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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: Update (November, 1987) on Major Toxicity Issues Related to Special Review. Request for Additional Teratology (Rabbit Dermal) Data.

TOX CHEM No.: 896E

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In response to your request to comment on the status of current toxicological issues related to the Special Review of triphenyltin hydroxide (TPTH), Toxicology Branch (TB) has prepared the following summary of outstanding issues for your consideration. In essence, TB believes there is sufficient concern at this time regarding potential developmental toxicity, immunotoxicity and inhalation hazard to warrant continuing TPTH in Special Review status.

cc. Lois Rossi, PM #21, Registration Division (TS-767)
Phil Hundemann, PM Team #21, Registration Division (TS-767)
Robert Zendzian, Toxicology Branch, HED (TS-769)
Roy Sjoblad, Toxicology Branch, HED (TS-769)
Gary Burin, SIS, HED (TS-769)

It is furthermore requested (based on the discussion in the following pages) that additional toxicity studies described in this memo be provided by the registrant as soon as possible. These studies are:

1. Dermal teratology in rabbits.*
2. Additional immunotoxicity studies.**
3. Subchronic inhalation study with rats.**

*SRB should request this study from the registrant as soon as possible. In requesting the registrant to provide this study, the instructions that the protocol should be submitted to TB for review should be included.

**SRB need not make special requests to the registrant to provide these studies. The registrant has already been informed that additional subchronic inhalational toxicity data are required (refer to J. Doherty memo dated August 27, 1987). TB has also recently reviewed protocols for additional immunotoxicity testing (refer to J. Doherty memo dated September 28, 1987) and assumes that the registrant is already preparing to provide the additional immunotoxicity data.

The major issues involving developmental, immuno, inhalational toxicity testing, dermal penetration and determining Margins of Safety (MOS) related to these effects are discussed separately on the following pages. In addition, a list of other data expected from the registrant is included.

ISSUES

1. Developmental Toxicity

A. Overview

The Registration Standard indicated that TPTH may be teratogenic in the rat. Subsequent data submissions by the registrant and the results of the Agency's own study conducted at the RTP facilities have now led TB to conclude that TPTH is not teratogenic to the rat at dose levels which produce significant maternal toxicity. The NOEL for maternal toxicity in the rat was determined to be 1.0 mg/kg/day.

A teratology study was also submitted using the rabbit as the test species (refer to J. Doherty review dated May 26, 1987). The rabbit dams were more sensitive than rat dams to the systemic toxicity effects of TPTH and a NOEL for maternal toxicity was set at 0.1 mg/kg/day with the LEL being 0.3 mg/kg/day (at this level dam body weight gain was decreased). At 0.9 mg/kg/ day, the highest level tested, there were slight but not statistically significant pup weight decreases. The pilot dose range finding study indicated that there were many resorptions at the dose level of 2 mg/kg/day. Thus, the NOEL for resorptions was set at 0.9 mg/kg/day, the highest dose level used in the definitive rabbit teratology study. TB recognizes that TPTH has the potential to cause fetal resorptions at dose levels of 2.0 mg/kg/day and higher via the oral route.

The Registration Standard also indicated that a rat multigeneration reproduction study showed that TPTH may affect testis size (weight) but the study was determined to be INVALID because only a summary report was provided.

The registrant submitted a second multi-generation reproduction study in rats and the NOEL was determined to be 0.25 mg/kg/day (refer to review by J. Doherty dated April 22, 1987). The LEL was set at 0.93 mg/kg/day with effects noted at this level consisting of decreases in liver and spleen weight and decreases in live litter size. At the next higher dose level (2.5 mg/kg/day) decreases in testis, thymus and ovary weights and body weights of both the pups and adults were noted. Thus, it is established that toxic responses to TPTH in developmental toxicity studies are noted at low dose levels (< 1 mg/kg/day) in rats and rabbits.

B. Determining the MOS for Developmental Toxicity

By relating the human dermal exposure estimates for pecan applicators (refer to D. Jaquith memo dated March 11, 1986) to the NOELs for developmental toxicity, Margins of Safety (MOSs) can be calculated. For example, when the NOEL for maternal toxicity from the rabbit teratology study (0.1 mg/kg/day) or the NOEL for maternal and systemic pup effects from the rat reproduction study (0.25 mg/kg/day) is related to the human dermal exposure estimate, the MOS is less than unity (J. Doherty review date pending). These MOS calculations utilized a dermal penetration factor of 34% (see item 4 below).

There are, however, several aspects of these MOS calculations that require further discussion as follows:

The results of oral toxicity studies in test animals were related to human dermal exposure utilizing a dermal penetration factor. This calculation was used because there are no dermal developmental toxicity studies.

TB believes that it would be highly preferable and more accurate, for the purpose of determining the MOS for developmental toxicity to use a NOEL from a dermal teratology study.

One reason for this is that since TPTH is absorbed slowly over time following dermal exposure, the tissue levels of TPTH may not reach the same levels as they would following an oral dose and, in fact, may not even accumulate to the critical levels necessary to cause maternal and/or developmental (resorptions) toxicity. Another reason is that maternal and/or developmental toxicity may possibly result from indirect effects of TPTH (for example gastrointestinal effects of TPTH might prevent absorption of essential nutrients).

In order to further assess the potential hazard of TPTH with regard to developmental toxicity, TB requests that the registrant provide a dermal teratology study with rabbits. Because of the unusual nature of the dermal absorption of TPTH, the protocol for this study should be reviewed by the Agency prior to initiating the study.

2. Immunotoxicity

[Note: Dr. Roy Sjoblad, microbiologist, TB, is coordinating the evaluation of the immunotoxicity data requirements.]

A. Overview

TB does not recognize at this time a NOEL for potential immunotoxic effects of TPTH. The LEL for guinea pigs, based on decreased leucocyte counts, is < 0.1 mg/kg/day (lowest dose tested, LDT). Based on decreases in immunoglobulin levels at all dose levels tested in subchronic feeding studies, the LEL in the rat is < 0.2 mg/kg/day and in the mouse is < 0.57 mg/kg/day.

The registrant has recently submitted protocols for additional immunotoxicity testing which were prepared in response to suggestions made by Dr. Sjoblad. TB has concurred with the procedures to be used in these studies but has also advised the registrant that further immunotoxicity testing may be required if these studies do not satisfy the Agency's concerns or if it is deemed necessary to have additional information for immunotoxicity risk assessment. Refer to review by J. Doherty dated September 28, 1987.

The issue of establishing a NOEL for potential immunotoxicity of TPTH is not resolved and is not expected to be resolved until the additional immunotoxicity testing is completed. TB does not expect these studies to be submitted to the Agency for at least another year. After receipt of these studies, TB will reassess the immunotoxicity issue for purposes of risk assessment.

B. Determining the MOS for Immunotoxicity

A NOEL for immunotoxicity has not been recognized by TB. A dose level of 0.1 mg/kg/day has already been recognized to result in decreased leucocyte counts in a guinea pig feeding study. Data with rats and mice also indicate that the LEL is in the range of 0.1 mg/kg/day. Utilizing these known effect levels to estimate a MOS already results in MOSs of less than unity. It is therefore expected that when a true NOEL level is established for immunotoxicity, the MOS will be less than unity.

An unresolved problem related to risk assessment for the immunotoxic potential of TPTH is that the studies currently designed to determine the NOEL are using rats and mice. Determining the NOEL for these species will not also establish a NOEL for guinea pigs. The reason that rats and mice were selected for these studies is because immunotoxicity assay methods are presently being validated with these species.

TB has no information on potential immunotoxicity resulting from dermal or inhalation exposure. Although additional studies utilizing these routes of exposure may possibly be required in the future, there is at the present time no requirement to submit such studies.

As suggested by Dr. Sjoblad, the overall issue of risk assessment for potential immunotoxicity of TPTH may have to be eventually settled by a Special Peer Review Panel.

3. Inhalation Toxicity

A. Overview

TPTH has an acute inhalation LC_{50} of 60.3 ug/l (Tox. Cat. I). This acute study also revealed that the exposed rats developed signs of lung pathological responses that persisted in the survivors to the study termination (13-14 days).

Subchronic inhalation toxicity studies have also indicated significant toxicity at low dose levels (1.1 ug/l). Neither of the two subchronic inhalation studies submitted thus far was considered to be acceptable, however, by the Agency. A third subchronic inhalation study with TPTH has been requested. Refer to the memo by J. Doherty dated August 27, 1987.

Because of indications of potential inhalation hazard, TB will request Exposure Assessment Branch (EAB) to estimate inhalation exposure to applicators and bystanders for all of the registered uses of TPTH.

B. Determining the MOS for Subchronic Inhalation Toxicity

In the absence of exposure data and a NOEL for inhalation toxicity, a MOS for inhalation exposure cannot be estimated at this time.

4. Dermal Penetration

[Note: Dr. Robert Zendzian, TB, is coordinating the dermal penetration data requirements and review.]

TPTH was found to pose special problems related to dermal penetration. For example, once applied to the skin, TPTH adheres and is slowly absorbed over the course of several days or more. The percentage absorption was determined to depend upon the amount applied. Refer to the memo from R. Zendzian dated May 26, 1987. Based on Dr. Zendzian's review, 34% can be used as the dermal penetration factor.

5. Current list of outstanding toxicity study data and/or information requested to be submitted by the registrant (as of November 2, 1987).

Study type	Reference*
81-6 Dermal sensitization - guinea pigs	October, 1987 (exact date pending).
82-4 Subchronic inhalation - rats	August 27, 1987.
83-1 Chronic feeding and oncogenicity - rats	Registration Standard, see also TB memo dated June 18; 1986.
83-1 Chronic feeding - nonrodent (Study has been reviewed and classified RESERVED pending receipt of additional information.).	October, 1987 (exact date pending).
83-2 Oncogenicity - mouse	Registration Standard, see also TB memo dated June 18, 1986.
83-3 Teratogenicity - rabbit (dermal)	This memo.
84-2 Mutagenicity - human lymphocyte cytogenetic assay.	August 18, 1986.
85-1 General metabolism - studies with ^{113}Sn or ^{119}Sn	August, 1987 (exact date pending).
Special studies - immunotoxicity	Registration Standard, see also TB memo dated September 28, 1987.

*Date of TB memorandum requesting the study.

SUMMARY

Available data utilizing oral developmental toxicity NOELs result in MOSs of less than unity. If dermal developmental toxicity studies were to be related to dermal exposure data, the MOS may be considerably higher. TB is requesting that the registrant provide a dermal rabbit teratology study.

It should be recognized that submission of the dermal teratology study may result in a higher MOS related to developmental toxicity only. There will remain, however, outstanding questions concerning the MOSs related to both immuno- and inhalation toxicity and exposure that the Agency must consider in evaluating the hazards associated with the uses of TPTH.

TB anticipates that when a NOEL is eventually established for immunotoxicity, the resulting MOS may be less than unity. The overall hazard assessment of TPTH is further complicated at this time because of the uncertainty of inhalation hazard due to incomplete information related to inhalation toxicity and exposure.