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[ESFENVALERATE]

Developmental Study (83-3b)

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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

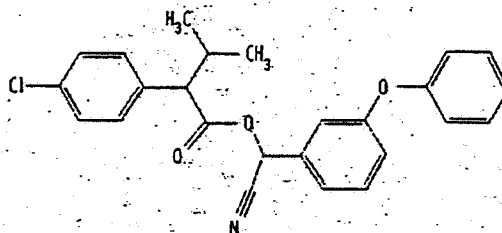
Source: Hazleton Research Products
Inc., Denver, Pennsylvania

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 19¹, 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 were analyzed 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 7².

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:

Group Mean Litter Basis

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

Proportional Litter Basis

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

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.

$$\text{X 100} \quad \text{}^a\text{Postimplantation Loss/Litter (\%)} = \frac{\text{No. Dead Fetuses, Resorptions (all)}}{\text{Litter No. Implantation Sites/Litter}}$$

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 visceraally 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 Wilson³ 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

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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 from table 7 in the study report (pp 45, 46)

** significantly different from 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 from 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 day 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

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Pages 9 through 17 are not included.

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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 no 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.