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**Name:** 1,5,9-Cyclododecatriene / cyclododeca-1,5,9-triene / 4904-61-4

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

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**Printing date:** 2019-09-03T12:16:50.316+09:00

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# 1,5,9-Cyclododecatriene

## CORE

### General information

#### Identification

**SUBSTANCE:** 1,5,9-Cyclododecatriene

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**UUID:** e16ca988-a4be-4cd9-9dc8-64a4e1e8f212

**Dossier UUID:**

**Author:** Dra

**Date:** 2018-03-08T10:44:51.697+09:00

**Remarks:**

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#### Substance name

1,5,9-Cyclododecatriene

#### Legal entity

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

### Identification of substance

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#### Reference substance

[cyclododeca-1,5,9-triene](#) / [cyclododeca-1,5,9-triene](#) / [4904-61-4](#) / [225-533-8](#)

**EC number**

225-533-8

**EC name**

EC Inventory

**CAS number**

4904-61-4

**CAS name**

**IUPAC name**

cyclododeca-1,5,9-triene

### Role in the supply chain

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#### Manufacturer

false

#### Importer

false

#### Only representative

false

#### Downstream user

false

# OECD

## Health Effects

### Repeated dose toxicity: oral

ENDPOINT\_STUDY\_RECORD: Repeated dose toxicity: oral.001

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**UUID:** 087b5c71-30cb-4926-bcde-a32e0e2f24b2

**Dossier UUID:**

**Author:** Dra

**Date:** 2018-03-09T15:41:10.203+09:00

**Remarks:**

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## Administrative data

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### 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

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### Reference

[Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test on ... / MHLW, Japan / study report](#)

### Data access

data published

## Materials and methods

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## Test guideline

**Qualifier**

according to

**Guideline**

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

**GLP compliance**

yes

## Test material

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**Test material information**

[1,5,9-Cyclododecatriene](#)

**Specific details on test material used for the study**

Purity: 94.7% (sum of isomers)

## Test animals

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**Species**

rat

common rodent species

**Strain**

other: CrI:CD(SD)

**Sex**

male/female

## Administration / exposure

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**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)

<b>Dose / conc.</b>	
60	mg/kg bw/day (actual dose received)
<b>Dose / conc.</b>	
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 at 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 administration 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 males 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 weights: 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**

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### **Results of examinations**

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#### **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 was observed in females in the 300 mg/kg group.

#### **Clinical biochemistry findings**

effects observed, treatment-related

#### **Description (incidence and severity)**

$\gamma$ -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

#### **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 hepatocytes in both sexes.

There were appearance of eosinophilic bodies in tubular epithelium caused by  $\alpha_2\mu$ -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**

<b>Key result</b>	false
<b>Dose descriptor</b>	NOAEL
<b>Effect level</b>	
12	mg/kg bw/day (actual dose received)
<b>Based on</b>	act. ingr.
<b>Sex</b>	male/female
<b>Basis for effect level</b>	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](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 cyclododeca-1, 5, 9-triene 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 cyclododeca-1, 5, 9-triene at 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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**UUID:** e351c082-0693-421e-aab6-f843c868f26c

**Dossier UUID:**

**Author:** Dra

**Date:** 2018-08-27T11:27:27.475+09:00

**Remarks:**

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## Administrative data

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### 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

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### Reference

[Reverse Mutation Test of 1,5,9-Cyclododecatriene on Bacteria. / MHLW, Japan / study report](#)

### Data access

data published

## Materials and methods

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### Test guideline

#### Qualifier

according to

#### Guideline

OECD Guideline 471 (Bacterial Reverse Mutation Assay)

in vitro gene mutation study in bacteria

### GLP compliance

yes

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**Type of assay**

bacterial reverse mutation assay  
in vitro gene mutation study in bacteria

**Test material**

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**Test material information**

[1,5,9-Cyclododecatriene](#)

**Specific details on test material used for the study**

Purity 96.6%

**Method**

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**Species / strain****Species / strain**

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 µg/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**

Acetone

**Controls****Solvent 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 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**

yes -S9 mix: 4.88 µg/plate, +S9 mix: 78.1 µg/plate

**Vehicle controls valid**

yes

**Positive controls valid**

yes

**Key result**

false

**Species / strain**

S. typhimurium TA 1535  
bacteria

**Metabolic activation**

with and without

**Genotoxicity**

negative

**Cytotoxicity**

yes -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**

yes -S9 mix: 9.77 µg/plate, +S9 mix: 156 µg/plate

**Vehicle controls valid**

yes

**Positive controls valid**

yes

**Key result**

false

**Species / strain**

S. typhimurium TA 98

bacteria

**Metabolic activation**

with and without

**Genotoxicity**

negative

**Cytotoxicity**

yes -S9mix: 9.77 µg/plate, +S9 mix: 156 µg/plate

**Vehicle controls valid**

yes

**Positive controls valid**

yes

**Key result**

false

**Species / strain**

S. typhimurium TA 1537

bacteria

**Metabolic activation**

with and without

**Genotoxicity**

negative

**Cytotoxicity**

yes -S9 mix: 4.88 µg/plate, +S9 mix: 39.1 µg/plate

**Vehicle controls valid**

yes

**Positive controls valid**

yes

**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. typhimurium* 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 78.1 µg/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

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

[http://dra4.nihs.go.jp/mhlw\\_data/home/pdf/PDF4904-61-4e.pdf](http://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF4904-61-4e.pdf)

## Applicant's summary and conclusion

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### 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* WP2 uvrA/pKM101 (OECD TG 471), negative results were obtained for cyclododeca-1, 5, 9-triene with or without metabolic activation.

## ENDPOINT\_STUDY\_RECORD: Genetic toxicity in vitro.002

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**UUID:** 86d5e6eb-2f49-4f10-a61d-c382dcf83394

**Dossier UUID:**

**Author:** Dra

**Date:** 2018-08-27T11:27:39.684+09:00

**Remarks:**

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## Administrative data

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### 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

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### 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

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### Test guideline

#### Qualifier

according to

#### Guideline

OECD Guideline 473 (In Vitro Mammalian Chromosome Aberration Test)

in vitro cytogenicity / chromosome aberration study in mammalian cells

### GLP compliance

yes

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**Type of assay**

in vitro mammalian chromosome aberration test  
in vitro cytogenicity / chromosome aberration study in mammalian cells

**Test material**

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**Test material information**

1,5,9-Cyclododecatriene

**Specific details on test material used for the study**

Purity 96.6%

**Method**

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**Species / strain**

**Species / strain**

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**

Acetone

**Controls**

**Negative controls**

yes

**Solvent controls**

yes

**Positive controls**

yes

**Positive control substance**

cyclophosphamide

+S9 mix



mitomycin C  
- S9 mix

**Details on test system and 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 polyploidy induced, the following criteria were employed. Appearance incidence of cell with chromosomal aberrations: Negative(-): less than 5%, Equivocal( $\pm$ ): 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**

yes

**Vehicle controls valid**

yes

**Negative controls valid**

yes

**Positive controls valid**

yes

**Key result**

false

**Species / strain**

other: Chinese hamster lung(CHL/IU) cells

**Metabolic activation**

with

**Genotoxicity**

ambiguous polyploidy

**Cytotoxicity**

yes

**Vehicle controls valid**

yes

**Negative controls valid**

yes

**Positive controls valid**

yes

**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**

yes

**Positive controls valid**

yes

**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 metabolic 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](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), cyclododeca-1, 5, 9-triene was clastogenic with metabolic activation and had weak potential to induce polyploidy with metabolic activation. Based on these results, cyclododeca-1, 5, 9-triene was judged to cause chromosomal aberration in vitro.

## Toxicity to reproduction

### ENDPOINT\_STUDY\_RECORD: Toxicity to reproduction.001

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**UUID:** bc99dfd6-e5f8-4f59-abe7-333bd20e3176

**Dossier UUID:**

**Author:** Dra

**Date:** 2018-03-12T09:34:44.545+09:00

**Remarks:**

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## Administrative data

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**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

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**Reference**

[Reverse Mutation Test of 1,5,9-Cyclododecatriene on Bacteria. / MHLW, Japan / study report](#)

**Data access**

data published

## Materials and methods

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**Test guideline**

**Qualifier**

according to

**Guideline**

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

**GLP compliance**

yes

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## Test material

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### 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: CrI: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 successful 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. Dams 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

<b>Dose / conc.</b>	
0	mg/kg bw/day (actual dose received)
<b>Dose / conc.</b>	
12	mg/kg bw/day (actual dose received)

<b>Dose / conc.</b>	
60	mg/kg bw/day (actual dose received)
<b>Dose / conc.</b>	
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 administration 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 males 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.

**Estrous 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 pups 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 implantation 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 liveborn 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**

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### **Results: P0 (first parental animals)**

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#### **General toxicity (P0)**

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##### **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 was observed in females in the 300 mg/kg group.

##### **Clinical biochemistry findings**

effects observed, treatment-related

##### **Description (incidence and severity)**

$\gamma$ -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 hepatocytes in both sexes.

There were appearance of eosinophilic bodies in tubular epithelium caused by  $\alpha_2\mu$ -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: estrous 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, implantation 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)

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### 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

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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](http://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF4904-61-4b.pdf)

## Applicant's summary and conclusion

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### 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 cyclododeca-1, 5, 9-triene 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 cyclododeca-1, 5, 9-triene was determined to be 60 mg/kg bw/day, at which maternal general toxicity was observed as described above.



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# References

## TEST\_MATERIAL\_INFORMATION: 1,5,9-Cyclododecatriene

---

**UUID:** a87598f4-1681-4f77-bb10-1b3effa8b6cd

**Dossier UUID:**

**Author:** Dra

**Date:** 2018-03-08T10:47:51.009+09:00

**Remarks:**

---

**Name**

1,5,9-Cyclododecatriene

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

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**UUID:** fa643fc0-02bc-4b23-a9b3-38dce416c64b

**Dossier UUID:**

**Author:** Dra

**Date:** 2018-03-08T16:53:19.716+09:00

**Remarks:**

---

## General information

---

**Reference Type**

study report

**Title**

Combined Repeated Dose Toxicity Study with the Reproduction/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/SeArchPageENG.jsp](http://dra4.nihs.go.jp/mhlw_data/jsp/SeArchPageENG.jsp)

**Testing facility**

Bozo Research Center Inc.

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# REFERENCE\_SUBSTANCE: cyclodo deca-1,5,9-triene

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**UUID:** ECB5-32e2ca12-bb3c-4055-929c-602a4bce5dc7

**Dossier UUID:**

**Author:** Dra

**Date:** 2018-03-08T10:45:13.650+09:00

**Remarks:**

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## General information

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**Reference substance name**

cyclododeca-1,5,9-triene

## Inventory

---

**Inventory name**

cyclododeca-1,5,9-triene

**Inventory**

EC

**Inventory number**

225-533-8

**CAS number**

4904-61-4

**Molecular formula**

C<sub>12</sub>H<sub>18</sub>

**Description**

## Reference substance information

---

**IUPAC name**

cyclododeca-1,5,9-triene

**Synonyms**

**Identity**

1,5,9-Cyclododecatriene

## CAS information

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**CAS number**

4904-61-4

## Molecular and structural information

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**Molecular formula**

C<sub>12</sub>H<sub>18</sub>

---

**Molecular weight**

162.2713

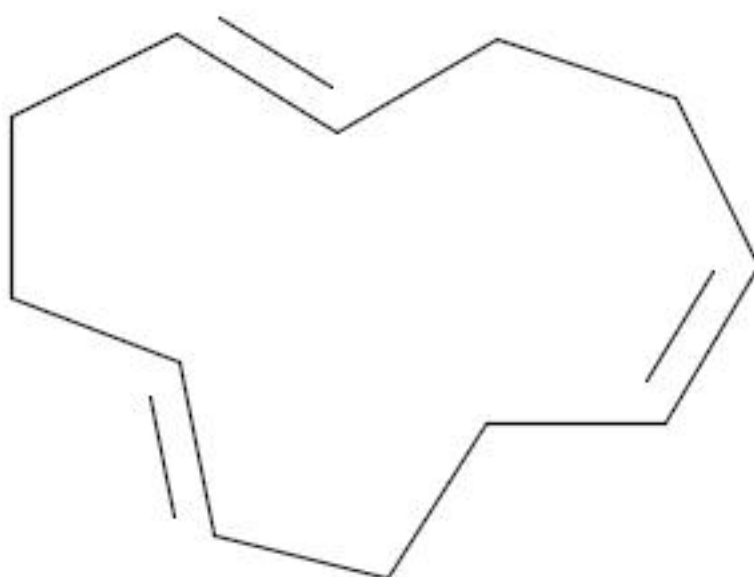
**SMILES notation**

C1\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**



# 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:** Dra

**Date:** 2018-03-08T15:29:36.699+09:00

**Remarks:**

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## General information

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**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/SeachPageENG.jsp](http://dra4.nihs.go.jp/mhlw_data/jsp/SeachPageENG.jsp)

**Testing facility**

Bozo Research Center Inc.

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# LEGAL\_ENTITY: National Institute of Health Sciences

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**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](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.

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## General information

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### 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](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

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### Other IT system identifiers

<b>IT system</b> LEO
<b>ID</b> 10767
<b>IT system</b> IUCLID4
<b>ID</b> 16558402024DIV750

## Contact information

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**Person**

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**First name**

Akihiko

**Organisation**

National Institute of Health Sciences, Japan

**Department**

Division of Risk Assessment

**Title**

Dr

**Country**

Japan

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

---

**UUID:** 6470f598-9801-49b9-8c09-d092c960b48f

**Dossier UUID:**

**Author:** Dra

**Date:** 2018-03-08T10:25:04.034+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](http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp)

**Testing facility**

Bozo Research Center Inc.