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

JAN 20 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Registration No. 8340-17 - Triphenyltin Hydroxide - Review of Protocols for Dermal Absorption (Extended Duration) and Placental Transfer With ^{14}C Triphenyltin Hydroxide.

TOX Chem No. 896E
TOX Project No. 2225
Record No. 178059

FROM: John Doherty 11/18/86
Toxicology Branch
Hazard Evaluation Division (TS-769C)

TO: Henry M. Jacoby, PM 21
Fungicide-Herbicide Branch
Registration Division (TS-767C)

THRU: Edwin Budd, Section Head
Toxicology Branch
Hazard Evaluation Division (TS-769C) 12/19/86 1/15/87

The American Hoechst Corporation (Somerville, New Jersey) has submitted protocols for proposed studies for determining the dermal penetration and the placental transfer of triphenyltin hydroxide (TPTH) radiolabeled with ^{14}C.

Toxicology Branch (TB) has reviewed these protocols and has the following comments. (Note: Copies of the protocols are attached.)

Dermal Absorption Study

This study is entitled "An extended duration dermal absorption study in rats with ^{14}C triphenyltin hydroxide." The study protocol was prepared by the Wil Research Laboratories, Inc., Ashland, Ohio and is Study No. Wil-39033 dated July 18, 1986.

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Review of this protocol was deferred to Dr. Robert Zendzian of TB. A copy of the referral memorandum together with his comments are also attached. Dr Zendzian has had telephone communications with Dr. Ed Carmines of the American Hoechst Corp. and discussed this protocol. Dr. Zendzian concurs that the protocol is appropriate with the modifications such as recovering the application sites after 10 hours (comment on Dr. Zendzian's memorandum).

Placental Transfer Study

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Important Note to Product Manager: TB has no record of requesting that this study be provided. Before the registrant is advised by EPA to conduct this study, the original justification for requesting this study should be rereviewed.

The following comments on the protocol are provided for the registrant's consideration should they eventually proceed and conduct this study.

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This study is entitled "A placental transfer study in rats with ^{14}C-triphenyltin hydroxide." The study protocol was prepared by the Wil Research Laboratories, Inc., Ashland, Ohio and is Study No. Wil-39032 dated July 18, 1986.

This study has two objectives, first to determine if TPTH enters the embryo via the placenta and the second is to determine if TPTH accumulates in the embryo during organogenesis if it does cross the placenta. To accomplish these objectives pregnant rats will be dosed with either of three dose levels of ^{14}C labeled TPTH as single doses on day 15 of gestation or as multiple doses on days 6 through 15 of gestation. All dams will be sacrificed 8 hours after the last dose or their single dose on day 15.

TB has the following comments on this study:

1. In general, the study itself appears to be well designed in terms of selection of the test strain of rat (Wistar which was also used in teratology studies), dosing route (oral, but see item 2 below)), dose levels (0, 1, 2.8, and 8.0 mg/kg), and number of rats per testing group.

2. Because of the poor gastrointestinal absorption of TPTH, the registrants should consider dosing at least

one or more extra groups intravenously (with at least a single dose and daily doses if possible) and proceding to assess for placental transfer.

3. The final report of this study must include a section on characterization of the radiolabelled material (if any) in the embryos or that which crosses the placenta. Such characterization should include at least determining if the metabolites contain tin.
In this regard it would be desirable to do the placental transfer study with ^{113}Sn TPTH if possible.

4. The protocol does not state how the various tissue samples will be assessed for radioactivity. Will the solid tissues such as the uterus, placenta, and fetuses be combusted and the ^{14}C trapped? If so, will this method be appropriate for TPTH? For example, have there been experiments demonstrating that ^{14}C TPTH is combusted to $^{14}CO_2$ so that it can be trapped, and what is the efficiency of detecting ^{14}C derived from TPTH by this method?

5. The protocol does not include provisions for accounting for the total dose of radioactivity applied. TB recommends that for at least two rats per dose group the urine, feces, and GI tract contents be quantitated for radioactivity. For example, the study should show what percentage was absorbed from the GI tract.

6. The 8-hour period between the dosing and sacrifice may not be sufficient time to assess for possible placental transfer following a single dose due to the slow rate of gastrointestinal absorption. TB suggests that information on the absorption and distribution of TPTH in rats be reviewed and in the final report of the study the basis for selecting 8 hours (or other time interval) be included.

7. It is unclear as to what the vehicle will be. On page 3 it is stated that the vehicle will be water On page 6 reference is made to corn oil (Mazola Oil) being the "control material." Because of the poor water solubility of TPTH, the test material might best be applied in small volumes of corn oil. (Note: The volume of administration in ml/kg was not provided.)

8. Dams dying or sacrificed in extremis and fetuses from abortions or premature deliveries should be assessed for placental transfer and embryo accumulation of radioactivity derived from the labelled TPTH.

9. Page 8, item 7 (sampling and analyses) is unclear. Does the statement "items 3, 4, 5, 6 will be pooled for each dam" mean that all such tissues or fetuses from each of the six dams will be put into a common pool for each dose level? If this is true, why is it necessary? Without additional explanation, this step does not seem to be a good practice. If it is not true, how does one go about pooling the placenta from a single dam.

10. The study should include assessments for radioactivity in the dams for at least the following: liver, kidney, brain, and fat for at least the high dose group dams.

Attachments:

Attachment

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INTRABRANCH MEMORANDUM

SUBJECT: Triphenyltin hydroxide: Request to review protocol for a special dermal absorption study with labelled (^{14}C) test material.

TOX PROJECT No. 2225
TOX CHEM No. 896E
Record No. 178058

FROM: John Doherty John Doherty 8/28/86
Toxicology Branch
Hazard Evaluation Division (TS-769)

TO: Robert Zendzian
Toxicology Branch
Hazard Evaluation Division (TS-769)

THRU: Edwin Budd Budd 8/28/86
Section Head
Toxicoogy Branch
Hazard Evaluation Division (TS-769)

Attached is a protocol entitled "An extended duration dermal absorption study in rats with ^{14}C-triphenyltin hydroxide" (Study No. WIL-39033, from the WIL Research Laboratories, Inc., Ashland Ohio).

Please review this protocol for appropriateness in defining the dermal absorption of triphenyltin hydroxide. In particular, please try to ascertain if the study as designed will give data useful in determining a dermal penetration factor for use in risk assesments with TPTH.

Please note that for purposes of logging TECH hours this is TOX Branch Project No. 2225.

Note: The due date for this action is 10/20/86.

Protocol OK
1 - 21 day groups application site should be re-covered after 10 hrs. [illegible]
[illegible] 8/29/86

TPTH toxicology review

Page _____ is not included in this copy.

Pages 6 through 27 are not included in this copy.

The material not included contains the following type of information:

___ Identity of product inert ingredients

___ Identity of product impurities

___ Description of the product manufacturing process

___ Description of product quality control procedures

___ Identity of the source of product ingredients

___ Sales or other commercial/financial information

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