Name: OECD_SIDS / SUBSTANCE : Methyl(2-pentyl-3-oxocyclopentyl)acetate / methyl (3-oxo-2-pentylcyclopentyl)acetate / 24851-98-7 Fri, 29 Nov 2024, 09:47:31+0900 /

Printing date: 2024-11-29T09:47:31.351+09:00

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DOSSIER:

UUID: 0
Dossier UUID:
Author:
Date: 2024-11-29T09:47:31.118+09:00
Remarks:

Dossier header

Dossier submission type

Name
OECD SIDS

Version
core 9.0

Name (given by user)

Dossier subject

Dossier subject
Methyl(2-pentyl-3-oxocyclopentyl)acetate / methyl (3-oxo-2-pentylcyclopentyl)acetate / 24851-98-7

Public name

Submitting legal entity
National Institute of Health Sciences

Dossier creation date/time
Fri, 29 Nov 2024, 09:47:31+0900

Used in category

LEGAL_ENTITY: National Institute of Health Sciences

UUID:	71368d76-19ad-4a2e-bc26-6c8ef515e6e3
Dossier UUID:	
Author:	
Date:	2024-05-29T16:58:20.759+09:00
Remarks:	

General information

Legal entity name
National Institute of Health Sciences

Methyl(2-pentyl-3-oxocyclopentyl)acetate

General information

Identification

SUBSTANCE: Methyl(2-pentyl-3-oxocyclopentyl)acetate

UUID: e9759c5c-5fd1-4ab8-826e-f112508a3e9d
Dossier UUID:
Author:
Date: 2023-01-12T15:46:47.000+09:00
Remarks:

Substance name
Methyl(2-pentyl-3-oxocyclopentyl)acetate

Identification of substance

Reference substance
methyl 3-oxo-2-pentylcyclopentaneacetate / methyl (3-oxo-2-pentylcyclopentyl)acetate / 24851-98-7 / 246-495-9

EC number	EC name
246-495-9	EC Inventory
CAS number	**CAS name**
24851-98-7	

IUPAC name
methyl (3-oxo-2-pentylcyclopentyl)acetate

Role in the supply chain

Manufacturer
false

Importer
false

Only representative
false

Downstream user
false

Toxicological information

Repeated dose toxicity

Repeated dose toxicity: oral

ENDPOINT_STUDY_RECORD: Repeated dose toxicity: oral. 001

UUID:	da25bb03-ee50-4b95-ac74-3a26d99e8c1c
Dossier UUID:	
Author:	
Date:	2023-01-31T10:01:06.000+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
false

Used for classification
false

Used for SDS
false

Reliability
1 (reliable without restriction)

Rationale for reliability incl. deficiencies
guideline study
Reliability 1

Cross-reference

Reason / purpose for cross-reference
reference to same study

Related information
OECD / Toxicity to reproduction / Toxicity to reproduction. 001 / Methyl(2-pentyl-3-oxocyclopentyl)acetate / methyl (3-oxo-2-pentylcyclopentyl)acetate / 24851-98-7

Data source

Reference

Combined repeated dose toxicity study with the reproductive/developmental toxicity screening test of / Ministry of Health, Labour and Welfare (MHLW), Japan / study report

Data access
data published https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF24851-98-7d.pdf

Materials and methods

Test guideline

Qualifier
according to guideline

Guideline
other: Guideline for Combined Repeated Dose Study with the Reproduction /Developmental Toxicity Screening Test in Mammalian Species (Chemical Substances Control Law of Japan)

GLP compliance
yes

Limit test
no

Test material

Test material information
Methyl(2-pentyl-3-oxocyclopentyl)acetate

Specific details on test material used for the study
- Name of test material (as cited in study report): methyl (2-pentyl-3-oxocyclopentyl) acetate
- Analytical purity: 98.35% (as the isomeric mixture)
- Storage condition of test material: sealed, cool place (actual temperature: 2 - 8°C)
- Stability under test conditions: The stability of test material was identified by analysis of the rema inder

Test animals

Species
rat
common rodent species

Strain
other: Crl:CD(SD)

Sex
male/female

Details on test animals or test system and environmental conditions
TEST ANIMALS
- Source: Charles River Japan, Inc., Atsugi Breeding Center.
- Age at study initiation: 10 weeks old
- Weight at study initiation: Male: 430 g (406-472 g), Female: 256 g (235-282 g)
- Housing: Animals were individually housed in bracket-type metallic wire-mesh cages (254W × 350D × 170H mm), from gestation day 17 to lactation day 4, Dams were bred individually or with individual littermates in plastic cages (340W x 400D x 185H mm) and bedding.
- Diet: Solid feed (NMF: Oriental Yeast Co., ltd.) was given ad libitum.
- Water: Tap water was given ad libitum.
- Acclimation period: 20 days
ENVIRONMENTAL CONDITIONS
- Temperature (°C): 23±3 (actual temperature: 22-24°C)
- Humidity (%): 50±20% (actual humidity: 50-59%)

- Air changes (per hr): 10-15
- Photoperiod (hrs dark / hrs light): 12 hr dark/12 hr light (light: 7:00-19:00)

Administration / exposure

Route of administration
oral: gavage

Vehicle
corn oil

Details on oral exposure
- Amount of vehicle (if gavage): 5 mL/kg
- Dosing volume: 5 mL/kg

Analytical verification of doses or concentrations
yes

Details on analytical verification of doses or concentrations
The concentrations of each suspension used at weeks 1 and 6 of administration were analyzed by GC. The results showed that the concentration of each suspension was 99.5 to 101.5% of the nominal concentration, and both values were within the acceptable range (concentration: percentage of nominal concentration, 100±10%)

Duration of treatment / exposure
Males: 42 days including 14 days pre-mating
Females (mating group): 41-46 days including 14 days pre-mating, mating and gestation periods and the days until day 4 of lactation
Female (non-mating group): 42 days

Frequency of treatment
Once/day, 7 days/week

Doses / concentrations

Dose / conc.	
0	mg/kg bw/day (actual dose received)
Dose / conc.	
100	mg/kg bw/day (actual dose received)
Dose / conc.	
300	mg/kg bw/day (actual dose received)
Dose / conc.	
1000	mg/kg bw/day (actual dose received)

No. of animals per sex per dose
Mating group: 12 animals/sex/dose (0, 100, 300 and 1000 mg/kg bw/day)
Non-mating group: 10 females/dose (0 and 1000 mg/kg bw/day)

Recovery group: 5 males/dose in the mating group and 5 females/dose in the non-mating groups (0 and 1000 mg/kg bw/day)

Control animals
yes, concurrent vehicle

Details on study design
- Dose selection rationale: Based on the results of a 14-day preliminary study, the high dose was 1000 mg/kg bw/day, which was expected to cause clear signs of toxicity, and the intermediate dose and low dose were set to 300 mg/kg bw/day and 100 mg/kg bw/day, respectively.

[14-day preliminary study]
A 14-day repeated dose oral toxicity test (Crl:CD(SD) rats, doses: 0, 250, 500, and 1000 mg/kg bw/day).
In the 1000 mg/kg bw/day group, males and females showed transient decreased body weight with decreased food consumption in early administration and increased liver weight, males showed increased kidney weight and recessed area in kidney and females showed high total cholesterol. In the 500 mg/kg bw/day group, females showed transient decreased body weight with decreased food consumption in early administration, and males and females showed increased liver weight.

- Rationale for animal assignment (if not random): Body weight-balanced randomization.

Examinations

Observations and examinations performed and frequency
CAGE SIDE OBSERVATIONS: Yes
- Time schedule: 3 times/day (before administration, immediately after administration and 1-3 hours after administration) during the administration period. Twice a day during the recovery period.

DETAILED CLINICAL OBSERVATIONS: Yes
- Time schedule:
Males in the mating group and females in the non-mating group: Once before the start of admi nistration, once every weekly during the administration and recovery periods.
Females in the mating group: Once a week during the pre-mating period, on designated days during mating, gestation, and lactation (Gestation Days (GDs) 1, 7, 14 and 20 for mated females, and L actation Day (LD) 4 for parturient females).

BODY WEIGHT: Yes
- Time schedule for examinations:
Males: Days 1, 8, 15, 22, 29, 36 and 42 of administration and on the day of necropsy, and Days 1, 8 and 14 of recovery and on the day of necropsy.
Females in the mating group: Days 1, 8 and 15 of administration, GDs 0, 7, 14 and 20, LDs 0 and 4 and the day of necropsy.
Females in the non-mating group: Days 1, 8, 15, 22, 29, 36 and 42 of administration and on the day of necropsy, and Days 1, 8 and 14 of recovery and on the day of necropsy.
FOOD CONSUMPTION AND COMPOUND INTAKE (if feeding study):
- Food consumption: Yes
Measurement of food consumption was conducted on all animals at the following frequencies:
Males: Days 2, 8, 15, 30, 36 and 42 of administration, and Days 1, 8 and 14 of recovery.
Females in the mating group: Days 2, 8 and 15 of administration, GDs 1, 7, 14 and 20, LDs 2 and 4.
Females in the non-mating group: Days 2, 8, 15, 30, 36 and 42 of administration, and Days 1, 8 and 14 of recovery.

OPHTHALMOSCOPIC EXAMINATION: No
HAEMATOLOGY: Yes
- Time schedule for collection of blood: At the end of administration period, or at the end of recovery period in both sexes
- Anaesthetic used for blood collection: isoflurane

- Animals fasted: Yes
- How many animals:
5 animals/sex/group
- Parameters examined: red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, reticulocyte perc entage, platelet count, white blood cell count, differential white blood cell count, absolute number of each white blood cell, prothrombin time, activated partial thromboplastin time, fibrinogen.

CLINICAL CHEMISTRY: Yes
- Time schedule for collection of blood: At the end of administration period, or at the end of recovery period in both sexes
- Animals fasted: Yes
- How many animals:
5 animals/sex/group
- Parameters checked: ALP, total bile acid, total cholesterol, triglyceride, phospholipids, total bilirubin, glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, calcium, inorganic phosphorus, total protein, albumin, A/G ratio, AST (GOT), ALT (GPT), LDH, γ-GTP

BLOOD HORMONE: No

URINALYSIS: Yes
- Time schedule for collection of urine: On the final week of administration (Days 38 to 39 of ad ministration) and on the final week of recovery (Days 10 to 11 of recovery)
- Metabolism cages used for collection of urine: Yes
A urine collector to collect four-hour urine samples under fasting but ad libitum drinking conditions, followed by collection of 20-hour urine samples under ad libitum feeding and drinking conditions.
- How many animals: 5 animals/group
- Parameters checked: pH, protein, ketones, glucose, occult blood, bilirubin, urobilinogen, color, sedim ent, urine volume (4-hour volume), osmotic pressure, sodium, potassium, chloride, urine volume (20-h our volume), water intake (24-hour volume)

NEUROBEHAVIOURAL (FUNCTIONAL) EXAMINATION: Yes
- Time schedule for examinations:
Males: On the final week of administration (Day 37 of administration), and on the final week of recovery (Day 9 of recovery).
Females in the mating group: LD 4 (Day 41 to Day 44 of administration)
Females in the non-mating group: On the final week of administration (Day 37 of administration), and on the final week of recovery (Day 9 of recovery).
- Dose groups that were examined:
All dose groups (5 animals/sex/group)
- Battery of functions tested:
1) Manipulative Test. Auditory response, approach response, touch response, tail pinch response, pupi llary reflex, aerial righting reflex, landing foot splay
2) Measurement of Grip Strength. Following manipulative test, grip strength of forelimb and hind limb was measured by CPU gauge MODEL-RX-5 (AIKOH Engineering Co., Ltd.).
3) Measurement of Motor Activity. Following measurement of grip strength, motor activity was measured by a motor activity sensor for experimental animals NS-AS01 (Neuro Science, Inc). The measurement was conducted for 1 hour, and measured values at 10-minute intervals and from 0 to 60 minutes were collected.

Sacrifice and pathology
GROSS PATHOLOGY: Yes
ORGAN WEIGHT: Yes [brain, pituitary, thyroids (including parathyroids), adrenal gland, thymus, spleen, heart, liver, kidney, testis, epididymis, prostate, seminal vesicles (including coagulating gland), ovary, uterus]

HISTOPATHOLOGY: Yes [cerebrum, cerebellum (including pons), sciatic nerve, spinal cord (thoracic), eyeball, optic nerve, Harderian gland*, pituitary, thyroid, parathyroid, adrenal glands, thymus, spleen,

submandibular lymph nodes, mesenteric lymph nodes, heart, thoracic aorta*, trachea, lung (includ ing bronchial), tongue*, larynx*, esophagus*, stomach, duodenum, jejunum, ileum (including payer's p atch), cecum, colon, rectum, submandibular gland, sublingual gland, liver, pancreas, kidney, bladder, testis, epididymis, ovary, uterus, vagina, prostate, seminal vesicles (including coagulating gland), skin (inguinal region)*, mammary gland (inguinal region)*, sternum* and femur (including bone marrows), femoral skeletal muscle, and Individual identification site (pinna with ear tag)*]
Asterisked organs and tissues are fixed and stored only.

Statistics
For quantitative data, the homogeneity of variances was first tested using the Bartlett method. If the variance was homogeneous, statistical differences between the treatment and control groups were a nalyzed using the Dunnett method. If not homogeneous, the steel method was used to test for statisti cal differences between each treatment group and the control group. For comparison of quantitative d ata between the two groups in the recovery study, homogeneity of variance was analyzed by the F-test . Then, if homogeneous, the Student's t-test was applied. If not, the Aspin-Welch t-test was used.
Regarding auditory response, approach response, touch response, tail pinch response, pupillary reflex, aerial righting reflex, Fisher's test was applied.

Results and discussion

Results of examinations

Clinical signs
effects observed, treatment-related

Description (incidence and severity)
[At the dosing period]:
[General condition of living and dead animals]:
In males and females, salivation was observed at 1000 mg/kg bw/day.
[At the recovery period]:
There were no effects related to the test substance in any groups.

Mortality
no mortality observed

Body weight and weight changes
effects observed, treatment-related

Description (incidence and severity)
[At the dosing period]:
In males, significantly decreased body weight gain was observed at 1000 mg/kg bw/day.
In mating females, significantly decreased body weight gain during gestation was observed at 1000 mg/kg bw/day.
In non-mating females, In mating females, significantly decreased body weight at day 15 of treatment and body weight gain during dosing period were observed at 1000 mg/kg bw/day.
[At the recovery period]:
In non-mating females, body weight gain was significantly increased at 1000 mg/kg bw/day.

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

Description (incidence and severity)
[At the dosing period]:
In males, food consumption was significantly decreased on day 2 and significantly increased on days 30, 36 and 42 of treatment at 1000 mg/kg bw/day.
In mating females, food consumption was significantly increased on pregnancy day 7 and lactation day 2 at 1000 mg/kg bw/day.
In non-mating females, food consumption was significantly increased on days 30 and 36 of treatment at 1000 mg/kg bw/day.

[At the recovery period]:
There were no changes related to the test substance in any groups.

Food efficiency
not examined

Water consumption and compound intake (if drinking water study)
not examined

Ophthalmological findings
not examined

Haematological findings
effects observed, treatment-related

Description (incidence and severity)
[At the end of dosing period]:
In non-mating females, significant decreases in red blood cell count, hemoglobin and hematocrit w ere observed at 1000 mg/kg bw/day.
[At the end of recovery period]:
There were no changes related to the test substance in any groups.

Clinical biochemistry findings
effects observed, treatment-related

Description (incidence and severity)
[At the end of dosing period]:
In males, a significant increase in ALP was observed at 1000 mg/kg bw/day.
In mating females, a significant increase in total cholesterol and a significant decrease in glucose we re observed at 1000 mg/kg bw/day.
In non-mating females, significant increases in ALT, total cholesterol, triglyceride and phospholipids, and a significant decrease in glucose was observed at 1000 mg/kg bw/day.
[At the end of recovery period]:
There were no changes related to the test substance in any groups.

Endocrine findings
not examined

Urinalysis findings
effects observed, treatment-related

Description (incidence and severity)
[At the dosing period]:
In males, significant increases in water intake and urine volume were observed at 1000 mg/kg bw/ day.
In non-mating females, significant increases in water intake and urine volume, and a significant decrease in osmotic pressure were observed at 1000 mg/kg bw/day.
[At the recovery period]:
There were no changes related to the test substance in any groups.

Behaviour (functional findings)
no effects observed

Immunological findings
not examined

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

Description (incidence and severity)
[At the end of dosing period]:

In males, a significant increase in relative weight of liver was observed at 300 and 1000 mg/kg bw/day, and significant increases in absolute weight of liver and relative weight of kidney were observed at 1000 mg/kg bw/day.
In mating females, a significant increase in absolute and relative weight of liver was observed at 300 and 1000 mg/kg bw/day, and a significant increase in relative weight of kidney was observed at 1000 mg/kg bw/day.
In non-mating females, significant increases in absolute and relative weight of liver and kidney were observed at 1000 mg/kg bw/day.
[At the end of recovery period]:
In non-mating females, a significant increase in absolute and relative weight of liver was observed at 1000 mg/kg bw/day.

Gross pathological findings
effects observed, treatment-related

Description (incidence and severity)
[At the end of dosing period]:
In mating females, white foci in the kidneys was observed at 1000 mg/kg bw/day.
[At the end of recovery period]:
There were no changes related to the test substance in any groups.

Neuropathological findings
not examined

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

Description (incidence and severity)
[At the end of dosing period]:
Liver:
Hypertrophy of centrilobular hepatocyte was observed at 300 and 1000 mg/kg bw/day in males and mating females and at 1000 mg/kg bw/day in non-mating females.

Kidney:
Focal dilatation of tubular was observed in mating females at 1000 mg/kg bw/day.

[At the end of recovery period]:
Liver:
Hypertrophy of centrilobular hepatocyte was observed in one male at 1000 mg/kg bw/day.

Histopathological findings: neoplastic
not examined

Effect levels

Key result
true

Dose descriptor
NOAEL

Effect level

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

Based on
test mat.

Sex
male/female

Basis for effect level
histopathology: non-neoplastic
hypertrophy of centrilobular hepatocyte was observed in males and females at 300 mg/kg bw/day.
organ weights and organ / body weight ratios
A significant increase in relative weight of liver was observed in males and females, and a significant increase in absolute weight of liver was observed in females at 300 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.

https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF24851-98-7d.pdf

Applicant's summary and conclusion

Conclusions
The NOAEL for repeated dose toxicity in this study was determined to be 100 mg/kg bw/day for males and females.

Executive summary

A combined repeated oral dose toxicity study with the reproduction/developmental toxicity screening test was performed according to a Japanese guideline (similar to OECD TG 422). Male and female rats (12 animals/sex/dose) were administered methyl (2-pentyl-3-oxocyclopentyl) acetate by gavage at 0 (vehicle: corn oil), 100, 300, and 1000 mg/kg bw/day. Males were administered for 42 days, including a 14-day premating period and subsequent mating period, whereas females in the mating group were administered for 41–46 days, including the 14-day premating, mating, and gestation periods, and until lactation day 4. Five males at the 0 and 1000 mg/kg bw/day were allocated to a recovery group and maintained for 14 days after the administration period. Ten additional females were administered at 0 and 1,000 mg/kg bw/day as a satellite group. These females were administered for 42 days without mating, and five females at 0 and 1000 mg/kg bw/day were allocated to a recovery group and maintained for 14 days after the administration period.

In the clinical signs, salivation was observed in males and females at 1000 mg/kg bw/day.

In the body weight, a significantly decreased body weight gain with decreased food consumption was observed in males in early administration and a significant decrease in body weight gain was observed in mating females during gestation and in non-mating females during administration at 1000 mg/kg bw/day.

In the food consumption, significant increase was observed in males and females at 1000 mg/kg bw/day.

In the urinalysis, significant increases in water intake and urine volume were observed in males and non-mating females, and a significant decrease in osmotic pressure was observed in non-mating females at 1000 mg/kg bw/day.

In the haematology, significant decreases in red blood cell count, hemoglobin and hematocrit were observed in non-mating females at 1000 mg/kg bw/day.

In the clinical chemistry, a significant increase in ALP was observed in males, a significant increase in total cholesterol and a significant decrease in glucose were observed in mating females, and significant increases in ALT, total cholesterol, triglyceride and phospholipids, and a significant decrease in glucose was observed in non-mating females at 1000 mg/kg bw/day.

In organ weights, weights of the liver and kidney were affected by the administration of the test substance. A significant increase in relative weight of liver was observed in males and mating females at 300 and 1000 mg/kg bw/day and in non-mating females at 1000 mg/kg bw/day, a significant increase in absolute weight of liver was observed in males and non-mating females at 1000 mg/kg bw/day and in mating females at 300 and 1000 mg/kg bw/day, a significant increase in relative weight of kidney was observed in males and mating and non-mating females at 1000 mg/kg bw/day, and a significant increase in absolute weight of kidney was observed in non-mating females at 1000 mg/kg bw/day.

In the gross pathology, white foci in the kidneys was observed in mating females at 1000 mg/kg bw/day.

In the histopathological examination, hypertrophy of centrilobular hepatocyte was observed in the liver at 300 and 1000 mg/kg bw/day in males and mating females, and at 1000 mg/kg bw/day in non-mating females, and focal dilatation of tubular was observed in the kidney at 1000 mg/kg bw/day in mating females.

In the recovery study, the changes observed duration of administration were reversible, decreasing or disappearing.

Based on these results, the NOAEL for repeated dose toxicity under the conditions of this study were determined to be 100 mg/kg bw/day for males and females, because hypertrophy of centrilobular hepatocyte and increased weight of liver were observed in males and females at 300 mg/kg bw/day.

Genetic toxicity

Genetic toxicity in vitro

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.001

UUID: c8e82795-985c-4b00-8955-9fa6aa7e08e4
Dossier UUID:
Author:
Date: 2023-01-31T09:57:43.000+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 Methyl(2-pentyl-3-oxocyclopentyl)acetate on Bacteria. / Ministry of Health, Labour and Welfare (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

Deviations
no

Qualifier
according to guideline

Guideline
JAPAN: Guidelines for Screening Mutagenicity Testing Of Chemicals
genetic toxicity in vitro, other

Deviations
no

GLP compliance
yes

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

Test material

Test material information
Methyl(2-pentyl-3-oxocyclopentyl)acetate

Specific details on test material used for the study
-Name of test material (as cited in study report): Methyl(2-pentyl-3-oxocyclopentyl)acetate
- Analytical purity: 98.35%
- Storage condition of test material: Seald and refrigerated (actual temperature: 2.9 - 5.7°C)
- Stability under test conditions: The stability of test material was identified by analysis of the remai
nder

Method

Species / strain

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

Species / strain / cell type
E. coli WP2 uvr A
bacteria

Metabolic activation
with and without

Metabolic activation system
S9 mix; SD male rat liver, induced by phenobarbital and 5,6-benzoflavone

Justification for deviation from the high dose level
-S9 mix:
9.77, 19.5, 39.1, 78.1, 156, 313 µg/plate (TA100, TA1535, TA98, TA1537 strains)
39.1, 78.1, 156, 313, 625, 1250 µg/plate (WP2uvrA strain)

+S9 mix:
9.77, 19.5, 39.1, 78.1, 156, 313 µg/plate (TA100, TA1535, TA98, TA1537 strains)
39.1, 78.1, 156, 313, 625, 1250 µg/plate (WP2uvrA strain)

Maximum concentration was established based on the result of the preliminary test at concentration up to 5000 ug/plate. In the preliminary test, the growth inhibition was observed at 313 µg/plate and a bove for S. typhimurium TA100, TA1535, TA98, and TA1537 with or without S9, at 1250 µg/plate and above for E. coli WP2uvrA strains with or without S9 mix.

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

Controls

Untreated negative controls
no

Negative solvent / vehicle controls
yes

True negative controls
no

Positive controls
yes

Positive control substance
other: -S9 mix: 2-(2-furyl)-3-(5-nitro-2-furyl) acrylamide (AF-2), sodium azide (SAZ) and 2-methoxy-6-chloro-9-[3-(2-chloroethyl)-aminopropylamino]acridine 2HCl (ICR-191) ;
+S9 mix: 2-aminoanthracene (2AA), benzo[a]pyrene (B[a]P)

Details on test system and experimental conditions
METHOD OF APPLICATION: Preincubation
DURATION- Preincubation period: 20 min at 37°C
- Exposure duration: 48 or 49.5 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 i ncrease was observed.

Statistics
no

Results and discussion

Test results

Key result
true

Species / strain
S. typhimurium TA 1535

bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
cytotoxicity -S9 mix: 313 µg/plate
+S9 mix: 313 µg/plate

Vehicle controls validity
valid

Positive controls validity
valid

Key result
true

Species / strain
S. typhimurium TA 1537
bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
cytotoxicity -S9 mix: 313 µg/plate
+S9 mix: 313 µg/plate

Vehicle controls validity
valid

Positive controls validity
valid

Key result
true

Species / strain
S. typhimurium TA 98
bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
cytotoxicity -S9 mix: 313 µg/plate
+S9 mix: 313 µg/plate

Vehicle controls validity
valid

Positive controls validity
valid

Key result
true

Species / strain
S. typhimurium TA 100
bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
cytotoxicity -S9 mix: 313 µg/plate
+S9 mix: 313 µg/plate

Vehicle controls validity
valid

Positive controls validity
valid

Key result
true

Species / strain
E. coli WP2 uvr A
bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
cytotoxicity -S9 mix: 625 µg/plate and above
+S9 mix: 625 µg/plate and above

Vehicle controls validity
valid

Untreated negative controls validity
not examined

Positive controls validity
valid

Any other information on results incl. tables

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

https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF24851-98-7e.pdf

Please also see the attached files (Tables in English)

Overall remarks, attachments

Attachments

Attached (sanitised) documents for publication
24851-98-7_Ames Tables.xlsx / 42.78 KB (application/vnd.openxmlformats-officedocument.spreadsheetml.sheet)

Applicant's summary and conclusion

Conclusions
Interpretation of results (migrated information): negative
In a bacterial reverse mutation assay using Salmonella typhimurium TA100, TA1535, TA98, and TA1537, and Escherichia coli WP2uvrA (OECD TG 471), methyl(2-pentyl-3-oxocyclopentyl)acetate was negative with or without metabolic activation.

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.002

UUID:	6eee9350-bafd-4c99-ba85-8aa3ed2299a0
Dossier UUID:	
Author:	
Date:	2023-01-12T15:46:47.000+09:00
Remarks:	

Administrative data

Endpoint
in vitro chromosome aberration study in mammalian cells

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

In Vitro Chromosomal Aberration Test of Methyl (2-pentyl-3-oxocyclopentyl) acetate on Cultured Chine / Ministry of Health, Labour and Welfare (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

Deviations
no

Qualifier
according to guideline

Guideline
JAPAN: Guidelines for Screening Mutagenicity Testing Of Chemicals
genetic toxicity in vitro, other

Deviations
no

GLP compliance
yes

Type of assay
other: in vitro mammalian chromosome aberration test

Test material

Test material information
Methyl(2-pentyl-3-oxocyclopentyl)acetate

Specific details on test material used for the study
-Name of test material (as cited in study report): Methyl(2-pentyl-3-oxocyclopentyl)acetate
- Analytical purity: 98.35%
- Storage condition of test material: Seald and refrigerated (actual temperature: 2 - 8°C)
- Stability under test conditions: The stability of test material was identified by analysis of the remainder

Method

Species / strain

Species / strain / cell type
Chinese hamster lung (CHL/IU)
mammalian cell line

Metabolic activation
with and without

Metabolic activation system
S9 mix; SD male rat liver, induced by phenobarbital and 5,6-benzoflavone

Justification for deviation from the high dose level
Cell growth inhibition study
-S9 mix (short-term treatment): 18.0, 35.9, 71.9, 144, 288, 575, 1150, 2300 ug/mL
+S9 mix (short-term treatment): 18.0, 35.9, 71.9, 144, 288, 575, 1150, 2300 ug/mL
-S9 mix (continuous treatment, 24hr): 18.0, 35.9, 71.9, 144, 288, 575, 1150, 2300 ug/mL
-S9 mix (continuous treatment, 48hr): 18.0, 35.9, 71.9, 144, 288, 575, 1150, 2300 ug/mL

Main study
-S9 mix (short-term treatment): 42.7, 64.0, 96.0, 144 ug/mL
+S9 mix (short-term treatment): 36.0, 27.7, 41.5, 72.0, 144, 288 ug/mL
-S9 mix (continuous treatment, 24hr): 42.7, 64.0, 96.0, 144 ug/mL
-S9 mix (continuous treatment, 48hr): 42.7, 64.0, 96.0, 144 ug/mL

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

Controls

Untreated negative controls
no

Negative solvent / vehicle controls
yes

True negative controls
no

Positive controls
yes

Positive control substance
cyclophosphamide
+S9
mitomycin C
-S9

Details on test system and experimental conditions
METHOD OF APPLICATION:
Exposure duration:
- [short-term treatment]: 6 hrs + 18 hrs
- [continuous treatment]: 24, 48 hrs
SPINDLE INHIBITOR: Colcemid
STAIN: Giemsa stain (2 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. Appearance incidence of cell with chromosomal aberrations: Negative (-): less than 5%, Equivocal(±): more than 5% and less than 10%, Positive(+): 10% and above

Statistics
no

Results and discussion

Test results

Key result
true

Species / strain
Chinese hamster lung (CHL/IU)
mammalian cell line

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
cytotoxicity

Vehicle controls validity
valid

Positive controls validity
valid

Additional information on results
RANGE-FINDING/SCREENING STUDIES (if applicable):
50% cell growth inhibition (IC50): 138 ug/mL (short-term treatment, +S9 mix), 97 ug/mL (short-term tr eatment, -S9 mix), 130 ug/mL (continuous treatment, 24hr), 113 ug/mL (continuous treatment, 48hr)

Any other information on results incl. tables

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

https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF24851-98-7f.pdf

Applicant's summary and conclusion

Conclusions
Interpretation of results (migrated information): negative with or without metabolic activation

In an in vitro chromosomal aberration test using CHL/IU cells (OECD TG 473), methyl (2-pentyl-3-oxocyclopentyl) acetate was negative with or without metabolic activation

Toxicity to reproduction

Toxicity to reproduction

ENDPOINT_STUDY_RECORD: Toxicity to reproduction. 001

UUID:	72e404ba-521a-4d35-bf2f-3c70bb5d55c1
Dossier UUID:	
Author:	
Date:	2023-01-31T10:00:30.000+09:00
Remarks:	

Administrative data

Endpoint
reproductive toxicity, other A combined repeated dose/reproductive developmental toxicity study

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

Cross-reference

Reason / purpose for cross-reference
reference to same study

Related information
OECD / Repeated dose toxicity: oral / Repeated dose toxicity: oral. 001 / Methyl(2-pentyl-3-oxocyclopentyl)acetate / methyl (3-oxo-2-pentylcyclopentyl)acetate / 24851-98-7

Data source

Reference

Combined repeated dose toxicity study with the reproductive/developmental toxicity screening test of / Ministry of Health, Labour and Welfare (MHLW), Japan / study report

Data access
data published https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF24851-98-7d.pdf

Materials and methods

Test guideline

Qualifier
according to guideline

Guideline
other: Guideline for Combined Repeated Dose Toxicity Study with the Reproduction /Developmental Toxicity Screening Test in Mammalian Species (Chemical Substances Control Law of Japan)

GLP compliance
yes

Limit test
no

Test material

Test material information
Methyl(2-pentyl-3-oxocyclopentyl)acetate

Specific details on test material used for the study
- Name of test material (as cited in study report): methyl (2-pentyl-3-oxocyclopentyl) acetate
- Analytical purity: 98.35% (as the isomeric mixture)
- Storage condition of test material: sealed, cool place (actual temperature: 2 - 8°C)
- Stability under test conditions: The stability of test material was identified by analysis of the rema inder

Test animals

Species
rat

Strain
other: Crl:CD(SD)

Sex
male/female

Details on test animals or test system and environmental conditions
TEST ANIMALS
- Source: Charles River Japan, Inc., Atsugi Breeding Center.
- Age at study initiation: 10 weeks old
- Weight at study initiation: Male: 430 g (406-472 g), Female: 256 g (235-282 g)
- Housing: Animals were individually housed in bracket-type metallic wire-mesh cages (254W × 350D × 170H mm), from gestation day 17 to lactation day 4, Dams were bred individually or with individual littermates in plastic cages (340W x 400D x 185H mm) and bedding.
- Diet: Solid feed (NMF: Oriental Yeast Co., ltd.) was given ad libitum.
- Water: Tap water was given ad libitum.
- Acclimation period: 20 days
ENVIRONMENTAL CONDITIONS
- Temperature (°C): 23±3 (actual temperature: 22-24°C)
- Humidity (%): 50±20% (actual humidity: 50-59%)
- Air changes (per hr): 10-15
- Photoperiod (hrs dark / hrs light): 12 hr dark/12 hr light (light: 7:00-19:00)

Administration / exposure

Route of administration
oral: gavage

Vehicle
corn oil

Details on exposure
- Amount of vehicle (if gavage): 5 mL/kg
- Dosing volume: 5 mL/kg

Details on mating procedure
- M/F ratio per cage:1/1
- Length of cohabitation: up to 5 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
The concentrations of each suspension used at weeks 1 and 6 of administration were analyzed by GC. The results showed that the concentration of each suspension was 99.5 to 101.5% of the nominal concentration, and both values were within the acceptable range (concentration: percentage of nominal concentration, 100±10%)

Duration of treatment / exposure
Males: 42 days including 14 days pre-mating
Females (mating group): 41-46 days including 14 days pre-mating, mating and gestation periods and the days until day 4 of lactation
Female (non-mating group): 42 days

Frequency of treatment
Once/day, 7 days/week

Doses / concentrations

Dose / conc.	
0	mg/kg bw/day (actual dose received)
Dose / conc.	
100	mg/kg bw/day (actual dose received)
Dose / conc.	
300	mg/kg bw/day (actual dose received)
Dose / conc.	
1000	mg/kg bw/day (actual dose received)

No. of animals per sex per dose
Mating group: 12 animals/sex/dose (0, 100, 300 and 1000 mg/kg bw/day)
Non-mating group: 10 females/dose (0 and 1000 mg/kg bw/day)
Recovery group: 5 males/dose in the mating group and 5 females/dose in the non-mating groups (0 and 1000 mg/kg bw/day)

Control animals
yes, concurrent vehicle

Details on study design
- Dose selection rationale: Based on the results of a 14-day preliminary study, the high dose was 1000 mg/kg bw/day, which was expected to cause clear signs of toxicity, and the intermediate dose and low dose were set to 300 mg/kg bw/day and 100 mg/kg bw/day, respectively.

[14-day preliminary study]
A 14-day repeated dose oral toxicity test (Crl:CD(SD) rats, doses: 0, 250, 500, and 1000 mg/kg bw/day).
In the 1000 mg/kg bw/day group, males and females showed transient decreased body weight with decreased food consumption in early administration and increased liver weight, males showed increased kidney weight and recessed area in kidney and females showed high total cholesterol. In the 500 mg/kg bw/day group, females showed transient decreased body weight with decreased food consumption in early administration, and males and females showed increased liver weight.

- Rationale for animal assignment (if not random): Body weight-balanced randomization.

Examinations

Parental animals: Observations and examinations
CAGE SIDE OBSERVATIONS: Yes
- Time schedule: 3 times/day (before administration, immediately after administration and 1-3 hours after administration) during the administration period. Twice a day during the recovery period.

DETAILED CLINICAL OBSERVATIONS: Yes
- Time schedule:
Males in the mating group and females in the non-mating group: Once before the start of admi nistration, once every weekly during the administration and recovery periods.
Females in the mating group: Once a week during the pre-mating period, on designated days during mating, gestation, and lactation (Gestation Days (GDs) 1, 7, 14 and 20 for mated females, and L actation Day (LD) 4 for parturient females).

BODY WEIGHT: Yes
- Time schedule for examinations:
Males: Days 1, 8, 15, 22, 29, 36 and 42 of administration and on the day of necropsy, and Days 1, 8 and 14 of recovery and on the day of necropsy.
Females in the mating group: Days 1, 8 and 15 of administration, GDs 0, 7, 14 and 20, LDs 0 and 4 and the day of necropsy.
Females in the non-mating group: Days 1, 8, 15, 22, 29, 36 and 42 of administration and on the day of necropsy, and Days 1, 8 and 14 of recovery and on the day of necropsy.
FOOD CONSUMPTION AND COMPOUND INTAKE (if feeding study):
- Food consumption: Yes
Measurement of food consumption was conducted on all animals at the following frequencies:
Males: Days 2, 8, 15, 30, 36 and 42 of administration, and Days 1, 8 and 14 of recovery.
Females in the mating group: Days 2, 8 and 15 of administration, GDs 1, 7, 14 and 20, LDs 2 and 4.
Females in the non-mating group: Days 2, 8, 15, 30, 36 and 42 of administration, and Days 1, 8 and 14 of recovery.

OPHTHALMOSCOPIC EXAMINATION: No
HAEMATOLOGY: Yes
- Time schedule for collection of blood: At the end of administration period, or at the end of recovery period in both sexes
- Anaesthetic used for blood collection: isoflurane
- Animals fasted: Yes
- How many animals:
5 animals/sex/group

- Parameters examined: red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, reticulocyte percentage, platelet count, white blood cell count, differential white blood cell count, absolute number of each white blood cell, prothrombin time, activated partial thromboplastin time, fibrinogen.

CLINICAL CHEMISTRY: Yes
- Time schedule for collection of blood: At the end of administration period, or at the end of recovery period in both sexes
- Animals fasted: Yes
- How many animals:
5 animals/sex/group
- Parameters checked: ALP, total bile acid, total cholesterol, triglyceride, phospholipids, total bilirubin, glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, calcium, inorganic phosphorus, total protein, albumin, A/G ratio, AST (GOT), ALT (GPT), LDH, γ-GTP

BLOOD HORMONE: No

URINALYSIS: Yes
- Time schedule for collection of urine: On the final week of administration (Days 38 to 39 of administration) and on the final week of recovery (Days 10 to 11 of recovery)
- Metabolism cages used for collection of urine: Yes
A urine collector to collect four-hour urine samples under fasting but ad libitum drinking conditions, followed by collection of 20-hour urine samples under ad libitum feeding and drinking conditions.
- How many animals: 5 animals/group
- Parameters checked: pH, protein, ketones, glucose, occult blood, bilirubin, urobilinogen, color, sediment, urine volume (4-hour volume), osmotic pressure, sodium, potassium, chloride, urine volume (20-hour volume), water intake (24-hour volume)

NEUROBEHAVIOURAL (FUNCTIONAL) EXAMINATION: Yes
- Time schedule for examinations:
Males: On the final week of administration (Day 37 of administration), and on the final week of recovery (Day 9 of recovery).
Females in the mating group: LD 4 (Day 41 to Day 44 of administration)
Females in the non-mating group: On the final week of administration (Day 37 of administration), and on the final week of recovery (Day 9 of recovery).
- Dose groups that were examined:
All dose groups (5 animals/sex/group)
- Battery of functions tested:
1) Manipulative Test. Auditory response, approach response, touch response, tail pinch response, pupillary reflex, aerial righting reflex, landing foot splay
2) Measurement of Grip Strength. Following manipulative test, grip strength of forelimb and hind limb was measured by CPU gauge MODEL-RX-5 (AIKOH Engineering Co., Ltd.).
3) Measurement of Motor Activity. Following measurement of grip strength, motor activity was measured by a motor activity sensor for experimental animals NS-AS01 (Neuro Science, Inc). The measurement was conducted for 1 hour, and measured values at 10-minute intervals and from 0 to 60 minutes were collected.

Oestrous cyclicity (parental animals)
Vaginal smears were collected from all females in the mating 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 all P male parental generations: testis weight, epididymis weight, histopathological examinations for testes, epididymides, seminal vesicle and ventral prostate.

Litter observations
PARAMETERS EXAMINED: The following parameters were examined in F1 offspring: Number and sex of pups, stillbirths, live births, postnatal mortality, presence of gross anomalies, and weight gain.
GROSS EXAMINATION OF DEAD PUPS: Yes, for external and internal abnormalities.

Postmortem examinations (parental animals)
METHOD OF SACRIFICED: All animals were sacrificed by exsanguination under isoflurane anesthesia.

SACRIFICE: Males in main groups and females in non-mating groups: On Day 43 (next day after the last administration), Maternal animals: on Day 5 of lactation, and Males and females recovery groups: on Day 15 of recovery.

GROSS PATHOLOGY: Yes

ORGAN WEIGHT: Yes [brain, pituitary, thyroids (including parathyroids), adrenal gland, thymus, spleen, heart, liver, kidney, testis, epididymis, prostate, seminal vesicles (including coagulating gland), ovary, uterus]

HISTOPATHOLOGY: Yes [cerebrum, cerebellum (including pons), sciatic nerve, spinal cord (thoracic), eyeball, optic nerve, Harderian gland*, pituitary, thyroid, parathyroid, adrenal glands, thymus, spleen, submandibular lymph nodes, mesenteric lymph nodes, heart, thoracic aorta*, trachea, lung (including bronchial), tongue*, larynx*, esophagus*, stomach, duodenum, jejunum, ileum (including payer's patch), cecum, colon, rectum, submandibular gland, sublingual gland, liver, pancreas, kidney, bladder, testis, epididymis, ovary, uterus, vagina, prostate, seminal vesicles (including coagulating gland), skin (inguinal region)*, mammary gland (inguinal region)*, sternum* and femur (including bone marrows), femoral skeletal muscle, and Individual identification site (pinna with ear tag)*]
Asterisked organs and tissues are fixed and stored only.

Postmortem examinations (offspring)
SACRIFICE
- The F1 offsprings were euthanized on PND4 by exsanguination under isoflurane anesthesia.
GROSS NECROPSY：Yes
- Gross necropsy consisted of external and internal examinations including the cervical, thoracic, and abdominal viscera.
HISTOPATHOLOGY / ORGAN WEIGTHS
- Not examined.

Statistics
For quantitative data, the homogeneity of variances was first tested using the Bartlett method. If the variance was homogeneous, statistical differences between the treatment and control groups were analyzed using the Dunnett method. If not homogeneous, the steel method was used to test for statistical differences between each treatment group and the control group. For comparison of quantitative data between the two groups in the recovery study, homogeneity of variance was analyzed by the F-test. Then, if homogeneous, the Student's t-test was applied. If not, the Aspin-Welch t-test was used. Regarding implantation index, stillborn index, live birth index, viability index and external abnormalities, Steel test was applied. Regarding copulation index, insemination index, fertility index, and delivery index, auditory response, approach response, touch response, tail pinch response, pupillary reflex, aerial righting reflex, Fisher's test was applied.

Reproductive indices
Each parameter was determined by the following equations:
Index of animals with abnormal estrous cycle (%) = No. of animals with abnormal estrous cycle / No. of animals examined) × 100
Copulation index (%) = (No. of copulated animals / No. of mated animals) × 100
Insemination index (%) = (No. of males which impregnated females / No. of copulated males) × 100
Fertility index (%) = (No. of pregnant females / No. of copulated females) × 100
Gestation index (%) = (No. of females which delivered liveborns / No. of pregnant females) × 100

Gestation length (days) = No. of days from pregnancy day 0 to parturition day
Implantation index (%) = (No. of implantation sites / No. of corpora lutea) × 100
Delivery index (%) = (No. of delivered pups / No. of implantation sites) × 100
Stillborn index (%) = (No. of stillborn / No. of delivered pups) × 100
External abnormalities (%) = (No. of delivered pups with external abnormalities / No. of delivered pu ps) × 100
Live birth index (%) = (No. of liveborn / No. of delivered pups) × 100
Sex ratio of delivered pups = No. of delivered males / No. of delivered pups
Sex ratio of liveborns = No. of liveborns males / No. of liveborns
Sex ratio of live pups on day 4= No. of live males on day 4/ No. of live pups on day 4

Offspring viability indices
Viability index on postnatal day 4 (%) = (No. of live pups on day 4 / No. of liveborns) × 100

Results and discussion

Results: P0 (first parental generation)

General toxicity (P0)

Clinical signs
effects observed, treatment-related

Description (incidence and severity)
See 7.5.1 Repeated dose toxicity. 001

Mortality
no mortality observed

Body weight and weight changes
effects observed, treatment-related

Description (incidence and severity)
See 7.5.1 Repeated dose toxicity. 001

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

Description (incidence and severity)
See 7.5.1 Repeated dose toxicity. 001

Food efficiency
not examined

Water consumption and compound intake (if drinking water study)
not examined

Ophthalmological findings
not examined

Haematological findings
effects observed, treatment-related

Description (incidence and severity)
See 7.5.1 Repeated dose toxicity. 001

Clinical biochemistry findings
effects observed, treatment-related

Description (incidence and severity)
See 7.5.1 Repeated dose toxicity. 001

Endocrine findings
not examined

Urinalysis findings
effects observed, treatment-related

Description (incidence and severity)
See 7.5.1 Repeated dose toxicity. 001

Behaviour (functional findings)
no effects observed

Immunological findings
not examined

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

Description (incidence and severity)
See 7.5.1 Repeated dose toxicity. 001

Gross pathological findings
effects observed, treatment-related

Description (incidence and severity)
See 7.5.1 Repeated dose toxicity. 001

Neuropathological findings
not examined

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

Description (incidence and severity)
See 7.5.1 Repeated dose toxicity. 001

Histopathological findings: neoplastic
not examined

Reproductive function / performance (P0)

Reproductive function: oestrous cycle
effects observed, treatment-related

Description (incidence and severity)
At 1000 mg/kg bw/day, abnormal estrous cycle was observed in females.

Reproductive function: sperm measures
no effects observed

Reproductive performance
effects observed, treatment-related

Description (incidence and severity)
At 1000 mg/kg bw/day, trends toward in a prolonged gestation length and a decreased delivery index were observed in females.

Details on results (P0)

General toxicity:
See 7.5.1 Repeated dose toxicity.001

Reproductive function / performance:

At 1000 mg/kg bw/day, abnormal estrous cycle was observed in 3 of 12 females, trend toward in a prolonged gestation length was observed in one female.

Effect levels (P0)

Key result
true

Dose descriptor
NOAEL

Effect level

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

Based on
test mat.

Sex
male/female

Basis for effect level
organ weights and organ / body weight ratios
See 7.5.1 Repeated dose toxicity. 001
histopathology: non-neoplastic
See 7.5.1 Repeated dose toxicity. 001

Key result
true

Dose descriptor
NOAEL

Effect level

1000 mg/kg bw/day (actual dose received)

Based on
test mat.

Sex
male

Basis for effect level
reproductive function (sperm measures)
No effects observed.
reproductive performance
No effects observed.

Key result
true

Dose descriptor
NOAEL

Effect level

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

Based on
test mat.

Sex
female

Basis for effect level
reproductive function (oestrous cycle)
Abnormal estrous cycle was observed in females at 1000 mg/kg bw/day,
reproductive performance
Trends toward in a prolonged gestation length and a decreased delivery index were observed in females at 1000 mg/kg bw/day,

Results: F1 generation

General toxicity (F1)

Clinical signs
no effects observed

Mortality / viability
no mortality observed

Body weight and weight changes
effects observed, treatment-related

Description (incidence and severity)
At 1000 mg/kg bw/day, a significant decreased body weight was observed in males and females on postnatal day 0.

Gross pathological findings
no effects observed

Details on results (F1)

No effects observed.

Effect levels (F1)

Key result
true

Dose descriptor
NOAEL

Generation
F1

Effect level

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

Based on
test mat.

Sex
male/female

Basis for effect level
body weight and weight gain
A significant decreased body weight was observed in males and females on postnatal day 0 at 1000 mg/kg bw/day,

Overall reproductive toxicity

Key result
false

Reproductive effects observed
no

Any other information on results incl. tables

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

https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF24851-98-7d.pdf

Applicant's summary and conclusion

Conclusions
In the combined repeated oral dose toxicity study with the reproduction/developmental toxicity screening test described above, abnormal estrous cycle and trends toward in a prolonged gestation length and a decreased delivery index were observed at 1000 mg/kg bw/day. With regard to effects on pups, in the 1000 mg/kg bw/day, decreased body weight was observed on postnatal day 0.
The NOAELs for the rat reproductive/developmental toxicity of methyl (2-pentyl-3-oxocyclopentyl) acetate were regarded as 1000 mg/kg bw/day for males, 300 mg/kg bw/day for females, and 300 mg/kg bw/day for pups.

References

Reference Substances

REFERENCE_SUBSTANCE: methyl 3-oxo-2-pentylcyclopentaneacetate

UUID: ECB5-06ffba49-3875-4943-a963-63a55879c17c
Dossier UUID:
Author:
Date: 2023-01-13T10:52:30.000+09:00
Remarks:

Reference substance name
methyl 3-oxo-2-pentylcyclopentaneacetate

IUPAC name
methyl (3-oxo-2-pentylcyclopentyl)acetate

Inventory

Inventory number

Inventory name
methyl 3-oxo-2-pentylcyclopentaneacetate

Inventory
EC Inventory

Inventory number
246-495-9

CAS number
24851-98-7

Molecular formula
C13H22O3

Description

CAS number
24851-98-7

Synonyms

Synonyms

Identity
Cyclopentaneacetic acid, 3-oxo-2-pentyl-, methyl ester

Identity
Cyclopentaneacetic acid, 3-oxo-2-pentyl-, methyl ester

Molecular and structural information

Molecular formula
C13H22O3

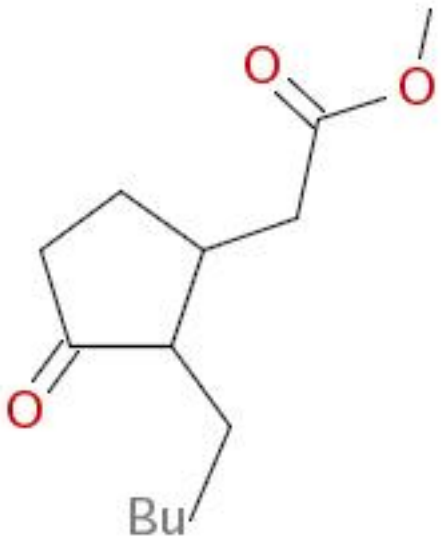
Molecular weight

226.312

SMILES notation
CCCCCC1C(CC(=O)OC)CCC1=O

InChI
InChI=1/C13H22O3/c1-3-4-5-6-11-10(7-8-12(11)14)9-13(15)16-2/h10-11H,3-9H2,1-2H3

Structural formula



Related substances

Group / category information
DSL Category: Organics

Test Materials

TEST_MATERIAL_INFORMATION: Methyl(2-pentyl-3-oxocyclopentyl)acetate

UUID: 6c0bb432-b446-4125-b774-803e77776540
Dossier UUID:
Author:
Date: 2023-01-13T10:52:35.000+09:00
Remarks:

Name
Methyl(2-pentyl-3-oxocyclopentyl)acetate

Composition

Composition

Type
Constituent

Reference substance
methyl 3-oxo-2-pentylcyclopentaneacetate / methyl (3-oxo-2-pentylcyclopentyl)acetate / 24851-98-7 / 246-495-9

EC number	EC name
246-495-9	EC Inventory

CAS number	CAS name
24851-98-7	

IUPAC name
methyl (3-oxo-2-pentylcyclopentyl)acetate

Concentration

98.35	% (v/v)

Literatures

LITERATURE: Combined repeated dose toxicity study with the reproductive/developmental toxicity screening test of Methyl (2-pentyl-3-oxocyclopentyl) acetate by oral administration in rats

UUID: ff279dc0-d84f-4942-90d7-2e8d70fb8e5e
Dossier UUID:
Author:
Date: 2023-01-17T09:05:29.000+09:00
Remarks:

General information

Reference Type
study report

Title
Combined repeated dose toxicity study with the reproductive/developmental toxicity screening test of Methyl (2-pentyl-3-oxocyclopentyl) acetate by oral administration in rats

Author
Ministry of Health, Labour and Welfare (MHLW), Japan

Year
2013

Bibliographic source
available in the web of Japan Existing Chemical Data Base (JECDB) https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF24851-98-7d.pdf

Testing facility
BoZo Research Center

Report date
2013-09-10

Report number
R-1106

LITERATURE: In Vitro Chromosomal Aberration Test of Methyl (2-pentyl-3-oxocyclopentyl) acetate on Cultured Chinese Hamster Cells.

UUID: ea4cf7be-7b1b-4fff-9926-d50d9c626d55
Dossier UUID:
Author:
Date: 2023-01-12T15:41:10.000+09:00
Remarks:

General information

Reference Type
study report

Title
In Vitro Chromosomal Aberration Test of Methyl (2-pentyl-3-oxocyclopentyl) acetate on Cultured Chinese Hamster Cells.

Author
Ministry of Health, Labour and Welfare (MHLW), Japan

Year
2013

Bibliographic source
Japan Existing Chemical Data Base (JECDB) https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF24851-98-7f.pdf

Testing facility
Bozo Research Center Inc.

Report date
2013-03-22

Report number
T-G061

LITERATURE: Reverse Mutation Test of Methyl(2-pentyl-3-oxocyclopentyl)acetate on Bacteria.

UUID: b9cd22c5-b18c-4e42-91a5-1b6020dc837b
Dossier UUID:
Author:
Date: 2023-01-12T15:17:29.000+09:00
Remarks:

General information

Reference Type
study report

Title
Reverse Mutation Test of Methyl(2-pentyl-3-oxocyclopentyl)acetate on Bacteria.

Author
Ministry of Health, Labour and Welfare (MHLW), Japan

Year
2013

Bibliographic source
Japan Existing Chemical Data Base (JECDB) https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF24851-98-7e.pdf

Testing facility
Bozo Research Center Inc.

Report date
2013-03-22

Report number
T-1113