Name: OECD_SIDS / SUBSTANCE : Benzyl(dimethyl)(octan-1-yl)ammonium chloride / N-benzyl-N,N-dimethyloctan-1-aminium chloride / 959-55-7 Wed, 26 Nov 2025, 09:34:42+0900 /

Printing date: 2025-11-26T09:34:43.291+09:00

Table of Contents

DOSSIER:

UUID: 0
Dossier UUID:
Author:
Date: 2025-11-26T09:34:42.908+09:00
Remarks:

Dossier header

Dossier submission type

Name
OECD SIDS

Version
core 9.0

Name (given by user)

Dossier subject

Dossier subject
Benzyl(dimethyl)(octan-1-yl)ammonium chloride / N-benzyl-N,N-dimethyloctan-1-aminium chloride / 959-55-7

Public name

Submitting legal entity
National Institute of Health Sciences

Dossier creation date/time
Wed, 26 Nov 2025, 09:34:42+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

Benzyl(dimethyl)(octan-1-yl)ammonium chloride

General information

Identification

SUBSTANCE: Benzyl(dimethyl)(octan-1-yl)ammonium chloride

UUID:	1a80329b-05d8-456f-9d9e-9dc5a1917f70
Dossier UUID:	
Author:	
Date:	2024-09-11T11:55:38.046+09:00
Remarks:	

Substance name
Benzyl(dimethyl)(octan-1-yl)ammonium chloride

Identification of substance

Reference substance
benzyldimethyloctylammonium chloride / N-benzyl-N,N-dimethyloctan-1-aminium chloride / 959-55-7 / 213-502-1

EC number	EC name
213-502-1	EC Inventory
CAS number	**CAS name**
959-55-7	

IUPAC name
N-benzyl-N,N-dimethyloctan-1-aminium chloride

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:	c0a1b5be-884f-401b-b2f8-831244dfd5c8
Dossier UUID:	
Author:	
Date:	2024-09-11T11:55:38.046+09:00
Remarks:	

Administrative data

Endpoint
short-term repeated dose toxicity: oral

Type of information
experimental study

Robust study summary
false

Used for classification
false

Used for SDS
false

Study period: start date
2013-01-15

End date
2013-07-11

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. / Benzyl(dimethyl)(octan-1-yl)ammonium chloride / N-benzyl-N,N-dimethyloctan-1-aminium chloride / 959-

Data source

Reference

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

Data access
data published

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
Benzyl(dimethyl)(octan-1-yl)ammonium chloride

Specific details on test material used for the study
- Name of test material (as cited in study report): Benzyl(dimethyl)(octan-1-yl)ammonium chloride
- Analytical purity: ≥95%
- Storage condition of test material: sealed, cool place (actual temperature: 3-7.3°C)
- Stability under test conditions: The stability of test material was identified by analysis of the remainder

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: 417 g (389-450 g), Female: 247 g (217-289 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 × 400D × 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: 21-23°C)

- Humidity (%): 50±20% (actual humidity: 39-56%)
- Air changes (per hr): 12-17
- Photoperiod (hrs dark / hrs light): 12 hr dark/12 hr light (light: 7:00-19:00)

Administration / exposure

Route of administration
oral: gavage

Vehicle
other: water for injection

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 HPLC. The results showed that the concentration of each suspension was 97.3 to 101.0% of the no minal 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): 41-47 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.	
15	mg/kg bw/day (actual dose received)
Dose / conc.	
50	mg/kg bw/day (actual dose received)
Dose / conc.	
150	mg/kg bw/day (actual dose received)

No. of animals per sex per dose
Mating group: 12 animals/sex/dose (0, 15, 50 and 150 mg/kg bw/day)
Non-mating group: 10 females/dose (0 and 150 mg/kg bw/day)

Recovery group: 5 males*/dose in the mating group and 5 females*/dose in the non-mating groups (0 and 150 mg/kg bw/day) *In the 150 mg/kg bw/day group, one male was sacrificed and one female died during the treatment period, resulting in four animals each.

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 150 mg/kg, which is the intermediate dose between the high and intermediate doses of the preliminary s tudy, and the intermediate and low doses were divided by a common ratio of 3, to 50 and 15 mg/kg respectively.

[14-day preliminary study]
A 14-day repeated dose oral toxicity test in Crl: CD(SD) rats, doses: 0, 10, 30, 100 and 300 mg/kg bw/ day). In the 300 mg/kg bw/day group, 3/5 of both males and females died from 6 to 14 days of treatm ent. In the 100 mg/kg dose group, dilatation of the digestive tract was observed, but there were no histological abnormalities.

- 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.
* Neutrophil, eosinophil, basophil, lymphocyte, monocyte and large unstained cells.

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 36 to 37 of admini stration) and on the final week of recovery (Days 8 to 9 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, s ediment, 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 38 of administration), and on the final week of recov ery (Day 10 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 38 of administration), and on the final week of recovery (Day 10 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.

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 (inclu ding bronchial), tongue*, larynx*, esophagus*, stomach, duodenum, jejunum, ileum (including payer's patch), cecum, colon, rectum, submandibular gland, sublingual gland, liver, pancreas, kidney, bladde r, testis, epididymis, ovary, uterus, vagina, prostate, seminal vesicles (including coagulating gland), skin (inguinal region), mammary gland (inguinal region), sternum (including bone marrows)*, femur (including bone marrows), femoral skeletal muscle, individual identification site (pinna with ear tag)*, and gross lesions]
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 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. R egarding 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)
CLINICAL SIGNS:
[Dead or sacrificed animals]
Dyspnea was observed at the 150 mg/kg bw/day group. The dyspnea was considered to be due to di rect respiratory stimulation by the test substance, such as aspiration.

[At the dosing period]
In surviving animals, no effects related to the test substance were observed in any of the groups.

[At the recovery period]
In one non-mating female, at the 150 mg/kg bw/day group, dyspnea was observed on day 3. The dyspnea was considered to be due to direct respiratory stimulation by the test substance, such as aspiration.

DETAILED CLINICAL OBSERVATIONS:
[At the dosing period]
In two males, at the 150 mg/kg bw/day group, transient salivation was observed.
In four mating females, at the 150 mg/kg bw/day group, transient salivation was observed during gestation period. The salivation was considered to be induced by the irritation of the test substance, because the test substance may damage the respiratory mucosa.
[At the recovery period]
There were no effects related to the test substance in any of the groups.

Mortality
mortality observed, treatment-related

Description (incidence)
In males, at 150 mg/kg bw/day group, one animal died and one animal was sacrificed on day 5, and one animal died on 32 days.
In mating females, at the 150 mg/kg bw/day group, one animal each died on days 5, 8 or 32 (day 15 of gestation).

In non-mating females, at the 150 mg/kg bw/day group, one animal died on day 12, and one animal was sacrificed on day 39.

Body weight and weight changes
effects observed, treatment-related

Description (incidence and severity)
[At the dosing period]
In males, significant decreases in body weight on or after day 29, and significant decreases in body weight gain during the dosing period were observed at 50 mg/kg bw/day and above.

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

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

Description (incidence and severity)
[At the dosing period]
In males, significantly lower food consumption was observed on day 2 at 50 mg/kg bw/day and above
.
In mating females, significantly lower food consumption was observed on day 2 at 150 mg/kg bw/day.

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

Food efficiency
not examined

Ophthalmological findings
not examined

Haematological findings
effects observed, treatment-related

Description (incidence and severity)
[At the end of dosing period]
In males, a significant decrease in fibrinogen was observed at 150 mg/kg bw/day.
In mating females, a significant decrease in fibrinogen was observed at 150 mg/kg bw/day.
In non-mating females, significant decreases in fibrinogen was observed at 150 mg/kg bw/day.

[At the end of recovery period]
There were no findings related to the test substance in any of the groups.

Clinical biochemistry findings
effects observed, treatment-related

Description (incidence and severity)
[At the end of dosing period]
In males, a trend towards decrease in total bile acid was observed at 150 mg/kg bw/day.
In mating females, significant decreases in total bile acid, sodium, and chloride were observed at 150 mg/kg bw/day.
In non-mating females, a significant decrease in total bile acid was observed at 150 mg/kg bw/day.

[At the end of recovery period]
There were no findings related to the test substance in any of the groups.

Endocrine findings
not examined

Urinalysis findings
effects observed, treatment-related

Description (incidence and severity)
[At the dosing period]
In males, brown urine was observed at 150 mg/kg bw/day.
In non-mating females, brown urine was observed at 150 mg/kg bw/day.

[At the recovery period]
There were no findings 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
no effects observed

Gross pathological findings
effects observed, treatment-related

Description (incidence and severity)
[Dead or sacrificed animals]
In males, large cecum and dark red discoloration of bronchus were observed at 150 mg/kg bw/day.
In mating females, large cecum and dark red discoloration of bronchus were observed at 150 mg/kg bw/day.
In non-mating females, large cecum and dark red discoloration of bronchus were observed at 150 mg/kg bw/day.

[At the end of dosing period]
In males, large cecum was observed at 50 mg/kg bw/day and above, and dark red focus of bronchus was observed at 150 mg/kg bw/day.
In mating females, large cecum was observed at 150 mg/kg bw/day.
In non-mating females, large cecum was observed at 150 mg/kg bw/day.

[At the end of recovery period]
There were no findings related to the test substance in any groups.

Neuropathological findings
not examined

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

Description (incidence and severity)
[Dead or sacrificed animals]
Lung:
Mild bronchial necrotizing inflammation or bronchiolo-alveolar inflammation, mild alveolar edema, and mild or severe tracheal necrotizing inflammation were observed at 150 mg/kg bw/day in males.
Mild or moderate bronchial necrotizing inflammation, mild alveolar edema, and mild or severe tracheal necrotizing inflammation were observed at 150 mg/kg bw/day in mating females.
Mild bronchial necrotizing inflammation, mild alveolar edema, and mild or severe tracheal necrotizing inflammation were observed at 150 mg/kg bw/day in non-mating females.
The respiratory damage was considered to cause of death or sacrifice. The respiratory effects could be caused by direct injury to the trachea and bronchial mucosa as a result of the test substance entering the respiratory tract, for example by aspiration.

[At the end of dosing period]
Lung:
Minimal bronchiolo-alveolar inflammation was observed at 150 mg/kg bw/day in males.
The respiratory effects could be caused by direct injury to the trachea and bronchial mucosa as a r esult of the test substance entering the respiratory tract, for example by aspiration.

Stomach:
Minimal or mild squamous hyperplasia of the forestomach was observed at 150 mg/kg bw/day in m ales. The hyperplasia could be induced by the irritation of the test substance.
[At the end of recovery period]
Lung:
Minimal bronchiolo-alveolar inflammation was observed at 150 mg/kg bw/day in males.
The respiratory effects could be caused by direct injury to the trachea and bronchial mucosa as a result of the test substance entering the respiratory tract, for example by aspiration.

Histopathological findings: neoplastic
not examined

Effect levels

Key result
true

Dose descriptor
NOAEL

Effect level

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

Based on
test mat.

Sex
male

Basis for effect level
body weight and weight gain
A decreased body weight gain was observed at 50 mg/kg bw/day.
food consumption and compound intake
A lower food consumption was observed at 50 mg/kg bw/day.

Key result
true

Dose descriptor
NOAEL

Effect level

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

Based on
test mat.

Sex
female

Basis for effect level
clinical biochemistry
A decreased total bile acid was observed in mating/non-mating females, and decreased sodium and chloride was observed in mating females at 150 mg/kg bw/day.
food consumption and compound intake
A lower food consumption was observed in mating females at 150 mg/kg bw/day.
gross pathology
A large cecum was observed in mating/non-mating females at 150 mg/kg bw/day.
haematology
A decreased fibrinogen was observed in mating and non-mating females at 150 mg/kg bw/day.
urinalysis
A brown urine was observed in non-mating females at 150 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/PDF959-55-7d.pdf

Applicant's summary and conclusion

Conclusions
The NOAEL for repeated dose toxicity in this study was determined to be 15 mg/kg bw/day for males and 50 mg/kg bw/day for 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 benzyl(dimethyl)(octan-1-yl)ammonium chloride by gavage at 0 (vehicle: water for injection), 15, 50, and 150 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 41–47 days, including the 14-day premating, mating, and gestation periods, and until lactation day 4. Five males at the 0 and 150 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 150 mg/kg bw/day as a satellite group. These females were administered for 42 days without mating, and five females at 0 and 150 mg/kg bw/day were allocated to a recovery group and maintained for 14 days after the administration period.

At 150 mg/kg bw/day, 2 males, 3 females in the mating group, and 1 female in the non-mating group died, and 1 male and 1 female in the non-mating group were sacrificed. Respiratory damage was considered to cause of death or sacrifice. The respiratory effects could be caused by direct injury to the trachea and bronchial mucosa as a result of the test substance entering the respiratory tract, for example by aspiration.

In the clinical signs, salivation was observed in males, mating females during gestation period and non-mating females during recovery period at 150 mg/kg bw/day. Dyspnea was observed during recovery period in non-mating females at 150 mg/kg bw/day.

In the body weights, decreased body weight and body weight gain were observed in males at 50 mg/kg bw/day and above.

In the food consumptions, transient but significant decrease was observed on day 2 in males at 50 mg/kg bw/day and above and mating females at 150 mg/kg bw/day.

In the urinalysis, brown urine was observed in males and non-mating females at 150 mg/kg bw/day.

In the haematology results, decreased fibrinogen was observed in males, mating females, and nonmating females at 150 mg/kg bw/day.

In the clinical chemistry results, decreased total bile acid was observed in males, mating females, and non-mating females, as well as decreased sodium and chloride were observed in mating females, at 150 mg/kg bw/day.

In the gross pathological examinations, a large cecum was observed in males at 50 mg/kg bw and above, and in mating and non-mating females at 150 mg/kg bw/day

In the histopathological examinations, minimal bronchiolo-alveolar inflammation was observed at 150 mg/kg bw/day in males. Squamous hyperplasia of the forestomach was observed in males at 150 mg/kg bw/day. The squamous hyperplasia of the forestomach could be induced by the irritation of the test substance.

In the recovery study, dyspnea was observed transiently in non-mating females at 150 mg/kg bw/day, and bronchiolo-alveolar inflammation in the lung was observed in males at the same dose at the end of recovery period. These findings were thought to be due to benzyl (dimethyl) (octan-1-yl) ammonium chloride entering the airways by aspiration or other reasons.

Genetic toxicity

Genetic toxicity in vitro

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.001.

UUID:	91f97d2b-1eca-420b-8fa7-03243ce84ecd
Dossier UUID:	
Author:	
Date:	2024-02-19T10:41:06.000+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

Study period: start date
2013-03-01

End date
2013-11-20

Reliability
1 (reliable without restriction)

Rationale for reliability incl. deficiencies
guideline study
Reliability 1

Data source

Reference

Reverse Mutation Test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride 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 (incl. QA statement)

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

Test material

Test material information
Benzyl(dimethyl)(octan-1-yl)ammonium chloride

Specific details on test material used for the study
-Name of test material (as cited in study report): Benzyl(dimethyl)(octan-1-yl)ammonium chloride
- Analytical purity: ≥95%
- Storage condition of test material: cold place (actual temperature: 3.6-6.0°C), airtight and moisture-proof
- Stability under test conditions: The stability of test material was identified by analysis of the remain der

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

Test concentrations
Main study 1
-S9 mix: 9.77, 19.5, 39.1, 78.1, 156, 313 µg/plate (All strains)
+S9 mix: 9.77, 19.5, 39.1, 78.1, 156, 313 µg/plate (All strains)

Main study 2
-S9 mix: 9.77, 19.5, 39.1, 78.1, 156, 313 µg/plate (TA100, TA1535, WP2uvrA, TA98 strains)
1.22, 2.44, 4.88, 9.77, 19.5, 39.1, 78.1, 156, 313 µg/plate (TA1537 strain)
+S9 mix: 9.77, 19.5, 39.1, 78.1, 156, 313 µg/plate (All strains)

High dose level used
no

Justification for deviation from the high dose level
Maximum concentration was established based on the result of the range-finding study at co ncentration up to 5000 ug/plate.
In this study, growth inhibition was observed at 313 µg/plate and above for all strains with or without metabolic activation.

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

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 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
false

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: 156 µg/plate and above

Vehicle controls validity
valid

Positive controls validity
valid

Key result
true

Species / strain
S. typhimurium TA 1537
bacteria

Metabolic activation
with and without

Genotoxicity
positive

Cytotoxicity / choice of top concentrations
cytotoxicity -S9 mix: 313 µg/plate; +S9 mix: 156 µg/plate and above

Vehicle controls validity
valid

Positive controls validity
valid

Key result
false

Species / strain
S. typhimurium TA 98
bacteria

Metabolic activation
with and without

Genotoxicity
negative

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

Vehicle controls validity
valid

Positive controls validity
valid

Key result
false

Species / strain
S. typhimurium TA 100
bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
cytotoxicity -S9 mix: 313 µg/plate
+S9 mix: 156 µg/plate and above

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
cytotoxicity -S9 mix: 313 µg/plate;
+S9 mix: 313 µg/plate

Vehicle controls validity
valid

Untreated negative controls validity
not examined

Positive controls validity
valid

Additional information on results
RANGE-FINDING/SCREENING STUDIES (if applicable):

Concentration: 19.5, 78.1, 313, 1250, 5000 ug/plate with and without S9mix
Growth inhibitions: Growth inhibition was observed in all strains at 313 µg/plate and above wit or without metabolic activation.
Precipitation: No test substance-related precipitation was observed at any concentration with or without metabolic activation.
Mutagenicity: No increase in the number of revertant colonies was observed in any strain with or wit hout metabolic activation.

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/PDF959-55-7e.pdf

Please also see the attached files (Tables in English)

Overall remarks, attachments

Attachments

Attached (sanitised) documents for publication
R5_959-55-7_Ames Tables.xlsx / 39.456 KB (application/vnd.openxmlformats-officedocument.spreadsheetml.sheet)

Applicant's summary and conclusion

Conclusions
Interpretation of results (migrated information): positive
In a bacterial reverse mutation assay using Salmonella typhimurium TA100, TA1535, TA98, and TA1537, and Escherichia coli WP2uvrA (OECD TG 471), benzyl(dimethyl)(octan-1-yl)ammonium chloride showed positive result in TA 1537 with or without metabolic activation.

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.002.

UUID:	fe392f62-216b-4c7f-8568-feb3db5f4e07
Dossier UUID:	
Author:	
Date:	2024-02-19T10:48:47.000+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

Study period: start date
2013-04-04

End date
2013-11-20

Reliability
1 (reliable without restriction)

Rationale for reliability incl. deficiencies
guideline study
Reliability 1

Data source

Reference

In Vitro Chromosomal Aberration Test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride on Cultured Ch / 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 (incl. QA statement)

Type of assay
other: in vitro mammalian chromosome aberration test

Test material

Test material information
Benzyl(dimethyl)(octan-1-yl)ammonium chloride

Specific details on test material used for the study
- Name of test material (as cited in study report): Benzyl(dimethyl)(octan-1-yl)ammonium chloride
- Analytical purity: ≥95%
- Storage condition of test material: sealed, cool place (actual temperature: 3-8°C)
- Stability under test conditions: The stability of test material was identified by analysis of the r emainder

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

Test concentrations
Cell growth inhibition study
-S9 mix (short-term treatment): 22.7, 45.3, 90.6, 181, 363, 725, 1450, 2900 ug/mL
+S9 mix (short-term treatment): 215, 322, 483, 725 ug/mL
-S9 mix (continuous treatment, 24hr): 22.7, 45.3, 90.6, 181, 363, 725, 1450, 2900 ug/mL
-S9 mix (continuous treatment, 48hr): 22.7, 45.3, 90.6, 181, 363, 725, 1450, 2900 ug/mL

Main study

-S9 mix (short-term treatment): 143, 215, 322, 483 ug/mL
+S9 mix (short-term treatment): 215, 322, 483, 725 ug/mL
-S9 mix (continuous treatment, 24hr): 71.6, 107, 161, 242, 363 ug/mL
-S9 mix (continuous treatment, 48hr): 11.3, 22.7, 45.3, 90.6, 181 ug/mL

High dose level used
no

Justification for deviation from the high dose level
Chromosomal aberration test was carried out at several different doses of test substance selected fr
om the result of cell growth inhibition study.
Cell-growth inhibition study was conducted up to the limited concentration of 2900 µg/mL (10 mM)
In this study, precipitation and more than 50% cell growth inhibition were observed.
(See Additional information on results)

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

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 Short-term treatment (+/-S9 mix): cytotoxicity; Continuous treatment (24hr/48hr): cytotoxicity

Vehicle controls validity
valid

Positive controls validity
valid

Additional information on results
RANGE-FINDING/SCREENING STUDIES (if applicable):
Cell-growth inhibition study was conducted up to the limited concentration of 2900 µg/mL (10 mM)
In this study, precipitation and more than 50% cell growth inhibition were observed.
- Precipitation:
Short term treatment (+S9 mix): above 1450 µg/mL
- More than 50% cell growth inhibition:
Short term treatment (+S9 mix): 725 µg/mL
Short term treatment (-S9 mix): 363 µg/mL
Continuous treatment (24 h): 363 µg/mL
Continuous treatment (48 h): 90.6 µg/mL
- 50% cell-growth inhibition:
Short term treatment (+S9 mix): 641 µg/mL
Short term treatment (-S9 mix): 357 µg/mL
Continuous treatment (24 h): 211 µg/mL
Continuous treatment (48 h): 67 µg/mL

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/PDF959-55-7f.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), benzyl(dimethyl)(octan-1-yl)ammonium chloride was negative with or without metabolic activation.

Toxicity to reproduction

Toxicity to reproduction

ENDPOINT_STUDY_RECORD: Toxicity to reproduction. 001.

UUID:	b8466337-1fbf-46eb-9e33-657d176d9f14
Dossier UUID:	
Author:	
Date:	2024-02-16T16:08:55.000+09:00
Remarks:	

Administrative data

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

Type of information
experimental study

Robust study summary
false

Used for classification
false

Used for SDS
false

Study period: start date
2013-01-15

End date
2013-07-11

Reliability
1 (reliable without restriction)

Cross-reference

Reason / purpose for cross-reference
reference to same study

Related information
OECD / Repeated dose toxicity: oral / Repeated dose toxicity: oral.001. / Benzyl(dimethyl)(octan-1-yl)ammonium chloride / N-benzyl-N,N-dimethyloctan-1-aminium chloride / 959-

Data source

Reference

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

Data access
data published

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
Benzyl(dimethyl)(octan-1-yl)ammonium chloride

Specific details on test material used for the study
- Name of test material (as cited in study report): benzyl(dimethyl)(octan-1-yl)ammonium chloride
- Analytical purity: ≥95%
- Storage condition of test material: sealed, cool place (actual temperature: 3-7.3°C)
- Stability under test conditions: The stability of test material was identified by analysis of the remainder

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: 417 g (389-450 g), Female: 247 g (217-289 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 × 400D × 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: 21-23°C)
- Humidity (%): 50±20% (actual humidity: 39-56%)
- Air changes (per hr): 12-17
- Photoperiod (hrs dark / hrs light): 12 hr dark/12 hr light (light: 7:00-19:00)

Administration / exposure

Route of administration
oral: gavage

Vehicle
other: water for injection

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 14 days
- Proof of pregnancy: vaginal plug / sperm in vaginal smear referred to as day 0 of pregnancy

Analytical verification of doses or concentrations
yes

Details on analytical verification of doses or concentrations
The concentrations of each suspension used at weeks 1 and 6 of administration were analyzed by HPLC. The results showed that the concentration of each suspension was 97.3 to 101.0% of the no minal 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): 41-47 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.	
15	mg/kg bw/day (actual dose received)
Dose / conc.	
50	mg/kg bw/day (actual dose received)
Dose / conc.	
150	mg/kg bw/day (actual dose received)

No. of animals per sex per dose
Mating group: 12 animals/sex/dose (0, 15, 50 and 150 mg/kg bw/day)
Non-mating group: 10 females/dose (0 and 150 mg/kg bw/day)
Recovery group: 5 males*/dose in the mating group and 5 females*/dose in the non-mating groups (0 and 150 mg/kg bw/day) *In the 150 mg/kg bw/day group, one male was sacrificed and one female died during the treatment period, resulting in four animals each.

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 150 mg/kg, which is the intermediate dose between the high and intermediate doses of the preliminary s tudy, and the intermediate and low doses were divided by a common ratio of 3, to 50 and 15 mg/kg respectively.

[14-day preliminary study]
A 14-day repeated dose oral toxicity test in Crl: CD(SD) rats, doses: 0, 10, 30, 100 and 300 mg/kg bw/ day). In the 300 mg/kg bw/day group, 3/5 of both males and females died from 6 to 14 days of treatm ent. In the 100 mg/kg dose group, dilatation of the digestive tract was observed, but there were no histological abnormalities.

- 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 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.
* Neutrophil, eosinophil, basophil, lymphocyte, monocyte and large unstained cells.

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 36 to 37 of admini stration) and on the final week of recovery (Days 8 to 9 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, s ediment, 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 38 of administration), and on the final week of recov ery (Day 10 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 38 of administration), and on the final week of recovery (Day 10 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: weights and histopathological examinations for testis, epididymis, prostate and seminal vesicles (including coagulating gland).

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 (including bone marrows)*, femur (including bone marrows), femoral skeletal muscle, individual identification site (pinna with ear tag)*, and gross lesions]
Asterisked organs and tissues are fixed and stored only.

Postmortem examinations (offspring)
SACRIFICE:
- The F1 offsprings were fixed on day 4 by immersion in Bouin's solution under isoflurane anesthesia and stored.

GROSS PATHOLOGY: Yes.
- Examination for external abnormalities.

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, delivery index, live birth index, stillborn index, external abnormalities and viability index on PND4 and, Steel test was applied. Regarding the index of animals with abnormal estrous cycle, copulation index, insemination index, fertility index, and gestation 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 G estation 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
mortality observed, treatment-related

Description (incidence)
See 7.5.1 Repeated dose toxicity. 001

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

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
no effects observed

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
no effects observed

Reproductive function: sperm measures
no effects observed

Reproductive performance
no effects observed

Details on results (P0)

General toxicity:
See 7.5.1 Repeated dose toxicity.001

Reproductive function / performance:
no effects observed

Effect levels (P0)

Key result
true

Dose descriptor
NOAEL

Effect level

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

Based on
test mat.

Sex
male/female

Basis for effect level
reproductive performance
No reproductive effects were observed in males and females up to 150 mg/kg bw/day.

Key result
true

Dose descriptor
NOAEL

Effect level

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

Based on
test mat.

Sex
male

Basis for effect level
body weight and weight gain
A decreased body weight gain was observed at 50 mg/kg bw/day.
food consumption and compound intake
A lower food consumption was observed at 50 mg/kg bw/day.

Key result
true

Dose descriptor
NOAEL

Effect level

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

Based on
test mat.

Sex
female

Basis for effect level
food consumption and compound intake
A lower food consumption was observed in mating females at 150 mg/kg bw/day.
haematology
A decreased fibrinogen was observed in mating and non-mating females at 150 mg/kg bw/day.
clinical biochemistry
A decreased total bile acid was observed in mating/non-mating females, and decreased sodium and chloride was observed in mating females at 150 mg/kg bw/day.
urinalysis
A brown urine was observed in non-mating females at 150 mg/kg bw/day.
gross pathology
A large cecum were observed in mating/non-mating females at 150 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
no effects observed

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

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

Based on
test mat.

Sex
male/female

Remarks on result
other: There were no effects on developmental parameters up to 150 mg/kg bw/day.

Overall reproductive toxicity

Key result
true

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/PDF959-55-7d.pdf

Applicant's summary and conclusion

Conclusions
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). There were no effects on the reproductive and developmental parameters up to 150 mg/kg bw/day. The NOAEL for the rat reproductive/developmental toxicity of benzyl(dimethyl)(octan-1-yl)ammonium chloride was regarded as 150 mg/kg bw/day, the highest dose tested.

References

Reference Substances

REFERENCE_SUBSTANCE: benzyldimethyloctylammonium chloride

UUID: ECB5-f37a36b2-dad2-46f1-9e8d-abf2b9446151
Dossier UUID:
Author:
Date: 2007-05-10T18:00:00.000+09:00
Remarks:

Reference substance name
benzyldimethyloctylammonium chloride

IUPAC name
N-benzyl-N,N-dimethyloctan-1-aminium chloride

Inventory

Inventory number

Inventory name
benzyldimethyloctylammonium chloride

Inventory
EC Inventory

Inventory number
213-502-1

CAS number
959-55-7

Molecular formula
C17H30N.Cl

Description

CAS number
959-55-7

Synonyms

Synonyms

Identity
Benzenemethanaminium, N,N-dimethyl-N-octyl-, chloride

Molecular and structural information

Molecular formula
C17H30N.Cl

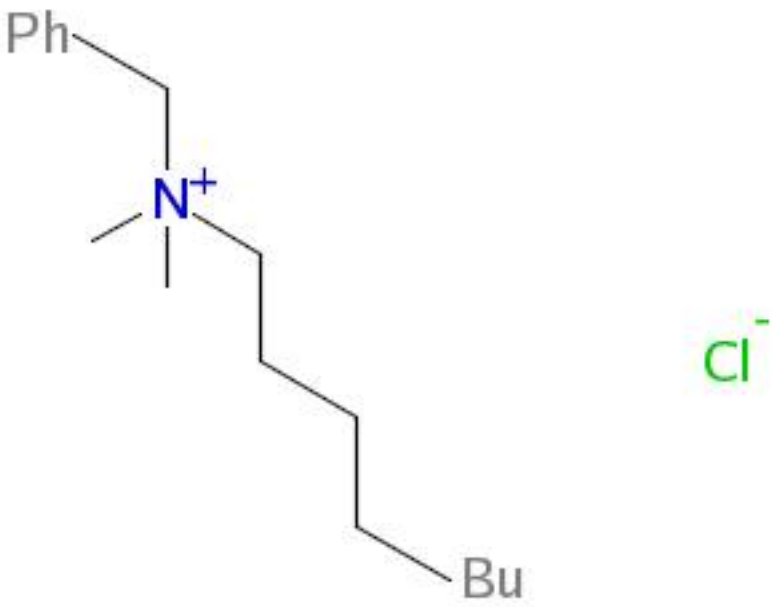
Molecular weight

283.8798

SMILES notation
[Cl-].CCCCCCCC[N+](C)(C)Cc1ccccc1

InChI
InChI=1/C17H30N.ClH/c1-4-5-6-7-8-12-15-18(2,3)16-17-13-10-9-11-14-17;/h9-11,13-14H,4-8,12,15-16H2,1-3H3;1H/q+1;/p-1

Structural formula



Test Materials

TEST_MATERIAL_INFORMATION: Benzyl(dimethyl)(octan-1-yl)ammonium chloride

UUID: e0b3ed42-969d-478d-ae46-776fc037714d
Dossier UUID:
Author:
Date: 2024-02-05T11:24:17.000+09:00
Remarks:

Name
Benzyl(dimethyl)(octan-1-yl)ammonium chloride

Composition

Composition

Reference substance
benzyldimethyloctylammonium chloride / N-benzyl-N,N-dimethyloctan-1-aminium chloride / 959-55-7 / 213-502-1

EC number	EC name
213-502-1	EC Inventory

CAS number	CAS name
959-55-7	

IUPAC name
N-benzyl-N,N-dimethyloctan-1-aminium chloride

Literatures

LITERATURE: Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of benzyl(dimethyl)(octan-1-yl) ammonium chloride by oral administration in rats

UUID: c368e44e-d420-45af-a105-c2f5970b87f6
Dossier UUID:
Author:
Date: 2024-02-14T16:24:13.000+09:00
Remarks:

General information

Reference Type
study report

Title
Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of benzyl(dimethyl)(octan-1-yl) ammonium chloride by oral administration in rats

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

Bibliographic source
Japan Existing Chemical Data Base (JECDB)
https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF959-55-7d.pdf

Testing facility
BoZo Research Center Inc.

Report date
2013-10-15

Report number
R-1102

LITERATURE: In Vitro Chromosomal Aberration Test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride on Cultured Chinese Hamster Cells.

UUID: f90de55d-5961-449d-87ce-4708d3a0cf69
Dossier UUID:
Author:
Date: 2023-08-02T14:00:55.000+09:00
Remarks:

General information

Reference Type
study report

Title
In Vitro Chromosomal Aberration Test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride 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/PDF959-55-7f.pdf

Testing facility
Bozo Research Center Inc.

Report date
2013-11-20

Report number
T-G057

LITERATURE: Reverse Mutation Test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride on Bacteria.

UUID: 07ca01a6-5c09-44ba-be84-c1a64a7bdefa
Dossier UUID:
Author:
Date: 2024-02-15T14:05:36.000+09:00
Remarks:

General information

Reference Type
study report

Title
Reverse Mutation Test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride 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/PDF959-55-7e.pdf

Testing facility
Bozo Research Center Inc.

Report date
2013-11-20

Report number
T-1109