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

JAN _9 1991

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Peer Review of Triphenyltin Hydroxide (TPTH), Tox. Chemical No. 896E

FROM: Victor Miller, V.M.
Peer Review Committee
Reproductive and Developmental Toxicity
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

TO: Louis Kerestesy, Review Manager
Special Review Branch (H7508C)
Special Review and Reregistration Division

and

Eric Ferris, Review Manager
Reregistration Branch (H7508C)
Special Review and Reregistration Division

and

Susan Lewis, Product Manager (Team 21)
Registration Division (H7505C)

The Peer Review Committee for Reproductive and Developmental Toxicity met to discuss the potential developmental toxicity of TPTH on July 12, 1990. The Committee concluded that TPTH is a developmental toxicant in rats, rabbits and hamsters with the lowest NOEL's in the rabbit at 0.1 mg/kg/day for maternal toxicity and 0.3 mg/kg/day for developmental toxicity. The lowest LEL's for developmental and maternal toxicity were also in the rabbit (0.9 and 0.3 mg/kg/day, respectively).

A. Individuals in Attendance:

1. Peer Review Committee: (Signatures indicates concurrence with the peer review unless otherwise stated.)

William L. Burnam

Reto Engler

Thomas F.X. Collins

Marcia van Gemert — Marcia van Gemert 12/4/90

Carole Kimmel — Carole A. Kimmel 12/17/90

Stephen Dapson — Stephen C. Dapson 12/4/90

Jim Rowe — Jim Rowe 11/30/90

Lawrence Chitlik — Lawrence D. Chitlik 12/24/90

David Anderson — David G. Anderson 12/5/90 ~~with comment~~ DGA

Jennifer Seed — J. Seed 12/18/90

2. Reviewers: (Non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report.)

John Doherty (Reviewer) — John Doherty 12/7/90 With Comments attached.

Roger Gardner (Section Head) — Roger Gardner 11-29-90

Karl Baetcke (Branch Chief) — Karl P. Baetcke 11/29/90

3. Peer Review Members in Absentia: (Committee members who were unable to attend the discussion; signatures indicate concurrence with the overall conclusions of the Committee.)

Penelope Fenner-Crisp — Penelope A. Fenner-Crisp 12/28/90

Jennifer Orme — ~~Jennifer Orme~~ 12/21/90

4. Other Attendees: (Observers) Ed Budd, Victor Miller, and Esther Saito.

B. Material Reviewed:

The material available for review consisted of a comprehensive summary of the available toxicology information on TPTH that was prepared by Dr. John Doherty, Review Section I, Toxicology Branch I. Included in this summary was information on developmental toxicity studies on the rat, rabbit and hamster and multigeneration reproduction studies with rats. Dr. Doherty also provided Data Evaluation Records (DER's) on developmental and reproduction studies with TPTH as well as toxicology "one-liners" for the chemical. The specific studies considered are as follows:

Report Investigation of Teratogenic and Toxic Potential of Technical Triphenyltin Hydroxide, performed by Cannon Laboratories, October 12, 1976, MRID No. 00086547

Evaluation of the Teratogenicity of Triphenyltin Hydroxide in the Sprague-Dawley Rat. Battelle Columbus Laboratories, dated June 25, 1981. Accession No. 070696.

Triphenyltin Hydroxide (TPTH) Developmental Toxicology Study. Robert J. Kavlock, Ph.D. (EPA, Health Effects Research Laboratory, Research Triangle Park, North Carolina), March 28, 1985

A Teratology Study in Rats with Triphenyltin Hydroxide. WIL Research Laboratories, Project No. WIL-39011, April 1, 1985, EPA Accession No. 257402.

One Generation Teratology and Reproductive Study in Rats with Triphenyltin Hydroxide. WIL Research Laboratories, Research Report dated June 4, 1985, Project No. WIL-39013, EPA Accession No. 258229.

An Embryotoxicity Study in Rabbits with Triphenyltin Hydroxide. WIL Research Laboratories, February 27, 1987, Project No. 39012, MRID No. 401048-01

The Evaluation of the Teratogenicity of Triphenyltin Hydroxide In the Syrian Golden Hamster. Battelle Colubus Laboratories, Febuary 10, 1982, Project No. N)723-0100. MRID No. 00094904.

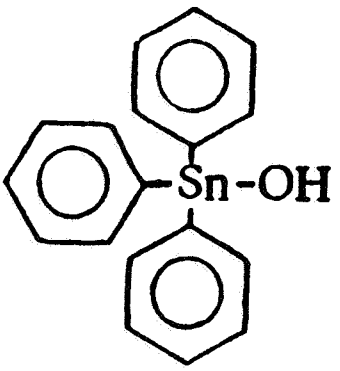
A Dietary Two-Generation Reproduction Study in Rats with Triphenyltin Hydroxide. WIL Research Laboratories, August 28, 1986, Project No. WIL-39022, Accession No. 264667 to 264676.

Reproduction Study with Triphenyltinhydroxide in Three Generations of Rats. Report No. R 2476. Central Instituut Voor Voedingoenderzook (August, 1967; MRID No. 00086548).

Draft Final Report on Range-finding Study for the Evaluation of Reproductive Effects of TPTH in the Wistar Rat. Project No. N0723-0400. Battelle Columbus Labs., dated July 22, 1982; EPA Acc. No. 071368, MRID No. 00125263.

C. Background Information:

Triphenyltin hydroxide (TPTH, see structure below) is used as a fungicide on sugarbeets, potatoes, peanuts, carrots and pecans. TPTH is also registered for use as an industrial preservative. Formulations include a 50% wettable powder, 19.7 and 40% flowable, and a 95% technical solid for industrial use. Overall application rates range from 1.5 to 12 oz. active ingredient per acre using ground, aerial, or sprinkler irrigation equipment. The registrant is American Hoechst Corporation (Somerville, New Jersey).



Triphenyltin Hydroxide (TPTH)

In a Registration Standard prepared in 1984, the Agency considered two developmental toxicity studies in the rat (Cannon, 1976, and Battelle, 1981) and another study in hamsters (Battelle Labs., February 10, 1982). These studies indicated that a no-effect level was not established for developmental toxicity in the rat (based on increased incidences of hydrocephalus and hydronephrosis). The effects were noted at lower dose levels than the no-observed-effect level (NOEL) indicated by the hamster developmental toxicity study, and the Agency requested additional developmental toxicity data.

A reproduction study (Central Instituut Voor Voedingoenderzook, August, 1967) was also considered in the Registration Standard. In that study, pups from groups given diets containing low levels of TPTH had increased spleen weights and lower testes weights in the absence of maternal toxicity. However, this study was classified invalid by the Agency, and raw data were needed to upgrade the study.

Based on results of the developmental toxicity studies, the Agency recommended in the Registration Standard that a Special Review of TPTH should be initiated. The chemical was also classified as a restricted use pesticide, and label warnings as well as a 24-hour reentry period were imposed. Additional data were also required to fill data gaps in product chemistry, residue chemistry, environmental fate, ecological effects, and toxicology.

The Position Document 1 issued on January 9, 1985, initiated the Special Review. In addition to developmental toxicity, the other effects of concern included immunotoxicity, reproductive toxicity, inhalation toxicity, and effects on nontarget organisms.

As part of its response to the Agency's request for additional toxicology data, the registrant submitted two developmental toxicity studies in the rat. The first (WIL, April 1, 1985) was larger than studies previously submitted (45 animals per group), and it evaluated a lower dose level than previous studies. The second rat

study (WIL, June 4, 1985) evaluated the same dose levels as the first new study, and it was specifically designed to evaluate potentially adverse effects of TPTH on growth and survival of offspring during lactation with emphasis on possible kidney effects. Neither of the new studies confirmed the effects of TPTH on urogenital or central nervous system development indicated by earlier studies.

The Agency also conducted a study specifically designed to evaluate the effects of TPTH on central nervous system and urogenital tract development in rats (EPA, 1985). This study included a postnatal phase in which potential effects on renal function were evaluated. There were slight effects noted on the central nervous system (hydrocephalus). Observed changes in renal morphology did not appear to be permanent, but effects on the morphology of developing ureters in the rat were described by the investigators as equivocal. The central nervous system and urogenital tract effects were observed with excessive maternal and developmental toxicity (i.e., mortality).

D. Summary of Relevant Data

1. Developmental Toxicity Studies

a. Rats

i. Cannon Labs Study (October 12, 1976; MRID #00086547)

Experimental Design

This study was determined to be invalid because of reporting deficiencies and discrepancies noted in Tables 1, 2, and 3 below. Also studies from Cannon Labs are regarded as invalid unless audited for Good Laboratory Practices compliance and determined to be valid.

Technical TPTH was administered in corn oil to five test groups of 20 pregnant Sprague-Dawley rats at dose levels of 0, 1.25, 5.0, 8.75 and 12.5 mg/kg/day each on days 6-15 of gestation by gavage.

Maternal Toxicity

No abnormal activity was noted in the two lower dose levels. The pregnant dams receiving 8.75 and 12.5 mg/kg/day exhibited significantly lower body weight gains than the other groups (see Table 1).

Table 1

Group Mean Maternal Body Weight Change (g) in Rats Given TPTH During Gestation (Cannon Labs, October 12, 1976).

Observation	Doses (mg/kg/day) 0	1.25	5.0	8.75	12.5
Gestation Days:					
0-6	23.3	26.0	29.2	24.8	29.5
6-11	26.2	26.6	23.8	10.7 *	10.6 *
11-15	19.9	24.7	27.4	18.1	6.6 *
15-20	76.8	66.6	67.5	47.8 *	24.4 *
0-20 +	146.2	144.7	148.4	111.5 *	68.6 *
0-20 ++	146.20	148.80	162.90	101.39	76.91

* These values were significantly different at $p < 0.01$ (Duncan's multiple range test).

\+ These data are from Table I in Part III of the Statistical Evaluation Section in the report. There is no explanation in the report for the discrepancies between these results and those from the Results Section of the report.

++ These data are from Table II in the Results Section of the report. There is no explanation in the original report for the discrepancies between these results and those from the Statistical Evaluation Section.

Developmental Toxicity

The 8.75 and 12.5 mg/kg/day dose levels caused significantly decreased fetal weight, increased fetal deaths and increased the number of resorptions (see Table 2).

Table 2

Summary of Fetal Mortality and Fetal Weight Results in Rats Given TPTH (Cannon Labs, October 12, 1976).

Observation	Doses (mg/kg/day) 0	1.25	5.0	8.75	12.5
No. pregnant	20	20	19 [a]	17 [b]	12 [c]
No. implants/dam	13.6	12.0	13.2	12.3	11.4
No. viable fetuses per litter	13.2	11.7	12.5	8.2 *	4.8 *
No. nonviable fetuses per litter	0	0	0.11	1.35 *	1.08 *
Resorptions per litter	0.50	0.30	0.58	2.71 *	5.58 *
Mean fetal weight (g)	3.93	4.06	3.80	3.38	2.42 *

[a] One animal was not pregnant.

[b] One animal aborted on gestation day 11, and two others aborted on day 16.

[c] According to the text of the report, three animals aborted, one each on gestation days 11, 12, and 15, and one animal died on day 18. Table V of the report indicated that five other animals had "possible abortions." There was no clear indication in the report that the animal that died on day 18 also aborted its litter.

* Significantly different from other groups, but no statistical test or p value was included with these data in the report.

Examination using the Wilson technique revealed hydronephrosis and hydrocephalus in all groups including the control (see Table 3 below).

Table 3

Incidence of Fetuses with Hydrocephalus or Hydronephrosis in Rats Given TPTH (Cannon Labs, October 12, 1976). *

Observation	Doses (mg/kg/day) 0	1.25	5.0	8.75	12.5
No. animals examined	94	75	73	47	20
Hydrocephalus	1	15	8	7	6
(%)	(1)	(20)	(11)	(15)	(30)
Hydronephrosis	2	5	12	16	2
(%)	(2)	(7)	(16)	(33)	(10)

* Incidences of fetal alterations by litter was not included in the original report.

ii. Battelle Labs. (June 25, 1981, MRID #00094903).

Experimental Design

The developmental toxicity potential of TPTH was evaluated by administering 0, 1.0, 2.8 and 8.0 mg/kg/day of the test compound in corn oil by gavage to 26 animals per dose group on days 5 to 19 of gestation.

Maternal Toxicity

Signs of toxicity observed in rats given the highest dose included rough coat, oral/nasal discharge, alopecia, diarrhea, ocular discharge, vaginal discharge, lethargy, hemorrhage from the vaginal area, and thinness. Body weight gain for this dose group was also significantly decreased during gestation (82 g compared with >130 g for the other test groups).

Developmental Toxicity

Litter size at the highest dose level (8 mg/kg/day) was decreased by 15% below control values, and fetuses weighed 22% less than controls. The number of dead and/or resorbed fetuses was increased in the 8 mg/kg dosed group (12%) compared to the control value (3%) (see Table 4).

Table 4

Summary of Selected Fetal Data from
Pregnant Rats (Battelle, June 25, 1981)

Observation	Doses (mg/kg/day) * 0	1.0	2.8	8.0
No. litters examined	20	20	20	18
Implantations per litter				
Mean	13	13	14	13
(S.D.)	(4)	(3)	(2)	(3)
Viable fetuses per litter				
Mean	13	12	13	11
(S.D.)	(4)	(3)	(3)	(3)
Fetal weight (g)				
Mean	3.50	3.54	3.50	2.72
(S.D.)	(0.39)	(0.56)	(0.60)	(0.43)
% Dead/resorbed fetuses per litter				
Mean	3	5	6	12
(S.D.)	(5)	(9)	(12)	(11)
No. implantation sites per no. corpora lutea				
Mean	0.88	0.78	0.86	0.79
(S.D.)	(0.27)	(0.20)	(0.17)	(0.21)

* No results of statistical analyses were noted.

No dose response was apparent relative to hydronephrosis. The incidence of hydroureter was 1 (1%), 7 (6%), 7 (6%) and 12 (12%) for the control, low, mid, and high dose test groups.

iii. EPA, Health Effects Research Laboratory (March 28, 1985).

Experimental Design

The experiment was divided into two phases with the animals assigned as shown in Table 5 below.

Table 5

Assignment of animals in the EPA Study
Dated March 28, 1985.

Phase	Doses (mg/kg/day) * 0	4	8
I	20	21	20
II **	22	23	0
II **	23	22	0
Total	66	66	20

* All pregnant rats were administered TPTH in doses of 0, 4, or 8 mg/kg/day by gastric intubation on gestation days seven through 20.

** All Phase I animals were used for fetal analyses; Phase II animals were divided such that approximately 30% were used for fetal analyses with the remaining 70% used for postnatal analyses. Phase II was accomplished in two separate groups of animals bred one week apart.

The objective of Phase I was to establish the potential of TPTH to induce alterations in the central nervous system and urogenital tract of fetuses and to set dose levels for the subsequent study. Phase II was designed to evaluate whether any developmental toxicity affected postnatal life. Two measures of renal function were applied to offspring in Phase II: 1) a renal concentrating test on either postnatal day 7, 8, 9 or 10 (in this strain birth normally occurs on the evening of day 22 of gestation and the following day is considered postnatal day 1 [PD1]) (approximately 25% of the pups in each litter were tested each day); and 2) serum and urine chemistries on either PD22 or 23 (approximately 50% of the pups in each litter on each day). At the conclusion of the latter test, the pups were sacrificed and examined for urogenital morphology.

Maternal Toxicity

Maternal toxicity was evident at the 8 mg/kg/day dose level as indicated by deaths among the dams (30% in the high dose group vs. 9% in the control group).

Developmental Toxicity

Decreased fetal weight, decreased postnatal pup weight gain and increased resorptions were noted (see Table 6 below).

During necropsy, a grading system was used to describe the morphological status of the cerebral ventricles, kidneys and ureters (see Table 6). Prenatal exposure to TPTH had a slight effect on the development of the fetal kidney and the ureter. This effect, which consisted of shifts to more severe grades for the kidney and ureter, was more pronounced in the prenatal experiment (Phase I) than in the postnatal experiment (Phase II).

Table 6

Effects of Prenatal TPTH Exposure on Fetal Development in the Rat (EPA, March 28, 1985).

Observation	Doses (mg/kg/day) 0	4	8
No. litters examined	17	18	7
No. fetuses	191	198	89
Postnatal weight gain (g)	43 ± 2 *	26 ± 4	-23 ± 10 *
Implantation sites (No. per dam)	13.1 ± 0.5	12.9 ± 0.3	13.0 ± 0.3
7 Prenatal mortality (%)	8.8 ± 1.6	9.7 ± 2.3	30.0 ± 12.1 *
Fetal weight (g)	4.2 ± 0.2	4.1 ± 0.2	2.9 ± 0.4 *
Cerebral ventricles grade (mean)	2.03 ± 0.01	2.03 ± 0.01	2.04 ± 0.01
% in grade 3	1.6	2.5	6.7
Kidney grades			
Right (mean)	1.71 ± 0.04	1.80 ± 0.04	1.58 ± 0.05
% in grade 2	63	70	56
% in grade 3	4	5	1
Left (mean)	1.65 ± 0.04	1.75 ± 0.04	1.46 ± 0.06
% in grade 2	59	66	44
% in grade 3	3	5	1
Ureter grade			
Right (mean)	t1.10 ± 0.02	1.29 ± 0.03	1.28 ± 0.05
% in grade 2	10	26	28
% in grade 3	0	2	0
Left (mean)	1.30 ± 0.03	1.50 ± 0.04	1.38 ± 0.05
% in grade 2	30	37	38
% in grade 3	0	7	0

* Statistically significant difference from control, $p < 0.05$.

The pups from the postnatal phase showed no treatment related impairment of renal function or morphology.

iv. WIL Laboratories (April 1, 1985; Acc. No. 257402).

Experimental Design

In this study, groups of 45 mated female Sprague-Dawley strain rats were given doses of 0, 0.35, 1.0, 2.8, or 8.0 mg/kg/day by gavage on gestation days 6-15.

Maternal Toxicity

Maternal effects included weight loss and poor condition at the 2.8 and 8.0 mg/kg/day dose levels. There was a 6-12% decrease in maternal body weights in the two highest dosed groups when compared to the control group (see Table 7); food consumption was also decreased for those two groups (decreased from control values by 10-22% in the 2.8 mg/kg group and up to 50% in the 8.0 mg/kg dosed group). Other signs of toxicity in the two highest dosed groups included lethargy, emaciation, anogenital staining, and red vaginal discharges.

Table 7

Summary of Mean Maternal Weight Change Data in Pregnant Rats (WIL Laboratories, April 1, 1985)

	Doses (mg/kg/day)				
Gestation Days	0	0.35	1.0	2.8	8.0
0-6	29	30	28	29	28
6-9	9	11	9	4 *	-7 **
9-12	17	17	18	15	8 **
12-16	26	29	26	26	12 **
16-20	56	58	59	60	59
6-16	52	57	53	45	13 **
6-20	108	115	114	105	72 **
0-20	137	145	141	134	100 **

* Statistically different from controls at $p < 0.05$ (Dunnett's test).

** Statistically different from controls at $p < 0.01$ (Dunnett's test).

Developmental Toxicity

Fetal effects included an increase in early resorptions and total litter resorptions at the highest dose level, and fetal

weight in that group was 11% less than that for fetuses from the control group. Litter size was also decreased at the 8.0 mg/kg/day dose level. These results are summarized in Table 8 below.

Table 8

Summary of Mean Fetal Survival Data
(WIL Laboratories, April 1, 1985)

Observation	Doses (mg/kg/day) 0	0.35	1.0	2.8	8.0
No. assigned	45	45	45	45	45
No. aborted	0	0	1	0	1
No. nongravid	4	6	4	6	9
No. total resorptions	0	0	0	1 +	4
No. litters with viable fetuses	41	39	40	38	31
Viable fetuses/dam					
Mean	13.9	14.1	13.9	13.2	11.4 *
(S. D)	(3.2)	(1.9)	(2.9)	(3.7)	(5.4)
Early resorptions/dam					
Mean	0.4	0.9 *	0.6	0.6	0.9 *
(S. D)	(0.7)	(0.8)	(0.8)	(2.4)	(4.8)
Late resorptions/dam					
Mean	0.0	0.0	0.0	0.1	0.1
(S. D)	(0.0)	(0.2)	(0.0)	(0.3)	(0.5)
Fetal weight (g) per litter					
Mean	3.6	3.7	3.7	3.6	3.2 *
(S. D)	(0.4)	(0.3)	(0.3)	(0.3)	(0.5)

\+ According to the report, this total litter resorption was induced by the pathological condition resulting from an intubation error.

* Statistically different from controls at $p < 0.05$.

Earlier studies investigated the potential for TPTH to cause kidney alterations, and the incidence of similar effects (undeveloped renal papillae and/or distended ureter) is summarized from the Data Evaluation Record and shown in Table 9 below. These

results indicated that no treatment-related effects on kidney development were noted.

Table 9

Number of Fetuses and Litters with Undeveloped Renal Papillae and/or Distended Ureters (WIL Laboratories, April 1, 1985)

Observation	Doses (mg/kg/day) 0	0.35	1.0	2.8	8.0
No. affected fetuses per no. examined (%)	20/285 (7.4)	20/275 (7.3)	10/278 (3.6)	20/257 (7.8)	14/201 (7.0)
No. affected litters per no. examined (%)	14/41 (34.2)	14/39 (35.9)	8/40 (20.0)	12/38 (31.6)	10/30 (33.3)

The increased incidence of unossified sternebrae #5 or #6 was reported to be statistically significant at the 8 mg/kg/day dose level (see Table 10). There were a total of 4 fetuses with hydrocephalus (one in the control and 2.8 mg/kg dose groups and two in two litters from the 8 mg/kg dose group).

Table 10

Number of Fetuses and Litters with Unossified Sternebrae (WIL Laboratories, April 1, 1985)

Observation	Doses (mg/kg/day) 0	0.35	1.0	2.8	8.0
No. affected fetuses per no. examined (%)	36/285 (12.6)	41/275 (14.9)	27/278 (9.7)	17/257 (6.6)	41/201 * (20.4)
No. affected litters per no. examined (%)	16/41 (39.0)	17/39 (35.9)	17/40 (42.5)	13/38 (34.2)	21/30 * (70.0)

* Statistically significant difference from controls at $p < 0.05$ (Fisher's Exact test).

v. WIL Laboratories (June 4, 1985; Acc No. 258229).

Experimental Design

The potential adverse effects of TPTH on the growth and survival of the offspring through lactation day 28 were investigated with special emphasis on the developmental morphology of the kidneys in the offspring.

Dose levels selected were 0, 0.35, 1.0, 2.8 and 8.0 mg/kg/day of TPTH in corn oil which was administered to four groups of 25 rats from gestation days 6 to 15. All females were allowed to litter naturally and rear the offspring until lactation day 21. On that day, all surviving females were sacrificed and necropsied.

Maternal Toxicity

No deaths were recorded among the maternal animals. Maternal body weight gain over the entire treatment period was significantly decreased in the highest dose group (see Table 11).

Table 11

Group Mean Maternal Body Weight Change (g) in Rats Given TPTH During Gestation (WIL Labs, June 4, 1985).

Observation	Doses (mg/kg/day) 0	0.35	1.0	2.8	8.0
Gestation Days:					
0-6	26	26	27	26	24
6-9	8	10	11	9	0 **
9-12	14	17	16	18	9 *
12-16	24	26	30	27	12 **
16-20	25	42	47 *	48 *	35
6-16	47	53	57 *	54	20 **
6-20	73	95 *	104 **	102 **	55
0-20	99	121 *	131 **	127 **	79

* These values were significantly different at $p < 0.05$ (Dunnett's test).

** These values were significantly different at $p < 0.01$ (Dunnett's test).

Hair loss was observed in all study groups but was reported to be slightly more extensive in the 8.0 mg/kg/day group. A few animals in this group were also reported to be lethargic.

Developmental Toxicity

There were no compound-related effects on litter parameters, but 12 females had total litter loss, five in the control group, one each in the 0.35 and 1.00 mg/kg/day groups and five in the 8.00 mg/kg/day group (see Table 12).

Table 12

Pregnancy Status in Rats Given TPTH During Gestation (WIL Labs, June 4, 1985).

Observation	Doses (mg/kg/day) 0	0.35	1.0	2.8	8.0
No. on study	25	25	25	25	25
No. not delivering by post-mating day 25:					
No. nongravid	3	2	1	2	7
No. gravid	0	0	0	0	1
No. normal deliveries	22	23	24	23	17
No. with total litter loss	5	1	1	0	5
Litters weaned	17	22	23	23	12
Total no. gravid	22	23	24	23	18

The kidneys of the offspring were weighed at the scheduled sacrifice on lactation day 28 and processed for histopathological evaluation. Organ weights of pups relative to final body weights were increased significantly at dose levels of 2.8 and 8.0 mg/kg/day for both males and females (see Table 13). There were no histopathological observations in this study which correlated with this finding (see Table 14).

Table 13

Summary of Pup Kidney Weight Results from a Postnatal Developmental Toxicity Study in Rats (WIL Labs., June 4, 1985).

Observation	Doses (mg/kg/day) 0	0.35	1.0	2.8	8.0
Males					
No. examined	73	106	125	109	54
Pup body weight (g)					
Mean	73.79	73.54	77.62 *	79.12 **	75.71
(S.D.)	(10.686)	(9.327)	(9.056)	(8.427)	(12.138)
Pup kidney weight (g)					
Mean	0.8901	0.9135	0.9409 *	1.0644 **	0.9727 **
(S.D.)	(0.13113)	(0.12239)	(0.11261)	(0.10097)	(0.14267)
Kidney/body wt. ratio					
Mean	1.208	1.244	1.215	1.275 **	1.296 **
(S.D.)	(0.0776)	(0.0833)	(0.0860)	(0.1131)	(0.13312)
Females					
No. examined	93	110	105	117	53
Pup body weight (g)					
Mean	70.49	68.94	71.57	72.49	69.14
(S.D.)	(8.256)	(9.113)	(6.816)	(7.780)	(9.144)
Pup kidney weight (g)					
Mean	0.8432	0.8512	0.8420	0.9030 **	0.8646
(S.D.)	(0.10532)	(0.11748)	(0.07874)	(0.08767)	(0.10245)
Kidney/body wt. ratio					
Mean	1.200	1.237	1.180	1.254 **	1.260 **
(S.D.)	(0.1001)	(0.0860)	(0.0864)	(0.1410)	(0.1522)

* These values were significantly different at $p < 0.05$ (Dunnett's test).

** These values were significantly different at $p < 0.01$ (Dunnett's test).

Table 14

Summary of Selected Pup Kidney Histopathology from a Postnatal Developmental Toxicity Study in Rats (WIL Labs., June 4, 1985).

Observation	Doses (mg/kg/day) 0	0.35	1.0	2.8	8.0
			Males		
No. of pups examined	73	106	125	109	54
Pelvic dilatation					
No. of pups	12	12	32	27	6
%	16.44	11.32	25.60	24.77	9.38
Unilateral hydronephrosis					
No. of pups	0	0	1	0	0
%	0	0	0.80	0	0
Tubular dilatation					
No. of pups	0	1	0	2	1
%	0	0.94	0	1.83	1.56
			Females		
No. of pups examined	93	110	105	117	53
Pelvic dilatation					
No. of pups	17	7	11	24	9
%	18.28	6.31	10.48	20.51	16.98
Unilateral hydronephrosis					
No. of pups	3	0	0	0	0
%	3.23	0	0	0	0
Tubular dilatation					
No. of pups	0	0	0	2	0
%	0	0	0	1.71	0

SGOT levels were significantly decreased in the females only, at all dose levels (significantly different from control group at 0.05 level using Dunnett's test). In the three highest dose groups in females (1.0, 2.8 and 8.0 mg/kg/day), they were significantly different from the control group at 0.01 level using Dunnett's test.

Increases in lactic dehydrogenase levels in both males and females were noted as being statistically significant in all but the lowest dose level i.e. 0.35 mg/kg/day.

b. Rabbits

WIL Research Laboratories (Feb. 27, 1987; MRID # 401048-01).

i. Pilot Study

Experimental Design

In a dose range-finding study TPTH was administered by gavage at levels of 0, 0.1, 1.0, 2.0, 4.0, 6.0, and 8.0 mg/kg to groups of six bred New Zealand White rabbits once daily from gestation days 6 through 18. Doses were administered in solutions of 1% aqueous carboxymethylcellulose at a volume of 1 ml/kg body weight.

Observations

Mean maternal body weight losses occurred throughout the treatment period in the 1.0, 2.0, 4.0, and 6.0 mg/kg/day dose groups. Maternal body weight gain was apparentlynot affected by treatment at the 0.1 mg/kg/day dose level, but all six does in the 8.0 mg/kg/day dose group died. Mean fetal body weights were decreased at 0.1 and 1.0 mg/kg/day when compared to the control group in this study. At higher doses (2, 4 and 6 mg/kg/day) there were total litter resorptions (see Table 15). These results were the basis for selection of the doses used in the definitive study described in the following section.

Table 15

Summary of Selected Maternal and Developmental Data from a Range-Finding Study with TPTH in Pregnant Rabbits (WIL, February 27, 1987). *

Observation	Doses (mg/kg/day)					
	0	1.0	2.0	4.0	6.0	8.0
No. on study	6	6	6	6	6	6
No. aborted	1	1	2	1	3	0
No. died		0	0	0	0	3
No. nongravid	1	0	1	0	0	0
Total resorptions	1	0	2	5	3	0
No. with viable fetuses	3	5	1	0	0	0

* Data from the 0.1 mg/kg/day dose group is not included in this table since no maternal toxicity was observed at that dose level.

ii. Definitive Study

Experimental Design

In the definitive study, potential maternal and developmental effects of TPTH were evaluated by administering dose levels of 0, 0.1, 0.3, and 0.9 mg/kg/day by gavage to groups of 22 bred New Zealand White rabbits. The animals were treated daily on gestation days 6 through 18 with appropriate concentrations of TPTH in 1% aqueous carboxymethylcellulose.

Maternal Toxicity

TPTH decreased maternal body weight gain and food consumption during the study (see Tables 16 and 17 below). Although decreased body weight gains in the 0.3 mg/kg dosed group were not statistically significant during the study, decreases were considerable from day 12 through the end of gestation (see Table 16). A statistically significant decrease was reported for the 0.3 mg/kg/day dosed group below the control group value for gestation days 0-29.

Table 15

Summary of Group Mean Maternal Body Weight Changes (g) in Pregnant Rabbits Treated with TPTH (WIL Laboratories, February 27, 1987).

Observation	Doses (mg/kg/day) 0	0.1	0.3	0.9
Days 0 - 6				
Mean	196	71 *	96	70 *
(S.D.)	(197)	(123)	(117)	(82)
Days 6 - 12				
Mean	83	98	79	-81 **
(S.D.)	(59)	(69)	(73)	(167)
Days 12 - 18				
Mean	64	85	3	-58 **
(S.D.)	(117)	(75)	(112)	(135)
Days 18 - 24				
Mean	44	47	-19	45
(S.D.)	(127)	(94)	(79)	(164)
Days 24 - 29				
Mean	-37	-32	-17	86 *
(S.D.)	(186)	(134)	(135)	(91)
Days 6 - 18				
Mean	147	184	82	-139 **
(S.D.)	(122)	(105)	(136)	(250)
Days 18 - 29				
Mean	8	15	-35	146 *
(S.D.)	(249)	(140)	(105)	(127)
Days 0 - 29				
Mean	350	276	143 **	93 **
(S.D.)	(192)	(169)	(203)	(217)

* Significantly different from the control group at $p < 0.05$ using Dunnett's test.

** Significantly different from the control group at $p < 0.01$ using Dunnett's test.

Table 17

Summary of Group Mean Maternal Food Consumption (g/animal/day) in Pregnant Rabbits Treated with TPTH (WIL Laboratories, February 27, 1987).

Observation	Doses (mg/kg/day) 0	0.1	0.3	0.9
Days 0 - 6				
Mean	160	175	166	161
(S.D.)	(34)	(24)	(28)	(23)
Days 6 - 12				
Mean	184	178	159	85 **
(S.D.)	(33)	(26)	(46)	(45)
Days 12 - 18				
Mean	165	166	109 **	57 **
(S.D.)	(34)	(35)	(53)	(47)
Days 18 - 24				
Mean	140	139	101 *	86 **
(S.D.)	(56)	(51)	(46)	(47)
Days 24 - 29				
Mean	93	98	88	126
(S.D.)	(71)	(55)	(43)	(27)
Days 6 - 18				
Mean	174	172	134 **	71 **
(S.D.)	(32)	(29)	(41)	(39)
Days 18 - 29				
Mean	119	122	95	106
(S.D.)	(56)	(47)	(37)	(31)
Days 0 - 29				
Mean	150	154	126 *	103 **
(S.D.)	(33)	(32)	(31)	(22)

* Significantly different from the control group at $p < 0.05$ using Dunnett's test.

** Significantly different from the control group at $p < 0.01$ using Dunnett's test.

Developmental Toxicity

The necropsy findings in the animals surviving to the scheduled sacrifice showed only a slight (10%) decrease (not statistically significant) in mean fetal body weight in the 0.9 mg/kg/day dose group without other significant effects on litter size (see Table 18 below).

Table 18

Summary of Selected Fetal Data from Pregnant Rabbits (WIL Laboratories, February 27, 1987) *

Observation	Doses (mg/kg/day) 0	0.1	0.3	0.9
No. of litters	20	19	22	19
Fetuses per doe				
Mean	6.1	6.9	7.3	6.8
(S.D.)	(3.9)	(3.2)	(2.7)	(3.0)
Fetal weight (g)				
Mean	40.4	41.0	41.0	36.1
(S.D.)	(6.1)	(6.9)	(6.0)	(7.2)

* No Statistically significant differences were noted with respect to fetal parameters according to the report.

There was also an increased incidence of fetuses (0/121, 1/132, 1/160, and 6/130 in the control, low, mid and high dose groups, respectively) and litters containing affected fetuses (0/17, 1/18, 1/21, and 3/18 in the control, low, mid and high dose 727groups, respectively) with hyoid unossified.

c. Hamsters

Battelle Columbus Laboratories, (Febuary 10, 1982, EPA Accession No. 070697).

Experimental Design

In this study, doses of 0, 2.15, 5.08 or 12 mg/kg/day were administered by gavage in saline solution containing 0.3% hydroxypropyl cellulose to groups of 25 pregnant Syrian hamsters. A positive control group of 25 animals received Vitamin A palmi-

tate. All doses and the controls were administered on gestation days 5 through 14 and the dams were sacrificed on day 15.

Maternal Toxicity

According to the report, maternal body weight gain was decreased among the high dose (12.0 mg/kg/day) dams when compared to the vehicle control group. (Numerical data were not readable in the available copies of the report.)

Developmental Toxicity

No developmental effect of TPTH was observed at the 2.15 and 5.08 mg/kg/day dose levels and the animals in these dose groups were not significantly different from the vehicle control group for fetal parameters examined. Among the high dose group (12.0 mg/kg/day), fetal weight was decreased, and the incidence of fetuses with minor skeletal alterations was significantly increased above that in the control group.

Decreases at 12 mg/kg/day were reported in the average number of viable fetuses per litter and the average weight of viable fetuses. The average percent dead or resorbed fetuses per litter reported for the mid and high dose groups was approximately double that reported for the control group. Selected fetal data are summarized in Table 19 below.

Table 19

Summary of Mean Fetal Survival Data in Hamsters (Battelle, February 10, 1982)

Observation	Doses (mg/kg/day) 0	2.15	5.08	12.0	Positive control
No. of litters	20	20	20	20	20
Viable fetuses/litter					
Mean	12.20	12.60	12.95	9.75 *	10.35 *
(S. D)	(3.05)	(2.90)	(2.82)	(4.31)	(3.57)
% Dead/resorbed fetuses per litter					
Mean	11.60	7.02	7.22	25.96	25.80
(S. D)	(16.40)	(9.56)	(11.37)	(30.56)	(21.03)
Fetal weight (g)					
Mean	1.94	1.99	2.03	1.75 *	1.76 *
(S. D)	(0.17)	(0.15)	(0.17)	(0.27)	(0.13)

* Statistically different from controls at p <= 0.001. (A list of statistical tests used in the study was included in the text, but the specific test used to determine p values for these results was not mentioned.)

2. Reproduction Studies

a. Central Instituut Voor Voedingoenderzook (August, 1967; MRID No. 00086548).

This study was considered invalid by the Agency because no raw data were presented with the original submission, and those data have not been provided to support upgrading of the study.

Experimental Design

The reproductive toxicity of TPTH was evaluated in a three generation reproduction study. Five groups of Wistar rats were given diets containing 0, 0.5, 1.0, 2.0 and 5.0 ppm TPTH. These rats were mated within their groups at 12 and 20 weeks after being started on the diet to produce F_1A and F_1B generations. F_1B offspring were selected to produce F_2A and F_2B litters in the next generation, and pups from F_2B litters were subsequently mated to produced F_3A and F_3B litters. Ten males and 10 females per group

were also selected from the F_1B and F_2B litters for a 90-day feeding study.

Parental Toxicity

According to the study report, the health and survival of the parental animals remained unaffected throughout the course of the experiment.

Reproductive Toxicity

Increased spleen weights in the F_1B and F_2B pups and decreased testicular weights in the F_2B pups were reported at dose levels of 1.0 ppm and higher. The weight differences in the spleen were not accompanied by pathological lesions, but decreased maturation of the testicle was noted by the investigators.

b. Battelle (July 22, 1982; EPA Acc. No. 071368).

Experimental Design

This one-generation study was performed to set dose levels for a definitive multigeneration reproduction study. Six groups of 10 male and 10 female Wistar strain rats were given diets containing 0, 12.5, 25, 50, 100 and 200 ppm. All rats were fed the test diets prior to mating and through the first day after parturition when they were sacrificed.

Parental Toxicity

Toxic signs included rough coat, hunched back, lethargy, nasal discharge, alopecia and a lower pregnancy rate. Those signs were noted chiefly in the 200 ppm group where the pregnancy rate was reported to be only 4 of 10 dams. Body weight was also decreased in the male animals at the 200 ppm dose level.

Reproductive Toxicity

At 100 ppm and 200 ppm pup survival was only 59.6% and 0%. The weight of the surviving pups at 100 ppm was decreased, and no live pups were found at 200 ppm. There were no gross abnormalities in the surviving pups, but the incidence of minimal to mild chronic nephrosis and mineralization was increased in the 100 ppm group. On the basis of these data the dose levels of 0, 5, 18.5 and 50 ppm were selected for the definitive study.

c. WIL Research Laboratories (August 28, 1986; EPA Acc No. 264667 to 264676).

Experimental Design

Five groups of 30 male and 30 female Wistar strain rats (F_0 animals) were given diets containing 0 (two groups), 5, 18.5 or 50 ppm TPTH. The animals received test diets for at least 70 days prior to mating and continuously through mating, gestation and lactation for the F_1 and F_2 generations, and the study included one mating per generation. F_0 and F_1 parental animals and F_1 and F_2 offspring (25/sex/group) were examined at necropsy for gross lesions; organs were weighed and tissues were evaluated for histopathological changes.

Parental Toxicity

F_0 and F_1 animals in the 50 ppm dose group exhibited reduced body weight, body weight gain and food consumption.

Developmental and Reproductive Effects

There were decreased pup body weights at weaning at the 50 ppm dose level. Spleen and liver weights were reduced in the 18.5 and 50 ppm dose groups (see Table 20).

Table 20

Summary of Group Mean Final Body Weights (g), Spleen and Liver Absolute Weights (g), and Relative Weights (Organ-to-Body Weight Weight Ratios) from a Rat Reproduction Study (WIL, August 28, 1985)

Observation	Doses (ppm)				
	0	0	5.0	18.5	50.0
F_1 Males					
Body weight	142.20	140.64	139.96	133.80	124.92 *
Spleen					
Absolute weight (g)	0.68	0.67	0.64	0.57 *	0.53 **
Relative weight	0.477	0.478	0.460	0.424	0.428
Liver					
Absolute weight (g)	7.35	7.66	7.45	6.94	6.85
Relative weight	5.166	5.436	5.311	5.170	5.485
F_1 Females					
Body weight	129.44	132.50	120.24	122.04	108.32 **
Spleen					
Absolute weight (g)	0.59	0.63	0.53	0.51	0.43 **
Relative weight	0.456	0.480	0.439	0.418	0.397
Liver					
Absolute weight (g)	6.77	6.80	6.06	6.19	5.56 **
Relative weight	5.214	5.195	5.010	5.062	5.102
F_2 Males					
Final body weight	69.77	68.33	68.68	65.20	48.80 **
Spleen					
Absolute weight (g)	0.32	0.34	0.33	0.28	0.18 **
Relative weight	0.463	0.493	0.482	0.427	0.375 **
Liver					
Absolute weight	3.29	3.21	3.26	2.99	2.31 **
Relative weight	4.694	4.682	4.754	4.581	4.753
F_2 Females					
Final body weight	63.00	59.89	63.40	57.32	44.18 **
Spleen					
Absolute weight (g)	0.29	0.29	0.31	0.24 *	0.15 **
Relative weight	0.460	0.481	0.487	0.418	0.346 **
Liver					
Absolute weight	2.92	2.79	2.88	2.53 *	2.07 **
Relative weight	4.619	4.649	4.544	4.400	4.702

* Significantly different from the control group at $p < 0.05$ using Dunnett's test.

** Significantly different from the control group at $p < 0.01$ using Dunnett's test.

Other organ weights were reduced in pups from the 50 ppm dose group as the result of generally decreased body weight. Exceptions to this observation included the testes and ovaries.

Testicular weights were reported as being decreased in an earlier study (Central Instituut Voor Voedingoenderzook, 1967) at dietary dose levels of 1.0 ppm or higher (see page 24). Testis weights in the 50 ppm dose group of this more recent study were reduced for the F_1 group pups (17-23% absolute, 7-12% for organ-to-body weight and 17-21% f9r organ-to-brain weight). The F_2 group pups also had testis weight decreases (absolute 22%, 19-21% relative to brain weight but an apparent increase of 2-9% for relative to body weight). The other groups did not show statistically significant differences.

Ovary weights were variable and an effect in the high dose group only was noted.

Thymus weight was decreased in the mid and high dose group (to as much as 39-43%) and this is considered possibly related to the immunotoxic effects of TPTH.

The organ weight changes were not reported to occur along with histopathological changes.

The mean litter size in the mid dose level was decreased 12% for the F_2 generation and the high dose was reduced 15% for the F_1 and 18% for the F_2 generation. Selected litter data are summarized in Table 21 below.

Table 21

Summary of Pup Survival Data from a Multigeneration Reproduction Study with TPTH in Rats (WIL Laboratories, August 28, 1986)

Observation	Doses (ppm)				
	0	0	5.0	18.5	50
F_1 Generation					
No. dead pups	1	15 **	2	3	7
Total no. pups	374	358	387	374	307
No. litters	29	27	29	30	28
Pups per litter	12.9	13.3	13.3	12.5	11.0 +
F_2 Generation					
No. dead pups	6	1	20 **	2	7
Total no. pups	387	439	354	341	338
No. litters	27	30	27	27	29
Pups per litter	14.3	14.6	13.1	12.6 +	11.7 ++

* Statistically different from controls at $p < 0.05$ level (Chi square test).

** Statistically different from controls at $p < 0.01$ level (Chi square test).

\+ Statistically different from controls at $p < 0.05$ level (Dunnett's test).

++ Statistically different from controls at $p < 0.01$ level (Dunnett's test).

E. Additional Toxicology Data on:

1. Acute, Subchronic, Chronic Effects.

The acute oral LD50 values in rats are 165 mg/kg for males and 156 mg/kg for females (EPA Accession No. 071364). Depending on the conditions of the study, the acute dermal toxicity LD50 values in rabbits was 3000 mg/kg (range: 1820-4950 mg/kg; EPA Accession No. 0083560) or was 127 mg/kg (EPA Accession No. #71364). The acute inhalation LC_{50} for rats was 60.3mg/m^3, with some deaths being

delayed. (Accession No. 071364). TPTH is corrosive to the eye (EPA Accession No. 071364).

Toxic effects observed in a 90-day rat feeding study (EPA Accession No. 261754) included decreased immunoglobulin levels at the lowest dose tested (4 ppm), and decreased food consumption and body weight gain at 100 ppm. Toxic effects observed in a 90-day mouse feeding study (EPA Accession No. 261753) included decreased immunoglobulin levels (at 4 ppm; the lowest dose tested), and increased liver weights at 100 ppm.

In a 1-year dog study (EPA Accession No. 402855-01), the NOEL was >18 ppm (the highest dose tested)

2. Carcinogenicity:

The Health Effects Division Peer Review Committee has evaluated the weight-of-evidence on TPTH and has classified the chemical as a Group B2-Probable Human Carcinogen. Quantification of the carcinogenicity risk was recommended.

These conclusions were based on the following: the significant increase in fatal pituitary gland adenomas in female Wistar rats and Leydig cell tumors in male Wistar rats (RCC, Switzerland; #046980; April 18, 1989; MRID No. 410857-02); and, the significantly increased incidence of hepatocellular adenomas and combined adenomas and/or carcinomas in male and female NMRI strain mice, and a significantly increasing dose-related trend for the incidence of hepatocellular carcinomas in female mice (RCC, Switzerland; #047002; April 14, 1989; MRID No. 410857-01). Other factors considered by the Peer Review Committee included: the uncommon spontaneous occurrence of hepatocellular carcinomas in female NMRI strain mice; tumor incidences were increased at relatively low dose levels of TPTH; and evidence for immunotoxicity of the chemical.

3. Mutagenicity.

Seven acceptable studies have been submitted with TPTH as the test substance. Six were negative, and one in vitro study was "borderline" positive. The marginal effect was not reproduced in the in vivo studies. Table 22 summarizes the mutagenicity study results.

Table 22

Summary of Mutagenicity Studies on TPTH

Study	Results
Bacterial---reverse mutation in S. typhimurium and E. coli (Huntingdon Res. Centre; #450/81A; July, 1981; EPA Acc. No. 071368).	Not mutagenic with and without metabolic activation.
Gene mutation in E. pombe (Inst. di Ricerche Biom. Antion Marxer, #M 889; August 20, 1985; EPA Acc. No. 259345).	Negative up to and including cytotoxic levels.
Mouse lymphoma forward mutation assay (Litton Bionetics Netherlands, #E09046; August, 1985; EPA Acc. No. 259345).	Borderline positive at 250 and 300 ng/ml in the presence of S-9 mix. Negative in the absence of S-9 at up to and including cytoxic levels.
Mouse micronucleus (in vivo) (RCC, Switzerland, #049552; August 5, 1985; EPA Acc. No. 259345).	Negative up to and including 77% of the LD_{50}, a dose level showing signs of toxicity.
In vivo cytogenetics in bone marrow cells of the Chinese hamster (Pharma, Germany; #86-1104; MRID No. 403711-02).	Negative at dose levels up to and including 80 mg/kg. Assessed at 12, 24 and 48 hours after dosing.
Gene conversion in S. cerevisiae D4 (Inst. di Ricerche Biom. Antion Marxer, #M 890; October 24, 1985; EPA Acc. No. 260962).	Negative up to and including 5 ug/ml without metabolic activation and 15 ug/ml with the S-9 activation system.
Unscheduled DNA synthesis in rat primary hepatocytes (Litton Bionetics; #20991; October, 1985; EPA Acc. No. 260962).	Negative at doses up to and including 0.5 ug/ml (cytotoxic dose).

4. Metabolism.

Studies (MRID Nos. 400294-05, -06, and-07) with 14C-ring labelled TPTH showed that most of the 14C is excreted in the feces. 14C excreted in the urine was identified mostly as benzene metabolites. A more recent study (MRID No. 413091-01 and -02) with 113Sn-labeled TPTH showed that about 25% can be absorbed from the gastrointestinal tract of male rats and about 12% is absorbed from

the gastrointestinal tract of female rats. The label did not selectively accumulate in the testes, pituitary glands, or the liver. The liver was among the organs showing the highest accumulation of the label.

5. Immunotoxicity.

Reports in the scientific literature show that organotin compounds, including TPTH, can suppress cell-mediated immune response in the rat (e.g., Vos J., et al., 1984, Toxicology, 29:325-336). Subchronic and chronic feeding studies submitted to the Agency indicate also that TPTH can cause reductions in immunoglobulin classes (i.e., IgG, IgM, and IgA). A study currently is being performed in mice and in rats to establish a NOEL for TPTH immunotoxicity.

6. Structure:Activity Relationships.

A developmental toxicity study in rabbits (EPA Acc. No. 252178) indicated that Tributyltin Oxide (TBTO) was associated with an increased incidence of cleft palate.

F. Discussion

Table 23 summarizes the lowest effect levels (LEL) and no-observed-effect levels (NOEL) as reported in each of seven developmental toxicity studies in three species considered by the Peer Review Committee. The discussion that follows generally represents the course of the Committee's discussion of those seven studies and three reproduction studies.

The first rat developmental toxicity study (Cannon Labs., Oct. 12, 1976) was determined to be invalid. However, Committee members noted that effects observed at the 8.75 and 12.5 mg/kg/day dose level included increased resorptions and decreased fetal body weight which were observed in other studies at lower dose levels.

The second rat study (Battelle, June 25, 1981), which is considered to be supplementary, also reported decreased fetal weight and increased resorptions, but this study failed to provide a NOEL for developmental effects based on an increased incidence of fetuses with hydroureter.

Table 23

Summary of No-Observed-Effect Levels (NOEL) and Lowest Effect Levels (LEL) (Expressed in mg/kg/day) as Reported in Developmental Toxicity Studies of TPTH. *

Study	Endpoint	LEL	NOEL
	Rats		
Cannon Labs., Oct. 12, 1976	Maternal toxicity: decreased body weight gain.	8.75	5.0
	Developmental toxicity: hydrocephalus and hydronephrosis.	1.25	None
Battelle, June 25, 1981.	Maternal toxicity: rough coat, oral/nasal discharge, alopecia, diarrhea, ocular discharge, vaginal discharge, lethargy, hemorrhage from the vaginal area, and thinness, and decreased body weight gain.	8.0	2.8
	Developmental toxicity: fetal mortality and decreased fetal weight; increased dead or resorbed fetuses; increased incidence of hydroureter, but no hydrocephalus was seen.	1.0	None
EPA, Health Effects Research Labs., RTP, March 28, 1985	Maternal toxicity: mortality.	8.0	4.0
	Developmental toxicity: decreased fetal weight, increased resorptions, increased severity of urogenital alterations (without increased incidence) and slightly increased incidence of hydrocephalus.	8.0	4.0
WIL, April 1, 1985	Maternal toxicity: decreased food consumption and body weight; lethargy, emaciation, anogenital staining, and red vaginal discharges.	2.8	1.0
	Developmental toxicity: increases in early resorptions, total litter resorptions, and incidence of unossified sternebrae; and decreased fetal weight.	8.0	2.8

* See text (pages 35, 37 and 38) for discussion of the quality and limitations of each study.

Table 23 (Continued)

Study	Endpoint	LEL	NOEL
	Rats (continued)		
WIL, June 4, 1985	Maternal toxicity: decreased body weight gain and increased incidence of hair loss.	2.8	1.0
	Developmental toxicity: increased absolute and relative kidney weights.	2.8	1.0
	Rabbits		
WIL, February 27, 1985	Maternal toxicity: decreased maternal body weight gain and food consumption.	0.3	0.1
	Developmental toxicity: decreased fetal body weight and increased incidence of fetuses with unossified hyoid.	0.9	0.3
	Hamsters		
Battelle, February 10, 1982	Maternal toxicity: decreased body weight gain.	12.0	8.75
	Developmental toxicity: decreased fetal weight; increased incidence of fetuses with skeletal alterations, dead and resorbed fetuses.	8.75	5.08

* See text (pages 35, 37 and 38) for discussion of the quality and limitations of each study.

The third study in rats was considered to be supplementary because it was specifically designed to evaluate the significance of central nervous system and urogenital effects observed in the two previous studies.

The results of the second and third studies failed to confirm the potential of TPTH to induce hydrocephalus in the rat, but all three studies suggested urogenital development may be affected by TPTH treatment.

Two additional developmental toxicity studies in the rat (WIL, April 1, 1985 and WIL, June 4, 1985) were considered by the Peer Review Committee. Neither of the new studies confirmed the effects

of TPTH on urogenital or central nervous system morphology indicated by earlier studies. The Committee agreed that these studies established the lowest NOEL for developmental toxicity in rats at 2.8 mg/kg/day based on increased early resorptions and decreased fetal weight and litter size observed at the 8.0 mg/kg dose level. The supplementary postnatal study (WIL, June 4, 1985) indicated that kidney weights of offspring in the 2.8 mg/kg/day dose group were increased without accompanying morphological changes.

In the discussion of the rabbit developmental toxicity study (WIL, February 27, 1985) some Committee members questioned the use of the 0.3 mg/kg/day dose level in the definitive study as a lowest effect level (LEL) based on decreased maternal body weight gain. Other Committee members commented that the variability in measured body weights and calculated body weight gains was so large that individual animal data should be examined before the mid dose level could be characterized as a NOEL for maternal toxicity.

It was also noted that mean body weight gains for low, mid and high dose groups during the pre-dosing period (days 0-6) were 64, 51, and 64% less than controls, respectively, and the low and high dose group decreases were statistically significant. These results suggested that body weight gain data from day 6 of gestation would be more appropriate to evaluation of the 0.3 mg/kg/day dose level with respect to maternal body weight gain.

Although decreased body weight gains in the 0.3 mg/kg dosed group were not statistically significant during the study, decreases were considerable from day 12 through the end of gestation (see Table 15, page 21). One Committee member indicated that subtracting the mean litter weight in the 0.3 mg/kg dosed group (7.3 fetuses/doe X 40.1 g/fetus = 293 g/doe) from the maternal weight gain during gestation days 6 through 29 (-35 g/doe + 82 g/doe = 47 g/doe) suggests a loss in maternal body weight (293 - 47 = 246 g lost/doe). A statistically significant difference was reported between the 0.3 mg/kg/day dosed group and the control group for the entire gestation period (days 0-29;). Based on the suggested loss in maternal body weight in the absence of significant decreases in fetal weight, the Committee concluded that the LEL for maternal toxicity is 0.3 mg/kg/day in the rabbit.

Committee members noted that many of the maternal and developmental effects observed in the hamster study (WIL, February 27, 1985) occurred at higher doses than those observed in the rat and rabbit studies.

One reproduction study (Central Instituut Voor Voedingoenderzook (August, 1967) is invalid because no raw data were presented with the original report, and those data have not been provided to support upgrading of the study. A second study is supplementary

because it was used to determine the doses to be used in the definitive study.

The definitive multigeneration reproduction study (WIL, August 28, 1986) indicated that the NOEL for developmental toxicity is 5 ppm in the diet (0.25 mg/kg/day), and the LEL was reported to be 18.5 ppm (0.93 mg/kg/day). Developmental effects included reduced spleen and liver weights without histopathological changes in offspring at the 18.5 ppm dose level. Parental toxicity was observed at the 50 ppm dose level (decreased body weight, body weight gain and food consumption) with a reported NOEL at 18.5 ppm (0.93 mg/kg/day). The Peer Review Committee noted that the developmental toxicity NOEL in the reproduction study was similar to that for maternal toxicity in the rabbit developmental study.

G. Weight of the Evidence

The Peer Review Committee considered the following points in its weight-of-evidence analysis of the available information on TPTH:

1. TPTH induced developmental toxicity in four studies in rats.

2. The chemical induced developmental toxicity in three species (rat, rabbit and hamster).

3. The endpoint that defined the LEL and NOEL for developmental effects was decreased fetal body weight which was consistently observed in all species tested.

4. The rabbit is the most sensitive species with a NOEL of 0.3 mg/kg/day and a LEL of 0.9 mg/kg/day for developmental toxicity (WIL, February 27, 1985).

5. Developmental toxicity occurred at or above maternally toxic levels in all three species.

6. The most sensitive species with respect to the maternal toxicity of TPTH is also the rabbit with a NOEL of 0.1 mg/kg/day.

7. A NOEL for increased spleen and liver weights observed in offspring from the multigeneration reproduction study with TPTH (5 ppm, 0.25 mg/kg/day) is approximately the same as the LEL for maternal toxicity in rabbits (0.3 mg/kg/day).

H. Conclusion

The Peer Review Committee concluded that TPTH is a developmental toxicant in rats, rabbits and hamsters with the lowest NOEL's in the rabbit at 0.1 mg/kg/day for maternal toxicity and 0.3 mg/kg/day for developmental toxicity. The lowest LEL for developmental toxicity is 0.9 mg/kg/day, and that for maternal toxicity is 0.3 mg/kg/day in the rabbit.

Note:

Subject: Additional corrections to the TPTH developmental toxicity Peer Review report.

From: John Doherty
Section I, Toxicology Branch I

To: Roger Gardner
Section Head
and
Karl Baetcke
Branch Chief
Toxicology branch I

The following adjustments should be made to the Peer Review of Triphenyltin Hydroxide Document.

page 2/3. The Battelle 1981 rat teratology study is not listed. The entry should be:

"Evaluation of the Teratogenicity of Triphenyltin Hydroxide (TPTH) in the Sprague-Dawley Rat" Battelle Columbus Laboratories, Project No.: NO723-0200, June 25, 1981. EPA MRID #00094903.

Note: Some of the study titles are listed in " " others are not. Also the project # and date for the WIL 4/1/85 study are in reverse order.

Draft is spelled drstf for the last entry.

The correct listing (to be consistent with the other listings) for the hamster study is as follows:

"The Evaluation of the Teratogenicity of Triphenyltin Hydroxide in the Syrian Golden hamster" Battelle Columbus Laboratories, February 10, 1982, Project No.: N)723-0100. MRID #00094904.

page 11, Table 6. David Anderson indicated that the weight gain data for the 4 mg/kg dose group is not indicated as being statistically significant. Kavlock's original report indicates that this is stat sig at 0.05 level. Please add a * to this entry (i.e. 26 $\pm$ 4*).

Table 6 does not indicate a 'slight" increase in cerebral ventricle grade. These data are very difficult to illustrate in this document without the comprehensive table such as the one prepared by Kavlock to show that there was a shift to a higher grade. The means are very close together and there was no statistical analysis.

In particular comparing the means of 1.71 and 1.65 for the right and left control kidneys with 1.58 and 1.46 for the right and left high dose kidneys implies that the opposite is true (there was a less degree of effect in the highest dose level tested).

You might consider replacing the mean scores with the percent in grade 2/3 as follows:

	Control	4 mg/kg	8 mg/kg
Cerebral ventricles			
percent in grade 3	1.6	2.5	6.7
Kidney			
percent in grade 2/3[1]			
right	63/4	70/5	56/1
left	59/3	66/5	44/1
Ureter			
Percent in grade 2/3[1]			
right	10/0	26/2	28/0
left	30/0	37/7	38/0

Note: One rat in the 4 mg/kg dose group had a kidney with grade 4. No other rats had this level.
[1] Data for grade 2 are presented in the numerator and for grade 3 presented in the denominator.

Observation. On reexamination of these data (today) I find that there is no real shift in the kidney but possibly a slight shift in the ureter. You may want to drop the kidney data from the Table 6.

Your reference to the severity grades for kidney effects being more pronounced in Phase I than in Phase II is not true. I rechecked Kavlock's paper and it is rather apparent that the ureter effect is similarly affected in Phase II as in Phase I. For example the controls were 42 and 58% for the right and left kidneys vs. 59 and 75% (differences of 17 and for both) for the 4 mg/kg/day group in Phase II. Whereas this difference is also 16 and 17 for Phase I (see Table above).

Overall I don't think there is enough data from Kavlock's study to go on to make a decision her. In particular, Phase I had only 10 and 30% while Phase II had 42 and 58% classified in grade 2. There is too wide a variation among the untreated animals and

probably subjective errors in classifying.

The last sentence of the paragraph on page 11 should be located after Table 6 since the content of this sentence is not related to Table 6 and contains important information about other experimental procedures.

page 32.

The following is a rewrite to accurately reflect the conclusions of the carcinogenicity Peer review report:

"the significant increases in fatal pituitary gland adenomas in female Wistar rats, and Leydig cell tumors in male Wistar rats; and, the significant increases in male and female NMRI mice of hepatocellular adenomas and combined hepatocellular (adenoma and/or carcinoma) tumors and, in female mice a positive trend for hepatocellular carcinomas".

page 35

Quality and limitations of each study are not discussed in the text.

page 35/36

The pertinent and relevant information on the rat MGR study NOEL and LEL were not included in this table. These should be presented!

page 38

Developmental toxicity in the rat MGR study (NOEL = 0.25 mg/kg and LEL = 0.93) is below the maternal toxicity in the rat for the developmental toxicity studies (NOEL = 1.0 mg/kg and LEL = 2.8 mg/kg). Thus item 5 of the W of E needs a qualifier. Perhaps item 5 should be dropped and add to item 7

.....(0.3 mg/kg/day) but is below the NOEL for maternal toxicity in rats (1.0 mg/kg/day).

Note:

I discussed Dave Anderson's comments with him. I pointed out where the data for hyoid ossifiation were in the text (on page 24). I already mentioned his other comment about stat sig of some of Kavlock's maternal body weight gain data. Dave said he would pull his comments out now that the corrections will be made and that he knows where the data was presented.