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

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

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MEMORANDUM

SUBJECT: EPA Id No.: 279-GREU and 000279-3027. Cypermethrin-S (FMC 56701): Application for registration of the technical product and 1.5 EC Insecticide and 1.5 EW Insecticide for registration on cotton, lettuce and pecans. Requirement for special neurotoxicity testing for cypermethrin and cypermethrin-S.

TOX CHEM No.: 271DE
PC No.: 129064
TOX PROJECT Nos.: 0-1854 and 1-2022
Submission Nos.: S381204 and S400902

FROM: John Doherty John Doherty 2/13/92
Section IV, Toxicology Branch I
Health Effects Division (H7509C)

TO: George LaRocca/Adam Heyward
Product Manager #15
Registration Division (H7505C)

THROUGH: Marion Copley, DVM, Section Head Marion Copley 3/3/92
Section IV, Toxicology Branch I
Health Effects Division (H7509C)

and

Karl Baetcke Karl Baetcke 2/24/92
Chief, Toxicology Branch I
Health Effects Division (H7509C)

I. CONCLUSION

A. Toxicology Branch has no objections to the conditional registering cypermethrin-S and its formulations (FMC 56701 1.5 EC and 1.5 EW Insecticide) for use on cotton, lettuce and pecans.

The conditions for registration of these products require that a chromosomal aberration study in vivo and special neurotoxicity studies series 81-8 and 82-7 (see under III.2 below) be provided within a reasonable period of time.

B. The neurotoxicity studies (series 81-8 and 82-7) if conducted with cypermethrin-S can be used to support the registration of cypermethrin but not vice-versa.

II. Action requested

The FMC Corporation (refer to letter from Alejandro Torres dated May 29, 1991) is requesting that the products FMC 56701 Technical, FMC 56701 1.5 EC Insecticide and FMC 56701 1.5 EW Insecticide (all are listed as EPA Reg. No. 279-) be registered for use on cotton, lettuce and pecans. FMC 56701 (cypermethrin-S) is a technical grade product that is enriched in the insecticidally active isomers of the product cypermethrin which is already registered on these commodities. A rat multi-generation reproduction study and a series of mutagenicity/ genetic toxicity studies were submitted for review. Additional data were submitted and reviewed earlier. In addition, TB has agreed to bridge certain data supporting the registration of cypermethrin for the registration of cypermethrin-S.

In an earlier inquiry concerning this registration of cypermethrin-S, the registrant (refer to letter from Dr. Donald A. Shaw dated August 28, 1990) wanted to clarify the need for special neurotoxicity testing (81-8 and 82-7) for both cypermethrin-S and cypermethrin. In particular, clarification was sought regarding if separate neurotoxicity studies would be required for both cypermethrin and cypermethrin-S or if studies conducted with one product could be used to support the registration of the other.

III. Toxicology Branch Comments

1. **Toxicology Summary.**

A Free Standing Summary of the toxicity data base for cypermethrin-S is attached. The registrant has provided all of the studies which HED currently considers appropriate for the registration of cypermethrin-S except for the new requirements for special neurotoxicity testing (81-8 and 82-7) and one additional mutagenicity/genetic toxicity study. These requirements are discussed below.

2. **Special Neurotoxicity Testing (81-8 and 82-7).**

In response to Dr. Shaw's inquiry, TB-I considered that the special neurotoxicity testing should be conducted with cypermethrin-S and these data can be used to support both cypermethrin and cypermethrin-S registrations. The registration of cypermethrin-S need not be delayed until the special neuro-

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toxicity data are generated but a reasonable time frame (i.e. 2 years) should be allowed for submission of these studies.

TB-I does not consider it necessary to require these studies prior to a full registration of cypermethrin-S because the toxicity data requirements for this chemical were defined several years ago (refer to three memos from TB dated Sept 7 and 8, and October 17, 1988) and cypermethrin-S can be regarded as an "older new chemical" rather than as a "new chemical".

The protocol for these neurotoxicity studies should be submitted to the Agency for review. The protocol should justify the route of exposure during testing. The protocol should also indicate what stains will be used to examine the peripheral nerves and other parts of the nervous system. Selection of these stains should be based on the types of neurotoxicity noted in earlier studies with high doses of cypermethrin.

3. **Mutagenicity/Genetictoxicity testing (84-2).**

Three mutagenicity/genetictoxicity studies were submitted and reviewed (see table below). Cypermethrin-S was determined to be weakly positive in one strain (TA100) at 3333, 5000 and 10,000 ug/plate in repeat assays. The bacterial gene mutation assay was determined to be acceptable. The unscheduled DNA synthesis and the in vitro mammalian cell gene forward mutation assay were determined to be acceptable and not to indicate mutagenicity/genetictoxicity.

In order to complete the mutagenicity/genetictoxicity data base requirements the registrant must submit an in vivo chromosomal aberration study. The registration of cypermethrin-S should not be delayed until this study is submitted. The study, however, should be submitted within a reasonable period of time (for example about one year from issuance of this notice).

3. **Product Labelling.**

The acute toxicity studies conducted to support the label signal word and precautionary statements were reviewed previously (refer to HED Document No.: 8482). The reviewer of these studies requested additional information regarding certain procedures used in the inhalation studies. The registrant has provided (via fax message sent Feb 2, 1992, refer to letter from Alejandro Torres of the FMC Company and January 31, 1992 fax message from Rusty R. Bush, Toxicologist of the Springborn Laboratories, Inc., copies of these messages are attached) this information.

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The following is in place of a supplemental DER for studies A90-3291 and A90-3200:

1. Volume of the test atmosphere samples for the determination of gravimetric and analytical concentrations.

This volume was stated by Mr. Bush as being 5 liters.

2. Filter pore size for the filters used in the gravimetric and analytical determinations.

The filter was described by Mr. Bush as being a Gelman Sciences, Inc. 25 mm extra thick glass fiber filter. The pore size of this filter was 0.3 u.

Receipt of this information allows these studies to be reclassified and upgraded to GUIDELINE. They satisfy the GUIDELINES requirements for an 81-3 study for these products.

5. **Studies reviewed.**

Study Identification	Toxicity Noted
83-4. Multi-generation reproduction-rats. Argus Laboratories, Study # 106-007, February 11, 199 1. MRID No.: 419682-04 (3 volumes). Classification: GUIDELINES	NOEL/LEL = 100/375 ppm. 375 ppm: decreased pup weight gain during lactation; decreased parental weight during lactation; threshold for clinical signs. At 750 ppm: decreased lactation index; pup and parental mortality and clinical signs. No specific reproductive effects. Dose levels tested: 0, 7.5, 25, 100, 375 and 750 ppm approximately 0, 0.5, 1.8, 7.4, 27, and 50 mg/kg/day.

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84-2. Ames test (Salmonella) Study No.: 89-3012, February 28, 1992. MRID No.: 419682-05 Classification: Acceptable	Weak mutagen effects noted at 10, 000, 5000 and 3333 ug/plate in absence of metabolic activation in Salmonella strain TA100 in two studies. Strains TA98, TA1535, TA1537 and TA 1538 did not indicate mutagenic effect in presence or absence of S-9 activation. Dose levels tested: 0, 100, 333, 1000, 3333, 5000 and 10,000 ug/plate.
84-2. CHO-HGPRT Mutation Assay. Study No.: A89-3013, February 1, 1990. MRID No.: 419682-06 Classification: Acceptable	Negative. Dose levels tested 0, 14, 45, 140, 450 1400 and 4500 ug/ml.
84-2. Unscheduled DNA Synthesis in Rat Primary Hepatocytes. Study No.: A89-3015., December 4, 1989. MRID No.: 419682-07 Classification: Acceptable	Negative. Dose levels tested 0, 1, 10, 25, 50, 100 (estimated limit of solubility), 400, 700 and 1000 ug/ml.

[FSTS-Cypermethrin-S, Feb, 1992]

FREE STANDING TOXICITY PROFILE

Chemical: cypermethrin-S
Edition: February 1992

Tox Chem No.: 271DE
PC No.: 109702

Series. Study Type	Study Available	Results/Comments	Document Number
81-1. Acute oral - rats MRID No.: 417761-15	G	Toxicity Category II	8482
81-2. Acute Dermal - rabbits MRID No.: 0099855	no	Bridged from cypermethrin. [Toxicity Category III Classification: MINIMUM]	4825
81-3. Acute inhalation - rats	no		
81-4. Primary eye - rabbits MRID No.: 0099855	no	Bridged from cypermethrin. [Toxicity category IV Classifiation: GUIDELINE]	4825
81-5. Primary dermal - rabbits MRID No.: 0099855	no	Bridged from cypermethrin. [Toxiicty Category IV] Classification: MINIMUM]	4825
81-6. Dermal sensitization - g. pig MRID No.: 070565	no	Bridged from cypermethrin. [Moderate sensitizer. Classification: MINIMUM] Note: Study with 18.9% formulation (1.5 EW) is positive for sensitization.]	2391 8482
81-7. Delayed neurotoxicity - hen	no	Not applicable.	
81-8. Special neurotoxicity - rat	no	Required as of February 1992	
82-1a. Subchronic oral - rat. MRID No.: 417761-01	M	NOEL/LEL = 250/500 ppm. Decreased body weight and gain and decreased food consumption. Dose levels tested: males: 0.7, 3.3, 10.2, 16.7, 33.7 and 68.0 mg/kg/day; females: 4.0, 11.7, 19.7, 38.4 and 79.5 mg/kg/day.	8865

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82-1b. Subchronic oral - nonrodent MRID No.: 099855	no	Bridged from cypermethrin. [NOEL/LEL = 500/1500 ppm: Diarrhea, anorexia and nerve symptoms. Levels tested 0, 5, 50, 500 amd 1500 ppm. Beagle dog. Classification: MINIMUM]	4825
82-2. 21-day dermal -rabbit MRID No.: 070564	no	Bridged from cypermethrin. [NOEL/LEL = 20/200 mg/kg/day. Liver pathology. Classification: MINIMUM]	2391
82-3. 90-day dermal	no	Not required at this time.	
82-4. 90-day inhalation	no	Not required at this time.	
82-5. 90-day neurotoxicity	no	Not applicable.	
82-6			
82-7. Neurotoxicity screen	no	Required as of February 1992	
83-1a. Chronic feeding - rat	no	See 82-5.	
83-1b. Chronic feeding - nonrodent MRID No.: 071069	no	Bridged from cypermethrin. [NOEL/LEL = 1/5 mg/kg/day. 5 mg/kg/day: GI disturbances. 15 mg/kg/day: nervous system disturbance. Levels tested 0, 1, 5 and 15 mg/kg/day. Beagle dog. Classification: CUIDELINE]	3249 5159 3647
82-2a. Oncogenicity - rat	no	See 82.5.	
82-2b. Oncogenicity - mouse	no	Special ad hoc Peer Review determined that this study should not be required.	
83-3a. Developmental toxicity - rat MRID No.: 417761-02	G	NOEL/LEL (maternal toxicity) = 12.5/25 mg/kg/day. At 25 mg/kg/day: ataxia, decreased weight gain, body staining and decreased food consumption. NOEL (developmental toxicity) $\geq$ 35 mg/kg/day (HDT). Dose levels tested: 0, 5, 12.5, 25 and 35 mg/kg/day.	8865

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83-3b. Developmental toxicity -rabbit MRID No.: 099855	no	Bridged from cypermethrin. [NOEL > 30 mg/kg/day (HDT). Levels tested 0, 10, and 30 mg/kg/day. Classification MINIMUM.]	4825
83-4. Multi generation reproduction-rat MRID No.: 419682-04	G	NOEL/LEL = 100/375 ppm. 375 ppm: decreased pup weight gain during lactation. 750 ppm: Pup and parental mortality and clinical signs. Approximately 0.5, 1.8, 7, 27, and 45 mg/kg/day.	
83-5. Combined chronic/onco MRID No.: 071070 and 071071	no	Bridged from cypermethrin. [NOEL/LEL = 150/1500 ppm. At 1500 ppm: weight loss, genral change in blood elements and cholesterol. Doses tested 0, 20, 150 and 1500 ppm. Classification: MINIMUM]	3249
84-2. Gene mutation MRID No.: 419682-05 MRID No.: 419682-06	2A	1. Regarded as weakly positive in S. typhimurium strain TA 100 at 3333, 5000 and 10,000 ug/plate in two experiments in absence of activation. Other strains not positive. 2. Not positive in CHO/ HGPRT in vitro mammalian gene mutation assay. 0, 1, 10, 25, 50, 100, 400, 700 and 1000 ug/ml.	
84-2. Chromosome aberration	no	Study required as of February 1992.	
84-2. Other mechanism genetic tox MRID No.: 419682-07.	1A	No unscheduled DNA synthesis in male rat liver primary hepatocyte cultures. Doses tested 0, 14, 45, 140, 450, and 4500 ug/ml.	
85-1. Metabolism MRID No.: 070565	no	Bridged from cypermethrin. [Extensive data base, overall classification MINIMUM.]	02391
85-2. Domestic animal safety		Refer to individual formulations for requirements.	

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85-3. Dermal Absorption	no	No data.	
85-. Nerve function/operant behavior	no	Not required at this time.	

G = a study classified as GUIDELINE is available. M = a study classified as MINIMUM is available. No = no study conducted with cypermethrin-S exists. A = a study classified as acceptable exists, if a number precedes the A there are that many acceptable studies for this category of testing. NOTE: Data in [ ] was derrived from cypermethrin and not cypermethrin-S.

Special Toxicology Issues and Problems.

1. **Labelling.** The labelling of all products containing cypermethrin-s must have precautionary statements which address the following:

1. Cypermethrin-S is a type II pyrethroid which may cause a tingling sensation and reddening of the skin if contact with skin is made with the product. The symptoms usually disappear if the affected area is washed with soap and water.

2. Studies with technical grade cypermethrin and a formulation containing cypermethrin-S indicate a dermal sensitization based on the guinea pig sensitization study. The label should contain the appropriate precautionary statements to warn against sensitization in some individuals. .

2. **Carcinogenicity.**

Cypermethrin-S is a refined product of cypermethrin which contains 8 isomers. Cypermethrin was determined to be a category C carcinogen based on lung tumors in female mice (Peer Review Report dated February 17, 1988). The uses of cypermethrin are not required to be supported by quantitative risk assessments based on a Q1*.

An ad-hoc Peer Review meeting was held to discuss the issue as to requiring an additional mouse carcinogenicity study with cypermethrin-s and it was determined that a study was not required. At this time cypermethrin-S is also regarded as a category C carcinogen and its uses are not required to be supported by quantitative risk assessments based on a Q1*.

3. **RfD.**

Cypermethrin-s has not been reviewed by the RfD committee as of January 1992.

4. **Non carcinogenic risk assessment.**

No special review triggers are recognized for cypermethrin and cypermethrin-S as of February, 1992.

5. **Mutagenicity/genetic toxicity comments.**

A chromosomal aberration study in vivo is required to complete the first tier of mutagenicity/genetic toxicity testing.

6. **Dermal Penetration.**

There is no data available on dermal penetration.

7. **Neurotoxicity Testing.**

Studies have been requested by HED to meet the criteria for 81-8 and 82-7 special neurotoxicity testing as of February 1992.

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