

US EPA ARCHIVE DOCUMENT

KB-319
TXR-1728

001728

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

354C

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DATE: 10/22/78

SUBJECT: EPA # 10182-7, PIRIMOR^R 50 W, application for amended registration, human safety evaluation of. Active ingredient is 2-(dimethylamino)-5,6-dimethyl-4-pyrimidinyl dimethylcarbamate, pirimicarb.

FROM: TB/HED

TO: PM (No. 16) Mr. Miller

Action requested: Add aerial use on potatoes.

Formulation: Contains 50% active ingredient (pirimicarb and 50% inert ingredients, each of which is cleared under 40 CFR 180.1001. (Proposed label for use on potatoes does not recommend addition of a wetting agent in spray tank.)

Petitioner: ICI Americas, Inc.

RECOMMENDATION: Grant requested amended registration, contingent on the formulation label being changed as followed: Following "Warning" label should read, "May be fatal if swallowed or absorbed through the skin. Causes eye irritation." Following "Hazards to Humans (& Domestic Animals) Warning," label should read, "Do not get in eyes, on skin, or on clothing. Avoid unnecessary exposure to spray mist. Wash thoroughly after handling."

- Comments:
1. Registration applicant should be advised that (formulation) supporting acute toxicity data are deficient, according to present TOX requirements (details are on pp. 2-4 of this memo.)
 2. Registration applicant should be advised that TOX data requirements previously communicated to him (cf. TB review of PP No. 7F1915, 4/7/77, by Dr. S. Chan) concerning need for further carcinogenicity data and for studies on bone-marrow cytology, antibody and anemia production and possible immunogenic sensitization must be fulfilled before any further tolerances can be considered. (FAO/WHO, 1976, also notes similar concerns and recommends specific types of studies they will require for further consideration; presently, only a temporary ADI for man, using a high safety factor, is estimated.)

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Review of pertinent clinical data:

Oral acute toxicity on formulation.

LD₅₀ (fed F rat) = 356 mg/kg
(308-414, 95% CI)

Groups of 6 F rats (young adults) each received single oral doses of 200, 250, 320, 400, or 500 mg/kg EW formulation ("PP.062 50% dispersible powder"); observed 14 days; LC₅₀ calculation by method of Thompson, 1947.

Toxic signs: Salivation, chromolachrymation, urination, defecation, miosis, and muscular fibrillation, leading to fasciculations and death. Plasma cholinesterase, 67% inhibited; RBC ChE, 92% inhib.

Source: Acc. No. 003890 (test 003), 10182-T(7), Vol. II, ref. 1C, Rept. TR/620, ICI Ltd., 11/6/67.

Classif.: SUPPLEMENTARY

Defic's: No male rats tested
No body weights reported
No autopsy done
Method of cholinesterase analysis, not reported
Rats not fasted

Dermal acute toxicity on formulation.

LD₅₀ (F rat) = more than
500 mg/kg

Two female rats (only) each received a single 24-hr exposure to 600 mg/kg formulation ("PP.062 dispersible powder, as a suspension in water") on shorn back, under occlusive dressing.

Toxic signs: None noted. (However, "toxic signs would be expected at ca. one g/kg.")

Source: Acc. No. 003890 (test 016), 10182-T(7), Vol. II., ref. 1C, Rept. TR/620, ICI Ltd., 11/6/67.

Classific.: SUPPLEMENTARY

Defic's.: No male rats (or rabbits) tested.
Too few rats used
Too few dose-levels used
Abraded skin not tested
No body weights given
No autopsy done

Acute inhalation toxicity on formulation. LC₅₀ (rats) = more than
20 mg/liter/hr

Four M and 4 F rats, only heads exposed, were placed in chamber with 20 mg/l heavy dust Pirimor dispersible powder, which contained ca. 9% respirable (i.e., particles with free-falling speed less than that of a 7.1-micrometer unit-density sphere) particles, for one hour.

Toxic signs: None shown. Plasma ChE, "40% inhibited;" RBC ChE, not significantly inhibited.

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INERT INGREDIENT INFORMATION IS NOT INCLUDED

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Source: Acc. No. 003890, (test 027), 10182-T(7), Vol. II, Ref. 6C, Rept. HO/IH/P/69, ICI Ltd., August, 1972

Classif.: CORE-MENINGOM

Defic's.: Too few rats
No. anal. value
test substance
concn. in air
No autopsy

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Primary Eye Irritation Draize score on formulation: (rabbit F) 2.9/110

Six F rabbits each received one drop (0.05 ml) of 50% dispersible powder formulation [JF2538 (Pirimor), ~~as a~~ suspension in water in left eye. Thus, each eye received ca. 25 mg formulation. Observed 7 days; scored, individually, acc. to Draize scale. (No eyes washed.)

Results: Two rabbits had transitory corneal opacity; 3 had transitory chemosis in conjunctivae.

Source: Acc. No. 094393, PP 5F1608, Vol. 1, Ref. 3C, Rept. HO/IH/P/87B, D. M. Ferguson, August, 1973.

Classif.: SUPPLEMENTARY

Defic's.: No males tested
Only 25 mg sample
tested in eye
Sample moistened
(not tested dry)

Primary Skin Irritation Draize score on formulation: (rabbit) 0.5

Irritant action of "Pirimor 50% dispersible powder formulation (JF 2538)" was determined on 4 rabbits, each with intact and abraded skin sites, "according to Draize (1959)." Details of procedure not supplied, except that Pirimor was applied as a 50% paste with water. Individual scores are given.

Source: Acc. No. 003890 (test 025) 10182-T(7), Vol. II, ref. 6C, Rept. HO/IH/P/69, ICI Ltd., Dec., 1972.

Classific.: SUPPLEMENTARY

Deficiency: Full details of procedure needed

Other studies:

Delayed neurotoxicity on tech grade:

(hen), negative at 25 mg/kg

Four adult hens each received a single oral dose of 25 mg/kg tech. PP. 062 (in range of oral LD₅₀ for hens); observed 21 days post-dosage.

Results: No delayed locomotor ataxia noted in any hen during 21 days.

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COMMENT: These TOX studies were classified because none were found classified in TB (Caswell) file (No. 359C) nor were any available from the PM, on request.

Taken at face value, they show the formulation to be in TOX Cat. II for oral and dermal acute toxicity and eye irritation and in TOX Category IV for acute inhalation toxicity and primary skin irritation.

We believe these studies in conjunction with others, are adequate to judge safety of proposed use (and proper labelling):

The oral acute toxicity value in rats agrees well with those in other species (done on technical grade) to backstop its placement in Cat. II, as does the reported lack of effect of 50 mg/kg/day to M^{tech. grade} and F rats in a 14-day repeated oral dose test.*

The dermal acute toxicity placement in Cat. II is, likewise, supported by reported lack of toxicity of a 14-day repeated dermal dose test in rabbits (tech. grade) (M and F) at 500 mg/kg/day.*

The delayed neurotoxicity test was negative in two separate trials in hens (one carried out as recommended by the British authorities) at a dosage rate of 25 mg/kg which is in the range of the LD₅₀ (oral) determined, preliminarily, by ICI personnel (see above review).*

The negative finding of teratogenicity of technical grade perimicarb (at 5 mg/kg/day) is also supported by lack of positive findings in teratologic or reproduction tests in rats and mice.*

* Cf. earlier reviews by Mr. R. Coberly, 7/1/75, PP No. 5F1608; cf., also, Joint Meeting of FAO/WHO on pesticides, 1976, "Pirimicarb," pp. 535-95

MLC 10/26/78

Mary L. Quaife, Ph.D., TB/HED
October 26, 1978

EB 11/3/78

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