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

Nov 7 1991

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Sumithrin. Review of Developmental Toxicity Study in Rabbits.

Tox. Chem. No. 652B
Project No. 1-1283

TO: Richard King, PM Team # 72
Special Review and
Reregistration Division (H7508C)

FROM: Pamela M. Hurley, Toxicologist Pamela M. Hurley 9/30/91
Section I, Toxicology Branch I
Health Effects Division (H7509C)

THRU: Roger L. Gardner, Section Head Roger L. Gardner 11-4-91 KR 11/5/91
Section I, Toxicology Branch I
Health Effects Division (H7509C)

Record No(s). S396171

Background and Request:

A developmental toxicity study on sumithrin in rabbits was submitted by Sumitomo Chemical Company, Limited as a generic data submission in support of reregistration (FIFRA '88). The Toxicology Branch (TB-I) was asked to review and comment on the study.

Toxicology Branch Response:

The Toxicology Branch (TB-I) has reviewed the developmental toxicity study. The study adequately satisfies the regulatory requirements for a developmental toxicity study in rabbits. It is classified as Core Minimum data. The following statement taken from the review is a summary of the study.

A developmental toxicity study was conducted in which New Zealand White rabbits were administered sumithrin via gavage at 0, 30, 100, 300, or 500 mg/kg/day during gestational days (GD) 7 through 19. Maternal toxicity was evidenced as increased incidences of clinical signs and abortions at 500 mg/kg/day. Consequently, the maternal NOEL and LOEL were 100 and 300 mg/kg/day, respectively.

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Developmental toxicity, observed at 500 mg/kg/day, was manifested as an increased incidence of fetuses with hydrocephaly. Consequently, the developmental NOEL and LOEL were 300 and 500 mg/kg/day, respectively.

SOP# 2000: **ATTACHMENT D**

Reviewer Assessment of Contractor Performance

TASK No. 3-67
DYN. No. 367-F

Chemical Name: Sumithrin

Study Type	Accession Number/MRID No.	Final DER Completion Date	EPA Reviewer Evaluation	Hours Spent Performing: Secondary Reviews	Hours Spent Performing: On-Site Visits
Developmental Rabbits	412300-03	8/28/91	No problems with review. It was fine.	8	0

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Reviewer Signature: Pamela M. Hurley

Section Head Initials: Roger Gaudin 11/4/91

lw

CONFIDENTIAL BUSINESS INFORMATION
DOES NOT CONTAIN
NATIONAL SECURITY INFORMATION (EO 12065)

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EPA No.: 68D80056
DYNAMAC No.: 367-F
TASK No.: 3-67F
August 29, 1991

DATA EVALUATION RECORD

SUMITHRIN

Developmental Toxicity Study in Rabbits

STUDY IDENTIFICATION: Nemec, M.D. A teratology study in rabbits with sumithrin. (Unpublished study No. WIL-118003 conducted by WIL Research Laboratories, Inc., Ashland, OH, and submitted by Sumitomo Chemical Company, Limited, Osaka, Japan; dated May 11, 1989.) MRID No. 412300-03.

APPROVED BY:

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

Signature: Terrence J. McLellan for

Date: Aug 29, 1991

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DATA EVALUATION RECORD

1. **CHEMICAL:** 3-phenoxybenzyl (1R)-cis/trans chrysanthemate.

2. **TEST MATERIAL:** Sumithrin, 94.1% purity; clear amber liquid; lot No. 61001.

3. **STUDY/ACTION TYPE:** Developmental toxicity study in rabbits.

4. **STUDY IDENTIFICATION:** Nemec, M.D. A teratology study in rabbits with sumithrin. (Unpublished study No. WIL-118003 conducted by WIL Research Laboratories, Inc., Ashland, OH, and submitted by Sumitomo Chemical Company, Limited, Osaka, Japan; dated May 11, 1989.) MRID No. 412300-03.

5. **REVIEWED BY:**

Pia Lindström, DPH
Principal Reviewer
Dynamac Corporation

Signature: Pia Lindström
Date: Aug 29, 1991

James R. Plautz, M.S.
Independent Reviewer
Dynamac Corporation

Signature: James R. Plautz
Date: August 29, 1991

6. **APPROVED BY:**

Nicolas P. Hajjar, Ph.D.
Department Manager
Dynamac Corporation

Signature: William L. McLellan for
Date: Aug 29, 1991

Esther Saito, Ph.D.
Section Head
Science Administration Section
Science Analysis and Coordination Branch
(H-7509C)

Signature: Roy Hardee Gar
Date: 11/4/91

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

MRID NUMBER: 412300-03.

TEST MATERIAL: Sumithrin, 94.1% purity; clear amber liquid; lot No. 61001.

SYNONYMS: S-2539-Forte, d-phenothrin.

STUDY NUMBER: WIL-118003.

SPONSOR: Sumitomo Chemical Company, Limited, Osaka, Japan.

TESTING FACILITY: WIL Research Laboratories, Inc., Ashland, OH.

TITLE OF REPORT: A Teratology Study in Rabbits with Sumithrin.

AUTHOR: Nemec, M.D.

REPORT ISSUED: May 11, 1989.

CONCLUSIONS: A developmental toxicity study was conducted in which New Zealand White rabbits were administered sumithrin via gavage at 0, 30, 100, 300, or 500 mg/kg/day during gestational days (GD) 7 through 19. Maternal toxicity was evidenced as increased incidences of clinical signs and abortions at 500 mg/kg/day and decreased body weight gain and food consumption during the treatment period at 300 and 500 mg/kg/day. Consequently, the maternal NOEL and LOEL were 100 and 300 mg/kg/day, respectively.

Developmental toxicity, observed at 500 mg/kg/day, was manifested as an increased incidence of fetuses with hydrocephaly. Consequently, the developmental NOEL and LOEL were 300 and 500 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 rabbits.

A. MATERIALS:

Test Compound:
- Purity: 94.1%.
- Description: Clear amber liquid.
- Lot No.: 61001.
- Contaminants: Not reported.

Vehicle: 0.5% aqueous methylcellulose (source: Dow Chemical Company).

Test Animals:
- Species: Rabbit.
- Strain: New Zealand White.
- Source: Hazleton Research Products, Denver, PA.
- Age: Approximately 5.5 months at study initiation.
- Weight: 3257-5249 g on GD 0.

B. STUDY DESIGN:

This study was designed to assess the potential of sumithrin to cause developmental toxicity in rabbits when administered daily via gavage from GD 7 through 19, inclusive.

Mating: Following 30 days of acclimation, females were artificially inseminated using semen from 10 males of the same strain and from the same supplier. Sperm motility (>50%) and concentration (>3 million motile sperm/mL) were determined before insemination. A volume of 0.25 to 0.50 mL of the diluted semen from each male was used to inseminate an equal number of females in each group. To ensure ovulation, each doe was given an iv injection of 100 USP units of human chorionic

gonadotropin (A.P.L. Ayerst Laboratories, Inc., NY, NY) immediately after the insemination. The day of insemination was designated day 0 of gestation.

Group Arrangement: Animals were randomly assigned to dose groups using a stratified block design based on body weight as follows:

Test Group	Dose Level (mg/kg/day)	Number Assigned per Group
Control	0	20
2	30	20
3	100	20
4	300	20
5	500	20

Dosing: Doses were administered daily via gavage on GD 7 through 19 in a volume of 5 mL/kg. The individual body weights recorded on GD 7 were used to provide the correct mg/kg/day dose. Dose suspensions (three batches) were prepared weekly in 0.5% aqueous methylcellulose and stored refrigerated. Analyses for stability and homogeneity had been performed on one batch used for the range-finding studies; analyses for concentration were performed on all three batches and dose levels used in the present study.

The selection of dose levels was based on the results of two range-finding studies. In the first study, five nonpregnant rabbits/group were administered sumithrin at 0, 250, 500, 1000, 2000, or 3000 mg/kg/day for 5 days; toxicity (clinical signs and reduced body weight and food consumption) was observed at 2000 and 3000 mg/kg/day. In the second study, seven pregnant rabbits/group were administered sumithrin at 0, 500, 1000, 2000, or 3000 mg/kg/day on GD 7 through 19; maternal toxicity (abortions, clinical signs, and reduced body weight and food consumption) and developmental toxicity (reduced fetal body weight and decreased viability) were observed at all dose levels.

Observations: Animals were observed twice daily for mortality, moribundity, general appearance, and behavior, and at 0, 1, and 4 hours postdosing for overt signs of toxicity. Females that aborted and/or died were necropsied, and gross findings and fetuses from these animals were preserved in 10% neutral buffered formalin for possible microscopic examination. Body weight were recorded on GD 0, 7, 8, 10, 13, 16, 19, 20, 23, 26,

and 29. Food consumption was recorded daily during the entire gestation. Females were sacrificed on GD 29 by an injection of T-61 Euthanasia solution, and litters were delivered by cesarean section. Examination of the dams at sacrifice included the following:

- Gross pathological observations;
- Number of corpora lutea;
- Number of implantation sites; and
- Number and location of resorptions (early and late) and live and dead fetuses.

Uteri from apparently nonpregnant animals were stained with 10% ammonium sulfide to detect early embryonic death.

All fetuses were examined in the following manner:

- Fetuses were weighed and sexed;
- External anomalies were recorded for all fetuses and included palate, eyes, and external orifices;
- Visceral anomalies were evaluated (including the heart and major vessels) using Staples' fresh dissection technique. The fetal heads were examined by a midcoronal slice; and
- Fetuses were evaluated for skeletal anomalies after staining with Alizarin Red S using a modification of Dawson's technique.

<u>Statistical Analysis</u>: The following methods were used.

- Maternal body weight, body weight gain, food consumption, numbers of viable fetuses, implantations, and corpora lutea, and fetal body weight--ANOVA and Dunnett's test;
- Fetal sex ratios--Chi-square test with Yates' correction factor;
- Numbers of early and late resorptions, dead fetuses, and postimplantation losses--Mann-Whitney U-test;
- Fetal and litter incidences of malformations and variations--Fisher's Exact test; and
- Incidence data including males/litter (%), resorptions (%), and implantation efficiency--Kruskall-Wallis and Terpstra-Jonckeere test for trend analysis.

Compliance:

- A Statement of No Data Confidentiality Claim, dated May 16, 1989, was provided;

- A signed Statement of Compliance with EPA and Japanese GLPs as well as MAFF (Ministry of Agriculture, Forestry, and Fisheries) guidelines for registering agricultural chemicals in Japan, dated May 11 and 30, 1989, was provided; and

- A signed Quality Assurance Statement, dated May 11, 1989, was provided.

C. RESULTS:

The following results were reported by the study author:

1. Test Material Analyses: Analyses for homogeneity of the test material in methylcellulose revealed mean sample homogeneity and concentration values between 98.3 and 109.0% of nominal concentrations; analyses for stability of the test material in methylcellulose after 11 days of refrigerated storage revealed individual values between 96.0 and 105.3% of nominal concentrations; and analyses of concentration of the test material in methylcellulose revealed mean values between 90.7 and 102.5% of nominal concentrations for the three batches.

2. Maternal Toxicity:

Mortality: At 300 mg/kg/day, one animal died on GD 20 following decreased defecation on GD 16-19; the cause of death was not determined. One animal from the control group was sacrificed *in extremis* on GD 7 following excessive weight loss on GD 0-7; necropsy revealed a thickened and reddened urinary bladder, which also had a white area (1.5 cm in diameter).

Abortion: Abortions occurred in the control (one doe; GD 21), 100- (three does; GD 24, 25, and 28), 300- (one doe; GD 29), and 500- (four does; GD 19, 22, 26, and 27) mg/kg/day dose groups. Necropsy revealed two females (at 100 and 500 mg/kg/day) with accentuation of lobular markings in the liver, one of which also had pale kidneys and dark red areas in the stomach (100 mg/kg/day); one female (at 500 mg/kg/day) with a clear fluid-filled thoracic cavity; and one female (at 100 mg/kg/day) with a necrotic hemorrhagic uterus and nine severely autolyzed late resorptions.

Clinical Observations: At 500 mg/kg/day, decreased defecation and urination were observed in an increased number of animals. Also at this dose level, green staining of the fur in the urogenital area was observed in three animals but was not seen at any other dose level. Additional clinical signs, occurring either as single events or in all study groups at similar frequencies, included alopecia, mucoid/soft stool, missing/malaligned upper incisors, diarrhea, swollen urogenital area, ocular discharge, and dried/wet red/tan/yellow anogenital staining.

Body Weight: A summary of maternal body weight gain for selected time intervals is presented in Table 1. At 500 mg/kg/day, body weight gain was consistently decreased; the decrease was significant ($p < 0.05$ or 0.01) for GD 7-13, 7-19, 7-20, 7-23, 7-26, and 20-23. At 300 mg/kg/day, body weight gain was slightly (but not significantly) decreased on GD 7-10. At 100 mg/kg/day, body weight gain was significantly decreased on GD 7-23 ($p < 0.05$) and 20-23 ($p < 0.01$). However, these decreases were not considered to be biologically meaningful because there was no dose-related trend in the 300 mg/kg/day dose group. Body weights (data not shown) never differed significantly between dose groups, including the control group.

Food Consumption: A summary of food consumption for selected time intervals is presented in Table 2. At 500 mg/kg/day, food consumption (g/kg/day) was consistently decreased on GD 7-26 (53-86% of controls) reaching a significant level ($p < 0.05$) on GD 19-20 and 20-23. At 300 mg/kg/day, food consumption was nonsignificantly decreased (81-85% of controls) on GD 8-20. At 100 mg/kg/day, food consumption was significantly decreased on GD 20-23 ($p < 0.05$). Again, as with the body weight gain data, the decrease in food consumption was not considered to be biologically meaningful at 100 mg/kg/day because there was no comparable decrease at 300 mg/kg/day.

Gross Pathological Observations: Accentuation of the lobular markings of the liver and dark red areas in the stomach were observed at all treatment levels, excluding the control group. The incidences of occurrence were not dose-related, however (0/18, 4/20, 6/17, 1/18 and 3/16 for liver and 0/18, 2/20, 2/17, 1/18 and 1/16 for stomach in controls, 30, 100, 300 and 500 mg/kg/day dose groups, respectively). Depressed/pale areas of the kidneys and fluid-filled midabdominal regions were noted as single events at 100 and 500 mg/kg/day, respectively.

Cesarean Section Observations: A summary of cesarean section data is presented in Table 3. No significant differences were observed between any dose levels for any parameter.

TABLE 1. Mean Body Weight Gain (g ± S.D.)[a]

Dose Group (mg/kg/day)	Prior to Dosing Period (GD 0-7)	Dosing Period (GD 7-19)	Post Dosing Period (GD 20-29)	Entire Gestation Period (GD 0-29)
0	53 ± 95/14[b]	85 ± 113/14	-48 ± 137/13	137 ± 195/13
30	98 ± 73/18	116 ± 109/18	-23 ± 183/18	198 ± 212/13
100	64 ± 82/17	59 ± 224/17	-138 ± 266/14	-41 ± 404/14
300	52 ± 82/19	3 ± 211/19	64 ± 188/17	169 ± 239/17
500	102 ± 98/16	-72 ± 250*/16	-56 ± 152/12	6 ± 371/12

[a]Data were extracted from Study No. WIL-118003, Table 4.

[b]Number of does weighed.

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

TABLE 2. Mean Food Consumption (g/kg/day ± S.D.)[a]

Dose Group (mg/kg/day)	Prior to Dosing Period (GD 0-7)	Dosing Period (GD 7-20)	Post Dosing Period (GD 20-29)	Entire Gestation Period (GD 0-29)
0	34 ± 5.9	33 ± 5.1	21 ± 6.1	29 ± 3.2
30	38 ± 6.0	35 ± 5.9	20 ± 8.6	31 ± 4.9
100	37 ± 4.4	32 ± 10.4	13 ± 12.2	27 ± 8.2
300	35 ± 5.4	28 ± 8.8	25 ± 7.6	29 ± 5.8
500	39 ± 4.9	25 ± 14.5	17 ± 11.2	27 ± 8.7

[a]Data were extracted from Study No. WIL-118003, Table 6.

TABLE 3. Cesarean Section Observations[a]

Parameter	Dose Level (mg/kg/day) 0	30	100	300	500
No. animals assigned	20	20	20	20	20
No. animals pregnant	14	18	17	19	16
Pregnancy rate (%)	70	90	85	95	80
Maternal wastage					
No. died or killed/pregnant	0	0	0	1	0
No. died/nonpregnant	1	0	0	0	0
No. nonpregnant	6	2	3	1	4
No. aborted	1	0	3	1	4
Total No. corpora lutea	125	173	169	160	117
Corpora lutea/doe	9.6 ± 2.9[b]	9.6 ± 2.6	12.1 ± 2.1	9.4 ± 3.3	9.8 ± 3.3
Total No. implantations	100	133	121	129	93
Implantations/doe	7.7 ± 2.9	7.4 ± 2.6	8.6 ± 3.3	7.6 ± 3.2	7.8 ± 2.3
Total No. live fetuses	88	126	110	120	77
Live fetuses/doe	6.8 ± 3.1	7.0 ± 2.7	7.9 ± 2.7	7.1 ± 3.2	6.4 ± 2.8
Total No. resorptions	12	7	10	9	16
Early	11	7	3	7	5
Late	1	0	7	2	11
Resorptions/doe	0.9 ± 0.8	0.4 ± 0.6	0.7 ± 1.0[c]	0.5 ± 0.7	1.3 ± 2.4
Total No. dead fetuses	0	0	1	0	0
Fetal weight/litter (g)	41.6 ± 5.8	43.7 ± 6.3	36.6 ± 10.3	42.4 ± 3.8	40.3 ± 7.1
Preimplantation loss (%)[c]	20.1	22.6	29.1	18.9	18.4
Postimplantation loss (%)[c]	17.6	5.8	7.0	11.3	15.1
Sex ratio (% male)[c]	44	47	50	50[d]	53

[a]Data were extracted from Study No. WIL-118003, Table 8 and individual animal data.

[b]Mean ± S.D.

[c]Recalculated by the reviewers to exclude the dead fetus.

[d]Sexes from one litter not available.

3. Developmental Toxicity:

A summary of incidences of malformations is presented in Table 4.

External Examinations: At 500 mg/kg/day, four fetuses (from three litters) exhibited hydrocephaly (with or without dome head) and one of those fetuses also had umbilical herniation of the intestines; at 300 mg/kg/day, one fetus exhibited carpal and/or tarsal flexure and another fetus (from a different litter) had microphthalmia and/or anophthalmia; and at 100 mg/kg/day, one fetus exhibited spina bifida and carpal and/or tarsal flexure. No variations were noted.

Visceral Examinations: Two fetuses (one in the control group and one in the 500-mg/kg/day group) exhibited heart and/or great vessel anomalies. Variations (data not shown), evident in all dose groups at similar incidences, included major blood vessels and retrocaval ureter. A single incident of hemorrhagic ring around the iris was noted at 500 mg/kg/day.

Skeletal Examinations: At 300 mg/kg/day, one fetus exhibited fused frontals; at 100 mg/kg/day, one fetus exhibited spherical rib enlargement; and at 30 mg/kg/day, one fetus exhibited fused ribs, while another fetus (from a different litter) exhibited forked ribs. Variations (data not shown), evident in all dose groups at similar incidences, included 13th rudimentary or 13th full rib(s), 27 presacral vertebrae, incomplete ossification in skull bone(s) and sternebrae, bent hyoid arch(es), and sternebrae with threadlike attachment. Malaligned sternebrae, 7th sternebrae, and accessory skull bone(s) occurred as single events in all dose groups except for the 500-mg/kg/day group.

D. REVIEWERS' DISCUSSION/CONCLUSIONS:

1. Acceptance Criteria: The reviewers have completed an Acceptance Criteria checklist (Attachment I) that is included with this evaluation. All criteria were satisfied. Criterion 1 was considered to be fulfilled, although the report did not state that the technical form of the test compound was used. The 94.1% purity of the test compound is consistent with the technical grade requirements of the guideline.

TABLE 4. Summary of Fetal Malformations[a]

Finding[b]	Dose Level (mg/kg/day) 0	30	100	300	500
No. fetuses (litters)	88 (12)	126 (18)	110 (14)	120 (16)	77 (11)
EXTERNAL OBSERVATIONS:					
Carpal and/or tarsal flexure	0	0	1	1	0
Spina bifida	0	0	1	0	0
Hydrocephaly (with or without dome head)	0	0	0	0	4 (3)
Umbilical herniation of intestines	0	0	0	0	1
Microphthalmia and/or anophthalmia	0	0	0	1	0
Total No. fetuses (litters) with external malformations	0	0	1	2 (2)	4 (3)
VISCERAL OBSERVATIONS:					
Heart and/or great vessel anomaly	1[c]	0	0	0	1[d]
Total No. fetuses (litters) with visceral malformations	1	0	0	0	1
SKELETAL OBSERVATIONS:[e]					
Spherical rib enlargement	0	0	1	0	0
Fused ribs	0	1	0	0	0
Forked ribs	0	1	0	0	0
Fused frontals	0	0	0	1	0
Vertebral anomaly with or without associated rib anomaly	0	0	0	1	0
Total No. fetuses (litters) with skeletal malformations	0	2 (2)	1	2 (2)	0
TOTAL NO. FETUSES (LITTERS) WITH ANY MALFORMATIONS	1	2 (2)	2 (2)	4 (4)	4 (3)

[a]Data were extracted from Study No. WIL-118003, Table 9.

[b]More than one finding may be observed in one fetus.

[c]Bulbous aorta: small interventricular defect in septum. Pulmonary trunk reduced in size with no opening into heart.

[d]Rudimentary atrium, left.

2. Test Material Analyses: Homogeneity and stability (11 days, refrigerated) of the test material in the vehicle were confirmed. Concentrations of the dosing suspensions were within ±10% of nominal values.

3. Maternal Toxicity: Maternal toxicity was evidenced by increased incidences of abortions and clinical signs at 500 mg/kg/day and decreased body weight gain and food consumption during the dosing period at 500 and 300 mg/kg/day.

   The four abortions occurring at 500 mg/kg/day were considered to be compound-related. In the dose range-finding study similar effects were observed; 4/7 does aborted at 500 mg/kg/day. On the other hand, the three abortions occurring at 100 mg/kg/day in the present study were considered to be spontaneous in nature, since no other signs of toxicity were evident at this dose level and abortions had not occurred in a dose-related manner (only one abortion was noted at 300 mg/kg/day). A comparison with historical control data further supports this conclusion; in all but one study (in which the vehicle was 1% polyvinyl alcohol solution), the number of abortions ranged from 2/36 to 3/17.

   Clinical signs similar to those in the present study (decreased defecation/urination and green staining around the urogenital area), decreased body weight, and reduced food intake had been observed in the range-finding study in a dose-related manner, thus indicating compound-related effects.

   Based on these results, the maternal NOEL and LOEL were 100 and 300 mg/kg/day, respectively.

4. Developmental Toxicity:

   a. Deaths/Resorptions: No compound-related effects were noted. At 500 mg/kg/day, a slight increase in the number of resorptions/doe was noted, which was mostly due to 100% resorptions in one animal. The number of resorptions/doe was, however, within the historical range, and the increase was not considered to be biologically relevant.

   b. Altered Growth: No compound-related effects were observed.

   c. Developmental Anomalies: At 500 mg/kg/day, four fetuses (from three litters) exhibited hydrocephaly; this malformation was not observed at any other dose level or among controls. This increase was not

statistically significant, but it was outside the range of the historical control data (historical range for fetal incidence: 0.0-3.0%; historical range for litter incidence: 0.0-5.6% versus present study; fetal incidence range: 5.2%; and litter incidence: 27%), therefore, it was considered to be a compound-related effect of biological significance.

Based on these results, the NOEL and LOEL for developmental toxicity w re 300 and 500 mg/kg/day, respectively.

5. Study Deficiency:

No gravid uterine weights were recorded; therefore, the corrected maternal body weight could not be calculated.

E. CLASSIFICATION: CORE Minimum Data.

Maternal NOEL = 100 mg/kg/day.
Maternal LOEL = 300 mg/kg/day.
Developmental Toxicity NOEL = 300 mg/kg/day.
Developmental Toxicity LOEL = 500 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.* YES Analysis for test material stability, homogeneity, and concentration in dosing medium.

7. YES Individual daily observations.

8. YES Individual body weights.

9. YES 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.