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EPA No.: 68D80056
DYNAMAC No.: 391-A
TASK No.: 3-91A
August 12, 1991

# DATA EVALUATION RECORD

## OXYFLUORFEN

## Developmental Toxicity Study in Rats

STUDY IDENTIFICATION: Solomon, H.M. and Romanello, A.S. Goal: Oral (gavage) developmental toxicity study in rats. (Unpublished study No. 90R-008 conducted and submitted by Rohm and Haas Company, Spring House, PA; dated February 15, 1991.) MRID No. 418065-01.

APPROVED BY:

Robert J. Weir, Ph.D.
Program Manager
Dynamac Corporation

Signature: Nicholas P. Hajjar for

Date: August 12, 1991

1/20

1. CHEMICAL: 2-chloro-1-(3-ethoxy-4-nitrophenoxy)-4-(trifluoromethyl)benzene.

2. TEST MATERIAL: Goal, 71.4% purity; reddish-brown solid; lot No. 2-0956.

3. STUDY/ACTION TYPE: Developmental toxicity study in rats.

4. STUDY IDENTIFICATION: Solomon, H.M. and Romanello, A.S. Goal: Oral (gavage) developmental toxicity study in rats. (Unpublished study No. 90R-008 conducted and submitted by Rohm and Haas Company, Spring House, PA; dated February 15, 1991.) MRID No. 418065-01.

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DATA EVALUATION RECORD

STUDY TYPE: Developmental Toxicity. Guideline §83-3.

MRID NUMBER: 418065-01.

TEST MATERIAL: Goal, 71.4% purity; reddish-brown solid; lot No. 2-0956.

SYNONYMS: Oxyfluorfen, Koltar, RH-2915.

STUDY NUMBER: 90R-008.

SPONSOR: Rohm and Haas Company, Spring House, PA.

TESTING FACILITY: Rohm and Haas Company, Spring House, PA.

TITLE OF REPORT: Goal: Oral (Gavage) Developmental Toxicity Study in Rats.

AUTHORS: Solomon, H.M. and Romanello, A.S.

REPORT ISSUED: February 15, 1991.

CONCLUSIONS: A developmental toxicity study was conducted in which Crl:CD BR rats were administered oxyfluorfen via gavage at 0, 15, 150, or 750 mg/kg/day during gestational days (GD) 6 through 15. Analytical chemistry results, however, indicated that the actual low-, mid-, and high-doses were approximately 18, 183, and 848 mg/kg/day, respectively. Maternal toxicity, observed at the mid- and high-dose levels, was manifested as an increased mortality rate and increased levels of alkaline phosphatase and SGOT (high-dose group), increased incidences of clinical signs (mid- and high-dose groups), and decreased body weight gain and food consumption during the dosing period (mid- and high-dose groups). Based on these results, the maternal NOEL and LOEL were 18 and 183 mg/kg/day, respectively.

Developmental toxicity, observed at the mid- and high-dose levels, was manifested as a 100% resorption rate (high-dose group) and increased numbers of resorptions, decreased fetal body weight, and increased incidences of visceral and skeletal anomalies (mid-dose group). Based on these results, the NOEL and LOEL for developmental toxicity were 18 and 183 mg/kg/day, respectively.

Classification: CORE Minimum Data. This study meets the minimum requirements set forth under EPA Guideline §83-3 for a developmental toxicity study in rats.

A. MATERIALS:

| | | |
|---|---|---|
| Test Compound: | Purity: | 71.4%. |
| | Description: | Reddish-brown solid. |
| | Lot No.: | 2-0956. |
| | Contaminants: | Not reported. |
| Vehicle: | Corn oil (Sigma Chemical Co., Lot 19F-0038). | |
| Test Animals: | Species: | Rat. |
| | Strain: | Crl:CD BR. |
| | Source: | Charles River, Breeding Laboratories Inc., Raleigh, NC. |
| | Age: | 55-63 days upon arrival. |
| | Weight: | 186-222 g upon arrival. |

B. STUDY DESIGN:

This study was designed to assess the potential of oxyfluorfen to cause developmental toxicity in rats when administered daily via gavage from GD 6 through 15, inclusive.

Mating: Following 14 days of acclimation, females were mated 1:1 with stock males of the same strain and source. Females were checked each morning for copulation plugs and abundance of

sperm (determined by vaginal lavage). The day on which a sperm plug and sufficient number (not specified) of sperm in the lavage were found was designated day 0 of gestation.

Group Arrangement: Animals were allocated to dose groups using a randomized block design based on GD 0 body weight as follows:

| Test Group | Dose Level (mg/kg/day) | Number Assigned per Group |
|---|---|---|
| Control | 0 | 27 |
| Low dose | 15 | 27 |
| Mid dose | 150 | 27 |
| High dose | 750 | 27 |

Dosing: Doses were administered daily via gavage on GD 6 through 15 in a volume of 5 mL/kg. The most recently recorded body weights were used to calculate the concentration of the doses, which were also adjusted for active ingredient. Doses were prepared daily by melting the test compound at 76°C, weighing out the appropriate amount, and then mixing it with warm corn oil (38°C) to achieve the desired concentrations. During dosing the suspensions were constantly stirred and kept warm (38°C). A sample from each dose level was collected during the beginning, midpoint, and end of the treatment period and analyzed for concentration. The stability of the compound in the vehicle was determined by analyzing samples that had been stored at room temperature for four hours. No homogeneity analyses were performed. Concentration of the doses was selected based upon the results of a previous study (No. 77RC-1107) conducted in the same strain of rats; however, these results were not reported.

Observations: Animals were observed daily for overt signs of toxicity (twice a day during dosing) in addition to morbidity and mortality checks on GD 0-5 and 16-19. Body weight was recorded on GD 0, 6, 8, 10, 13, 16, and 20. Food consumption was recorded on GD 0, 6, 10, 16, and 20. Hematology and clinical chemistry parameters were evaluated on GD 20. On GD 20, females were anesthetized with carbon dioxide, blood was drawn from the abdominal aorta, and the animals were subsequently sacrificed by exsanguination. Litters were delivered by cesarean section. Examination of the dams at sacrifice included the following:

- Gross pathology observations of the abdominal and thoracic cavities;

- Liver weights were recorded and selected samples were stored in neutral buffered formalin for possible future evaluation;

- Number of corpora lutea;

- Number of implantation sites; and

- Numbers of resorptions (early and late) and live and dead fetuses.

Uteri from apparently nonpregnant animals were stained with ammonium sulfide to detect early embryo loss.

Fetuses were examined in the following manner:

- Individual fetuses were weighed and sexed;

- External anomalies were recorded;

- Approximately one-half of the fetuses were examined for visceral alterations using Staples' technique (1974), and fetal heads were evaluated using the technique of Barrow and Taylor (1969); and

- All fetuses were examined for skeletal alterations using Dawson's technique (1926).

Statistical Analysis: The following methods were used:

- Maternal body weight, weight change, food consumption, liver weight, and hematology and serum chemistry--ANOVA and Dunnett's test;

- Incidences of pregnancy and maternal death, clinical signs, maternal necropsy findings, and number of totally resorbed litters--Fisher's Exact test; and

- Numbers of corpora lutea, implantation sites, live and dead fetuses, and resorptions, fetal body weight, and incidence of fetal alterations --Mann-Whitney U-test or Fisher's Exact test.

Compliance:

- A signed Statement of No Data Confidentiality Claim, dated February 21, 1991, was provided;

- A signed Statement of Compliance with EPA and OECD GLPs was provided but not dated; and

- A signed Quality Assurance Statement was provided but not dated.

C. RESULTS:

The following results were reported by the study authors.

1. Test Material Analysis: Analyses conducted on dosing solutions prepared on days 6, 17, and 23 of the study revealed the following results (range of % of target concentrations): the 0-mg/kg/day group, 100%; the 15-mg/kg/day, 111-168%; the 150-mg/kg/day, 106-138%; and the 750-mg/kg/day, 95.3-136% (see Reviewers' Conclusions for further discussion). Stability was confirmed after 4 hours storage in room temperature.

2. Maternal Toxicity:

Mortality: In the high-dose group, a significant increase was observed in the mortality rate. Fifteen animals were found dead and one animal was killed in extremis. All animals were confirmed pregnant. (For necropsy findings, see Gross Pathology Observations.)

Abortion: No abortions were observed.

Clinical Observations: A summary of selected clinical observations is presented in Table 1. No clinical signs were observed during the predosing period (GD 0-5, data not shown). During the dosing period (Table 1), incidences of the following clinical observations were significantly increased in the high-dose group: hunched, lethargic appearance, stained perineum, muzzle, and abdomen, stained cageboard, vaginal discharge, alopecia, and soft/mucoid/scant feces. In the mid-dose group, significant increases included stained cageboard and soft/scant feces. Incidences of alopecia and soft/mucoid feces remained significantly increased in the high-dose group during the postdosing period (GD 16-20; data not shown).

Body Weight: A summary of maternal body weight gain for selected intervals is presented in Table 2. Due to the high mortality rate in dams from the high-dose group, body weight gain for this group was not calculated. In dams from the mid-dose group, body weight gain was significantly decreased on GD 6-8 ($p < 0.05$); it was (nonsignificantly)

TABLE 1. Incidences of Selected Maternal Clinial Signs on GD 6-15[a]

| Findings | Dose Level (mg/kg/day) | | | |
|---|---|---|---|---|
| | 0 | 15 | 150 | 750 |
| Hunched | 0 | 0 | 0 | 9* |
| Ataxia | 0 | 0 | 0 | 4 |
| Lethargic | 0 | 0 | 0 | 11* |
| Perineum, stained brown | 0 | 0 | 1 | 18* |
| Perineum, stained yellow | 0 | 0 | 1 | 17* |
| Perineum, stained stained red | 0 | 0 | 0 | 3 |
| Vaginal discharge, red | 1 | 0 | 4 | 15* |
| Cageboard, stained yellow | 0 | 1 | 24* | 25* |
| Cageboard, stained red | 0 | 0 | 0 | 8* |
| Pale extremities | 0 | 0 | 0 | 3 |
| Muzzle, stained tan/brown | 0 | 0 | 0 | 15* |
| Alopecia | 0 | 0 | 4 | 8* |
| Abdomen, stained brown | 0 | 0 | 0 | 7* |
| Feces, soft | 0 | 0 | 9* | 26* |
| Feces, mucoid | 0 | 0 | 1 | 26* |
| Feces, scant | 0 | 0 | 5* | 17* |

[a]Data were extracted from Study No. 90R-008, Table 2.

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

TABLE 2. Mean Body Weight Gain (g ± S.E.)[a]

| Dose Group (mg/kg/day) | Prior to Dosing Period (GD 0-6) | Dosing Period (GD 6-16) | Post Dosing Period (GD 16-20) | Corrected Body Weight (GD 6-20)[b] |
|---|---|---|---|---|
| 0 | 33.9 ± 2.0 | 54.1 ± 2.6 | 63.5 ± 2.2 | 40.4 ± 2.4 |
| 15 | 34.1 ± 1.8 | 59.2 ± 2.2 | 68.4 ± 1.8 | 42.7 ± 2.0 |
| 150 | 30.5 ± 1.9 | 50.2 ± 2.9 | 57.8 ± 3.6 | 42.8 ± 2.4 |
| 750 | -[c] | - | - | - |

[a]Data were extracted from Study No. 90R-008, Tables 4 and 5.

[b]Terminal body weight - uterine weight - GD 6 body weight.

[c]Not calculated due to the high mortality rate in this dose group.

increased by approximately 20% on GD 8-13 (data not shown). Slight decreases were noted in dams from the mid-dose group on GD 13-16 (10%, data not shown), 6-16 (7%, Table 2), and 16-20 (9%, Table 2). No differences were noted between the control, low-, and mid-dose groups in corrected body weight gain.

Food Consumption: A summary of food consumption is presented in Table 3. Due to the high mortality rate in dams from the high-dose group, food consumption for this group was not calculated. In dams from the mid-dose group, food consumption was significantly decreased on GD 6-10.

Gross Pathology Observations: A summary of maternal necropsy findings is presented in Table 4. A significantly increased incidence of intestine, reddened and filled with yellow mucus and slightly increased incidences of stomach and intestine filled with black material were observed in dams from the high-dose group. Since these findings only occurred in animals that were found dead, they were considered postmortem changes rather than effects of the test compound.

Hematology, Serum Chemistry, and Liver Weights: In dams from the high-dose group, the following hematology parameters were significantly increased: leucocytes ($p < 0.01$), mean cell volume ($p < 0.05$), and platelets ($p < 0.01$); among serum chemistry parameters, alkaline phosphatase ($p < 0.05$) and SGOT ($p < .0.01$) levels were significantly increased. No compound-related effects were observed in maternal liver weights.

Cesarean Section Observations: A summary of cesarean section data is presented in Table 5. In all dams that survived in the high-dose group, total litter resorption occurred. In dams from the mid-dose group, the number of resorptions was significantly increased; consequently the % postimplantation loss increased. Fetal body weight was significantly decreased in the mid-dose group.

3. Developmental Toxicity:

Incidences of external, visceral, and skeletal alterations are presented in Tables 6, 7, and 8.

External Examinations: Malformations were observed in one fetus from the control group (vestigial tail and anal atresia) and one fetus from the mid-dose group (body, anasarca; Table 6). No variations were noted.

Visceral Examinations: One malformation was observed in a fetus from the low-dose group (ventricular septal defect;

TABLE 3. Mean Food Consumption (g/animal/day ± S.E.)[a]

| Dose Group (mg/kg/day) | Prior to Dosing Period (GD 0-6) | Dosing Period (GD 6-10) | Dosing Period (GD 10-16) | Post Dosing Period (GD 16-20) |
|---|---|---|---|---|
| 0 | 24.1 ± 1.2 | 19.4 ± 0.5 | 22.9 ± 0.7 | 29.0 ± 0.7 |
| 15 | 24.3 ± 0.8 | 20.5 ± 0.4 | 21.9 ± 0.5 | 29.2 ± 0.6 |
| 150 | 27.0 ± 1.3 | 15.6 ± 1.0* | 22.2 ± 0.4 | 30.3 ± 0.6 |
| 750 | -[b] | - | - | - |

[a]Data were extracted from Study No. 90R-008, Table 6.

[b]Not calculated due to the high mortality rate in this dose group.

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

TABLE 4. Incidences of Maternal Necropsy Findings[a]

| Findings | Dose Level (mg/kg/day) | | | |
|---|---|---|---|---|
| | 0 | 15 | 150 | 750 |
| Abdominal cavity, mesenteric lymph nodes reddened | 0 | 0 | 0 | 4 |
| Cecum, filled with yellow mucus | 0 | 0 | 0 | 4 |
| Colon, filled with yellow fluid | 0 | 0 | 0 | 2 |
| Stomach, pyloric region, black material attached to mucosa | 0 | 0 | 0 | 7* |
| Stomach, pyloric region, mucosa reddened | 0 | 0 | 0 | 13* |
| Stomach, filled with black material | 0 | 0 | 0 | 3 |
| Stomach, enlarged 2x normal size | 0 | 0 | 0 | 3 |
| Kidney, dilated renal pelvis | 2 | 0 | 1 | 0 |
| Intestine, reddened and filled with yellow mucus | 0 | 0 | 0 | 8* |
| Intestine, filled with black material | 0 | 0 | 0 | 4 |
| Intestine, filled with yellow mucus | 0 | 0 | 0 | 3 |
| Uterus, brown mucoid material | 2 | 0 | 0 | 1 |
| Uterus, filled with clear fluid | 2 | 0 | 0 | 0 |
| Cervix, filled with brown mucoid material | 1 | 1 | 2 | 1 |

[a]Data were extracted from Study No. 90R-008, Table 7.

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

TABLE 5. Cesarean Section Observations[a]

| Parameter | Dose Level (mg/kg/day) | | | |
|---|---|---|---|---|
| | 0 | 15 | 150 | 730 |
| No. animals assigned | 27 | 27 | 27 | 27 |
| No. animals pregnant | 21[b] | 25 | 24 | 26 |
| Pregnancy rate (%) | 81 | 93 | 89 | 96 |
| Maternal wastage | | | | |
| No. died/pregnant | 0 | 0 | 0 | 16* |
| No. nonpregnant | 5 | 2 | 3 | 1 |
| No. aborted | 0 | 0 | 0 | 0 |
| Total corpora lutea[c] | 375 | 444 | 455 | 179[e] |
| Corpora lutea/dam | 17.9 ± 0.5[d] | 17.8 ± 0.6 | 19.0 ± 0.8 | 17.9 ± 0.7 |
| Total implantations[c] | 310 | 391 | 368 | 148[e] |
| Implantations/dam | 14.8 ± 0.6 | 15.6 ± 0.5 | 15.3 ± 0.9 | 14.8 ± 1.6 |
| Total live fetuses[c] | 291 | 378 | 303 | 0 |
| Live fetuses/dam | 13.9 ± 0.6 | 15.1 ± 0.5 | 12.6 ± 1.1 | 0 |
| Total resorptions[c] | 19 | 13 | 65 | 148 |
| Early | 19 | 13 | 65 | 148 |
| Late | 0 | 0 | 0 | 0 |
| Resorptions/dam | 0.9 ± 0.3 | 0.5 ± 0.1 | 2.7 ± 0.7* | - |
| Total dead fetuses | 0 | 0 | 0 | 0 |
| Fetal weight/litter (g) | 3.65 ± 0.11 | 3.68 ± 0.07 | 3.07 ± 0.11* | - |
| Preimplantation loss (%) | 16.4 | 11.1 | 9.6 | - |
| Postimplantation loss (%)[c] | 5.6 | 3.3 | 20.4 | - |
| Sex ratio (% male)[c] | 53.1 | 52.5 | 50.7 | - |

[a]Data were extracted from Study No. 90R-008, Table 8 and Appendix 9.

[b]One dam excluded from calculation due to unknown GD 0.

[c]Calculated by the reviewers.

[d]Mean ± S.E.

[e]Only dams surviving to term included in calculation.

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

TABLE 6. Incidences of Fetal External Malformations and Variations[a]

| Findings[b] | Dose Level (mg/kg/day) 0 | 15 | 150 | 750 |
|---|---|---|---|---|
| No. fetuses (litters) examined | 291 (21) | 378 (25) | 303 (24) | 0 |
| Malformations | | | | |
| Body, anasarca | 0 | 0 | 1 | - |
| Tail, vestigial | 1 | 0 | 0 | - |
| Anal atresia | 1 | 0 | 0 | - |
| Total No. fetuses (litters) with external malformations | 1 | 0 | 1 | - |
| Variations | | | | |
| Total No. fetuses (litters) with external malformations | 0 | 0 | 0 | - |

[a]Data were extracted from Study No. 90R-008, Tables 9 and 12.

[b]More than one type of anomaly may be found in one fetus.

Table 7). Variations were noted in one fetus from the control group and twelve fetuses (four litters) from the mid-dose group (vessel variations).

Skeletal Examinations: Malformations were observed in one fetus from the control group (lumbar and sacral vertebrae) and in twentyfive fetuses from twelve litters in the mid-dose group (bent scapula and/or bent limbs and fused sternebrae; Table 8). Variations were noted in eight fetuses (six litters) from the control group, nine fetuses (five litters) from the low-dose group, and twelve fetuses (ten litters) from the mid-dose group. They included extra ossification site and rudimentary rib in the lumbar vertebrae and misaligned sternebrae. The incidence of skeletal retardations (data not shown) was significantly increased for fetuses from the mid-dose group. Affected sites included thoracic vertebrae and pelvic bones (ossified partially or unossified) and ribs (wavy).

D. REVIEWERS' DISCUSSION/CONCLUSIONS:

1. Acceptance Criteria: The reviewers have completed an Acceptance Criteria check list (Attachment I) to be included with the evaluation of the study. Criterion 6 (analytical chemistry data) was satisfied (i.e., the analyses were conducted and the data were reported); however, the variations in the results greatly exceeded the commonly accepted ± 10% of target concentration. All other criteria were satisfied.

2. Test Material Analyses: Stability of the test compound in the vehicle was demonstrated; homogeneity was not analysed. Analyses of the dosing solutions revealed concentrations between 95 and 168% of nominal values. Within each dose group the average variation from the target concentration approximated +120%, except for the low-dose group at study day 23 when the concentration averaged +163% of target (15 mg/kg/day). From the analytical chemistry information available in Appendix 2 (Report No. 90R-008), it was apparent that the analytical results were representative of the test material concentration in the dosing suspensions. Therefore, the actual dosages administered to the animals approximated 18 mg/kg/day (123% for the low-dose group; results from study day 23 excluded), 183 mg/kg/day (122%) for the mid-dose group, and 848 mg/kg/day (113%) for the high-dose group.

   A dose-range study was conducted but no information was provided regarding analyses of the dosing solutions. A comparison between analytical results from the dose-range study and this definitive study may indicate a potential

TABLE 7. Incidences of Fetal Visceral Malformations and Variations[a]

| Findings[b] | Dose Level (mg/kg/day) 0 | 15 | 150 | 750 |
|---|---|---|---|---|
| No. fetuses (litters) examined | 152 (21) | 194 (25) | 158 (24) | 0 |
| Malformations | | | | |
| Heart, ventricular septal defect | 0 | 1 | 0 | - |
| Total No. fetuses (litters) with visceral malformations | 0 | 1 | 0 | - |
| Variations | | | | |
| Great vessels, left carotid arises from innominate | 1 | 0 | 12 (4) | - |
| Blood vessels, right branch of pulmonary artery displaced | 0 | 0 | 1 | - |
| Total No. fetuses (litters) with visceral variations | 1 | 0 | 12 (4) | - |

[a]Data were extracted from Study No. 90R-008, Tables 10 and 13.

[b]More than one type of anomaly may be found in one fetus.

TABLE 8. Incidences of Fetal Skeletal Malformations and Variations[a]

| Findings[b] | Dose Level (mg/kg/day) 0 | 15 | 150 | 750 |
|---|---|---|---|---|
| No. fetuses (litters) examined | 291 (21) | 378 (25) | 302 (24) | 0 |
| **Malformations** | | | | |
| Lumbar vertebrae, agenesis | 1 | 0 | 0 | - |
| Lumbar vertebrae, centrum, agenesis | 1 | 0 | 0 | - |
| Sacral vertebrae, agenesis | 1 | 0 | 0 | - |
| Scapula, bent | 0 | 0 | 22 (10*) | - |
| Sternebrae, fused | 0 | 0 | 3 (3) | - |
| Forelimb, humerus bent | 0 | 0 | 13 (8*) | - |
| Forelimb, radius bent | 0 | 0 | 12 (7*) | - |
| Forelimb, ulna bent | 0 | 0 | 9 (6*) | - |
| Hindlimb, femur bent | 0 | 0 | 2 (2) | - |
| Hindlimb, fibula bent | 0 | 0 | 1 | - |
| Total No. fetuses (litters) with skeletal malformations | 1 | 0 | 25 (12*) | - |
| **Variations** | | | | |
| Lumbar vertebrae, extra ossification site | 4 (2) | 6 (2) | 0 | - |
| Lumbar vertebrae, rudimentary rib | 0 | 1 | 0 | - |
| Sternebrae, misaligned | 4 (4) | 3 (3) | 12 (10) | - |
| Total No. fetuses (litters) with skeletal variations | 8 (6) | 9 (5) | 12 (10) | - |

[a]Data were extracted from Study No. 90R-008, Tables 11 and 14.

[b]More than one type of anomaly may be found in one fetus.

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

mixing problem in the preparation of the dosing suspensions.

3. Maternal Toxicity: Compound-related maternal toxicity was observed in a dose-related manner at the mid- and/or high-dose levels, and was manifested as mortality, clinical signs, decreased body weight gain and food consumption, and increased levels of alkaline phosphatase and SGOT.

   Selected hematology parameters (leukocytes, mean cell volume, and platelets) were significantly increased in animals from the high-dose group. However, these increases were not considered by the study authors to be effects of the test compound because the values were still within the normal range. Since historical control data were not submitted, the reviewers could not confirm this.

   Based on these results and the actual administered doses, the maternal NOEL and LOEL were 18 and 183 mg/kg/day, respectively.

4. Developmental Toxicity:

   a. Deaths/Resorptions: Compound-related effects were observed at the mid- and high-dose levels. In dams surviving the highest dose, the resorption rate was 100%; in dams from the mid-dose group, the number of resorptions was still significantly increased when compared to controls.

   b. Altered Growth: Compound-related effects included decreased fetal body weight and increased incidences of skeletal retardations (probably a secondary effect of reduced body weight) and were observed in fetuses from the mid-dose group.

   c. Developmental Anomalies: Compound-related anomalies included skeletal malformations (scapula, limbs and sternebrae) and variations (great vessels and sternebrae) and were observed in fetuses from the mid-dose group.

   Based on these results and the actual administered doses, the developmental NOEL and LOEL were 18 and 183 mg/kg/day, respectively.

5. Reporting Deficiencies:

   No analysis for homogeneity of the test compound in the vehicle was performed.

No historical control data were submitted for the clinical chemistry data.

No data were submitted for the range-finding study.

E. CLASSIFICATION: CORE Minimum Data.

Maternal NOEL = 18 mg/kg/day.
Maternal LOEL = 183 mg/kg/day.
Developmental Toxicity NOEL = 18 mg/kg/day.
Developmental Toxicity LOEL = 183 mg/kg/day.

F. RISK ASSESSMENT: Not applicable.

ATTACHMENT I

83-3 Teratology Studies

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?

| | | |
|---|---|---|
| 1. | YES | Technical form of the active ingredient tested. |
| 2. | YES | At least 20 pregnant animals/dose group for mice, rats, or hamsters are available. At least 12 pregnant animals/dose group for rabbits are available (three test groups and control group). |
| 3. | YES | At the high dose, overt maternal effects such as slight weight loss are reported (or a limit dose is given, 1,000 mg/kg). |
| 4.* | YES | At the low dose, no developmental toxicity is reported. |
| 5. | YES | Dosing duration is at least during the period of major organogenesis, but may extend up to one day prior to term. |
| 6.* | Y/N | Analysis for test material stability, homogeneity, and concentration in dosing medium. |
| 7. | YES | Individual daily observations. |
| 8. | YES | Individual body weights. |
| 9. | NO | Individual food consumption. |
| 10. | YES | Necropsy on all animals. |
| 11. | YES | Individual uterine examination, including numbers of fetal deaths, early and late resorptions, and viable fetuses per sex. |
| 12. | YES | All ovaries examined to determine number of corpora lutea. |
| 13. | YES | Individual litter weights and/or individual fetal weights/sex/litter. |
| 14. | YES | Individual fetal external examination. |
| 15. | YES | Individual fetal skeletal examination for 1/3 to 1/2 of each litter for rodents and all for rabbits. |
| 16. | YES | Individual fetal soft tissue examination. |

Criteria marked with a * are supplemental, may not be required for every study.