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

FEB 5 1988

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Mevinphos. Amended Section 18, Emergency Exemption for the Use of Phosdrin™ 4EC (EPA Reg. No. 35247-AA) to Control Aphids on Loose-Heading Chinese Cabbage in the State of California.

EPA No. 88-CA-12 Project No. 8-0368
Record No. 212541 Tox. Chem. No. 160B
40 CFR §180.157

TO: Donald R. Stubbs, PM #41
Emergency Response Section
Registration Division (TS-767c)

FROM: John E. Whalan, D.A.B.T., Toxicologist
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769c)

2-4-88

THRU: Edwin R. Budd, Section Head
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769c)

The state of California has requested an Emergency Specific Exemption for the use of Phosdrin™ 4EC (mevinphos) on Loose-Heading Chinese Cabbage to control green peach aphid. A maximum of 3000 acres of crop will be treated with a maximum of 9000 pounds of active ingredient. It will be applied with aerial or ground equipment at a rate of 0.5 to 2.0 pints of Phosdrin per acre (0.25 to 1.0 lbs a.i./acre). The reentry interval is 72 hours, and the preharvest interval is 4 days. The effective date of this exemption is February 10, 1988 through January 30, 1989. The Registrant has no residue data for this proposed use of Phosdrin.

The database that had been used to define the ADI and regulate the use of mevinphos is old, incomplete, poorly documented, and unreliable. When the Toxicology Branch recently drafted a chapter for the Mevinphos Registration Standard, these data were found to be completely inadequate. These old studies do suggest that mevinphos is a potent cholinesterase inhibitor, however. The only acceptable study is a recently submitted rat teratology study. In the absence of substantiating data, an ADI could not be defined. Copies of the One-Liners and an Amendment to the Toxicology Chapter of the Mevinphos Registration Standard are attached. These documents describe the paucity of the database.

Accident reports from California list mevinphos as one of the five most dangerous pesticides used in that state. This fact, coupled with the lack of a toxicity database, make it impossible for the Toxicology Branch to approve any further uses of this pesticide - even for emergency use.

Tox Chem No. 160B File Last Updated _____ Current Date 8-18-87

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
2-Year Feeding - rat; Tunstall Laboratory; Report #TLGR.0043.71; Project #T507521/27; 10-71. MRID #81217	Phosdrin (60.2% cis-isomer)	225524-C	Tentative ChE NOEL's: Plasma & RBC = 0.019 mg/kg/day Brain = 0.186 mg/kg/day Clinical signs: Negative Clinical pathology: Decreases in plasma, RBC, and brain cholinesterase. Gross pathology: Reportedly no lesions. Decreases in spleen and testicular weights. Histopathology: Not evaluable. The report failed to distinguish between benign and malignant tumors. Levels tested: 0 (veh. control), 0.37, 1.11, 3.71, and 11.14 ppm (0, 0.019, 0.056, 0.186, and 0.557 mg/kg/day) (orally in feed) in Carworth Farm E strain.		Supplementary
2-Year Feeding - dog; Tunstall Laboratory; Report #TLGR.0052.71; Project #T507521/27; 12-71. MRID #81218	Phosdrin (60.2% cis-isomer)	225524-D	Tentative ChE NOEL's: Plasma & RBC = 0.025 mg/kg/day Brain = 0.25 mg/kg/day Clinical signs: Vomiting, anorexia Clinical pathology: Decreases in plasma, RBC, and brain cholinesterase. Gross pathology: Not reported. Possible increases in heart weight in females and testicular weights. Histopathology: Not evaluable. Levels tested: 0 (veh. control), 0.025, 0.075, 0.25, and 0.75 mg/kg/day (orally via gelatin capsules) in beagles.		Supplementary

Tox Chem No. 160B | File Last Updated _____ | Current Date 8-18-87

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD50, LC50, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Teratology - rat; Bio/dynamics, Inc., Report # N/A, Project # 85-3009, 3-1-87 MRID #402014-01	Mevinphos tech. (66.5% cis-isomer, 21.2% trans-isomer)	N/A	Maternal NOEL = 0.20 mg/kg/day Maternal LEL = 0.75 mg/kg/day (tremors) Fetotoxic NOEL >1.00 mg/kg/day Embryotoxic NOEL >1.00 mg/kg/day Teratogenic NOEL >1.00 mg/kg/day A/D Ratio <0.75 Clinical signs: Tremors, excessive lacrimation and salivation, chromodacrhorrhea, anogenital staining, and soft stools. Levels tested: 0 (vehicle control), 0.20 0.75, 1.00 mg/kg/day (orally) in Sprague-Dawley CD strain.		Guideline
Teratology - rabbit; Tunstall Laboratory; Report #TLGR.0016.74; Exp. #491; 4-74 MRID #81216	Phosdrin (71.6% cis-isomer, 17.1% trans-isomer)	225524-B	The NOEL and LEL values could not be defined because of report deficiencies. Clinical signs: A low-dose doe died on an unspecified day with hemorrhaged gastric mucosa. The high-dose does had occasional mild tremors, salivation, and "signs of organophosphate toxicity." Teratogenic effect: There did not appear to be any compound-related anomalies at doses that elicited maternal toxicity. Levels tested: 0 (vehicle control), 0.3, and 1.0 mg/kg/day (gelatin capsule) in banded Dutch strain.		Supplementary
3-Gen. reproduction-rat Hill Top Research, Inc.; Project # P-5; 10-24-67 MRID #68959	Phosdrin (60.0% cis-isomer, 40% related compounds)	091197-A	The presentation of the results is inadequate for evaluation. Levels tested: 0 (vehicle control), 1.2, and 24 ppm; 0, 0.06, and 1.2 mg/kg/day orally in feed) in Charles River CD strain.		Supplementary

Tox Chem No. 160B | File Last Updated _____ | Current Date 8-18-87

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Mutagenic - chromosome aberration in mouse bone marrow cells; Tunstall Laboratory; Report #TLGR.0008.74; Exp #533; 2-74 MRID #97540	Phosdrin (70.0% cis-isomer)	246595-A	Phosdrin was not toxic and not mutagenic at the doses used. Levels tested: 0 (vehicle control), 1.5, and 3.0 mg/kg/2 days with Phosdrin, and 100 mg/kg/2 days with cyclophosphamide (positive control) (orally) in pathogen-free CF_1 strain.		Unacceptable
Mutagenic - dominant lethal assay; Tunstall Laboratory; Report #TLGR.0031.74; 7-74 MRID #97541	Phosdrin (70.0% cis-isomer)	246595-B	Phosdrin was not toxic and not mutagenic at the doses used. Levels tested: 1.5, 3.0, and 6.0 mg/kg (orally) in pathogen-free CF_1 strain mice.		Unacceptable

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Amendment to the Toxicology Chapter of the Mevinphos Registration Standard

Tox. Chem. No. 97

TO: Harvey Warnick
Deputy Branch Chief
Insecticide and Rodenticide Branch
Registration Division (TS-767c)

FROM: John E. Whalan, D.A.B.T., Toxicologist
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769c)

John E Whalan 12-18-87

THRU: Robert P. Zendzian Ph.D.
Registration Standard Coordinator
Toxicology Branch
and
William Burnam, Deputy Chief
Toxicology Branch

12/15/87

W.H. Burnam 12/22/87

Attached is an amendment to the Toxicology Chapter of the Registration Standard for mevinphos (Phosdrin™). Mevinphos was found to inhibit cholinesterase at low doses in two Core Supplementary chronic studies. During a December 17, 1987 meeting to discuss mevinphos as a candidate for Special Review, the Toxicology Branch learned that mevinphos is a major cause of accidental pesticide poisoning. Prudence dictates that the Registration Standard be amended to include a study which will evaluate cholinesterase inhibition following dermal exposure.

cc Rispin

5

C. DATA GAPS

Mevinphos is registered, and tolerances have been issued for the control of insects in 45 crops (see 40 CFR 180.157). The following Guideline toxicology studies are required for registration:

81-1 Acute Oral Toxicity
81-2 Acute Dermal Toxicity
81-3 Acute Inhalation Toxicity
81-4 Primary Eye Irritation
81-5 Primary Dermal Irritation
81-6 Dermal Sensitization
81-7 Acute Delayed Neurotoxicity
81-X Acute Dermal (to define lethality, toxicity, and ChE NOEL's)

82-1 Subchronic Oral, two species (rodent and nonrodent)
82-2 Subchronic Dermal (21-day)
82-5 Subchronic Neurotoxicity (conditionally in hen and/or mammal)

83-1 Chronic Toxicity, two species (rodent and nonrodent)
83-2 Oncogenicity, two species
83-3 Teratogenicity, two species
83-4 Reproduction

84-2 Mutagenicity (full battery)

85-1 Metabolism

Based on these toxicity data requirements, the following Guideline Toxicology studies have been identified as data gaps for Mevinphos, and are therefore required:

81-1 Acute Oral Toxicity
81-2 Acute Dermal Toxicity
81-3 Acute Inhalation Toxicity
81-4 Primary Eye Irritation
81-5 Primary Dermal Irritation
81-6 Dermal Sensitization
81-7 Acute Delayed Neurotoxicity
81-X Acute Dermal (to define lethality, toxicity, and ChE NOEL's)

82-1 Subchronic Oral, two species (rodent and nonrodent) [1]
82-2 Subchronic Dermal (21-day)
82-5 Subchronic Neurotoxicity (conditionally in hen and/or mammal)

83-1 Chronic Toxicity, two species (rodent and nonrodent)
83-2 Oncogenicity, two species
83-3 Teratogenicity (rabbit)
83-4 Reproduction

84-2 Mutagenicity (full battery)

85-1 Metabolism

1 This requirement is waived since chronic studies are required.

D. ADI REASSESSMENT

The Agency attempted to reassess the ADI for mevinphos in April, 1987. At that time, John Whalan recommended that any discussion of an ADI be tabled until a registration standard could be drafted because of the meager and dubious nature of the data base. This motion carried.

The initial ADI for mevinphos was based on a 2-year dog feeding study. On the basis of plasma and erythrocyte cholinesterase inhibition, the NOEL in this study was defined as 0.025 mg/kg/day. A safety factor of 10 was used to calculate the ADI of 0.0025 mg/kg/day. The ChE LEL in this study was defined as 0.075 mg/kg/day. When this study was originally reviewed, it was classified Core Minimum. In the course of preparing this registration standard, the study was reviewed anew. There were serious report deficiencies which made the study unevaluable. Because it was not possible to define NOEL and LEL doses, the study has been reclassified as Core Supplementary.

Seven studies were reevaluated for this standard. All but one of them (a rat teratology study) were unacceptable. It was the decision of the Toxicology Branch RFD/ADI Committee, which met again in October, 1987, that there were insufficient data to establish an ADI for mevinphos.

E. TOXICOLOGICAL ISSUES

Mevinphos is a potent cholinesterase inhibitor. It is currently registered for use on 45 crops, although there are virtually no acceptable toxicity data to support these registrations. There is a potential for accidental poisoning, with neurologic involvement, of applicators and farmers who are not protected. In addition to the required guideline studies, an additional Acute Dermal Toxicity study is required to define NOEL's for cholinesterase inhibition, toxicity and lethality. This study will be performed using the most sensitive sex as determined in the guideline acute dermal toxicity study. The Toxicology Branch should be consulted prior to initiating this study.

Mevinphos is a mixture of alpha (cis-, or E-) isomer, and beta (trans-, or Z-) isomers; the insecticidal potency of the alpha-isomer is approximately 100-fold that of the beta-isomer (Merck Index - 10th Edition). The studies reviewed for this Registration Standard report using test articles with alpha isomer concentrations ranging from 60.0% to 71.6%. It is not known whether the observed cholinesterase inhibition was due to the alpha or beta isomers of mevinphos, or the impurities.

Table A
GENERIC DATA REQUIREMENTS FOR MEVINPHOS

Data Requirement	Composition[1]	Use Patterns[2]	Does EPA Have Data To Satisfy This Requirement? (Yes, No, or Partially)?	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)?
§158.135 Toxicology					
ACUTE TESTING:					
81-1 Acute Oral - Rat	TGAI	A,B,C,D,E	No	—	Yes
81-2 Acute Dermal	TGAI	A,B,C,D,E	No	—	Yes
81-3 Acute Inhalation - Rat	TGAI	A,B,C,D,E	No	—	Yes
81-4 Eye Irritation - Rabbit	TGAI	A,B,C,D,E	No	—	Yes
81-5 Dermal Irritation - Rabbit	TGAI	A,B,C,D,E	No	—	Yes
81-6 Dermal Sensitization - Guinea Pig	TGAI	A,B,C,D,E	No	—	Yes
81-7 Acute Delayed Neurotoxicity - Hen	TGAI	A,B,C,D,E	No	—	Yes
81-X Acute Dermal/ChE	TGAI	A,B,C,D,E	No	—	Yes [3]
SUBCHRONIC TESTING:					
82-1 90-Day Feeding -					
Rodent	TGAI	A,B,C,D,E	No	—	No [4]
Nonrodent	TGAI	A,B,C,D,E	No	—	No [4]
82-2 21-Day Dermal	TGAI	A,B,C,D,E	No	—	Yes

Table A
GENERIC DATA REQUIREMENTS FOR MEVINPHOS

Data Requirement	Composition[1]	Use Patterns[2]	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)?	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)?
§158.135 Toxicology (cont.)					
82-3 90-Day Dermal	TGAI	A,B,C,D,E	No	—	No [5]
82-4 90-Day Inhalation	TGAI	A,B,C,D,E	No	—	Yes [6]
82-5 90-Day Neurotoxicity -					
Hen	TGAI	A,B,C,D,E	No	—	Yes [7]
Mammal	TGAI	A,B,C,D,E	No	—	Yes [8]
CHRONIC TESTING:					
83-1 Chronic Toxicity -					
Rodent	TGAI	A,B,C,D,E	No	—	Yes
Nonrodent	TGAI	A,B,C,D,E	No	—	Yes
83-2 Oncogenicity -					
Rat	TGAI	A,B,C,D,E	No	—	Yes
Mouse	TGAI	A,B,C,D,E	No	—	Yes
83-3 Teratogenicity -					
Rat	TGAI	A,B,C,D,E	Yes	402014-01	No
Rabbit	TGAI	A,B,C,D,E	No	—	Yes

Table A
GENERIC DATA REQUIREMENTS FOR MEVINPHOS

Data Requirement	Composition[1]	Use Patterns[2]	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)?	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)?
§158.135 Toxicology (cont.)					
83-4 Reproduction	TGAI	A,B,C,D,E	No	—	Yes
MUTAGENICITY TESTING:					
84-2 Gene Mutation	TGAI	A,B,C,D,E	No	—	Yes
84-2 Chromosome Aberration	TGAI	A,B,C,D,E	No	—	Yes
84-2 Other Mechanism of Mutagenicity	TGAI	A,B,C,D,E	No	—	Yes
SPECIAL TESTING:					
85-1 General Metabolism	PAI or PAIRA	A,B,C,D,E	No	--	Yes

1 Composition: TGAI = Technical Grade of the Active Ingredient; PAI = Pure Active Ingredient; PAIRA = Pure Active Ingredient, Radio-labelled; Choice = Choice of several test substances determined on a case-by-case basis.

2 The Use Patterns are coded as follows: A = Terrestrial, Food Crop; B = Terrestrial, Non-Food; C = Aquatic, Food Crop; D = Aquatic Non-Food; E = Greenhouse, Food Crop; F = Greenhouse, Non-Food; G = Forestry; H = Domestic, Outdoor; I = Indoor; IP = Industrial Preservative.

3 An Acute Dermal Toxicity study is required which defines NOEL's for cholinesterase inhibition, toxicity, and lethality. The most sensitive sex will be used as determined in the guideline acute dermal toxicity study.

4 This requirement is waived since chronic studies are required.

5 Not required because of the nature of the exposure pattern.

6 Required to support use in greenhouses.

7 Requirement is contingent upon results of acute delayed neurotoxicity study in hens.

8 If neurotoxic lesions are found in mammalian studies, a subchronic neurotoxicity study in mammals may be required.