, 100, 300, and 1,000 mg/kg bw/day) (OECD TG 422), no effects of this substance on reproductive and developmental parameters were observed at 1,000 mg/kg bw/day. NOAEL for the rat reproductive/developmental toxicity of diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate was regarded as 1,000 mg/kg bw/day, the highest dose tested.

References

TEST_MATERIAL_INFORMATION: 3021-65-5

UUID: 067f67f4-1be1-3618-a6f5-8540a6c179db

Dossier UUID:

Author: SuperUser

Date: 2017-02-15T15:48:17.000+09:00

Remarks:

Name

3021-65-5

Composition

Type

Constituent

Reference substance

3021-65-5 / 3021-65-5

EC number

EC name

CAS number

CAS name

IUPAC name

3021-65-5

Other characteristics

Details on test material

- Name of test material (as cited in study report): diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate
- Purity: 100.0%
- Lot/batch No.: 6803
- Storage condition of test material: in a hermetically sealed and light-resistant container at cool (2-8 °C) place
- Stability under test conditions: The stability of test material was identified by analysis of the remainder.

LITERATURE: Combined repeat dose and reproductive/developmental toxicity screening test of diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate by oral administration in rats

UUID: a3ee5596-6157-3898-81d6-64f2a82d1a72

Dossier UUID:

Author: SuperUser

Date: 2017-02-15T15:47:28.000+09:00

Remarks:

General information

Reference Type

study report

Title

Combined repeat dose and reproductive/developmental toxicity screening test of diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate by oral administration in rats

Author

MHLW Japan

Year

2009

Bibliographic source

available in the web of Japan Existing Chemical Data Base (JECDB) at http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp

Testing facility

BoZo Research Center

LITERATURE: Combined repeat dose and reproductive/developmental toxicity screening test of diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate by oral administration in rats

UUID: 5871efdc-ac0e-3345-bf1f-4eaf58d59637

Dossier UUID:

Author: SuperUser

Date: 2017-02-15T15:50:34.000+09:00

Remarks:

General information

Reference Type

study report

Title

Combined repeat dose and reproductive/developmental toxicity screening test of diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate by oral administration in rats

Author

MHLW, Japan

Year

2009

Bibliographic source

available in the web of Japan Existing Chemical Data Base (JECDB) at http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp

Testing facility

BoZo Research Center

REFERENCE_SUBSTANCE: diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

UUID: ECB5-399f7091-4bb7-447c-b011-267f474d9c96

Dossier UUID:

Author: SuperUser

Date: 2016-12-21T15:14:55.000+09:00

Remarks:

General information

Reference substance name

diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Inventory

Inventory name

diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Inventory

EC

Inventory number

221-146-3

CAS number

3012-65-5

Molecular formula

C₆H₈O₇.2H₃N

Description

Reference substance information

IUPAC name

diammonium hydrogen citrate

Synonyms

Identity

1,2,3-Propanetricarboxylic acid, 2-hydroxy-, diammonium salt

Identity

1,2,3-Propanetricarboxylic acid, 2-hydroxy-, diammonium salt

Identity

1,2,3-Propanetricarboxylic acid, 2-hydroxy-, diammonium salt

CAS information

CAS number

3012-65-5

Related substances**Group / category information**

DSL Category: Organics

Molecular and structural information**Molecular formula**C₆H₈O₇·2H₃N**Molecular weight**

225.1772

SMILES notation[NH4+].[NH4+].OC(CC(=O)[O-])(CC(=O)[O-])C(=O)[O-]**InChI**

InChI=1/C6H8O7.2H3N/c7-3(8)1-6(13,5(11)12)2-4(9)10;;/h13H,1-2H2,(H,7,8)(H,9,10)(H,11,12);2*1H3/p-1

Structural formula

TEST_MATERIAL_INFORMATION: d diammonium hydrogen citrate / 3012-65-5 / 221-146-3

UUID: 80817e13-2fe0-3773-a70c-2e2ef08eef5c

Dossier UUID:

Author: SuperUser

Date: 2017-02-15T15:51:02.000+09:00

Remarks:

Name

diammonium hydrogen citrate / 3012-65-5 / 221-146-3

Composition

Type

Constituent

Reference substance

diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate / diammonium hydrogen citrate / 3012-65-5 / 221-146-3

EC number

221-146-3

EC name

EC Inventory

CAS number

3012-65-5

CAS name

IUPAC name

diammonium hydrogen citrate

Other characteristics

Details on test material

- Name of test material (as cited in study report): diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate
- Analytical purity: 100.0%
- Lot/batch No.: 6803
- Stability under test conditions: The stability of test material was identified by analysis of the remainder.
- Storage condition of test material: At a cold place (temperature 2~7°C) in a refrigerator, with a stopper.

TEST_MATERIAL_INFORMATION: d diammonium hydrogen citrate / 3012-65-5 / 221-146-3

UUID: 728e8f1d-e1e7-346c-9964-b1a2bf419c50

Dossier UUID:

Author: SuperUser

Date: 2017-02-15T15:50:34.000+09:00

Remarks:

Name

diammonium hydrogen citrate / 3012-65-5 / 221-146-3

Composition

Type

Constituent

Reference substance

diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate / diammonium hydrogen citrate / 3012-65-5 / 221-146-3

EC number

221-146-3

EC name

EC Inventory

CAS number

3012-65-5

CAS name

IUPAC name

diammonium hydrogen citrate

Other characteristics

Details on test material

- Name of test material (as cited in study report): diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate
- Purity: 100.0%
- Impurities (identity and concentrations):
- Lot/batch No.: 6803
- Stability under test conditions: Stable
- Storage condition of test material: Refrigeration
- Dosing solution storage condition: Room temperature
- Other: The dosing solution was used within 10 days of preparation.

TEST_MATERIAL_INFORMATION: d diammonium hydrogen citrate / 3012-65-5 / 221-146-3

UUID: 9020a79f-ddd7-3adc-82b6-1e1c8c476fdf

Dossier UUID:

Author: SuperUser

Date: 2017-02-15T15:49:29.000+09:00

Remarks:

Name

diammonium hydrogen citrate / 3012-65-5 / 221-146-3

Composition

Type

Constituent

Reference substance

diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate / diammonium hydrogen citrate / 3012-65-5 / 221-146-3

EC number

221-146-3

EC name

EC Inventory

CAS number

3012-65-5

CAS name

IUPAC name

diammonium hydrogen citrate

Other characteristics

Details on test material

- Name of test material (as cited in study report): diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate
- Analytical purity: 100.0%
- Lot/batch No.: 6803
- Storage condition of test material: in a hermetically sealed and light-resistant container at cool (2-8 °C) place
- Stability under test conditions: The stability of test material was identified by analysis of the remainder.

LITERATURE: In Vitro Chromosomal Aberration Test of diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate on Cultured Chinese Hamster Cells.

UUID: ed9f5c39-923d-3218-a027-aa04dad90a22

Dossier UUID:

Author: SuperUser

Date: 2017-02-15T15:49:29.000+09:00

Remarks:

General information

Reference Type

study report

Title

In Vitro Chromosomal Aberration Test of diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate on Cultured Chinese Hamster Cells.

Author

MHLW, Japan

Year

2011

Bibliographic source

Japan Existing Chemical Data Base (JECDB)

Testing facility

Safety Research Institute for Chemical Compounds Co., Ltd.

LEGAL_ENTITY: National Institute of Health Sciences

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

Dossier UUID:

Author: SuperUser

Date: 2019-09-03T10:05:28.255+09:00

Remarks: Disclaimer: The contents in this document were created based on the MHLW (Ministry of Health, Labour and Welfare) peer reviewed study reports (in Japanese) in JECDB (Japan Existing Chemical Database) at http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp. Authorship is in the Division of Risk Assessment, the National Institute of Health Sciences, and the contents do not reflect any official MHLW opinions or any other regulatory policies.

General information

Legal entity name

National Institute of Health Sciences

Remarks

Disclaimer: The contents in this document were created based on the MHLW (Ministry of Health, Labour and Welfare) peer reviewed study reports (in Japanese) in JECDB (Japan Existing Chemical Database) at http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp. Authorship is in the Division of Risk Assessment, the National Institute of Health Sciences, and the contents do not reflect any official MHLW opinions or any other regulatory policies.

Identifiers

Other IT system identifiers

IT system LEO
ID 10767
IT system IUCLID4
ID 16558402024DIV750

Contact information

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Postal code

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Region / State

Kanagawa

Country

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Contact persons

Person

Hirose, Akihiko; National Institute of Health Sciences, Japan

Last name

Hirose

First name

Akihiko

Organisation

National Institute of Health Sciences, Japan

Department

Division of Risk Assessment

Title

Dr

Country

Japan

LITERATURE: Reverse Mutation Test of diammonium hydrogen 2-hydroxypropane -1,2,3-tricarboxylate on Bacteria.

UUID: 435d0925-d6a4-3611-87a0-697e7ce9d1bb

Dossier UUID:

Author: SuperUser

Date: 2017-02-15T15:48:17.000+09:00

Remarks:

General information

Reference Type

study report

Title

Reverse Mutation Test of diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate on Bacteria.

Author

MHLW, Japan

Year

2011

Bibliographic source

Japan Existing Chemical Data Base (JECDB)

Testing facility

Safety Research Institute for Chemical Compounds Co., Ltd.

LITERATURE: Single Dose Oral Toxicity Test of diammonium hydrogen 2-hydroxypropane -1,2,3-tricarboxylate in Rats

UUID: 711f2de5-2173-37ae-b376-f1c8b65aca3e

Dossier UUID:

Author: SuperUser

Date: 2017-02-15T15:51:02.000+09:00

Remarks:

General information

Reference Type
publication

Title
Single Dose Oral Toxicity Test of diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate in Rats

Author
MHLW

Year
2011

Bibliographic source
available in the web of Japan Existing Chemical Data Base (JECDB) at http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp

Testing facility
Safety Research Institute for Chemical Compounds Co., Ltd.