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

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11/6/84

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Petition No. 3F2823: Registrant's responses to previous reviews by TB. Review of responses concerning the embryotoxicity, immunotoxicity and reproduction studies with triphenyltin hydroxide.
Tox. Chem No. 896E
Accession No. 072734

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THRU: Edwin R. Budd, Section Head
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Budd 11/6/84

BACKGROUND: American Hoechst Co. has requested establishment of tolerances for triphenyltin hydroxide (TPTH) on soybean seed and soapstock. Previous reviews of TPTH by Toxicology Branch (TB) (see J. Doherty reviews dated: 7/25/80, 4/28/82, 8/11/83) have indicated several types of toxicity potential caused by TPTH and also indicated deficiencies in the studies used to support registrations and tolerances for TPTH.

The current action contains the registrant's responses submitted in attempt to partially satisfy the deficiencies in the toxicity data indicated by TB (see memorandum by J. Doherty, 8/11/83). These responses are evaluated below.

RECOMMENDATION: TB feels that the toxicologic data does not scientifically support the requested tolerances for TPTH at this time.

REGISTRANTS RESPONSES:

1. Embryotoxicity in rats

Initial concern of TB: TPTH may be a teratogen because of the presence of hydronephrosis (HN) and hydroureter (HU) in the fetuses.
Registrant's Response: The company has submitted historical data by study/date for years 1970-1983 from the laboratory of Pharma Research

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Toxicology at HOECHST AG in Frankfurt. There is some variability in the occurance of HN and HU in the control rats.

The registrant described in brief, the methods, results and summary of the study performed by Battelle Labs as well as from an earlier teratology study performed by Cannon Lab. (1976). The summary of the Cannon study concluded that: 1) HN and hydrocephalus (HC) were due to delayed development and 2) a NOEL was not established. The summary of the Battelle study stated that fetal and maternal toxicity were present only in the high dose group (8.0 mg/kg). The only significant fetal soft tissue lesion was HU, also present only at 8.0 mg/kg. The company felt that the 1.0 and 2.8 mg/kg (low and mid dose) groups were similar to controls and that hydroureter was indicative of maternal toxicity rather than a teratogenic effect of TPTH. Individual fetus and litter data for HU and HN were also included in this action.

A letter from Battelle's principal research scientist indicated that after review of the data, HN and HU were not associated with: 1) time of sacrifice, 2) weight of fetuses, 3) uterine location, 4) fetal age or development. She concluded with, "Unfortunately these results leave us without a clearer understanding of the mechanism of induction of HU/HN."

TB comments and conclusions: There have been two teratology studies. There was a strong dose response for both HC and HN with no NOEL in the first study (by Cannon, 1976). This indicated that TPTH may have teratogenic potential.

Dose (mg/kg/day)	number of fetuses exam.	% of fetuses with: HC	HN
0	94	1	2
1.25	75	20	7
5.00	73	11	16
8.75	47	15	34
12.5	20	30	30

Both lesions may be either: 1) due to delayed development (as the registrant states) or 2) teratogenic effects. The latter is more likely however, because maternal toxicity occured only at the two highest doses while fetal lesions occured at all treatment levels. The only method for distinguishing between the two mechanisms would be special teratology studies including postnatal examination.

The enclosed historical data is not from the laboratory that performed the second study (Battelle Columbus Laboratory, Columbus, Ohio) therefore it is of limited value for determining whether the occurance of HU at the mid and low doses is relevant. To be useful the data needs to be from Battelle Columbus Labs. In the absence of appropriate historical controls, TB has compared the treatment values to the study controls. The high, mid and low dose frequencies of HU indicate a biologically relevant teratogenic effect. HN occurs only with HU except in 1 fetus in the control and 1 at 2.8 mg/kg/day. HU and HN ranged from mild to severe with most of the lesions graded as moderate. There was no dose related change in severity for either lesion.

Dose (mg/kg/day)	number of fetuses exam.	% of fetuses with: HU	HN	HU &/or HN*
0	131	.7	1.4	1.4
1	118	6.0	5.0	6
2.8	123	6.5	2.0	7
8	96	12.5	4.0	12.5

* fetuses were counted only once

The conclusions are:

1) HU is a teratogenic effect in the second study. HN and HC may be teratogenic effects in the first study.
2) Further studies are needed to determine an NOEL for all three lesions (see details in conclusion # 9).
3) TB is concerned by the presence of HC in the first study but not in the second. The registrant should give a possible explaination for this discrepency. What was the grading system for HC (or dilated ventricals) in both studies?
4) A related Triphenyltin compound (triphenyltin acetate) resulted in HU ("Effects of Triphenyltin Acetate on Pregnancy in the Rat", by E. Giavini, M. Prate and C. Vismara; Bull. of Environ. Contamin. and Tox., 24: 936-939, 1980).
5) TB is also concerned by a dose related increase of HN in the first study not present in the second study. HU appears to be the lesion of concern in the second study. The company should submit a detailed definition, description and grading system (including diagrams if necessary) of the terms HN and HU as used by both contract laboratories.
6) Were the fetuses examined for HU at Cannon and was it observed in the study?
7) TB needs the individual fetus and litter data, including all malformations, variations and notes for Battelle's rat the Syrian Golden Hamster teratology studies. Please include the number of fetuses and litters affected with HN and HC and fetuses and litters examined.
8) TB understands that Cannon Labs. is now out of business, however, TB still needs historical data from both Cannon Labs. (1972-1977) and Battelle Columbus Labs. (1977-1982) for HC, HU and HN, listed by study, with data by fetus and litter (number of affected and number examined) for the same strain and vehical used in their respective TPTH teratology studies.
9) In view of the previous 8 conclusions, TB strongly recommends that an additional rat teratology study by gavage, be performed. The study should include: 1. Twice the number of dams used for a usual teratology study: 2. levels lower than those previously used to determine a NOEL; 3. levels to confirm prior test results; 4. a postnatal examination of half of the fetuses (they should be allowed to survive for at least 21 days - weaning). Although special attention should be given to HC, HU and HN, the examination should not be limited to these parameters. This study will aid in determining the teratogenic NOEL and whether the lesions are due to toxicity as the registrant suggests. TB would be agreeable to review a protocol for this special study prior to study initiation if requested by the registrant.

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2. Reproduction study

Initial concern of TB: The reproduction study was only a pilot and therefore classified as core-supplementary. No acceptable reproduction study has been submitted.

Registrant's response: The registrant feels that this study, although a pilot reproduction study should be "... interpreted as a three-month study also....", since it was designed to answer questions raised in a previous 90 day-rat feeding study. A complete blood count, selected organ weights and histopathology (control and high dose) were performed on the adults. No treatment related changes were reported in organ weights and histopathology; white blood cell changes were observed only in the high dose females.

TB comments and conclusions: The previous review of this study (see review by J. Doherty, 7/22/83) adequately addressed the additional information. This study, if reviewed as a 90-day study would also be classified as core-supplementary due to the lack of urinalysis and clinical biochemistry data. The previous review also stated that all rats were sacrificed after parturition rather than at 90 days. An acceptable reproductive study and 90 day rat feeding study still need to be submitted. If the reproduction study is in progress, TB strongly recommends that in addition to routine procedures, special attention be paid to ureteral and renal conformation at the time of sacrifice of the offspring.

3. Immunotoxicity

Initial concern of TB: TB determined that two of the studies submitted to assess the immunotoxicity of TPTH did not adequately assess the problem.

Registrant's response to study 1 - rat study: The 2.5 mg/kg/day dose "represents an extreme safety margin to the maximal expected applicator exposure level.

TB comments and conclusions to study 1 - rat study: While the study indicates a large margin of safety it does not answer the original reviewer's question - "Can TPTH affect the thymus?" Although the study does provide useful information, levels that show some other form of toxicity should be used.

Registrant's Response to study 2 - mouse study: The method was that used by the National Toxicology Program (NTP). A review of the data indicates that the effects produced were not dose related and of no toxicological significance.

A letter from Al Munson, PhD, Quintox, Inc., concluded that:

1) Spleen weight and spleen cell number were erratic due to proliferation and the effect of TPTH on a proliferating system should be studied separately. The lowest effect level (LEL) with respect to the antibody forming cell (AFC) response in the spleen was 10 mg/kg.

2) There is not enough data about the mitogen response to support TB's statement that the immune system (as it relates to mitogenesis) does not always follow a dose response. Five chemicals evaluated for the NTP support the dose response pattern.

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3) Leukocyte counts, although lower than controls, did not evidence a dose response. Interpretation of this decrease should be withheld until other toxicological studies with TPTH are reviewed and confirm an effect on peripheral white blood cells.

TB comments and conclusions to study 2 - mouse study: TB cannot agree with the registrant's claim that the effects produced were of no toxicological significance. TB does agree with Dr. Munson's conclusions that: 1) the LEL for AFC response is 10 mg/kg; 2) the mitogen data may not indicate a treatment related response; 3) the leukocyte depression, when considered without data from other studies is inconclusive. It should be noted that a leucocyte depression was noted in the high dose (200 ppm) females in the pilot reproduction study (Wistar rats) (see J. Doherty review, 8/11/83) characterized by a marked relative and absolute neutropenia and mild lymphopenia. The NOEL for immunotoxicity, as measured by the AFC response would be 5 mg/kg.

COMMENTS:

1. The following is a list of studies noted as data gaps in the TB chapter of the Registration Standard for triphenyltin hydroxide:

° Mouse oncogenicity study - The TB needs the additional data requested (see memorandum by J. Doherty, 8/11/83) concerning the uterine lesions.

° Rat oncogenicity study

° Rat teratology study by gavage with a "post natal phase" - TPTH is considered a teratogen (hydroureter and possibly for hydronephrosis and hydrocephalus). A NOEL has not been established. Additional historical control data and further studies are necessary to clarify the NOEL for TPTH (see the conclusions in part 1 of this memorandum - embryotoxicity in rats).

° Rabbit teratology study by gavage

° Dermal teratology study - requirement is contingent upon results of the previous two teratology studies.

° Immunotoxicity -
   a. TB has determined that the rat study submitted to assess the immunotoxicity of TPTH still does not adequately address the question.
   b. TB has determined that the NOEL for the mouse study is 5 mg/kg for the AFC response.
   c. The registrant is strongly encouraged to discuss their protocol(s) with TB prior to performing the study(ies).

° Reproduction study

° 90 day rat feeding study

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- 90 day dog feeding study
- 90 day inhalation study - TB is still waiting for the complete histopathology report (see memorandum by J. Doherty, 8/11/83).
- Chronic dog feeding study
- Chronic rat feeding study
- Sensitization study - Guinea pig
- General metabolism
- Mutagenesis studies
  a. Chromosome aberration study
  b. Other genotoxic effects (ie. dominant lethal)
- Dermal absorption study
- The Exposure Assessment Branch will indicate which studies will be required in order to accurately estimate applicator exposure (dermal and inhalation).

2. There is no study available which TB accepts as appropriate for setting the ADI (see memorandum by J. Doherty, 3/21/84).