CASWELL FILE

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

005917

MAY 28 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Reg. No. 8340-17. Triphenyltin hydroxide: Review of pilot and definitive rabbit teratology studies.

TOX CHEM No.: 896E
TOX PROJECT No.: 7-0564
Record No.: 192657

FROM: John Doherty 5/22/87
Toxicology Branch
Hazard Evaluation Division (TS-769)

TO: Lois Rossi
Product Manager #21
Registration Division (TS-767)

THRU: Edwin Budd
Section Head
Toxicology Branch
Hazard Evaluation Division (TS-769) Budd 5/27/87 5/28/87

The American Hoechst Corporation has submitted rabbit teratology studies (a pilot and a definitive study) with the fungicide triphenyltin hydroxide (TPTH) in order to fulfill the data requirements as indicated in the Registration Standard for this chemical. The studies were reviewed by Toxicology Branch (TB) and the following comments apply.

1. The NOEL for potential teratogenic effects was established as being 0.9 mg/kg/day in the rabbit. Higher dose levels, such as > 1 mg/kg/day are toxic to the dams and result in decreased fetus size and resorptions as indicated by the pilot study. Total resorptions were noted at 4 mg/kg/day.

   A LEL for resorptions was assigned by TB as 2 mg/kg/day.

40104801

2. TPTH was not demonstrated to be teratogenic in this species. Although TPTH was suspected as possibly inducing cleft palate based on the results of a study with another organotin compound, no indications of TPTH induced increases in cleft palate were evident in this study.

3. The data requirement for a rabbit teratology study is considered to be fulfilled.

4. The low dose levels for maternal toxicity (NOEL of 0.1 mg/kg/day and LEL of 0.3 mg/kg/day) and for potential to induce resorptions (NOEL of 0.9 mg/kg/day and LEL of 2.0 mg/kg/day) must be taken into consideration in assessing the overall toxicity and potential hazards resulting from the use of TPTH.

2

STUDIES REVIEWED

Study	Result	CORE Classification
Teratology - rabbits (Pilot study)	Maternal Toxicity: NOEL ≥ 0.1 mg/kg/day (est.) LEL = 1.0 mg/kg/day, body weight decreases (<10%); at 2.0 mg/kg/day body weight decreases (>10%), resorptions (most dams), severe pup weight decreases; at 4.0, 6.0 and 8.0 mg/kg/day total resorptions and at the two highest levels deaths. Fetotoxicity: NOEL ≥ 1.0 mg/kg/day LEL = 2.0 mg/kg/day, decreased pup weight, resorptions, pup deaths. Teratogenicity: Not fully evaluated.	SUPPLEMENTARY
Teratology - rabbits (Definitive study)	Maternal Toxicity: NOEL = 0.1 mg/kg/day LEL = 0.3 mg/kg/day, body weight gain decreases. Fetotoxicity: NOEL ≥ 0.9 mg/kg/day (HDT) slight but not statistically significant pup weight decrease at this level. Teratogenicity: NOEL ≥ 0.9 mg/kg/day (HDT).	GUIDLEINES

005917

Reviewed By: J.D. Doherty John Doherty 5/22/87
Section II, Toxicology Branch (TS-769C)
Secondary Reviewer: E.R. Budd
Section II, Toxicology Branch (TS-769C)

DATA EVALUATION REPORT

Study Type: Teratology - Rabbit (Pilot) TOX Chem. No.: 896E

Accession Number: 401048-01 MRID No.: N/A

Test Material: Triphenyltin Hydroxide

Synonyms: TPTH, fentinhydroxid

Study Number(s): WIL-39031

Sponsor: American Hoechst Corporation

Testing Facility: Wil Research Laboratories

Title of Report: A Range-Finding Embryotoxicity Study in Rabbits With Triphenyltin Hydroxide

Author(s): Rodwell, D.E.

Report Issued: February 27, 1987

Conclusions:

Maternal Toxicity:
NOEL > 0.1 mg/kg/day (estimated)
LEL = 1.0 mg/kg/day, body weight decreses (< 10%);
at 2.0 mg/kg/day, body weight decreases (> 10%), resorptions (most dams), severve pup weight decreases;
at 4.0, 6.0 and 8.0 mg/kg - total resorptions and deaths.

Fetotoxicity:
NOEL = 1.0 mg/kg/day
LEL = 2.0 mg/kg/day, decreased pup weight, resorptions, pup deaths.

Teratogenic:
Not fully evaluated.

Classification: Core-Supplementary

Special Review Criteria (40 CFR 154.7): N/A

REVIEW

This study was designed as a pilot study in order to provide information useful in selecting the dosage levels for the definitive teratogenicity study in this species.

The basic experiment consisted of six groups of six female New Zealand White rabbits which were scheduled to be dosed at either 0, 1.0, 2.0, 4.0, 6.0, or 8.0 mg/kg TPTH per day. Subsequently, a seventh group of six rabbits were dosed with 0.1 mg/kg/day. The test material was dissolved in 1% aqueous carboxymethylcellulose and was administered to the rabbits on days 6 to 18 of gestation (13 consecutive daily doses) via stomach tube. On day 29 of gestation the surviving females were scheduled for sacrifice via an intravenous injection of T-61® Euthanasia solution).

Results:

1. Maternal Effects

All of the does receiving 8.0 mg/kg and three of the six receiving 6 mg/kg/day died as a result of treatment with TPTH (deaths were noted on days 11 to 24 of gestation). Five abortions were reported, but there was no dose relationship noted between incidences of abortion and dosage. There were 5, 5, 4, 5, 3, 0, and 6 does available which delivered and were examined at day 29 for the control, 1.0, 2.0, 4.0, 6.0, 8.0, and 0.1 mg/kg/day dose groups.

There were a variety of behavioral and/or clinical signs reported in the treated does. The more noticeable signs were lethargy, emaciation respiratory rales, decreased defecation (all dose levels, but apparently a lesser effect in the 0.1 mg/kg dose group), decreased urination, and red excreta.

Body Weight

Mean body weight of the dams was decreased (-6%) in the group receiving 1.0 mg/kg/day and progressively larger decreases in body weight were noted with increases in dose level. At day 18 (last day of treatment with TPTH), the mean body weight of the dams in the group receiving 0.1 mg/kg/day was equivalent to the control group but at day 29 the mean body weight for this group was 5% less than the control.

Cesarian Section Data

There were no viable fetuses in the groups receivng 4.0, 6.0, or 8.0 mg/kg/day. The dams in the high-dose group died

and in the 4.0 and 6.0 mg/kg/day groups had total resorptions. Only one female in the group receiving 2.0 mg/kg/day had viable fetuses, but the body weight of these fetuses was severely decreased. The other gravid females in this group had total (early) resorptions.

There were no definite effects on the postimplantation data for either the groups receiving 1.0 or 0.1 mg/kg/day but evaluation of these parameters was confounded because of the variation of the control group relative to the historical control data available. For example, mean implantation loss in the control group was high relative to the historical control data. Also, mean litter size was small for the control group when compared to the test group receiving 0.1 and 1.0 mg/kg/day, giving the appearance of reduced mean litter weight in the test groups.

2. Teratogenic Evaluation

(Limited to visual external examination only.) Only three fetuses were reported as having visible malformations. Two fetuses in the group receiving 1.0 mg/kg/day were reported as having omphalocele. A control group fetus was reported as having micrognathia and hydrocephaly. No incidences of cleft palate were evident.

3. Necropsy

[Limited report provided.] Necropsy of the nine rabbits which died as a result of TPTH treatment revealed that deaths were due to "overt toxicity." This term is too nonspecific to be helpful to TB in assessing how TPTH caused the deaths of the rabbits.

Conclusion:

This study is SUPPLEMENTARY. The study provides useful range-finding information important in selecting the dose levels for the definitive teratology study in this species. A conclusion made by the the testing laboratory was that a dose level of 1.0 mg/kg/day "would be excessive" for a definitive embryotoxicity study in rabbits apparently based on the decreases in body weight of the dams at this level.

TB notes that the definitive embryotoxicity study should carefully check for the presence of omphalocele.

005917

Reviewed By: J.D. Doherty John Doherty 5/22/87
Section II, Toxicology Branch (TS-769C)
Secondary Reviewer: E.R. Budd
Section II, Toxicology Branch (TS-769C)

DATA EVALUATION REPORT

Study Type: Teratology - Rabbit TOX Chem. No.: 896E

Accession Number: 401048-01 MRID No.: N/A

Test Material: Triphenyltin Hydroxide

Synonyms: TPTH, fentinhydroxid

Study Number(s): WIL-39012

Sponsor: American Hoechst Corporation

Testing Facility: WIL Research Laboratories

Title of Report: An Embryotoxicity Study in Rabbits With Triphenyltin Hydroxide

Author(s): Rodwell, D.E.

Report Issued: February 27, 1987

Conclusions:

Maternal Toxicity:
NOEL = 0.1 mg/kg/day
LEL = 0.3 mg/kg/day, body weight gain decrease.

Fetotoxicity:
NOEL $\geq$ 0.9 mg/kg/day (HDT), slight but not statisticaly significant body weight decrease at this level.

Teratogenic:

NOEL $\geq$ 0.9 mg/kg/day (HDT).

Classification: Core-GUIDELINES

Special Review Criteria (40 CFR 154.7): N/A

REVIEW

Basic Protocol:

Four groups of New Zealand White rabbits were impregnated artificially using semen extracted from mature males. The semen from one male was used to inseminate two females. Apparently by error, the semen from one male was used to inseminate four females in the group dosed with 0.9 mg/kg/day of TPTH. Each of the four groups consisted of 22 females. Immediately after deposition of the semen in the anterior region of the vagina, each female was dosed with an intravenous injection of human chorionic gonadotropin to ensure ovulation.

The four dosed groups consisted of a control group dosed with 1% aqueous carboxymethylcellulose and three treatment groups receiving either 0.1, 0.3, and 0.9 mg/kg/day of TPTH in 1% aqueous carboxymethylcellulose. No positive control group was included. The rabbits were dosed by gastric intubation on days 6 through day 18 of gestation and received 13 doses. On day 29 of gestation the rabbits were sacrificed by intravenous injection of T-61® Euthanasia solution and their uterine contents examined.

Teratologic Evaluation consisted of a detailed external examination of each fetus. Each fetus was then sexed internally and examined viscerally by a modification of the procedure developed by Staples which included the heart and major blood vessels. The fetuses were then skinned and fixed in 95% isopropyl alcohol for eventual skeletal examination.

Results:

1. Effects in the Dams (Maternal Toxicity)

Body weight was reported to be decreased in both the mid (0.3) and high (0.9 mg/kg/day) dose groups. The mid-dose group did not reach statistical significance when data for various intervals (i.e., predosing, during dosing and postdosing) but when the 0 to 29 day weight gain was compared with the control group it was 59 percent lower and statistically significant. The high-dose group was 73 percent lower and also statistically significant. The weight gain decrease for the high-dose group was largest during the dosing period and after this period the dams in the high-dose group actually gained more weight than the controls.

Food consumption decrements paralleled the body weight changes. The study reports that "reduced defecation" was also evident in the mid- and high-dose groups and was apparently related to the decreased food consumption.

8

There were four abortions. Two in the high-dose group (on days 23 and 27), low-dose group (day 26) and control group (day 29). The study report states that the abortions in the high-dose group "may be due to test article related maternal toxicity." Such a conclusion is not necessarily justified based on the data provided. For example, the abortions in this group occurred after test article administration and when the rabbits were regaining their lost weight.

Necropsy of the dams revealed that a single dam in the high-dose group had "dark red areas" in the stomach. A similar finding was noted in a single dam in the pilot study.

On gestation day 29 the dams were examined for sex of the pups, viable fetuses, dead fetuses, early and late resorptions, postimplantation loss, implantation sites, corpora lutea, pre-implantation loss, fetal weight, and for number of gravid females. There were 121, 132, 161, and 130 viable fetuses for the control, low-, mid-, and high-dose groups. There were no dead fetuses. Mean fetal weight for the high-dose group was slightly lower (-11%) than the controls and the report maintained that this decrease in weight gain was related to the decrease in weight gain in the dams. This 11 percent decrease was not statistically significant and the weight of the pups in this group was within the historical control limits. The data for early resorptions and postimplantation loss for the high-dose group appeared to indicate more incidences than the controls, no test chemical effect was evident, and the low- and mid-dose groups were also higher than the controls but not in a dose related manner.

The NOEL for maternal toxicity is 0.1 mg/kg/day. At the LEL (0.3 mg/kg/day) there is body weight decrease.

2. Teratologic Evaluation (Fetotoxicity and Teratogenic Effects)

There were 1, 6, 3, and 4 rabbit pups delivered with malformations in the control, low-, mid-, and high-dose test groups. The malformation frequency was within the range of historical control for this strain of rabbit (based on appended historical control data). Skeletal findings included that there were six incidences of "hyoid body and/or arches unossified" in the high-dose group but not in the control and one each in the low- and mid-dose groups. The laboratory implies that this anomaly results from the decreased body weight gain in the dams.

No incidences of cleft palate were reported. Note: TPTH was considered as a chemical that might induce cleft palate because another organotin chemical was found to be associated with increased incidence of this anomaly in rats.

There were also no incidences of omphalocele reported in this study. The pilot study indicated the possibility of treatment related increases in this anomaly.

The NOEL for fetotoxic and teratogenic effects is $\geq$ 0.9 mg/kg/day (HDT).

Conclusion:

This study is CORE-GUIDELINES. The following one liner applies.

Maternal Toxicity:
NOEL = 0.1 mg/kg/day
LEL = 0.3 mg/kg/day, body weight gain decreases.

Fetotoxicity:
NOEL $\geq$ 0.9 mg/kg/day (HDT), slight but statistically significant body weight decrease at this level

Teratogenic:
NOEL $\geq$ 0.9 mg/kg/day (HDT).