Name: COMPLETE / SUBSTANCE : 1,5,9-Cyclododecatriene / cyclododeca-1,5,9-triene / 4904-61-4 Fri, 16 Dec 2022, 15:45:15+0900 /

Legal entity owner: National Institute of Health Sciences

Printing date: 2022-12-16T15:45:16.079+09:00

Table of Contents

DOSSIER:

UUID: 0
Dossier UUID:
Author:
Date: 2022-12-16T15:45:15.882+09:00
Remarks:

Dossier header

Dossier submission type

Name
Complete table of contents

Version
core 7.0

Name (given by user)

Dossier subject

Dossier subject
1,5,9-Cyclododecatriene / cyclododeca-1,5,9-triene / 4904-61-4

Public name

Submitting legal entity
National Institute of Health Science

Dossier creation date/time
Fri, 16 Dec 2022, 15:45:15+0900

Used in category

LEGAL_ENTITY: National Institute of Health Science

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

General information

Legal entity name
National Institute of Health Science

1,5,9-Cyclododecatriene

CORE

General information

Assessment approach (assessment entities)

FIXED_RECORD: Assessment approach

UUID:	1382ab58-1ccf-3c1d-831b-9e6fb534512c
Dossier UUID:	
Author:	
Date:	2018-03-08T10:44:51.000+09:00
Remarks:	

OECD

Health Effects

Repeated dose toxicity: oral

ENDPOINT_STUDY_RECORD: Repeated dose toxicity: oral.001

UUID:	087b5c71-30cb-4926-bcde-a32e0e2f24b2
Dossier UUID:	
Author:	
Date:	2022-12-16T15:42:26.917+09:00
Remarks:	

Administrative data

Endpoint
short-term repeated dose toxicity: oral

Type of information
experimental study

Adequacy of study
key study

Robust study summary
true

Used for classification
false

Used for SDS
false

Reliability
1 (reliable without restriction)

Rationale for reliability incl. deficiencies
guideline study
Reliability 1

Data source

Reference

Combined Repeated Dose Toxicity Study with theReproduction/Developmental Toxicity Screening Test on / MHLW, Japan / study report

Data access
data published

Materials and methods

Test guideline

Qualifier
according to guideline

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

GLP compliance
yes

Test material

Test material information
1,5,9-Cyclododecatriene

Specific details on test material used for the study
Purity: 94.7% (sum of isomers)

Test animals

Species
rat
common rodent species

Strain
other: Crl:CD(SD)

Sex
male/female

Administration / exposure

Route of administration
oral: gavage

Vehicle
corn oil

Analytical verification of doses or concentrations
yes

Duration of treatment / exposure
males: 42 days, females: 41-46 days from 14 days before mating to day 4 of lactation

Frequency of treatment
once a day

Doses / concentrations

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

Dose / conc.	
12	mg/kg bw/day (actual dose received)

Dose / conc.	
60	mg/kg bw/day (actual dose received)

Dose / conc.	
300	mg/kg bw/day (actual dose received)

No. of animals per sex per dose
12 animals/sex/dose

Control animals
yes, concurrent vehicle

Details on study design
- Dose selection rationale:
Dose finding study: Rats were dosed the test substance at 0, 100, 300, and 1000 mg/kg/day for 14 days. Two males died at 1000 mg/kg bw/day. Shiver and reduced body weight gain were observed a t 1000 mg/kg bw/day. At 300 mg/kg bw/day and higher, hyperactivity was found. At 100 mg/kg bw/ day and higher, there were slight decreased food consumption and increased liver weight. Based on the dose finding study, the highest dose for the main test was set as 300 mg/kg bw/day, and middle and low doses were set as 60 and 12 mg/kg bw/day with a common ratio of 3.

- Post-exposure recovery period in satellite groups: 14 days

Examinations

Observations and examinations performed and frequency
Clinical observation performed and frequency: General condition was observed 3 times a day during the administration period (before dosing, and immediately after and approximately 2 hours after dosing) and once a day (in the morning) during the recovery period.
Body weights were determined on days 1, 4, 8, 11, 15, 18, 22, 25, 29, 32, 36, 39 and 42 of adminis tration for males and on days 1, 4, 8, 11 and 15 of administration, days 0, 4, 7, 11, 14, 17 and 20 of gestation and days 0 and 4 of lactation for females, and the day of necropsy in males and females . In addition, males and females in the recovery groups were weighed on days 1, 4, 8, 11 and 14 of recovery and on the day of necropsy.
Food consumption was determined on days 1, 4, 8, 11, 15, 32, 36, 39 and 42 of administration for male s and on days 1, 4, 8, 11 and 15 of administration, days 1, 4, 7, 11, 14, 17 and 20 of gestation and days 2 and 4 of lactation in females, but it was not determined during the mating period for males and females. In addition, it was determined on days 1, 4, 8, 11 and 14 of recovery for males and females in the recovery groups.

Sacrifice and pathology
Necropsy: Detailed macroscopic examination was then conducted on the organs/tissues throughout the body of each animal, including the external appearance, head, thorax and abdomen.
Measurement of organ weighs: The brain, thyroids (including parathyroids), adrenals, thymus, spleen, heart, liver, kidneys, testes, epididymides were determined.
Histopathological examination: The liver in both sexes and the kidney in males of all groups, the cerebrum, cerebellum, pituitary, spinal cord (thoracic), sciatic nerve, thyroids, parathyroids, adrenals, thymus, spleen, submandibular lymph node, mesenteric lymph node, heart, lung (including bronchus), duodenum, jejunum, ileum, cecum, colon, rectum, liver, kidneys, urinary bladder, testes, epididymides, ovaries, uterus, seminal vesicles, sternum (including bone marrow), femur (including bone marrow)

in males and females at 0 and 300 mg/kg. In addition, all gross pathological lesions of all animals were examined.

Statistics
Statistical methods: Dunnett's test for continuous data and Dunnett-type mean rank test for quantal data were used.

Results and discussion

Results of examinations

Clinical signs
effects observed, treatment-related

Description (incidence and severity)
Salivation caused by irritation from the test article was observed during the administration period in both sexes in the 300 mg/kg group. Salivation was observed sporadically at approximately 2 hours after administration from week 3 of administration.

Mortality
no mortality observed

Body weight and weight changes
effects observed, treatment-related

Description (incidence and severity)
Reduced body weight gain was observed in males during the administration period and in females from day 14 of gestation in the 300 mg/kg group.

Food consumption and compound intake (if feeding study)
no effects observed

Haematological findings
effects observed, treatment-related

Description (incidence and severity)
At the end of administration period, prolongation of prothrombin time in males in the 60 mg/kg group , and prolongation of prothrombin time and activated partial thromboplastin time and high value in f ibrinogen in males in the 300 mg/kg group were observed. Additionally, a low value in white blood cell count with low values in lymphocyte and neutrophil counts and basophil percentage and count was observed in females in the 300 mg/kg group.

Clinical biochemistry findings
effects observed, treatment-related

Description (incidence and severity)
γ-GTP, total protein, and albumin were increased at 300 mg/kg bw/day in males. AST, ALT, and creatin ine were decreased at 300 mg/kg bw/day in females.

Urinalysis findings
no effects observed

Behaviour (functional findings)
no effects observed

Description (incidence and severity)
Manipulative test, measurements of grip strength and motor activity: No test article-related changes were observed in males or females.

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

Description (incidence and severity)
At the end of the administration period, high value in the liver weight in both sexes in the 300 mg/kg group was observed. High value in the liver weight without hypertrophy of centrilobular hepatocytes in females in the 60 mg/kg group was observed. Additionally, high value in the kidney weight was observed in males in the 300 mg/kg group.

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

Description (incidence and severity)
At the end of the administration period, histopathology revealed hypertrophy of centrilobular hepa tocytes in both sexes.
There were appearance of eosinophilic bodies in tubular epithelium caused by α2μ-globulin in 1, 2 and 5 males in the 12, 60 and 300 mg/kg groups, respectively, and the incidence was increased in the 300 mg/kg group.

Effect levels

Key result
false

Dose descriptor
NOAEL

Effect level

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

Based on
act. ingr.

Sex
male/female

Basis for effect level
haematology
prolonged PT in males at 60 mg/kg bw/day
organ weights and organ / body weight ratios
increased liver weight in females at 60 mg/kg bw/day

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/PDF4904-61-4b.pdf

Applicant's summary and conclusion

Conclusions
Based on the effects on the liver of cyclododeca-1, 5, 9-trieneat 60 mg/kg bw/day, the NOAEL for its repeated-dose toxicity was determined to be 12 mg/kg bw/day in rats.

Executive summary

A combined repeated oral dose toxicity study with the reproduction/developmental toxicity screening test was performed in accordance with OECD TG 422. Male and female rats (12 animals/sex/dose) were administered 1,5,9-cyclododecatriene at 0 (vehicle: corn oil), 12, 60, and 300 mg/kg bw/day. Males were dosed for 42 days, including a 14-day pre-mating period and subsequent mating period. Females were dosed for 42–53 days, including 14-day pre-mating, mating, and gestation periods, and until lactation day 4. Five out of 12 males dosed at 0 and 300 mg/kg bw/day were treated as a recovery group. Reduced body weight gain was observed in both sexes in the 300 mg/kg bw/day group. Regarding hematological parameters, prolongation of prothrombin time in males in the 60 and 300 mg/kg bw/day groups as well as activated partial thromboplastin time and a high level of fibrinogen in males in the 300 mg/kg bw/day group were observed. High liver weights were also observed in both sexes at 300 mg/kg bw/day and in females at 60 mg/kg bw/day. Moreover, histopathological analysis revealed hypertrophy of centrilobular hepatocytes at 300 mg/kg bw/day. These changes were either not found or the degree and incidence were reduced after the recovery period. Based on the effects on the liver of 1,5,9-cyclododecatriene 60 mg/kg bw/day, the NOAEL for its repeated-dose toxicity was determined to be 12 mg/kg bw/day in rats.

Genetic toxicity in vitro

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.001

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Dossier UUID:	
Author:	
Date:	2022-12-16T15:43:21.627+09:00
Remarks:	

Administrative data

Endpoint
in vitro gene mutation study in bacteria

Type of information
experimental study

Adequacy of study
key study

Robust study summary
false

Used for classification
false

Used for SDS
false

Reliability
1 (reliable without restriction)

Rationale for reliability incl. deficiencies
guideline study
Reliability 1

Data source

Reference

Reverse Mutation Test of 1,5,9-Cyclododecatriene on Bacteria. / MHLW, Japan / study report

Data access
data published

Materials and methods

Test guideline

Qualifier
according to guideline

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

GLP compliance
yes

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

Test material

Test material information
1,5,9-Cyclododecatriene

Specific details on test material used for the study
Purity 96.6%

Method

Species / strain

Species / strain / cell type
S. typhimurium TA 1535, TA 1537, TA 98, TA 100 and E. coli WP2
bacteria

Metabolic activation
with and without

Metabolic activation system
S9 mix: Rat liver, induced with phenobarbital and 5,6-benzoflavone

Test concentrations with justification for top dose
-S9 mix: 0, 0.15, 0.31, 0.61, 1.22, 2.44, 4.88 µg/plate(TA100, TA1535, TA1537)
0, 0.61, 1.22, 2.44, 4.88, 9.77, 19.5 µg/plate(TA98, WP2 uvrA)
+S9 mix: 0, 2.44, 4.88, 9.77, 19.5, 39.1, 78.1 µg/plate(TA strains)
0, 9.77, 19.5, 39.1, 78.1, 156, 313 µg/plate(WP2 uvrA)
Maximum concentration was established based on the result of the preliminary test at concentration up to 5000 ug/plate. In this test, the growth inhibition was observed at 4.88 µg/plate and above for S. typhimurium TA100, 1535 and 1537 without S9 mix, at 19.5 µg/plate and above for S. typhimurium TA98 and E. coli WP2 uvrA without S9 mix, at 78.1 µg/plate and above for S. typhimurium TA strains with S9 mix and at 313 µg/plate and above for E. coli WP2 uvrA with S9 mix.

Vehicle / solvent
Acetone

Controls

Negative solvent / vehicle controls
yes

Positive controls
yes

Positive control substance
sodium azide
without S9 mix (TA 1535)
benzo(a)pyrene
with S9 mix (TA100, TA98, TA1537)
other: without S9 mix:2-(2-Furyl)-3-(5-nitro -2-furyl)acrylamide (TA100, TA98, WP2uvrA), with S9 mix: 2-Aminoanthracene (TA1535, WP2 uvrA)

Details on test system and experimental conditions
METHOD OF APPLICATION: Preincubation

DURATION- Preincubation period: 20 min at 37°C
- Exposure duration:48 hrs
NUMBER OF PLATES: 3
NUMBER OF REPLICATIONS: 2
DETERMINATION OF CYTOTOXICITY- Method: other: growth inhibition

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

Statistics
not used

Results and discussion

Test results

Key result
false

Species / strain
S. typhimurium TA 100
bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
cytotoxicity -S9 mix: 4.88 µg/plate, +S9 mix: 78.1 µg/plate

Vehicle controls validity
valid

Positive controls validity
valid

Key result
false

Species / strain
S. typhimurium TA 1535
bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
cytotoxicity -S9 mix: 4.88 µg/plate, +S9 mix: 39.1 µg/plate

Key result
false

Species / strain
E. coli WP2 uvr A pKM 101

bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
cytotoxicity -S9 mix: 9.77 µg/plate, +S9 mix: 156 µg/plate

Vehicle controls validity
valid

Positive controls validity
valid

Key result
false

Species / strain
S. typhimurium TA 98
bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
cytotoxicity -S9mix: 9.77 µg/plate, +S9 mix: 156 µg/plate

Vehicle controls validity
valid

Positive controls validity
valid

Key result
false

Species / strain
S. typhimurium TA 1537
bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
cytotoxicity -S9 mix: 4.88 µg/plate, +S9 mix: 39.1 µg/plate

Vehicle controls validity
valid

Positive controls validity
valid

Additional information on results
There were no precipitation in any test concentration.

Cytotoxic concentration: Growth inhibition was observed at 4.88 µg/plate and above for S. typh imurium TA100, TA1535 and TA1537 without S9 mix, at 9.77 µg/plate and above for S. typhimurium TA98 and E. coli WP2 uvrA without S9 mix, at 39.1 µg/plate and above for S. typhimurium TA1535 and TA1537 with S9 mix, at 78.1µg/plate and above for S. typhimurium TA100 and TA98 with S9 mix and at 156 µg/plate and above for E. coli WP2 uvrA with S9 mix.
Genotoxic effects:

Any other information on results incl. tables

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

http://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF4904-61-4e.pdf

Tables (in English) are attachted to this document. Please download the export file to see the Tables.

Overall remarks, attachments

Attachments

Attached (sanitised) documents for publication
4904-61-4_Ames Tables.xlsx / 34.59 KB (application/vnd.openxmlformats-officedocument.spreadsheetml.sheet)

Applicant's summary and conclusion

Conclusions
Genotoxic effects:
With metabolic activation: Negative
Without metabolic activation: Negative

Executive summary

In the bacterial reverse mutation assay using S. typhimurium TA100, TA1535, TA98, and TA1537, and E. coli WP2uvrA/pKM101 (OECD TG 471), negative results were obtained for 1,5,9-cyclododecatriene with or without metabolic activation.

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.002

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Dossier UUID:
Author:
Date: 2022-12-16T15:44:03.408+09:00
Remarks:

Administrative data

Endpoint
in vitro cytogenicity / chromosome aberration study in mammalian cells

Type of information
experimental study

Adequacy of study
key study

Robust study summary
true

Used for classification
false

Used for SDS
false

Reliability
1 (reliable without restriction)

Rationale for reliability incl. deficiencies
guideline study
Reliability 1

Data source

Reference

In Vitro Chromosomal Aberration Test of on 1,5,9-Cyclododecatriene Cultured Chinese Hamster Cells. / MHLW, Japan / study report

Data access
data published

Materials and methods

Test guideline

Qualifier
according to guideline

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

GLP compliance
yes

Type of assay
in vitro mammalian chromosome aberration test
in vitro cytogenicity / chromosome aberration study in mammalian cells

Test material

Test material information
1,5,9-Cyclododecatriene

Specific details on test material used for the study
Purity 96.6%

Method

Species / strain

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

Metabolic activation
with and without

Metabolic activation system
S9 mix: Rat liver, induced with phenobarbital and 5,6- benzoflavone

Test concentrations with justification for top dose
-S9 mix(short-term treatment): 0, 44.0, 57.2, 74.4, 96.7 µg/mL
+S9 mix(short-term treatment): 0, 13.8, 19.4, 27.1, 37.9, 53.1 µg/mL

Preliminary study
0, 13.3, 26.6, 53.1, 106, 213, 425, 850, 1700 µg/mL (=10 mM)

50% growth inhibition was observed
at 53.1 µg/mL with S9 mix
at 106 µg/mL without S9 mix
at 65.8 µg/mL 24h
at 63.5 µg/mL 48 h

Vehicle / solvent
Acetone

Controls

Untreated negative controls
yes

Negative solvent / vehicle controls
yes

Positive controls
yes

Positive control substance
cyclophosphamide
+S9 mix

mitomycin C
- S9 mix

Details on test system and experimental conditions
METHOD OF APPLICATION: Exposure duration: [short-term treatment]:6 hrs + 18 hr,
STAIN: Giemsa stain (3 v/v%) for 15 min.
NUMBER OF REPLICATIONS: 2
NUMBER OF CELLS EVALUATED: 100 + 100 cells /concentration
DETERMINATION OF CYTOTOXICITY- Method: relative total growth

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

Statistics
Not used

Results and discussion

Test results

Key result
false

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

Metabolic activation
with

Genotoxicity
positive clastogenicity

Cytotoxicity / choice of top concentrations
cytotoxicity

Vehicle controls validity
valid

Untreated negative controls validity
valid

Positive controls validity
valid

Key result
false

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

Metabolic activation
with

Genotoxicity
ambiguous polyploidy

Cytotoxicity / choice of top concentrations
cytotoxicity

Vehicle controls validity
valid

Untreated negative controls validity
valid

Positive controls validity
valid

Key result
false

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

Metabolic activation
without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
cytotoxicity

Vehicle controls validity
valid

Untreated negative controls validity
valid

Positive controls validity
valid

Additional information on results
Increase in structural and numerical chromosomal aberrations was observed in the short-term treatment with metabolic activation, while not observed in the short-term treatment without metabo lic activation.

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/PDF4904-61-4f.pdf

Applicant's summary and conclusion

Conclusions
Positive with S9 mix

Executive summary

In an in vitro chromosomal aberration test using CHL/IU cells (OECD TG 473), 1,5,9-cyclododecatriene was clastogenic with metabolic activation and had weak potential to induce

polyploidy with metabolic activation. Based on these results, 1,5,9-cyclododecatriene was judged to cause chromosomal aberration in vitro.

Toxicity to reproduction

ENDPOINT_STUDY_RECORD: Toxicity to reproduction.001

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Author:	
Date:	2022-12-16T15:44:47.259+09:00
Remarks:	

Administrative data

Endpoint
screening for reproductive / developmental toxicity

Type of information
experimental study

Adequacy of study
key study

Robust study summary
true

Used for classification
false

Used for SDS
false

Reliability
1 (reliable without restriction)

Rationale for reliability incl. deficiencies
guideline study
Reliability 1

Data source

Reference

Reverse Mutation Test of 1,5,9-Cyclododecatriene on Bacteria. / MHLW, Japan / study report

Data access
data published

Materials and methods

Test guideline

Qualifier
according to guideline

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

GLP compliance
yes

Test material

Test material information
1,5,9-Cyclododecatriene

Specific details on test material used for the study
Purity: 94.7% (sum of isomers)

Test animals

Species
rat

Strain
other: Crl:CD(SD)

Sex
male/female

Administration / exposure

Route of administration
oral: gavage

Vehicle
corn oil

Details on mating procedure
Males and females in the same dose group of the main groups were co-housed overnight on a one-to-one basis after the end of the pre-mating administration period. Copulation was considered s uccessful if the formation of vaginal plugs or presence of sperm in vaginal smears was confirmed the following morning. The length of the mating period for the same male and female was 4 days at maximum.
Delivery and delivery/lactation status: All copulated females were allowed to deliver spontaneously and examined for any abnormality of delivery. Dams which completed delivery were observed for clearance of placenta and amnion, and the end of delivery was designated as day 0 of lactation. D ams were then allowed to nurse their liveborn pups until day 4 of lactation and examined for lactation status using the gathering of pups, nesting and lactating as indicators

Analytical verification of doses or concentrations
yes

Duration of treatment / exposure
males: 42 days, females: 41-46 days from 14 days before mating to day 4 of lactation

Frequency of treatment
once a day

Doses / concentrations

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

Dose / conc.	
12	mg/kg bw/day (actual dose received)

Dose / conc.	
60	mg/kg bw/day (actual dose received)

Dose / conc.	
300	mg/kg bw/day (actual dose received)

No. of animals per sex per dose
12 animals/sex/dose

Control animals
yes, concurrent vehicle

Examinations

Parental animals: Observations and examinations
Clinical observation performed and frequency: General condition was observed 3 times a day during the administration period (before dosing, and immediately after and approximately 2 hours after dosing) and once a day (in the morning) during the recovery period.
Body weights were determined on days 1, 4, 8, 11, 15, 18, 22, 25, 29, 32, 36, 39 and 42 of adminis tration for males and on days 1, 4, 8, 11 and 15 of administration, days 0, 4, 7, 11, 14, 17 and 20 of gestation and days 0 and 4 of lactation for females, and the day of necropsy in males and females . In addition, males and females in the recovery groups were weighed on days 1, 4, 8, 11 and 14 of recovery and on the day of necropsy.
Food consumption was determined on days 1, 4, 8, 11, 15, 32, 36, 39 and 42 of administration for male s and on days 1, 4, 8, 11 and 15 of administration, days 1, 4, 7, 11, 14, 17 and 20 of gestation and days 2 and 4 of lactation in females, but it was not determined during the mating period for males and females. In addition, it was determined on days 1, 4, 8, 11 and 14 of recovery for males and females in the recovery groups.

Oestrous cyclicity (parental animals)
Vaginal smears were collected from all females in the main groups and microscopically examined every day (in the morning) from the day after the start of administration until the day copulation was confirmed. Vaginal smear pictures were classified as proestrus, estrus, metestrus and diestrus and examined for the frequency of estrus and interval between estruses (estrous cycle).

Postmortem examinations (offspring)
The numbers of liveborn pups and stillborn pups were counted on the day of birth. After liveborn pu ps were examined for any external abnormality, sexed and weighed, dams were allowed to nurse their pups. Liveborn pups were observed for mortality once daily until day 4 after birth. All liveborn pups were exsanguinated after measurement of body weight on day 4 after birth, necropsied and examined for any abnormality in organs/tissues, including those in the head, thorax and abdomen. Individual body weights of liveborn pups were recorded, and the average body weight per litter was calculated by sex.
Pathological examinations were performed.

Statistics
Dunnett's test for continuous data, Dunnett-type mean rank test for quantal data and chi-square test with Yates' continuity correction or chi-square test with Yates' continuity correction for other data were used.

Reproductive indices
No. of copulated animals, No. of males that impregnated females, No. of pregnant females, No. of females that delivered liveborn pups, estrous cycle, gestational length, No.of corpora lutea, No. of im plantation sites, total No. of liveborn and stillborn pups, No. of liveborn pups, sex ratio on day 0 and

day 4 after birth, copulation index (No. of copulated animals / No. of animals housed together x 100), insemination index (No. of pregnant females / No. of copulated males x 100), fertility index (No. of pregnant females / No. of copulated females x 100), delivery index (No. of females that delivered liv eborn pups / No. of pregnant females x 100), implantation index (No. of implantation sites / No. of corpora lutea x100), stillbirth index (No. of stillborn pups / No. of pups born x 100)

Offspring viability indices
Index of external abnormalities (No. of pups with external abnormalities / No. of pups born x 100), live birth index (No. of liveborn pups / No. of pups born x 100), and viability index on day 4 after birth (No. of live pups on day 4 after birth / No. of liveborn pups x 100) were determined.

Results and discussion

Results: P0 (first parental generation)

General toxicity (P0)

Clinical signs
effects observed, treatment-related

Description (incidence and severity)
Salivation caused by irritation from the test article was observed during the administration period in both sexes in the 300 mg/kg group. Salivation was observed sporadically at approximately 2 hours after administration from week 3 of administration.

Mortality
no mortality observed

Body weight and weight changes
effects observed, treatment-related

Description (incidence and severity)
Reduced body weight gain was observed in males during the administration period and in females from day 14 of gestation in the 300 mg/kg group.

Food consumption and compound intake (if feeding study)
no effects observed

Haematological findings
effects observed, treatment-related

Description (incidence and severity)
At the end of administration period, prolongation of prothrombin time in males in the 60 mg/kg group , and prolongation of prothrombin time and activated partial thromboplastin time and high value in fibrinogen in males in the 300 mg/kg group were observed. Additionally, a low value in white blood cell count with low values in lymphocyte and neutrophil counts and basophil percentage and count w as observed in females in the 300 mg/kg group.

Clinical biochemistry findings
effects observed, treatment-related

Description (incidence and severity)
γ-GTP, total protein, and albumin were increased at 300 mg/kg bw/day in males. AST, ALT, and creatinine were decreased at 300 mg/kg bw/day in females.

Urinalysis findings
no effects observed

Behaviour (functional findings)
no effects observed

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

Description (incidence and severity)
At the end of the administration period, high value in the liver weight in both sexes in the 300 mg/kg group was observed. High value in the liver weight without hypertrophy of centrilobular hepatocytes in females in the 60 mg/kg group was observed. Additionally, high value in the kidney weight was observed in males in the 300 mg/kg group.

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

Description (incidence and severity)
At the end of the administration period, histopathology revealed hypertrophy of centrilobular hepa tocytes in both sexes.
There were appearance of eosinophilic bodies in tubular epithelium caused by α2μ-globulin in 1, 2 and 5 males in the 12, 60 and 300 mg/kg groups, respectively, and the incidence was increased in the 300 mg/kg group.

Reproductive function / performance (P0)

Reproductive function: oestrous cycle
no effects observed

Reproductive performance
effects observed, treatment-related

Description (incidence and severity)
A low value in the number of liveborn pups was observed in the 300 mg/kg group. There were no test article-related effects on the estrous cycle, number of elapsed days until copulation, copulation index, insemination index or fertility index. In addition, no test article-related effects were observed in the delivery index, duration of gestation, numbers of corpora lutea and implantation sites, implantatio n index, stillborn index, birth index or sex ratio. No abnormalities were found in the lactation status during the lactation period.

Effect levels (P0)

Key result
false

Dose descriptor
NOAEL

Effect level

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

Based on
act. ingr.

Sex
male/female

Basis for effect level
other: a significantly low value of the number of liveborn pups at 300 mg/kg bw/day

Results: F1 generation

General toxicity (F1)

Mortality / viability
mortality observed, treatment-related

Description (incidence and severity)
A significantly low value of the number of liveborn pups was observed in the 300 mg/kg bw/day group.

Body weight and weight changes
no effects 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/PDF4904-61-4b.pdf

Applicant's summary and conclusion

Conclusions
A significantly low value of the number of liveborn pups was observed in the 300 mg/kg bw/day group. No other effects were observed for fertility and development. The NOAEL for the rat reproductive/developmental toxicity of cyclododeca-1, 5, 9-triene was determined to be 60 mg/kg bw/day, at which maternal general toxicity was observed as described above.

Executive summary

A combined repeated oral dose toxicity study with the reproduction/developmental toxicity screening test was performed in accordance with OECD TG 422. Male and female rats (12 animals/sex/dose) were administered 1,5,9-cyclododecatriene at 0 (vehicle: corn oil), 12, 60, and 300 mg/kg bw/day. Males were dosed for 42 days, including a 14-day pre-mating period and subsequent mating period. Females were dosed for 42–53 days, including 14-day pre-mating, mating, and gestation periods, and until lactation day 4. Five out of 12 males dosed at 0 and 300 mg/kg bw/day were treated as a recovery group. Reduced body weight gain was observed in both sexes in the 300 mg/kg bw/day group. Regarding hematological parameters, prolongation of prothrombin time in males in the 60 and 300 mg/kg bw/day groups as well as activated partial thromboplastin time and a high level of fibrinogen in males in the 300 mg/kg bw/day group were observed. High liver weights were also observed in both sexes at 300 mg/kg bw/day and in females at 60 mg/kg bw/day. Moreover, histopathological analysis revealed hypertrophy of centrilobular hepatocytes at 300 mg/kg bw/day. These changes were either not found or the degree and incidence were reduced after the recovery period. A significantly low value of the number of liveborn pups was observed in the 300 mg/kg bw/day group. No other effects were observed for fertility and development. The NOAEL for the rat reproductive/developmental toxicity of 1,5,9-cyclododecatriene was determined to be 60 mg/kg bw/day, at which maternal general toxicity was observed as described above.

DOMAIN

Substance

SUBSTANCE: 1,5,9-Cyclododecatriene

UUID: e16ca988-a4be-4cd9-9dc8-64a4e1e8f212
Dossier UUID:
Author:
Date: 2022-12-16T15:45:04.247+09:00
Remarks:

Substance name
1,5,9-Cyclododecatriene

Legal entity
National Institute of Health Sciences / Kawasaki / Japan

Identification of substance

Reference substance
cyclododeca-1,5,9-triene / cyclododeca-1,5,9-triene / 4904-61-4 / 225-533-8

EC number	EC name
225-533-8	EC Inventory
CAS number	**CAS name**
4904-61-4	
IUPAC name	
cyclododeca-1,5,9-triene	

Role in the supply chain

Manufacturer
false

Importer
false

Only representative
false

Downstream user
false

References

Reference Substances

REFERENCE_SUBSTANCE: cyclododeca-1,5,9-triene

UUID: ECB5-32e2ca12-bb3c-4055-929c-602a4bce5dc7
Dossier UUID:
Author:
Date: 2018-03-08T10:45:13.000+09:00
Remarks:

Reference substance name
cyclododeca-1,5,9-triene

IUPAC name
cyclododeca-1,5,9-triene

Inventory

Inventory number

Inventory name
cyclododeca-1,5,9-triene

Inventory
EC Inventory

Inventory number
225-533-8

CAS number
4904-61-4

Molecular formula
C12H18

Description

CAS number
4904-61-4

Synonyms

Synonyms

Identity
1,5,9-Cyclododecatriene

Molecular and structural information

Molecular formula
C12H18

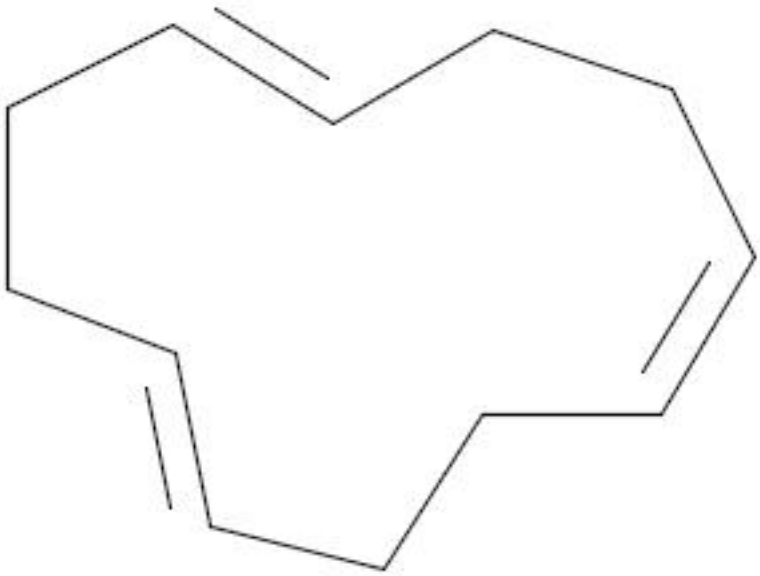
Molecular weight

162.2713

SMILES notation
C1C\C=C\CC\C=C\CC\C=C/1

InChI
InChI=1/C12H18/c1-2-4-6-8-10-12-11-9-7-5-3-1/h1-2,7-10H,3-6,11-12H2

Structural formula



Test Materials

TEST_MATERIAL_INFORMATION: 1,5,9-Cyclododecatriene

UUID:	a87598f4-1681-4f77-bb10-1b3effa8b6cd
Dossier UUID:	
Author:	
Date:	2018-03-08T10:47:51.000+09:00
Remarks:	

Name
1,5,9-Cyclododecatriene

Literatures

LITERATURE: Combined Repeated Dose Toxicity Study with theReproduction/Developmental Toxicity Screening Test on 1,5,9-CYCLODODECATRIENE

UUID: fa643fc0-02bc-4b23-a9b3-38dce416c64b
Dossier UUID:
Author:
Date: 2018-03-08T16:53:19.000+09:00
Remarks:

General information

Reference Type
study report

Title
Combined Repeated Dose Toxicity Study with theReproduction/Developmental Toxicity Screening Test on 1,5,9-CYCLODODECATRIENE

Author
MHLW, Japan

Year
2008

Bibliographic source
Japan Existing Chemical Data Base (JECDB) http://dra4.nihs.go.jp/mhlw_data/jsp/Se archPage ENG.jsp

Testing facility
Bozo Research Center Inc.

LITERATURE: In Vitro Chromosomal Aberration Test of on 1,5,9-Cyclododecatriene Cultured Chinese Hamster Cells.

UUID: 190607e5-f62e-4c0d-8caa-6826131d2902
Dossier UUID:
Author:
Date: 2018-03-08T15:29:36.000+09:00
Remarks:

General information

Reference Type
study report

Title
In Vitro Chromosomal Aberration Test of on 1,5,9-Cyclododecatriene Cultured Chinese Hamster Cells.

Author
MHLW, Japan

Year
2008

Bibliographic source
Japan Existing Chemical Data Base (JECDB) http://dra4.nihs.go.jp/mhlw_data/jsp/Sea rchPage ENG.jsp

Testing facility
Bozo Research Center Inc.

LITERATURE: Reverse Mutation Test of 1,5,9-Cyclododecatriene on Bacteria.

UUID: 6470f598-9801-49b9-8c09-d092c960b48f
Dossier UUID:
Author:
Date: 2018-03-08T10:25:04.000+09:00
Remarks:

General information

Reference Type
study report

Title
Reverse Mutation Test of 1,5,9-Cyclododecatriene on Bacteria.

Author
MHLW, Japan

Year
2008

Bibliographic source
Bibliographic source JECDB http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp

Testing facility
Bozo Research Center Inc.

Legal Entities

LEGAL_ENTITY: National Institute of Health Sciences

UUID: IUC4-b036ff75-0f3c-323b-b200-ed5f46cf5101
Dossier UUID:
Author:
Date: 2022-11-07T15:49:29.000+09:00
Remarks:

General information

Legal entity name
National Institute of Health Sciences

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

Address

Address 1
Tonomachi 3-25-26

Address 2
Kawasaki-ku

Postal code
210-9501

Town
Kawasaki

Region / State
Kanagawa

Country
Japan
JP

Identifiers

Other IT system identifiers

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

ID
16558402024DIV750