CASWELL FILE

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

SEP 28 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Reg. No. 8340-17 - Triphenyltin hydroxide: Review of protocols for rat and mouse immunotoxicity studies.

TOX CHEM No.: 896E
TOX PROJECT No.: 7-0907
Record No.: 199177

FROM: John Doherty 9/11/87
Toxicology Branch
Hazard Evaluation Division (TS-769)

TO: Lois Rossi
Product Manager #21
Registration Division (TS-767)

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

9/14/87

THRU: Theodore Farber, Ph.D.
Branch Chief
Toxicology Branch
Hazard Evaluation Division (TS-769)

Theodore M. Farber
9/14/87

The American Hoechst Corporation has submitted to the Agency for review copies of protocols for testing for potential immunotoxicity of triphenyltin hydroxide (TPTH). These protocols were prepared by the registrant and their consulting laboratories in response to the recommendations made by Dr. R. Sjoblad of Toxicology Branch (TB). Refer to the memo from R. Sjoblad to E. Budd and J. Doherty dated December 20, 1985.

These protocols were referred to Dr. Sjoblad for review and a copy of his comments is attached. Refer to memo from R. Sjoblad to E. Budd dated September 10, 1987, attached. It is suggested that a copy of Dr. Sjoblad's memo be forwarded to the registrant.

In addition to the comments made by Dr. Sjoblad, TB wishes to remind the registrant that it is their responsibility to provide a study that will be scientifically acceptable to the Agency and that indications of immunotoxicity resulting from this study may require additional immunotoxicity testing as deemed to be necessary for risk assessment (refer also to the last paragraph of Dr. Sjoblad's review attached).

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SEP 10 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Review of proposed immunotoxicity testing protocols for triphenyltin hydroxide (TPTH) as submitted by American Hoechst Corporation.

TO: Ed Budd
Head, Review Section II

FROM: Roy D. Sjoblad, Ph.D.
Microbiologist, Mission Support Staff

R D. Sjoblad 9/10/87

THROUGH: Reto Engler, Ph.D.
Chief, Mission Support Staff

EPA ID No.: 8340-17

Caswell No.: 896E

Record No.: 199177

Tox. Branch Project No.: 7-0907

Background:

American Hoechst Corporation has submitted by letter (June 30, 1987, from B. Volger to L. Rossi) protocols for a pilot study to establish appropriate dose levels for subsequent immunotoxicity studies. The registrant states that the protocols "...concur with Dr. Sjoblad's recommendations (see H. Jacoby's letter dated August 4, 1986)." The purpose of the immunotoxicology study is to establish a NOEL for TPTH on cells of the immune system.

Studies proposed:

Range-finding:

Male and female Fisher 344 rats and $B_6C_3F_1$ mice will be exposed to technical grade TPTH via the diet for 28 days. TPTH dose levels proposed for the rat are 0, 1, 5, 25, and 125 ppm. Dose levels proposed for the mouse originally were 0, 5, 20, 80, and 320 ppm, however, handwritten amendments to these proposed dose levels were made, but were illegible in the copy provided. Ten male and ten female animals are to be included in each dose group. Test animals will be approximately 6 weeks old at the initiation of dosing.

The following parameters are to be evaluated: mortality, physical examination, body weights, organ weights (kidneys, liver, lungs, spleen, thymus), food consumption, and hematology (hemoglobin, hematocrit, erythrocyte count, total and differential

leucocyte count, platelet count, MCH, MCV, MCHC).

A complete necropsy will be conducted on all animals that die or are sacrificed on study, and on all others at termination of the study. Tissues and organ samples will be saved for possible future examination.

Immunotoxicology:

Male and female Fisher 344 rats and $B_6C_3F_1$ mice will be exposed to technical grade TPTH via the diet for 28 days. The dose levels will be determined from the pilot feeding studies. There will be 15 male and 15 female animals per dose group. Ten male and ten female test animals will be sacrificed and analyzed after 28 consecutive days of dosing. Five male and female test animals will be utilized in a recovery study, and will be sacrificed at 28 days after the last dosing with TPTH. Three dose levels, and a 0 ppm dose level, are proposed.

The following parameters will be evaluated: body and organ weights, food consumption, organ weights, hematology (see Discussion below), and total and viable splenocyte and thymocyte count, T- and B-lymphocyte enumeration, and bone marrow total and differential cell count (see Discussion below).

Discussion:

1. The specific organ weights and hematological parameters to be evaluated in the immunotoxicology study were not mentioned, however, this reviewer presumes that they will be analogous to those proposed in the range-finding study. The Registrant should address this presumption.

2. Specific protocols for the immunological parameters were not provided. Instead, laboratory SOP reference numbers were provided for all the immunological parameters proposed for monitoring. The Registrant should submit the protocols to the Agency.

3. Two separate laboratories will be conducting the studies: one will perform the general toxicological analyses and the bone marrow differential cell counts. The other laboratory will evaluate the specific immunotoxicological endpoints.

4. The proposed protocols are consistent with those suggested by R.D. Sjoblad in 12/20/85 Memorandum to E. Budd and J. Doherty.

5. The dose level amendments for mice in the range-finding study are illegible, and a clear copy should be submitted to the Agency.

6. The Fischer 344 rat is proposed for use as a test animal, however, most previous studies have employed the Wistar rat. The Wistar rat should be used as the test animal since it previously has been shown to be sensitive to effects of TPTH.

7. Three dose levels are proposed in the immunotoxicity testing portion of the study. Consideration should be given to using four or more dose levels.

Recommendation:

If sufficiently well-done, the proposed studies should provide an estimate of a NOEL for effects of TPTH on T- and B-lymphocytes in the rat and the $B_6C_3F_1$ mouse after exposure, via the diet, to TPTH for 28 days. The Registrant

should address the above [redacted] Discussion points. The Registrant also has provided the Agency with a study (January 15, 1986) which showed that TPTH caused statistically significant ($p < 0.01$), decreasing, dose-related trends for IgG, IgA, and IgM in male and female mice. The Registrant should include measurement of these parameters in the immunotoxicity study, and should submit protocols to the Agency. The protocols should include use of a sensitive, quantitative method for measuring immunoglobulin levels.

Any additional immunotoxicity studies with TPTH that may be required will, in large part, be based on the NOELs established in the above-proposed studies, and on the perceived necessity for a risk-evaluation due to immunotoxic effects of TPTH.