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

MAY 31 1989

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Parathion, Domestic Animal Safety

TO: Dennis Edwards PM-12
Registration Division (H7505C)

FROM: Robert P. Zendzian Ph.D., 5/19/89
Acting Head, Rev Sec I
Toxicology Branch I
Health effects Division (H7509C)

THROUGH: Edwin Budd
Acting Chief
Toxicology Branch I

Compound; Paration | Tox Chem #637 | Accession #410313-01

Registration #4787-3 | Registrant; Chemnova | Tox Project #9-1126

Action Requested

In response to the parathion registration standard the registrant has submitted the following document;

Review of the literature on toxicological effects of ethyl parathion; J. Pascarella, Jellinek, Schwartz, Connolly & Freshman Inc, Project ID 208, March 7, 1989, MRID 410313-01

Conclusions

In relation to the parathion registration standard toxicology data requirments;

1. Data requirement 85-2 is satisfied. Parathion is clearly established as Toxicity Catagory I by the dermal route.

1. Data requirement 85-3 acute inhalation toxicity is in error. Parathion is clearly established as Toxicity Catagory I by the inhalation route. No further data is required.

3. The registration standard requirement for Domestic Animal Safety data (86-1) is in error. This data is required only for End Use Products to be used on domestic animals. Therefore it is not a requirement for technical parathion and

should not be be required by the standard.

Discussion

This action is somewhat confusing. The cover letter states; "On behalf of A/S Cheminova (DK-7620, Lemvig, Denmark), I am submitting four copies of a literature review on toxicological effects of ethyl parathion as it relates to domestic animal safety. This literature review satisfies data requirement 85-2, required by the December 15, ethyl parathion Registration Standard."

The parathion registration standard lists 81-2 acute oral toxicity as a data gap and states "4/ An acceptable review of the available literature will satisfy these requirements." However the toxicology chapter notes that this is not a data gap, the requirement having been waived (Arce, memo, 9/21/84). Parathion is clearly established as a Toxicity catagory I poison by the dermal route in numerous studies. The Agency considers this matter as well established and the data requirement as having been satisfied.

It should also be noted that this same situation exists for 81-3 acute inhalation toxicity, it is required by the standard and not by the toxicology chapter. The standard is in error, Parathion is well established as a Toxicity Catagory I poison by the inhalation route and no further data are required.

In relation to the mention of Domestic Animal Safety, both the toxicology chapter and the standard list this as a data gap and require data. This is in error, domestic animal safety data is required only for End Use Products to be used on domestic animals. Therefore it is not a requirement for technical parathion and should not be be required by the toxicology chapter or by the standard.

Attachments

Table A generic data requirements for parathion from the Standard
Table A generic data requirements for parathion from the Toxicology Chapter

Registration Standard

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

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§158.135 Toxicology (continued)						
CHRONIC TESTING:						
83-1 - Chronic Toxicity - 2 species	TGAI	A,C,E				
- Rodent, and			Yes	GS00155011	No[7]	
- Non-rodent (Dog)			Yes	00093896	No[8]	
83-2 - Oncogenicity Study - 2 species	TGAI	A,C,E				
- Rat (preferred), and			Yes	GS00155011	No	
- Mouse (preferred)			Partially	GS00155012	Yes	50 Months
83-3 - Teratogenicity - 2 species:	TGAI	A,B,C,D,E,F				
- Rat			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 metalxolites must be examined.

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

Toxicology Chapter

TABLE A
GENERIC DATA REQUIREMENTS FOR PARATHION

Data Requirement §158.135 Toxicology	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)? 3/
ACUTE TESTING:					
81-1 - Oral LD_{50} - Rat	TGAI	A,B,C,D,E,F,G,H	Yes	Cannon Lab. 3/7/1979, 5/28/1980	No
81-2 - Dermal LD_{50}	TGAI	A,B,C,D,E,F,G,H	No	_	No (4)
81-3 - Inhalation LC_{50} - Rat	TGAI	A,B,C,D,E,F,G,H	No	_	No (4)
81-7 - Acute Delayed Neurotoxicity - Hen	TGAI	A,B,C,D,E,F,G,H	No	_	No (5)
SUBCHRONIC TESTING:					
82-1 - 90-Day Feeding - Rodent, Non-rodent	TGAI	A,C,E,	Yes	00072407, 00071671 00071670	No
82-2 - 21-Day Dermal - Rabbit	TGAI	A,E,F,G	No	_	Yes (6)
82-3 - 90-Day Dermal - Rabbit	TGAI		No	_	Yes (6)
82-4 - 90-Day Inhalation - Rat	TGAI		No	_	Yes (6)
82-5 - 90-Day Neurotoxicity- Hen/Mammal	TGAI		No	_	No (5)

1. Composition: TGAI = Technical grade of the active ingredient.
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 no later than _____.
4. Previously waived (A. Arce, memo dated 9/21/1984).
5. Data are available in the open literature indicating that parathion is not a delayed neurotoxin.
6. Contingent upon the outcome of the worker exposure analysis.

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 Section 3(c)(2)(B)? 2/
§158.135 Toxicology (continued)					
CHRONIC TESTING:					
83-1 - Chronic Toxicity - 2 species: Rodent and Non-rodent	TGAI	A,C,E	Yes	Bio/dynamics #77-2055 00093896	Yes (4)
83-2 - Oncogenicity Study - 2 species: Rat and Mouse preferred	TGAI	A,C,E	Partially	Bio/dynamics #77-2055	Yes (5)
83-3 - Teratogenicity - 2 species	TGAI	A,B,C,D,E,F,G,H,I	Yes	Bio/dynamics #82-2644 #82-2660	No
83-4 - Reproduction, 2-generation - Rat	TGAI	A,B,C,D,E,F,G	Yes	Bio/dynamics #80-2457	Yes (6)
MUTAGENICITY TESTING					
84-2 - Gene Mutation	TGAI	A,B,C,D,E,F,G,I	No		Yes (7)
84-2 - Chromosomal Aberration	TGAI	A,B,C,D,E,F,G,I	No		Yes (7)
84-2 - Other Mechanisms of Mutagenicity	TGAI	A,B,C,D,E,F,G,I	Partially	Stanford Res Inst EPA-600/L-77-028	Yes (7)

1. Composition: TGAI = Technical grade of the active ingredient.
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 no later than _____.
4. The registrant(s) must provide reasonable and acceptable approaches to determine the "no-observed effect level" for cholinesterase inhibition in the chronic-dog study, and for the eye toxicity based on functional impairment in the chronic-rat study. The mechanism of abnormal gait in female rats and sciatic nerve degeneration in male rats must be addressed.

5. Oncogenicity study in another species may not be required. Although the oncogenicity study in the mouse does not meet the Agency's current standard, nevertheless, it did not elicite a positive response that may warrant another study in this species. However, historical background of the spontaneous tumor incidence in the rat are required.
6. The study is currently classified as Core-Supplementary, additional information are required for the re-evaluation of the study. Upon the receipt and evaluation of these additional data the study may be elevated to Core-Minimum.
7. Data are required for all three categories a) gene mutation, b) chromosomal aberration, and c) other mechanisms of mutagenicity. Testing should include plant metabolites and some photoalteration products in addition to the parent compound (see F. 2&4). The test battery should include (and not be limited to) an in vitro mammalian gene mutation a and at least one in vivo mammalian gene mutation assay, and at least one in vivo mammalian assay (preferrably mouse micronucleus). The possibility of nitrosoamine formation of some plant metabolites should be examined.

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 Section 3(c)(2)(B)? 3/
§158.135 Toxicology (continued)					
SPECIAL TESTING					
85-1 - General Metabolism	PAI or PAIRA		No	-	Yes (4)
85-2 - Domestic Animal Safety	Choice		No	-	Yes
85-X - Other Studies			No	-	Yes (5)

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=Aqautic, 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 no later than _____.
4. An acceptable summary of literature materials may satisfy this requirment.
5. a. Product integrity study on granular formulations. b. Worker exposure profiles to include all subjects of the application and other common farming practices. d. Rate of percutaeous absorption. e. Residue data on the photodegradation products with respect to their nature and magnitude in the plant residues as well as their toxicological significance. f. Other testing may be required based upon the review of certain residue data.