



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

CASWELL FILE

006415

OCT 30 1987

OFFICE OF  
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Reg. NO.: 8340-15 - Triphenyltin hydroxide:  
Review of guinea pig sensitization study.

TOX CHEM No.: 896E  
TOX PROJECT No.: 7-1038  
Record No.: 202168

FROM: John Doherty *John Doherty* 10/29/87  
Toxicology Branch  
Hazard Evaluation Division (TS-769)

TO: Lois Rossi  
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THRU: Edwin Budd  
Section Head  
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Hazard Evaluation Division (TS-769)

*Budd*  
*10/29/87*

Background

The Toxicology Branch chapter of the Registration Standard for triphenyltin hydroxide (TPTH) identified a dermal sensitization study as a data gap. The registrant previously submitted a dermal sensitization study with guinea pigs to fulfill this requirement but Toxicology Branch (TB) determined that the study was unacceptable (refer to review by J. Doherty dated August 22, 1985, for EPA Reg. No. 8340-15). The current submission includes an additional dermal sensitization study with guinea pigs and an overview of the potential dermal sensitization properties of TPTH prepared by Dr. E. L. Carmines. These documents were reviewed and the following comments apply.

When the earlier dermal sensitization study was reviewed (refer to August 22, 1985 review), it was noted that the study report maintained that TPTH was a "very slight sensitizing agent" on the albino guinea pig under the conditions of the study (modified Buehler procedure). Toxicology Branch (TB), however, determined that the study was NOT ACCEPTABLE and that additional dermal sensitization data would have to be provided. TB considered that the borderline response noted in the earlier study was not sufficient in itself to classify TPTH as a skin sensitizer.

It was stated in the August 22, review that "additional studies using one or more methods to assess for skin sensitization must be conducted. In the future studies, the positive control must give a positive response". The registrant was advised of this requirement when the actual TB review was sent with EPA's cover letter concerning the review of the earlier dermal sensitization study (refer to H. Jacoby letter to American Hoechst Co, dated November 25, 1985). The inclusion of the positive control was considered to be important by TB because the positive control in the earlier study gave only a weak or borderline response that was nearly the same or only slightly higher than the response to TPTH.

#### Toxicology Branch Comments.

1. The submitted study was reviewed and determined to be CORE SUPPLEMENTARY.

Refer to DER attached.

2. The study did not include a positive control even though the previous review from TB (refer to J. Doherty review dated August 22, 1987) specifically requested that a positive control be included.
3. The Agency is currently confronted with three dermal sensitization studies, one of which was determined to show indications that TPTH is a sensitizer. Of the remaining studies, the first study was not acceptable to the Agency (refer to the TB chapter of the Registration Standard for TPTH) and the second study (current review), did not include a positive control.

TB has determined that since one study showed that TPTH may cause a dermal sensitization effect, future studies must include a positive control.

Therefore, an additional dermal sensitization study which includes a positive control must be provided in order to resolve the potential dermal sensitization of TPTH.

The registrant is requested to survey the literature on types of dermal sensitization studies used by regulatory agencies and select another study type (besides the Maximisation study type already submitted) and send a proposed protocol to EPA for review. The protocol should contain the rationale for selection of this study type. If the registrant desires to repeat the modified Buehler assay (i.e. the study type which was reviewed in the August 22, 1987 review from TB, copy attached), it should be clearly understood that a repeat of this study must clearly distinguish a response between TPTH and the positive control.

4. TB has read the document entitled "Summary Sensitizing Potential in TPTH" as prepared by Dr. E.L. Carmines (dated July 30, 1987).

It is noted that Dr. Carmines concluded that "based on the results of this study and the previous studies it can be concluded that TPTH is not a sensitizer"\*. [Note no DER was prepared for this summary report.]

TB does not consider that the available data base fully defines the dermal sensitization potential of TPTH. The fact that the maximisation test utilized Freund's Adjuvant does not necessarily mean that the study was most appropriate for testing for the dermal sensitization effects of TPTH in particular. The maximisation test is only a maximisation test for some but not all compounds.

5. Lastly, TB is especially concerned with the potential for TPTH to affect the immune system and dermal sensitization is one aspect of this system. Thus, TB is justified in requesting the additional dermal sensitization studies as above.

\*There is apparently some confusion among the registrant's staff concerning the dermal sensitization potential of TPTH because the cover memo with this submission as prepared by Dr. Bert Volger (dated August 24, 1987) states that "The results indicate that TPTH is a skin sensitizer". This statement is a contradiction of the summary made by Dr. Carmines.

Reviewed by: J.D. Doherty  
Section II, Tox. Branch (TS-769C)  
Secondary reviewer: E.R. Budd  
Section II, Tox. Branch (TS-769C)

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DATA EVALUATION REPORT

STUDY TYPE: 81-6 Dermal Sensitization  
guinea pigs

TOX. CHEM. NO.: 896E

ACCESSION NUMBER: 403180-01

MRID NO.: Not provided

TEST MATERIAL: Triphenyltin hydroxide

SYNONYMS: TPTH

STUDY NUMBER(S): 87.0080

SPONSOR: American Hoechst Corporation

TESTING FACILITY: Pharma Research Toxicology and Pathology  
Hoechst Aktiengesellschaft 6230, Frankfurt Germany

TITLE OF REPORT: Fentin-hydroxide-Active Ingredient Technical (Code:  
HOE 02964 OF ZD97 0004) Testing for Sensitizing  
Properties in the Pirbright-White Guinea Pig  
in a Maximisation Test.

AUTHOR(S): Dr. K.-H. Diehl and Dr. K.-H. Leist

REPORT ISSUED: February 13, 1987

CONCLUSIONS:

No evidence that TPTH causes dermal sensitization was evident  
from this study.

Classification: core-SUPPLEMENTARY [No positive control group  
was included in the study.]

Special Review Criteria (40 CFR 154.7) - N/A

## REVIEW

### Basic Procedures

Pirbright-White guinea pigs (males, about 10 weeks old and with an average weight of 377 gm) obtained from HOECHST AG, Kast-ergrund, SPF breeding colony were used in this study. The test material (TPTH, 97.2% purity) was applied to the prepared skin of the guinea pig via either intradermic injection or dermal application after being dissolved in semiliquid paraffin. The paraffin mixture was further diluted with Fruend's Original Adjuvant and physiological saline. No positive control was included in the study.

### Preliminary studies

#### 1. Primary non-irritant concentration (dermal application).

Topical applications (0.5 ml in a cellulose bandage) of 10, 1 0.2, 0.02 and 0.002% TPTH diluted in semisolid paraffin were applied to the backs of each of two guinea pigs and kept in place for 24 hours.

The study report states (the individual animal data were not provided) that no signs of irritation were seen at concentrations of 0.02% and below. Higher concentrations resulted in well defined erythema and "lightish discoloration of the patch-covered area".

Based on these data a concentration of 0.02% was chosen for the challenge treatment.

#### 2. Tolerance of intradermic injections.

Intradermic injections (twice) of 5, 1, 0.2, 0.02 and 0.002% solutions of TPTH in semiliquid paraffin were injected twice to guinea pigs and the pigs were observed for reactions.

The 5, 1 and 0.2% solutions each showed moderate to severe erythema and oedema. The solutions of 0.02% and 0.002% solutions exhibited well defined erythema and slight oedema.

The 0.02% solution was selected for the intradermic injections in the main test.

Main Study

The guinea pigs (35) were prepared by shaving over a dorsal area 4 x 6 cm in the vicinity of the shoulders. The induction treatment (20 pigs treated with TPTH) consisted of making intradermic injections (twice) at three sites within the shaved area on day 1 as follows:

Site 1	2 x 0.1 ml	50% Fruend's Adjuvant
Site 2	2 x 0.1 ml	0.02% solution of TPTH in paraffin
Site 3	2 x 0.1 ml	0.02% solution of TPTH in 50% Fruend's Adjuvant

The control (10 pigs) and "escort" (5 pigs) were treated as follows:

Site 1	2 x 0.1 ml	50% Fruend's Adjuvant
Site 2	2 x 0.1 ml	semiliquid paraffin
Site 3	2 x 0.1 ml	50% Freund's Adjuvant

On days 1-7, the application area was examined for local reactions.

On day 9, the dermal induction treatment was made which consisted of application of 0.5 ml of the test substance (0.2% TPTH) to the control and treatment groups and vehicle only (semiliquid paraffin) to the "escort" group in a 2 x 4 cm cellulose patch which was applied around the intradermic injection sites. The application was kept in place for 48 hours (until day 11) under occlusion with an impermeable film and elastic bandage.

On days 12-21. The pigs in the control and treatment groups were held for observation.

On days 15-18. The challenge treatment of the "escort" group was made. No erythema or oedema were reported.

On day 22. The control and TPTH treated groups were challenged by preparing areas 5 x 5 cm by shaving each flank and 0.5 ml of the test substance (0.02% TPTH in paraffin) was applied to each left flank. The right flank was left untreated.

The treated guinea pigs showed no "abnormalities on the treated skin after challenge to indicate that TPTH treatment resulted in a sensitization reaction".

Other aspects of the general condition of the guinea pigs on this study were also noted. The treated guinea pigs showed no clinical signs of intoxication. Their body weights were not affected. The intradermic injections with Freund's Adjuvant (with or without cotreatment with the test substance) were reported to cause well defined erythema and slight oedema and the sites of injection was in some cases dry, chapped and hardened.

#### CONCLUSION.

This study is CORE SUPPLEMENTARY. No evidence that TPTH treatment resulted in dermal sensitization was demonstrated.

It should be noted, however, that no positive control was included. A previous memo from TB (refer to J. Doherty memo dated August 22, 1987) specifically indicated that a positive control should be included in the study.