8-5-91

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

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Developmental Toxicity Study of Ordram® in the Rabbit

TO: Ernie Dobbins PM 52
SRRD (H7508C)

FROM: Karen E. Whitby, Ph.D.
Section, II
Toxicology Branch II/(HED) (H7509C)

THRU: K. Clark Swentzel 8/5/91
Section Head
Toxicology Branch II/(HED) (H7509C)

and

Marcia van Gemert, Ph.D. 8/5/91
Chief, Toxicology Branch II/(HED) (H7509C)

HED Project No. 1-1888 Caswell No. 444

The Data Evaluation Report for the subject developmental toxicity study is attached.

Action Requested

Review the rabbit teratology study 83-3(b) for Ordram®.

Study Title and Conclusion

A Teratology Study in New Zealand White Rabbits with Ordram®

EPA TRID (Accession) No. 4700-210-15

Ordram® was administered in corn oil to presumed pregnant New Zealand White Rabbits by gavage at 0, 2, 20, and 200 mg/kg. Maternal toxicity was observed at 200 mg/kg as an increased incidence of abortions, a significant reduction in maternal body weight change of all does during days 14-21, and significantly increased absolute and relative liver weights. Necropsy findings indicated a treatment related non-significant increase in the number of does with dark brown livers. Developmental toxicity was

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observed at the 200 mg/kg level as reduced ossification of the sternebrae. The reduction in extra paired ribs at 200 mg/kg may also indicate a delay in fetal development. Furthermore, the percentage of pregnant does with live fetuses at term was 94, 93, 85, and 71% for the 0, 2, 20, and 200 mg/kg groups respectively. The percentage of pregnant does that aborted was 6, 7, 8, and 24% respectively for the 0, 2, 20, and 200 mg/kg groups.

Core Classification: Core-Minimum Data

Maternal NOEL = 20 mg/kg
Maternal LOEL = 200 mg/kg
Developmental Toxicity NOEL = 20 mg/kg
Developmental Toxicity LOEL = 200 mg/kg

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GUIDELINE: §83-3

Primary Review by: Karen E. Whitby, Ph.D.
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(H7509C)

Secondary Review by: K. Clark Swentzel 2/5/91
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DATA EVALUATION RECORD

Study Type: Teratology - Developmental Toxicity
Species: Rabbit
Guideline: §83-3

EPA Identification No.s: EPA TRID (Accession) No. 4700-210-15
EPA Pesticide Chemical Code 041402
Caswell No. 444
HED Project No. 1-1888

Test Material: Ordram® Technical

Synonyms: Molinate

Sponsor: Stauffer Chemical Company
Environmental Health Center
400 Farmington Avenue
Farmington, Connecticut 06032

Study Number(s): T-11866

Testing Facility: Stauffer Chemical Company
Environmental Health Center
Farmington, Connecticut 06032

Title of Report: A Teratology Study in New Zealand White Rabbits with Ordram®

Author(s): J.L. Minor, M.S.

Report Issued: June 6, 1985

Study Dates: November 12, 1984 (Study In-Life Initiation)
December 20, 1984 (Study In-Life Termination)

Bibliographic Citation: Minor, J.L., (1985) A Teratology Study in New Zealand White Rabbits with Ordram® Report No. T-11866 (Stauffer Chemical Company Environmental Health Center Farmington, Commecticut 06032)

Conclusions: Ordram® was administered in corn oil to pres:med

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pregnant New Zealand White Rabbits by gavage at 0, 2, 20, and 200 mg/kg. Maternal toxicity was observed at 200 mg/kg as an increased incidence of abortions, a significant reduction in maternal body weight change of all does during days 14-21, and significantly increased absolute and relative liver weights. Necropsy findings indicated a treatment related non-significant increase in the number of does with dark brown livers. Developmental toxicity was observed at the 200 mg/kg level as reduced ossification of the sternebrae. The reduction in extra paired ribs at 200 mg/kg may also indicate a delay in fetal development. Furthermore, the percentage of pregnant does with live fetuses at term was 94, 93, 85, and 71% for the 0, 2, 20, and 200 mg/kg groups respectively. The percentage of pregnant does that aborted was 6, 7, 8, and 24% respectively for the 0, 2, 20, and 200 mg/kg groups.

Core Classification: Core-Minimum Data

Maternal NOEL = 20 mg/kg
Maternal LOEL = 200 mg/kg
Develcpmental Toxicity NOEL = 20 mg/kg
Developmental Toxicity LOEL = 200 mg/kg

A. Materials

A copy of the "materials and methods" section from the investigators report is appended.

1. Test Compound:

| | |
|---|---|
| Chemical Name: | S-ethyl hexahydro-1H-azepine-1-carbothioate |
| Molecular Formula: | $C_9H_{17}NOS$ |
| Molecular Weight: | 187.3 |
| Purity: | 98.8% |
| Source: | de Guigne Technical Center<br>Stauffer Chemical Co.<br>Richmond, CA |
| Description: | amber liquid |
| Lot No.: | EHC-0469-29 |
| Stability: | stable under ambient temperatures and pressures. Ordram® was stored under ambient temperatures in this study. |

2. Vehicle(s): Corn oil (source not provided)

3. Test Animal(s):

| | |
|---|---|
| Species: | rabbit |
| Strain: | New Zealand White [Dla:(NZW) SPF)] |
| Source: | Dutchland Laboratories, Inc.<br>Denver, PA. |
| Age: | 26 - 29 weeks (at cohabitation) |
| Weight: | at receipt not provided |

Animals were quarantined for at least three weeks before mating. During this time the animals were examined by the study veterinarian.

B. Study Design

This study was designed to assess the developmental toxicity potential of Ordram® when administered by oral intubation to rabbits on gestation days 7 through 19, inclusive.

1. Mating

Seventy virgin females were mated with males (number not given) to obtain 65 pregnant females. Females were considered pregnant when matings were observed visually. Females were assigned to the study after one successful mating. A second mating was performed for each female with a second buck on the same day and was usually successful. The day of mating was considered day 0 of gestation.

2. Group Arrangement

Females were assigned to the study groups so as to eliminate any

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bias due to the day animals were mated, the sire, or the day 0 body weight.

| Test Group | Dose Level (mg/kg) | Number Assigned |
|---|---|---|
| Control | 0 | 16 |
| Low Dose | 2 | 16 |
| Mid Dose | 20 | 16 |
| High Dose | 200 | 17 |

3. Dosing

All doses were in a volume of 0.5 mL/kg of body weight/day prepared at the beginning of the study by a weight/volume method. Corrections to dosing solutions were not made for purity. All dosing solutions were analyzed for concentration. Stability was analyzed for the 4.0 mg/mL solution (LDT) over the study period. Dosing was based on gestation day 7 body weight.

4. Observations

The animals were examined for clinical signs daily. Body weights were recorded days 0, 7, 14, 21, and 29. Feed consumption was measured days 0-7, 7-14, 14-21, and 21-29.

Dams were sacrificed on day 29 of gestation by sodium pentobarbital injection. Females were examined for macroscopic changes in all organs of the thoracic and abdominal cavities. The liver, kidneys, spleen, adrenals, ovaries, and intact reproductive tract were weighed. Paired organs were weighed together. Placentas of live fetuses for each litter were weighed collectively. The number of corpora lutea, fetuses, and resorptions were recorded.

All fetuses were weighed and examined for external abnormalities. Fetuses which weighed less than 3/4 of the mean litter weight were designated as calculated runts. Viable fetuses were sacrificed by intrathoracic injection of sodium pentobarbital. The head of each fetus was removed and fixed in Bouin's fixative for exam by a modified Wilson technique (1965). The trunk of each fetus was examined, and the sex determined, by a modified Staples technique (1974). The fetuses were then eviscerated and processed for skeletal examination by a modification of the Kimmel (1981) technique.

Historical control data were provided to allow comparison with concurrent controls.

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5. Statistical Analysis

Enumeration data for each dose group, such as doe anomalies were evaluated for significance by the Fisher exact probability test (Siegel, 1956), with Bonferroni's correction for multiple comparisons to a single control value (Ingelfinger, 1983). Enumeration data for each litter, such as fet. anomalies and number of corpora lutea per doe were analyzed by the Mann-Whitney U two-sample rank test (Goldstein, 1967). Quantitative or continuous data, such as body weights and feed consumption were analyzed by the one-way analysis of variance (Steel and Torrie, 1960) and the Dunnett's t-test (Dunnett, 1964). The fiducial limit of 0.05 was employed in all statistical tests.

6. Compliance

A signed Statement of Confidentiality Claim was not provided (the title page of the report indicates that the report is the property of Stauffer Chemical Company. It must not be copied in whole or in part, nor the information shown herein disclosed to third parties. All pages of the report are stamped Stauffer confidential and proprietary - do not copy.)

A signed Statement of Compliance with EPA GLP's was not provided.

A signed Quality Assurance Statement was provided (pg 4).

C. Results

1. Analyses of Dosing Solutions

Dosing solutions were prepared November 7, 1984 and used for the thirteen days of treatment. Analyses were performed on November 8, 1984. The study started November 12, 1984. The stability analyses was performed with the 4.0 mg/mL solution, which was blended November 7, 1984. The final stability analyses were performed on December 20, 1984.

TABLE 1: Concentration Analyses

| Theoretical Concentration (mg/mL) | Actual Concentration (mg/mL) Sample Number | | | Mean Measured Concent. (mg/mL) | R.S.D. |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | | |
| 4 | 4.08 | 4.01 | 3.96 | 4.02 | (1.50%) |
| 40 | 41.6 | 41.4 | 40.7 | 41.2 | (1.15%) |
| 400 | 407 | 396 | 416 | 406.3 | (2.46%) |

R.S.D. = relative standard deviation and is a measure of homogeneity. (Extracted from table 1 in report T-11866, p. 20.)

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TABLE 2: Stability Analyses

| Temp. | Final Concentration (mg/mL) | | | | |
|---|---|---|---|---|---|
| | Number of Days | | | | |
| | 7 | 13 | 28 | 35 | 42 |
| 4° C | 4.0(0) | 4.1(-2.5) | 4.1(-2.5) | 4.0(0) | 4.0(0) |
| No. of Samples | 3 | 3 | 3 | 2 | 3 |
| Room Temp. | 3.9(2.5) | 4.1(-2.5) | 4.1(-2.5) | 4.0(0) | 4.0(0) |
| No. of Samples | 3 | 3 | 3 | 3 | 3 |

() = % loss (Extracted from table 2 report T-11866 p. 21.)

The results above indicate that the actual concentrations were within +/- 4% of the theoretical. The stability analyses indicate that the loss of the test material was no greater than -2.5%.

2. Maternal Toxicity

a. Mortality

Only one female died during this study. This animal was in the 20 mg/kg group. The cause of death could not be determined at necropsy.

b. Clinical Observations

The only finding during daily clinical observations which was treatment related was an increase in the number of abortions prior to sacrifice, which was not reported as being statistically significant.

c. Body Weight

The investigators supplied the following data:

TABLE 3: Maternal Body Weight Gain (g)[a]

| Dose (mg/kg): | Days 0-7 | Days 7-14 | Days 14-21 | Days 21-29 | Corrected Body Weight Gains 7-14[1] | Entire[2] |
|---|---|---|---|---|---|---|
| 0 | 225 | 123 | -65 | -2.4 | -345.3 | 3959 |
| 2.0 | 205 | 122 | 27 | -144 | -334.5 | 3829 |
| 20.0 | 163 | 68 | 30 | -71 | -428.2 | 3817 |
| 200.0 | 226 | 175 | -185 | 71 | -260.4 | 4080 |

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1 = bodyweight gain days 7-14 minus gravid uterus weight.
2 = corrected bodyweight = day 29 gestation (terminal) bodyweight minus gravid uterine weight
a = Data for does with viable fetuses extracted from (study number T-11866 tables 5 and 7, and appendices 5 and 7 pp. 26, 28 and 87-88, 95-102)
(Some of the above values were calculated by this reviewer.)

The data in the above table represent the does with live fetuses. There were no statistically significant differences found for maternal body weight change of does with live fetuses. The greatest body weight loss occurred in the 200 mg/kg group (HDT) during days 14-21. When all does were included in the analysis, significance was detected ($p<0.05$) days 14-21 in the 200 mg/kg group. This significant loss of body weight may have been related to the four does in this group that aborted [there were four other does in this group whose weight loss ranged from -520 to -439 that did not abort (one of these does had a totally resorbed litter)].

d. Food Consumption

The investigators supplied the following data:

TABLE 4: Food Consumption Data (g/day)[a]

| Dose Group (mg/kg/day) | | Gestation Day Interval | | | |
|---|---|---|---|---|---|
| | | 0-7 | 7-14 | 14-21 | 21-29 |
| 0 | Mean<br>S.D.<br>N | 196.9<br>32.9<br>15 | 154.5<br>2 .8<br>15 | 120.6<br>72.6<br>15 | 97.0<br>53.9<br>13 |
| 2 | Mean<br>S.D.<br>N | 196.2<br>31.4<br>13 | 154.8<br>29.8<br>13 | 117.2<br>60.1<br>12 | 89.7<br>38.4<br>9 |
| 20 | Mean<br>S.D.<br>N | 203.2<br>31.3<br>13 | 160.8<br>18.2<br>10 | 127.4<br>60.4<br>11 | 57.4<br>52.1<br>7 |
| 200 | Mean<br>S.D.<br>N | 199.1<br>41.2<br>15 | 161.7<br>42.0<br>15 | 82.5<br>74.4<br>9 | 82.0<br>64.8<br>16 |

[a] Extracted from report T-11866, table 9 p. 30.

No significant differences were found when comparing the feed consumption of the control with treated groups. However, the 200 mg/kg group consumed 32% less than the control group days 14-21. This is apparently related to the decreased weight in these

animals during the same time period.

e. Gross Pathological Observations

Necropsy findings indicated a treatment related non-significant increase in the number of does with dark brown livers. No other treatment related or significant findings were noted at necropsy. There was a dose related significant increase in absolute and relative liver weight in the 200 mg/kg does compared to the control. No other dose related or significant alterations were noted for organ weights.

TABLE 5: Mean Organ Weights

| Absolute Wt. (g) Relative Wt. (%) | | 0 mg/kg | 2 mg/kg | 20 mg/kg | 200 mg/kg |
|---|---|---|---|---|---|
| Whole Body | | 4427 | 4285 | 4314 | 4516 |
| Adrenals | Abs. Wt | 0.524 | 0.516 | 0.559 | 0.520 |
| | Rel. Wt. | 0.012 | 0.012 | 0.013 | 0.012 |
| Kidneys | Abs. Wt. | 19.415 | 18.621 | 19.213 | 20.363 |
| | Rel. Wt. | 0.439 | 0.435 | 0.447 | 0.455 |
| Liver | Abs. Wt. | 99.471 | 105.468 | 107.783 | 119.666* |
| | Rel. Wt. | 2.242 | 2.471 | 2.500 | 2.677* |
| Ovaries | Abs. Wt. | 1.012 | 1.031 | 0.901 | 0.925 |
| | Rel. Wt. | 0.023 | 0.024 | 0.021 | 0.020 |
| Placentas | Abs. Wt. | 56.855 | 55.141 | 62.506 | 57.089 |
| | Rel. Wt. | 1.289 | 1.292 | 1.449 | 1.264 |
| Repro. | Abs. Wt. | 468.61 | 456.18 | 496.49 | 435.30 |
| Tract | Rel. Wt. | 10.612 | 10.684 | 11.504 | 9.654 |
| Spleen | Abs. Wt. | 1.710 | 1.692 | 1.550 | 1.920 |
| | Rel. Wt. | 0.039 | 0.039 | 0.036 | 0.042 |
| Uterus | Abs. Wt. | 75.61 | 67.61 | 67.64 | 66.40 |
| | Rel. Wt. | 1.703 | 1.582 | 1.566 | 1.490 |

Extracted from report T-11866, tables 10 and 11, pp.31-34.
* Significantly different from the control group ($p<0.05$).

f. Cesarean Section Observations

All of the data in the table for cesarean section observations represent does with viable fetuses on day 29 of gestation. The overall

fertility rate in this study was 93.8%. Doe 746 died on gestation day 27, neither the text, individual necropsy findings, individual clinical observations, individual organ weights, or individual intrauterine data indicate whether or not this doe was pregnant. However, table 2 on page 22 indicates that the percent pregnant for the 20 mg/kg group was 81% (13/16) which would infer that she was pregnant (of the 16 animals in the group, 3 were not pregnant, and one aborted). Due to the absence of data for this pregnancy, this pregnancy was not included in the data in the table for cesarean section observations. Four does in the 200 mg/kg group aborted. One doe in the 200 mg/kg group had a litter of ten that was totally resorbed. The data for these five does in the 200 mg/kg group were not included in the cesarean section observation table.

When considering all does (including those which aborted), the number of non-viable fetuses for the 0, 2, 20, and 200 mg/kg groups were 8, 11, 4, and 26 respectively. It was not possible to include these in the calculation of the percent preimplantation and postimplantation loss, because the individual data do not contain the number of corpora lutea or implants for these does, but merely the number of non-viable fetuses. Therefore, the accuracy of these indices is ambiguous.

Furthermore, the individual intrauterine data indicate that 2, 1, 3, and 3 does in the 0, 2, 20, 200 mg/kg groups had a higher number of implants than corpora lutea. For this reason these litters were not included in the calculation of preimplantation loss. This further reduces the weight which should be placed on this endpoint. The historical control data provided with this study present mean values for the number of corpora lutea and implants. It is not possible to determine whether individual animals would present similar findings. In the current study, the mean number of implants is less than the mean number of corpora lutea. The only statistically significant finding for the cesarean section observation data is a significant increase in the number of viable fetuses in the 20 mg/kg group relative to the control. The relationship of this finding to the possible twinning (3 does with a greater number of implants than corpora lutea) is unclear. However, it is the opinion of this reviewer that the higher number of implants than corpora lutea is due to technical error.

In the 200 mg/kg group, 4 does aborted and there were 13 does with implants (one litter of ten was totally resorbed); and 12 does with live fetuses. The percentage of pregnant does with live fetuses at term was 94, 93, 85, and 71% for the 0, 2, 20, and 200 mg/kg groups respectively.

TABLE 6: Cesarean Section Observations[a]

| Dose (mg/kg): | 0 | 2 | 20 | 200 |
|---|---|---|---|---|
| #Animals Assigned | 16 | 16 | 16 | 17 |
| #Animals Mated/Inseminated | 16 | 16 | 16 | 17 |
| # Pregnant (%) | 16(100) | 15(94) | 13(81) | 17(100) |
| Maternal Wastage | | | | |
| #Died | 0 | 0 | 1 | 0 |
| #Non pregnant | 0 | 1 | 3 | 0 |
| #Aborted | 1 | 1 | 1 | 4 |
| #Premature Delivery | 0 | 0 | 0 | 0 |
| N | 15 | 14 | 11 | 12 |
| Total Corpora Lutea | 154 | 138 | 111 | 115 |
| Corpora Lutea/Doe | 10.3 | 9.9 | 10.1 | 9.6 |
| Total Implantation | 130 | 120 | 110 | 101 |
| Implantations/Doe | 8.7 | 8.6 | 10.0 | 8.4 |
| Total Live Fetuses | 115 | 116 | 107 | 96 |
| Live Fetuses/Doe | 7.7 | 8.3 | 9.7* | 8.0 |
| Total Resorptions | 15 | 3 | 3 | 7 |
| Early | 9 | 0 | 2 | 3 |
| Late | 6 | 3 | 1 | 4 |
| Resorptions/Doe | 1.0 | 0.2 | 0.3 | 0.2 |
| Total Dead Fetuses | 0 | 1 | 0 | 0 |
| Dead Fetuses/Doe | 0.0 | 0.1 | 0.0 | 0.0 |
| Mean Fetal Weight (gm) | 40.5 | 38.2 | 35.7 | 38.6 |
| Preimplantation Loss(%) | 19.6 | 15.5 | 7.5 | 18.7 |
| Postimplantation Loss(%) | 10.3 | 3.1 | 2.3 | 4.8 |
| Sex Ratio (% Female) | 46 | 45 | 50 | 45 |

[a] = Data extracted from report no. T-11866 tables 2 and 12 p. 22 and 35 and appendix 9 pp. 115-118

* Significantly different from the control group ($p<0.05$).

2. Developmental Toxicity

TABLE 7: External Examinations[a]

| Dose (mg/kg): | 0 | 2 | 20 | 200 |
|---|---|---|---|---|
| #pups(litters) examined | 115(15) | 116(14) | 107(11) | 96(12) |
| Observations[+] | | | | |
| Abdomen Dark | 0(0) | 0(0) | 2(1) | 0(0) |
| Hematoma, Hindlimbs | 0(0) | 0(0) | 4(1) | 0(0) |
| Pale | 0(0) | 0(0) | 0(0) | 1(1) |
| Runt | 2(1) | 0(0) | 0(0) | 0(0) |
| Spina Bifida | 0(0) | 1(1) | 0(0) | 0(0) |

[+] some observation may be grouped together
[a] fetal (litter) incidence

Data extracted from report no. T-11866 table 13 pp. 36-37 and appendix 11 pp. 127-192

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TABLE 8: Visceral Examinations[a]

| Dose (mg/kg): | 0 | 2 | 20 | 200 |
|---|---|---|---|---|
| #pups(litters) examined | 115(15) | 116(14) | 107(11) | 96(12) |
| Observations[+] | | | | |
| Eye- | | | | |
| Retina Convoluted Both | 3(2) | 0(0) | 0(0) | 0(0) |
| Retina Convoluted Both Moderate | 2(1) | 0(0) | 0(0) | 0(0) |
| Retina Convoluted Left | 0(0) | 0(0) | 1(1) | 1(1) |
| Retina Convoluted Right | 2(2) | 1(1) | 4(4) | 2(2) |
| Hindbrain- | | | | |
| Cystic Dilatation | 6(5) | 5(3) | 3(2) | 4(1) |
| Cystic Dilatation, Moderate | 2(1) | 0(0) | 0(0) | 0(0) |
| Lat. Vent. Dilated, Moderate | 1(1) | 0(0) | 0(0) | 0(0) |
| Lat. Vent. Dilated | 0(0) | 4(1) | 1(1) | 1(1) |
| Olfactory Lobes- | | | | |
| Reduced Both | 0(0) | 0(0) | 3(1) | 0(0) |
| Spinal Cord- | | | | |
| Cystic Dilation | 1(1) | 0(0) | 0(0) | 0(0) |
| Gallbladder- | | | | |
| Absent | 1(1) | 0(0) | 1(1) | 0(0) |
| Pale | 0(0) | 1(1) | 0(0) | 0(0) |
| Enlarged | 4(2) | 1(1) | 0(0) | 0(0) |
| Enlarged, Moderate | 1(1) | 0(0) | 0(0) | 0(0) |
| Reduced | 5(4) | 2(2) | 5(1) | 5(4) |
| Reduced, Extreme | 0(0) | 1(1) | 0(0) | 0(0) |
| Reduced, Moderate | 0(0) | 0(0) | 2(2) | 1(1) |
| Kidney- | | | | |
| Pelvis Dilated, Both | 0(0) | 1(1) | 0(0) | 0(0) |
| Pelvis Dilated, Left | 0(0) | 0(0) | 0(0) | 1(1) |
| Pelvis Dilated, Right | 0(0) | 1(1) | 1(1) | 1(1) |
| Liver- | | | | |
| Dark, Moderate | 0(0) | 0(0) | 1(1) | 0(0) |
| Pale | 0(0) | 4(1) | 0(0) | 0(0) |
| Spleen- | | | | |
| Enlarged | 0(0) | 3(1) | 1(1) | 2(1) |
| Enlarged, Moderate | 1(1) | 0(0) | 0(0) | 0(0) |
| Pale | 0(0) | 0(0) | 0(0) | 1(1) |
| Reddened | 0(0) | 3(1) | 0(0) | 0(0) |
| Thoracic Cavity Fluid Filled | 0(0) | 0(0) | 1(1) | 0(0) |
| Pericardium, Fluid Filled | 1(1) | 2(2) | 0(0) | 0(0) |

[+] some observation may be grouped together
[a] fetal (litter) incidence
Data extracted from report no. T-11866 table 14 pp. 38-46 and appendix 11 pp. 127-192

TABLE 9: Skeletal Examinations[a]

| Dose (mg/kg): | 0 | 2 | 20 | 200 |
|---|---|---|---|---|
| #pups(litters) examined | 115(15) | 116(14) | 107(11) | 96(12) |
| Lumbar Vert.- | | | | |
| Absent | 1(1) | 0(0) | 1(1) | 2(1) |
| Lateral Process Absent Right | 0(0) | 0(0) | 1(1) | 0(0) |
| Presacral Extra Vert. | 1(1) | 6(3) | 1(1) | 1(1) |
| Rib(s)- | | | | |
| Absent | 0(0) | 0(0) | 0(0) | 1(1) |
| Branched | 0(0) | 0(0) | 0(0) | 2(2) |
| Bulbous Thickening | 0(0) | 0(0) | 1(1) | 0(0) |
| Fused | 0(0) | 0(0) | 0(0) | 2(2) |
| Extra, Full-Sized, Both | 26(9) | 40(11) | 25(8) | 14(5) |
| Extra, Full-Sized, Left | 1(1) | 5(3) | 4(4) | 3(3) |
| Extra, Full-Sized, Right | 7(6) | 9(6) | 3(2) | 3(2) |
| Extra, Rudi., Both | 3(2) | 1(1) | 6(4) | 1(1) |
| Extra, Rudi., Left | 2(2) | 4(4) | 4(3) | 2(2) |
| Extra, Rudi., Right | 1(1) | 5(4) | 2(2) | 4(4) |
| Extra, Short, Both | 16(11) | 6(4) | 10(6) | 6(2) |
| Extra, Short, Left | 12(9) | 11(6) | 5(3) | 7(4) |
| Extra, Short, Right | 5(3) | 3(2) | 4(3) | 5(4) |
| Spina Bifida | 0(0) | 1(1) | 0(0) | 0(0) |
| Sternebrae- | | | | |
| Incomplete Oss., 5th | 75(15) | 57(14) | 57(11) | 39(9) |
| Incomplete Oss., Other | 13(8) | 11(4) | 13(7) | 3(2) |
| Unossified, 5th | 9(6) | 16(6) | 15(3) | 25(7) |
| Unossified, Other | 9(6) | 9(6) | 2(1) | 5(3) |
| Lobed | 0(0) | 0(0) | 1(1) | 0(0) |
| Split | 2(2) | 2(2) | 1(1) | 1(1) |

+ some observation may be grouped together
[a] fetal (litter) incidence
Data extracted from report no. T-11866 table 14 pp. 45-49 and appendix 11 pp. 127-192

The mean litter percent was calculated from the group mean value for each individual litter incidence by dividing the no. of pups affected by the number of pups examined X 100. There was a significant decrease ($p<0.05$) in the mean litter percent of bilateral extra short ribs in the 2 and 200 mg/kg groups relative to the control. This finding does not appear to be biologically significant, as the incidence is within their historical control range. Examination of the data as total extra paired ribs (full, short, and rudimentary combined) yields a incidence in the 200 mg/kg group which is lower than the historical control range, and

may be interpreted as a slight developmental delay.

There was a significant treatment related decrease ($p<0.05$) in the mean litter percent of incompletely ossified 5th sternebrae in the 2, 20, and 200 mg/kg groups relative to the control. The mean litter percent was also significantly reduced for other sternebrae incompletely ossified in the 200 mg/kg group. The decreased incidence of incomplete ossification of the 5th sternebrae and other sternebrae was not considered by this reviewer to be biologically significant. The incidence of unossified 5th sternebrae in the 200 mg/kg group was not statistically significant, yet the finding is reported by the authors as higher than that observed in their historical control, and therefore may be indicative of delayed development.

D. Discussion/Conclusions

1. Maternal Toxicity:

One female in the 20 mg/kg group died in this study. The cause of death could not be determined. Maternal toxicity was observed at the 200 mg/kg level by way of the increased incidence of abortions, a significant reduction in maternal body weight change of all does during days 14-21, and significantly increased absolute and relative liver weights. Necropsy findings indicated a treatment related non-significant increase in the number of does with dark brown livers.

2. Developmental Toxicity:

a. Deaths/Resorptions:

There was no treatment related or significant effect on fetal deaths or resorptions. However, the percentage of pregnant does with live fetuses at term was 94, 93, 85, and 71% for the 0, 2, 20, and 200 mg/kg groups respectively. The percentage of pregnant does that aborted was 6, 7, 8, and 24% respectively for the 0, 2, 20, and 200 mg/kg groups.

b. Altered Growth:

There were no significant or treatment related alterations in fetal growth.

c. Developmental Anomalies:

A delay in fetal development was indicated at the 200 mg/kg level by reduced ossification of the sternebrae. The reduction in extra paired ribs at 200 mg/kg may also indicate a delay in fetal development.

d. Malformations:

No significant increase was noted in malformations.

E. Study Deficiencies:

1. The report does not contain a signed Statement of Compliance with EPA GLP's.

F. Core Classification: Core-Minimum Data.

Maternal NOEL = 20 mg/kg
Maternal LOEL = 200 mg/kg
Developmental Toxicity NOEL = 20 mg/kg
Developmental Toxicity LOEL = 200 mg/kg

**APPPENDIX I**

**Materials and Methods**

Page _____ is not included in this copy.

Pages 19 through 33 are not included in this copy.

The material not included contains the following type of information:
Identity of product inert ingredients.

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