Name: OECD_SIDS / SUBSTANCE : 1-Ethoxy-2-(2-methoxyethoxy)ethane / 1-ethoxy-2-(2-methoxyethoxy)ethane / 1002-67-1 Wed, 26 Nov 2025, 09:42:29+0900 /

Printing date: 2025-11-26T09:42:30.283+09:00

Table of Contents

DOSSIER:

UUID: 0
Dossier UUID:
Author:
Date: 2025-11-26T09:42:29.966+09:00
Remarks:

Dossier header

Dossier submission type

Name
OECD SIDS

Version
core 9.0

Name (given by user)

Dossier subject

Dossier subject
1-Ethoxy-2-(2-methoxyethoxy)ethane / 1-ethoxy-2-(2-methoxyethoxy)ethane / 1002-67-1

Public name

Submitting legal entity
National Institute of Health Sciences

Dossier creation date/time
Wed, 26 Nov 2025, 09:42:29+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

1-Ethoxy-2-(2-methoxyethoxy)ethane

General information

Identification

SUBSTANCE: 1-Ethoxy-2-(2-methoxyethoxy)ethane

UUID: 69249661-45c9-4b4b-aa31-c30eb97682b5
Dossier UUID:
Author:
Date: 2025-08-08T15:14:52.224+09:00
Remarks:

Substance name
1-Ethoxy-2-(2-methoxyethoxy)ethane

Identification of substance

Reference substance
1-ethoxy-2-(2-methoxyethoxy)ethane / 1-ethoxy-2-(2-methoxyethoxy)ethane / 1002-67-1 / 213-690-5

EC number	EC name
213-690-5	EC Inventory
CAS number	**CAS name**
1002-67-1	

IUPAC name
1-ethoxy-2-(2-methoxyethoxy)ethane

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:	c6da73f4-d911-4fc9-8289-440cf4b1af70
Dossier UUID:	
Author:	
Date:	2024-09-11T11:58:13.459+09:00
Remarks:	

Administrative data

Endpoint
short-term repeated dose toxicity: oral

Type of information
experimental study

Adequacy of study
key study

Robust study summary
false

Used for classification
false

Used for SDS
false

Study period: start date
2013-09-26

End date
2014-03-26

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. / 1-Ethoxy-2-(2-methoxyethoxy)ethane / 1-ethoxy-2-(2-methoxyethoxy)ethane / 1002-67-1

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)

Version / remarks
similar to OECD TG422

GLP compliance
yes (incl. QA statement)

Limit test
no

Test material

Test material information
1-Ethoxy-2-(2-methoxyethoxy)ethane

Specific details on test material used for the study
- Name of test material (as cited in study report): 1-Ethoxy-2-(2-methoxyethoxy)ethane
- Analytical purity: 100.0% (capillary-column GC)
- Storage condition of test material: sealed, light-shielded at room temperature (actual temperature: 15.8-24.6°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: 376.3-449.2 g, Female: 217.0-292.9 g
- Housing: Animals were individually housed in bracket-type metallic wire-mesh cages (220W × 270D×190H mm), from gestation day 18 to lactation day 4, Dams were bred individually or with individ ual
- littermates in plastic cages (350W × 400D × 180H mm) and bedding.
- Diet: Solid feed (CE-2: CLEA Japan Inc.) was given ad libitum.
- Water: Tap water was given ad libitum.
- Acclimation period: 15 days

ENVIRONMENTAL CONDITIONS
- Temperature (°C): 21.0-25.0 (actual temperature: 22.0-24.5°C)
- Humidity (%): 40.0-75.0% (actual humidity: 50.0-73.5%)
- Air changes (per hr): 15
- Photoperiod (hrs dark / hrs light): 12 hr dark/12 hr light (light: 7:00-19:00)

Administration / exposure

Route of administration
oral: gavage

Vehicle
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 test suspension used at day1 of administration were analyzed by HPLC. The results showed that the concentration of each test suspension was 98.5 to 100.0% of the n ominal concentration.

Duration of treatment / exposure
Males: 42 days including 14 days pre-mating
Females (mating group): 41-46 days including 14 days pre-mating, mating and gestation periods and the days until day 4 of lactation (non-mated females: 52 days including 14 days pre-mating, and non-parturient females: until equivalent day 25 of gestation)
Female (non-mating group: satellite 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.	
62.5	mg/kg bw/day (actual dose received)

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

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

No. of animals per sex per dose
Mating group: 12 animals/sex /dose (0, 62.5, 250, and 1000 mg/kg bw/day)
Non-mating group (satellite group): 10 females/dose (0 and 1000 mg/kg bw/day)
Recovery group: 5 males/dose in the mating group (0 and 1000 mg/kg bw/day) and 5 females/dose in the non-mating groups (0 and 1000 mg/kg bw/day)

Control animals
yes, concurrent vehicle

Details on study design
- Dose selection rationale: Based on the results of a 14-day preliminary study, the highest dose was 1000 mg/kg, which is the amount limit, and the intermediate and low doses were divided by a common ratio of 4, to 250 and 62.5 mg/kg respectively.

[14-day preliminary study]
A 14-day repeated dose oral toxicity test (Crl:CD(SD) rats, males and females, doses: 0, 250, 500 or 1000 mg/kg bw/ day. The increased liver weights and the decreased MCHC were observed in males at 500 mg/kg bw/day and above, decreased locomotor activity and HGB were observed in males and females at 1000 mg/kg bw/day, and decreased hematocrit and total protein were observed in males at 1000 mg/kg bw/day, but all of these changes were mild.
- Rationale for animal assignment (if not random): Body weight-balanced randomization.

Examinations

Observations and examinations performed and frequency
CAGE SIDE OBSERVATIONS: Yes
- Time schedule: 2 or more times/day (before administration, after administration) during the administ ration period. At least once a day during the recovery period.

DETAILED CLINICAL OBSERVATIONS: Yes
- Time schedule:
Males: At the end of acclimation period, Days 8, 15, 24, 30, 36, and 42 of administration and Days 7 an d 14 of recovery period.
Females in the mating groups: At the end of acclimation period and Days 8, 15, 24, 30, 36, and 42* of administration period. (*Note: For delivered females, once during lactation period (lactation day 0 to day 4).)
Females in the non-mating groups (satellite group): At the end of acclimation period, Days 8, 15, 24, 30, 36, and 42 of administration and Days 7 and 14 of recovery period.

BODY WEIGHT: Yes
- Time schedule for examinations:
Males: Days 1, 4, 7, 14, 21, 28, 35, and 42 of administration period and on the day of necropsy, and Days 1, 7 and 14 of recovery period and on the day of necropsy.
Females in the mating groups: Days 1, 4, 7, and 14 of administration period, Days 0, 7, 14, and 20 of gestation, Days 0 and 4 of lactation, and on the day of necropsy. For unmated females, Days 21, 28, 35, 42 and 49 of administration period and on the day of necropsy.
Females in the non-mating groups (satellite group): Days 1, 4, 7, 14, 21, 28, 35, and 42 of administra tion period and on the day of necropsy, and Days 1, 7 and 14 of recovery period and on the day of ne cropsy.

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 1-2, 7-8, 14-15, 29-30, 35-36 and 41-42 of administration period. Days 6-7 and 12-13 of recovery period.
Females in the mating groups: Days 1-2, 7-8 and 14-15 of administration period. Days 0-1, 7-8, 14-15, and 20-21 of gestation period. Days 3-4 of lactation period. For unmated females, Days 29-30, 35-36, 41-42 and 48-49 of administration period.
Females in the non-mating groups (satellite group): Days 1-2, 7-8, 14-15, 21-22, 29-30, 35-36 and 41-42 of administration period. Days 6-7 and 12-13 of recovery period.

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: Pentobarbital sodium
- Animals fasted: Yes
- How many animals:
5 animals/sex/group
- Parameters examined: red blood cell count (RBC), white blood cell count (WBC), differential white blood cell count, reticulocyte ratio, hemoglobin (HGB), mean corpuscular volume (MCV), platelet count, hematocrit, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), activated partial thromboplastin time (APTT), prothrombin time (PT)

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: total protein, albumin, A/G ratio, glucose, total cholesterol, triglyceride, phospholipids, AST, ALT, γ-GTP, LDH, bile acid, blood urea nitrogen, creatinine, total bilirubin, ALP, inorganic phosphorus, calcium, sodium, potassium, chloride

BLOOD HORMONE: No

URINALYSIS: Yes
- Time schedule for collection of urine: : On the final week of administration (Day 37 of administration) and on the final week of recovery (Day 13 of recovery) in males and females in the non-mating groups (satellite group).
- Metabolism cages used for collection of urine: Yes
- How many animals: 5 animals/group
- Parameters checked:
4-hour urine sample: color, turbidity, pH, occult blood, protein, glucose, ketone, urobilinogen, bilirubin, urinary sediments
24-hour urine sample: urine volume, specific gravity, sodium, potassium, chloride

NEUROBEHAVIOURAL (FUNCTIONAL) EXAMINATION: Yes
- Time schedule for examinations:
Males: On the final week of administration (Manipulative Test: Day 42, Measurement of Grip Strength and Motor Activity: Day 39). No examinations were performed during the recovery period.
Females in the mating group: On the final week of administration
Females in the non-mating groups (satellite group): On the final week of administration (Manipulative Test: Day 42, Measurement of Grip Strength and Motor Activity: Day 39). No examinations were performed during the recovery period.

- Dose groups that were examined: All dose groups (5 animals/sex/group) (excluding the 1000 mg/kg bw/day group of mating females)
- Battery of functions tested:
1) Manipulative Test. Prayer's reaction, pupillary reflex, visual placing, startle reaction, withdrawal reflex, eyelid reflex, and righting reflex.
2) Measurement of Grip Strength. Grip strength of forelimb and hindlimb were measured by grip strength meter, Chatillon (Columbus Instruments, LLC).
3) Measurement of Motor Activity. Motor activity was measured by a motor activity sensor for experimental animals, SUPER-MEX (Muromachi Kikai. Co., Ltd.). The measurement was conducted for 20 min.

Sacrifice and pathology
METHOD OF SACRIFICED: All animals were sacrificed by exsanguination under pentobarbital sodium anesthesia.

SACRIFICE:
Males of mating groups and females of non-mating groups (satellite group):
On day 43 (next day after the last administration).
Females of mating groups:
Delivered case: On day 5 of lactation period.
Undelivered case: On equivalent to day 26 of gestation period.
Unmated case: On day 53 (next day after the last administration).
All litters died case: On the day all litters died.
Males and females of recovery groups:
On day 15 of recovery period.

GROSS PATHOLOGY: Yes
ORGAN WEIGHT: Yes [brain, thyroid gland (including parathyroid gland), thymus, heart, liver, kidney, spleen, adrenal gland, testis, epididymis, prostate (ventral), seminal vesicles (including coagulating gland), ovary, uterus]
Note: The organ weights of the dams those all litters died, unmated females and non-delivered females were excluded from the evaluation.
HISTOPATHOLOGY: Yes [brain, spinal cord, pituitary gland, eyeball (Harderian gland), submandibular gland, sublingual gland, trachea, thyroid gland, parathyroid gland, thymus, heart, lung, bronchus, liver, kidney, spleen, pancreas, adrenal gland, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, submandibular lymph node, mesenteric lymph node, testis, epididymis, prostate, seminal vesicle and coagulating gland, ovary, uterus, vagina, urinary bladder, femur and femur marrow, skeletal muscle, sciatic nerve, and gross abnormalities site]

Statistics
Changes in estrous cyclicity, copulation index and fertility index were analyzed by Fisher’s test (significance level = 0.05).
Graded pathological data was analyzed by Mann-Whitney’s U test and pathological data with number of positive and negative animals was analyzed by one-sided Fisher’s test (significance level = 0.05).
In females, the tests were only performed on the animals necropsied on day 5 of lactation.
These data were analyzed using F-test for homogeneity of variance. The Student’s t-test and the Aspin-Welch’s t-test were conducted for homogenous and non-homogenous distribution, respectively to compare the control and individual treatment groups. Three or more groups setting, these data were analyzed using Bartlett’s test for homogeneity of distribution. The Dunnett’s multiple comparison test after the ANOVA and the Dunnett’s-type mean rank sum test after Kruskal-Wallis’s H test were conducted for homogenous and non-homogenous distribution, respectively to compare the control and individual treatment groups. Significance level was set at 0.05 compared with the control group and among the groups.

Results and discussion

Results of examinations

Clinical signs
effects observed, treatment-related

Description (incidence and severity)
[At the dosing period]:
In males, at the 1000 mg/kg bw/day group, decrease in locomotor activity and transient salivation were observed.
In mating females, at the 1000 mg/kg bw/day group, decrease in locomotor activity was observed before delivery, and transient salivation was observed during pregnancy and lactation.
In non-mating females (satellite group), at the 1000 mg/kg bw/day group, decrease in locomotor activity was observed.

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

Mortality
no mortality observed

Body weight and weight changes
effects observed, treatment-related

Description (incidence and severity)
[At the dosing period]
In mating females, significant decreases in body weight gain during pregnancy was observed at 1000 mg/kg bw/day.

[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 1-2 and 41-42 at 1000 mg/kg bw /day.
In mating females, significantly lower food consumption was observed on day 3-4 of lactation at 250 mg/kg bw/day. (Note: In the 1000 mg/kg bw/day group, food consumption data during lactation were not reported because all the litters died and the dams were sacrificed on day 1 of lactation.)
In non-mating females (satellite group), significantly lower food consumption was observed on day 7-8 and 41-42 at 1000 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 reticulocyte ratio was observed at 250 mg/kg bw/day and above, a nd significant decreases in HGB and hematocrit were observed at 1000 mg/kg bw/day.
In non-mating females (satellite group), significant decreases in HGB, hematocrit, MCHC, platelet count and reticulocyte ratio were observed at 1000 mg/kg bw/day.

[At the end of recovery period]
There were no changes 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, significant decrease in total protein and increase in γ-GTP were observed at 1000 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, significant decrease in potassium and chloride ion concentrations were observed at 1000 mg/kg bw/day.

[At the recovery period]
In non-mating females (satellite group), significant decreases in specific gravity and sodium, pota ssium, and chloride ion concentrations were observed at 1000 mg/kg bw/day.

Behaviour (functional findings)
no effects observed

Immunological findings
not examined

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

Description (incidence and severity)
[At the dosing period]
In males, significant decrease in absolute and relative weight of thymus, epididymides and ventral prostate, and significant increase in relative weight of liver and kidney were observed at 1000 mg/kg bw/day.
In non-mating females (satellite group), significant decrease in absolute and relative weight of t hymus, and significant increase in relative weight of liver and kidney were observed at 1000 mg/kg b w/day.

[At the recovery period]
In males, significant increase in relative weight of the liver and significant decrease in absolute weight of the epididymis (left) was observed at 1000 mg/kg bw/day.

Gross pathological findings
effects observed, treatment-related

Description (incidence and severity)
[At the end of dosing period]
Thymus:
Small thymus was observed at 1000 mg/kg bw/day in males and 250 mg/kg bw/day in mating femal es.

Epididymis:
Bilateral edema was observed at 1000 mg/kg bw/day in males.

Prostate:
Small prostate was observed at 1000 mg/kg bw/day in males.

Testis:
Bilateral edema and small testis were observed at 1000 mg/kg bw/day in males.

Note: No litters survived to day 4 of lactation at the 1000 mg/kg bw/day. Therefore, in this dose, gross pathological findings of mating female at the end of dosing period was not available.

[The dams those all litters died]
2/8 females in the 1000 mg/kg bw/day group had enlarged spleen.

[Undelivered females]
3/4 females in the 1000 mg/kg bw/day group and 1/1 female in the 250 mg/kg bw/day were infertile, while 1/4 females in the 1000 mg/kg bw/day group had implantation scars.
Dilatation of the uterine lumen was observed in one infertile female in the 1000 mg/kg bw/day group.
[Unmated females]
There were no abnormal findings at 250 mg/kg bw/day.

[At the end of recovery period]
Epididymis:
Bilateral Edema and unilateral or bilateral small epididymis were observed at 1000 mg/kg bw/day in males.

Testis:
Bilateral Edema and unilateral or bilateral small testis were observed at 1000 mg/kg bw/day in males.

Neuropathological findings
not examined

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

Description (incidence and severity)
[At the end of dosing period]
Thymus:
Very slight to slight medullary atrophy was observed at 1000 mg/kg bw/day in males and non-mating females (satellite group).

Liver:
Very slight to slight hypertrophy of centrilobular hepatocytes was observed at 250 mg/kg bw/day and above in males, and 1000 mg/kg bw/day in non-mating females (satellite group).
Very slight to slight ground glass appearance of hepatocytes was observed at 1000 mg/kg bw/day in males and non-mating females (satellite group).
Hypertrophy of centrilobular hepatocytes and ground glass appearance of hepatocytes were also observed in mating females that lost all the litter at 1000 mg/kg bw/day.

Testis:
Slight exfoliation of spermatid and sperm, very slight multinucleated giant cell, and very slight to slight vacuolation of the germ cell layer in the bilateral seminiferous tubules were observed at 1000 mg/kg bw/day in males.

Epididymis:
Slight or very slight cell debris and decreased sperm in the bilateral lumen were observed at 1000 mg/kg bw/day in males.

Prostate:
Very slight decreased liquid content in the bilateral lumen was observed at 1000 mg/kg bw/day in males.

[At the end of recovery period]
Testis:
Very slight to moderate exfoliation of spermatocyte, spermatid and sperm, and vacuolation of the germ cell layer in the bilateral seminiferous tubules were observed at 1000 mg/kg bw/day in males.

Epididymis:
Very slight to moderate cell debris and very slight to moderate decreased sperm in the unilateral or bilateral lumen were observed at 1000 mg/kg bw/day in males.

Histopathological findings: neoplastic
not examined

Effect levels

Key result
true

Dose descriptor
NOAEL

Effect level

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

Based on
test mat.

Sex
male

Basis for effect level
haematology
A significant decrease in reticulocyte ratio was observed at 250 mg/kg bw/day and above.
histopathology: non-neoplastic
Hypertrophy of centrilobular hepatocytes was observed at 250 mg/kg bw/day and above.

Key result
true

Dose descriptor
NOAEL

Effect level

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

Based on
test mat.

Sex
female

Basis for effect level
food consumption and compound intake

A significantly lower food consumption was observed on day 3 of lactation at 250 mg/kg bw/day.
Note: In mating females, food consumption data during lactation in the 1000 mg/kg bw/day group were not reported because all the litters died and the dams were sacrificed on day 1 of lactation.

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/PDF1002-67-1d.pdf

Applicant's summary and conclusion

Conclusions
The NOAEL for repeated dose toxicity in this study was determined to be 62.5 mg/kg bw/day for males and females.

Executive summary

A combined repeated oral dose toxicity study with the reproduction/developmental toxicity screening test was performed according to a Japanese guideline (similar to OECD TG 422). Male and female rats (12 animals/sex/dose) were administered 1-ethoxy-2-(2-methoxyethoxy)ethan by gavage at 0 (vehicle: water for), 62.5, 250, and 1000 mg/kg bw/day.

Males were administered for 42 days, including a 14-day premating period and subsequent mating period, whereas females in the mating group were administered for 41–46 days, including the 14-day premating, mating, and gestation periods, and until lactation day 4. Five males at the 0 and 1000 mg/kg bw/day were allocated to a recovery group and maintained for 14 days after the administration period. Ten additional females were administered at 0 and 1000 mg/kg bw/day as a satellite group. These females were administered for 42 days without mating, and five females at 0 and 1000 mg/kg bw/day were allocated to a recovery group and maintained for 14 days after the administration period.

In the clinical signs, transient salivation was observed in males and mating females during pregnancy and lactation at 1000 mg/kg bw/day. The salivation was considered to be induced by the irritation of the test substance, because the no neurotoxic effects were observed during detailed clinical observations or functional examination. Decrease in locomotor activity was observed in males, mating females before delivery, and non-mating females (satellite group) at 1000 mg/kg bw/day.

In the body weights, decreased body weight gain, probably related to litter loss in utero or fetal growth inhibition was observed in mating females during pregnancy at 1000 mg/kg bw/day.

In the food consumptions, transient but significant decrease was observed on day 1-2 and 41-42 in males and on day 7-8 and 41-42 in non-mating females (satellite group) at 1000 mg/kg bw/day, and on day 3-4 of lactation in mating females at 250 mg/kg bw/day. In mating females, food consumption data during lactation were not reported because all the litters died and the dams were sacrificed on day 1 of lactation at 1000 mg/kg bw/day.

In the urinalysis, decreased potassium and chloride ion concentrations were observed in males at 1000 mg/kg bw/day. At the recovery period, decreased specific gravity and sodium, potassium, and chloride ion concentrations were observed in non-mating females (satellite group) at 1000 mg/kg bw/day.

In the haematology results, in males, decreased reticulocyte ratio was observed at 250 mg/kg bw/day and above, and decreased HGB and hematocrit were observed at 1000 mg/kg bw/day. In non-mating females (satellite group), decreased HGB, hematocrit, MCHC, platelet count and reticulocyte ratio were observed at 1000 mg/kg bw/day.

In the clinical biochemistry results, decreased total protein and increased γ-GTP were observed in males at 1000 mg/kg bw/day.

In the organ weights, decreased absolute and relative weights of the thymus and increased relative weights of the liver and kidney were observed in males and non-mating females (satellite group) at 1000 mg/kg bw/day. In males, decreased the epididymides and ventral prostate weights were also observed at 1000 mg/kg bw/day. At the recovery period, increased relative weight of the liver and decreased absolute weight of the epididymis (left) was observed in males at 1000 mg/kg bw/day.

In the histopathological examination, atrophy of the thymic medulla was observed in males and non-mating females (satellite group) at 1000 mg/kg bw/day. Hypertrophy of centrilobular hepatocytes was observed in males at 250 mg/kg bw/day and above, and in mating females that lost all the litter and non-mating females (satellite group) at 1000 mg/kg bw/day. Ground glass appearance of hepatocytes was observed in mating females that lost all the litter and non-mating females (satellite group) at 1000 mg/kg bw/day. Exfoliation of spermatid and sperm, multinucleated giant cell, and vacuolation of the germ cell layer in the seminiferous tubules of the testis, cell debris and decreased sperm in the lumen of the epididymis, and decreased liquid content in the lumen of the prostate were observed in males at 1000 mg/kg bw/day. At the end of recovery period, exfoliation of spermatocyte, spermatid and sperm, and vacuolation of the germ cell layer in the seminiferous tubules of the testis, and cell debris and decreased sperm in the lumen of the epididymis were observed in males at 1000 mg/kg bw/day.

Genetic toxicity

Genetic toxicity in vitro

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.001..

UUID:	984b6e2d-4f9b-473a-9f04-0cfdcb2f4822
Dossier UUID:	
Author:	
Date:	2024-02-19T10:33:04.000+09:00
Remarks:	

Administrative data

Endpoint
in vitro gene mutation study in bacteria

Type of information
experimental study

Robust study summary
false

Used for classification
false

Used for SDS
false

Study period: start date
2013-08-27

End date
2014-03-11

Reliability
1 (reliable without restriction)

Rationale for reliability incl. deficiencies
guideline study
Reliability 1

Data source

Reference

Reverse Mutation Test of 1-Ethoxy-2-(2-methoxyethoxy)ethane 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
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
1-Ethoxy-2-(2-methoxyethoxy)ethane

Specific details on test material used for the study
-Name of test material (as cited in study report): 1-Ethoxy-2-(2-methoxyethoxy)ethane
- Analytical purity: 100.0% (capillary-column GC)
- Storage condition of test material: sealed, light-shielded at room temperature (actual temperature: 17.0-24.6°C)
- Stability under test conditions: The stability of test material was identified by analysis of the remainder.

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
-S9 mix: 313, 625, 1250, 2500, 5000 µg/plate (All strains)
+S9 mix: 313, 625, 1250, 2500, 5000 µg/plate (All strains)

High dose level used
yes

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) (TA100, WP2uvrA, TA98), Sodium azide (SAZ) (TA1535) and 9-Aminoacridine (9 AA) (TA1537)
+S9 mix: 2-Aminoanthracene (2AA) (TA1535, WP2uvrA), Benzo[a]pyrene (B[a]P) (TA100, TA98, TA1537)

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: 2
NUMBER OF REPLICATIONS: 2
DETERMINATION OF CYTOTOXICITY
- Method: other: growth inhibition

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

Statistics
no

Results and discussion

Test results

Key result
true

Species / strain
S. typhimurium TA 1535
bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
no cytotoxicity nor precipitates, but tested up to recommended limit concentrations

Vehicle controls validity
valid

Untreated negative controls validity
not examined

True negative controls validity
not examined

Positive controls validity
valid

Key result
true

Species / strain
S. typhimurium TA 1537
bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
no cytotoxicity nor precipitates, but tested up to recommended limit concentrations

Vehicle controls validity
valid

Untreated negative controls validity
not examined

True negative controls validity
not examined

Positive controls validity
valid

Key result
true

Species / strain
S. typhimurium TA 98
bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
no cytotoxicity nor precipitates, but tested up to recommended limit concentrations

Vehicle controls validity
valid

Untreated negative controls validity
not examined

True negative controls validity
not examined

Positive controls validity
valid

Key result
true

Species / strain
S. typhimurium TA 100
bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
no cytotoxicity nor precipitates, but tested up to recommended limit concentrations

Vehicle controls validity
valid

Untreated negative controls validity
not examined

True negative controls validity
not examined

Positive controls validity
valid

Key result
true

Species / strain
E. coli WP2 uvr A
bacteria

Metabolic activation
with and without

Genotoxicity
negative

Cytotoxicity / choice of top concentrations
no cytotoxicity nor precipitates, but tested up to recommended limit concentrations

Vehicle controls validity
valid

Untreated negative controls validity
not examined

True negative controls validity
not examined

Positive controls validity
valid

Additional information on results
RANGE-FINDING/SCREENING STUDIES (if applicable):
Concentration: 1.50, 5.00, 15.0, 50.0, 150, 500, 1500, 5000 ug/plate with and without S9mix
Growth inhibitions: No growth inhibition was observed in any strains with or without metabolic acti vation.
Precipitation: No test substance-related precipitation was observed at any concentration with or witho ut metabolic activation.
Mutagenicity: No increase in the number of revertant colonies was observed in any strain with or without 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/PDF1002-67-1e.pdf

please also see the attached files (Tables in English)

Overall remarks, attachments

Attachments

Attached (sanitised) documents for publication
R5_1002-67-1_Ames Tables.xlsx / 22.247 KB (application/vnd.openxmlformats-officedocument.spreadsheetml.sheet)

Applicant's summary and conclusion

Conclusions
Interpretation of results (migrated information): negative
In a bacterial reverse mutation assay using Salmonella typhimurium TA100, TA1535, TA98, and TA 1537, and Escherichia coli WP2uvrA, 1-ethoxy-2-(2-methoxyethoxy)ethane was negative with or wit hout metabolic activation.

ENDPOINT_STUDY_RECORD: Genetic toxicity in vitro.002..

UUID:	388cdc26-0f26-4e24-84dc-12c0f81125a2
Dossier UUID:	
Author:	
Date:	2025-08-08T15:14:52.224+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
2013-08-27

End date
2014-03-11

Reliability
1 (reliable without restriction)

Rationale for reliability incl. deficiencies
guideline study
Reliability 1

Data source

Reference

In Vitro Chromosomal Aberration Test of 1-Ethoxy-2-(2-methoxyethoxy)ethane on Cultured Chinese Hamst / Ministry of Health, Labour and Welfare (MHLW), Japan / study report

Data access
data published

Materials and methods

Test guideline

Qualifier
according to guideline

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

Version / remarks
Simiral to OECD TG 473 (In Vitro Mammalian Chromosomal Aberration Test)

Deviations
no

GLP compliance
yes (incl. QA statement)

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

Test material

Test material information
1-Ethoxy-2-(2-methoxyethoxy)ethane

Specific details on test material used for the study
- Name of test material (as cited in study report): 1-Ethoxy-2-(2-methoxyethoxy)ethane
- Analytical purity: 100.0% (capillary-column GC)
- Storage condition of test material: sealed, light-shielded at room temperature (actual temperature: 17.0-24.6°C)
- Stability under test conditions: The stability of test material was identified by analysis of the remaind er.

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:
0.023, 0.047, 0.094, 0.19, 0.38, 0.75, 1.5 mg/mL
Main study:
-S9 (short-term treatment): 0.19, 0.38, 0.75, 1.5 mg/mL
+S9 (short-term treatment): 0.19, 0.38, 0.75, 1.5 mg/mL
-S9 (continuous treatment, 24hr): 0.19, 0.38, 0.75, 1.5 mg/mL

High dose level used
yes

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 hr,
- [continuous treatment]: 24 hrs
SPINDLE INHIBITOR: Colcemid
STAIN: Giemsa stain (3 v/v%) for 8 min.
NUMBER OF REPLICATIONS: 2
NUMBER OF CELLS EVALUATED:
- frequency of cells with structural chromosomal aberrations: 100 + 100 cells /concentration
- frequency of cells with numerical chromosome aberration: 400 + 400 cells /concentration

DETERMINATION OF CYTOTOXICITY
- Method: relative total growth

Evaluation criteria
The frequency of cells with structural chromosomal aberrations and polyploid cells was tested for si gnificance by Fisher's exact test (one-sided test, P<0.01) between the negative control and test sub stance treated groups. The results of these tests were used as a reference for a comprehensive evalu ation, taking into account biological considerations.

Statistics
Yes

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
no cytotoxicity nor precipitates, but tested up to recommended limit concentrations

Vehicle controls validity
valid

Untreated negative controls validity
not examined

True negative controls validity
not examined

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 1.5 mg/mL (10 mM)
Cell growth inhibition: No cell growth inhibition effect of 50% or more was observed under all treatment conditions.
Precipitation: No precipitation was observed in all treatments.

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/PDF1002-67-1f.pdf

Applicant's summary and conclusion

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

An in vitro chromosomal aberration test using CHL/IU cells (Similar to OECD TG 473) showed that 1-ethoxy-2-(2-methoxyethoxy)ethane was negative with or without metabolic activation.

Toxicity to reproduction

Toxicity to reproduction

ENDPOINT_STUDY_RECORD: Toxicity to reproduction.001.

UUID: cdeb42a5-d7bb-48e5-8570-7f13b629dc5b
Dossier UUID:
Author:
Date: 2024-02-20T11:53:09.000+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
2013-09-26

End date
2014-03-26

Reliability
1 (reliable without restriction)

Rationale for reliability incl. deficiencies
guideline study
Reliability 1

Cross-reference

Reason / purpose for cross-reference
reference to same study

Related information
OECD / Repeated dose toxicity: oral / Repeated dose toxicity: oral.001. / 1-Ethoxy-2-(2-methoxyethoxy)ethane / 1-ethoxy-2-(2-methoxyethoxy)ethane / 1002-67-1

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)

Version / remarks
similar to OECD TG422

GLP compliance
yes (incl. QA statement)

Limit test
no

Test material

Test material information
1-Ethoxy-2-(2-methoxyethoxy)ethane

Specific details on test material used for the study
- Name of test material (as cited in study report): 1-Ethoxy-2-(2-methoxyethoxy)ethane
- Analytical purity: 100.0% (capillary-column GC)
- Storage condition of test material: sealed, light-shielded at room temperature (actual temperature: 15.8-24.6°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)

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: 376.3-449.2 g, Female: 217.0-292.9 g
- Housing: Animals were individually housed in bracket-type metallic wire-mesh cages (220W × 270D×190H mm), from gestation day 18 to lactation day 4, Dams were bred individually or with individual
- littermates in plastic cages (350W × 400D × 180H mm) and bedding.
- Diet: Solid feed (CE-2: CLEA Japan Inc.) was given ad libitum.
- Water: Tap water was given ad libitum.
- Acclimation period: 15 days

ENVIRONMENTAL CONDITIONS
- Temperature (°C): 21.0-25.0 (actual temperature: 22.0-24.5°C)
- Humidity (%): 40.0-75.0% (actual humidity: 50.0-73.5%)
- Air changes (per hr): 15
- Photoperiod (hrs dark / hrs light): 12 hr dark/12 hr light (light: 7:00-19:00)

Administration / exposure

Route of administration
oral: gavage

Vehicle
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 test suspension used at day1 of administration were analyzed by HPLC. The results showed that the concentration of each test suspension was 98.5 to 100.0% of the n ominal concentration.

Duration of treatment / exposure
Males: 42 days including 14 days pre-mating
Females (mating group): 41-46 days including 14 days pre-mating, mating and gestation periods and the days until day 4 of lactation (non-mated females: 52 days including 14 days pre-mating, and non-parturient females: until equivalent day 25 of gestation)
Female (non-mating group: satellite 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.	
62.5	mg/kg bw/day (actual dose received)
Dose / conc.	
250	mg/kg bw/day (actual dose received)
Dose / conc.	
1000	mg/kg bw/day (actual dose received)

No. of animals per sex per dose
Mating group: 12 animals/sex /dose (0, 62.5, 250, and 1000 mg/kg bw/day)
Non-mating group (Satellite group): 10 females/dose (0 and 1000 mg/kg bw/day)

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

Control animals
yes, concurrent vehicle

Details on study design
- Dose selection rationale: Based on the results of a 14-day preliminary study, the highest dose was 1000 mg/kg, which is the amount limit, and the intermediate and low doses were divided by a common ratio of 4, to 250 and 62.5 mg/kg respectively.

[14-day preliminary study]
A 14-day repeated dose oral toxicity test (Crl:CD(SD) rats, males and females, doses: 0, 250, 500 or 1000 mg/kg bw/ day. The increased the liver weight and the decreased MCHC were observed in ma les at 500 mg/kg bw/day and above, decreased locomotor activity and HGB were observed in males and females at 1000 mg/kg bw/day, and decreased hematocrit and total protein were observed in m ales at 1000 mg/kg bw/day, but all of these changes were mild.

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

Examinations

Parental animals: Observations and examinations
CAGE SIDE OBSERVATIONS: Yes
- Time schedule: 2 or more times/day (before administration, after administration) during the administ ration period. At least once a day during the recovery period.

DETAILED CLINICAL OBSERVATIONS: Yes
- Time schedule:
Males: At the end of acclimation period, Days 8, 15, 24, 30, 36, and 42 of administration and Days 7 an d 14 of recovery period.
Females in the mating groups: At the end of acclimation period and Days 8, 15, 24, 30, 36, and 42* of administration period. (*Note: For delivered females, once during lactation period (lactation day 0 to day 4).)
Females in the non-mating groups (satellite group): At the end of acclimation period, Days 8, 15, 24, 30, 36, and 42 of administration and Days 7 and 14 of recovery period.

BODY WEIGHT: Yes
- Time schedule for examinations:
Males: Days 1, 4, 7, 14, 21, 28, 35, and 42 of administration period and on the day of necropsy, and Days 1, 7 and 14 of recovery period and on the day of necropsy.
Females in the mating groups: Days 1, 4, 7, and 14 of administration period, Days 0, 7, 14, and 20 of gestation, Days 0 and 4 of lactation, and on the day of necropsy. For unmated females, Days 21, 28, 35, 42 and 49 of administration period and on the day of necropsy.
Females in the non-mating groups (satellite group): Days 1, 4, 7, 14, 21, 28, 35, and 42 of administra tion period and on the day of necropsy, and Days 1, 7 and 14 of recovery period and on the day of ne cropsy.

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 1-2, 7-8, 14-15, 29-30, 35-36 and 41-42 of administration period. Days 6-7 and 12-13 of recovery period.
Females in the mating groups: Days 1-2, 7-8 and 14-15 of administration period. Days 0-1, 7-8, 14-15, and 20-21 of gestation period. Days 3-4 of lactation period. For unmated females, Days 29-30, 35-36, 41-42 and 48-49 of administration period.
Females in the non-mating groups (satellite group): Days 1-2, 7-8, 14-15, 21-22, 29-30, 35-36 and 41-42 of administration period. Days 6-7 and 12-13 of recovery period.

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: Pentobarbital sodium
- Animals fasted: Yes
- How many animals:
5 animals/sex/group
- Parameters examined: red blood cell count (RBC), white blood cell count (WBC), differential white blood cell count, reticulocyte ratio, hemoglobin (HGB), mean corpuscular volume (MCV), platelet c ount, hematocrit, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), activated partial thromboplastin time (APTT), prothrombin time (PT)

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: total protein, albumin, A/G ratio, glucose, total cholesterol, triglyceride, phospholipids, AST, ALT, γ-GTP, LDH, bile acid, blood urea nitrogen, creatinine, total bilirubin, ALP, inorganic phosphorus, calcium, sodium, potassium, chloride

BLOOD HORMONE: No

URINALYSIS: Yes
- Time schedule for collection of urine: On the final week of administration (Day 37 of administration) and on the final week of recovery (Day 13 of recovery) in males and females in the non-mating groups (satellite group).
- Metabolism cages used for collection of urine: Yes
- How many animals: 5 animals/group
- Parameters checked:
4-hour urine sample: color, turbidity, pH, occult blood, protein, glucose, ketone, urobilinogen, bilirubin, urinary sediments
24-hour urine sample: urine volume, specific gravity, sodium, potassium, chloride

NEUROBEHAVIOURAL (FUNCTIONAL) EXAMINATION: Yes
- Time schedule for examinations:
Males: On the final week of administration (Manipulative Test: Day 42, Measurement of Grip Strength and Motor Activity: Day 39). No examinations were performed during the recovery period.
Females in the mating group: On the final week of administration
Females in the non-mating groups (satellite group): On the final week of administration (Manipulative Test: Day 42, Measurement of Grip Strength and Motor Activity: Day 39). No examinations were performed during the recovery period.
- Dose groups that were examined: All dose groups (5 animals/sex/group) (excluding the 1000 mg/kg bw/day group of mating females)
- Battery of functions tested:
1) Manipulative Test. Prayer's reaction, pupillary reflex, visual placing, startle reaction, withdrawal ref lex, eyelid reflex, and righting reflex.
2) Measurement of Grip Strength. Grip strength of forelimb and hindlimb were measured by grip stren gth meter, Chatillon (Columbus Instruments, LLC).
3) Measurement of Motor Activity. Motor activity was measured by a motor activity sensor for experi mental animals, SUPER-MEX (Muromachi Kikai. Co., Ltd.). The measurement was conducted for 20 min.

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. The average days of recurrence of estrous cycle and the frequency of animals deviated the normal estrus cycle during treatment period were calculated for each group.

Sperm parameters (parental animals)
Parameters examined in all P male parental generations: organ weight of testis, epididymis, prostate (ventral) and seminal vesicles, histopathological examinations for testis, epididymis, prostate, se minal vesicle and 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 pentobarbital sodium anesthesia.

SACRIFICE:
- Males of mating groups and females of non-mating groups (satellite group):
On day 43 (next day after the last administration).
- Females of mating groups:
Delivered case: On day 5 of lactation period.
Undelivered case: On equivalent to day 26 of gestation period.
Unmated case: On day 53 (next day after the last administration).
Case where all the litters died: On the day all litters died.
- Males and females of recovery groups:
On day 15 of recovery period.
GROSS PATHOLOGY: Yes

ORGAN WEIGHT: Yes [brain, thyroid gland (including parathyroid gland), thymus, heart, liver, kidney, spleen, adrenal gland, testis, epididymis, prostate (ventral), seminal vesicles (including coagulating gland), ovary, uterus]
Note: The organ weights of the dams those all litters died, unmated females and non-delivered female s were excluded from the evaluation.

HISTOPATHOLOGY: Yes [brain, spinal cord, pituitary gland, eyeball (Harderian gland), submandibular gland, sublingual gland, trachea, thyroid gland, parathyroid gland, thymus, heart, lung, bronchus, liver, kidney, spleen, pancreas, adrenal gland, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, submandibular lymph node, mesenteric lymph node, testis, epididymis, prostate, seminal vesicle and coagulating gland, ovary, uterus, vagina, urinary bladder, femur and femur marrow, skeletal muscle, sciatic nerve, and gross abnormalities site]

Postmortem examinations (offspring)
SACRIFICE
- The F1 offsprings were euthanized on postnatal day 4 by exsanguination under sevoflurane anesthesia.

GROSS NECROPSY
- Gross necropsy consisted of external and internal examinations including the cervical, thoracic, and abdominal viscera.

HISTOPATHOLOGY / ORGAN WEIGTHS
- Not examined.

Statistics
Changes in estrous cyclicity, copulation index and fertility index were analyzed by Fisher's test (s ignificance level = 0.05).
Graded pathological data was analyzed by Mann-Whitney's U test and pathological data with number of positive and negative animals was analyzed by one-sided Fisher's test (significance level = 0.05).
In females, the tests were only performed on the animals necropsied on day 5 of lactation.
These data were analyzed using F-test for homogeneity of variance. The Student's t-test and t he Aspin-Welch's t-test were conducted for homogenous and non-homogenous distribution, res pectively to compare the control and individual treatment groups. Three or more groups setting, thes e data were analyzed using Bartlett's test for homogeneity of distribution. The Dunnett's multiple c omparison test after the ANOVA and the Dunnett's-type mean rank sum test after Kruskal-Wallis's H test were conducted for homogenous and non-homogenous distribution, respectively to compare the control and individual treatment groups. Significance level was set at 0.05 compared with the control group and among the groups.

Reproductive indices
Each parameter was determined by the following equations:
Copulation index (%) = (No. of copulated pares / No. of mated pares) × 100
Fertility index (%) = (No. of fertile males / No. of copulated pares) × 100
Delivery index (dams, %) = (No. of dams with live offspring / No. of pregnant dams) × 100
Implantation index (%) = (No. of implantation scars / No. of corpora lutea) × 100
Sex ratio = No. of male offspring / (No. of male offspring + No. of female offspring)
Delivery index (offspring) = (No. of offspring at birth/ No. of implantation scars) × 100
Birth index = (No. of live offspring at birth/No. of implantation scars) × 100
Live birth index = (No. of live offspring at birth/No. of offspring at birth) × 100

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

Results and discussion

Results: P0 (first parental generation)

General toxicity (P0)

Clinical signs
effects observed, treatment-related

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

Mortality
no mortality observed

Body weight and weight changes
effects observed, treatment-related

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

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

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

Food efficiency
not examined

Ophthalmological findings
not examined

Haematological findings
effects observed, treatment-related

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

Clinical biochemistry findings
effects observed, treatment-related

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

Endocrine findings
not examined

Urinalysis findings
effects observed, treatment-related

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

Behaviour (functional findings)
no effects observed

Immunological findings
not examined

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

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

Gross pathological findings
effects observed, treatment-related

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

Neuropathological findings
not examined

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

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

Histopathological findings: neoplastic
not examined

Reproductive function / performance (P0)

Reproductive function: oestrous cycle
effects observed, treatment-related

Description (incidence and severity)
At 1000 mg/kg bw/day, prolonged estrous cycle and increased frequency of abnormal estrous cycle were observed in females.

Reproductive function: sperm measures
no effects observed

Reproductive performance
effects observed, treatment-related

Description (incidence and severity)
At 1000 mg/kg bw/day, mating was confirmed in all pairs, but three were infertile. At 250 mg/kg bw/day, mating was not confirmed in one pair and one further case was infertility.
At 1000 mg/kg bw/day, significantly prolonged gestation length, decreased delivery index (dam) and implantation index were observed.

Details on results (P0)

General toxicity:
See 7.5.1 Repeated dose toxicity.001

Reproductive function / performance:
At 1000 mg/kg bw/day, prolonged estrous cycle and increased frequency of abnormal estrous cycle were observed in females.
At 1000 mg/kg bw/day, mating was confirmed in all pairs, but three were infertile. At 250 mg/kg bw/day, mating was not confirmed in one pair and one further case was infertility.
At 1000 mg/kg bw/day, significantly prolonged gestation length, decreased delivery index (dam) and implantation index were observed.

Effect levels (P0)

Key result
true

Dose descriptor
NOAEL

Effect level

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

Based on
test mat.

Sex
male/female

Basis for effect level
reproductive function (oestrous cycle)
Prolonged estrous cycle, increased frequency of abnormal estrous cycle, prolonged gestation length, decreased delivery index (dam) and implantation index were observed at 1000 mg/kg bw/day.

Key result
true

Dose descriptor
NOAEL

Effect level

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

Based on
test mat.

Sex
male

Basis for effect level
haematology
A significant decrease in reticulocyte ratio was observed at 250 mg/kg bw/day and above.
histopathology: non-neoplastic
Hypertrophy of centrilobular hepatocytes was observed at 250 mg/kg bw/day and above.

Key result
true

Dose descriptor
NOAEL

Effect level

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

Based on
test mat.

Sex
female

Basis for effect level
food consumption and compound intake
A significantly lower food consumption was observed on day 3 of lactation at 250 mg/kg bw/day.
Note: In mating females, food consumption data during lactation in the 1000 mg/kg bw/day group were not reported because all the litters died and the dams were sacrificed on day 1 of lactation.

Results: F1 generation

General toxicity (F1)

Clinical signs
effects observed, treatment-related

Description (incidence and severity)
At 1000 mg/kg bw/day, luck of nursing was observed on postnatal day 0 in one of the two litters and all the offsprings died on day 1 of lactation in both cases.

Mortality / viability
mortality observed, treatment-related

Description (incidence and severity)
At 1000 mg/kg bw/day, significantly decreased delivery index (offspring), number of offspring at bir th, number of live offspring at birth, birth index, and live birth index, and increased number of dead offspring were observed. The viability index on postnatal day 4 showed 0%.

Body weight and weight changes
no effects observed

Gross pathological findings
no effects observed

Effect levels (F1)

Key result
true

Dose descriptor
NOAEL

Generation
F1

Effect level

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

Based on
test mat.

Sex
not specified

Basis for effect level
mortality
Significantly decreased delivery index (offspring), number of offspring at birth, number of live off spring at birth, birth index, and live birth index, and increased number of dead offspring were obse rved at 1000 mg/kg bw/day.

Overall reproductive toxicity

Key result
false

Reproductive effects observed
no

Any other information on results incl. tables

Figures and Tables (in English) are available in the following full report of the study. https:// dra4.nihs.go.jp/mhlw_data/home/pdf/PDF1002-67-1d.pdf

Applicant's summary and conclusion

Conclusions
In the combined repeated oral dose toxicity study with the reproduction/developmental toxicity scree ning test described above, prolonged estrous cycle, prolonged gestation length, decreased delivery i ndex (dam), and decreased implantation index were observed at 1000 mg/kg bw/day. With regard to effects on pups, in the 1000 mg/kg bw/day, significantly decreased delivery index (offspring), number of offspring at birth, number of live offspring at birth, birth index, and live birth index, and increased number of dead offspring were observed at 1000 mg/kg bw/day.
Although not included in the reproductive/developmental toxic effects, treatment-related effects on male reproductive organs have been reported.
The NOAELs for the rat reproductive/developmental toxicity of 1-ethoxy-2-(2-methoxyethoxy)ethan we re regarded as 250 mg/kg bw/day for males and females, and pups.

References

Reference Substances

REFERENCE_SUBSTANCE: 1-ethoxy-2-(2-methoxyethoxy)ethane

UUID: ECB5-51a4559c-6ce8-4122-8a9a-36eb0f65680a
Dossier UUID:
Author:
Date: 2007-05-10T18:00:00.000+09:00
Remarks:

Reference substance name
1-ethoxy-2-(2-methoxyethoxy)ethane

IUPAC name
1-ethoxy-2-(2-methoxyethoxy)ethane

Inventory

Inventory number

Inventory name
1-ethoxy-2-(2-methoxyethoxy)ethane

Inventory
EC Inventory

Inventory number
213-690-5

CAS number
1002-67-1

Molecular formula
C7H16O3

Description

CAS number
1002-67-1

Synonyms

Synonyms

Identity
1-ethoxy-2-(2-methoxyethoxy)ethane

Identity
Ethane, 1-ethoxy-2-(2-methoxyethoxy)-

Molecular and structural information

Molecular formula
C7H16O3

Molecular weight

148.2001

SMILES notation
CCOCCOCCOC

InChI
InChI=1/C7H16O3/c1-3-9-6-7-10-5-4-8-2/h3-7H2,1-2H3

Structural formula

Related substances

Group / category information
USEPA Category: Ethylene Glycol Ethers;Neutral Organics

Test Materials

TEST_MATERIAL_INFORMATION: 1-Ethoxy-2-(2-methoxyethoxy)ethane

UUID:	697d34bb-1dc4-4875-bd71-a0fe96d35387
Dossier UUID:	
Author:	
Date:	2023-08-02T10:18:34.000+09:00
Remarks:	

Name
1-Ethoxy-2-(2-methoxyethoxy)ethane

Literatures

LITERATURE: Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 1-ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

UUID: 9bce2188-07f8-4f13-90d9-85d7d5edcda7
Dossier UUID:
Author:
Date: 2024-02-14T15:23:28.000+09:00
Remarks:

General information

Reference Type
study report

Title
Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 1-ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Year
2014

Bibliographic source
Japan Existing Chemical Data Base (JECDB)
https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF1002-67-1d.pdf

Testing facility
the Hatano Research Institute, Food and Drug Safety Center

Report date
2014-03-26

Report number
R-13-002

LITERATURE: In Vitro Chromosomal Aberration Test of 1-Ethoxy-2-(2-methoxyethoxy)ethane on Cultured Chinese Hamster Cells.

UUID: c5160761-eb99-4657-9952-141141ff8e80
Dossier UUID:
Author:
Date: 2024-02-09T14:14:28.000+09:00
Remarks:

General information

Reference Type
study report

Title
In Vitro Chromosomal Aberration Test of 1-Ethoxy-2-(2-methoxyethoxy)ethane on Cultured Chinese Hamster Cells.

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

Year
2014

Bibliographic source
Japan Existing Chemical Data Base (JECDB)
https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF1002-67-1f.pdf

Testing facility
the Hatano Research Institute, Food and Drug Safety Center

Report date
2014-03-11

Report number
G-13-018

LITERATURE: Reverse Mutation Test of 1-Ethoxy-2-(2-methoxyethoxy)ethane on Bacteria.

UUID: ce89875f-d95e-40fb-995a-7cce47feacc3
Dossier UUID:
Author:
Date: 2023-08-02T10:17:31.000+09:00
Remarks:

General information

Reference Type
study report

Title
Reverse Mutation Test of 1-Ethoxy-2-(2-methoxyethoxy)ethane on Bacteria.

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

Year
2014

Bibliographic source
Japan Existing Chemical Data Base (JECDB)
https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF1002-67-1e.pdf

Testing facility
the Hatano Research Institute, Food and Drug Safety Center

Report date
2014-03-11

Report number
M-13-038