RP-519
TXR-1251

001731

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

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

DATE: February 18, 1981

SUBJECT: Pirimor (Pirimicarb); Additional Oncogenicity Data.
(Caswell 359 C)

FROM: George Z. Ghali, Ph.D.
Toxicology Branch, HED (TS-769)

TO: William Miller (PM 16)
Registration Division (TS-767)

THRU: William Burnam, Acting Branch Chief
Toxicology Branch, HED (TS-769)

Action Requested:

Review of preliminary data submitted by ICI Americas, Inc. for the oncogenicity of pirimicarb in mice.

Background

Pirimicarb [2-(dimethylamino)-5,6-dimethyl-4-pyrimidinyl dimethylcarbamate] is registered for use on potatoes and various ornamental plants. Amended registration applications and tolerance petitions have been submitted for uses on a range of leafy vegetables, alfalfa, cotton, apples and pecans. It is also being tested under Experimental Use Permit No. 10182-EUP-2. In connection with the above registration and pending petitions, a life time feeding study in mouse was initiated and a preliminary report was submitted to the EPA for review for a possible carcinogenic potential.

The subject study was initiated as the result of 1976 meeting of the joint FAO/WHO Expert Committee on Pesticide Residues. The committee has reviewed four two-year studies in the rat and one in the mouse [submitted to the EPA in 1975 and 1977 (EPA Reg. No. 10182-7 and Pesticide Petitions No. 5F1608 and 7F1915)]. The committee expressed interest in a further carcinogenicity study in an appropriate species using a currently acceptable protocol.

179

aterials and Methods:

Five groups of Alderly Park Swiss-derived mice of each sex were used in this study. Sixty animals were used per each group. The test chemical was incorporated in the diet at the level of 200, 400 and 1600 ppm for up to 96 weeks. Two control groups were used for each sex. No further details for the experimental design and conditions were given in the preliminary report.

Results:

Liver tumor:

The incidence of liver tumor has been increased in the treated animals at all dosage levels in a dose related manner (Table 1).

Pulmonary adenoma:

The compound has increased the incidence of pulmonary adenoma in both males and females especially at the highest dosage level (1600 ppm) as shown in Table 1.

Lymphosarcoma:

There is a good evidence suggesting that th compound has possibly disturbed the spontaneous lymphosarcoma profile in this strain of mice (Table 1).

Discussion and Conclusion:

Although the preliminary report did not provide enough data, there was enough evidence suggesting that pirimicarb is a hepatic, pulmonary and possibly a lymphatic carcinogen.

Recommendations:

1. There is a presumptive evidence from data submitted to the Agency as per the letter to William Miller dated October 31, 1980 (Re: Primor 50W, EPA Reg. No. 10182-7, Additional Toxicology Study) suggesting that the compound is oncogenic.

   Toxicology Branch considers this data as possible 6, (a), (2) data and request all data on this study to be submitted for review.

2. In a second letter to Mr. William Miller dated December 5, 1980 (Re: Pirimor Insecticide Containing Pirimicarb Voluntary Cancellation), ICI Americas, Inc. requested EPA to approve the continued sale and distribution of existing stock of pirimor 50W, (approximately [redacted] pounds of a.i.) (Reg. No. 10182-7) in commerce until the supplies are exhausted or for one year after the effective date of the cancellation, whichever is earlier.

   In order for the Toxicology Branch to be able to estimate the hazard of this quantity of a possible oncogen, the forerequested study data will necessarily have to be reviewed for this hazard assessment.

3. Toxicology Branch has no objection to the cancellation of the existing ICI registration for pirimicarb containing products, and the withdrawal of all pending applications for ammended registration and all pending petitions for tolerances for this insecticide as requested by ICI Americas, Inc. as per letter of December 5, 1980.

Table 1

Pirimicarb: Lifetime Feeding Study in the Mouse
Major Neoplastic Findings

Total Number of Tumor Bearing Animals (Intercurrent Deaths Plus Terminal Kill)

	Males					Females				
	0 (control)	0 (control)	200 ppm	400 ppm	1600 ppm	0 (control)	0 (control)	200 ppm	400 ppm	1600 ppm
	60	60								
Total Liver Nodules	7	15	18	18	32	3	2	7	9	9
Subdivided as follows:										
Type A Nodules	3	9	5	9	15	1	2	3	6	4
Type B Nodules	4	6	13	8	17	2	0	3	3	5
Indeterminate Nodules	0	0	0	1	0	0	0	1	0	0
	7	15	18	18	32	3	2	7	9	9
Pulmonary Adenoma	9	8	9	8	17	9	4	9	11	18
Lymphosarcoma	13	15	13	13	14	11	25	18	18	24

*The study was initiated with 60 animals per sex per group.

ICI Americas Inc.

001731

Registration And
Regulatory Affairs
Department

HAND DELIVERED

October 31, 1980

Mr. William H. Miller
Product Manager (16)
Registration Division (TS-767)
U.S. Environmental Protection Agency
Washington, DC 20460

Dear Mr. Miller:

Re: PIRIMOR 50W
EPA Reg. No. 10182-7
Additional Toxicology Study

PIRIMOR products (containing pirimicarb) are registered for use on potatoes and various ornamental plants. Amended registration applications and tolerance petitions have been submitted for uses on a range of leafy vegetables, alfalfa, cotton, apples and pecans. PIRIMOR is also currently being tested under Experimental Use Permit No. 10182-EUP-2 under a crop destruct clause. In connection with this registration and these pending petitions, the preliminary results of a further toxicology study (lifetime feeding study in the mouse) with pirimicarb are herein being submitted for consideration of EPA.

The subject study was initiated as a result of the 1976 meeting of the Joint FAO/WHO Expert Committee on Pesticide Residues. That Meeting concluded that, although it was not unduly concerned about the carcinogenic potential of the compound, it wished to see a further carcinogenicity study undertaken in an appropriate species using a currently acceptable protocol.

The oncogenicity data reviewed by the FAO/WHO Committee in 1976 are those which ICI has submitted to the EPA in 1975 and 1977 (under EPA Reg. No. 10182-7 and Pesticide Petition Nos. 5F1608 and 7F1915). They comprise four two-year studies in the rat and one in the mouse. Since there were four previous studies in the rat but only one in the mouse, the mouse was chosen for this additional study. There are no outstanding questions from the Agency to ICI on the previous studies.

5

In the study which was initiated as a result of the FAO/WHO review, five groups of Alderley Park Swiss-derived mice (60 per sex per group) were fed diets containing pirimicarb at levels of 0 (2 groups), 200, 400 and 1600 ppm for up to 96 weeks. Several different tumor types were found in all groups. Lymphosarcoma was apparently the cause of an increased mortality in the 1600 ppm females. However, as this condition first appeared in controls, and as the incidence varied markedly between the two control groups, this finding is not considered by ICI to be an effect of pirimicarb. There was a statistically significant increase (as determined by Logrank analysis) in the incidence of liver nodules and pulmonary adenomas in both sexes at 1600 ppm compared to controls (Table 1). However, these increases in common tumor types at the highest dose level must be viewed against the high background levels of these neoplasms in the study as a whole and against their known variability in the mouse. They must also be viewed in the light of the lack of adverse findings during mutagenicity studies and in the light of the findings of the five previous long-term rodent studies on pirimicarb. On this basis, ICI concludes that these results should not be regarded as indicating that the compound is carcinogenic.

A report of the study is in preparation and will be submitted to the EPA as soon as it is available.

Respectfully submitted,

James M Wagner

J. M. Wagner
Pesticide Regulatory Specialist

RER/JWM/dmp/V/W/A29-30

Rec'd EPA
11/3/80

6

#359C

ICI Americas Inc.

Registration And
Regulatory Affairs
Department

HAND DELIVERED

December 5, 1980

001731

Mr. William H. Miller
Product Manager Team 16
Registration Division (TS-767)
U.S. Environmental Protection Agency
Washington, DC 20460

Dear Mr. Miller:

Re: PIRIMOR® Insecticide
Containing Pirimicarb
Voluntary Cancellation

The purpose of this letter is to officially request that EPA cancel all existing ICI registrations for products containing the insecticide pirimicarb. We also wish to withdraw all pending applications for amended registration and all pending petitions for tolerances for this insecticide. The basis for this request is as follows.

Pirimicarb is a selective insecticide with its pesticidal value primarily in controlling aphids. This narrow spectrum of activity results in a relatively small sales potential for the product.

In attempting to obtain approval for the planned additional outlets, ICI has experienced delays and expenses well beyond those it had originally anticipated. Further delays and expenses can be expected as a result of the ongoing preparation and review of registration data.

ICI Americas therefore requests EPA to take the following actions:

1. ICI requests that EPA cancels the registrations for the following products:

   (1) Pirimicarb Technical Insecticide
   EPA Reg. No. 10182-15

   (2) PIRIMOR 50W Insecticide
   EPA Reg. No. 10182-7

Wilmington, Delaware 19897 Phone (302) 575-3000

001731

(3) PIRIMOR 50WP Insecticide
EPA Reg. No. 10182-16

ICI requests that EPA approve the continued sale and distribution of existing stocks of PIRIMOR 50W (Reg. No. 10182-7) in commerce until the supplies are exhausted or for one year after the effective date of the cancellation, whichever is earlier. ICI's current inventory for all product labeled under EPA Reg. No. 10182-7 is [redacted] pounds of the 50% formulation (equivalent to [redacted] pounds of active ingredient). [redacted] of Pirimor 50WP, Reg. No. 10182-16.

2. Under 40 CFR Part 180.8, ICI requests that the following petitions be withdrawn without prejudice:

(1) Pesticide Petition No. 7F1915/Food Additive Petition No. 9H5224; originally filed January 10, 1977 for tolerances of pirimicarb on cabbage, lettuce, brussels sprouts, cauliflower, bell peppers and chili peppers.

(2) Pesticide Petition No. 9F2175; originally filed on March 2, 1979 for tolerances for pirimicarb on alfalfa and pecans.

(3) Pesticide Petition No. 9F2235/Food Additive Petition No. 9H5232; originally filed July 20, 1979 for tolerances for pirimicarb on apples and cotton.

(4) Pesticide Petition No. 9G2119/10182-EUP-RA; originally filed April 20, 1979 for temporary tolerance for pirimicarb on pecans.

(5) Pesticide Petition No. 9G2257/Food Additive Petition 9H5238; originally filed August 23, 1979 for temporary tolerances of pirimicarb on apples, cotton, cabbage, lettuce and peppers.

8

001731

ICI regrets having to take this course of action, but finds that the product's limited sales volume could not support the product through further anticipated delays and expenses in obtaining EPA approvals.

Sincerely,

Robert E Ridsdale

R. E. Ridsdale, Ph.D
Director
Registration and Regulatory Affairs

RER/JMW/bmw/M33-35

CC: Mr. Douglas C. Campt
Director
Registration Division

Mr. Frank Sanders
Section Head
Insecticide - Rodenticide Branch

9