UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

009428

APR 15 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: ID. No. 001965, Vancide TH, 90 Day Dermal Study and Developmental Toxicity Study in Rats

Tox. Chem. No.: 481B
Project No.: 20309
Record No. : S406018

FROM: Melba S. Morrow, D.V.M. MSM 1/29/92
Review Section II, Toxicology Branch I
Health Effects Division (H7509C)

TO: John Lee, PM 31
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THRU: Joycelyn E. Stewart, Ph.D. 3/6/92 KB 3/9/92
Acting Section Head, Review Section II
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Health Effects Division (H7509C)

CONCLUSIONS:
We have reviewed the 90 day dermal toxicity and the developmental toxicity studies and have the following comments:

**82-3 90 Day Dermal Toxicity Study in Rats**

The study is classified as core guideline. When administered topically to male and female rats at doses of 10, 30 and 100 mg/kg/day, Vancide was associated with severe dermal irritation and slight decreases in body weight at the highest dose tested. The systemic NOEL was 30 mg/kg and the LOEL was 100 mg/kg. The dermal NOEL was less than 10 mg/kg based on gross observation of dermal irritation which was confirmed histologically by the prtesence of hyperplasia, hyperkeratosis, inflammation, sebaceous gland hyperplasia and eschar formation.

**83-3 Developmenta' Toxicity Study in Rats**

When Vancide TH wa administered to pregnant rats on gestation days 6-15 at doses of 0, 10, 75 and 150, the maternal LOEL was 150 mg/kg/day base on decreased weight gain. The maternal NOEL

was 75 mg/kg/day. The developmental NOEL was less than 10 mg/kg based on the observed significant positive trend in the pup and litter incidences of dilated renal pelvises and bilateral convoluted ureters. At the highest dose tested, there was a significant increase in the occurence of dilated renal pelvises ($p \leq 0.05$) and bilateral convoluted ureters ($p \leq 0.01$) when compared to controls.

The registrant did not provide any historical control data to which the results of this study could be compared. The registrant is requested to supply historical control information so that an adequate review of the data can be made. When the data are reviewed, the study may be upgraded to core minimum, and /or presented to the Developmental Peer Review Committee to determine its developmental toxicity potential.

This study is classified as core supplementary.

Copies of the DERs are attached for your reference.

**Reviewed by:** Melba S. Morrow, D.V.M. MSM 1/27/92
Section II, Tox. Branch I (H7509C)
**Secondary Reviewer:** Joycelyn E. Stewart, Ph.D. JES 1/27/92
Section II, Tox. Branch I (H7509C)



## DATA EVALUATION REPORT

**STUDY TYPE:** 90 Day Dermal Toxicity Study -Rats

**GUIDELINE #:** 82-3

**TOX. CHEM. #:** 418B

**MRID #:** 418583-01

**TEST MATERIAL:** Vancide TH

**SYNONYMS:** Hexahydro-1,3,5- triethyl-s-triazine

**STUDY NUMBERS:** 240810

**SPONSOR:** R.T. Vanderbilt Co.,Inc.
Norwalk, Connecticut

**TESTING FACILITY:** Exxon Biomedical Sciences, Inc.
East Millstone, N.J.

**TITLE OF REPORT:** 90 Day Subchronic Dermal Toxicity Study in Rats (Vancide TH)

**AUTHOR:** Gary W. Trimmer

**REPORT ISSUED:** April 19, 1991

**CONCLUSIONS:**

Under the conditions of the study, Vancide TH, when administered topically to male and female Crl:CDBR rats, at doses of 10, 30 and 100 mg/kg, caused severe dermal irritation in both sexes and slight decreases in body weight (7%) at the highest dose tested. The systemic NOEL was 30 mg/kg and the systemic LOEL was 100 mg/kg. The dermal NOEL was < 10 mg/kg based on the gross observation of dermal irritation which was confirmed histologically. Dermal irritation was characterized by hyperplasia, hyperkeratosis, inflammation, sebaceous gland hyperplasia and eschar formation.

CLASSIFICATION: Guideline
TOX. CATEGORY: N/A

**MATERIALS:**

Vancide TH, (hexahydro 1,3,5-triethyl-s-triazine) a colorless liquid with a purity of 96.6% was the test material. The lot number of the test material used in this study was M-TH-9K-318. The carrier vehicle was reverse osmosis water.

The test animals were Crl:CDBR (Sprague Dawley) rats. Fifty two males and 52 females were supplied by Charles River Laboratories. At the start of the study, males were approximately 7 weeks of age and weighed from 257.4 to 317.6 grams. Females were approximately 9 weeks of age and weighed from 193.6 to 243.3 grams.

**METHODS:**

After completing a 13 day acclimation period, animals were individually housed in environments which provided a 12 hour light/dark cycle. Room temperatures were maintained at 68 to 76° F and the relative humidity ranged from 40 to 70%. Water and food were provided ad libitum. Animals were randomly assigned to one of the following treatment groups:

| Group | Dose (mg/kg) | # Animals | |
|---|---|---|---|
| | | M | F |
| 1 | 0 | 13 | 13 |
| 2 | 10 | 13 | 13 |
| 3 | 30 | 13 | 13 |
| 4 | 100 | 13 | 13 |

In each group, three animals per sex per group were dosed for the first four weeks for the purpose of serving as replacement animals. These were sacrificed on day 29.

Twenty four hours prior to the initial topical application, an area from the shoulders to the lumbar region was clipped on each animal. This clipped area was divided into quadrants. For the remainder of the study, the hair was clipped from this area on Sundays. The test material was applied to approximately 10% of the body surface area in one of the prepared quadrants. Daily applications were rotated from quadrant to quadrant. After the material was applied with a gauze patch, the patch was wrapped with COBAN. Material was left in contact with the skin for 6 hours and afterward, the residual material was removed with a paper towel and was washed with reverse osmosis water. This procedure was repeated for 5 days a week for the next 13 weeks.

Animals were checked twice daily from Monday thru Friday for morbidity and mortality. On Saturdays, Sundays and holidays, these observations were made only once daily. Dermal irritation was observed and evaluated using the method described by Draize.

Body weights were recorded on day 0 of the study and on Mondays prior to the administration of the test material. Food consumption was recorded weekly and ophthalmoscopic examinations were conducted prior to the initiation of the study and one week prior to the termination of the study. Hematology and serum chemistry samples were collected on day 31 and at study termination.

The following checked parameters were evaluated (* indicates those parameters required under Subdivision F Guidelines):

x Hematocrit (HCT) *
x Hemoglobin (HGB) *
x Leukocyte count (WBC)*
x Erythrocyte count ( RBC)*
x Platelet count *
x Leukocyte differential*
Mean corpuscular hemaglobin
Mean corpuscular hemaglobin concentration
Mean corpuscular volume
Reticulocytes

Blood clotting measurements:
Thromboplastin time
Clotting time
Prothrombin time

Electrolytes:
x Calcium *
x Chloride *
Magnesium
x Phosphorus *
x Potassium *
x Sodium *

Enzymes:
Creatinine phosphokinase
x Alkaline phosphatase
Lactic dehydrogenase
x SGPT (ALT)
x SGOT (AST)
Gamma glutamyl transferase
Glutamate dehydrogenase
Cholinesterase

Other Serum Chemistry Values:
x Albumen
x Blood creatinine
x BUN
x Cholesterol
Globulin
x Glucose
x Total Bilirubin
x Total protein
Triglycerides
Serum protein electrophoresis

At the end of the study, animals were weighed, anesthetized with methoxyflurane and sacrificed by exsanguination. Animals were evaluated for gross pathological changes. Tissues and organs were collected from control and high dose animals and from those which died during the study. Lung, liver kidney and any gross lesions were also collected from low dose animals.

The following CHECKED (x) tissues were collected for histological examination. Weighed organs are designated by (xx)

| Digestive system | Cardiovasc./Hemat. | Neurologic |
|---|---|---|
| Tongue | x Aorta | xx Brain |
| x Salivary glands | xx Heart | x Periph. nerves |
| x Esophagus | x Bone marrow | x Spinal cord |
| x Stomach | x Lymph nodes | |
| x Duodenum | x Spleen | |
| x Jejunum | x Thymus | Glandular |
| x Ileum | | x Parathyroids |
| x Cecum | | x Adrenals |
| x Colon | Urogenital | x Thyroid |
| Rectum | xx Kidneys | xx Pituitary |
| | x Urinary bladder | x Mammary |
| xx Liver | xx Testes | |
| Gall bladder | x Epididymides | Other |
| x Pancreas | x Prostate | x Bone |
| | Seminal vesicle | x Skin |
| Respiratory | xx Ovaries | x Skel. muscle |
| x Trachea | x Uterus | x All gross lesions |
| xx Lung | Vagina | x Eyes |
| Nose | | |
| Pharynx | | |
| Larynx | | |

**STATISTICAL ANALYSIS:**

Mean body weight, mean weekly food consumption, serum chemistry parameters, hematology parameters, mean organ weights and organ: body weight ratios were subjected to a statistical analysis. Bartlett's test for equal variance was conducted at 1% level of significance. Other tests (ANOVA, Dunnett's, Kruskall-Wallis, Dunn's and Jonckheere's) were conducted at 1% and 5% levels of significance.

**QUALITY ASSURANCE:**

A Statement of Quality Assurance dated 4/16/91 were provided in the submission along with a statement of compliance with GLPs dated 4/17/91.

**RESULTS:**

Three females died during the study (1 control, 1 mid and 1 high dose). The death in the control animal was believed to be caused by renal and urinary bladder problems. This was confirmed upon gross and histologic examination of this animal. Mortalities reported in the mid and high dose groups were believed to be associated with dosing procedures.

On day 36 of the study, all high dose animals were sacrificed because of the severity of the dermal irritation. Dermal symptoms in these animals included erythema, eschar, desquamation, necrosis, exfoliation and ulceration.

Females in the high dose group were reported to have the most severe dermal lesions. In these animals, no healing was observed after the weekend periods when the test material was not administered. In animals in groups 2 and 3, some healing was present after the weekends. In group 2, slight erythema with eschar was observed. In group 3, severe erythema with eschar was observed. Exfoliation, necrosis, desquamation and ulceration were reported in the mid dose (group 3) animals. In the control group, irritation was minimal. These animals had only a few observations of slight erythema during the 13 weeks.

Body Weight:

A dose related decrease in mean body weight was reported in males. A statistically significant decrease (7%) in body weight was reported for males in the high dose group when compared to controls. Although there was no statistical significance in mean body weights in the low and mid dose groups, there appeared to be a linear response to the dose of Vancide when these groups were compared to controls.

No differences in mean body weights were reported for females in any of the treated groups when compared to controls. (See Table I).

Food Consumption

In the mid and high dose males, mean weekly food consumption was statistically lower than controls on day 14. This was the only reported difference in food consumption reported for males. In females, a statistical significance was reported for animals in the mid and high dose groups on day 35; however, the significance was the result of an increase in food consumption reported for these animals.

Hematology and Serum Chemistry

Statistically significant differences were reported in the interim evaluation in both sexes of animals in the high dose group for hemoglobin and hematocrit. Red blood cell counts were also lower in the high dose group when compared to controls and platelet counts were higher. In high dose females, white blood cell counts were also higher than controls during the interim evaluation. At the end of the study, no significant differences were reported for any of the hematology parameters.

In all treated males, albumen, calcium, total protein, sodium and chloride values were statistically lower than controls at the interim evaluation. Phosphorus values were statistically decreased in group 3 males. Potassium, AST and ALT values were lower than controls in group 4 animals.

In females, significant differences reported for albumen, BUN calcium, glucose, total protein, sodium, chloride and potassium during the interim. Most of these values were higher than controls with the exception of albumen and total protein in high dose animals.

Terminal serum chemistry values revealed lower albumen, sodium, calcium and total protein values in group 2 and 3 males. Group 2 males also had lower chloride and potassium levels when compared to controls. In females in group 3, phosphorus was increased and bilirubin and cholesterol were decreased when compared to controls. In group 2 females, decreases in total protein and cholesterol were reported. (See Table II for hematology and serum chemistry values).

Gross/ Histopathology

No significant differences were reported for organ weights. Relative increases were reported for liver and lung weights in females without statistical significance when compared to controls.

Histologically, there were no treatment related lesions reported with the exception of those reported for the skin. In the skin, there was an increased incidence in hyperplasia and hyperkeratosis of the epidermis of the skin in both sexes. Sebaceous gland hyperplasia and dermal inflammatory cell infiltrations were also increased. Other lesions included eschar formation, focal dermal fibrosis, focal epidermal necrosis and focal sebaceous gland necrosis.

**DISCUSSION:**

Based on the results of this study the dermal NOEL was < 10 mg/kg. At the lowest dose tested there was dermal irritation and histological dermal lesions characterized by hyperplasia, hyperkeratosis, inflammation, sebaceous gland hyperplasia and eschar formation.

Observations made with regard to serum chemistry and hematology values in both sexes appear to be incidental findings that are not biologically significant. No significant differences were reported for the hematology values at the end of the study and the serum chemistry values that were statistically significant at both the interim and terminal evaluations, were within the range of normal values.

The systemic NOEL was 30 mg/kg and the systemic LOEL was 100 mg/kg based on severe dermal irritation in both sexes and decreased body weight reported in high dose males. At the highest dose tested , both sexes of animals had to be sacrificed on day 36 due to the severity of the dermal lesions.

This study satisfies the guideline (82-3) requirements for a 90 day dermal toxicity study.

TABLE I
MEAN BODY WEIGHT (g)

| Males Day | Dose Level (mg/kg) 0 | 10 | 30 | 100 |
|---|---|---|---|---|
| 0 | 273.9 | 273.8 | 276.3 | 271.4 |
| 7 | 312.7 | 314.9 | 314.3 | 303.5 |
| 14 | 347.9 | 354.6 | 336.9 | 325.1* |
| 21 | 376.9 | 380.8 | 368.2 | 350.5* |
| 28 | 402.5 | 408.6 | 390.7 | 374.7* |
| 35 | 410.4 | 419.3 | 402.9 | 383.6* |
| 42 | 430.6 | 443.2 | 416.4 | a |
| 63 | 418.8 | 499.1 | 456.7 | |
| 84 | 511.9 | 524.5 | 490.1 | |
| 91 | 514.0 | 532.9 | 497.6 | |

| Females Day | Dose Level (mg/kg) 0 | 10 | 30 | 100 |
|---|---|---|---|---|
| 0 | 217.8 | 216.6 | 215.7 | 218.7 |
| 7 | 227.1 | 225.7 | 226.2 | 233.7 |
| 14 | 241.6 | 240.9 | 231.9 | 245.7 |
| 21 | 245.8 | 256.9 | 243.3 | 255.8 |
| 28 | 257.2 | 260.8 | 250.7 | 262.5 |
| 35 | 262.1 | 256.7 | 263.6 | 268.9 |
| 42 | 265.1 | 268.7 | 268.9 | a |
| 63 | 288.0 | 281.1 | 287.3 | |
| 84 | 295.0 | 295.2 | 297.6 | |
| 91 | 294.3 | 291.3 | 295.9 | |

Data extracted from Table II of report.
* = $p \leq 0.05$
a = animals in the high dose group were sacrificed on day 35.

TABLE II
INTERIM HEMATOLOGY and SERUM CHEMISTRY PARAMETERS

**Hematology**

**Males**

| Dose group (mg/kg) | Parameters HCT | HGB | RBC | WBC | platelets |
|---|---|---|---|---|---|
| 0 | 50.3 | 16.8 | 7.9 | 11.6 | 1100 |
| 100 | 47.1* | 15.7** | 7.53* | 12.5 | 1463 |
| **Females** | | | | | |
| 0 | 48.4 | 15.7 | 7.51 | 7.9 | 1373 |
| 100 | 44.8** | 14.4** | 6.90* | 12.2** | 1454 |

**Serum Chemistry**

**Males**

| Parameter | Dose Group (mg/kg) 0 | 10 | 30 | 100 |
|---|---|---|---|---|
| Albumen | 4.2 | 3.9** | 4.0* | 3.7** |
| Calcium | 10.4 | 9.9** | 9.9** | 9.5** |
| ALT | 61.9 | 57.4 | 51.8 | 46.8** |
| AST | 164.3 | 156.8 | 148.3 | 130.2** |
| T protein | 7.6 | 7.0** | 7.0** | 6.8** |
| Sodium | 154.8 | 148.6** | 147.5** | 147.2** |
| Chloride | 113.1 | 107.9** | 108.0** | 108.1** |
| Potassium | 4.9 | 4.5 | 4.5 | 4.4* |

Data for this table taken from Table 4 of submission
* = $p \leq 0.05$; ** = $p \leq 0.01$

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Primary Review by: Melba S. Morrow, D.V.M. MSM 2/24/92
Review Section II, TBI

Secondary Review by: Joycelyn E. Stewart, Ph.D. JES 4/24/92
Section Head, Review Section II, Toxicology Branch I/HED

DATA EVALUATION RECORD

Study Type: Teratology - Developmental Toxicity
Species: Rats
Guideline: 83-3

EPA Identification No.s: EPA MRID (Accession) No.: 41865701
EPA ID No.: 009165
EPA Record No.: S406018
Caswell No.: 418B
HED Project No.: 2-0309

Test Material: MRD89-408

Synonyms: Vancide TH

Sponsor: R.T. Vanderbilt
Norwalk, Connecticut

Study Number(s): 240834

Testing Facility: Exxon Biomedical Sciences
East Millstone, N.J.

Title of Report: Developmental Toxicity Study in Rats with Vancide TH

Author(s): Bruce K. Beyer

Report Issued: April 26, 1991

Conclusions: Under the conditions of the study, Vancide TH, when administered to pregnant female rats at doses of 0, 10, 75 and 150 mg/kg from gestation days 6-15, caused decreased weight gain at the highest dose tested. The NOEL for maternal toxicity was 75 mg/kg/day.

The NOEL for developmental toxicity was less than 10 mg/kg based on statistically significant increases in the incidences of bilateral convoluted ureters ($p \leq 0.01$) and dilated renal pelvises ($p \leq 0.05$), both of which were accompanied by a significant positive trend.

Core Classification: Supplementary. No historical control data were supplied by the investigators and this would be needed to determine whether there is an association with the administration



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of the test material and the occurence of renal abnormalities. In addition, a developmental NOEL was not obtained in this study.

Materials

Test Compound: Vancide TH
Purity: 96.6%
Description: Colorless liquid
Lot No.: Not provided (batch # 2)

Vehicle(s): Reverse osmosis water

Test Animal(s): Species:Rats
Strain: Crl:CDBR (Sprague Dawley)
Source: Charles River Labs
Age: Approx. 60 days at mating
Weight: Females 181-258 g

Study Design

This study was designed to assess the developmental toxicity potential of Vancide TH when administered by gavage to pregnanat female rats on gestation days 6 through 15, inclusive.

Mating

Animals were mated on a 1 male to 1 female ratio. Pairs were housed together and when mating was confirmed by either the presence of a copulatory plug or by the presence of sperm in the vagina females were removed. Assignment to treatment groups was done in the order of mating.

Group Arrangement:

| Test Group | Dose Level (mg/kg) | Number Assigned |
|---|---|---|
| Control | 0 | 25 |
| Low Dose | 10 | 25 |
| Mid Dose | 75 | 25 |
| High Dose | 150 | 25 |

Dosing:

All doses were in a volume of 5 ml/kg of body weight/day prepared during the dosing period. The dosing solutions were analyzed for concentration and stability. Dosing was based on most recent body weight.

Stability and Concentration

Samples of Vancide TH in reverse osmosis water were analysed by HPLC for verification of concentration and stability. Stability analysis was performed on the test material at concentrations of 0.2% and 3.0% . Duplicate samples were analyzed and mean values were reported.

Analysis for concentration was conducted weekly. Duplicate samples were also collected and mean values were reported. Concentration analysis was performed on samples taken from test groups in this developmental study.

Observations

The animals were checked for mortality or abnormal condition twice daily during the treatment period. Food consumption and body weights were recorded prior to selection and on day 0, 6, 9, 12, 15, 18 and 21 of gestation. Observations for clinical signs of toxicity were conducted daily. Dams were sacrificed on day 21 of gestation by carbon dioxide asphyxiation.

At sacrifice, uterine weights (with ovaries) were recorded. Uterine contents were examined and the number of implants, live and dead fetuses, malformed fetuses, corpora lutea, and late and early resorptions were recorded. Uteri of non-pregnant rats were stained with ammonium sulfate to determine pregnancy status. All abnormal tissues were saved in 10% neutral buffered formalin for possible histological evaluation.

Live fetuses were euthanized by sodium pentobarbital injection. All fetuses were weighed and examined for gross abnormalities and the sex was determined. Half of the fetuses in each treatment group were decapitated and preserved in Bouin's solution. The heads from these animals were checked for abnormalities and the viscera was examined by dissection. The remaining half of the fetuses were eviscerated and the skeletons were stained with Alizarin red in order to determine the presence of skeletal malformations and variations.

Historical data were not provided to allow for comparison with concurrent controls.

Statistical analysis

Data were statistically analysed using Cochran's transformation followed by arc, sine transformation. Bartlett's test for homogeneity of variance was applied with a level of significance of 1 or 5%. ANOVA was used to analyze variances and if significant, Dunnett's test was applied. Linear regression was

conducted to determine if there was a dose response. If variances were not equal, Kruskall- Wallis test was performed. Jonkheere's test was performed for ordered response and rank- sum comparison was conducted to determine which test groups differed from controls. Chi square, 2 X 2 Fisher's exact and Armitage test for linear trend were also conducted.

Compliance

A signed Statement of Confidentiality Claim was provided.

A signed Statement of compliance with EPA GLP's was provided.

A signed Quality Assurance Statement was provided. (Dated 4/26/91)

Results

Maternal Toxicity

Mortality

Deaths were reported in controls (1/25), mid (2/25) and high (6/25) dose groups. The deaths in all of these animals were believed to be associated with the incorrect gavaging technique.

Clinical Observations

The incidence of moist rales was higher in the mid and high dose groups when compared to controls. Dry rales was also reported in several animals in the high dose group with the first observation being made on day 9 of the study. These observations were made both during the treatment period and during the period when Vancide was not being administered; therefore, rales was not considered to be compound related.

Body Weight

The high dose group gained significantly less (39%) than controls during the treatment period. Lower body weights were also reported for the mid dose group for the entire gestation period; however these values were not statistically significant.

The investigators supplied the following data:

Table I: Body Weight Gains (grams)[a]

| Group: | Prior to Dosing Period | Dosing Period | Post Dosing Period | Entire Gestation Period | Corrected Body Weight Gains Dosing P.[1] | Entire[2] |
|---|---|---|---|---|---|---|
| Control | 36.0 | 46.7 | 100.3 | 183.0 | -63.1 | 73.2 |
| LDT | 35.8 | 49.6 | 98.2 | 183.6 | -55.6 | 78.4 |
| MDT | 37.4 | 47.3 | 92.3 | 177.6 | -65.7 | 64.0 |
| HDT | 33.8 | 28.9** | 98.6 | 161.3 | -79.8 | 52.6* |

[1] = corrected body weight gain for dosing period = body weight gain for dosing period minus gravid uterus weight.
[2] = corrected body weight gain for entire gestation period = body weight gain for entire gestation period minus gravid uterus weight.
a = Data extracted from Table 3, page 33.
* = $p \leq 0.05$
** = $p \leq 0.01$

Food Consumption

Food consumption was higher for the low and mid dose groups during the dosing period and for the low dose group during the post dosing interval. This translated into higher food consumption for these two groups for the entire gestation period. Slightly lower food consumption was reported for the high dose animals throughout the study; however, this finding was not considered statistically significant.

The investigators supplied the following data:

Table II: Food Consumption Data (grams)[a]

| Group: | Prior to Dosing Period | Dosing Period | Post-Dosing Period | Entire Gestation Period |
|---|---|---|---|---|
| Control | 145.8 | 221.0 | 173.4 | 538.7 |
| LDT | 145.4 | 231.8 | 207.1 | 584.3 |
| MDT | 151.1 | 241.0* | 167.0 | 559.1 |
| HDT | 138.1 | 204.6 | 158.0 | 500.7 |

[a] = Data extracted from Table 4
* = $p \leq 0.05$

Stability and Concentration

Stability of the test material in reverse osmosis water was confirmed for up to 8 days. Approximately 94% of the nominal concentration was recovered when the test material was refrigerated for the 8 day period. The concentration of Vancide TH was within 10% of the nominal concentration , with the exception of one sample in the low dose group. During the third week of analysis, the concentration was less than 88% of the nominal concentration; however, on the following week, the concentration in this same dose group was 97% of the targeted concentration.

Gross Pathological Observations

No treatment related lesions were present in maternal animals at sacrifice. Most animals had no abnormalities, while lesions observed in the cervical lymph nodes, lung, liver, kidney, skin and fur were reported as either single observances or at incidences that would not suggest an association with the compound.

In the high dose animals, fluid was present in the thoracic cavity (4/25). A tear was observed in the esophagus of 5/25 animals in this group and was probably related to incorrect gavaging techniques.

Cesarean section Observations

Post implantation loss was higher in treated groups when compared to controls; however, only the low dose group had a statistically significant value. This was believed to be an incidental finding because statistical significance was not present at the two higher dose group.

Table III: Cesarean Section observations[a]

| Dose | 0 | 10 | 75 | 150 |
|---|---|---|---|---|
| #Animals Assigned | 25 | 25 | 25 | 25 |
| #Animals Mated/Inseminated[b] | 25 | 25 | 25 | 25 |
| Pregnancy Rate (%) | 100 | 100 | 100 | 100 |
| Maternal Wastage | | | | |
| #Died | 1 | 0 | 1 | 6 |
| Total Corpora Lutea | 427.0 | 426.0 | 430.0 | 355.00 |
| Corpora Lutea/dam | 17.8 | 17.0 | 18.7 | 18.68 |
| Total Implantation | 397.0 | 393.0 | 399.0 | 324.0 |
| Implantations/Dam | 15.9 | 15.7 | 17.3 | 17.0 |
| Total Live Fetuses | 388.0 | 364.00 | 384.0 | 304.0 |
| Live Fetuses/Dam | 15.5 | 14.56 | 16.7 | 16.0 |
| Total Resorptions | 9.00 | 29.00 | 15.00 | 20.00 |
| Resorptions/Dam | .38 | 1.16 | .65 | 1.05 |
| Total Dead Fetuses | | | | |
| Dead Fetuses/Dam | 0 | 0 | 0 | 0 |
| Mean Fetal Weight (gm) | 5.2 | 5.33 | 5.03 | 4.98 |
| Preimplantation Loss(%) | 10.7 | 8.80 | 6.60 | 8.20 |
| Postimplantation Loss(%) | 2.2 | 6.9* | 3.80 | 6.10 |
| Sex Ratio (% Male) | 47.7 | 48.0 | 46.30 | 48.10 |

[a] = Data extracted from Table 6 and 7 and Appendix E.

b = animals dying prior to completion of the study were not included in the C section data. C-section data are based on 24, 25, 24 and 19 animals for groups 1, 2, 3 and 4, respectively.

* = $p \leq 0.05$

2. Developmental Toxicity

No differences were reported for fetal body weights when treated animals were compared to controls. External variations were reported which included protruding tongue, swollen hind paws with hematoma, and stunted fetuses. There was no statistical difference in treated groups for these observations.

Malformations were observed in control, low and mid dose groups and included exencephaly, micrognathia, omphalocele and thread like tail. No malformations were reported in the high dose group.

An increase in the occurence on hypoplastic sternebrae was reported for animals in the low and mid dose groups. There was a statistically significant increase in both the fetal and litter incidence of this anomaly. The fetal incidence of unossified sternebrae was statistically increased in the mid dose group when compared to controls. This was probably an incidental finding since ther was no similar observation at the highest dose tested.

Visceral variations were reported for all four groups. The most commonly observed variation involved the kidney and included dilated renal pelvises and convoluted and /or distended ureters. There was a statistically significant increase in this observation in the high dose pups and a treatment related trend was observed for the occurence of dilated renal pelvises and for bilateral convoluted ureters.

## Table IV: External Examinations

| Observations | Dose Group 0 | 10 | 75 | 150 |
|---|---|---|---|---|
| #pups(litters) examined | 373(24) | 364(25) | 384(23) | 304(19) |
| #pups(litters) affected | 0(0) | 1(1) | 2(2) | 0(0) |
| hematoma | 0 | 0 | 1 | 0 |
| Stunted growth | 0 | 1 | 0 | 0 |
| protruding tongue | 0 | 0 | 1 | 0 |

## Visceral Examinations

| Observations | 0 | 10 | 75 | 150 |
|---|---|---|---|---|
| #pups(litters) examined | 186(24) | 182(25) | 193(23) | 152(19)* |
| #pups(litters) affected | 28(11) | 35(15) | 31(14) | 40(14) |
| Individual Observations: | | | | |
| Dilated renal pelvis[t] | 6(4) | 10(6) | 13(8) | 17(10)* |
| Bilateral convoluted ureter [t] | 8(4) | 9(6) | 17(8) | 21(9)** |
| Bilateral distended ureter | 5(3) | 10(6) | 9(5) | 13(7) |

## Skeletal Examinations

| Observations | Control | Low Dose | Mid Dose | High Dose |
|---|---|---|---|---|
| #pups(litters) examined | 197(24) | 182(25) | 192(23) | 152(19) |
| #pups(litters) affected | 74(19) | 77(21) | 98(22) | 53(15) |
| Individual Observation | | | | |
| Hypoplastic Hyoid | 33(13) | 19(8) | 14(5) | 8(3) |
| Hypoplastic Sternebrae | 8(5) | 22(10)* | 51(17)** | 15(9) |
| Unossified Sternebrae | 6(3) | 9(4) | 18(5)* | 3(2) |

t = trend indicated, Armitage test.
* = $p \leq 0.05$
** = $p \leq 0.01$
Data extracted from Table 8.

Discussion/Conclusions

Based on the results of this study, when Vancide TH was administered orally on gestation days 6 -15, the maternal NOEL was 75 mg/kg and the maternal LOEL was 150 mg/kg based on decreased body weight gain. The developmental NOEL was less than 10 mg/kg based on the observed significant positive trend in the incidence of bilateral convoluted ureters and dilated renal pelvises.

The study is classified as core supplemetary. Historical control data should be provided to determine whether the renal observations in the pups are related to the administration of the test material. Once the data are received, the study may be upgraded to core minimum and /or presented to the Developmental Peer Review Committee.