Name: OECD_SIDS / SUBSTANCE : azoicCC5 / 91-96-3 / N,N'-(3,3'-dimethylbiphenyl-4,4'-diyl)bis(3-oxobutanamide) / 91-96-3 Fri, 16 Dec 2022, 15:32:37+0900 /

Legal entity owner: National Institute of Health Sciences

Printing date: 2022-12-16T15:32:37.316+09:00

Table of Contents

DOSSIER:

UUID: 0
Dossier UUID:
Author:
Date: 2022-12-16T15:32:37.188+09:00
Remarks:

Dossier header

Dossier submission type

Name
OECD SIDS

Version
core 7.0

Name (given by user)

Dossier subject

Dossier subject
azoicCC5 / 91-96-3 / N,N'-(3,3'-dimethylbiphenyl-4,4'-diyl)bis(3-oxobutanamide) / 91-96-3

Public name

Submitting legal entity
National Institute of Health Science

Dossier creation date/time
Fri, 16 Dec 2022, 15:32:37+0900

Used in category

LEGAL_ENTITY: National Institute of Health Science

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

General information

Legal entity name
National Institute of Health Science

azoicCC5 / 91-96-3

General information

Identification

Identification

SUBSTANCE: azoicCC5 / 91-96-3

UUID:	deab6e64-fa59-4831-94d9-2fe3d795e5ab
Dossier UUID:	
Author:	
Date:	2022-12-16T15:32:17.590+09:00
Remarks:	

Substance name
azoicCC5 / 91-96-3

Legal entity
National Institute of Health Sciences / Kawasaki / Japan

Identification of substance

Reference substance
N,N'-(3,3'-dimethylbiphenyl-4,4'-ylene)di(acetoacetamide) / N,N'-(3,3'-dimethylbiphenyl-4,4'-diyl)bis(3-oxobutanamide) / 91-96-3 / 202-111-1

EC number	EC name
202-111-1	EC Inventory
CAS number	**CAS name**
91-96-3	

IUPAC name
N,N'-(3,3'-dimethylbiphenyl-4,4'-diyl)bis(3-oxobutanamide)

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:	d24f470f-836b-4aaf-9786-1ea1dc1c0df4
Dossier UUID:	
Author:	
Date:	2020-10-09T09:59:51.000+09:00
Remarks:	

Administrative data

Endpoint
short-term repeated dose toxicity: oral repeated dose 28-day oral toxicity study in rodents

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

A 28-day repeat dose oral toxicity test of azoicCC5 in rat with a recovery period of 2 weeks / Ministry of Health, Labour and Welfare(MHLW), Japan / publication

Data access
data published

Materials and methods

Test guideline

Qualifier
according to guideline

Guideline
OECD Guideline 407 (Repeated Dose 28-Day Oral Toxicity Study in Rodents)

Deviations
no

GLP compliance
yes

Test material

Specific details on test material used for the study
azoicCC5 / 91-96-3

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 Laboratories Japan, Inc. Atsugi
- Age at study initiation: 6 weeks
- Weight at study initiation: Males: 201-223 g; Females: 141-168 g
- Housing: bracket-type metallic wire-mesh cages (W 250 × D 350 × H 200 mm)
- Diet: ad libitum
- Water: ad libitum
- Acclimation period: 7 days

ENVIRONMENTAL CONDITIONS
- Temperature (°C): 20-23 (acceptable range:23±3 °C)
- Humidity (%): 48-62 (acceptable range:50±20 %)
- Air changes: 10-15 times / hr
- Photoperiod: 12 hrs dark / 12 hrs light

Administration / exposure

Route of administration
oral: gavage

Vehicle
methylcellulose

Details on oral exposure
PREPARATION OF DOSING SOLUTIONS: Test substance was suspended in Methyl cellulose 400cP fo r injection.

Vehicle
- Name: 0.5 w/v% Methyl cellulose 400cP
- Lot Number: 8K74
- Manufacturer: Wako pure Chemical Industries, Ltd.
- Storage Conditions: Refrigeration (refrigerator, measured temperature: 3 to 6°C)

Analytical verification of doses or concentrations
yes

Details on analytical verification of doses or concentrations
Test solutions were prepared at least once in 8 days and used within 7 days of preparation.
The test solutions to be used for week 1 or week 4 of administration were analyzed for concentration by HPLC method at Gotemba Laboratory, Bozo Research Center Inc.
The results showed that the concentrations were 95.5 to 105.0% of the nominal concentrations (acceptable range: 100 ± 10% of the nominal value), which were all within the acceptable range.

Duration of treatment / exposure
28 days

Frequency of treatment
Once/day, 7 days/week

Doses / concentrations

Dose / conc.	
0	mg/kg bw/day (actual dose received)
Dose / conc.	
8	mg/kg bw/day (actual dose received)
Dose / conc.	
40	mg/kg bw/day (actual dose received)
Dose / conc.	
200	mg/kg bw/day (actual dose received)
Dose / conc.	
1000	mg/kg bw/day (actual dose received)

No. of animals per sex per dose
6 or 12 animals/sex/dose as a main dose group
6 out of 12 animals at 0 and 1000 mg/kg bw/day were treated as a recovery group

Control animals
yes
yes, concurrent vehicle
0.5 w/v% Methyl cellulose 400cP

Details on study design
- Dose selection rationale: Doses in this test were set based on the results of the following dose s etting study: a 14-day repeated dose oral toxicity test (doses: 0, 300, and 1000 mg/kg bw/day).

The main changes observed were food consumption and organ weight of all males at >= 100 mg/kg bw/day and changes in hematological examination in females in the >=300 mg/kg bw/day group. However, the relationship with azoicCC5 is uncertain.
Therefore, the highest dose in this study was set at 1000 mg/kg bw/day, with a high dose at 200 mg/kg bw/day, a middle dose of 40 mg/kg bw/day group and a low dose of 8 mg/kg bw/day, using the common ratio of approximately 5.

- Rationale for animal assignment : Body weight-balanced randomization
- Post-exposure recovery period in recovery groups: 14 days

Examinations

Observations and examinations performed and frequency
CAGE SIDE OBSERVATIONS:
Yes
Males and females: 3 times/day during the administration period (before and after dosing) , once a da y during the recovery period.
DETAILED CLINICAL OBSERVATIONS:
Yes

Other examinations
BODY WEIGHT:
Yes
Time schedule for examinations: Males /females (main/recovery group): All animals were weighed before administration on days 1, 4, 7, 10, 14, 17, 21, 24 and 28 of administration and on days 1, 3, 7, 10 and 14 of recovery, and the day of necropsy (after ca. 16h-fasting).

FOOD CONSUMPTION AND COMPOUND INTAKE (if feeding study):
yes
Males /females (main/recovery group): on days1, 7, 14, 21, and 28 during the administration period, and on days 7 and 14 during the recovery period.

OPHTHALMOSCOPIC EXAMINATION:
yes

HAEMATOLOGY:
Yes

- Time schedule for collection of blood: Blood was collected on the day of necropsy
- Anaesthetic used for blood collection: Yes (ether)
- Animals fasted: Yes, 16-20h
- How many animals: all animals, 6 sex/dose/group

CLINICAL CHEMISTRY:
Yes
Time schedule for collection of blood: Same as hematology
- Animals fasted: Same as hematology
- How many animals: Same as hematology
- Parameters checked in table were examined.

URINALYSIS:
Yes

- Time schedule for collection of urine: on weeks 4 of the administration period and weeks 2 of the recovery period.
- Metabolism cages used for collection of urine: Yes
- Animals fasted: 4-hour urine under fasting diet ad libitum
  20- hour urine under diet and water ad libitum

Statistics
The data were analyzed for homogeneity of variance by the Bartlett test. If variances were homogeneous, data was analyzed by the Dunnett test, whereas heterogeneous data was analyzed by the Steel test ($p<0.05$ and $p<0.1$, two-sided).
2 groups: The data were analyzed for homogeneity of variance by the F test. If variances were homo geneous, data was analyzed by the Student t test, whereas heterogeneous data was analyzed by the Aspin-Welch t test ($p<0.05$ and $p<0.1$, two-sided).

Results and discussion

Results of examinations

Clinical signs
no effects observed

Mortality
no mortality observed

Body weight and weight changes
effects observed, treatment-related

Description (incidence and severity)
1) Administration period

At 40 mg/kg bw/day, low body weight was significantly observed in males from day 7 to day 28 of the administration period and in females on days 24 and 28 of the administration period.
At 200 mg/kg bw/day and 1000 mg/kg bw/day in males, low body weights were observed from day 4 to day 28 of the administration period.
At 200 mg/kg bw/day in females, low body weights were observed on day 28 of the administration period.
At 1000 mg/kg bw/day in females, low body weights were observed from day 17 to day 28 of the administration period.

In the 40 mg/kg bw/day and above groups, low body weight gain was significantly observed in males and females.

At 8 mg/kg bw/day, there was a trend toward lower values in males throughout the treatment period.

2) Recovery period
At 1000 mg/kg bw/day, low body weights were significantly observed in males from day 1 to day 14 of recovery period, and in females on day 1 of recovery period.

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

Description (incidence and severity)
Significant low food consumption was observed in males at 40 mg/kg bw/day, females from day 7 to day 28 of the administration period, females at 40 mg/kg bw/day, females on days 21 and 28 of the administration period, females at 200 mg/kg bw/day, females on days 7 and 28 of the administration period, and females at 1000 mg/kg bw/day on days 21 and 28 of the administration period.

At 1000 mg/kg bw/day, lower food consumption was significantly observed in males on day 7 of rec overy period.

Food efficiency
not examined

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

Haematological findings
no effects observed

Description (incidence and severity)
1) End of the administration period

Low fibrinogen levels were significantly observed in males at 40 mg/kg bw/day and above.
A significant reduction in prothrombin time was observed in males at 40 mg/kg bw/day and 200 mg/ kg bw/day.
At 200 mg/kg bw/day, high hemoglobin and hematocrit values and low reticulocyte percentage were s ignificantly observed in males.
Significantly lower eosinophil counts for the percentage of leukocytes and eosinophil numbers in l eukocytes fractions were observed in males at 40 mg/kg bw/day and 200 mg/kg bw/day.

These changes were considered to be spontaneous because hematology changes were mild and not observed in high dose groups.

2) End of the recovery period

Significantly lower red blood cell counts and higher reticulocyte percentages were observed in males at 1000 mg/kg bw/day.
At 1000 mg/kg bw/day, higher platelet counts were significantly observed in females.
At 1000 mg/kg bw/day, a low lymphocyte percentage and a high neutrophil percentage were sign ificantly observed in males.
At 1000 mg/kg bw/day, low eosinophil proportions and high neutrophil counts in differential real coun ts were significantly observed in females.
At 1000 mg/kg bw/day, a significantly higher number of neutrophils was observed in males in the f ractionated real number.

These changes were considered to be spontaneous because hematology changes were not dose dependent.

Clinical biochemistry findings
no effects observed

Description (incidence and severity)
A significant increase in phospholipids was observed in males at 40 mg/kg bw/day and in males and females at 1000 mg/kg bw/day at the end of the administration period.
High levels of phospholipids were observed in males at 200 mg/kg bw/day.

At 1000 mg/kg bw/day, high levels of total cholesterol were observed in males and females.

It was indicated that the effect of the administration of azoicCC5 to the liver was indicated. These changes disappeared after the recovery period.

At the end of the administration period, low ALT was observed in females at 40 mg/kg bw/day, and low ALP was observed in females at 40 mg/kg bw/day, females at 1000 mg/kg, and males at 1000 mg/kg bw/day.

These were considered insignificant because they were all very mild and not high, suggestive of disabi lity.

At the end of the recovery period, high AST and ALT levels were observed in males at 1000 mg/kg bw/ day. These changes were considered incidental because they were minimal in severity and were not observed at the end of the administration period.

A high potassium level was observed in males at 1000 mg/kg bw/day. However, it was considered to be spontaneous because there was no change in other electrolytes and it was not observed at the end of the administration period.

Urinalysis findings
effects observed, treatment-related

Description (incidence and severity)
No qualitative abnormalities were observed in either sex in each test article treatment group on week 4 of the administration period.
Small water consumption were significantly observed in males at 40 mg/kg bw/day and higher and in females at 1000 mg/kg bw/day on week 4 of the administration period.
Low urinary volume were significantly observed in males at 1000 mg/kg bw/day on week 4 of the administration period.

These changes were considered to be spontaneous because these were recovered by withdraw.

Behaviour (functional findings)
no effects observed

Description (incidence and severity)
At 1000 mg/kg bw/day, a high landing open leg width was significantly observed in males at week 2 of recovery period.
At 1000 mg/kg bw/day, a significant increase in locomotor activity was observed in females between 0 and 60 minutes of measurement at week 2 of recovery period.
These changes were considered to be spontaneous.

Organ weight findings including organ / body weight ratios
no effects observed

Description (incidence and severity)
At the end of the treatment period, higher relative liver weights were observed in males at 40 mg/kg bw/day and in females at 200 mg/kg bw/day.

At the end of the administration period, low absolute thymus weights were observed in males at 200 mg/kg bw/day.
There were no abnormalities at the end of the recovery period, and recovery was observed.

At the end of the administration or recovery period, low absolute weights were observed in the brain, heart, spleen, kidney, and ovary, and high relative weights were observed in the brain, heart, spleen, testis, and epididymis in the organ weights.
These changes were considered to be secondary to the inhibition of body weight gain.

At the end of treatment, low absolute adrenal weights were observed in females at 1000 mg/kg bw/ day and males at each dose level, and low relative adrenal weights were observed in males at 40 mg/ kg bw/day.

At the end of the recovery period, low absolute weights were observed in males at 1000 mg/kg bw/da y.

These changes were considered to be incidental because they were minimal in severity and were usu ally observed.

Gross pathological findings
no effects observed

Description (incidence and severity)
At the end of the recovery period, centrilobular hepatocyte hypertrophy was observed in the liver of males at 1000 mg/kg bw/day. However, the degree and frequency of hepatocyte hypertrophy were alleviated and were no longer observed after withdrawal of administration, showing reversibility.

At the end of administration or at the end of the recovery period, there were focal depressed foci and cysts in the kidney, focal white foci in the spleen, small testes, focal elevated foci in the forestomach, and dark red foci in the glandular stomach.

All changes were judged to be spontaneous based on their appearance status, etc.

Effect levels

Key result
true

Dose descriptor
NOAEL

Effect level

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

Based on
test mat.

Sex
male/female

Basis for effect level
body weight and weight gain
food consumption and compound intake
histopathology: non-neoplastic
centrilobular hypertrophy of hepatocytes
organ weights and organ / body weight ratios

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/PDF91 -96 -3b.pdf

Applicant's summary and conclusion

Conclusions
.Based on the effects in the liver observed at 40 mg/kg bw/day, the NOAEL for the repeated-dose toxi city of azoic CC5 in rats was determined to be 8 mg/kg bw/day.

Executive summary

The repeated-dose toxicity of azoic CC5 was evaluated in rats according to the OECD TG 407. Male and female rats (6 or 12 animals/sex/dose) were treated with 0 [vehicle: 0.5% (w/v) methylcellulose solution], 8, 40, 200, and 1000 mg/kg bw/day azoic CC5 for 28 days. Six of the 12 animals/sex receiving 0 and 1,000 mg/kg bw/day were selected for a 14-day recoverygroup.

No treatment-related deaths were observed for either sex. For both sexes, decreased food consumption, body weight, and body weight gain were observed in the groups receiving ≥40 mg/kg bw/day. Water intake was decreased in males receiving ≥40 mg/kg bw/day as well as females receiving 1,000 mg/kg bw/day. Urine volume was decreased in males receiving 1,000 mg/kg bw/day. Blood chemistry analysis showed increased total cholesterol and phospholipid levels in both sexes treated with 1000 mg/kg bw/day. The relative weight of the liver was increased in males receiving ≥40 mg/kg bw/day and females receiving ≥200 mg/kg bw/day. Histopathological analysis revealed centrilobular hepatocellular hypertrophy in both sexes treated with ≥40 mg/kg bw/day. Following withdrawal of treatment, the changes observed during or at the end of the administration period were no longer observed, and were thus reversible. Based on the effects in the liver observed at 40 mg/kg bw/day, the NOAEL for the repeated-dose toxicity of azoic CC5 in rats was determined to be 8 mg/kg bw/day.

ENDPOINT_STUDY_RECORD: Repeated dose toxicity: oral.002

UUID: d6ea4fa5-213f-4942-8c18-5e60661852e4
Dossier UUID:
Author:
Date: 2020-10-09T10:35:05.000+09:00
Remarks:

Administrative data

Endpoint
repeated dose toxicity: oral, other oral combined repeated dose and reproduction / developmental screening

Type of information
experimental study

Adequacy of study
key study

Robust study summary
false

Used for classification
false

Used for SDS
false

Reliability
1 (reliable without restriction)

Rationale for reliability incl. deficiencies
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 / azoicCC5 / 91-96-3 / N,N'-(3,3'-dimethylbiphenyl-4,4'-diyl)bis(3-oxobutanamide) / 91-96-

Remarks
Toxicity to reproduction.001

Data source

Reference

A reproduction/developmental toxicity screening test in rats treated orally with azoicCC5 / Ministry of Health, Labour and Welfare(MHLW), Japan / publication

Data access
data published

Materials and methods

Test guideline

Qualifier
according to guideline

Guideline
other: Guideline for reproduction/developmental toxicity screening test in rats (Chemical Substa nces Control Law of Japan)

GLP compliance
yes

Test material

Specific details on test material used for the study
azoicCC5 / 91-96-3

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 Laboratories Japan, Inc. Atsugi
- Age at study initiation: 10 weeks
- Weight at study initiation: Males: 371-442 g; Females: 222-264 g
- Housing: bracket-type metallic wire-mesh cages (W 250 × D 380 × H 180 mm)
- Diet: ad libitum
- Water: ad libitum
- Acclimation period: 15 days

ENVIRONMENTAL CONDITIONS
- Temperature (°C): 20-24 (acceptable range:22±3 °C)
- Humidity (%): 38-70 (acceptable range:50±20 %)
- Air changes: 10-15 times / hr
- Photoperiod: 12 hrs dark / 12 hrs light

Administration / exposure

Route of administration
oral: gavage

Vehicle
methylcellulose

Details on oral exposure
PREPARATION OF DOSING SOLUTIONS: Test substance was dissolved in methyl cellulos for injection.

Vehicle
- Name: 0.5 w/v% Methyl cellulose 400cP
- Lot Number: WEK5883
- Manufacturer: Wako pure Chemical Industries, Ltd.
- Storage Conditions: Refrigeration (refrigerator, measured temperature: 3.3 to 10°C)

Details on analytical verification of doses or concentrations
Test solutions were prepared at least once in 8 days and used within 7 days of preparation.
The test solutions to be used for day 1 or day 42 of administration were analyzed for concentration by IR method
The results showed that the concentrations were 94.0 to 100.0% of the nominal concentrations (acceptable range: 100 ± 10% of the nominal value), which were all within the acceptable range.

Duration of treatment / exposure
Males were dosed for 42 days, including a 14-day pre-mating period and subsequent mating period.
Females were dosed for 40–49 days, including 14-day pre-mating, mating, and gestation periods, and until lactation day 3.

Frequency of treatment
Once/day, 7 days/week

Doses / concentrations

Dose / conc.	
0	mg/kg bw/day (actual dose received)
Dose / conc.	
2.5	mg/kg bw/day (actual dose received)
Dose / conc.	
10	mg/kg bw/day (actual dose received)
Dose / conc.	
40	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
In a 28-day repeated-dose oral toxicity study (dose: 8, 40, 200, 1000 mg/kg/day), decreased body wei ght gain, decreased food consumption, and hepatic centrilobular hepatocellular hypertrophy were observed in both sexes at doses 40 mg per kg/day, and increased liver weights were observed in males (doses 200 mg/kg) and females (doses 200 mg/kg).

Therefore, the highest dose in this study was set at 40 mg/kg bw/day, a middle dose of 10 mg/kg bw/day group and a low dose of 2.5 mg/kg bw/day, using the common ratio of approximately 4.
- Rationale for animal assignment (if not random): Body weight-balanced randomization

Examinations

Observations and examinations performed and frequency
CAGE SIDE OBSERVATIONS: Yes
Males and females: 3 times/day during the administration period (before and after dosing) , once a day during the recovery period.
DETAILED CLINICAL OBSERVATIONS: Yes
BODY WEIGHT: Yes
Time schedule for examinations: Males /females (main/recovery group): All animals were weighed before administration on days 1, 3, 7, 14, 21, 28, 35 and 42 of administration.
FOOD CONSUMPTION AND COMPOUND INTAKE (if feeding study):Yes
Time schedule for examinations: Males /females (main/recovery group): All animals were weighed before administration on days 1, 3, 7, 14, 21, 28, 35 and 42 of administration.
OPHTHALMOSCOPIC EXAMINATION: yes
HAEMATOLOGY: No
CLINICAL CHEMISTRY: No
URINALYSIS: No

Statistics
The data were analyzed for homogeneity of variance by the Bartlett test. If variances were homogeneous, data was analyzed by the Dunnett test, whereas heterogeneous data was analyzed by the Kruskal-Wallis test ($p<0.05$). If variances were homogeneous, data was analyzed by the Steel ($p<0.1$).

Results and discussion

Results of examinations

Clinical signs
effects observed, non-treatment-related

Description (incidence and severity)
In the 10 mg/kg bw/day group, Red urine was observed in one male from Day 29 to Day 43, but it was not a dose-related change.

Mortality
no mortality observed

Body weight and weight changes
effects observed, treatment-related

Description (incidence and severity)
In males, in the 40 mg/kg bw/day group, body weight gain was suppressed during the treatment period, and significant decreases in body weight after Day 2 and significant decreases in body weight gain were observed during the treatment period.
At 2.5 mg/kg bw/day and 10 mg/kg bw/day groups, in males, no effects were observed.

In females in the 40 mg/kg bw/day group, body weight gain was suppressed during gestation, and body weight gain was significantly lower than that in the control group.

In the 10 mg/kg bw/day and 40 mg/kg bw/day groups, significantly lower body weights were obse rved at 4 days of lactation period.

Body weight gain tended to be lower in the 2.5 mg/kg bw/day group than in the control group, and was significantly lower in the 2.5 mg/kg bw/day group during lactation period.
Body weight and body weight gain during the 14 days before mating were not significantly different between each dose group and the control group.

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

Description (incidence and severity)
In males, in the 40 mg/kg/day group, a tendency toward lower food consumption was observed in the administration period, and lower food consumption was significantly observed after day 7 of administration.
In 2.5 mg/kg bw/day and 10 mg/kg bw/day groups, in males, food consumption was not significantly different compared with the control group.

Females tended to have lower food consumption of gestation and lactation period in the 10 mg/kg bw/day group.
Lower food consumption was significantly observed in the 10 mg per kg/day group on day 14 of gestation and day 4 of lactation period, and in the 40 mg/kg bw/day group on days 7, 14 and 4 of ges tation.

There were no statistically significant differences in the 2.5 mg/kg bw/day group compared with the c ontrol group, but there was a tendency toward lower food consumption on the day 4 of lactation perio d.
During the 14 days before mating, food consumption was not significantly different between each d ose group and the control group.

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

Description (incidence and severity)
Higher relative liver weights were observed in males at 10 mg/kg bw/day and at 40 mg/kg bw/day.
At 40 mg/kg bw/day, in males, testicular relative higher weight and, lower absolute seminal vesicle weight were observed.
No effect was observed at 2.5 mg/kg bw/day in males.

Higher relative liver weights were observed in females at 40 mg/kg bw/day.
No effect was observed at 2.5 mg/kg bw/day and 10 mg/kg bw/day in males.

Gross pathological findings
effects observed, treatment-related

Description (incidence and severity)
In the 10 and 40 mg/kg bw/day groups, unilateral renal pelvis dilatation was observed in two males a nd one male, respectively.
In the 2.5 mg/kg bw/day group, no effects were observed in any of the animals.
In the control group, a unilateral caudal yellowish white mass was observed in the epididymis in one animal.

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

Description (incidence and severity)
In males, slight centrilobular hepatocellular hypertrophy was observed in the liver in 11 of 12 animals in the 40 mg/kg bw/day group.

Minimal granulomas in the liver and minimal and mild inflammation in the prostate were spontane ously observed in a few rats in each group, but the spontaneous changes are often observed in rats a nd were not considered to be dose-related effect.

Minor dilatation of the renal pelvis was observed in 2 animals (males) in the 10 mg/kg bw/day group and 1 animal (male) in the 40 mg/kg bw/day group, both of which were unilateral changes and these changes were considered to be spontaneous.

There was mild sperm granuloma in the epididymis in one male and minimal seminiferous tubule atro phy in the testis and minimal cellular debris in the lumen of the epididymis in the other male in the control group.

Minimal granulomas in the liver were observed in 1 female each in the control group and the 40 mg/ kg bw/day group, but considered to be spontaneous changes.

No abnormal findings were observed in an infertile female in the 2.5 mg/kg bw/day group.

Target system / organ toxicity

Key result
false

Lowest effective dose / conc.

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

System
cardiovascular

Organ
liver

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/PDF91-96-3c.pdf

Applicant's summary and conclusion

Executive summary

The reproductive and developmental toxicity of azoic CC5 was evaluated in a reproduction/ developmental toxicity screening test in rats (OECD TG 421). In this study, azoic CC5 was administered via oral gavage at doses of 0 [vehicle: 0.5% (w/v) methylcellulose solution], 2.5, 10, and 40 mg/kg bw/ day. Males (12/dose) were treated for 42 days, including a 14-day premating period and subsequent mating period, while females (12/dose) were treated for 40–49 days, including 14-day premating, mating, and gestation periods, until lactation day 3. No deaths were observed due to treatment in either sex. Decreased food consumption, body weight, and body weight gain were observed in males treated with 40 mg/kg bw/day and females treated with≥10 mg/kg bw/day. At doses of≥2.5 mg/kg bw/day, body weight gain and body weight decreased in females during the lactation period. An increased relative liver weight was observed in males treated with≥10 mg/kg bw/day and females treated with 40 mg/kg bw/day, and centrilobular hepatocellular hypertrophy was observed in males treated with 40 mg/kg bw/day.

Genetic toxicity

Genetic toxicity in vitro

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.001

UUID:	863194e1-9eee-4ae3-a921-064fe82084ac
Dossier UUID:	
Author:	
Date:	2020-10-09T12:26:45.000+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

A reverse mutation test of azoicCC5 using bacteria / Ministry of Health, Labour and Welfare(MHLW), Japan / publication

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

Principles of method if other than guideline
“Study Methods on New Chemical Substances, etc." (Chemical Substances Control Law of Japan)

GLP compliance
yes

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

Test material

Specific details on test material used for the study
azoicCC5 / 91-96-3

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 (PB) and 5,6-benzoflavone (BF)

Test concentrations with justification for top dose
To set the dose levels for the main tests, the 50 mg/mL solution was diluted 4 times using a common ratio of 4 and a total of 7 dose levels were selected (1.22, 4.88, 19.5, 78.1, 313, 1250 and 5000 µg/plate) in the dose-selection test.
In the dose-selection test, growth inhibition by the test substance was observed at 313 µg/plate and above for S. typhimurium TA strains without metabolic activation, at 313 µg/plate and above for S. typhimurium TA1537 with metabolic activation, and at 1250 µg/plate and above for S. typhimurium TA100, TA1535, TA98 with metabolic activation. Neither precipitation of nor coloration by the test substance on the plate was observed at any dose level irrespective of the presence or absence of metabolic activation.
Therefore, in the main tests, the lowest dose levels at which cell growth inhibition was observed in the dose-selection test were set as the highest dose levels 313 µg/plate for S. typhimurium TA strains without metabolic activation, 1250 µg/plate for S. typhimurium TA1535 with metabolic activation, and a total of 6 dose levels were selected by 5-step dilution using a common ratio of 2.

Test were set as the highest dose levels 5000 µg/plate for E.coli WP2 uvrA with or without metabolic activation, and a total of 5 dose levels were selected by 4-step dilution using a common ratio of 2.
Test were set as the highest dose levels 5000 µg/plate for S. typhimurium TA100, TA98 and a total of 8 dose levels were selected by 7-step dilution using a common ratio of 2.

Vehicle / solvent
DMSO

Controls

Untreated negative controls
no

Negative solvent / vehicle controls
yes

True negative controls
no

Positive controls
yes

Positive control substance
sodium azide
benzo(a)pyrene
other: 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide (AF-2) 2-Methoxy-6-chloro-9-[3-(2-chloroethyl)-a minopropylamino]acridine.2HCl (ICR-191) 2-Aminoanthracene (2AA)

Details on test system and experimental conditions
METHOD OF APPLICATION: Preincubation
DURATION
- Preincubation period: 20 min

Exposure duration: ca. 50 hours
NUMBER OF REPLICATIONS: 3

Results and discussion

Test results

Key result
false

Species / strain
S. typhimurium TA 100
bacteria

Metabolic activation
with

Genotoxicity
positive

Cytotoxicity / choice of top concentrations
cytotoxicity growth inhibition: 1250 µg/plate

Vehicle controls validity
valid

Positive controls validity
valid

Key result
false

Species / strain
S. typhimurium TA 98
bacteria

Metabolic activation
with

Genotoxicity
positive

Cytotoxicity / choice of top concentrations
cytotoxicity growth inhibition: 1250 µg/plate

Vehicle controls validity
valid

Positive controls validity
valid

Key result
false

Species / strain
S. typhimurium TA 1535
bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
cytotoxicity growth inhibition: 625 µg/plate with metabolic activation growth inhibition: 313 µg/plate without metabolic activation

Vehicle controls validity
valid

Positive controls validity
valid

Key result
false

Species / strain
S. typhimurium TA 1537
bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
cytotoxicity growth inhibition: 156 µg/plate without metabolic activation growth inhibition: 313 µg/plate with metabolic activation

Vehicle controls validity
valid

Positive controls validity
valid

Key result
false

Species / strain
E. coli WP2 uvr A
bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
no cytotoxicity

Vehicle controls validity
valid

Positive controls validity
valid

Any other information on results incl. tables

Tables in English are attached.

Applicant's summary and conclusion

Conclusions
In a bacterial reverse mutation assay using S. typhimuriumTA100, TA1537, TA1537, TA98 and E.coli, azoicCC5 was positive with metabolic activation for TA100 and TA98.

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.002

UUID:	156c0482-e51e-4368-88bd-c4746faac9d6
Dossier UUID:	
Author:	
Date:	2019-05-23T13:40:44.000+09:00
Remarks:	

Administrative data

Endpoint
in vitro cytogenicity / chromosome aberration study in mammalian cells

Type of information
experimental study

Adequacy of study
key study

Robust study summary
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

Chromosome aberration test in cultured chinese hamster cells treated with azoicCC5 / Ministry of Health, Labour and Welfare(MHLW), Japan / publication

Data access
data published

Materials and methods

Test guideline

Qualifier
according to guideline

Guideline
OECD Guideline 473 (In Vitro Mammalian Chromosomal Aberration Test)
in vitro cytogenicity / chromosomal aberration study in mammalian cells (from 26 September 2014)

Deviations
no

GLP compliance
yes

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

Test material

Specific details on test material used for the study
azoicCC5 / 91-96-3

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 (PB) and 5,6-benzoflavone (BF)

Test concentrations with justification for top dose
+S9 mix(short-term treatment): 0, 30.1, 60.2, 120, 241, 481, 963, 1930, 3850 μg/mL
-S9 mix(short-term treatment): 0, 30.1, 60.2, 120, 241, 481, 963, 1930, 3850 μg/mL
-S9 mix(24hr-continuous treatment): 0, 30.1, 60.2, 120, 241, 481, 963, 1930, 3850 μg/mL
-S9 mix(48hr-continuous treatment): 0, 30.1, 60.2, 120, 241, 481, 963, 1930, 3850 μg/mL

Cell-growth inhibition test was conducted up to the limited concentration of 3850 μg/mL (10 mM)
-Short term treatment, +S9 mix: concentration of 50% cell-growth inhibition was determined as 200.7 μg/mL
-Short term treatment, -S9 mix: concentration of 50% cell-growth inhibition was determined as above 3850.0 μg/mL

-Continous treatment (24 h): concentration of 50% cell-groth inhibition was determined as above 481.0 μg/mL
-Continous treatment (48 h): concentration of 50% cell-groth inhibition was determined as 963.0 μg/mL

Vehicle / solvent
injection solvent

Controls

Positive controls
yes

Positive control substance
cyclophosphamide
mitomycin C

Details on test system and experimental conditions
Exposure duration: [continuous treatment]: 24, 48 hrs [short-term treatment]:6 hrs + 18 hr

SPINDLE INHIBITOR: Colcemid
NUMBER OF REPLICATIONS: 2
NUMBER OF CELLS EVALUATED: 200 cells / dose
DETERMINATION OF CYTOTOXICITY
- Method: relative total growth

Evaluation criteria
For the evaluation of the frequencies of structural aberrations and of polyploidy induced, the following criteria were employed.
Appearance incidence of cells with chromosomal aberrations: Negative (-): < 5%; equivocal (±): 5 -10% ; positive (+): > 10%.
Finally, the substance is positive when the incidence is considered to be dose-related and reprod ucible.

Statistics
not use

Results and discussion

Test results

Key result
false

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

Metabolic activation
with and without

Genotoxicity
negative structural aberration

Cytotoxicity / choice of top concentrations
cytotoxicity >50% cell growth inhibitation: 200.7 ug/mL with S9 (short) , Cytotoxicity: no with S9(24h continuous, 48h continuous), Cytotoxicity: no without S9

Vehicle controls validity
valid

Positive controls validity
valid

Key result
false

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

Metabolic activation
without

Genotoxicity
positive chromosome numerical aberrations. Metabolic activation: with negative, chromosome numerical aberrations

Cytotoxicity / choice of top concentrations
cytotoxicity >50% cell growth inhibitation: 200.7 ug/mL with S9 (short) , Cytotoxicity: no with S9(24h continuous, 48h continuous), Cytotoxicity: no without S9

Vehicle controls validity
valid

Positive controls validity
valid

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/PDF91-96-3f.pdf

Applicant's summary and conclusion

Executive summary

It was concluded that azoicCC5 is positive without metabolic actination for chromosome numerical aberration under the conditions of this study.

Toxicity to reproduction

Toxicity to reproduction

ENDPOINT_STUDY_RECORD: Toxicity to reproduction.001

UUID:	214c87ea-ba7e-4027-8326-b826854455d6
Dossier UUID:	
Author:	
Date:	2022-12-16T15:32:17.590+09:00
Remarks:	

Administrative data

Endpoint
screening for reproductive / developmental toxicity

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.002 / azoicCC5 / 91-96-3 / N,N'-(3,3'-dimethylbiphenyl-4,4'-diyl)bis(3-oxobutanamide) / 91-96-

Remarks
Repeated dose toxicity: oral.002

Data source

Reference

A reproduction/developmental toxicity screening test in rats treated orally with azoicCC5 / Ministry of Health, Labour and Welfare(MHLW), Japan / publication

Data access
data published

Materials and methods

Test guideline

Qualifier
according to guideline

Guideline
other: Guideline for reproduction/developmental toxicity screening test in rats (Chemical Substa nces Control Law of Japan)

GLP compliance
yes

Test material

Specific details on test material used for the study
azoicCC5 / 91-96-3

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 Laboratories Japan, Inc. Atsugi
- Age at study initiation: 10 weeks
- Weight at study initiation: Males: 371-442 g; Females: 222-264 g
- Housing: bracket-type metallic wire-mesh cages (W 250 × D 380 × H 180 mm)
- Diet: ad libitum
- Water: ad libitum
- Acclimation period: 15 days

ENVIRONMENTAL CONDITIONS
- Temperature (°C): 20-24 (acceptable range:22±3 °C)
- Humidity (%): 38-70 (acceptable range:50±20 %)
- Air changes: 10-15 times / hr
- Photoperiod: 12 hrs dark / 12 hrs light

Administration / exposure

Route of administration
oral: gavage

Vehicle
other: 0.5 w/v% Methyl cellulose

Details on mating procedure
- M/F ratio per cage: 1/1
- Length of cohabitation: up to 2 weeks
- Proof of pregnancy: vaginal plug / sperm in vaginal smear referred to as day 0 of pregnancy

Analytical verification of doses or concentrations
yes

Duration of treatment / exposure
Males were dosed for 42 days, including a 14-day pre-mating period and subsequent mating period. Females were dosed for 40–49 days, including 14-day pre-mating, mating, and gestation periods, and until lactation day 3.

Frequency of treatment
Once/day, 7 days/wee

Doses / concentrations

Dose / conc.	
0	mg/kg bw/day (actual dose received)
Dose / conc.	
2.5	mg/kg bw/day (actual dose received)
Dose / conc.	
10	mg/kg bw/day (actual dose received)
Dose / conc.	
40	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
In a 28-day repeated-dose oral toxicity study (dose: 8, 40, 200, 1000 mg/kg/day), decreased body wei ght gain, decreased food consumption, and hepatic centrilobular hepatocellular hypertrophy were observed in both sexes at doses 40 mg per kg/day, and increased liver weights were observed in males (doses 200 mg/kg) and females (doses 200 mg/kg).
Therefore, the highest dose in this study was set at 40 mg/kg bw/day, a middle dose of 10 mg/kg bw/ day group and a low dose of 2.5 mg/kg bw/day, using the common ratio of approximately 4.

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

Examinations

Parental animals: Observations and examinations
CAGE SIDE OBSERVATIONS: Yes
Males and females: 3 times/day during the administration period (before and after dosing) , once a day during the recovery period.

DETAILED CLINICAL OBSERVATIONS: Yes

BODY WEIGHT: Yes
Time schedule for examinations: Males /females (main/recovery group): All animals were weighed b efore administration on days 1, 3, 7, 14, 21, 28, 35 and 42 of administration.
FOOD CONSUMPTION AND COMPOUND INTAKE (if feeding study):Yes
Time schedule for examinations: Males /females (main/recovery group): All animals were weighed before administration on days 1, 3, 7, 14, 21, 28, 35 and 42 of administration.

OPHTHALMOSCOPIC EXAMINATION: yes

HAEMATOLOGY: No

CLINICAL CHEMISTRY: No

URINALYSIS: No

Oestrous cyclicity (parental animals)
yes

Sperm parameters (parental animals)
no examin

Postmortem examinations (parental animals)
yes

Postmortem examinations (offspring)
yes

Statistics
The data were analyzed for homogeneity of variance by the Bartlett test. If variances were homogeneous, data was analyzed by the Dunnett test, whereas heterogeneous data was analyzed by the Kruskal-Wallis test ($p<0.05$). If variances were homogeneous, data was analyzed by the Steel ($p<0.1$).

Reproductive indices
Fertility index (%) = (No. of pregnant females/No. of copulated females) × 100
Implantation index (%) = (No. of implantation sites/No. of corpora lutea) × 100
Birth index (%) = (Number of live pups on day 0 after birth/ No. of implantation sites) ×100
Sex ratio = No. of liveborn male pups/(No. of liveborn male pups + No. of liveborn female pups)
External abnormalities (%) = (No. of pups with external abnormalities/No. of liveborn pups) × 100

Offspring viability indices
Viability index = (Number of live pups on day 0 after birth/Number of live pups born) ×100
Viability index = (Number of live pups on day 4 after birth/ Number of live pups on day 0 after birth) ×100

Results and discussion

Results: P0 (first parental generation)

General toxicity (P0)

Clinical signs
no effects observed

Description (incidence and severity)
In the 10 mg/kg bw/day group, red urine was observed in one male from Day 29 to Day 43, but it was n ot a dose-related change.

No effects were observed in females before mating, in pregnancy period, to day 4 of lactation.

Mortality
no mortality observed

Body weight and weight changes
effects observed, treatment-related

Description (incidence and severity)
In males, in the 40 mg/kg bw/day group, body weight gain was suppressed during the treatment period, and significant decreases in body weight after Day 2 and significant decreases in body weight gain were observed during the treatment period.
At 2.5 mg/kg bw/day and 10 mg/kg bw/day groups, in males, no effects were observed.

In females in the 40 mg/kg bw/day group, body weight gain was suppressed during gestation, and body weight gain was significantly lower than that in the control group.

In the 10 mg/kg bw/day and 40 mg/kg bw/day groups, significantly lower body weights were obse rved at 4 days of lactation period.
Body weight gain tended to be lower in the 2.5 mg/kg bw/day group than in the control group, and was significantly lower in the 2.5 mg/kg bw/day group during lactation period.
Body weight and body weight gain during the 14 days before mating were not significantly different between each dose group and the control group.

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

Description (incidence and severity)
In males, in the 40 mg/kg/day group, a tendency toward lower food consumption was observed on the administration period, and lower food consumption was significantly observed after day 7 of administration.
In 2.5 mg/kg bw/day and 10 mg/kg bw/day groups, in males, food consumption was not significantly different compared with the control group.

Females tended to have lower food consumption of gestation and lactation period in the 10 mg/kg bw/day group.
Lower food consumption was significantly observed in the 10 mg per kg/day group on day 14 of gestation and day 4 of lactation period, and in the 40 mg/kg bw/day group on days 7, 14 and 4 of ges tation.

There were no statistically significant differences in the 2.5 mg/kg bw/day group compared with the c ontrol group, but there was a tendency toward lower food consumption on the day 4 of lactation perio d.
During the 14 days before mating, food consumption was not significantly different between each d ose group and the control group.

Food efficiency
not examined

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

Description (incidence and severity)
Higher relative liver weights were observed in males at 10 mg/kg bw/day and at 40 mg/kg bw/day.
At 40 mg/kg bw/day, in males, testicular relative higher weight and, lower absolute seminal vesicle weight were observed.
No effect was observed at 2.5 mg/kg bw/day in males.

Higher relative liver weights were observed in females at 40 mg/kg bw/day.
No effect was observed at 2.5 mg/kg bw/day and 10 mg/kg bw/day in males.

Gross pathological findings
no effects observed

Description (incidence and severity)
In the 10 and 40 mg/kg bw/day groups, unilateral renal pelvis dilatation was observed in two males a nd one male, respectively.
In the 2.5 mg/kg bw/day group, no effects were observed in any of the animals.
In the control group, a unilateral caudal yellowish white mass was observed in the epididymis in one animal.

Histopathological findings: non-neoplastic
no effects observed

Description (incidence and severity)
In males, slight centrilobular hepatocellular hypertrophy was observed in the liver in 11 of 12 animals in the 40 mg/kg bw/day group.

Minimal granulomas in the liver and minimal and mild inflammation in the prostate were spontane ously observed in a few rats in each group, but the spontaneous changes are often observed in rats a nd were not considered to be dose-related effect.
Minor dilatation of the renal pelvis was observed in 2 animals (males) in the 10 mg/kg bw/day group and 1 animal (male) in the 40 mg/kg bw/day group, both of which were unilateral changes and these changes were considered to be spontaneous.

There was mild sperm granuloma in the epididymis in one male and minimal seminiferous tubule atro phy in the testis and minimal cellular debris in the lumen of the epididymis in the other male in the control group.

Minimal granulomas in the liver were observed in 1 female each in the control group and the 40 mg/ kg bw/day group, but considered to be spontaneous changes.

Reproductive function / performance (P0)

Reproductive function: oestrous cycle
no effects observed

Reproductive performance
no effects observed

Effect levels (P0)

Key result
false

Dose descriptor
LOAEL

Effect level

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

Based on
test mat.

Sex
female

Basis for effect level
body weight and weight gain
weight gain the during lactation period

Results: F1 generation

General toxicity (F1)

Clinical signs
no effects observed

Mortality / viability
mortality observed, non-treatment-related

Description (incidence and severity)
Deaths occurred by 4 days of small number of nursing in the control, 2.5 mg/kg bw/day, and 10 mg/kg bw/day groups.

However, there was no significant difference in survival at postnatal days 0 and 4 between each dose group and the control group.
In addition, no abnormalities were observed in the general condition of the live pups in all groups of animals.

Body weight and weight changes
effects observed, treatment-related

Description (incidence and severity)
Body weight tended to be lower on days 0 and 4 of lactation in both sex in the 40 mg/kg bw/day group .
Low body weights were significantly observed in males at postnatal day 4.

Organ weight findings including organ / body weight ratios
no effects observed

Gross pathological findings
no effects observed

Any other information on results incl. tables

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

http://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF91-96-3c.pdf

Applicant's summary and conclusion

Conclusions
A NOAEL could not be identified, as decreases were observed in body weight gain or body weight in fe males during the lactation period at all doses. The LOAEL of the reproductive/developmental toxicity was determined to be 2.5 mg/kg bw/day

Executive summary

The reproductive and developmental toxicity of azoic CC5 was evaluated in a reproduction/ developmental toxicity screening test in rats (OECD TG 421). In this study, azoic CC5 was administered via oral gavage at doses of 0 [vehicle: 0.5% (w/v) methylcellulose solution], 2.5, 10, and 40 mg/kg bw/ day. Males (12/dose) were treated for 42 days, including a 14-day premating period and subsequent mating period, while females (12/dose) were treated for 40–49 days, including 14-day premating, mating, and gestation periods, until lactation day 3.

No deaths were observed due to treatment in either sex. Decreased food consumption, body weight, and body weight gain were observed in males treated with 40 mg/kg bw/day and females treated with ≥ 10 mg/kg bw/day. At doses of ≥ 2.5 mg/kg bw/day, body weight gain and body weight decreased in females during the lactation period. An increased relative liver weight was observed in males treated with ≥ 10 mg/kg bw/day and females treated with 40 mg/kg bw/day, and centrilobular hepatocellular hypertrophy was observed in males treated with 40 mg/kg bw/day. No changes were observed in reproductive organs, and fertility was not also affected by azoic CC5 treatment up to 40 mg/kg bw/day. Decreased body weight was observed in male and female pups at 40 mg/kg bw/day. A NOAEL could not be identified, as decreases were observed in body weight gain or body weight in females during the lactation period at all doses. The LOAEL of the reproductive/developmental toxicity was determined to be 2.5 mg/kg bw/day.

References

Reference Substances

REFERENCE_SUBSTANCE: N,N'-(3,3'-dimethylbiphenyl-4,4'-ylene)di(acetoacetamide)

UUID: ECB5-56083fb4-e319-4a67-8709-6d9e90c5a45b
Dossier UUID:
Author:
Date: 2007-05-10T18:00:00.000+09:00
Remarks:

Reference substance name
N,N'-(3,3'-dimethylbiphenyl-4,4'-ylene)di(acetoacetamide)

IUPAC name
N,N'-(3,3'-dimethylbiphenyl-4,4'-diyl)bis(3-oxobutanamide)

Inventory

Inventory number

Inventory name
N,N'-(3,3'-dimethylbiphenyl-4,4'-ylene)di(acetoacetamide)

Inventory
EC Inventory

Inventory number
202-111-1

CAS number
91-96-3

Molecular formula
C22H24N2O4

Description

CAS number
91-96-3

Synonyms

Synonyms

Identity
4',4'''-Bi-o-acetoacetotoluidide

Identity
Butanamide, N,N'-(3,3'-dimethyl[1,1'- biphenyl]-4,4'-diyl)bis[3-oxo-

Identity
Butanamide, N,N'-(3,3'-dimethyl[1,1'-biphenyl]-4,4'-diyl)bis[3-oxo-

Molecular and structural information

Molecular formula
C22H24N2O4

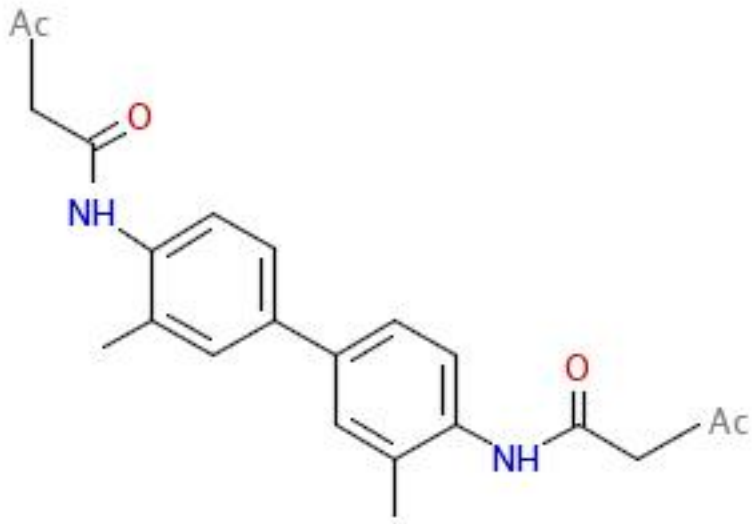
Molecular weight

380.437

SMILES notation
CC(=O)CC(=O)Nc1ccc(cc1C)c2ccc(NC(=O)CC(=O)C)c(C)c2

InChI
InChI=1/C22H24N2O4/c1-13-9-17(5-7-19(13)23-21(27)11-15(3)25)18-6-8-20(14(2)10-18)24-22(28)12-16(4)26/h5-10H,11-12H2,1-4H3,(H,23,27)(H,24,28)

Structural formula



Related substances

Group / category information
DSL Category: Organics
USEPA Category: Neutral Organics

Literatures

LITERATURE: A 28-day repeat dose oral toxicity test of azoicCC5 in rat with a recovery period of 2 weeks

UUID:	69996741-ab00-4a90-b22f-d8c0c4d5c218
Dossier UUID:	
Author:	
Date:	2019-05-21T16:34:03.000+09:00
Remarks:	

General information

Reference Type
publication

Title
A 28-day repeat dose oral toxicity test of azoicCC5 in rat with a recovery period of 2 weeks

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

Year
2010

LITERATURE: A reproduction/developmental toxicity screening test in rats treated orally with azoicCC5

UUID: f1b78e01-f648-4224-b9e5-ee5c90c0a92e
Dossier UUID:
Author:
Date: 2019-05-21T16:43:24.000+09:00
Remarks:

General information

Reference Type
publication

Title
A reproduction/developmental toxicity screening test in rats treated orally with azoicCC5

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

Year
2014

LITERATURE: A reverse mutation test of azoicCC5 using bacteria

UUID:	b6f59530-ae88-4db6-a15e-67063d6f6c98
Dossier UUID:	
Author:	
Date:	2019-05-21T16:44:20.000+09:00
Remarks:	

General information

Reference Type
publication

Title
A reverse mutation test of azoicCC5 using bacteria

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

Year
2009

LITERATURE: Chromosome aberration test in cultured chinese hamster cells treated with azoicCC5

UUID:	11588660-92af-46a6-a923-3549cfbe90b0
Dossier UUID:	
Author:	
Date:	2019-05-22T11:15:52.000+09:00
Remarks:	

General information

Reference Type
publication

Title
Chromosome aberration test in cultured chinese hamster cells treated with azoicCC5

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

Year
2008

Legal Entities

LEGAL_ENTITY: National Institute of Health Sciences

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

General information

Legal entity name
National Institute of Health Sciences

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

Address

Address 1
Tonomachi 3-25-26

Address 2
Kawasaki-ku

Postal code
210-9501

Town
Kawasaki

Region / State
Kanagawa

Country
Japan
JP

Identifiers

Other IT system identifiers

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

ID
16558402024DIV750