UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

009081

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

**MEMORANDUM**

SUBJECT: Esfenvalerate (S-1844) and Fenvalerate (S-5602) - Submission of A Comparative Mammalian (Rat) Neurotoxicity Study (EPA ID No. 352-515)

Tox Chem Nos: 77A, 268J
Project No.: 0-1983
Submission No.: S383635
PC No.: 109301

FROM: William B. Greear, M.P.H. William B. Greear 1/21/92
Review Section IV, Toxicology Branch I
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THRU: Marion P. Copley, D.V.M., Section Head Marion Copley 1/22/92
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I. CONCLUSIONS:

The study titled "Comparative Neurotoxicity of S-1844 and S-5602: Effects of Single Oral Administration" (LLT-50-0003) has been evaluated and has been designated Core-Supplementary. The sponsor should address the problem with the autolysis of animals that died within 24 hours of dosing when the animals were observed frequently on the day of dosing. This study will be taken in consideration with the other neurotoxicity studies in determining its acceptability in satisfying 81-8*5*s acute neurotoxicity study in rats.

II. REQUESTED ACTION:

Under a cover letter dated September 24, 1990, Robert W. Freerksen of E.I. du Pont de Nemours & Company has submitted a comparative mammalian neurotoxicity study, which the company recently obtained, for the Agency's information.

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Reviewed by: William B. Greear, M.P.H. William B. Greear 1/21/92
Review Section IV, Toxicology Branch I (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M.
Review Section IV, Toxicology Branch I (H7509C) Marion Copley 1/22/92

DATA EVALUATION REPORT

Study Type: Comparative Mammalian Neurotoxicity - Rat 81-8 55

TOX Chem Nos. 77A, 268J
PC No.: 109301
MRID No.: 416378-01

Test Material: (1) S-1844
(2) S-5602

Synonyms: (1) Esfenvalerate
(2) Fenvalerate

Study Number: LLT-50-0003

Sponsor: E.I. du Pont de Nemours & Company
Wilmington, DE

Testing Facility: Laboratory of Biochemistry and Toxicology
Sumitomo Chemical Company, Ltd.

Title of Report: Comparative Neurotoxicity of S-1844 and S-5602: Effects of Single Oral Administration

Author: Terishuge Kato, Shunji Hosokawa, Yasuyoshi Okuno, Yuichiro Koyama, Tomoyuki Yamada

Report Issued: December 27, 1985

Conclusion:

S-1844: 5 mg/kg - No effects
20 mg/kg - Muscular fibrillation, salivation and ataxia
360 mg/kg - Mortality, clinical signs of nervous system involvement (ataxia, tremors, etc.), histological lesions of the nervous system (peripheral nerve and spinal cord)

S-5602: 20 mg/kg - No effects
80 mg/kg - Muscular fibrillation
360 mg/kg - Mortality, clinical signs of nervous system involvement (ataxia, tremors, etc.), histological lesions of the nervous system (peripheral nerve and spinal cord).

Classification:

Core-Supplementary. This study was well conducted and provides useful information but does not meet the criteria set forth in the EPA guidelines, such as perfusion of the nervous system, or quantitative measurement of motor activity.

This study by itself would not satisfy the requirement for the Guideline Series 81-8 Acute Neurotoxicity in rats study. (mammalian)

A. Materials:

1a. Test Compound #1 - S-1844 - Description: Brownish oily liquid or solid; Batch No.: PKG-85036; Purity: 94.5 percent; Contaminants: Not reported.

1b. Test Compound #2 - S-5602 - Description: Yellow brownish viscous liquid; Batch No.: 41028; Purity: 95.5 percent; Contaminants: Not reported.

2. Test Animals - Species: Rat; Strain: Crj:CD(SD); Age: 6 weeks old; Weight: Males - 242.7 to 245.2 g; Females - 160.0 to 161.5 g; Source: Charles River Japan, Inc., Kanagawa.

B. Study Design:

1. Animal Assignment - Animals were assigned to the following test groups:

| | | Dose-Group | Number of Animals | |
|---|---|---|---|---|
| Group | Compound | (mg/kg) | Male | Female |
| I | Control | 0 | 8 | 8 |
| II | S-1844 | 5 | 8 | 8 |
| III | S-1844 | 20 | 8 | 8 |
| IV | S-1844 | 20 | 16 | 16 |
| V | S-5602 | 20 | 8 | 8 |
| VI | S-5602 | 80 | 8 | 8 |
| VII | S-5602 | 360 | 16 | 16 |

2. Dose Preparation - Doses were selected on the basis of an acute oral $LD_{50}$ study on S-1844 in which the $LD_{50}$ was determined to be 88.5 mg/kg and the no-effects dose based on clinical signs was 5 mg/kg. Dose levels of S-5602 were raised to 4X to adjust for the Aα isomer. The single doses were administered by gavage at a rate of 5 mL/kg. The vehicle used was corn oil. Corn oil was administered to controls at a rate of 5 mg/kg. The optical isomer ratios of the test material used are indicated in Table 1.

Table 1. Test Material

| Test Material | Purity (%) | Optical Isomer Ratio Aα | Aβ | Bα | Bβ |
|---|---|---|---|---|---|
| S-1844 | 94.5 | 87.2 | 7.4 | 4.8 | |
| S-5602 | 95.5 | 24.2 | 25.4 | 26.3 | 24.1 |

The chemical structures are indicated in Attachment 1.

3. Animals received food (CD-2 Type) and water ad libitum except for the fasting period (of unreported duration). The animals were housed two per cage in hanging-type aluminum cages with wire-mesh floors under specific pathogen-free environmental conditions in a room that was maintained at a temperature of 24 ± 2 °C, relative humidity of 55 ± 19 percent, and 8:00 to 20:00 hours illumination.

4. Statistics - Body weight was analyzed by the F-test. If differences were not significant, Student's t-test was used. Fisher-Behrens test was applied when differences were not significant. Mean slip angle (MSA) and relative mean slip angle (RMSA) were analyzed using the Mann-Whitney U-test. RMSA = body weight x sin (MSA).

5. Quality assurance was conducted at three time periods between August 5 and December 20, 1985. The QAU statement was signed by Masanori Takatsuka on December 27, 1985.

C. Methods and Results:

1. Observations - Animals were inspected for signs of toxicity and mortality at 1/2, 1, 2, 4, 6, 8, and 24 hours after dosing and daily thereafter for up to 2 weeks.

Results - Table 2 indicates the mortality observed in the study. All deaths in the 90 mg/kg S-1844 and 360 mg/kg S-5602 groups occurred within 1 day.

Table 2 - Mortality Observed

| Test Group | Test Material | Dose (mg/kg) | Number of Deaths/ Number of Animals | |
|---|---|---|---|---|
| | | | Male | Female |
| I | Control | 0 | 0/8 | 0/8 |
| II | S-1844 | 5 | 0/8 | 0/8 |
| III | S-1844 | 20 | 0/8 | 0/8 |
| IV | S-1844 | 90 | 2/16 | 1/16 |
| V | S-5602 | 20 | 0/8 | 0/8 |
| VI | S-5602 | 80 | 0/8 | 0/8 |
| VII | S-5602 | 360 | 1/16 | 4/16 |

Control males exhibited diarrhea, soft feces during the first 8 hours after dosing (suggesting the amount of vehicle administered may have been at a rate of 5 mL/kg, not 5 mg/kg), alopecia, and scab formation beginning on Day 4 and persisting until Day 14. One female control exhibited diarrhea 1 hour postdosing.

S-1844 Groups

Males and females in the 5 mg/kg group showed no signs indicative of toxicity. Two males and two females in the 20 mg/kg group exhibited muscular fibrillation 8 hours after dosing. Salivation and ataxia were also observed in one or more animals within 8 hours after dosing. Compound-related signs were absent by Day 1. The majority of males and females in the 90 mg/kg group displayed salivation, tremors, muscular fibrillation, limb paralysis, urinary incontinence, ataxia, and irregular respiration within 8 hours after dosing. The earliest sign observed was muscular fibrillation in one female after 1 hour. Other clinical signs of toxicity included loss of righting reflex, hypersensitivity to sound, and hunched posture. No signs of toxicity were observed 2 days after dosing except for ataxia and swelling of the hind leg which was exhibited in one

female on Days 13 and 14. The latent ataxia and swelling of the leg of 1 of 32 animals was probably not treatment related.

S-5602 Groups

No signs of toxicity were observed in the S-5602 20 mg/kg group that could be related to compound administration. Muscular fibrillation was observed in several animals in the 80 mg/kg group within 8 hours after dosing (earliest sign was at 4 hours). No signs indicative of toxicity were observed after Day 1. Muscular fibrillation, salivation, and ataxia were observed within 2 hours postdosing in the 360 mg/kg group. Additional clinical signs of toxicity observed within the first day postdosing included tremors, limb paralysis, loss of righting reflex, irregular respiration, and urinary incontinence. No signs of toxicity were observed after Day 1.

2. Body Weight - Individual body weights were determined prior to dosing (Day 0) on Days 1, 2, 3, 7, and 14 after dosing.

Results - Males in the 90 mg/kg S-1844 and the 360 mg/kg S-5602 group exhibited significantly decreased body weights on Days 1 to 3 and Days 1 to 7 after dosing, respectively. Females in the 360 mg/kg S-5602 group had significantly lower body weights on Day 1 (See Table 3). However, females in the 360 mg/kg S-5602 group had body weight gain that was comparable to the controls over the 14-day period.

Table 3. Group Mean Body Weight (g)

| Sex | Dose Level (mg/kg) | Day 0 | 1 | 2 | 3 | 7 | 14 | Gain (g) |
|---|---|---|---|---|---|---|---|---|
| Male | | | | | | | | |
| Control | 0 | 245.2 | 272.1 | 281.1 | 288.5 | 317.5 | 362.7 | 117.5 |
| S-1844 | 5 | 242.8 | 266.5 | 278.6 | 287.0 | 316.9 | 362.7 | 119.5 |
| | 20 | 243.9 | 261.8 | 274.5 | 281.9 | 314.2 | 360.2 | 116.2 |
| | 90 | 242.7 | 250.0* | 254.0** | 274.1** | 304.4 | 352.1 | 108.4 |
| S-5602 | 20 | 243.4 | 266.0 | 277.5 | 287.3 | 315.6 | 362.6 | 119.2 |
| | 80 | 243.1 | 262.1 | 274.0 | 282.8 | 310.9 | 354.0 | 110.9 |
| | 360 | 241.7 | 249.1* | 263.4** | 273.7** | 300.1** | 348.6 | 106.8 |
| Female | | | | | | | | |
| Control | 0 | 161.2 | 178.4 | 183.0 | 187.0 | 198.3 | 216.3 | 55.1 |
| S-1844 | 5 | 161.5 | 178.9 | 183.7 | 188.7 | 200.0 | 219.7 | 58.2 |
| | 20 | 161.1 | 178.1 | 181.5 | 188.0 | 202.1 | 224.5 | 63.4 |
| | 90 | 160.8 | 168.7 | 180.1 | 185.5 | 197.0 | 216.9 | 55.8 |
| S-5602 | 20 | 160.0 | 176.6 | 180.1 | 184.5 | 195.0 | 212.2 | 52.2 |
| | 80 | 160.2 | 175.5 | 182.2 | 184.5 | 196.6 | 218.7 | 58.4 |
| | 360 | 160.0 | 170.3** | 180.9 | 185.7 | 196.6 | 215.3 | 54.3 |

*Statistical significance at $p < 0.05$.
**Statistical significance at $p < 0.01$.

3. Functional Testing (Slip Angle) - The test was conducted on all surviving animals on Days 0, 3, 7 and 14. Each rat was placed on a wooden inclined plane with its head facing up the slope and increasing the angle until it could not maintain a stationary position. The test was repeated three times at each sampling time to arrive at an average mean slip angle.

Results - Unremarkable.

4. Sacrifice and Pathology - All animals that died or were sacrificed at scheduled termination were subjected to gross pathological examination and the following tissues were examined microscopically:

| | |
|---|---|
| Medulla oblongata | Spinal cord - cervical thoracic |
| Cerebellum | lumbosacral |
| Hypothalamus | Proximal peripheral nerves - |
| Cerebrum | sciatic |
| | Distal peripheral nerves - |
| | tibial |

The tissues were stained with H&E, luxol fast blue, and silver nitrate.

a. Gross Pathology - Unremarkable. However, it was stated that most animals that died were autolyzed. [This is puzzling since all animals in the 90 mg/kg S-1844 and 360 mg/kg S-5602 groups died within 24 hours and the animals were inspected frequently (at 1/2, 1, 2, 4, 6, 8 and 4 hours) during the first day.] The sponsor should address the autolysis problem in rats that died within 24 hours of dosing when the animals were frequently observed on the day of dosing.

b. Microscopic Pathology

(1) Non-neoplastic

Results - No microscopic lesions that could be related to treatment were observed in the brain of all terminally sacrificed animals. Slight axonal degeneration and/or demyelination of the cervical and/or thoracic spinal cords was observed in one or two males and females in the 20 and 90 mg/kg/day S-1844 group, in one male in each of the 80 and 360 mg/kg S-5602 groups, and in one male in the 5 mg/kg S-1844 group. Demyelination, axonal degeneration, and Schwann cell proliferation were observed to occur with a higher frequency

in animals in the 90 mg/kg S-1844 group (33-71%) and the 360 mg/kg S-5602 group (27-73%) than in the other treatment groups (see Tables 4 and 5). In addition, the severity of the lesions in these two groups was grade 2-3 compared to 1 in the other treatment groups. Although the investigator states that there was no effect on the spinal cord, the animals with the severest lesions of the peripheral nerves were the only animals in the 90 mg/kg S-1844 and 360 mg/kg S-5602 groups with lesions in the spinal cord. Therefore, this reviewer believes that the spinal cord was a target organ in the highest dose S-1844 and S-5602 groups.

(2) Neoplastic - None

D. Discussion:

Mortality was increased in males and females in the 90 mg/kg S-1844 and 360 mg/kg S-5602 groups. Males and females in the 90 mg/kg S-1844 and 360 mg/kg S-5602 groups exhibited demyelination, axonal degeneration, and Schwann cell proliferation of distal and proximal peripheral nerves. Muscular fibrillation, salivation and ataxia were observed in the 20 mg/kg S-1844 group within 8 hours of dosing. Muscular fibrillation was the only toxic sign observed in the 80 mg/kg S-5602 group. It occurred within the first 8 hours after dosing. Additional signs of toxicity, including tremors, limb paralysis, loss of righting reflex, irregular respiration, urinary incontinence, hypersensitivity to sound and/or hunched posture, were observed in the 90 mg/kg S-1844 and 360 mg/kg S-5602 groups. Compound-related signs of toxicity were not observed 2 days after dosing. Body weight of males in the 90 mg/kg S-1844 and 360 mg/kg S-5602 groups were decreased during the first week after dosing. In those, one or two animals in these two groups in which the lesions were severe, there were additional lesions, demyelination and/or axonal degradation of the cervical and/or thoracic spinal cords.

Attachment

Table 4. Incidence (%) of Histopathological Lesions of the Nervous System in Males

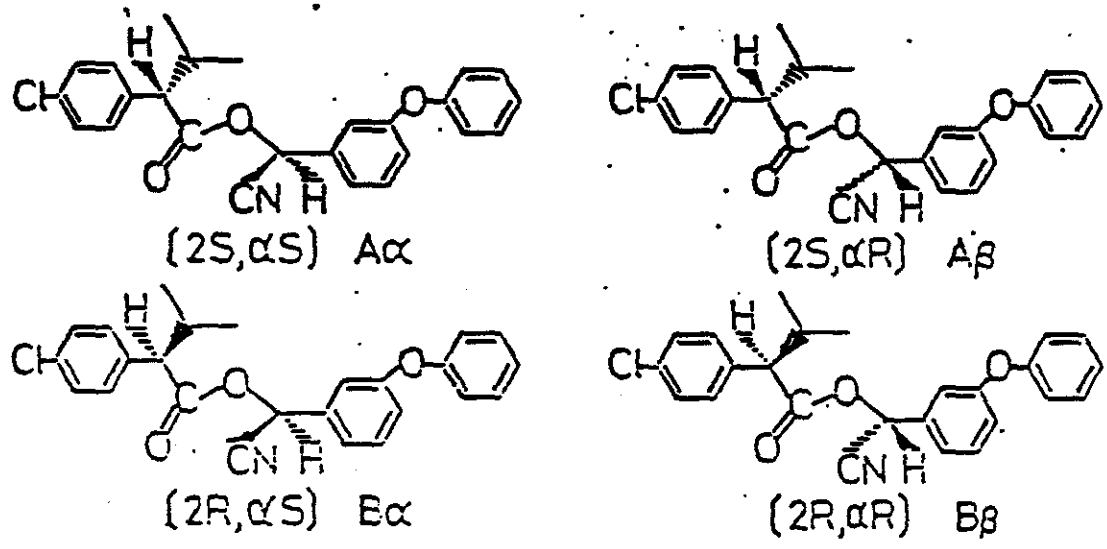
| Tissue/Lesion | Group (mg/kg) Control 0 | S-1844 5 | S-1844 20 | S-1844 90 | S-5602 20 | S-5602 80 | S-5602 360 |
|---|---|---|---|---|---|---|---|
| **Cervical Spinal Cord** | | | | | | | |
| - Demyelination | | 1/8 (13) | | 1/14 (7) | | | 1/15 (7) |
| - Axonal degeneration | | | | 1/14 (7) | | | 1/15 (7) |
| - Gliosis | | 1/8 (13) | | 1/14 (7) | | | 1/15 (7) |
| **Thoracic Spinal Cord** | | | | | | | |
| - Demyelination | | | 1/8 (13) | 1/14 (7) | | 2/8 (25) | 1/15 (7) |
| - Axonal degeneration | | | 1/8 (13) | 1/14 (7) | | 2/8 (25) | 1/15 (7) |
| - Gliosis | 3/8 (38) | | | 6/14 (43) | | 2/8 (25) | 1/15 (7) |
| **Lumbosacral Spinal Cord** | | | | | | | |
| - Demyelination | | | | 1/14 (7) | | | |
| - Axonal degeneration | | | | 1/14 (7) | | | |
| - Gliosis | | | | 1/14 (7) | | | |
| **Peripheral Nerve (Proximal)** | | | | | | | |
| - Demyelination | 2/8 (25) | 3/8 (38) | 3/8 (38) | 9/14 (64) | 3/8 (38) | 3/8 (38) | 12/15 (75) |
| - Axonal degeneration | | 2/8 (25) | 3/8 (38) | 11/14 (79) | 1/8 (15) | 3/8 (38) | 12/15 (75) |
| - Schwann cell proliferation | | | | 6/14 (43) | | | 5/15 (33) |
| **Peripheral Nerve (Distal)** | | | | | | | |
| - Demyelination | 2/8 (25) | 1/8 (13) | 1/8 (13) | 10/14 (71) | 1/8 (13) | | 11/15 (73) |
| - Axonal degeneration | 1/8 (13) | | 1/8 (13) | 9/14 (64) | | | 9/15 (60) |
| - Schwann cell proliferation | 1/8 (13) | | | 6/14 (43) | | | 4/15 (27) |

Table 5. Incidence (%) of Histopathological Lesions of the Nervous System in Females

| Tissue/Lesion | Group (mg/kg) Control 0 | S-1844 5 | S-1844 20 | S-1844 90 | S-5602 20 | S-5602 80 | S-5602 360 |
|---|---|---|---|---|---|---|---|
| **Cervical Spinal Cord** | | | | | | | |
| - Demyelination | | | | 1/15 (7) | | | |
| - Axonal degeneration | | | 1/8 (13) | 1/15 (7) | | | |
| - Gliosis | | | | 4/15 (27) | 1/8 (13) | | |
| **Thoracic Spinal Cord** | | | | | | | |
| - Demyelination | | | | 2/15 (13) | | | |
| - Axonal degeneration | | | | 2/15 (13) | | | |
| - Gliosis | 2/8 (25) | | 3/8 (38) | 5/15 (33) | 1/8 (13) | | 3/12 (25) |
| **Lumbosacral Spinal Cord** | | | | | | | |
| - Demyelination | | | | | | | |
| - Axonal degeneration | | | | | | | |
| - Gliosis | | | | | | | |
| **Peripheral Nerve (Proximal)** | | | | | | | |
| - Demyelination | 1/8 (13) | | 3/8 (38) | 9/15 (60) | 1/8 (13) | | 5/12 (42) |
| - Axonal degeneration | 1/8 (13) | | 2/8 (25) | 9/15 (60) | | 1/8 (13) | 5/12 (42) |
| - Schwann cell proliferation | 1/8 (13) | | 3/8 (38) | 8/15 (53) | | | 3/12 (25) |
| **Peripheral Nerve (Distal)** | | | | | | | |
| - Demyelination | 2/8 (25) | | | 8/15 (53) | 1/8 (13) | | 6/12 (50) |
| - Axonal degeneration | 1/8 (13) | | | 9/15 (60) | 1/8 (13) | | 6/12 (50) |
| - Schwann cell proliferation | 1/8 (13) | | | 5/15 (33) | | | 2/12 (17) |

## Appendix B Chemical identity of isomers

**Chemical identity of isomers is as follows:**




Four chiral isomers of fenvalerate