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

FEB 4 1986

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Triphenyltin Hydroxide: Request for additional studies to clarify potential immunotoxicity.

FROM: John Doherty 1/3/86 TOX CHEM No. 896E
Toxicology Branch
Hazard Evaluation Division (TS-769)

TO: Henry Jacoby
Product Manager #21
Registration Division (TS-767)

THRU: Edwin R. Budd
Section Head
Toxicology Branch
Hazard Evaluation Division (TS-769)

1/21/86
2/4/86

The fungicide triphenyltin hydroxide (TPTH) has been implicated as being immunotoxic (refer to the Toxicology Branch Chapter of the Registration Standard for this pesticide). Toxicology Branch (TB), however, does not consider that the existing data base demonstrates a NOEL for immunotoxic effects.

Problems related to the assessment of the immunotoxicity of TPTH were discussed with the company representatives at a meeting on December 12, 1985. During this meeting the companies were advised that TB would make recommendations for a series of tests to be conducted in an attempt to clarify the NOEL for the effects of TPTH on the immune system. Dr. Roy Sjoblad, TB microbiologist, has devised a set of recommendations as indicated in the attached memorandum.

Please advise the registrants of the attached requests for additional immunotoxicity testing with TPTH as recommended by Dr. Sjoblad.

cc: DR. R. Sjoblad
Ms. B. Shackleford

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MEMORANDUM

Subject: Recommended studies for establishing a NOEL for triphenyltin hydroxide on cells of the immune system.

To: Edwin Budd
Head, Review Section II
Toxicology Branch

John Doherty, Ph.D.
Toxicologist
Toxicology Branch

From: Roy D. Sjoblad, Ph.D. R.D.S. 12/20/85
Microbiologist
Toxicology Branch (TS 769C)

Background

Several reports (referenced and summarized by Drs. Diehl and Leist; letter from Hoechst; October 10, 1985) have indicated that oral administration of TPTH to rodents causes a suppression in numbers of certain cellular components of the immune system (i.e. splenocytes, eosinophils, circulating lymphocytes, and monocytes). In vitro tests established that TPTH, at >0.04 ug/ml, reduces the viability of thymocytes. A number of ex vivo functional tests have been performed, and where detected, positive results would be consistent with a mechanism of direct toxicity of TPTH to cellular components of the immune system.

At present, a NOEL for the effect of TPTH on cells of the immune system has not been established. In a report submitted by Hoechst ("Immunological study in male mice", Quintox Inc., Study No. QU/THAN, May 17, 1982, Document No. A25501) spleen cell numbers and spleen weights of mice treated at the lowest dose (2.5 mg TPTH/kg) were significantly lower than controls.

Recommended studies

The following should be evaluated in male and female rodents, so as to establish a NOEL for TPTH on certain cellular components of the immune system.

1) Hematology: particularly, total leucocyte counts and leucocyte differential.

2) Thymus: particularly, total and viable thymocyte count

3) Spleen: particularly, total and viable splenocyte count, T- and B-cell differential.

4) Bone marrow: particularly, a total and differential cell count.

5) Body weights and food consumption.

6) Organ weights, particularly, the spleen, thymus, and liver; and organ:body weight ratios.

The following are recommended as part of the protocols for the study. Female and male mice and rats should be used as the test animals. Newly weaned rats should be used, and the mice should be no more than 6 weeks old at the beginning of the study. With the mouse, strain $B_6C_3F_1$ is recommended, since it was used in the Quintox study. At least ~~20~~ 10 animals (~~10~~ 5 of each sex) of each species should be included in each dose group. TPTH (technical; purity >96%) should be administered by mixing in with the diet. Dosing should be for a period of 4 weeks. The lowest dose should have no effect on the above parameters, while the highest dose should cause some level of measurable toxicity. Test animals should be observed daily, and any clinical signs of toxicity should be recorded. S.D.D. 1/8/86

Consideration should be given to appropriate preservation of splenic, thymic, bone marrow, and liver tissues for possible histopathological examination. It is recommended that appropriate satellite groups of test animals be included in the study to evaluate recovery from, persistence of, or delayed occurrence of immunotoxic effects.

It is urged that protocols for the study be forwarded to the EPA for approval, before the study is conducted. Any questions concerning the study design may be submitted, through the product manager, to Dr. Roy D. Sjoblad.

Dr. Ralph Smialowicz (Immunologist, EPA, Research Triangle Park, N.C.) concurs with the recommended test requirements as set forth in this Memorandum.