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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Malathion Ocular Effects

FROM: Brian Dementi, Ph.D., D.A.B.T. Brian Dementi 4/12/90
Review Section I
Toxicology Branch-I (IRS)
Health Effects Division (H7509C)

TO: Edwin F. Tinsworth, Director
Special Review and Registration Division (H7508C)

THRU: Karl P. Baetcke, Chief Karl Baetcke 4/12/90
Toxicology Branch-I (IRS)
Health Effects Division (H7509C)

In view of the fact that malathion is a member of the chemical class, organophosphates, and the attendant realization that exposures to agents of this chemical class can elicit potentially serious ocular (opthamological) effects, Tox Branch I recommends that an ocular testing requirement be introduced as an addendum to the requirement for the rat chronic/carcinogenicity study for malathion. The Registrant should consult with HED staff to develop the protocol for addressing the histopathological evaluation of eye tissue and other facets of this effect.

Furthermore, since this a generic issue, respecting all organophosphates, Tox Branch I recommends ocular testing for all organophosphates.

flower, celery, cherries, clover, collards, carrots, cranberries, currants, cucumbers, dates, eggplant, endive, filbert, figs, garlic, kale, kohlrabi, mangoes, melons, mustard greens, olives, onions, peaches, peas, pineapples, plums, prunes, pumpkins, quince, rape, rutabaga, safflower, spinach, squash, sunflowers, swiss chard, turnips, vetch, walnuts and ornamentals. It is unlikely that these future crop reviews will add endangered species to the list thus far established, due to the broad geographical distribution of the crops already reviewed.

Endangered species labeling statements are included in the section of this document entitled "Required Labeling--Environmental Hazards Statement", and "Required Labeling--Endangered Species Restrictions". There is one label statement for crops, one for pasture/rangeland and one for mosquito larvicide uses. The label statements for crops and pasture/rangeland indicate that the user must obtain the EPA Endangered Species Bulletin before using the parathion product. The mosquito larvicide products do not contain a reference to an EPA Endangered Species Bulletin. Mosquito larvicides are applied by mosquito abatement districts which will be required to contact endangered species specialists for guidance prior to use.

11. Ocular effects data

The Agency is requiring parathion registrants to submit additional subchronic studies, such as electroretinograms and direct corneal measurements, to determine the potential for parathion to cause retinal degeneration and changes in corneal shape and structure.

2

Rationale: Recent studies as well as historical data have clearly implicated the organophosphates in general and parathion in particular, in such eye effects as retinal degeneration and myopia. Because of this concern the Agency has required under a separate Data Call-In Notice dated November 27, 1985, the submission of additional subchronic studies, such as electroretinograms and direct corneal measurements. These studies are to be conducted on both the rat and dog and are to be of 1-year duration. These data will provide additional information necessary to determine the potential for parathion to cause retinal degeneration and changes in corneal shape and structure.

12. Sciatic nerve effects data

The Agency is requiring parathion registrants to submit additional sciatic nerve effects studies to determine the NOEL for these effects.

Rationale: The observation of abnormal gait in the hind limbs of female rats treated with 50 ppm parathion (the highest dose tested) in a recent rat chronic feeding study (GS00155011) prompted special histopathological examination of the sciatic nerves in animals tested at the high dose level. These examinations showed compound-related toxicity such as loss of myelinated fibers with increased perivascular myelin debris and Schwann cell proliferation, degenerative changes characterized as cholesterol clifts, myelin ovoids, myelin sheath ballooning, and loss of myelinated fibers in the males. The teased nerve fiber preparation showed significant degenerative differences

between control and test animals at the high dose in both sexes. However, since the special histopathological examinations were not performed on the test animals which received low and intermediate doses, a NOEL for these sciatic nerve effects could not be established. Because of this concern the Agency has required under a separate Data Call-In Notice dated November 27, 1985, the submission of additional sciatic nerve effects studies. These data will provide additional information necessary to determine the NOEL for parathion related sciatic nerve effects.

13. Spray drift data

The Agency is imposing pesticide spray drift data requirements for parathion products. The data being required include droplet size spectrum studies, field evaluation of pesticide drift and granular integrity studies.

Rationale: The Agency is concerned about hazards to nontarget organisms (fish and wildlife, domestic animals and humans) caused by drift from aerial and ground air-blast applications of parathion. Many of the parathion exposure/poisoning related incidents reported to the Agency have been related to drift. In addition, granular particle sizes are known to be reduced inside the packaging material. The smaller granules are more likely to drift and pose an inhalation hazard to loaders and fieldworkers. These data will help the Agency evaluate the potential for drift to occur when parathion is used in aerial and ground air-blast operations. Review of these data may lead to further regulatory action.

4

TABLE A
GENERIC DATA REQUIREMENTS FOR PARATHION

Data Requirement	Composition[1]/	Use Pattern[2]/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA § 3(c)(2)(B)? Timeframes for Data Submission[3]/
§158.135 Toxicology (continued)					
ACUTE TESTING:					
81-1 - Oral	TGAI	A,B,C,D,E,F	Yes	00053120, GS00155009	No
81-2 - Dermal	TGAI	A,B,C,D,E,F	No	-	Yes[4]/ 9 Months
81-3 - Inhalation	TGAI	A,B,C,D,E,F	No	-	Yes[4]/ 9 Months
81-7 - Acute Delayed Neurotoxicity	TGAI	A,B,C,D,E,F	No	-	Yes[4]/ 9 Months
SUBCHRONIC TESTING:					
82-1 - 90-Day Feeding - Rodent, Non-rodent	TGAI	A,C,E,	Yes	00072409, 00071671 00071670	No
82-2 - 21-Day Dermal - Rabbit	TGAI	A,B,C,D,E,F	No	-	Reserved[6]/
82-3 - 90-Day Dermal - Rabbit	TGAI	A,B,C,D,E,F	No	-	Reserved[6]/
82-4 - 90-Day Inhalation - Rat	TGAI	A,B,C,D,E,F	No	-	Reserved[6]/
82-5 - 90-Day Neurotoxicity - Hen/Mammal	TGAI	-	No	-	Reserved[5]/
82-6 - Special Subchronic Testing - 2 species - Rat,	TGAI	A,C,E	No	-	Yes[7]/
- Dog			No	-	Yes[8]/

TABLE A
GENERIC DATA REQUIREMENTS FOR PARATHION

Data Requirement	Composition[1]/	Use Pattern[2]/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA § 3(c)(2)(B)? Timeframes for Data Submission[3]/	
§158.135 Toxicology (continued)						
CHRONIC TESTING:						
83-1 - Chronic Toxicity - 2 species - Rodent, and	TGAI	A,C,E	Yes	GS00155011	No[7]/	
- Non-rodent (Dog)			Yes	00093896	No[8]/	
83-2 - Oncogenicity Study - 2 species - Rat (preferred), and	TGAI	A,C,E	Yes	GS00155011	No	
- Mouse (preferred)			Partially	GS00155012	Yes	50 Months
83-3 - Teratogenicity - 2 species: - Rat	TGAI	A,B,C,D,E,F	Yes	GS00155013	No	
- Rabbit			Yes	GS00155014	No	
83-4 - Reproduction - Rat 2-generation	TGAI	A,B,C,D,E,F	Yes	GS00155015	Yes[9]/	39 Months
MUTAGENICITY TESTING						
84-2 - Gene Mutation (Ames Test)	TGAI	A,B,C,D,E,F	No	-	Yes[10]/	9 Months
84-2 - Structural Chromosomal Aberration	TGAI	A,B,C,D,E,F	No	-	Yes[10]/	12 Months
84-4 - Other Genotoxic Effects	TGAI	A,B,C,D,E,F	Partially	GS00155010	Yes[10]/	12 Months

TABLE A
GENERIC DATA REQUIREMENTS FOR PARATHION

Data Requirement	Composition[1]/	Use Pattern[2]/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA § 3(c)(2)(B)? Timeframes for Data Submission[3]/	
§158.135 Toxicology (continued)						
SPECIAL TESTING						
85-1 - General Metabolism	PAI or PAIRA		No	-	Yes[11]/	24 Months
85-2 - Dermal Penetration	Choice		No	-	Yes	12 Months
86-1 - Domestic Animal Safety	Choice		No	-	Yes	24 Months

1/ Composition: PAI = Pure active ingredient; PAIRA = Pure active ingredient, radiolabelled; 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.

3/ Data must be submitted within the indicated timeframes, which begin on the date of the Guidance Document (see front cover for this date).

4/ An acceptable review of the available literature will satisfy these requirements.

5/ This test is only required if the substance is shown to be a delayed neurotoxin in test 81-7.

6/ Contingent upon the outcome of the worker exposure analysis (see reentry section).

7/ The data below were requested in a 3(c)(2)(B) Notice dated November 27, 1985. The registrant(s) must provide reasonable and acceptable approaches to determine the "no-observed-effect level" for the eye toxicity based on possible functional retinal impairment. The Agency is prepared to accept studies such as electroretinograms to assess these effects (data must be submitted by March 27, 1987). The mechanism of abnormal gait in female rats and sciatic nerve degeneration including determination of a NOEL in rats must be addressed (data must be submitted no later than July 27, 1986). These data (eye and sciatic nerve) have been received and are being evaluated.

§158.135 Toxicology (continued)

8/ The data listed below were requested in a 3(c)(2)(B) Notice dated November 27, 1985. The registrant(s) must provide reasonable and acceptable approaches to determine the "no-observed-effect level" for cholinesterase inhibition in the chronic dog study (data are to be submitted no later than November 27, 1987). Additionally, reasonable and acceptable approaches to determine the eye toxicity based on functional retinal impairment must be provided. The Agency is prepared to accept studies such as electroretinograms to assess these effects (data are to be submitted no later than March 27, 1987).

9/ The LEL and NOEL values could not be assessed because there were critical omissions of data. Three of the four pup parameters (decreased pup viability in high-dose F_2 pups , and combined weighted average body weight gains for F_1, and F_2 pups during lactation) were of equivocal biological significance, and compound-related parental toxicity was not observed.

10/ Data are required for all three categories. Testing must include plant metabolites and some photoalteration products in addition to the parent compound). The test battery must include (but not be limited to) an in vitro mammalian gene mutation, at least one in vivo mammalian gene assay, and at least one in vivo mammalian assay (preferrably mouse micronucleus). The possibility of nitrosoamine formation of some plant metabolites must be examined.

11/ An acceptable summary of literature materials may satisfy this requirement.