6-22-94 (22)

[ESFENVALERATE] Developmental Study (83-3a)

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DATA EVALUATION RECORD

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

TOX. CHEM. NO.: 268J

P.C. CODE: 109303

11454

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.

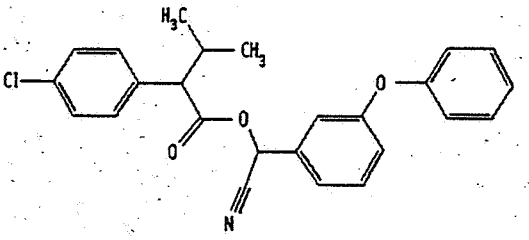
Special Review Criteria (40 CFR 154.7) None

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

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B. PROCEDURES AND STUDY DESIGN:

This study was designed to assess the developmental toxicity potential of S-1844 when administered 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

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

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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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ESFENVALERATE

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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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