7-29-92

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

JUL 29 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: EPA ID# 083601. Triphenyltin hydroxide: Review of a proposed rabbit dermal developmental toxicity study[1].

TOX CHEM No.: 896E
PC No.: 083601
Barcode: D180335
Submission No.: S421166

FROM: John Doherty 7/24/92
Section IV, Toxicology Branch I
Health Effects Division (H7509C)

TO: Mike Beringer
Product Manager #61
Special Review and Reregistration Division
(H7508W)

THROUGH: Marion Copley, DVM, Section Head 7/24/92
Section IV, Toxicology Branch I
Health Effects Division (H7509C)

I. CONCLUSION

The registrants may conduct the rabbit dermal developmental toxicity study at their discretion. TB-I cautions that the irritant properties of TPTH may confound the study and the rabbits may require special handling to prevent stress related effects in the dam and on development. TB-I recommends that the pilot dose range finding study should be conducted with pregnant rabbits. Lastly, the results of the pilot dose range finding study should be evaluated to assure that the dose levels for the main study can be used to calculate MOEs significantly different from using the existing oral developmental toxicity data base.

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[1]The dermal penetration protocol submitted with this action will be reviewed by R. Zendzian.

II. ACTION REQUESTED

The registrants of triphenyltin hydroxide (TPTH) have proposed to conduct a dermal developmental toxicity study with rabbits in order that these data can be used to more directly calculate risk assessments and Margins of Exposure (MOEs) for developmental toxicity. The dermal developmental toxicity study is considered by the registrants to be more appropriate for MOE calculations because the dermal route is the exposure pathway of concern to field workers. The registrants believe that the dermal developmental toxicity study will preclude the need to use a theoretical dermal penetration factor to correct for oral/dermal exposure differences. TB-I has reviewed the proposed protocol and the following comments apply.

III. Toxicology Branch Comments

1. **General**

It is the registrant's responsibility to provide a study consistent with current guidelines for a series 83-3 developmental toxicity study. TB-I will comment only on the special aspects of the study related to TPTH.

2. **Special problem of the irritant properties of TPTH**

TPTH is an irritant and this can be expected to compound the study. In general, pregnant rabbits do not react well to handling and the stress of confinement associated with dermal applications (i.e. using Elizabethan collars to prevent oral intake) often leads to abortions and/or other complications. The irritant properties of TPTH will likely further compound the stress on the rabbits and possibly result in a dose related increase in stress related reactions including abortions. The animal handlers should try to acclimate the rabbits to the handling and Elizabethan collars prior to application of the test material.

The irritant properties of TPTH may require that alternate sites of application be used rather than applying the test material to the same specific site each time. Based on the 21 day dermal study in rats (ACC. No.: 258230, review date Aug. 22, 1985, HED Document No.: 4624), dose levels as low as 5 mg/kg/day resulted in significant dermal irritation (erythema, edema, scabbing, atonia, fissuring and/or blanching). The proposed low dose of 1 mg/kg/day for the rabbit study is lower but rabbit skin is thinner and probably more susceptible to irritation.

3. **Dose Range finding study**

The dose range finding study to determine the dose levels should be conducted with pregnant rabbits rather than nonpregnant rabbits because this will help to determine the ability of the pregnant rabbit to tolerate the test material. The dose range finding study should also address the need for including more than the suggested 18 dams per dose level to account for possible loss of pregnant dams due to the irritation caused by TPTH and handling the rabbits.

Upon completion of the dose range finding study, the registrant should assess the dose levels to be used in the main development toxicity study in terms of the existing rabbit developmental toxicity data. It should then be determined if the MOE resulting from direct use of these proposed dose levels (assuming the highest dose level tested will be used for MOE calculations whether or not developmental toxicity is noted at this dose level) will be significantly different from the MOEs obtained by indirect methods from the oral developmental toxicity study currently being used.

Note: The proposed protocol was discussed at a meeting between the registrant and their consultants and TB-I staff and the Special Review Team on Thursday July 23, 1992. The registrant's were advised of the above comments from TB-I. They defended their approach to do the pilot study with non-pregnant rabbits and concurred with TB-I's concerns for the possibility that the irritant effects of TPTH may confound the assay. Although, TB-I still considers that the pilot study with pregnant rabbits would be more meaningful, it is not essential that they use rabbits in this condition. In addition, Robert Zendzian of HED introduced the possibility of conducting the study with a formulation rather than the technical grade of the active ingredient. The registrant, however, expressed their preference for using the technical grade material prior to adjourning the meeting.

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June 24, 1992

Mr. Mike Beringer
Review Manager
Special Review Branch, SRRD
U.S. Environmental Protection Agency
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Dear Mr. Beringer:

I am writing on behalf of the registrants of triphenyltin hydroxide (TPTH), Hoechst Celanese Corporation, Elf ATOCHEM North America, Inc., and Griffin Corporation, to provide the draft protocol outlines for the TPTH rabbit dermal developmental toxicity study and ^{113}Sn-labeled TPTH rat dermal absorption studies that were promised in the TPTH registrants' June 1, 1992, letter to Daniel M. Barolo of EPA. The registrants welcome comments from the Agency regarding the planned studies and any suggested improvements in experimental design. We request a meeting with Agency scientists to discuss the rationale and details of these critical studies.

As discussed in the June 1, 1992, letter, the rabbit dermal developmental toxicity study is intended to provide a dermal no-observed effect level (NOEL) for maternal and developmental effects in rabbits. The dermal route is the most appropriate route of administration for this study because the TPTH exposure pathway of concern is dermal rather than oral. This dermal-study NOEL would replace the NOEL (for maternal effects) from the oral rabbit teratology toxicity study that is currently being used by EPA as the basis for its worker exposure hazard assessment for TPTH. We believe that the new study will preclude the need to use a theoretical dermal penetration factor to correct for the oral/dermal exposure differences. We also believe that the results from a dermal rabbit teratology study, when compared with those of the oral rabbit teratology toxicity study, will provide a better basis for comparing oral and dermal toxicity than would results from the previously proposed 90-day dermal toxicity study because of the clearly defined toxic endpoints in the rabbit oral study.

In addition, we believe that the dermal absorption study will provide useful data to replace some of the assumptions used in the derivation of the dermal penetration factors. As currently used (especially when combined), these assumptions lead to a potentially exaggerated estimate of both dermal penetration and systemic dose resulting from dermal exposures. We plan to develop data that may be used either to validate or to refute these assumptions.

Hoechst

We have reviewed Dr. Robert Zendzian's case study, dated October 11, 1991, titled "Triphenyltin Hydroxide, Determination of a Systemic Dose Following Oral or Dermal Dosing, Comparison Factors for an Oral NOEL and a Dermal Exposure." We found this study to be useful and appreciate EPA's providing us an opportunity to review it. In this study Dr. Zendzian examines the oral metabolism and dermal absorption studies with TPTH to derive the dermal penetration factors. Dr. Zendzian interprets the studies as follows:

> The first study with ^{14}C-labeled TPTH used a single-day (10-hour) exposure with doses of 0.1, 1.0, and 10 mg/kg/body weight (applied doses of 0.0008, 0.009, or 0.121 mg/cm^3). Absorption in this study (including material retained on the skin) was 37, 34, or 38 percent of the dose, respectively (measured as ^{14}C-radioactivity). However, the majority of the ^{14}C-labeled material was retained on the skin.
>
> To examine the disposition of the material on the skin, a second dermal absorption study was done using a single-day, 10-hour exposure followed by sampling for 21 days. The doses in this study were identical to those in the first study in terms of mg/kg body weight, but the surface area covered was smaller, so the doses (on a mg/cm^3 basis) were 0.002, 0.026, or 0.240 mg/cm^3. The corresponding maximum systemic absorptions (not including the relatively small percentage retained on the washed skin) over time were 34, 16, or 16 percent of the administered dose, respectively (measured as ^{14}C-radioactivity).
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> Dr. Zendzian used data from the oral metabolism studies to estimate rates of excretion and concluded that the rate of excretion was roughly comparable to the rate of absorption (penetration through the skin). He also concluded that the maximum systemic concentrations were 3.2, 3.2, and 2.6 percent of the administered dose. However, there was an incomplete recovery of label in this study, and factoring in the missing material as presumably systemically absorbed led to a worst-case assumption that 50 percent of the total dose was systemically absorbed and that the maximum systemic concentration (taking absorption and excretion into consideration) was 11 percent of the applied dose. In addition, assuming that there would be identical maximal systemic absorption following repeat administration of material led to a projected systemic concentration of 27 percent of the applied dose following a multiple dermal application.
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> The following major assumptions were made by EPA to reach the foregoing conclusions.
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> 1. Any residue of TPTH on skin that cannot be washed off will be absorbed dermally.
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> 2. The dermally absorbed chemical contains tin, which involves the following assumptions:
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>   - significant metabolism does not occur in the skin;
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>   - the ^{14}C label in the feces found in dermal studies is organotin material; and

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- urinary excretion of the ^{14}C label represents dermally absorbed organotin;

3. "Missing" material that was not recovered or otherwise accounted for is systemically absorbed organotin material.

4. Complete absorption results from each repeated dermal exposure because the receptors in the skin do not have a saturation point.

5. Metabolism and pharmacokinetics would follow the same pattern after dermal exposure as after oral exposure, so the $T_{1/2}$ excretion (determined from the oral metabolism study to be 60 hours) would also apply for dermal exposures.

It is our opinion that these assumptions, particularly when combined, lead to a potentially exaggerated estimate of both dermal penetration and systemic dose resulting from dermal exposures. The proposed dermal absorption study with ^{113}Sn will provide data either to be used in place of or to confirm the above assumptions, with the exception of number 4, which would necessitate a repeated dose study. Depending on the results of the single-exposure dermal absorption study that is described in detail in the enclosed outline, we will examine the feasibility of performing additional studies, particularly to address point 4. It should be noted that we have identified only two laboratories with the capabilities for undertaking this study using the labeled tin isotope.

The TPTH registrants believe that the data provided from both of the planned studies will provide a better basis for derivation of dermal penetration factors. As noted earlier, the registrants welcome comments from the Agency regarding these studies and any suggested improvements in experimental design.

Please do not hesitate to contact me if you have any questions or concerns.

Sincerely,

Bert Volger /PN (JSC, Inc.)

Berthold Volger, Ph.D.

Enclosures

cc: John Doherty, EPA
Robert Zendzian, EPA
Karl Baetcke, EPA
Jack Skwara, ATOCHEM
Vern White, Griffin

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