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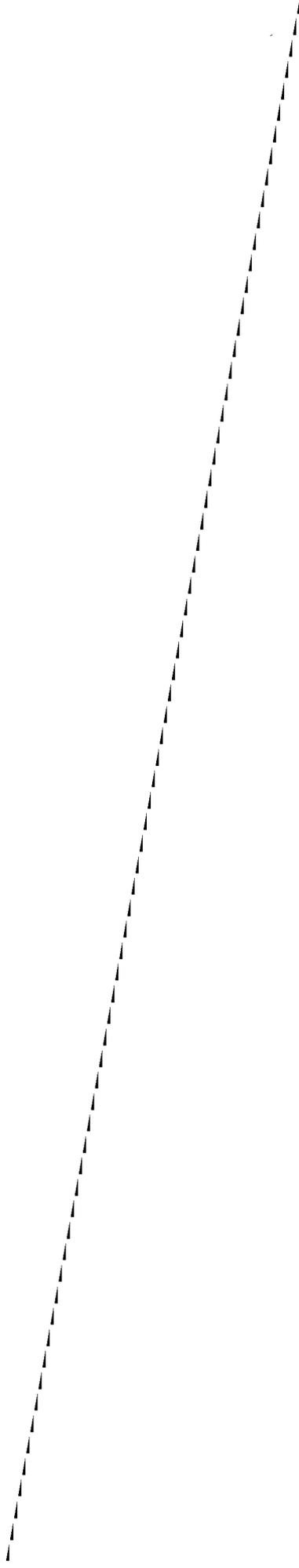
TSCA NON-CONFIDENTIAL BUSINESS INFORMATION

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19 August 2010

FYI EPA report.doc
page 1 (2)

For Your Information Submission

Substance: Tricyclodecanedimethanol (CAS No. 26160-83-8/26896-48-0)

Subject: Results of a combined 28-day repeated dose toxicity study with the reproduction/developmental toxicity screening test of Tricyclodecanedimethanol (TCD Alcohol DM ;CAS No. 26160-83-8/26896-48-0) in rats by oral gavage.

This submission does not contain confidential information.

OXEA GmbH is submitting results of combined 28-day repeated dose toxicity study with the reproduction/developmental toxicity screening test of TCD Alcohol DM (CAS No. 26160-83-8/26896-48-0) in rats by oral gavage, conducted by Notox B.V., 's-Hertogenbosch, Netherlands on behalf of OXEA GmbH, Oberhausen, Germany. The substance is primarily used as monomer.

The purpose of this study was to evaluate the potential toxic effects of the test substance when administered to rats for a minimum of 28 days and to evaluate the potential of the test substance to affect male and female reproductive performance such as gonadal function, mating behaviour, conception, parturition and early postnatal development according to the OECD guideline 422.

We have now received a preliminary robust study summary (see included), based on which the study does not meet TSCA 8(e) reporting requirements. We voluntarily submit the information for your information.

Experimental Results

TCD Alcohol DM was administered by daily oral gavage to male and female Wistar Han rats at dose levels of 150, 350 and 600 mg/kg/day. Males were exposed for 2 weeks prior to mating, during mating, and up to termination (for 28 days). The females were exposed for 2 weeks prior to mating, during mating, during post-coitum, and at least 4 days of lactation (for 42-53 days).

Formulation analysis showed that the formulations were prepared accurately and homogeneously, and were stable for at least 6 hours at room temperature.

Parental results

No toxicologically significant changes were noted in any of the parental parameters investigated in this study (i.e. clinical appearance, functional observations, body weights, food consumption, haematology and clinical biochemistry parameters, macroscopic examination, organ weights, and microscopic examination).

At 600 mg/kg/day, creatinine values were increased for animals of both sexes, and urea and total bilirubin levels were higher for females only.

Total bilirubin was also higher for females at 350 mg/kg/day, and glucose levels were dose-dependently reduced for males of all treatment groups.

These changes were generally slight in nature (i.e. within the normal range or slightly exceeding the range), and occurred in the absence of any corroborative morphological changes indicative of organ dysfunction. Therefore, the changes in clinical biochemistry parameters were not considered to be toxicologically relevant.

Reproductive/Developmental results

No reproductive/developmental toxicity was observed at any dose level.

Conclusion

In conclusion, treatment with TCD Alcohol DM by oral gavage in male and female Wistar Han rats at dose levels of 150, 350 and 600 mg/kg body weight/day revealed no parental toxicity up to 600 mg/kg body weight/day. No reproduction and developmental toxicity was observed for treatment up to 600 mg/kg body weight/day.

Based on these results, a parental, reproductive and developmental No Observed Adverse Effect Level (NOAEL) of 600 mg/kg/day was derived.

OXEA GmbH understands that reporting of the results from this study under FYI rather than TSCA 8(e) is in accordance with EPA's policy.

If you have any questions, please contact:

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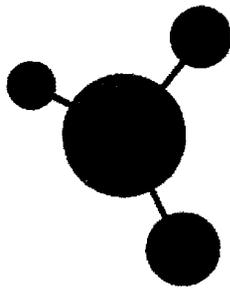
kind regards



(Dr. G. Becker)

Enclosure:

Robust Study Summary of Report NOTOX B.V., No. 491996 - F.M. van Otterdijk, Combined 28-day repeated dose toxicity study with the reproduction/developmental toxicity screening test of TCD Alcohol DM in rats by oral gavage.



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INTERNATIONAL UNIFORM CHEMICAL INFORMATION DATABASE

Printing Date 2010-08-17 12:28:47 CEST

Restriction of specific regulatory purposes

Confidentiality

Owner TCD ALCOHOL DM (TS 199737) / tricyclodecanedimethanol / tricyclo[2.2.2.2~1,4~]decane-2,5-diylidimethanol / 26896-48-0 / NOTOX B.V. / 's-Hertogenbosch / Netherlands

Legal entity owner NOTOX B.V. / 's-Hertogenbosch / Netherlands

Endpoint study record: Repeated dose toxicity: oral.NOTOX 491996

UUID IUC5-c27982d0-a67e-4fa6-90fe-e616d770f3a2
Dossier UUID 0
Author ZMA / NOTOX B.V. / 's-Hertogenbosch / Netherlands
Date 2010-08-17 12:19:13 CEST
Remarks

Administrative Data

Purpose flag key study; robust study summary
Study result type experimental result **Study period** 16 November 2009 - 08 January 2010
Reliability 1 (reliable without restriction)
Rationale for reliability incl. deficiencies This study has been performed according to OECD and/or EC guidelines and according to GLP principles.

Data source

Reference

Reference type	Author	Year	Title	Bibliographic source	Testing laboratory	Report no.	Owner company	Company study no.	Report date
study report	F.M. van Otterdijk, M.Sc.	2010	Combined 28-day repeated dose toxicity study with the reproduction/developmental toxicity screening test of TCD Alcohol DM in rats by oral gavage		NOTOX B.V., Hambakenwetering 7, 5231 DD, 's-Hertogenbosch, The Netherlands.	491996	OXEA Deutschland GmbH Otto-Roelen Strasse 3 46147 OBERHAUSEN Germany		2010-08-08

Materials and methods

Test type

combined repeated dose and reproduction / developmental screening

Limit test

no

Test guideline

Qualifier	Guideline	Deviations
according to	OECD Guideline 422 (Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test)	no
according to	other guideline: The United States Environmental Protection Agency (EPA) Health Effects Test Guidelines OPPTS 870.3650, Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test, July 2000.	no

GLP compliance

yes

Test materials

Identity of test material same as for substance defined in section 1 (if not read-across)

yes

Test material identity

Identifier	Identity
CAS number	26160-83-8
CAS number	26896-48-0

Details on test material

- Name of test material (as cited in study report): TCD Alcohol DM
 - Molecular formula (if other than submission substance): C12H20O2
 - Molecular weight (if other than submission substance): 196.28
 - Substance type. Clear colourless very viscous liquid
 - Physical state: liquid
 - Analytical purity. 99%
 - Lot/batch No. Tank 31
 - Expiration date of the lot/batch: 19 August 2010
 - Stability under test conditions Stable
 - Storage condition of test material. At room temperature in the dark
 - Other
- Alternative CAS: 26896-48-0
 Specific Gravity / Density ~1.107 g/cm3 (20°C)
 pH: Neutral

Confidential details on test material

none

Test animals**Species**

rat

Strain

other: CrI:WI(Han)

Sex

male/female

Details on test animals and environmental conditions**TEST ANIMALS**

- Source: Charles River Laboratones France, L'Arbresle Cedex, France

- Age at study initiation: Approximately 11 weeks.

At the start of treatment the animals were 11 weeks instead of 10 weeks old. A slight deviation in age does not affect the study integrity. Mating started shortly after the animals had attained full sexual maturity according to the OECD 422 guideline.

- Weight at study initiation: no data

- Fasting period before study: no

- Housing:

Pre-mating: Animals were housed in groups of 5 animals/sex/cage in Macrolon cages (MIV type, height 18 cm)

Mating: Females were caged together with males on a one-to-one-basis in Macrolon cages (MIII type, height 18 cm).

Post-mating: Males were housed in their home cage (Macrolon cages, MIV type, height 18 cm) with a maximum of 5 animals/cage. Females were individually housed in Macrolon cages (MIII type, height 18 cm).

Lactation: Pups were kept with the dam until termination in Macrolon cages (MIII type, height 18 cm).

General: Sterilised sawdust as bedding material (Litalabo, S.P.P S., Argenteuil, France) and paper as cage-enrichment (Enviro-dri, Wm. Lillico & Son (Wonham Mill Ltd), Surrey, United Kingdom) were supplied. Certificates of analysis were examined and then retained in the NOTOX archives. During activity monitoring, animals were housed individually in Macrolon cages (MIII type; height 15 cm) with sterilised sawdust as bedding material. No cage-enrichment was provided during activity monitoring.

Health check F0: A health inspection was performed prior to commencement of treatment to ensure that the animals were in a good state of health.

- Diet (e.g. ad libitum): ad libitum

- Water (e.g. ad libitum): ad libitum

- Acclimation period: At least 5 days prior to start of treatment.

ENVIRONMENTAL CONDITIONS

- Temperature (°C): 17.8 – 21.4°C

- Humidity (%): 32 - 94%

Temporary deviations from the minimum level of temperature and from the minimum and maximum level relative humidity occurred in the animal room. Laboratory historical data do not indicate an effect of the deviations

- Air changes (per hr): approximately 15 air changes per hour

- Photoperiod (hrs dark / hrs light): 12 hours artificial light and 12 hours darkness per day. Temporary fluctuations from the light/dark cycle (with a maximum of 1 hour) occurred due to performance of pupillary reflex tests in the room. Based on laboratory historical data, these fluctuations were considered not to have affected the study integrity.

IN-LIFE DATES: From: 16 November 2009 To: 08 January 2010

Administration / exposure**Route of administration**

oral: gavage

Vehicle

other: 20% (w/w) Ethylacetate (density 0.902 g/mL) in propylene glycol (density 1.036 g/mL)

Details on oral exposure**PREPARATION OF DOSING SOLUTIONS:**

Formulations (w/w) were prepared daily within 6 hours prior to dosing and were homogenised to a visually acceptable level. The test substance was suspended in ethylacetate to form a homogenous suspension. Subsequently, propylene glycol was added under constant stirring. Adjustment was made for the density of the vehicle (ethylacetate and propylene glycol) and for the test substance (1.107 g/cm³).

VEHICLE

- Justification for use and choice of vehicle (if other than water): Based on trial formulations performed at NOTOX

- Concentration in vehicle: 30, 70 and 120 mg/mL

- Dose volume: 5 mL/kg body weight. Actual dose volumes were calculated according to the latest body weight.

Analytical verification of doses or concentrations

yes

Details on analytical verification of doses or concentrations

Analyses were conducted during the treatment phase, according to a validated method (NOTOX project 491999). Samples of formulations were analyzed for homogeneity (highest and lowest concentration) and accuracy of preparation (all concentrations). Stability in vehicle over 6 hours at room temperature was also determined (highest and lowest concentration).

The accuracy of preparation was considered acceptable if the mean measured concentrations were 90-110% of the target concentration. Homogeneity was demonstrated if the coefficient of variation was ≤ 10%. Formulations were considered stable if the relative difference before and after storage was maximally 10%.

Results

The concentrations analysed in the formulations of Group 2, Group 3 and Group 4 were in agreement with target concentrations (i.e. mean accuracies between 90% and 110%).

The formulations of Group 2 and Group 4 were homogeneous (i.e. coefficient of variation $\leq 10\%$) and the entire range of formulations were stable when stored at room temperature for at least 6 hours

Duration of treatment / exposure

Males were exposed for 28 days, i.e. 2 weeks prior to mating, during mating, and up to termination. Females were exposed for 42-53 days, i.e. during 2 weeks prior to mating, during mating, during post-coitum, and during at least 4 days of lactation. Female no 60 (group 2) and no 78 (group 4) were not dosed during littering

Frequency of treatment

Once daily for 7 days per week, approximately the same time each day with a maximum of 6 hours difference between the earliest and latest dose. Animals were dosed up to the day prior to scheduled necropsy.

Doses/concentrations

0, 150, 350 and 600 mg/kg/day

No. of animals per sex per dose

10

Control animals

yes, concurrent vehicle

Details on study design

- Dose selection rationale: Dose levels were based on results of the dose range finding study (NOTOX Project 492082). See attachment in the result section of this file
- 5 animals/sex/group were randomly selected at allocation for functional observations, clinical pathology, macroscopic examination (full list), organ weights (full list) and histopathology.
- Males: the first 5 males per group
- Females: with live offspring only

Positive control

no

Examinations

Observations and examinations performed and frequency

CAGE SIDE OBSERVATIONS: Yes

- Time schedule: At least twice daily (early morning/late afternoon)

DETAILED CLINICAL OBSERVATIONS: Yes

- Time schedule: At least immediately after dosing, detailed clinical observations were made in all animals. Once prior to start of treatment and at weekly intervals this was also performed outside the home cage in a standard arena. Arena observations were not performed when the animals were mating, or housed individually

BODY WEIGHT: Yes

- Time schedule for examinations: Males and females were weighed on the first day of exposure and weekly thereafter. Mated females were weighed on Days 0, 4, 7, 11, 14, 17 and 20 post-coitum, and during lactation on Days 1 and 4
- For one female of Group 4 no body weight was determined during the post-coitum period as mating of this female was overlooked. Body weights were determined during the mating period and sufficient food consumption data was available to make a thorough assessment.

FOOD CONSUMPTION: Yes

- Weekly, for males and females. Food consumption was not recorded during the mating period. Food consumption of mated females was measured on Days 0, 4, 7, 11, 14, 17 and 20 post-coitum and on Days 1 and 4 of lactation.
- For one female of Group 4 no food consumption was determined during the post-coitum period as mating of this female was overlooked. Sufficient food consumption data is available to make a thorough assessment.

FOOD EFFICIENCY: Yes

- (food consumption per animal per day/ average body weight per cage)*1000

WATER CONSUMPTION AND COMPOUND INTAKE (if drinking water study): No

OPHTHALMOSCOPIC EXAMINATION: No

HAEMATOLOGY: Yes

- Time schedule for collection of blood: immediately prior to scheduled post mortem examination, between 7.00 and 10.30 a.m.
- Anaesthetic used for blood collection: Yes (iso-flurane)
- Animals fasted: Yes, but water was provided.
- How many animals: 5 animals/sex/group (females: with live offspring only).
- Parameters checked were: White blood cells, Differential leucocyte count (neutrophils, lymphocytes, monocytes, eosinophils, basophils), Red blood cells, Reticulocytes, Red blood cell distribution width, Haemoglobin, Haematocrit, Mean corpuscular volume, Mean corpuscular haemoglobin, Mean corpuscular haemoglobin concentration, Platelets, Prothrombin time, Activated Partial thromboplastin time.

CLINICAL CHEMISTRY: Yes

- Time schedule for collection of blood: immediately prior to scheduled post mortem examination, between 7.00 and 10.30 a.m.
- Animals fasted: Yes, but water was provided.
- How many animals: 5 animals/sex/group (females: with live offspring only).
- Parameters checked were: Alanine aminotransferase, Aspartate aminotransferase, Alkaline phosphatase, Total Protein, Albumin, Total Bilirubin, Urea, Creatinine, Glucose, Cholesterol, Sodium, Potassium, Chloride, Calcium, Inorganic Phosphate, Bile acids

URINALYSIS: No

NEUROBEHAVIOURAL EXAMINATION: Yes

- Time schedule for examinations: The selected males were tested during Week 4 of treatment and the selected females were tested during lactation (all before blood sampling)
- Dose groups that were examined: all
- Battery of functions tested: hearing ability, pupillary reflex, static righting reflex, grip strength and motor activity test.

Sacrifice and pathology

SACRIFICE

All animals were fasted overnight (with a maximum of approximately 22 hours) prior to planned necropsy, but water was provided. Animals surviving to scheduled necropsy were deeply anaesthetised using iso-flurane vapor (Abbott Laboratories Ltd., Hoofddorp, The Netherlands) and subsequently exsanguinated. Necropsy was conducted on the following days:

Females which delivered: Lactation Days 5-6.

Female which failed to deliver. Post-coitum Day 29 (female with evidence of mating)

Males: Following completion of the mating period (a minimum of 28 days of dose administration)

Female which died spontaneously: As soon as possible after death, within 24 hours.

Several males were necropsied later than after a maximum of 20 hours fasting, i.e. with a maximum of approximately 2 hours. The fasting period was only slightly longer and was not considered to have adversely affected the clinical laboratory, macroscopic or microscopic findings.

One female which failed to deliver was necropsied on Day 29 Post-coitum instead of between Days 25-27. Female was not pregnant. An extended treatment duration was not considered to have adversely affected overall interpretation of the study results

GROSS PATHOLOGY: Yes

All animals were subjected to macroscopic examination of the cranial, thoracic and abdominal tissues and organs, with special attention being paid to the reproductive organs. Descriptions of all macroscopic abnormalities were recorded. The number of former implantation sites and corpora lutea was recorded for all paired females.

Samples of the following tissues and organs were collected and fixed in 10% buffered formalin (neutral phosphate buffered 4% formaldehyde solution, Klinipath, Duiven, The Netherlands):

Selected 5 animals/sex/group and one Female of Group 2 that died spontaneously:

Identification marks: not processed, Ovaries, Adrenal glands, (Pancreas), (Aorta), Peyer's patches (jejunum, ileum) if detectable, Brain (cerebellum, mid-brain, cortex), Pituitary gland, Caecum, Preputial gland, Cervix, Prostate gland, Clitoral gland, Rectum, Colon, (Salivary glands - mandibular, sublingual), Duodenum, Sciatic nerve, Epididymides*, Seminal vesicles including coagulating gland, Eyes with optic nerve (if detectable) and Harderian gland*, Skeletal muscle, (Skin), Female mammary gland area, Spinal cord (cervical, midthoracic, lumbar), Femur including joint, Spleen, Heart, Sternum with bone marrow, Ileum, Stomach, Jejunum, Testes*, Kidneys, Thymus, (Larynx), Thyroid including parathyroid (if detectable), (Lacrimal gland, exorbital), (Tongue), Liver, Trachea, Lung, infused with formalin, Urinary bladder, Lymph nodes (mandibular, mesenteric), Uterus, (Nasopharynx), Vagina, (Oesophagus), All gross lesions.

All remaining animals and one Female of Group 3 which failed to deliver:

Cervix, Prostate gland, Clitoral gland, Seminal vesicles including coagulating gland, Epididymides*, Testes*, Ovaries, Uterus, Preputial gland, Vagina, Identification marks, not processed, All gross lesions.

*Fixed in modified Davidson's solution (prepared at NOTOX using Formaldehyde 37-40%, Ethanol, Acetic acid (glacial)(all Merck, Darmstadt, Germany) and Milli-Ro water (Millipore Corporation, Bedford, USA)) and transferred to formalin after fixation for at least 24 hours.

Tissues/organs mentioned in parentheses were not examined by the pathologist, since no signs of toxicity were noted at macroscopic examination

ORGAN WEIGHTS: Yes

The following organ weights and terminal body weight were recorded from the following animals on the scheduled day of necropsy:

Selected 5 animals/sex/group (females: with live offspring only). Adrenal glands, Spleen, Brain, Testes, Epididymides, Thymus, Heart, Uterus (including cervix), Kidneys, Prostate*, Liver, Seminal vesicles including coagulating glands*, Ovaries, Thyroid including parathyroid*. *weighed when fixed for at least 24 hours.

HISTOTECHNOLOGY: Yes

All organ and tissue samples, as defined under Histopathology (following), were processed, embedded and cut at a thickness of 2-4 micrometers and stained with haematoxylin and eosin (Klinipath, Duiven, The Netherlands).

Of the selected 5 males of the control and high dose group, additional slides of the testes were prepared to examine staging of spermatogenesis. The testes were processed, sectioned at 3-4 micrometers, and stained with PAS/haematoxylin (Klinipath, Duiven, The Netherlands).

HISTOPATHOLOGY: Yes

The following slides were examined by a pathologist.

-The preserved organs and tissues of the selected 5 animals/sex of Groups 1 and 4.

-The additional slides of the testes of the selected 5 males of Groups 1 and 4 to examine staging of spermatogenesis.

-The preserved organs and tissues of one Female of Group 2 that died spontaneously.

-All gross lesions of all animals (all dose groups).

-The reproductive organs* of all animals that failed to mate, conceive, sire or deliver healthy pups:

Group 2 One male and one female (female was found dead at littering)

Group 3 One male and one female (failed to conceive/sire)

All abnormalities were described and included in the report. An attempt was made to correlate gross observations with microscopic findings.

* Reproductive organs included the cervix, clitoral gland, coagulation gland, epididymides, ovaries, preputial gland, prostate gland, seminal vesicles, testis, uterus, and vagina.

Inadvertently, a few tissues were not available for histopathology. Reasons for missing a few tissues included that these tissues were not discernable at necropsy or trimming, or were erroneously not collected at necropsy. Missing tissues are listed in raw data and pathology report. Sufficient data was available for histopathological evaluation

Statistics

The following statistical methods were used to analyse the data.

-If the variables could be assumed to follow a normal distribution, the Dunnett-test (Dunnett, 1955) (many-to-one t-test) based on a pooled variance estimate was applied for the comparison of the treated groups and the control groups for each sex.

-The Steel-test (Miller, 1981) (many-to-one rank test) was applied if the data could not be assumed to follow a normal distribution.

-The Fisher Exact-test (Fisher, 1950) was applied to frequency data.

All tests were two-sided and in all cases $p < 0.05$ was accepted as the lowest level of significance.

Group means were calculated for continuous data and medians were calculated for discrete data (scores) in the summary tables. Test statistics were calculated on the basis of exact values for means and pooled variances. Individual values, means and standard deviations may have been rounded off before printing. Therefore, two groups may display the same printed means for a given parameter, yet display different test statistics values.

Any other information on materials and methods incl. tables

See attachment for summary of dose range finding study (NOTOX Project492082).

Results and discussions

Results of examinations

Clinical signs and mortality

no effects

Body weight and weight gain

no effects

Food consumption and compound intake (if feeding study)

no effects

Food efficiency

no effects

Water consumption and compound intake (if drinking water study)

not examined

Ophthalmoscopic examination

not examined

Haematology

no effects

Clinical chemistry

yes (The following (statistically significant) changes in clinical biochemistry parameters distinguished treated animals from control animals - Higher creatinine in males* and females at 600 mg/kg/day, - Higher total bilirubin in females at 350* and 600* mg/k)

Urinalysis

not examined

Neurobehaviour

no effects

Organ weights

no effects

Gross pathology

no effects

Histopathology: non-neoplastic

no effects

Histopathology: neoplastic

no effects

Details on results

CLINICAL SIGNS AND MORTALITY:

No mortality occurred during the study period that was considered to be related to treatment with the test substance.

One female at 150 mg/kg/day died during delivery. No cause of death could be determined for this animal. Since no further mortality occurred among this dose group or in the other dose groups, this death was considered to be unrelated to treatment.

No clinical signs indicative of treatment-related toxicity were noted during the observation period

Salivation observed among all animals at 350 and 600 mg/kg/day and at lower incidence at 150 mg/kg/day was considered to be a physiological response (eg. to taste of the formulation) rather than a sign of systemic toxicity, considering the nature and minor severity of the effect and its time of occurrence (i.e. after dosing).

Rales, and at lower incidence lethargy, shallow or laboured respiration, piloerection, uncoordinated movements and hunched posture were observed among the dose groups without a clear dose-related incidence. The occurrence of these signs was of an intermittent/transient nature (i.e. not related to the duration of treatment) and were therefore not considered to be toxicologically relevant

A single female at 350 mg/kg was noted with a swelling of the left and right axillary regions for a few days during the post-coitum and lactation periods. Upon macroscopic examination this animal was found with a hard, gray-white nodule in the subcutis of the axillary region which was determined to be an adenocarcinoma of the mammary gland at histopathological examination. This was not considered to be treatment-related.

Other incidental findings consisted of a wound, scabbing and alopecia of various body parts. The incidence of these findings occurred within the background range of findings encountered for rats of this age and strain, which are housed and treated under the conditions of this study. No toxicological relevance was therefore ascribed to these observations.

BODY WEIGHT AND WEIGHT GAIN:

No toxicologically relevant changes in body weights and body weight gain were noted.

The slightly lower mean body weights and body weight gain of males at 600 mg/kg/day during the pre-mating and mating period (achieving a level of statistical significance on several occasions) remained within the range considered normal for rats of this age and strain, and thus were not toxicologically relevant.

Other statistically significant changes in body weight (gain) occurred in the absence of a dose- and time-related trend, and were of a very slight nature. These changes consisted of a lower body weight of females at 350 mg/kg/day on Day 1 of lactation, and a higher body weight gain of females at 150 and 600 mg/kg/day on Day 4 of the Post-coitum phase. No toxicological relevance was ascribed to these changes.

One female at 350 mg/kg/day showed a notable weight loss on Day 7 of the Post-coitum phase as (14%). As the incidence of this finding was unrelated to the dose, this was considered to be without toxicological relevance.

FOOD CONSUMPTION.

No treatment-related changes in food consumption before or after allowance for body weight were noted.

The statistically significant higher absolute and relative food consumption of females at 600 mg/kg/day over Days 0-4 of the Post-coitum phase was slight in nature and was absent during the remainder of the Post-coitum and Lactation period. No toxicological relevance was ascribed to these changes.

Two females at 350 mg/kg/day showed a severely reduced food intake during the Post-coitum phase on Days 7-11 and 4-7 respectively. As these were incidental occurrences, no toxicological relevance was ascribed to these changes.

HAEMATOLOGY:

No toxicologically relevant changes occurred in haematological parameters of treated rats.

Any statistically significant changes in haematological parameters were considered to be of no toxicological relevance as these occurred in the absence of a dose-related trend and/or remained within the range considered normal for rats of this age and strain. These changes consisted of lower mean corpuscular haemoglobin concentrations (MCHC) for males at 150, 350 and 600 mg/kg/day, and higher reticulocyte counts and lower haemoglobin levels for females at 350 mg/kg/day.

Any notably high or low individual haematological values occurred in the absence of a dose-related incidence, and were considered to be of no toxicological relevance. These individual variations included higher relative neutrophil counts and lower lymphocyte counts in male no. 23 (Group 3) and female no. 53 (Group 2), and higher red cell distribution width (RDW) in male no. 35 (Group 4).

CLINICAL CHEMISTRY

The following (statistically significant) changes in clinical biochemistry parameters distinguished treated animals from control animals:

- Higher creatinine in males* and females at 600 mg/kg/day,
 - Higher total bilirubin in females at 350* and 600* mg/kg/day,
 - Higher urea in females at 600 mg/kg/day,
 - Lower glucose levels in males at 150, 350 and 600 mg/kg/day.
- * exceeding the range considered normal for rats of this age and strain.

The statistically significant higher sodium levels for males at 350 mg/kg and chloride levels for males at 150 and 600 mg/kg/day were considered to be of no toxicological relevance as they occurred in the absence of a treatment-related distribution and remained within the range considered normal for rats of this age and strain.

These changes were generally slight in nature (i.e. within the normal range or slightly exceeding the range), and occurred in the absence of any corroborative morphological changes indicative of organ dysfunction. Therefore, the changes in clinical biochemistry parameters were not considered to be toxicologically relevant.

NEUROBEHAVIOUR

Hearing ability, pupillary reflex, static righting reflex and grip strength were normal in all animals.

No toxicologically relevant changes in motor activity were observed.

Locomotor activity for females at 350 and 600 mg/kg/day appeared higher than controls. The higher counts for both the high and low sensors for these females were largely driven by one female in each of the two groups with notably high sensor counts (nos. 85 and 73, respectively). When the data were re-calculated excluding the sensor counts for these females, high sensor values were similar to control values, whilst low sensor values still appeared higher for females at 350 and 600 mg/kg/day, being statistically significant for females at 600 mg/kg/day. However, the means remained within the range considered normal for rats of this age and strain, and clinical signs did not support these variations. Therefore, no toxicological relevance was ascribed to these variations.

ORGAN WEIGHTS:

No toxicologically significant changes were noted in organ weights and organ to body weight ratios.

The statistically significant higher kidney to body weight ratio of males at 600 mg/kg/day was considered to be without toxicological relevance since the mean remained within the normal range for rats of this age and strain, no dose-related increase in absolute kidney weights was observed among male dose groups, and no histopathological correlates were found. The higher testes to body weight of males at 600 mg/kg/day occurred due to a lower terminal body weight since absolute weights were similar to control levels.

The statistically significant lower liver to body weight ratios of males and adrenal to body weight ratios of females at 150 mg/kg/day occurred in the absence of a dose-related trend, and were therefore considered to not be toxicologically relevant.

Other organ weights and organ to body weight ratios among the dose groups were similar to control levels.

GROSS PATHOLOGY.

Macroscopic observations at necropsy did not reveal any alterations that were considered to be toxicologically relevant.

One female at 350 mg/kg/day (no. 63), showed a gray-white hard nodule of the left axillary region subcutis. This finding corresponded to a swelling of the axillary region noted during the in-life phase, and to an adenocarcinoma of the mammary gland which was not considered to be treatment related.

The female that died spontaneously at 150 mg/kg/day (no. 51) was noted with yellowish contents of the gastro-intestinal tract, several reddish foci on the thymus, red discoloration of the mandibular lymph nodes, and cloudiness of both eyes. No relationship with treatment was established for these findings.

Incidental findings included alopecia and/or scabbing of various body parts, reddish foci on the lungs, stomach and/or thymus, reddish or red-brown discoloration of the liver, thymus, reddish discoloration of the mesenteric lymph node, irregular surface of the forestomach, a red-brown or tan focus on the clitoral gland, and accentuated lobular pattern of the liver. The incidence of these findings was within the background range of findings that are encountered among rats of this age and strain, did not show a dose-related incidence trend. These necropsy findings were

therefore considered to be of no toxicological significance.

No macroscopic abnormalities were noted among surviving females at 150 mg/kg/day

HISTOPATHOLOGY:

There were no treatment-related microscopic findings.

One female at 600 mg/kg (no. 73) had minimal forestomach inflammation, hyperplasia and hyperkeratosis and slight forestomach edema. In the absence of any other forestomach lesions in the animals at this dose level, and considering that this finding sometimes occurs in this type of study, it was not considered to be treatment-related.

One female at 350 mg/kg (no. 63) had a mammary gland adenocarcinoma which correlated to the gray-white nodule finding recorded upon macroscopic examination. Although mammary gland adenocarcinoma is a rare finding at this age, mammary gland lesions are one of the most commonly occurring natural neoplastic lesions in this rat strain. As such, this finding was regarded as not treatment-related.

All other microscopic findings recorded were considered to be within the normal range of background pathology encountered in Wistar-Han rats of this age and strain.

No abnormalities were seen in the reproductive organs of suspected non-fertile animals which could account for infertility and the assessment of the integrity of the spermatogenic cycle did not provide any evidence of impaired spermatogenesis.

Any other information on results incl. tables

none

Overall remarks, attachments

Overall remarks

See attachment for the results of the Dose range finding study (NOTOX Project 492082)

Attached background material

Attached document	Remarks
491996 Dose range finding study.pdf / 65.17 KB (application/pdf)	

Applicant's summary and conclusion

Conclusions

TCD Alcohol DM was administered by daily oral gavage to male and female Wistar Han rats at dose levels of 150, 350 and 600 mg/kg/day. Males were exposed for 2 weeks prior to mating, during mating, and up to termination (for 28 days). The females were exposed for 2 weeks prior to mating, during mating, during post-coitum, and at least 4 days of lactation (for 42-53 days).

Formulation analysis showed that the formulations were prepared accurately and homogeneously, and were stable for at least 6 hours at room temperature.

Parental results:

No toxicologically significant changes were noted in any of the parental parameters investigated in this study (i.e. clinical appearance, functional observations, body weights, food consumption, haematology and clinical biochemistry parameters, macroscopic examination, organ weights, and microscopic examination).

At 600 mg/kg/day, creatinine values were increased for animals of both sexes, and urea and total bilirubin levels were higher for females only. Total bilirubin was also higher for females at 350 mg/kg/day, and glucose levels were dose-dependently reduced for males of all treatment groups. These changes were generally slight in nature (i.e. within the normal range or slightly exceeding the range), and occurred in the absence of any corroborative morphological changes indicative of organ dysfunction. Therefore, the changes in clinical biochemistry parameters were not considered to be toxicologically relevant.

Reproductive/Developmental results:

No reproductive/developmental toxicity was observed at any dose level.

In conclusion, treatment with TCD Alcohol DM by oral gavage in male and female Wistar Han rats at dose levels of 150, 350 and 600 mg/kg body weight/day revealed no parental toxicity up to 600 mg/kg body weight/day. No reproduction and developmental toxicity was observed for treatment up to 600 mg/kg body weight/day.

Based on these results, a parental, reproductive and developmental No Observed Adverse Effect Level (NOAEL) of 600 mg/kg/day was derived.



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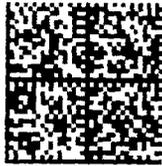
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