CASWELL FILE

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

004578

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPTC, 6(a)(2) Submission re Cardio-Toxicity at One Year in a Two-Year Rat Study

TO: Robert Taylor PM 25
Registration Division (TS-767)

FROM: Robert P. Zendzian PhD, Acting head
Review Section IV
Toxicology Branch
HED (TS-769)

WDB 4-8-85

THROUGH: Theodore M. Farber PhD, Chief
Toxicology Branch

Compound EPTC — Tox Chem #435

Registration #748-223, -222 — Registrant PPG Industries

Accession #257014, 15 & 16

Action Requested

1. Review and comment on a study submitted by the Registrant under the provisions of sec 6(a)(2).

Two year Oral Feeding Study of the Oncogenicity and Chronic Toxicity of EPTC in Rats One-Year Status Report (Hazleton).

2. Review the following studies.

A Three Month Subchronic Oral Dietary Toxicity Study of EPTC in Beagle Dogs (Bio/dynamics)

Acute Delayed Neurotoxicity Study with EPTC Technical in the Domestic Hen (Huntingdon)

Conclusion

1. The one-year status report of the two year rat study reports a dose-related degenerative cardiomyopathy at all doses in the males and at the intermediate and high dose in the females. Both incidence and severity increased with

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004578

Recommendation

Toxicology Branch repeats its recommendation from the memo of 4/8/85.

1. Considering the rarity of compound induction of the lesion, cardiomyopathy, and its life threatening potential, Toxicology Branch will have its ad Hoc Committee review the evidence on this compound. Until the committee has completed its evaluation Toxicology Branch recommends that no actions be approved on this compound.

2. This submission will be added to the previous submission of the final report of the chronic rat study and will be reported in detail with that report. Record #127492, Acession #s 254335, 36, 37 & 38.

Background

EPTC has been sponsored as a pesticide by PPG Industries (#747-223, -222) and Stauffer (#476-2140). A previous memo (Zendzian, April 1985, copy attached) points out that a compound-related cardiomyopathy has been identified in the one-year status report of a two-year rat feeding study submitted by PPG Industries. This memo concludes;

"The data on hand show that EPTC produces a cardiomyopathy in rats following short term exposure by the oral and inhalation routes. Compound-induced cardiac toxicity is an extremely rare observation in toxicity testing in animals. Cardiac toxicity of the type reported is potentialy an extremely serious life-threationing effect."

Report Submitted by Stauffer under §6(a)(2)

The report of the rereading of the histopathology slides of the cardiac tissue concludes;

"It was concluded that chronic myocarditis and thrombosis occured more frequently and with greator severity in rats of the high dose group (125mg/kg/day) when compared to rats of the control group. The no effect level appeared to be test group 3 (25mg/kg/day)."

Considering previnusly submitted data on this ccmpound and this report it is concluded that the effect is compound related. A detailed evaluation of this submission will be included with the reveiw of the origional report of the study.

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A similar cardiomyopathy had been seen in the subchronic study, however only the acute lesions were present after 3 months on test."

Conclusion

The data on hand show that EPTC produces a cardio-myopathy in rats following short term exposure by the oral and inhalation routes. Compound-induced cardiac toxicity is an extremely rare observation in toxicity testing in animals. Cardiac toxicity of the type reported is potentialy an extremely serious life-threationing effect.

co

Dr Engler

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