Manufacturing process information may be entitled to confidential treatment

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

001487

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

DATE: MAR 2 1982

SUBJECT: EPA Reg. No. 279-3013 and 279-3014: Permethrin, Notice of Change in Manufacturing Process that Results in Change in the cis and trans Isomer Composition.

TOX Chem. No. 652BB

FROM: John Doherty 2/4/82
Toxicology Branch/HED (TS-769)

TO: F. D. R. Gee, PM #17
Registration Division (TS-767)

THRU: Orville E. Paynter, Ph.D. OEP 3/1/82
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769)

The FMC Corporation has modified their manufacturing process so that the technical preparation of permethrin will be [redacted] (45:55 to 55:45). The old manufacturing process resulted in a [redacted] composition (35:65 to 45:55).

In order to support this change in composition, the company has submitted acute and subchronic toxicity tests which are reviewed herein (see below). (These studies are in EPA Acc. No. 242899, 242900, 242901, and 242902).

Conclusions:

1. Toxicology Branch has no objection to changing the manufacturing process as indicated.

2. The studies submitted were reviewed and found to be Core Minimum or Guidelines.

3. A separate memo from Mr. B. Litt (see B. Litt memo, EPA Reg. No. 279-3013 and 279-3014, dated May 29, 1981) addressed the mathematical expectation for possible oncogenic effects of changes in the cis and trans ratio. This memo addressed only the issue of the oncogenic effects resulting from cis and/or trans isomers of permethrin.

4. A list of the known impurities for the new [redacted] preparation of permethrin (identified as FMC 33297 55/45 and as FMC 458101) is appended to this review (see page 7).

5. Toxicology Branch does not anticipate, at this time, that additional toxicity studies will be required to support registration and tolerance requests for permethrin resulting from this revised manufacturing process.

Comparison of "New" and "Old" Preparation of Permethrin as Produced by the FMC Corporation

	NEW	OLD
	[redacted]	[redacted]
1. Acute Oral LD50, rats	Tox Cat. III	Tox Cat. IV **
2. Acute Dermal LD50, rabbit	Tox Cat. III	Tox Cat. III**
3. Primary Eye Irritation, rabbit	Tox Cat. IV	(Not irritating)**
4. Primary Skin Irritation, rabbit	Draize Score 0.5, Tox Cat. IV	(Not irritating)**
5. 90-Day Oral Feeding, rat	NOEL = 100 ppm (liver weight changes at 500 ppm, [redacted] HDT)	NOEL = 20 ppm, at 100 ppm some evidence of increased liver weight ***
6. 90-Day Capsule Feeding, dog	NOEL = 50 mg/kg/day at 364 mg/kg/day (HDT) definite signs of nervous system stimulation (M&F), decreased body weights (M), increased SAP (M), increased liver weights (M).	NOEL = 5 mg/kg/day, at 50 mg/kg/day some slight liver changes without histopathological lesions, at 500 mg/kg effects were more pronounced***

* all studies in this review.
** see R. Engler review March 4, 1977, PP 6G1769, and 279-EUP-60.
*** see R. Engler review May 10, 1976, PP 6F1769.

The above table shows that the change in manufacturing process results in no really significant changes in toxicity. For example, the changes in the liver for the old preparation are only "slight" at 50 mg/kg/day (for dogs) and 100 ppm (for rats).

7

001487

Summary of Studies Reviewed

	Study	Results	Core Classification
1.	Acute Oral LD50, rats CSE, March 19, 1980 0245A	3.58 (2.45-5.24) gm/kg/males (M) 2.28 (1.79-2.90) gm/kg/females (F) Toxicity Category III	Guidelines
2.	Acute Dermal LD50, rabbits CSE, 0245B, March 19, 1980	> 2.0 gm/kg Toxicity Category III	Minimum
3.	Primary Eye Irritation, rabbits, CSE, 0245C, March 19, 1980	No corneal involvement Toxicity Category IV	Guidelines
4.	Primary Dermal Irritation, rabbits CSE, 0245D, March 19, 1980	Draize Score 0.5 Toxicity Category IV	Guidelines
5.	90-Day Oral Feeding, rats FDRL, 6363, April 3, 1980	NOEL = 100 ppm, (Liver weight changes at 500 ppm).	Guidelines
6.	90-Day Capsule Feeding, dog FDRL, 6338, June 3, 1980	NOEL = 50 mg/kg/day. At higher doses stimulation of the nervous system (M & F), decreased body weights (M), increased SAP (M), increased liver weights (M).	Guidelines

1. Acute Oral Toxicity in Rats (FMC 33297 55/45):

Cosmopolitan Safety Evaluation, March 19, 1980; Study No. 0245A.

Groups of at least 5 male and 5 female rats [Tac N (SD) FBR] were dosed with 1.0, 1.4, 1.75, 2.0, 2.25, 2.5, 3.0, 3.5, 3.6, 4.0 or 4.5 gm/kg of body weight by gavage, and observed for 14 days. The test material was administered undiluted.

Results:

At doses of 1.75 gm/kg and above, the obvious clinical signs included tremors and clonic convulsions. The LD50's of:

Males = 3.58 (2.45-5.24) gm/kg
Females = 2.28 (1.79-2.90) gm/kg

were calculated (95% confidence limits). Necropsy was not remarkable except for yellow fluid in the intestines of some animals.

This test is Core Guidelines. Toxicity Category III.

3

2. Acute Dermal Toxicity Study - Rabbit LD50 (FMC 33297 55/45)

Cosmopolitan Safety Evaluation, March 19, 1980, Study No. 0245B.

Five male and five female rabbits were prepared and dosed with 2.0 gm/kg of test material (permethrin 55/45 described as a solid, the material was heated and applied undiluted). The animals were observed for 14 days.

No deaths or clinical signs of intoxication developed. Necropsy was unremarkable. An LD50 of > 2.0 gm/kg is established.

This test is Core Minimum. Only a single dose was used. Toxicity Category III.

3. Primary Eye Irritation Study in Rabbits (FMC 33297 55/45)

Cosmopolitan Safety Evaluation, March 19, 1980, Study No. 0245C.

Nine New Zealand rabbits were dosed with 0.1 ml of test material (permethrin 55/45). The test material was received as a solid but was melted to a liquid and instilled into their eyes, the temperature of the test material at instillation was 37°C. The eyes of three of the test animals were washed 20 seconds after instillation.

Results:

No corneal involvement developed. Transient irritation of the conjunctivae developed.

This test is Core Guidelines. Toxicity Category IV.

4. Primary Dermal Irritation Study in Rabbits (FMC 33297 55/45)

Cosmopolitan Safety Evaluation, March 19, 1980, Study No. 0245D.

Six New Zealand rabbits were prepared and 0.5 ml of test material was applied to intact and abraded areas of their skin and kept in place for 24 hours.

A Draize score of 0.5 was determined.

Core Guidelines, Toxicity Category IV.

5. Evaluation of the Subchronic Toxic Effects of FMC 45801 when Administered in the Diet to Long Evans Rats Over a Ninety-Day Period

Food and Drug Research Laboratories, Inc., April 3, 1980, Study No. 6363.

Five groups of Long-Evans rats, 30 males and 30 females per group, were fed 0, 50, 75, 100 or 500 ppm of FMC 45801 in their diets for 13 weeks. The main groups consisted of 20 animals per sex per dose and a satellite group of 10 animals per sex per dose was maintained for periodic blood sampling. Pretest data was determined by sacrificing 5 rats/sex prior to the initiation of the study.

Results:

1. No significant adverse reactions to the test chemical were reported. No adverse effects on body weight resulted. No consistant patterns of adverse effects in food consumption resulted.

2. Haematology - determined at pretest, and after 6 and 13 weeks of feeding. No effects on total and differential leucocyte counts, erythrocyte counts, hemoglobin, hematocrit, platelet count, or clotting time resulted.

3. Clinical chemistry - determined at pretest, and after 6 and 13 weeks of feeding. No effects on alkaline phosphatase, urea nitrogen, glutamate pyruvate transaminase, glutamate oxaloacetate transaminase, lactate dehydrogenase, glucose, total and direct bilirubin, total cholesterol, albumin, globulin, total protein, calcium or potassium resulted to indicate a toxic response to the test chemical.

4. Urinalysis - determined at pretest and after 6 and 13 weeks of feeding. No efffects related to pH, specific gravity, urobilinogen, appearance of occult blood, protein, bilirubin, ketones, glucose or microscopic examination resulted to indicate a toxic response to the test chemical.

5. Organ weight - at termination - only liver weights showed apparent responses to the test chemical. The high dose group males were 15% (absolute) and 6% (relative) heavier, the high dose group females were 13% (absolute) and 6% (relative) lighter than their control groups.

Note: In the female groups there were often less than 20 animals available for organ weight determination because several died during blood extraction.

5

6. Gross Necropsy - on all animals, no significant abnormalities were reported. However, there were increases in "dark" spleens in females as noted by this reviewer in the high dose group.

7. Histopathology - control and high dose groups only for most tissues. However, the heart, liver and spleen for all animals were examined. No adverse effects were reported as resulting in a dose dependent manner to suggest a toxic response to the test chemical. Only one tumor was reported in the high dose female group (fibrosarcoma).

Conclusion: This study is classified as Core Guidelines. A NOEL of 100 ppm is assigned (at 500 ppm, liver weight was affected).

6. 90 Day Subchronic Oral Dosing Study with FMC 45801 in Beagle Dogs.

Food and Drug Research Laboratories, June 3, 1980, Study No. 6338.

Four groups of Beagle dogs (6 males and 6 females per dose group) were dosed by gelatin capsules with 0, 5, 50 or 364 mg/kg/day of the test chemical designated as FMC 45801. The high dose group initially received 500 mg/kg/day, but due to severe reaction (nervous system effects) to the chemical, the dose was reduced to 364 mg/kg/day on day 9 of dosing. Note: on day 72, five dogs in the middle dose group (50 mg/kg/day) received an incorrect dose (they were given the high dose level).

Results:

1. Signs of CNS toxicity (stimulation) were evident in the high dose group when dosed with either 500 or 364 mg/kg/day.

The 50 mg/kg/day dose groups showed some signs of toxicity to the nervous system in response to treatment. For example, Table 8 shows that males developed "eye twitching" as early as day 31 and "muscle tremors/twitching" on day 53. On day 81 several other symptoms of nerve intoxication were reported but the report states that these symptoms were noted in dogs that may have received the high dose level instead of the scheduled 50 mg/kg. However, the report states that the error in dosing happened on day 72. Table 9 indicates that as many as 4 male dogs in the mid dose group developed the "eye twitching" and 3 dogs developed "muscle tremors/twitching". Table 8 and 9 show that one female dog was affected.

Toxicology Branch has assigned a NOEL of 50 mg/kg/day for development of observable effects on the nervous system. The minor symptoms of nervous system stimulation which develop at this level are not considered to occur frequently enough or to be of sufficient magnitude to be toxicologically significant.

2. Body Weight - The high dose male group gained less weight. Other groups were reported as not being affected. Food consumption: no consistant significant patterns were observed.

3. Hematology - (Sampled at initiation, and at 3, 6, 10 and 13 weeks, animals were fasted 14-16 hours prior to sampling). No dose related changes in total and differential leucocyte counts, erythrocyte counts, hemoglobin, hematocrit or platelet count were noted.

4. Clinical Chemistry - (Sampled at initiation, and at 3, 6, 10 and 13 weeks, animals were fasted 14-16 hours prior to sampling). The parameters evaluated included: alkaline phosphatase, urea nitrogen, glutamate pyruvate transaminase, glutamate oxaloacetate transamimase, lactate dehydrogenase, glucose, total and direct bilirubin, total cholesterol, albumin, globulin, total protein, calcium and potassium.

   Alkaline phosphatase levels were increased in the high dose male group at 3, 6, and 13 weeks: At 10 weeks this enzyme level was higher but statistical significance was not attained.

5. Urinalysis - (Initially and at 3, 6, 10 and 13 weeks, animals were fasted 14-16 hours prior to sampling). No differences were found related to pH, sediment, specific gravity, urobilinogen, appearance, occult blood, protein, bilirubin, ketones, or glucose.

6. Organ Weights - Liver weight in males was statistically significantly increased (31%) for the high dose level only. Liver weight in females was higher (18%) but statistical significance was not attained.

   The report states that the increases in liver weight in males correlated with the increases in alkaline phosphatase in male dogs.

7. Eye Examinations - (Initiation and at termination). All findings were reported as being within normal limits.

8. Pathology - No significant gross or microscopic abnormalities that developed in a dose dependent manner were reported.

   The pathology report consists of a table of macroscopic observations, a table of microscopic observations and a table of parallel gross and microscopic findings.

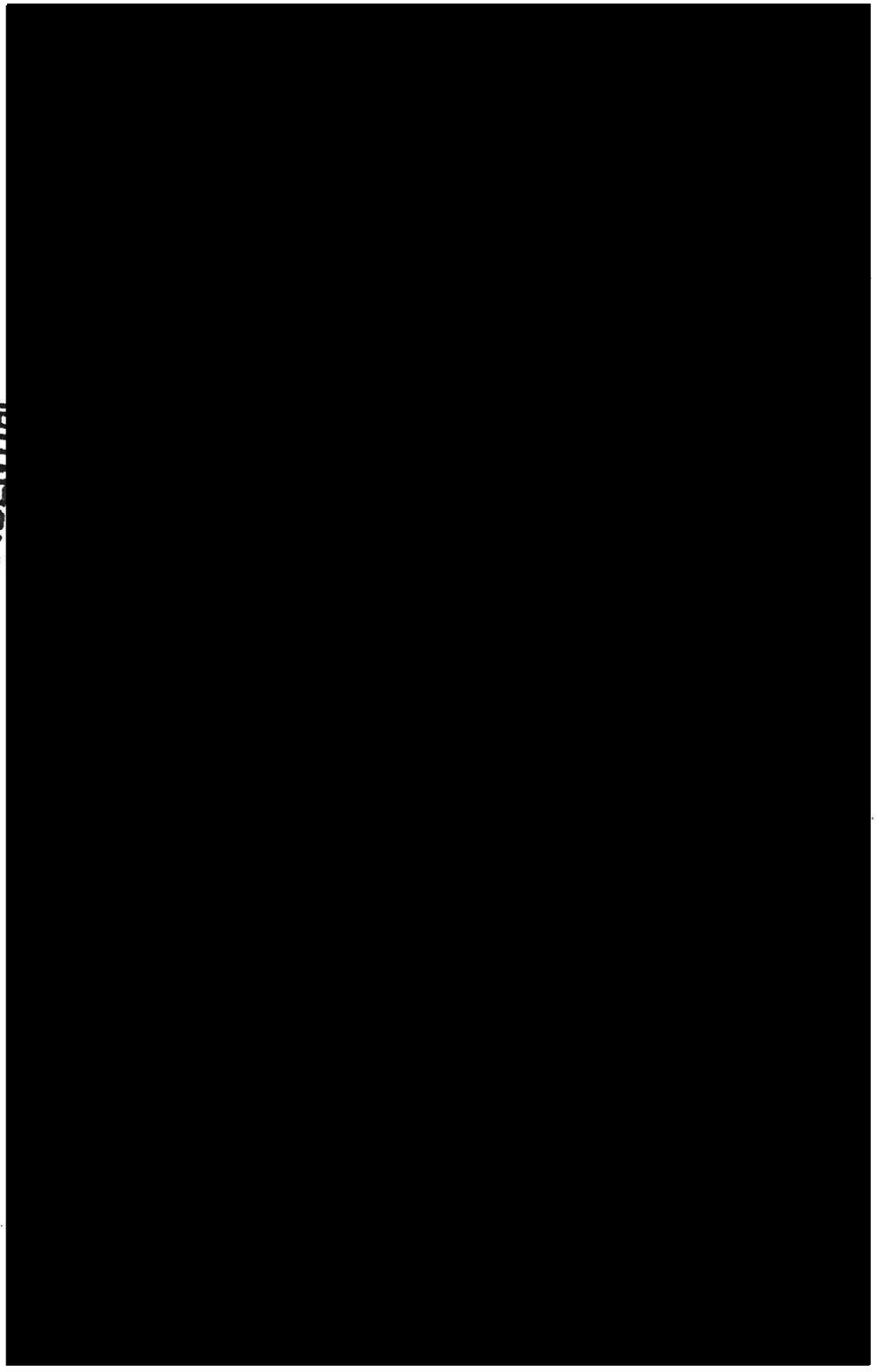
Conclusion:

This study is Core Guidelines. The NOEL is 50 mg/kg/day. At higher doses, definite signs of stimulation of the nervous system develop.

This study has an unresolved issue regarding the actual day on which the animals were misdosed.

001487

IMPURITIES IN
TECHNICAL PERMETHRIN COMPOSITION



CONFIDENTIAL

CONFIDENTIAL

Manufacturing process information may be entitled to confidential treatment

* See page 2 Section A, EPA Accession No 242899.

OPP:HED:TOX: J.DOHERTY:sb 4/28/81 X73710 Rm. 814 CM 2 #1

8