3-22-95

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

MAR 22 1995

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

**MEMORANDUM**

SUBJECT: Esfenvalerate - Submission of Developmental Toxicity Studies in Rats and Rabbits (EPA ID #000352-00515)

Tox Chemical No.: 263
PC No.: 109303
DP Barcode.: D204051
Submission No.: S467236

FROM: William B. Greear, M.P.H. William B. Greear 1/23/95
Review Section IV, Toxicology Branch-I
Health Effects Division (7509C)

TO: George LaRocca/John Hebert, PM#13
Insecticide-Rodenticide Branch
Registration Division (7505C)

THRU: John D. Doherty, Ph.D., Acting Section Head
Review Section IV, Toxicology Branch I
Health Effects Division (7509C)

2/13/95

I. Conclusions

The esfenvalerate developmental toxicity studies in rats and rabbits are acceptable and satisfy the guideline requirements for series 83-3(a)(b) developmental toxicity studies.

II. Requested Action

The Registration Division requests that Toxicology Branch-I evaluate the following two studies:

- "A Developmental Toxicity Study of S-1344 in Rats", Study No. WIL-118010, 1/10/91, MRID 43211504 (main). 43211502 (range-finding)
- "A Developmental Toxicity Study of S-1344 in Rabbits," Study No. WIL-118013, 10/10/90, MRID 43211503 (main), 43211501 (range-finding)

III. Discussion

The results of the evaluation of the developmental toxicity studies are provided below:

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- Developmental Toxicity Study in Rats

Esfenvalerate was administered to groups of 25 Sprague Dawley Crl:CD®BR female rats by gavage at doses of 0, 2.5, 5.0, 10.0 or 20.0 mg/kg/day from gestation days 6 through 15 (pilot study doses were 1.0, 2.0, 3.0, 4.0, 5.0 and 20 mg/kg/day).

Maternal toxicity was observed at all doses in the main study. At 2.5 mg/kg/day there were behavioral/CNS clinical signs including erratic jerking and extension of forelimbs (22/25 rats), rapid side-to-side head movement (19/25 rats), and excessive grooming (22/25 rats). At 5 mg/kg/day there was also hindlimb jerking and soft or mucoid stools. At 10 mg/kg/day hypersensitivity to touch and tremors were also seen. At 20 mg/kg/day there were high carriage, goosestepping ataxia, ataxia and convulsions. Incidence and frequency increased with increasing dose. Most signs were observed at 4 hours post dosing but resolved by the next day. At 20 mg/kg/day some signs were observed as early as 1 hour post dosing. The pilot study had similar types of signs at 4 mg/kg/day and above but no signs at 3 mg/kg/day and below. **The NOEL is 2.0 mg/kg/day (from the pilot study) and the LEL is 2.5 mg/kg/day based on behavioral/CNS clinical signs.**

There was no evidence of developmental toxicity at any dose. **The NOEL is 20 mg/kg/day, the highest dose tested.**

This study is classified core-minimum. This study satisfies the guideline requirement for a developmental study (83-3a) in rats.

Special Review Criteria (40 CFR 154.7) None

- Developmental Toxicity Study in Rabbits

Esfenvalerate was administered to groups of 20 New Zealand White female rabbits by gavage at doses of 0, 3.0, 10.0 or 20.0 mg/kg/day from gestation days 7 through 19 (pilot study doses were 0,2.0, 3.0, 4.0, 4.5, 5.0 or 20.0 mg/kg/day).

Maternal toxicity was observed at all doses in the main study. At 3.0 mg/kg/day there were behavioral/CNS clinical signs including erratic jerking and extension of forelimbs (11/20 rabbits), rapid side-to-side head movement (2/20 rabbits), excessive grooming (11/20 rabbits) and sneezing (3/20 rabbits). At 10.0 mg/kg/day there was also hindlimb jerking and hypersensitivity to touch. At 20.0 mg/kg/day there were tremors, ataxia, diarrhea, decreased defecation

and urination. Incidence and frequency increased with increasing dose. Most signs were observed at 1 to 4 hours post dosing and lasting to the next day for rabbits in the 10.0 and 20.0 mg/kg/day groups. The pilot study had similar types of signs at 3.0 mg/kg/day and above but no signs at 2.0 mg/kg/day. Body weight, body weight gain and food consumption were also decreased in the 10 and 20 mg/kg/day group in the main study. Body weight and food consumption changes were not observed in the pilot study. **The NOEL is 2.0 mg/kg/day (from the pilot study) and the LEL is 3.0 mg/kg/day based on behavioral/CNS clinical signs.**

There was no evidence of developmental toxicity at any dose. **The NOEL is equal to or greater than 20.0 mg/kg/day, the highest dose tested. The LEL is greater than 20.0 mg/kg/day.**

This study is classified **core-guideline.** This study satisfies the guideline requirement for a developmental study (83-3b) in rabbits.

Special Review Criteria (40 CFR 154.7) None

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OFFICE OF PESTICIDES/HED/TOX
ONELINERS

P. C. No: 109303 TOXCHEM NO.: 268J Chemical Name: Esfenvalerate

| CITATION | MATERIAL | MRID NUMBER | RESULTS | TOX CAT | CORE GRADE DOC.# |
|---|---|---|---|---|---|
| Develop. (83-3a)<br>Species: rat<br>Lab. Name: Will Res. Lab.<br>Study No: WIL-118010<br>Date: 1/10/91 | S-1844 (esfenvalerate) Purity 97.1% a.i. | 432115-04 (main)<br>432115-02 (pilot) | Dose levels: Administered to Sprague Dawley Crl:CD®BR rats by gavage were 0, 2.5, 5.0, 10.0 or 20.0 mg/kg/day. (pilot study doses were 1.0, 2.0, 3.0, 4.0, 5.0 and 20 mg/kg/day)<br><br>Maternal NOEL = 2.0 mg/kg/day (taken from the pilot study)<br>Maternal LOEL = 2.5 mg/kg/day based on behavioral/CNS clinical signs including erratic jerking and extension of forelimbs (22/25 rats), rapid side-to-side head movement (19/25 rats), and excessive grooming (22/25 rats).<br>At 5 mg/kg/day there was also hindlimb jerking and soft or mucoid stools. At 10 mg/kg/day hypersensitivity to touch and tremors were also seen. At 20 mg/kg/day there were high carriage, goosestepping ataxia, ataxia and convulsions. Incidence and frequency increased with increasing dose.<br><br>Developmental Toxicity NOEL $\geq$ 20 mg/kg/day<br>Developmental Toxicity LOEL > 20 mg/kg/day | | minimum |

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# U.S. ENVIRONMENTAL PROTECTION AGENCY
# OFFICE OF PESTICIDES/HED/TOX
# ONELINERS

P. C. No: 109303 TOXCHEM NO.: 268J Chemical Name: Esfenvalerate

| CITATION | MATERIAL | MRID NUMBER | RESULTS | TOX CAT | CORE GRADE DOC.# |
|---|---|---|---|---|---|
| Develop. (83-3b)<br>Species: rabbit<br>Lab. Name: Wil Res. Lab.<br>Study No: WIL-118013<br>Date: 10/10/90 | S-1844 (esfenvalerate) Purity 97.1% a.i. | 432115-03 (main)<br>432115-01 (pilot) | Esfenvalerate was administered to groups of 20 New Zealand White female rabbits by gavage at doses of 0, 3.0, 10.0 or 20.0 mg/kg/day from gestation days 7 through 19 (pilot study doses were 0, 2.0, 3.0, 4.0, 4.5, 5.0 or 20.0 mg/kg/day).<br><br>Maternal toxicity was observed at all doses in the main study. At 3.0 mg/kg/day there behavioral/CNS clinical signs including erratic jerking and extension of forelimbs (11/20 rabbits), rapid side-to-side head movement (2/20 rabbits), excessive grooming (11/20 rabbits) and sneezing (3/20 rabbits). At 10.0 mg/kg/day there was also hindlimb jerking and hypersensitivity to touch. At 20.0 mg/kg/day there were tremors, ataxia, diarrhea, decreased defecation and urination. Incidence and frequency increased with increasing dose. Most signs were observed at 1 to 4 hours post dosing and lasting to the next day for rabbits in the 10.0 and 20.0 mg/kg/day groups. The pilot study had similar types of signs at 3.0 mg/kg/day and above but no signs at 2.0 mg/kg/day. Body weight, body weight gain and food consumption were also decreased in the 10 and 20 mg/kg/day group in the main study. Body weight and food consumption changes were not observed in the pilot study. **The NOEL is 2.0 mg/kg/day (from the pilot study) and the LEL is 3.0 mg/kg/day based on behavioral/CNS clinical signs.**<br><br>There was no evidence of developmental toxicity at any dose. **The NOEL is equal to or greater than 20.0 mg/kg/day, the highest dose tested. The LEL is greater than 20.0 mg/kg/day.** | | guideline |

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[ESFENVALERATE] Developmental Study (83-3b)

EPA Reviewer: William B. Greear, M.P.H., D.A.B.T. William B. Greear, Date 10/21/94
Review Section 4, Toxicology Branch 1 (7509C)
EPA II° Reviewer: Marion Copley, D.V.M., D.A.B.T. Marion Copley, Date 11/14/94
Review Section 4, Toxicology Branch 1 (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Developmental Study - Rabbit (83-3b)

TOX. CHEM. NO.: 268J

P.C. CODE: 109303

MRID No.: 432115-03 (main), 432115-01 (RF)

TEST MATERIAL: Esfenvalerate

SYNONYMS: S-1844 (Sumitomo), ASANA (DuPont), DPX-YB656-84 (DuPont), (S)-alpha-cyano-3-phenoxybenzyl (S)-2-(4-chlorophenyl)-3-methylbutyrate

STUDY NUMBER(S): WIL-118013

SPONSOR: Sumitomo Chemical Company, Ltd.

TESTING FACILITY: Wil Research Laboratories, Ashland, Oh.

TITLE OF REPORT: A Developmental Toxicity Study of S-1844 in Rabbits

AUTHOR(S): Mark D. Nemec, BS

REPORT ISSUED: 10/10/90

EXECUTIVE SUMMARY

Esfenvalerate was administered to groups of 20 New Zealand White female rabbits by gavage at doses of 0, 3.0, 10.0 or 20.0 mg/kg/day from gestation days 7 through 19 (pilot study doses were 0, 2.0, 3.0, 4.0, 4.5, 5.0 or 20.0 mg/kg/day).

Maternal toxicity was observed at all doses in the main study. At 3.0 mg/kg/day there were behavioral/CNS clinical signs including erratic jerking and extension of forelimbs (11/20 rabbits), rapid side-to-side head movement (2/20 rabbits), excessive grooming (11/20 rabbits) and sneezing (3/20 rabbits). At 10.0 mg/kg/day there was also hindlimb jerking and hypersensitivity to touch. At 20.0 mg/kg/day there were tremors, ataxia, diarrhea, decreased defecation and urination. Incidence and frequency increased with increasing dose. Most signs were observed at 1 to 4 hours post dosing and lasting to the next day

for rabbits in the 10.0 and 20.0 mg/kg/day groups. The pilot study had similar types of signs at 3.0 mg/kg/day and above but no signs at 2.0 mg/kg/day. Body weight, body weight gain and food consumption were also decreased in the 10 and 20 mg/kg/day group in the main study. Body weight and food consumption changes were not observed in the pilot study. **The NOEL is 2.0 mg/kg/day (from the pilot study) and the LEL is 3.0 mg/kg/day based on behavioral/CNS clinical signs.**

There was no evidence of developmental toxicity at any dose. **The NOEL is equal to or greater than 20.0 mg/kg/day, the highest dose tested. The LEL is greater than 20.0 mg/kg/day.**

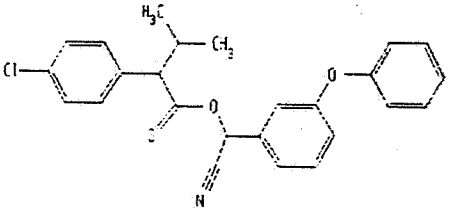
This study is classified **core-guideline.** This study satisfies the guideline requirement for a developmental study (83-3b) in rabbits.

Special Review Criteria (40 CFR 154.7) None

## I. MATERIALS AND METHODS

### A. MATERIALS:

1. Test Material: S-1844
   Description: viscous, clear brown liquid
   Lot/Batch #: 71219
   Purity: 97.1 % a.i. (dose calculations assumed 100 %)
   Stability of compound: considered stable at room temperature
   CAS #: 66230-04-4
   Structure:



2. Vehicle: 100 % Mazola Corn Oil Lot/Batch Oct 1490A, Supplier: Best Foods, CPC International, Inc.

3. Test animals: Species: Rabbit
   Strain: New Zealand White
   Age and weight when bred:
   2.835-4.145 kg, sexually mature adults
   Source: Hazleton Research Products Inc., Denver, Pennsylvania
   Housing: individually (except during mating)
   Environmental conditions (actual): Temperature: 64° - 74°F
   Humidity: 25% - 69%
   Air changes: ~10-15/hour

Photoperiod: 12 hr light/12 hr dark

Acclimation period: 8 weeks

B. PROCEDURES AND STUDY DESIGN:

This study was designed to assess the developmental toxicity potential of S-1844 when administered by gastric intubation to female rabbits on gestation days 7 through 19[1], inclusive. Does were sacrificed on day 29 of gestation.

1. Mating: Rabbits were artificially inseminated on day 0G (day 0 of gestation) with semen from 10 resident males. Semen from 1 male was used for 2 females in each group. Females were given 100 U.S.P. Units of human chorionic gonadotropin immediately following insemination by intravenous injection.

2. Animal Assignment and dose selection is presented in table 1. Assignment of pregnant dams was random using a computer generated randomization procedure with stratification for body weight.

TABLE 1 Animal Assignment

| Test Group | Dose Level (mg/kg) | Number Assigned |
|---|---|---|
| Vehicle Control | 0 | 20 |
| Low Dose | 3.0 | 20 |
| Mid Dose | 10.0 | 20 |
| High Dose | 20.0 | 20 |

3. Dose selection rationale: a) Dose selection was based on a range finding study conducted at WIL Labs. (study number WIL-118012, data not presented). Doses were 0, 5.0, 10.0, 20.0 and 30.0 mg/kg/day. There were 2 mortalities and 1 abortion at the high dose and clinical signs of toxicity noted at all dose levels. At 10 mg/kg/day there was inhibition of body weight gain and food consumption for the first 3 days of dosing These effects continued throughout the study in the 20.0 and 30.0 mg/kg/day doses. It was noted that "fetal body weight tended to be decreased at a dosage of 30.0 mg/kg/day."
b) The dose selection and conclusions are also supported by a pilot developmental

[1] 1 female from the 20 mg/kg/day group was inadvertently administered test material on day 20G. This was not considered by the lab. to effect the outcome of the study (appears to be a reasonable conclusion by TB1).

toxicity study (MRID 432115-01, Haskell Lab. Rept. # 43-94) that was conducted after completion of the main study. (for details see APPENDIX 1)

NOTE: This pilot was completed by DuPont prior to their becoming aware of a previously conducted developmental rabbit study with Esfenvalerate (by Sumitomo).

4. Dosing: All doses were in a volume of 0.5 ml/kg of body weight/day prepared 2 times during the dosing period. The dosing suspensions wereanalyzed for concentration and found to be within 10 % of nominal. Stability analyses were conducted on these preparations after 1, 7 and 14 days. The mean concentrations ranged from 93.1 to 102%. Dosing was based on the body weight on gestation day 7[2].

C. OBSERVATIONS:

1. Maternal Observations and Evaluations - The animals were checked for mortality or clinical signs twice daily. In addition animals were observed for pharmacotoxic signs at dosing and about 4 hours later. Body weight was recorded on days 0G, 7G, 8G, 10G, 13G, 16G, 19G, 20G 23G, 26G and 29G. Food consumption (gms/rat/day and gms/kg/day) was recorded daily throughout gestation. Weights during gestation were also calculated minus the gravid uterus. Dams were sacrificed on day 29G by intravenous injection of T-61[R]Euthanasia solution. Examinations at sacrifice consisted of: weighing of the gravid uterus; examination of the thoracic, abdominal and pelvic cavities; correlation of post mortem findings with ante mortem comments and abnormalities; counting of number of corpora lutea on each ovary; recording number and location of all fetuses, early and late resorptions. Uteri with no evidence of macroscopic nidation were examined for early implantation loss using 10% ammonium sulfide solution. Uterine data were summarized using the following 2 methods:

$$\text{Group Mean Litter Basis: Postimplantation Loss/Litter} = \frac{\text{No. Dead Fetuses, Resorptions (all)/Group}}{\text{No. Cravid Females/Group}}$$

$$\text{Proportional Litter Basis: Summation per Group (\%)} = \frac{\text{Postimplantation Loss/Litter (\%)}^{a}}{\text{No. of Litters/Group}}$$

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[2] On one day the does were inadvertently dosed based on their most recent weight rather than day 7G. Based on the dosing error volumes described in the report it is unlikely that the study conclusions were altered.

[a]Postimplantation Loss/Litter (%) = No. Dead Fetuses, Resorptions (all)/Litter X 100

No. Implantation Sites/Litter

2. Fetal Evaluations - The fetuses were examined in the following manner: weighed and sexed with internal confirmation. Also conducted were external examination and crown-rump measurement. Each fetus was examined viscerally by a modification of the Stuckhardt and Poppe fresh dissection technique which includes the heart and major vessels. Kidneys were also examined and graded for renal papillae development by the method of Woo and Hoar. Heads from about 1/2 of the fetuses/doe were fixed in Bouin's fixative for soft-tissue examination by the Wilson[3] technique. Heads from the remaining 1/2 were examined with a mid-coronal slice. All fetuses were eviscerated, fixed in alcohol, macerated in potassium hydroxide and stained with Alizarin Red S for skeletal examination. Both variations and malformations were recorded. Data were summarized by, a) incidence of a finding both as a % of the # of fetuses and # of litters available for examination in the group and, b) the litter as the basic unit calculating the # of affected fetuses/litter on a proportional basis.

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

D. STATISTICAL ANALYSIS: The statistical analysis methods are attached (taken from page 21 of the report).

E. COMPLIANCE: Signed and dated GLP and Quality Assurance statements were provided.

## II. RESULTS

### A. MATERNAL TOXICITY

1. Mortality - One 20 mg/kg/day group rabbit died on 17G. This did not appear to be treatment related.

2. Clinical Observations - Clinical signs of toxicity occurred in all treatment groups. These were primarily observed 1 to 4 hours post dosing and persisting through the daily examinations prior to dosing on the following day at 10.0 and 20.0 mg/kg/day. In the low dose group (**3.0 mg/kg/day**) signs were limited to the following transient

[3] Wilson, J.G., Embryological Consideration in Teratology, J.G. Wilson and Warkany, eds. Teratology - Principles and Techniques, The University of Chicago Press, Chicago, Illinois, 1965

behavioral/CNS signs.

| | |
|---|---|
| erratic jerking and extension of forelimbs | 11/20 rabbits |
| rapid side-to-side head movement | 2/20 rabbits |
| excessive grooming | 11/20 rabbits |
| sneezing | 3/20 rabbits |

At **10.0 mg/kg/day** there was also:

| | |
|---|---|
| hindlimb jerking | 6/20 rabbits |
| hypersensitivity to touch | 1/20 rabbits |

In addition, at **20.0 mg/kg/day:**

| | |
|---|---|
| tremors | 10/20 rabbits |
| ataxia | 9/20 rabbits |
| diarrhea | 2/20 rabbits |

Some signs (behavioral/CNS) occurred within 1 hour. Other signs of toxicity at 20.0 mg/kg/day were decreased defecation and urination.

Signs of toxicity observed at lower doses occurred with increased frequency and in more rats as the dose increased. When this is taken in combination with the results of the pilot study, it appears that 3.0 mg/kg/day is the LEL ,since there were also effects observed in 9/14 at 3.0 mg/kg/day in the same strain of rabbit. The NOEL for clinical signs (for 83-3b) can be considered to be 2.0 mg/kg/day.

3. Body Weight - Body weight (see Table 2) and weight gain were only effected in the 20.0 mg/kg/day group during the treatment period (primarily between days 7-10G ($p \leq 0.01$). Mean gravid uterine weights were not affected by treatment.

TABLE 2 Body Weight Gains (grams)[a]

| Dose (mg/kg/day) Test interval | 0 | 3.0 | 10.0 | 20.0 |
|---|---|---|---|---|
| 0-7G | 149 | 187 | 179 | 151 |
| 7-10G | 15 | -18 | -108** | -207** |
| 16-19G | 57 | 45 | 17 | 11 |
| 0-29G | 316 | 406 | 272 | 312 |

a) data taken form table 7 in the study report (pp 45, 46)
** significantly different form controls at 0.01 level, 2-tailed Dunnett's test

4. Food Consumption - Food consumption (see Table 3) was decreased for rabbits in the 10.0 and 20.0 mg/kg/day groups during 7-8G, 8-10G and 10-13G (see Table 3).

TABLE 3 Food Consumption (g/animal/day)[a]

| Dose (mg/kg/day) Test interval | 0 | 3.0 | 10.0 | 20.0 |
|---|---|---|---|---|
| 0-7G | 147 | 164 | 154 | 148 |
| 7-10G | 140 | 131 | 87** | 40** |
| 10-13G | 148 | 151 | 110* | 64** |
| 0-29G | 134 | 145 | 128 | 120 |

a data taken form table 9 in the study report (pp 48, 49)
* significantly different from controls at 0.05 level, 2-tailed Dunnett's test
** significantly different from controls at 0.01 level, 2-tailed Dunnett's test

5. Gross Pathology - There were no treatment related findings at necropsy.

6. Cesarean Section Data - One rabbit in the 20.0 mg/kg/group aborted on day 24G. One animal in the 3 mg/kg/day group aborted on day 24G. One control group female aborted on dy 25G (see tables 29 and 30 attached from the study report pp 53-56). A treatment related response could not be established.

B. DEVELOPMENTAL TOXICITY:

1. External Examination - There were no treatment related effects (see attached table 14, 16 taken from the study report).

2. Visceral Examination - There were no treatment related effects (see attached table 14, 16 taken from the study report).

3. Skeletal Examination - There were no treatment related effects (see attached table 14, 16 taken from the study report).

## III. DISCUSSION

### A. MATERNAL TOXICITY:

Maternal toxicity occurred in all doses (including 3.0 mg/kg/day - the LDT) in the main developmental study. In the pilot study, maternal toxicity expressed as behavioral abnormalities was observed at 3.0 mg/kg/day, but not at 2.0 mg/kg/day. The registrant's suggestion to combine data from these two studies in order to determine a NOEL for developmental toxicity in the rat appears reasonable. In the pilot study there were similar clinical (behavioral and CNS) observed at 3.0 mg/kg/day, but not at 2.0 mg/kg/day. This similarity in the data supports the use of a NOEL based on the pilot study. Therefore the NOEL for developmental toxicity is 2.0 mg/kg/day and the LEL is 3.0 mg/kg/day based on clinical signs (behavioral/CNS).

### B. DEVELOPMENTAL TOXICITY:

There were no treatment related effects in any developmental parameter including fetal death, resorptions, size, variations and malformations. This is consistent with the limited data available from the recent pilot study discussed in the appendix 1.

### C. STUDY DEFICIENCIES:

None.

D. CORE CLASSIFICATION: Core-guideline

Maternal NOEL = 2.0 mg/kg/day
Maternal LOEL = 3.0 mg/kg/day based on behavioral/CNS clinical signs.
Developmental Toxicity NOEL $\geq$ 20 mg/kg/day
Developmental Toxicity LOEL > 20 mg/kg/day

ESFENVALERATE TOX R 011454

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Pages 14 through 22 are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

X FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

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[ESFENVALERATE] Developmental Study (83-3b)

APPENDIX 1 - Pilot Developmental Rabbit Study

**Title:** Pilot Developmental Toxicity Study of DPX-YB656-84 in Rabbits
**Author:** SM Murray
**Sponsor:** DuPont Agricultural Products, EI du Pont de Nemours and Company
**Testing Facility:** Haskell Laboratory
**Completion Date:** 4/15/94
**Study Number:** Haskell Lab. Rept. No. 43-94
**MRID:** 432115-01
**Composition/Purity:** 98.8% weight % total isomers by analysis; 84.8 weight % S,S isomer by analysis

NOTE: This pilot was completed prior to becoming aware of a previously conducted developmental rabbit study with Esfenvalerate.

**Methods:** Pregnant New Zealand White rabbits were dosed with Esfenvalerate in cottonseed oil by gavage (10.0 mL/kg). Fourteen pregnant dams/group received 0, 2.0, 3.0, 4.0, 4.5, 5.0 or 20.0 mg/kg/day (days 7-19 of gestation). Test formulation was checked for concentration and homogeneity during the study. Mating was 1:1 until copulation was confirmed (day 1G). Dams were observed for clinical signs and mortality daily. They were weighed on days 3G, 7-20G, 24G and 22G. Food was weighed daily from day 3-29G. Animals were sacrificed on day 29G. The uterus was examined for types of implants and live/dead fetuses. Live fetuses were sexed, weighed and examined for external alterations. It appears that there was no examination for visceral and skeletal changes.

**Results:** One female in each of the control and 20.0 mg/kg/day groups died or was sacrificed in a moribund condition. Body weight was decreased (not significant) (179%) at 20.0 mg/kg/day. Food consumption was significantly decreased (41%) in the 20.0 mg/kg/day group at the beginning of the dosing period (7-10G). Clinical signs (see attached table 4 taken from the study report) were limited to excessive grooming behavior at 3.0 mg/kg/day and above. At 5 mg/kg/day the incidence of head shaking significantly increased. In addition, several (4/14) animals in the 20 mg/kg/day group had sores and/or scabs on their necks.

There was n evidence of developmental toxicity in this pilot study.

Therefore the NOEL for maternal toxicity was 2.0 mg/kg/day in this study with a LEL of 3.0 mg/kg/day. The NOEL for developmental toxicity (based on limited examination) was greater than 20 mg/kg/day.

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[ESFENVALERATE]

Developmental Study (83-3a)

EPA Reviewer: Marion Copley, DVM, DABT
Review Section 4, Toxicology Branch 1 (7509C)
EPA II° Reviewer: Myron Ottley, PhD
Review Section 4, Toxicology Branch 1 (7509C)

Marion Copley, Date 6/22/94
Myron Ottley, Date 6/22/94

DATA EVALUATION RECORD

STUDY TYPE: Developmental Study - Rat (83-3a)

TOX. CHEM. NO.: 268J

P.C. CODE: 109303

MRID No.: 432115-04 (main), 432115-02 (RF)

TEST MATERIAL: Esfenvalerate

SYNONYMS: S-1844 (Sumitomo), ASANA (DuPont), DPX-YB656-84 (DuPont), (S)-alpha-cyano-3-phenoxybenzyl (S)-2-(4-chlorophenyl)-3-methylbutyrate

STUDY NUMBER(S): WIL-118010

SPONSOR: Sumitomo Chemical Company, Ltd.

TESTING FACILITY: Wil Research Laboratories, Ashland, Oh.

TITLE OF REPORT: A Developmental Toxicity Study of S-1844 in Rats

AUTHOR(S): Mark D. Nemec, BS

REPORT ISSUED: 1/10/91

EXECUTIVE SUMMARY

Esfenvalerate was administered to groups of 25 Sprague Dawley Crl:CD®BR female rats by gavage at doses of 0, 2.5, 5.0, 10.0 or 20.0 mg/kg/day from gestation days 6 through 15 (pilot study doses were 1.0, 2.0, 3.0, 4.0, 5.0 and 20 mg/kg/day).

Maternal toxicity was observed at all doses in the main study. At 2.5 mg/kg/day there were behavioral/CNS clinical signs including erratic jerking and extension of forelimbs (22/25 rats), rapid side-to-side head movement (19/25 rats), and excessive grooming (22/25 rats). At 5 mg/kg/day there was also hindlimb jerking and soft or mucoid stools. At 10 mg/kg/day hypersensitivity to touch and tremors were also seen. At 20 mg/kg/day there were high carriage, goosestepping ataxia, ataxia and convulsions. Incidence and frequency increased with increasing dose. Most signs were observed at 4 hours post dosing but resolved by the

next day. At 20 mg/kg/day some signs were observed as early as 1 hour post dosing. The pilot study had similar types of signs at 4 mg/kg/day and above but no signs at 3 mg/kg/day and below. **The NOEL is 2.0 mg/kg/day (from the pilot study) and the LEL is 2.5 mg/kg/day based on behavioral/CNS clinical signs.**

There was no evidence of developmental toxicity at any dose. **The NOEL is 20 mg/kg/day, the highest dose tested.**

This study is classified core-minimum. This study satisfies the guideline requirement for a developmental study (83-3a) in rats.

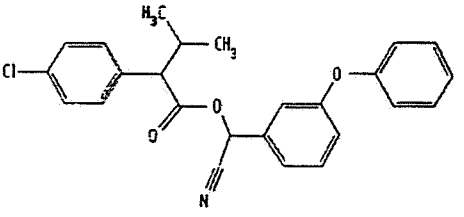
Special Review Criteria (40 CFR 154.7) None

## I. MATERIALS AND METHODS

### A. MATERIALS:

1. Test Material: S-1844
   Description: viscous, clear brown liquid
   Lot/Batch #: 71219
   Purity: 97.1 % a.i. (dose calculations assumed 100 %)
   Stability of compound: considered stable at room temperature
   CAS #: 66230-04-4

   Structure



2. Vehicle: 100 % Mazola Corn Oil
   Lot/Batch not given, Supplier: Best Foods, CPC International, Inc.

3. Test animals: Species: Rat
   Strain: Sprague Dawley Crl:CD®BR
   Age and weight when bred:
   222-308 gm, 83-94 days old
   Source: Charles River Breeding Laboratories, Inc., Portage, Michigan
   Housing: individually (except during mating)
   Environmental conditions: Temperature: 65° - 73°F
   Humidity: 23% - 55%
   Air changes: ~10
   Photoperiod: 12 hr light/12 hr dark
   Acclimation period: 10 days

B. EDURES AND STUDY DESIGN:

tudy was designed to assess the developmental toxicity potential of S-1844 when ... red by gavage to female rats on gestation days 6 through 15, inclusive. Dams were sacrificed on day 20.

1 Mating: Rats were housed with one female and male per cage until there was evidence of mating. Each male was used to impregnate only one female in this study. A copulatory plug in the vagina or sperm in a vaginal smear was considered evidence of mating. This was considered day 0 of gestation (0G).

2. Animal Assignment and dose selection is presented in table 1. Assignment of pregnant dams was random using a computer generated randomization procedure with stratification for body weight.

TABLE 1 Animal Assignment

| Test Group | Dose Level (mg/kg) | Number Assigned |
|---|---|---|
| Control | 0 | 25 |
| Low Dose | 2.5 | 25 |
| Mid Dose 1 | 5.0 | 25 |
| Mid Dose 2 | 10.0 | 25 |
| High Dose | 20.0 | 25 |

3. Dose selection rationale: Dose selection is supported by a pilot developmental toxicity study (MRID 432115-02, Haskell Lab. Rept. # 36-94) that was conducted after completion of the main study. (for details see APPENDIX 1)

NOTE: This pilot was completed by DuPont prior to becoming aware of a previously conducted developmental rat study with Esfenvalerate (by Sumitomo).

Fifteen pregnant dams received 0, 1.0, 2.0, 3.0, 4.0, 5.0 or 20.0 mg/kg/day (days 7-16 of gestation). Maternal toxicity occurred at 4.0 mg/kg/day and above consisting of abnormal gait (mobility) and reduced maternal weight gain (4/15 rats at 4.0 mg/kg/day and 3/15 rats at 5 mg/kg/day). At 20 mg/kg/day there was an increase in adverse clinical signs including: abnormal gait or mobility, incoordination, hind limb spasms, tremors, salivation, periocular staining, and diarrhea. Therefore **the NOEL for maternal toxicity was 3 mg/kg day in this study and the LEL was 4 mg/kg/day based on clinical signs.**

There was no effect on the reproductive parameters or evidence of developmental toxicity in this pilot study.

4. Dosing: All doses were in a volume of 5 ml/kg of body weight/day prepared 3 times during the dosing period. The dosing solutions were analyzed for concentration and found to be within 10 % of nominal (with one exception). Previous data indicated that the solution was stable (14 days) and homogeneous using the same methods used in this study. Dosing was based on the body weight on gestation day 6.

C. OBSERVATIONS:

1. Maternal Observations and Evaluations - The animals were checked for mortality or clinical signs several timed daily. Body weight and food consumption (gms/rat and gms/kg) were recorded on days 0G, 6G, 9G, 12G, 15G, 16G and 20G. Dams were sacrificed on day 20G by $CO_2$ inhalation. Examinations at sacrifice consisted of: weighing of the gravid uterus; examination of the thoracic, abdominal and pelvic cavities; correlation of post mortem findings with ante mortem comments and abnormalities; counting of number of corpora lutea on each ovary; recording number and location of all fetuses, early and late resorptions. Early implantation loss was examined for using 10% ammonium sulfide solution in uteri with no evidence of nidation.

2. Fetal Evaluations - The fetuses were examined in the following manner: weighed; sexed; sex; external examination; crown-rump measurement; 1/2 of viable fetuses/dam were fixed for soft-tissue examination by the Wilson[1] technique. The rest were eviscerated, fixed in alcohol, macerated in potassium hydroxide and stained with Alizarine Red S for skeletal examination.

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

D. STATISTICAL ANALYSIS: The statistical analysis methods are attached (taken from page 20 of the report).

E. COMPLIANCE: Signed and dated GLP and Quality Assurance statements were provided.

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[1] Wilson, J.G., Embryological Consideration in Teratology, J.G. Wilson and Warkany, eds. Teratology - Principles and Techniques, The University of Chicago Press, Chicago, Illinois, 1965

II. RESULTS

A. MATERNAL TOXICITY

1. Mortality - There were no deaths on study.

2. Clinical Observations - Clinical signs of toxicity occurred in all treatment groups. These were primarily observed at 4 hours post dosing but not present the following morning (except as noted).

In the low dose group **(2.5 mg/kg/day)** signs were limited to the following transient behavioral/CNS signs.

| | |
|---|---|
| erratic jerking and extension of forelimbs | 22/25 rats |
| rapid side-to-side head movement | 19/25 rats |
| excessive grooming | 22/25 rats |

At **5 mg/kg/day** there was also:

| | |
|---|---|
| hindlimb jerking | 1/25 rats |

One rat each had soft or mucoid stool.

At **10 mg/kg/day:**

| | |
|---|---|
| hypersensitive to touch | 5/25 rats |
| tremors | 1/25 rats |

One rat each with mucoid feces or diarrhea. Several rats also had mydriasis.

In addition, at **20 mg/kg/day**:

| | |
|---|---|
| high carriage | 23/25 rats |
| goosestepping ataxia | 8/25 |
| ataxia | 14/25 |
| convulsions | 4/25 |

Some signs (behavioral/CNS) occurred within 1 hour at this dose. Other signs of toxicity at this dose included uro- and anogenital matting, and a red or clear discharge around the eyes in a few animals.

Signs of toxicity observed at lower doses occurred with increased frequency and in more rats as the dose increased. When this is taken in combination with the results of the range finding study, it appears that 2.5 mg/kg/day is the LEL since in a newer pilot study, there were no effects observed in 15/15 rats at 2 and 3 mg/kg/day in the same strain of rat. However in the newer pilot study there were similar clinical signs observed at 4 mg/kg/day and up. Therefore the NOEL for clinical signs (for 83-3a) can be considered to be 2 mg/kg/day.

3. Body Weight - Body weight and weight gain were only effected in the 20 mg/kg/day group during the treatment period (primarily between days 12-15G ($p \leq 0.01$). Mean gravid uterine weights were not affected by treatment.

TABLE 2 Body Weight Gains (grams)[a]

| Dose (mg/kg/day) Test interval | 0 | 2.5 | 5.0 | 10.0 | 20.0 |
|---|---|---|---|---|---|
| 0-6G | 25 | 26 | 26 | 25 | 25 |
| 6-15G[b] | 26 | 26 | 25 | 24* | 24* |
| 16-20G | 28 | 28 | 28 | 27 | 27 |
| 0-20G | 27 | 27 | 27 | 26 | 26 |

a data taken form table 9 in the study report (pp 44, 45)
b treatment period
* significantly different form controls at 0.05 level, 2-tailed Dunnett's test

4. Food Consumption

There were no treatment related changes in food consumption.

5. Gross Pathology - There were no treatment related findings at necropsy.

6. Cesarean section Data - There were no abortions or early deliveries. there were no treatment related effects observed in the cesarean data (see tables 12 and 13 attached from the study report pp 49-52).

B. DEVELOPMENTAL TOXICITY:

1. External Examination - There were no treatment related effects (see attached table 14, 16 taken from the study report).

2. Visceral Examination - There were no treatment related effects (see attached table 14, 16 taken from the study report).

3. Skeletal Examination - There were no treatment related effects (see attached table 14,

16 taken from the study report). Although there was an increase 14th rib in fetus and litters ($p < 0.05$) in the high dose, there was no other corroborating evidence of toxicity (ie. no decrease in fetal body weight or increase in other variations). Therefore this is not considered biological significant.

## III. DISCUSSION

### A. MATERNAL TOXICITY:

Maternal toxicity occurred in all doses (including 2.5 mg/kg/day - the LDT) in the main developmental study. However, subsequent to the conduct of this study, a new pilot study was conducted using similar dose levels and the same strain of rat. The registrant's suggestion to combine data from these two studies in order to determine a NOEL for developmental toxicity in the rat appears reasonable. In the pilot study there were similar clinical (behavioral and CNS) observed at 4 mg/kg/day but not at 3 mg/kg/day or below. this similarity in the data supports the use of a NOEL based on the pilot study. Therefore the NOEL for developmental toxicity is 2.0 mg/kg/day and the LEL is 2.5 mg/kg/day based on clinical signs (behavioral/CNS).

### B. DEVELOPMENTAL TOXICITY:

There were no treatment effects in any developmental parameter including fetal death, resorptions, size, variations and malformations. This is consistent with the limited data available from the recent pilot study discussed in the appendix 1.

### C. STUDY DEFICIENCIES:

- Historical control data were not included in this study however there were no changes that warranted examination of this data.

### D. CORE CLASSIFICATION: Core-minimum

Maternal NOEL = 2.0 mg/kg/day
Maternal LOEL = 2.5 mg/kg/day based on behavioral/CNS clinical signs.
Developmental Toxicity NOEL $\geq$ 20 mg/kg/day
Developmental Toxicity LOEL > 20 mg/kg/day

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_____ A draft product label.

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APPENDIX 1 - Pilot Developmental Rat Study

**Title:** Pilot Developmental Toxicity Study of DPX-YB656-84 in Rats
**Author:** SM Murray
**Sponsor:** DuPont Agricultural Products, EI du Pont de Nemours and Company
**Testing Facility:** Haskell Laboratory
**Completion Date:** 3/31/94
**Study Number:** Haskell Lab. Rept. No. 36-94
**MRID:** 432115-02
**Composition/Purity:** 98.8% weight % total isomers by analysis; 84.8 weight % S,S isomer by analysis

NOTE: This pilot was completed prior to becoming aware of a previously conducted developmental rat study with Esfenvalerate.

**Methods:** Pregnant Crl:CD®BR rats were dosed with Esfenvalerate in cottonseed oil by gavage (10.0 mL/kg). Fifteen pregnant dams received 0, 1.0, 2.0, 3.0, 4.0, 5.0 or 20.0 mg/kg/day (days 7-16 of gestation). Test formulation was checked for concentration and homogeneity during the study. Mating was 1:1 until copulation was confirmed (day 1G). Dams were observed for clinical signs and mortality daily. They were weighed on days 1G, 7-17G and 22G. Food was weighed approximately every other day. Animals were sacrificed on day 22G. The uterus was examined toe types of implants and live/dead fetuses. Live fetuses were sexed, weighed and examined for external alterations. It appears that there was no examination for visceral and skeletal changes.

**Results:** There was no mortality. Body weight (see attached table 1 taken from the study report) was decreased at 5 mg/kg/day and above. Food consumption was not significantly depressed, however, there was a slight decrease in the high dose during the dosing period followed by a slight increase during the post dosing period. This may indicate a rebound. Clinical signs (see attached table 3 taken from the study report) were limited to abnormal gait or mobility at 4 and 5 mg/kg/day on about 20 % of the rats. At 20 mg/kg/day, 90 % were affected. In addition at 20 mg/kg/day there were tremors in 20 % of the rats, diarrhea in 73 %. One rat had other signs including salivation, periocular staining, incoordination and hind limb spasms.

There was no evidence of developmental toxicity in this pilot study.

Therefore the NOEL for maternal toxicity was 3 mg/kg/day in this study, LEL of 4 mg/kg/day. The NOEL for developmental toxicity (based on limited examination) was 20 mg/kg/day.

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