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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Triphenyltin hydroxide: Rebuttal comments to PD 1 and request for additional immunotoxicity studies.

TOX CHEM No. 896E

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and

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Background:

On January 9, 1985, EPA issued a Notice of Special Review (50 FR 1107) of pesticide products containing the active ingredient triphenyltin hydroxide (TPTH). In response to this Notice of Special Review, the registrants of TPTH in the United States (American Hoechst Corporation, Duphar, Griffin Corporation, M & T Chemicals, Inc. and Wesley Industries, Inc.) have prepared a rebuttal addressing the toxicity issues concerning teratology, oncogenicity in mice, reproduction study with rats and immunotoxicity. Below are Toxicology Branch's response to comments made in the rebuttal concerning these issues.

Before discussing the individual items as below, a general comment should be made regarding TB's review process related to INVALID studies. TB does not use INVALID studies to fill the data requirements for registration and tolerance setting for pesticides. When a study that has been determined to be INVALID,

or if the CORE Classification is RESERVED, for technical or procedural reasons, it is TB's prerogative to use the data until valid studies either confirm the observations in that study or demonstrate a lesser degree of toxicity.

For three of the four issues which the registrants addressed, part of their rebuttal was that EPA based the Special Review on studies which were called INVALID (or for which the classification was RESERVED). Such a tactic on the part of the registrants is not a rebuttal at all.

The following are comments related to specific toxicity problems mentioned in PDl associated with TPTH.

1. Teratogenicity

TB's concerns related to the teratogenic potential of TPTH in rats have been resolved. The studies conducted by the registrants at the Wil Laboratories (1985) and the study conducted at EPA's Research Triangle Park facilities provided sufficient data to assure that TPTH is not teratogenic in rats at dose levels up to and including 8.0 mg/kg/day. This level results in maternal toxicity. Refer to the attached reviews of these studies for additional information.

A teratology study with rabbits is still required (refer to the TPTH registration standard).

2. Oncogenicity in Mice

The registrants have not provided a sufficient rebuttal to dismiss TB's concerns related to oncogenicity in mice. TB recognizes that the Cannon study (1979) suffers from both procedural and reporting problems but has not previously declared this study INVALID. CORE Classification of this study is RESERVED (refer to the Registration Standard for TPTH dated March 27, 1984). When studies are classified as RESERVED, the registrant must provide additional information to TB so that the review may be completed. When this study was originally reviewed in 1983, and again when the Registration Standard was prepared in 1984, the registrants were asked to prepare and submit the following detailed information:

1. Complete description of the lesion(s) described as "endometrial hyperplasia" and "endometrial hyperplasia with cysts" in the uterus. In addition, it should be clearly stated by the examining pathologist that these lesions are not considered by him to be neoplastic.

2. Individual animal pathology sheets which show on the same page (two or more pages for some animals may be necessary) both the gross and microscopic findings. The time of death (and cause if known) must also be included on these individual animal data sheets.

3. A revised summary table which shows the neoplastic and nonneoplastic findings from all of the mice actually examined for each group. (Note: Tables XV-XVIII include only those mice surviving the 18-month dosing period.)

4. A summary table tabulating the behavioral reactions during the in-life phase of the study.

5. A summary table tabulating the gross necropsy findings.

6. Results of the diet analyses performed twice during the first month and "quarterly" thereafter.

The registrants have not provided the above information.

The Cannon study report shows that at all dose levels, the female mice were reported as having lesions in the uterus described as "endometrial hyperplasia" and "endometrial hyperplasia with cysts." The pathologist responsible for this report listed these lesions in the table of neoplastic findings. Hyperplasias are not normally considered neoplastic lesions. TB must have this issue resolved before use of TPTH is toxicologically supported.

The pathologist responsible for classifying the hyperplastic lesions as neoplastic should be found and requested to provide a revised report reclassifying the lesions as nonneoplastic and justify his classification. This, however, would not eliminate TB's concern for adverse effects noted in this study. For example, the uterus is a reproductive organ and no NOEL for the hyperplasias (LEL < 7.0 ppm) has been established (based on available information).

The registrants have stated (p. 20) that "American Hoechst obtained the Cannon slides from the contract lab for reevaluation of the uterine findings, over one-half of the slides were missing, and reevaluation was not possible." On this basis the study must be considered INVALID. Inspite of this classification, the findings must be considered as potential adverse effects of TPTH until a VALID study demonstrates otherwise to TB's satisfaction.

An additional study with the same strain of mouse should be submitted.

Lastly, the NCI mouse oncogenicity study was classified as SUPPLEMENTARY. NCI studies are only occasionally used to meet the oncogenicity data requirement by TB. NCI studies are given even less weight when other available studies with the same chemical indicate potential oncogenic effects.

3. Reproductive Effects.

The reproduction study which TB reviewed in 1980 (i.e., the Central Institut voor Voedingoenderzock, 1977) indicated reduction in testicular weights in the pups. Based on available information, a NOEL of 0.5 ppm and a LEL of 1.0 ppm were assigned for this lesion. This study was determined to be INVALID because it was submitted in summary form only. Without additional supporting data, TB must consider the findings of this study as potential adverse effects of TPTH until a valid study demonstrates otherwise.

The registrants have not presented the original data so that independent statistical evaluations can be made for this study. The study may not be upgraded to valid status without this data. The registrants have not submitted a second study. Thus, TB does not agree with their statement (p.21) that "there is no basis for regulatory concern regarding reproductive effects."

4. Immunotoxicity.

The Office of Toxic Substance (OTS) was requested to review the issue of potential immunotoxicity associated with TPTH (see J. Doherty memo to I. Baumel) OTS concurred with TB (refer to the memo dated August 30, 1985 from I. Baumel to J. Doherty) in that available data show that TPTH is immunotoxic and that no NOEL is established. Survey of the published literature on alkyltin compounds has indicated that these agents are immunotoxic (for example see the review by A.H. Penninks and W. Seinen in Immunotoxicology Academic Press, 1983) and that the immunotoxicity may result from the cyotoxicity effects of these agents on lymphocytes. In particular the T-lymphocytes are susceptible to di-n-butyltin dichloride and di-n-octyltin dichloride and the immune reactions in which T-lymphocytes participate are compromised by these agents. The bone marrow is apparently not a target organ and the B-lymphocytes are apparently not affected by the organotin derivatives. It is assumed that TPTH may also act on the T-lymphocytes as do the the prototype di-n-butyl and di-n-octyl derivatives.

As of October 1985, the registrants have not provided a detailed rebuttal to TB's position that the special immunotoxicity study in mice (Quintox, May 17, 1982) does not demonstrate a NOEL for immunotoxic effects (see J. Doherty review dated August 11, 1983 for PP 3F2823/FAP 3H5384 and comments related to immunotoxicity made in the TPTH Registration Standard). In order to further assess the potential of TPTH to affect the immune system, the following studies are requested.

90 day feeding studies with both sexes of mice The following end-points must be carefully evaluated:

i. body weight and behavioral reactions,

ii. organ weights-all major organs and especially including the spleen and thymus. Absolute and relative (to both body and brain weight) organ weights must be determined,

iii. hematology-both red blood cell and white blood cell (total and differential) counts must be presented,

iv. serum chemistry-quantitation of immunogloblin levels of IgG, IgM, IgA, and IgE,

v. histopathology of thymus and spleen and any other organ showing obvious gross pathology and/or weight change,

vi. evaluation of splenic lymphocyte function, i.e. mitogen stimulated lymphoproliferation, mixed lymphocyte reaction and natural killer cell activity,

vii. response to immunization with T-lymphocyte dependent antigen to sheep erythrocytes,

viii. susceptibility of test animals to bacterial infection, (i.e. Listeria monocytogenes).

The dose levels chosen must be such that the high dose groups show signs of systemic toxicity and that the low dose group clearly show a NOEL for potential effects on the immune system. A positive control should be included.

Although this test system is extensive, TB is requesting these studies because the chemical family to which TPTH belongs (organo tin derivatives) is known to be immunotoxic and the studies submitted to date have not clearly demonstrated a NOEL. Should the sbove set of immunotoxicity studies indicate a significant impairment of the immune system, a series of second tier studies may be necessary to determine recovery from any immunotoxicity that may be caused by TPTH.

In addition to the above, a dermal sensitization study with guinea pigs (Buehler test) is also required (refer to the Registration Standard) to assess delayed type hypersensitivity.