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

004681

FILE COPY

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SEP 25 1985

MEMORANDUM

SUBJECT: SS Pydrin Insecticide 1.9 Emulsible Concentrate
EPA File Symbol 201-URI
Active Ingredient: 33.4% Technical SS Pydrin Insecticide (MO 70616)

and

Technical SS Pydrin Insecticide (MO 70616)
EPA File Symbol 201-URO
Active Ingredient: 80.0% Fenvalerate (75% SS Isomer)

Tox CHEM No. 77A

FROM: William B. Greear William B. Greear 9/18/85
Section VII, Toxicology Branch
Hazard Evaluation Division (TS-769C)

TO: Adam Heyward, PM Team #15
Insecticide/Rodenticide Branch
Registration Division (TS-767C)

THRU: Albin B. Kocialski, Ph.D., ABK 9/24/85
Supervisory Pharmacologist
Section VII, Toxicology Branch
Hazard Evaluation Division (TS-769C)

and

Theodore M. Farber, Ph.D.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769C)

The Shell Chemical Company is seeking registrations for a new Pydrin technical (Technical SS Pydrin Insecticide) and a new formulation of Pydrin (SS Pydrin Insecticide 1.9 Emulsible Concentration) which is made from the new technical. As it is currently

SEP 28 1985

290

registered, Pydrin is a racemic mixture composed of four stereoisomers present in equal proportions. The four isomers are identified as: A-alpha or SS, B-alpha or RS, A-beta or SR, and B-beta or RR. However, only one of the four stereoisomers possesses significant insecticidal activity. This isomer is referred to as the A-alpha isomer or the SS isomer. The currently registered Pydrin technical (SD 43775) contains a minimum of 18 percent of the SS isomer. Due to new manufacturing techniques, the new Pydrin technical (MO 70616) would contain a minimum of 75 percent of the SS isomer.

The toxicity studies submitted in support of the two new registrations are listed below together with their Core classification and toxicity category. (The Data Evaluation Records are located in Appendix #1.)

SS Pydrin Insecticide 1.9 Emulsible Concentrate (EPA File Symbol 201-URI). The acute battery of toxicological studies for the new SS Pydrin 1.9 EC formulation are reported as a 2.4 EC formulation. The 2.4 EC formulation reported is 2.4 lbs total of the 4 isomers per gallon and contains 1.9 lbs of the single isomer, A-alpha, per gallon.

Study	Tox. Category/Results	Classification
Acute Oral LD_{50} - rat	II	Guideline
Acute Dermal LD_{50} - rabbit	III	Guideline
Primary Eye Irritation - rabbit	I	Guideline
Primary Skin Irritation - rabbit	I	Minimum Data
Skin Sensitization - guinea pig	Sensitizer	Minimum Data

Technical SS Pydrin Insecticide (MO 70616) (EPA File Symbol 201-URO)

Study	Tox. Category/Results	Classification
Acute Oral LD_{50} - rat	II	Guideline
Subchronic Oral - rat (3-month)	NOEL = 50 ppm	Minimum Data

Four metabolism studies (2 on SD-43775; 2 on SD-92459*) were submitted and found to be acceptable. The results of these studies are summarized in Appendix #1. Several reprints focusing on the neurological effects attributed to fenvalerate and the metabolism of fenvalerate were included in the submission and are summarized in Appendix #1. Additionally, several reports were submitted that pertain to the toxicity of materials that contain various proportions of the A-alpha, A-beta, B-alpha, and B-beta isomers. These reports are listed in Appendix #2. Some of these reports have previously been evaluated in support of the currently registered products, e.g., Pydrin 2.4 EC (EPA Reg. No. 201-401). The remainder of these reports have not yet been evaluated but will be evaluated as necessary in order to support other regulatory actions.

The toxicological data submitted on SS Pydrin Insecticide 1.9 Emulsible Concentrate are incomplete. Because multiple sprayings of certain crops such as cotton may be required (as indicated on the label), workers will be repeatedly exposed to the formulation. Unless the sponsor can demonstrate that under conditions of use, inhalable liquid particles of aerodynamic diameter of 15 micrometers or less will not be produced, an acute inhalation toxicity study on the formulation should be submitted for evaluation. The appropriate precautionary labeling cannot be determined until the Toxicology Branch's (TB's) concern over the lack of an acute inhalation study on the formulation has been ameliorated. (It should be noted that the precautionary labeling for ocular and dermal effects will need revision because the formulation is corrosive and is a skin sensitizer.) Another concern with this formulation is the use of two alternate, inert ingredients, [redacted] and [redacted] Currently, TB has no identification of the components of these products. The components must be identified in order to determine if they are exempted from the requirement of a tolerance under 40 CFR 180.1001.

The toxicological data submitted on Technical SS Pydrin Insecticide (MO 70616), a manufacturing-use product, are also incomplete. To date, only an acute oral LD_{50} study and a subchronic oral toxicity study in rats have been submitted. In order to determine the appropriate precautionary statements to use on the label, the following studies will need to be submitted for evaluation:

* SD-92459 is another material developed by the Shell Chemical Co. that is "Y-rich". It contains 45% A-alpha, 5% B-alpha, 5% A-beta and 45% B-beta isomers.

7 7/92

1. Acute Dermal Toxicity
2. Primary Eye Irritation
3. Primary Dermal Irritation

The main purpose for conducting a second subchronic rat study was to provide information with which to compare the toxicity of the new, enriched Pydrin technical (approximately 75 percent SS isomer content) with the currently registered, racemic Pydrin technical (approximately 18 percent SS isomer content). The toxicological manifestations observed in each of the two subchronic studies that utilized either the new Pydrin technical or the currently registered Pydrin technical will be described below, followed by a discussion of how the new study will impact on the acceptable daily intake (ADI) for fenvalerate.

Subchronic Study on MO 70616 in Rats

All animals (both sexes) in the 500 ppm group, several animals (both sexes) in the 300 ppm group and one male in the 150 ppm group exhibited signs of neurological dysfunction. Several animals in the 500 ppm group had areas around the base of the tail that were identified as dermatitis. Body weight gain was decreased in males and females in the 500 ppm group. Males and females in the 500 and 300 ppm groups exhibited slight hypertrophy of the parenchymal cells of the parotid salivary gland. A few of the animals in the 500 ppm group had hypertrophy of the submaxillary salivary glands. Some of the males in the 500 ppm group had slight hypertrophy of the parenchymal cells of the pars intermedia of the pituitary gland. The no-observable-effect level (NOEL) was established at 50 ppm. The LOEL was 150 ppm based on signs of neurological dysfunction.

Subchronic Study on SD 43775 in Rats - (see memorandum of R. Engler dated June 10, 1976).

Mortality was increased in males and females in the 2,000 ppm group. Body weight gain was decreased in males and females in the 1,000 and 2,000 ppm groups. The relative weight of the liver was increased in females in the 500, 1,000 and 2,000 ppm groups. The relative weight of the kidney was increased in all groups of treated animals except for males in the 125 ppm group. Animals in the 1,000 and 2,000 ppm groups had elevations in BUN (blood urea nitrogen). The NOEL was set at 125 ppm.

Impact on ADI

Because the petitioner intends to use the new enriched Pydrin technical in manufacturing end-use products for use on crops, it is necessary to make a quantitative adjustment to

the ADI to reflect the increased toxicity of the new Pydrin technical. Therefore, the NOEL established in the subchronic toxicity study in rats with the new Pydrin technical will be used to calculate the ADI. A 100-fold safety factor will be employed in the calculation. TB is aware that a 2,000-fold (currently 1,000-fold) safety factor has been routinely used in calculating PADIs (provisional acceptable daily intakes) from subchronic studies. The rationale for using the 100-fold safety factor rather than the 1,000-fold safety factor is as follows. The NOEL established for the subchronic toxicity study with the new enriched Pydrin technical was based on clinical signs of neurological dysfunction which was the most sensitive indicator of toxicity in the study. It is also believed that this neurological dysfunction is probably transient. In this subchronic study one male rat in the 150 ppm group exhibited "jerky leg movements" at weeks 11 and 12, but was normal at weeks 13 and 14. Additionally, several animals in the 300 ppm group displayed "jerky leg movements" during some point in the study but this toxic sign was not present during the last few weeks of the study. In a previous 24-month rat study a hind limb weakness (a sign of neurological dysfunction) was observed in several animals but appeared to be reversible. Based on the most sensitive indicator of toxicity, neurological dysfunction, TB is reasonably certain that the NOEL of 50 ppm in the subchronic toxicity study with the new, enriched Pydrin technical would probably reflect the NOEL for chronic toxicity. Therefore, a 100-fold safety factor will be used. The ADI calculation is shown below:

$$\text{ADI (mg/kg/day)} = \frac{\text{NOEL (mg/kg/day)}}{\text{Safety Factor}} \qquad \text{NOEL} = 50 \text{ ppm} = 2.5 \text{ mg/kg/day}$$

$$\text{ADI} = \frac{2.5 \text{ mg/kg/day}}{100} = 0.025 \text{ mg/kg/day}$$

The maximum permissible intake (MPI) will be calculated by multiplying the ADI of 0.025 mg/kg/day by the weight of a 60 kg human to yield on MPI of 1.5 mg/day.

Conclusions

1. The Toxicology Branch (TB) recommends that the sponsor conduct an acute inhalation toxicity study on SS Pydrin 1.9 Emulsible Concentrate and submit the study for evaluation or demonstrate that under conditions of use inhalable liquid particles of aerodynamic diameter of 15 micrometers or less will not be produced. Only after the satisfactory resolution of this concern, will TB be able to properly evaluate the precautionary statements on the label. (TB recognizes that this formulation is a sensitizer and must be labeled accordingly - "May cause allergic reactions.")

2. TB has no identification of two alternate inert ingredients in SS Pydrin 1.9 Emulsible Concentrate: [redacted] The components of these products must be identified so a determination can be made whether the components are exempted from the requirement of a tolerance under 40 CFR 180.1001.

3. In order to determine the appropriate precautionary statements to use on the label for Technical SS Pydrin Insecticide (MO 70616), the following studies should be submitted for evaluation:

1. Acute Dermal Toxicity
2. Primary Eye Irritation
3. Primary Dermal Irritation

4. When Technical SS Pydrin Insecticide and SS Pydrin - Insecticide Emulsible Concentrate are registered, the maximum permissible intake (MPI) will be calculated using the rat no-observable-effect level (NOEL) of 50 ppm which was determined in a subchronic (13-week) feeding study. This NOEL is equivalent to 2.5 mg/kg/day. The application of a safety factor of 100 results in a calculated acceptable daily intake (ADI) of 0.025 mg/kg/day and an MPI of 1.5 mg/kg/day for a 60 kg human.

5. With respect to the 13-Week Subchronic Feeding Study of MO 70616 in Rats (Report #227A-101-030-84; Dated December 10, 1984), the petitioner should forward information to the Agency which describes the "self-inflicted trauma" which caused the deaths of 3 females in the 500 ppm group.

6. The precautionary labeling needs to reflect the results of the acute toxicity studies. Please refer to 40 CFR 162.10 for the appropriate wording.

APPENDIX 1

DATA EVALUATION RECORD

Subject: Comparative Oral Toxicity of Technical MO 70616 and Technical SD 43775 in Rats

Test Material: Technical MO 70616 (WRC Tox Sample No. 730A)
Technical SD 43775 (WRC Tox Sample No. 77D)

EPA File Symbol: 201-URI

Accession No.: 254114

Purity: Technical MO 70616 - 97% parent isomers (85% A-alpha isomer)
Technical SD 43775 - 92% parent isomers (23% A-alpha isomer)

Testing Facility: Westhollow Research Center
Houston, TX 77082

Report No.: 6155M/WTP-243 (Ref. LR-15718, pp. 98-100)

Report Date: March 19, 1984

Authors: M. M. Bilsback, C. M. Parker, H. C. Wimberly

Classification: Guideline (both tests)

Toxicity Category: Technical MO 70616 (Category II)
Technical SD 43775 (cannot be categorized)

Materials and Methods:

Ninety Fischer 344 rats, obtained from Harlan Sprague-Dawley, Inc., Indianapolis, Indiana, were acclimated to the laboratory for 18 days and were then randomly distributed to groups containing 5 animals/sex/group. Fasted mean group body weight ranged from 163.8 g to 166.1 g for females and from 231.8 g to 235.3 g for males. The animals were caged in an environment in which the temperature ranged from 20.0 to 22.2 °C and the relative humidity ranged from 26 to 57 percent. A 12-hour on 12-hour off light cycle was maintained. The test materials were administered as a suspension in corn oil at a constant dose volume of 2.5 ml/kg. Technical MO 70616 was administered at 38, 92, 213, and 380 mg/kg. Technical SD 43775 was administered at 150, 370, 850, and 1500 mg/kg. One control group of five animals/ sex was employed. Animals were observed hourly for a 6-hour period following dosing and twice daily for the remainder of the 14-day period (females) or 15-day period (males). Body weights were determined on days 0, 7, and 14. All animals surviving until termination were sacrificed and necropsied. The LD_{50} for Technical MO 70616 was calculated by the method of Finney.

Results:

The following table provides information on the dose levels at which mortality occurred:

		Number Dead/Number Treated		
Test Substance	Dose(mg/kg)	Males	Females	Combined
Technical MO 70616	38	3/5	0/5	3/10
	92	4/5	4/5	8/10
	180	5/5	5/5	10/10
	380	5/5	5/5	10/10
Technical SD 43775	150	0/5	0/5	0/10
	370	3/5	2/5	5/10
	850	2/5	0/5	2/10
	1500	0/5	1/5	1/10

In those rats dosed with Technical MO 70616, all deaths occurred within 24 hours of dosing. All but one death occurred within 24 hours of dosing with Technical SD 43775. Clinical signs of toxicity attributed to Technical MO 70616 and Technical SD 43775 were similar and consisted primarily of ataxia and/or incoordination, tremors, convulsions, and hypersensitivity to touch and sound. Other signs observed were hyperactivity, lacrimation, depressed myotactic reflex, polyuria, hunched posture, and prostration. In surviving rats, clinical signs of toxicity were reversed within 3 to 5 days. Body weights were not affected by treatment. The following findings, noted at necropsy, were related to treatment: yellow- and red-stained hair, mucosal abrasions, dehydration, darkened liver, distension of the stomach with gas and fluid, presence of yellow-green fluid in the cecum and white mesenteric lymph nodes.

Conclusions:

Technical MO 70616 LD_{50} = 87.2 mg/kg

Technical SD 43775 LD_{50} could not be calculated.

Toxicity Category:

Technical MO 70616 is Category II.

Technical SD 43775 cannot be categorized.

Classification: Guideline (for both test substances)*

*It is noted that the test conducted on Technical SD 43775 is of such a nature that an LD_{50} cannot be determined or predicted with any degree of certainty. Thus, it cannot be used to satisfy a regulatory requirement.

DATA EVALUATION RECORD

Subject: Acute Oral Toxicity of MO 70616 2.4 EC in the Rat

Test Material: MO 70616 2.4 EC (WRC Tox Sample No. 731A)

EPA File Symbol: 201-URI

Accession No.: 254116

Purity: 29.8% of which 85% is the A-alpha isomer

Testing Facility: Westhollow Research Center
Houston, TX 77082

Report No.: 6155M/WTP-244

Report Date: February 20, 1984

Authors: C. M. Parker, T. H. Gardiner, Gary Van Gelder

Classification: Guideline

Toxicity Category: Category II

Materials and Methods:

Fifty Fischer 344 rats, obtained from Harlan Sprague-Dawley, Inc., Indianapolis, Indiana, were acclimated to the laboratory for 23 days and were then randomly distributed to groups containing 5 animals/sex. Fasted mean group body weights ranged from 164.0 g to 169.6 g for females and from 244.4 g to 252.6 g for males. The animals were caged in an environment in which the temperature ranged form 18.9 to 21.1 °C and the relative humidity ranged from 22 to 51 percent. A 12-hour on 12-hour off light cycle was maintained. The test material was administered as a suspension in deionized water at a constant dose volume of 2.5 ml/kg. MO 70616 2.4 EC was administered at 25, 51, 110, and 244 mg/kg. One control group of five animals/sex was employed. Animals were observed hourly for a 6-hour period following dosing and twice daily for the remainder of the 14-day observation period. Body weights were determined on days, 0, 7, and 14. All surviving animals were sacrificed at termination and necropsied. The LD_{50} was calculated by the Log Probit method.

Results:

The following table provides information on the dose levels at which mortality occurred:

	Number Dead/Number Treated		
Dose(mg/kg)	Males	Females	Combined
25	0/5	0/5	0/10
51	0/5	0/5	0/10
110	5/5	5/5	10/10
244	5/5	5/5	10/10

Rats dosed at 110 and 244 mg/kg died within 3 to 5 hours after dosing. Clinical signs of toxicity consisted primarily of ataxia, incoordination, tremors, convulsions, and hypersensitivity to touch and sound. Other signs sometimes observed were lacrimation, hyperactivity, diarrhea, prostration, hunched posture, salivation, and depressed myotactic reflex. Occasionally, a few female rats vocalized when touched. Body weight gain was not affected by treatment. The following findings were noted at necropsy in animals in the 110 and 244 mg/kg groups: tan/yellow- and red-stained haircoat, dehydration, darkened liver, presence of green opaque fluid in the large intestine, distension of the stomach and small intestine with gas and fluid, and pale green digested material in the lumen of the cecum.

Conclusion: LD_{50} = 75.2 (57.2 to 93.1) mg/kg

Toxicity Category: Category II

Classification: Guideline

VI

300

DATA EVALUATION RECORD

Subject: Comparative Acute Dermal Toxicity of MO 70616 2.4 EC and SD 43775 2.4 EC in the Rabbit ($ADLD_{50}$ Study)

Test Material: MO 70616 2.4 EC (WRC Tox. Sample No. 731A, January 11, 1984)
SD 43775 2.4 EC (WRC Tox. Sample No. 78B, January 11, 1984)

EPA File Symbol: 201-URI

Accession No.: 254116

Purity: MO 70616 2.4 EC - 29.8% parent isomers (84% A-alpha isomer)
SD 43775 2.4 EC - 30.5% parent isomers (22.8% A-alpha isomer)

Testing Facility: Stillmeadow, Inc.
Biological Testing Laboratory
Houston, TX 77036

Report No: 3207-84 (6155 M/WTP-245)

Report Date: February 14, 1984

Authors: R. J. Sabol, E. J. Sabol, R. Mendez

Classification: Guideline

Toxicity Category: III

Materials and Methods:

Eighty New Zealand White albino rabbits, obtained from Camm Research Lab Animals, Wayne, New Jersey, were acclimated to laboratory conditions for at least 2 weeks and were randomly assigned to five groups containing five animals/sex. Mean group body weights ranged from 2.505 kg to 2.530 kg for females and from 2.485 kg to 2.520 kg for males. Twenty-four hours prior to treatment the back of the trunk of each animal was clipped. MO 70616 2.4 EC was applied to a surgical gauze patch at 0.12, 0.29, 0.66, 1.2 and 2.0 ml/kg and the patch then placed on the skin of the exposed area. SD 43775 2.4 EC treated animals were treated similarly but at doses of 0.98, 2.25 and 4.0 ml/kg. An Ace bandage was wrapped around the trunk of each animal and the animals were returned to their cages. The elastic bandage was removed 24 hours after treatment and the remaining test material was wiped off with a moist cloth. The animals were observed at 1, 2, 4, 6, and 24 hours after treatment, and twice daily through day 14. Individual body weights were recorded initially and on days 7 and 14. All animals received a gross necropsy. Observations for dermal reactions were made 24 hours after exposure and on day 14.

Results:

The following table provides information on the dose levels at which mortality occurred.

Test Substance	Dose (ml/kg)	Males	Females	Combined
SD 43775 2.4 EC	0.98	0/5	0/5	0/10
	2.25	0/5	1/5	1/10
	4.0	0/5	1/5	1/10
MO 70616 2.4 EC	0.12	0/5	1/5	1/10
	0.29	0/5	0/5	0/10
	0.66	0/5	1/5	1/10
	1.2	0/5	0/5	0/10
	2.0	0/5	0/5	0/10

SD 43775 2.4 EC:

One female in each of the 2.25 and 4.0 ml/kg groups died during the study. Treated animals exhibited diarrhea, decreased defecation, and loss of hind limb coordination. Slight to moderate erythema and edema were observed in animals of all treatment groups at 24 hours. After 14 days, very slight erythema or edema was present in a few animals in each group. Body weight gain was not affected by treatment. At necropsy, the following findings were noted: signs of diarrhea, serosal blood vessels pronounced on entire gastrointestinal tract, discoloration of the contents of the gastrointestinal tract, intestinal tract distended with gas, discoloration of liver, and discoloration of the intestinal mucosa.

MO 70616 2.4 EC:

One female in each of the 0.12 and 0.66 mg/kg groups died during the study. Treated animals displayed decreased defecation, diarrhea, loss of fore and/or hind limb coordination, loss of righting reflex, body tremors, and salivation. Erythema and edema was present at 24 hours and ranged from barely perceptible to moderate. The response was dose-related. After 14 days, erythema and/or edema was barely perceptible in a few animals in several of the treatment groups. Body weight was decreased in females in the 2.0 ml/kg group over the 14-day period. At necropsy the following findings were noted: signs of diarrhea, nasal discharge, polyuria, epistaxis, salivation, pronounced serosal blood vessels on intestinal tract, discoloration of the contents of the gastrointestinal tract, gas in the gastrointestinal tract, and liquid in the abdominal cavity.

Conclusion:

LD_{50} of SD 43775 2.4 EC > 4.0 ml/kg
LD_{50} of MO 70616 2.4 EC > 2.0 ml/kg

Toxicity Category:

SD 43775 2.4 EC is Category III

MO 70616 2.4 EC is Category III

Classification: Guideline (for both test substances)

DATA EVALUATION RECORD

Subject: Primary Skin Irritation of MO 70616 2.4 EC in the Rabbit

Test Material: MO 70616 2.4 EC (WRC Tox Sample No. 731A)

EPA File Symbol: 201-URI

Accession No.: 254115

Purity: MO 70616 2.4 EC - 29.8% parent isomers
(84% A-alpha isomer)

Testing Facility: Westhollow Research Center
Houston, TX 77082

Report No: 6155M/WTP-247 (Ref. LR-14578, pp. 26-28)

Report Date: March 8, 1984

Authors: T. D. Merritt and C. M. Parker

Classification: Minimum Data

Toxicity Category: I

Materials and Methods:

Six New Zealand White rabbits (3 males, 3 females) obtained from Camm Research Lab Animals, Wayne, New Jersey, were acclimated to the laboratory for 27 days. Animals were maintained in a room with a temperature of 17.8 to 18.9 °C and humidity at 40 to 73 percent. Body weights ranged from 2.7 to 4.0 kg at initiation of the study. Twenty-four hours prior to application of the test material, the back of each rabbit was clipped free of hair. A 0.5 ml sample of the test material was applied to a 1 inch square piece of surgical gauze and then placed on the exposure site on the back of the animal. The patches were held in place with tape and the entire trunk was covered with Saran Wrap. The trunk was then wrapped with an Ace bandage which was left in place for 4 hours at which time the dressings were removed and the test sites wiped with a moist cloth. After removal of the dressings, the test sites were evaluated. The test sites were also evaluated at 72 hours and at 4 days.

Results:

On examination at 4 hours, very little to no erythema or edema was observed at the test sites. At 72 hours, animals exhibited well-defined areas of erythema and edema. One animal developed areas of eschar at the test site. At day 7, very little improvement

at the test sites had occurred when compared to the 72-hour evaluations. The one animal with eschar at 72 hours still had the lesion present at 7 days. At 72 hours, the mean score for erythema and edema combined was 5.0 out of 8.0.

Conclusions:

The test material produced moderate irritation at 72 hours. (A 24-hour reading was not obtained.)

Toxicity Category: I (Based on the presence of eschar in one animal at 72 hours and at 7 days, the test material is considered to be corrosive and will be ranked as a Category I dermal irritant.)

Classification: Minimum Data

Note: All animals were exposed for less than 4 hours, by as much as 25 minutes. Although the duration of exposure was somewhat insufficient, the results were conclusive. Therefore, the study will be classified as Minimum Data rather than Supplementary.

DATA EVALUATION RECORD

Subject: Eye Irritation of MO 70616 2.4 EC in the Rabbit

Test Material: MO 70616 2.4 EC (WRC Tox Sample No. 731A)

EPA File Symbol: 201-URI

Accession No.: 254115

Purity: MO 70616 2.4 EC - 29.8% parent isomers (84% A-alpha isomer)

Testing Facility: Westhollow Research Center
Houston, TX 77082

Report No.: 6155M/WTP-246 (Ref. LR-14579, pp. 29-31)

Report Date: March 8, 1984

Authors: T. D. Merritt and C. M. Parker

Classification: Guideline

Toxicity Category: Category I

Materials and Methods:

Nine New Zealand White rabbits (3 males, 6 females) obtained from Camm Research, Wayne, New Jersey, were acclimated to the laboratory for 27 days. Animals were maintained in a room with a temperature of 17.8 to 20.0 °C and humidity of 40 to 73 percent. Body weights ranged from 2.6 to 3.4 kg. Prior to testing, the eyes of each rabbit were examined for lesions with a 1 percent solution of fluorescein. On the day of treatment, one-tenth ml of the test material was placed in the right eye of each rabbit. The eye was then held closed for several seconds. Three female rabbits received an eye wash with 300 ml of tap water 30 seconds after instillation of the test material. The remaining six rabbits did not receive an eye wash. Ocular examinations were made at 1 hr and at 1, 2, 3, 7, 14, and 21 days after treatment.

Results:

All of the 9 animals developed corneal opacities. Corneal opacity was present in 1 rabbit in the nonwashed group at 21 days. All rabbits developed conjunctivitis and two rabbits showed effects on the iris. The maximum mean irritation score obtained was 39.3/110 at 24 hours in the nonwashed group and 33.7 in the washed group at 24 hours. Washing the eyes did not significantly reduce the irritation score at the 1-hr and 1-, 2-, and 3-day readings. However, washing seemed to reduce the irritation score at the 7-, 14-, and 21-day readings.

Conclusions:

Due to the extended corneal involvement, the test material should be considered to be a severe ocular irritant.

Toxicity Category: Category I

Classification: Guideline

DATA EVALUATION RECORD

Subject: Guinea Pig Skin Sensitization of MO 70616 2.4 EC

Test Material: MO 70616 2.4 EC (WRC Tox Sample No. 731A)

EPA File Symbol: 201-URI

Accession No.: 254115

Purity: 29.8% parent isomers (84% A-alpha isomer)

Testing Facility: Stillmeadow, Inc.
Biological Testing Laboratory
Houston, TX 77036

Report No.: 3196-83/WTP-248

Report Date: February 14, 1984

Authors: R. J. Sabol and E. J. Sabol

Classification: Minimum Data

Materials and Methods:

Twenty male and 20 female short-haired Hartley Albino guinea pigs, obtained from Camm Research Lab Animals, Wayne, NJ, were equilibrated in the laboratory. Five males and five females were randomly selected and assigned to each of four treatment groups. Animals were placed five per sex in suspended wire bottom galvanized cages. Bedding (paper) was changed daily and animals were moved to clean cages weekly. Guinea pig chow and tap water were available ad libitum. Group I animals (vehicle control) were treated with deionized water. Group II animals (positive control) were treated with a 0.1 percent solution of 2,4-dinitrochlorobenzene in diethyl ether. Group III animals (test group) were treated with a 10.0 percent w/v solution of the test material in deionized water. Group IV animals (irritation control) were treated with a 10.0 percent w/v solution of the test material in deionized water. Forty-eight hours prior to the treatment, the back of the trunk of each animal was clipped free of hair. Approximately 24 hours prior to treatment, Neet hair remover was applied to the exposure area of each animal and then was removed 5 to 15 minutes later. Group I, II, and III animals were treated on days 1, 8, and 15 by placing 0.5 ml of the appropriate material on a 5/8 x 9/8 inch gauze patch which was secured to the back the left front quadrant of the exposure area with a piece of adhesive tape. The trunk of each animal was then covered with polyethylene film for a 6-hour period. At the end of the exposure period, the patches were removed and the

animals returned to their cages. The same test site was used on each animal on all treatment days. On day 29, all animals (including Group IV animals) were treated in an identical manner as the previous 3 treatment days with the addition of a second test site (which also received a patch containing 0.5 ml of the appropriate material) located on the right rear quadrant of the exposure area. On day 36, the animals were again treated as on day 29, however, the test site was located more to the right anterior quadrant of the exposure area. Observations of the exposure sites were made 24 and 48 hours after treatment. Individual body weights were recorded on days 0, 7, 14, 21, 28, and 35.

Results:

No skin reactions were observed in animals in the vehicle control group. Animals in the positive control group had scores of 1.69 for the first virgin challenge site and 3.06 for the original test site for the first challenge on day 29. (The maximum score that can be obtained is 4.00.) Scores of 1.81 and 3.33 were obtained at the second virgin challenge site and original test site, respectively, for the second challenge on day 36. The average skin reaction scores for the irritation control group was 0.00 for both virgin treatment sites for the challenge treatment and 0.00 for the new virgin test site and 0.25 for the previously treated test site for the second challenge. One animal in this group died. Gross necropsy revealed that the small intestine was filled with gas and a red-brown mucoid material, and the stomach and cecum were filled with dark green mucoid material. Skin reaction scores for the test group were 0.08 for the first virgin challenge site and 0.53 for the original test site. Scores were 0.55 for the second virgin challenge site and 1.28 for the original test site for the final challenge on day 36. Skin reaction scores at virgin sites primarily reflected scores in females because males did not have skin reactions at virgin sites in the test group. It was also noted that on the third application of the induction period skin reactions occurred in the test group. Females were affected to a greater extent than males. Body weight gain was depressed in females in the test group and in males in the irritation control group.

Conclusions:

The test material is a skin sensitizer in female Hartley strain albino guinea pigs.

Classification: Minimum Data*

* The test is a modification of the Bühler topical closed patch technique, however, fewer than the recommended 20 test animals were used. Additionally, the challenge

applications were made at 1 and 2 weeks after the last induction application instead of the recommended 2 and 3 weeks after the last induction application. There is also an error in the report. In one section the positive control is stated to be 0.5 ml of a 0.1 percent w/v solution of 2,4-dinitrochlorobenzene in diethyl ether, but in another section it is referred to as 0.5 ml of a 0.05 w/v solution of 2,4-dinitrochlorobenzene in ethyl alcohol. These are very minor deficiencies, but they detract from the study. Therefore, a "Guideline" classification cannot be supported.

2
310

DATA EVALUATION RECORD

Subject: Subchronic (13-Week) Feeding Study of MO 70616 in the Rat for the Shell Development Company, Houston, Texas

Chemical: SS Fenvalerate (Pydrin)

Accession No.: 257018, 257019, 257020

Laboratory: T.P.S., Inc., Mt. Vernon, Indiana

Study No./Report Date: 227A-101-030-84/December 20, 1984

Test Material/Purity: MO 70616 - WRC Tox Sample No. 730B/98.7% of the parent isomers of which 84% was the A-alpha isomer

Testing Period:: June 12, 1984 - September 17, 1984

Classification: Minimum Data

Materials and Methods:

Animals:

Thirty-four day-old male and female Sprague-Dawley rats were obtained from Camm Research, Wayne, New Jersey, and acclimated to the laboratory for a 28-day period prior to assignment to control and treatment groups. The rats placed on treatment were selected from a larger group of animals on the basis of body weight, body weight gain, and pretest physical examinations, including ophthalmoscopy. The rats were segregated by sex, assigned to test groups using a computer generated random list, and identified individually by ear punch. Additionally, 10 rats/sex were randomly selected to provide a pretest baseline reference for hematologic and serum chemistry values and assessment of pathogen burden prior to initiation of the study. Ten rats/sex were also randomly selected to provide clinical chemistry calibration values at the interim (5 rats/sex) and terminal (5 rats/sex) evaluations. Rats were assigned to groups as indicated below:

Group	Male Rats	Female Rats	Treatment
TP 1	30	30	Control
TP 2	30	30	50 ppm
TP 3	30	30	150 ppm
TP 4	30	30	300 ppm
TP 5	30	30	500 ppm

Environment:

All animals were caged in the same room. Rats were caged individually during the study in stainless steel cages with wire mesh bottoms and automatic watering systems. Cages were changed and the racks were rotated in position in the room at 2-week intervals. The flush pans under each cage were manually rinsed twice per day after observing whether feed had been spilled. The temperature was maintained at 23 ± 2 °C and humidity at 50 ± 10 percent. The lighting cycle was established at 12 hours on and 12 hours off. Room air was changed 10 to 15 times per hour. Water samples were taken prior to initiation of the study and shortly after termination and sent to Lancaster Laboratories, Lancaster, Pennsylvania, for chemical analysis for heavy metals, pesticides, and organic materials.

Test Diets:

The basal diet was Purina Certified Rodent Chow Meal #5002, which was analyzed by the Ralston Purina Company prior to initiation of the study for chlorinated and organophosphorus pesticides, heavy metals and PCB's. The test material (MO 70616) was kept refrigerated prior to incorporation into test diets. To prepare 90 kg of each test diet, the correct amount of the test material was dissolved in 150 ml of acetone and then mixed with 3 kg of basal diet in a 20 qt. Univex mixer until the acetone had evaporated. A premix weighing 10 kg was then made by mixing the contents of the Univex mixer with the appropriate amount of basal diet in a 60 qt. Hobart mixer for 20 minutes. The premix was later added to a Day ribbon mixer containing sufficient basal diet to make 90 kg of test diet and mixed for 60 minutes. Samples of each test diet were taken for analysis by the Shell Development Company for concentration of test material and for homogeneity. A second batch of test diets weighing 50 or 60 kg was similarly prepared. Test diets were stored at room temperature until used. Animals were provided their diets ad libitum. Each week the feeders were weighed, and were replaced with clean feeders containing the appropriate test diet.

Observations and Measurements:

Animals were observed twice daily and received weekly clinical examinations by a veterinarian. Blood from 10 rats/sex at pretest, 10 rats/sex/group at interim necropsy, 15 rats/sex/group at termination, and 5 rats/sex used for calibration at interim necropsy and at termination were evaluated. The hematologic evaluations included hematocrit, hemoglobin, erythrocyte count, erythrocyte indices (MCV, MCHC, MCH), total and differential leukocyte counts, erythrocyte morphology and platelet count. From the same animals cited above the following clinical chemistry determinations were made from their serum: sodium, phosphorus,

calcium, potassium, serum lactic dehydrogenase, serum glutamic pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), glucose, blood urea nitrogen, total bilirubin, total cholesterol, serum alkaline phosphatase, albumin, globulin, albumin/globulin ratio, and total protein. Prior to interim and terminal sacrifices, urine was collected from those animals scheduled for necropsy. The urine was examined for volume, gross appearance, glucose, ketones, pH, albumin, specific gravity, urobilinogen, bilirubin, and occult blood. After 7 weeks, 99 of the 100 male and female rats selected for the interim necropsy and, after 13 weeks, 144 of the 150 male and female rats selected for the terminal necropsy were sacrificed. (The difference between scheduled and actual number of animals sacrificed at these times was due to unexpected deaths and moribund sacrifices.)

Selection of animals for necropsy was based on random distribution lists. After an overnight fast, the animals were weighed and euthanatized with carbon dioxide gas. The external surface, all offices, the cranial cavity, carcass, the external and cut surfaces of the brain and spinal cord, the nasal cavity and paranasal sinuses, the thoracic, abdominal, and pelvic cavities with their associated organs and tissues, and the neck with its associated tissues and organs were examined grossly. The following organs were weighed: lungs, liver, kidneys, heart, testes with epididymides or uterus with cervix, and brain (including stem). The following tissues from all the control and high-dose animals were routinely processed, embedded in Paraplast, sectioned, stained with hematoxylin and eosin, and examined microscopically: brain (3 transverse sections - 1 section through the frontal cortex and basal ganglia, 1 section through the parietal cortex and thalamic area, and one section through the cerebellum and medulla oblongata), spinal cord (3 transverse sections - one section through the cervical area, thoracic area, and lumbar area), sciatic nerve (4 sections - proximal and distal areas of the left and right nerves), tibial nerves (2 sections), plantar nerves (2 sections), right median nerve, eyes, pituitary, adrenals, thyroid, parathyroid, parotid salivary gland, mandibular lymph node, mesenteric lymph node, external iliac lymph node, thymus, esophagus, trachea, aorta, heart, lungs with mainstem bronchi, liver (3 sections), kidneys (longitudinal section of left and transverse section of right, both through papillae), spleen, urinary bladder, testes, prostate, epididymis, ovaries, oviducts, uterus, cervix, stomach (a section from the fundus and pylorus), pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, skin, mammary gland (right inguinal from females only), femur (bone marrow), costochondral junction (right third rib), and other tissues with gross lesions. Sections from the pituitary, parotid salivary glands, lungs with mainstem bronchi, liver and kidneys were processed and evaluated for 25 male and 25 female animals in the 3 lower dose groups designated for the interim and terminal necropsies. Forty-nine of the 50

713

rats selected for electron microscopy were weighed, anesthetized with sodium pentobarbital, and then perfused with saline and 2 percent glutaraldehyde buffer solution. The brain, the right and left sciatic, tibial, and plantar nerves, a section of dorsal lumbar skin, and spinal cord were removed and fixed. The tissues were sectioned as follows: brain 1 to 2 mm sections through the frontal cortex and basal ganglia, one through the parietal cortex and thalamic area, and one through the cerebellum and medulla oblongata; spinal cord - 1 to 2 mm sections from the cervical, thoracic, and lumbar regions; sciatic, tibial and plantar nerves - 1 to 2 mm sections from right and left nerves; and dorsal lumbar skin - 1 to 2 mm sections. (It was not explained from which dose groups these animals came.) Electron microscopy was conducted on the tissues from one animal.

Statistics:

Weekly body weights were evaluated by analysis of covariance. Differences between control and treated group values for weekly body weights, estimated food consumption, hematologic and serum chemistry values, organ weights, and quantitative urinalysis data were analyzed for statistical significance by the method of Dunnett.

Results:

Clinical Signs:

One male in the 150 ppm group exhibited jerky leg movements during week 11 of the study. One female in the 150 ppm group developed alopecia on the forelimbs during week 6 and had spread to the thoracic area by week 13. In the 300 ppm group, 18 males and 24 females had jerky leg movements at some point in time during the study. One female rat in this group also had an unsteady gait from week 5 through 8. All rats in the 500 ppm had jerky leg movements and/or unsteady gait at some time during the course of the study. Additionally, 3 males and 1 female rat in the 500 ppm group had a scab-covered area at the base of the tail at the end of the study. One male rat in this group had hair loss of the forelimbs from weeks 2 through 6. One female in this group had stained hair in the urogenital area from weeks 4 to 6 and one female had a rough hair coat from weeks 8 to 11. Four female rats in this group appeared to be hypersensitive to sound during a portion of the study and one female rat appeared to be hyperactive from weeks 11 to 14. By the end of week 1, jerky leg movements and unsteady gaits were first detected in several animals in the 500 ppm group. When examined, animals with jerky leg movements shook their forepaws in a fanning motion as the forelimb was raised from the table surface. Flexion of the hind limbs was prolonged or exaggerated, and during ambulation the limb was momentarily suspended and held posteriorly. Return of the limb

to the table surface was delayed. The gait was unsteady or uncoordinated in some affected animals. The severity of these signs appeared to be dose-related. The most severely affected animals in the 500 ppm group were hypersensitive to sound and had body tremors and/or convulsions eventually followed by death. Prior to death, nonspecific signs such as rough hair coat and scabs on the tail were observed in a few females in the 500 ppm group.

Body Weight and Food Consumption:

Male mean group body weight gain was decreased in animals fed 300 and 500 ppm in the diet from week 1 through week 6 when compared to the control group. Female mean group body weight gain was decreased in animals fed 500 ppm in the diet from week 1 through 5. Mean group food consumption was decreased in males in the 500 ppm group from week 1 through week 6. Mean group food consumption was decreased in females administered 500 ppm in the diet from week 1 through week 5. When food consumption was analyzed on a grams per kilogram body weight basis, males in the 500 ppm group exhibited an increase in relative food consumption from week 6 through week 13. In females, relative food consumption was increased in the group fed 500 ppm during weeks 6, 7, 8, 10, and 13.

Hematology:

There was a slight reduction in the erythrocyte count of females in the 500 ppm group at week 8. The remaining results obtained for test groups at week 8 compared favorably to those obtained for control animals. At termination of the study, there was a significant reduction in the hematocrit for all male test groups compared with the control group. However, when compared to mean hematocrit value obtained for the calibration group, no difference was apparent. Additionally, a dose-response relationship for the decrease in the hematocrit was not present. The erythrocyte count for males in the 300 ppm group and the mean hemoglobin levels for males in the 300 and 500 ppm groups were significantly lower than the values obtained for control males. However, when compared to males in the calibration group, no difference was discerned. These differences are sporadic and do not appear to be biologically significant.

Clinical Chemistry:

Males in the 500 ppm group exhibited a decrease in phosphorus levels when compared to all other groups of males at week 8. This is probably a spurious value since phosphorus levels were comparable among all groups at termination of the study. Females in the 500 ppm group had a decrease in potassium levels at week 8 which was attributed to slight hemolysis of the blood. When

nb 1 215

compared to control males, all treated male groups exhibited slight decreases in glucose and total protein (primarily reflected as a decrease in globulin levels) at termination. However, when compared to values obtained for males in the calibration group, no differences were apparent. There was a very slight decrease in total protein (represented primarily as globulin levels) in females in the 500 ppm group. However, the level of total protein in females in this group was similar to females in the calibration group and was not considered to be biologically significant.

Urinalysis:

The specific gravity was increased in males and females in the 500 ppm group at weeks 7 and 13. The specific gravity was also increased in females in the 300 ppm group at week 13. Urobilinogen was slightly elevated in males and females in the 500 ppm group and in females in the 300 ppm group at week 7. Additionally, urobilinogen was increased in females in the 300 and 500 ppm groups at week 13. The above-mentioned findings are considered to be minor and are of questionable biological significance.

Necropsy:

At the interim sacrifice, 99 of the 100 selected animals for necropsy displayed no pattern of lesions that could be attributed to administration of the test material. One of the selected rats died prior to the interim sacrifice but had no lesions attributable to treatment. At terminal sacrifice, 6 of the 150 animals selected for necropsy died during the study. Five animals were females in the 500 ppm group of which 3 were reported to have died from self-inflicted trauma. The sixth animal in the 300 ppm group had accidentally fallen and succumbed to a skull fracture. Of the animals that survived to termination, 1 female in the 300 ppm group and 3 animals (2 males, 1 female) in the 500 group had scab-covered areas in the skin around the base of the tail. The other findings noted appeared not be related to treatment.

Organ Weights:

At the interim sacrifice, male and female rats in the 500 ppm group had a decrease in the absolute weight of the heart. Males in the 500 ppm group also exhibited a slight decrease in the absolute and relative weight of the liver. The relative weight of the brain was slightly increased in males in the 300 ppm group and was significantly increased in males in the 500 ppm group. The relative weight of the brain was also increased in females in the 300 and 500 ppm groups. Females in the 150, 300, and 500 ppm groups also had increases in the relative weight of the kidney. At termination, the absolute weight of the uterus

was elevated in females in the 500 ppm group. The relative weight of the brain was increased in males and females in the 500 ppm group. Additionally, the relative weight of the kidneys was increased in males in the 300 and 500 ppm groups. These changes are minor, some do not show a dose-response relationship, and many reflect differences in body weights among the control and treated animals.

Histopathology:

At interim sacrifice, 2 of 10 male rats in the 500 ppm group had slight hypertrophy at the parenchymal cells in the pars intermedia of the pituitary gland. Slight hypertrophy of the parenchymal cells of the parotid salivary gland was observed in 4 of 10 males and 4 of 10 female rats in the 500 ppm group. One female with parotid salivary gland hypertrophy also exhibited slight hypertrophy of the submaxillary salivary glands. At terminal sacrifice, 3 of 15 male rats in the 500 ppm group had slight hypertrophy of the parenchymal cells in the pars intermedia of the pituitary gland. One of 15 male and 2 of 15 female rats in the 300 ppm group and 6 of 15 male and 4 of 15 females rats in the 500 ppm groups exhibited slight hypertrophy of the parenchymal cells of the parotid salivary gland. One male in the 500 ppm group with hypertrophy of the parotid salivary gland also had gross and microscopic evidence of hypertrophy of the submaxillary glands Slight to moderate dermatitis was observed in 1 female rat in the 300 ppm group and in 3 rats (2 males, 1 female) in the 500 ppm group in the scab areas (noted at necropsy) near the back of the tail. The lesions mentioned above were not observed in animals in the control, 50, or 150 ppm groups and are considered to be related to treatment.

Discussion and Conclusions:

All animals in the 500 ppm group, several animals in the 300 ppm group, and one animal in the 150 ppm group had one or more clinical signs characteristic of neurological dysfunction. Several animals in the 500 ppm group had scabs around the base of the tail that were histologically identified as areas of dermatitis. Body weight gain was decreased in males and females in the 500 ppm group and in females in the 300 ppm group. Food consumption was decreased although relative food consumption was increased in animals in the 500 ppm group. At necropsy, male rats in the 500 ppm group exhibited slight hypertrophy of the parenchymal cells of the pars intermedia of the pituitary gland. Males and females in the 500 ppm group exhibited slight hypertrophy of the parenchymal cells of the parotid salivary gland and a few of these animals also had hypertrophy of the submaxillary salivary glands. A few animals in the 300 ppm group had hypertrophy of the parenchymal cells of the parotid salivary gland. The observations cited above are considered to be related to treatment.

Note: Although sections of salivary gland were not examined in the low- and intermediate-dose groups, the occurrence of hypertrophy of the parenchymal cells of the submaxillary salivary glands was so low (1 male, 1 female) in the 500 ppm group, it is unexpected that the lesion would be observed in animals in the lower-dose groups.

LEL = 150 ppm (based on neurological signs)

NOEL = 50 ppm

Classification: Minimum Data

Recommendations: The sponsor should forward information to the Agency which describes the "self-inflicted trauma" which caused the deaths of 3 females in the 500 ppm group.

Summary of Literature Articles

1. Verschoyle, R.D.; Alderidge, W.N. (1980) Structure-activity relationship of some pyrethroids in rats. Arch. Toxicol. 45:325-329.

An approximate lethal dose of fenvalerate (and other pyrethroids) dissolved in glycerol formal was injected into the tail vein of female albino Porton derived Wistar rats weighing approximately 180 g. Fenvalerate-treated rats displayed the CS syndrome, which is characterized by "initial pawing and burrowing behavior, followed within 2 to 5 minutes by profuse salivation, coarse whole body tremor, increased startle response and abnormal locomotion involving the hind limbs. The coarse tremor progresses into a sinuous writhing of the whole body (choreoathetosis) which gradually becomes more violent and is enhanced by sensory stimuli. As a terminal event chronic seizures are occasionaly observed. No increase in core temperature occurs..." Some generalizations concerning structure-activity relationships can be made. The CS syndrome has only been observed with compounds having the α-cyano-3-phenoxybenzyl alcohol group in their structure.

2. Vijverberg, H.P.M.; Ruigt, G.S.F.; van der Bercken J. (1982) Structure-related effects of pyrethroid insecticides on the lateral-line sense organ and on peripheral nerves of the clawed from, Xenopus laevis. Pestic. Biochem. Pysiol. 18:315-324.

Pyrethroids without an α-cyano group (permethrin, cismethrin, and bioresmethrin) induce short trains of nerve impulses in the lateral-line sense organ of Xenopus laevis. In peripheral nerves they induce a depolarizing afterpotential with repetitive firing. Pyrethroids with an α-cyano-3-phenoxybenzyl alcohol group (cypermethrin, fenopropathrin, deltamethrin, and fenvalerate) induce very long trains of nerve impulses which may last for seconds and may contain hundreds or thousands of impulses. These α-cyano group pyrethroids do not cause repetitive firing in peripheral nerves. Instead, they induce a quickly reversible, stimulus frequency-dependent suppression of the action potential. The large differences in neurotoxic effects are attributed to the presence or absence of the α-cyano group. The duration of nerve impulse trains induced by both classes of pyrethroids increases substantially when the temperature is lowered. Additionally, the effects of both classes of pyrethroids on nerve action potentials are more pronounced to their effect on motor fibers. It was concluded that both classes of pyrethroids primarily interact with the sodium channels and that their principal action is to induce repetitive firing, which is due to a prolonging of the transient increase in sodium permeability of the nerve membrane during excitation.

30
719

3. Butterworth, S.T.G.; Hend, R.W. (1983) Peripheral Nerve Lesions Induced by Large Doses of Pyrethroid Insecticide in Rats. Neuropath. Appl. Neurobio. (in press).

"Permethrin, cypermethrin, fenpropathrin and fenvalerate were administered orally to rats either in the diet or as single doses. When given in large quantities, sufficient to kill some of the treated animals, all of these compounds produced sporadic Wallerian degeneration in the sciatic and posterior tibial nerves. The neuropathy was never severe and was not seen in animals given pyrethroids in doses less than the lethal range. In a feeding study in which peripheral nerve degeneration was found, no lesions were seen in the brain or spinal cord. In feeding studies ranging in duration from five weeks to two years there was no evidence of cumulative neurotoxicity."

4. Parker, C.M., Albert, J.R.; Van Gelder, G.A.; Patterson, D.R.; Taylor, J.L. (1984) Neuropharmacologic and neuropathologic effect of fenvalerate in mice and rats. Fundam. Appl. Toxicol. (in press).

"B6C3F_1 mice and Sprague-Dawley rats displayed the characteristic signs of pyrethroid intoxication following single oral doses ranging from 56 to 320 mg/kg and 133 to 1000 mg/kg fenvalerate, respectively. The LD_{50}'s for mice and rats were 180 and 776 mg/kg, respectively, with corn oil as the vehicle. Signs of neurologic deficit such as splayed gait, tremors, ataxia and hind limb incoordination were observed at doses of $\geq$ 100 mg/kg (mice) and $\geq$ 133 mg/kg (rats) within 1 to 8 hours after dosing. These signs had disappeared in most animals within 72 hours. Slight peripheral nerve fiber damage was detected in surviving mice and rats sacrificed 10 days after dosing. The incidence and severity were dose-related at doses $\geq$ 56 and $\geq$ 180 mg/kg; however even at lethal doses, evidence was lacking for the presence of nerve lesions in several animals. Thus, two distinct neurologic effects were observed: a reversible ataxia/incoordination and a neuropathologic effect manifested as sparse axonal damage in peripheral nerve."

5. Ohkawa, H., Kaneko, H., Tsuji, H. and Miyamoto, J. (1979) Metabolism of fenvalerate (Sumicidin®) in rats. J. Pesticide Sci. 4:143-155

"On either a single oral dose or 5 consecutive daily doses, the metabolism of fenvalerate [α-cyano-3-phenoxybenzyl-2-(4-chlorophenyl)isovalerate] and the (S)-acid ester isomer in male rats was rapid, and the acid moiety and the aromatic portion of the alcohol moiety were almost completely eliminated from the body within several days. The CN group of the alcohol moiety was rapidly converted mainly to thiocyanate

which retained relatively longer in selective tissues including skin and hair. Fenvalerate and the (S)-acid isomer yielded two fecal ester metabolites which resulted from hydroxylation at the 4'- and 2'-phenoxy positions. Other significant metabolites were 3-phenoxybenzoic acid and its hydroxy derivatives (free and conjugates) from the alcohol-labeled compound, 3-(4-chlorophenyl)isovaleric acid and its hydroxy derivatives (free, lactones and conjugates) from the acid-labeled compound, and thiocyanate and CO_2 from the CN-labeled compounds. There were no apparent differences in the nature and amount of metabolites, and in the patterns of ^{14}C excretion and tissue residues between fenvalerate and the (S)-acid isomer."

6. Kaneko, H., Ohkawa, H., and Miyamoto, J. (1981) Comparative metabolism of fenvalerate and the (2S,αS)-isomer in rats and mice J. Pesticide Sci. 6:317-326.

"On single oral administration of each of the ^{14}C-acid, -alcohol and -CN-labeled preparations of fenvalerate [(RS)-α-cyano-3-phenoxybenzyl-(RS)-2-(4-chlorophenyl)isovalerate] and the [2S,αS]-isomer at 4.2 to 30 mg/kg, the radiocarbon from the acid and alcohol moieties was almost completely eliminated from the body of rats and mice, and the ^{14}C tissue residues were generally very low. On the other hand, radiocarbon from the CN-labeled preparations was somewhat slowly excreted and higher ^{14}C residues were found in the hair, skin and stomach contents. There were no apparent differences in the total ^{14}C recovery, biological half-life and ^{14}C tissue residues in the two compounds or sexes. Two weeks pre-feeding of 500 ppm unlabeled fenvalerate resulted in more complete elimination of the radiocarbon from the body and lower ^{14}C tissue residues in rats and mice given a single dose of CN-labeled fenvalerate, as compared with the non-feeding treatment. Both fenvalerate and the [2S,αS]-isomer were similarly metabolized mainly by oxidation at the 2'- and 4'-phenoxy positions of the alcohol and at the C-2 and C-3 positions of the acid moiety, cleavage of the ester linkage, conversion of the CN group to SCN- and CO_2, and conjugation of the resultant carboxylic acids and phenols with glucuronic acid, sulfuric acid and/or amino acids. Although no significant differences in the nature or amount of metabolites were seen between the sexes, dose levels or isomers, the following remarkable species differences were found: 1) taurine conjugate of 3-phenoxybenzoic acid was found in mice, but not in rats, 2) 4'-hydroxylation of the alcohol moiety and sulfate conjugate of 3-(4'-hydroxyphenoxy)benzoic acid occurred to greater extents in rats than in mice and, 3) a greater amount of thiocyanate was excreted in mice than in rats."

APPENDIX #2

REFERENCES

*1. Albert, J. R. and L. M. Summitt, Acute Oral and I. P. Toxicity of WL 43775 (6-1-0-0) in Male and Female Mice (Preliminary Assay) Shell Development Company, Modesto, CA, TIR 74-020-76, 1976.

*2. Walker, B. J., Hend, R. W. and S. Linnett, Toxicity Studies on the Insecticide WL 43775: Summary of Results of Preliminary Experiments, Shell Research Ltd., Sittingbourne, UK, TLGR 42.75, July, 1975.

*3. Summitt, L. M. and J. R. Albert, Determination of the Acute Oral Lethality of WL 43775 (6-1-0-0) in the Male and Female Mouse, Shell Development Company, Modesto, CA, TIR 74-017-76, 1976.

*4. Sumitomo Chemical Company, Programs for Safety Evaluation of an Insecticidal S-5602, Sumitomo Chemical Company, Osaka, Japan, Report dated August, 1976.

*5. Parker, C. M., Albert, J. R. and J. L. Taylor, Species Susceptibility of PYDRIN Insecticide in the Rat, Mouse, Hamster and Rabbit, Shell Development Company, Houston, TX, RIR-118, 1978.

*6. Summitt, L. M. and J. R. Albert, Oral Lethality of WL 43775 in the Rat, Shell Development Company, Modesto, CA, TIR 74-019-76, 1976.

*7. Hart, E. R., Acute Oral Toxicity (LD_{50}) in Hamsters with SD 43775 Technical, Litton Bionetics, Inc., Falls Church, VA, 1976.

*8. Parker, C. M., Acute Toxicity Studies with Technical SD 92459 (WRC Tox. Sample No. 14200-61-59A), Shell Development Company, Houston, TX, RIR-114, 1981.

*9. Parker, C. M., Acute Oral Toxicity and Neuropathology of WRC Toxicology Sample No. 14200-61-59A (SD 92459) in the Rat, Shell Development Company, Houston, TX, RIR-115, 1981.

* Studies previously submitted to the Agency.

*10. Cassidy, S. L. and D. G. Clark, Toxicology of WL 43775: Acute Toxicity, Skin and Eye Irritancy of S 5602A (L 46967) Technical Material. Shell Research Ltd., Sittingbourne, UK, TLGR 0176.78, 1978.

11. Parker, C. M., Bilsback, M. M. and H. C. Wimberly, Acute Oral Toxicity of Technical Mo 70489 in the Rat, Shell Development Company, Houston, TX, RIR-355, 1984.

12. Butterworth, S. T. G. and S. L. Cassidy, Toxicity of Insecticides: Acute Oral Toxicity and Neuropathological Effects of SD 47443 in Rats, Shell Research Ltd., Sittingbourne, UK, TLGR 79.058, 1979.

13. Cassidy, S. L., Toxicology of Insecticides: Acute Oral LD_{50} (Rat), Percutaneous LD_{50} (Rat and Rabbit), Skin and Eye Irritancy and Skin Sensitizing Potential of SD 47443 (S-5602), Shell Research Ltd., Sittingbourne, UK, TLGR 31.79, 1979.

*14. Parker, C. M., Acute Toxicity Study of PYDRIN 2.4 EC, Shell Development Company, Houston, TX, RIR-152, 1981.

*15. Harrison, W. A. and C. W. Mastri, Acute Toxicity Studies with SD 43775, Code 5-2-8-6 2.4 EC, Industrial Biotest Laboratories, Northbrook, IL, IBT 601-07418, 1975.

*16. Harrison, W. A. and C. W. Mastri, Acute Toxicity Studies with SD 43775 Code 6-1-14-1 2.4 EC, Industrial Biotest Laboratories, Northbrook, IL, IBT 8530-08500, 1976.

17. Coombs, A. D. and Carter, B. I., Toxicity Studies on the Insecticide WL 43775: Acute Toxicity, Skin and Eye Irritancy Potential of the Emulsifiable Concentrate FX 3368, Shell Research Ltd., Sittingbourne, UK, TLGR 99.75, 1975.

*18. Parker, C. M., Acute Oral Toxicity Study with PYDRIN 4 OS, Shell Development Company, Houston, TX, RIR-314, 1983.

* Studies previously submitted to the Agency.

*19. Parker, C. M., Acute Oral Toxicity of SD 92459 1.2 EC (WRC Tox. Sample No. 14200-113-406A), Shell Development Company, Houston, TX, RIR-111, 1981.

*20. Eisenlord, G., SD 43775 Toxicology: Acute and Repeated (14-Day) Dermal Toxicity in the Rabbit, Hine Laboratories, Inc., San Francisco, CA, 1975. M-259-75.

21. Albert, J. R., Acute Dermal Toxicity of a 2.4 EC Formulation of PYDRIN Insecticide in the Rabbit, Shell Development Company, Houston, TX, RIR-133, 1981.

*22. Parker, C. M., Acute Toxicity Studies with PYDRIN 4 OS (WRC Tox. Sample No. 707A), Shell Development Company, Houston, TX, RIR-297, 1983.

23. Parker, C.M., Acute Dermal Toxicity of MO 70489 2.4 EC in the Rabbit, Shell Development Company, Houston, TX, RIR-357, 1984.

*24. Albert, J. R., Acute Dermal Toxicity of 1.2 EC Formulation of SD 92459 in the Rabbit, Shell Development Company, Houston, TX, RIR-137, 1981.

*25. Parker, C. M., Acute Dermal Toxicity of SD 92459 1.2 EC (WRC Tox. Sample No. 14200-113-406A), Shell Development Company, Houston, TX, RIR-110, 1981.

*26. Okuno, Y., Kadota, T. and J. Miyamoto, Eye and Skin Irritation of S 3206 and S 5602 in Rabbits, Sumitomo Chemical Company, Osaka, Japan, Report dated August, 1975.

*27. Okuno, Y., Kadota, T. and J. Miyamoto, Skin Sensitization Study of S 3206 and S 5602 in Guinea Pigs, Sumitomo Chemical Company, Osaka, Japan, Report dated August, 1975.

*28. Parker, C. M., Comparative Toxicity Study of Two PYDRIN 2.4 EC's and Their Formulation Blanks, Shell Development Company, Houston, TX, RIR-153, 1981.

* Studies previously submitted to the Agency.

29. Parker, C. M., Skin Sensitization Potential of the PYDRIN 2.4 EC Formulation in Guinea Pigs, Shell Development Company, Houston, TX, TIR-471, 1981.

*30. Parker, C. M., Acute Skin Irritation Study of SD 92459 1.2 EC (WRC Tox. Sample No. 14200-113-406A), Shell Development Company, Houston, TX, RIR-109, 1981.

*31. Parker, C. M., Acute Eye Irritation Study of SD 92459 1.2 EC (WRC Tox. Sample No. 14200-113-406A), Shell Development Company, Houston, TX, RIR-112, 1981.

*32. Parker, C. M., Skin Sensitization Study of SD 92459 1.2 EC (WRC Tox. Sample No. 14200-113-406A), Shell Development Company, Houston, TX, RIR-113, 1981.

*33. Jud, V. A. and C. M. Parker, Eye Irritation of PYDRIN 2.4 EC in the Rabbit, Shell Development Company, Houston, TX, RIR-260, 1982.

34. Okuno, Y. and J. Miyamoto, Isomerism of Fenvalerate and Granuloma Formation (Interim Results), Sumitomo Chemical Company, Osaka, Japan, Report dated November, 1983.

35. Dewar, A. J. and B. J. Moffett, Toxicity Studies on the Insecticide WL 47443. Preliminary Biochemical and Functional Studies on the Neurotoxicity of WL 47443 to Rats Including a Comparison with the Neurotoxicity of WL 43775, Shell Research Ltd., Sittingbourne, UK, TLGR 30.78, 1978.

* Studies previously submitted to the Agency.