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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Registration No. 8340-17 - Triphenyltin Hydroxide: Review of a Two-Generation Reproduction Study in Rats.

Tox Chem. No.: 896E
Tox Project No.: 2308
Record No.: 180471

FROM: John Doherty John Doherty 4/20/87
Toxicology Branch
Hazard Evaluation Division (TS-769C)

TO: Phil Hundemann, PM Team 21
Fungicide-Herbicide Branch
Registration Division (TS-767C)

THRU: Edwin Budd
Section Head, Toxicology Branch
Hazard Evaluation Division (TS-769C)

Budd 4/20/87

Background

The American Hoechst Corporation (Somerville, NJ) has submitted a multigeneration reproduction study with rats to fulfill the data gap for triphenyltin hydroxide (TPTH) indicated in the Toxicology Branch (TB) chapter of the Registration Standard for this chemical.

Previous reviews of a reproduction study and other studies have indicated that TPTH may affect the size of the testes and the weight of the spleen (refer to the TB chapter of the Registration Standard dated March 27, 1984). The multigeneration reproduction study previously submitted was determined to be INVALID because the study was available in summary form only. Thus, the registrants were asked to submit the original data or provide another study.

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A range-finding study designed to select the dose levels for the main study was conducted by the Battelle Laboratory and previously reviewed by TB (see J. Doherty review dated August 11, 1984 for PP#3F2823/FAP#3H5384). This study indicated that TPTH demonstrated adverse reproductive effects at dose levels of 100 ppm and above. Subsequently, the registrants submitted a protocol for the main study which was also reviewed by TB (see J. Doherty review dated June 18, 1985 for EPA Registration No. 8340-17).

TB Comments

1. The study has been reviewed and found to be CORE GUIDELINES.

2. The study was assigned a NOEL of 5 ppm by TB. This differs from the study report which assigns a NOEL of 18.5 ppm.

   TB has determined that there is evidence of decreased live litter size, and decreases in the weights of both the liver and spleen of pups at the dose level of 18.5 ppm such that a lower NOEL is more appropriately assigned.

   There were no specific effects of TPTH on the actual reproductive performance. (Note: the decrease in live litter size is considered to be a generalized systemic toxicity response rather than a specific reproductive response).

3. The decrease in spleen weight is consistent (but at a higher level) with the observation in the previous reproduction study. The change in spleen weight as well as the change in the thymus weight (definitely evident at 50 ppm in the weanlings) may relate to the potential immunotoxicity of TPTH although there were no specific data in this study which showed that the immunosystem of the rats on the study was affected.

4. A NOEL (18.5 ppm) was established in this study for decrease in testis weight. The observation in the previous 3-generation reproduction study that testes weight was decreased at dose levels in the range of 1 ppm was not confirmed in this study.

Reviewed by: John Doherty
Section II, Toxicology Branch (TS-769C)
Secondary reviewer: Edwin Budd
Section II, Toxicology Branch (TS-769C)

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DATA EVALUATION REPORT

Study Type: 83-4; Multigeneration Reproduction, Rats

Tox. Chem. No.: 896E
MRID No.: None

Accession Nos.: 264667, 264668, 264669, 264670, 264671, 264672, 264673, 264674, 264675, 264676

Test Material: Triphenyltin Hydroxide, 97.2% pure.

Synonyms: TPTH

Study Number(s): WIL-39022

Sponsor: Hoechst AG

Testing Facility: Wil Research Laboratories
Ashland, Ohio

Title of Report: A Dietary Two-Generation Reproduction Study in Rats with Triphenyltin Hydroxide

Author(s): Wil Staff Report (Dean E. Rodwell, study director).

Report Issued: August 28, 1986

Conclusions:

NOEL = 5 ppm

at 18.5 ppm — decreases in liver and spleen weight of pups and decrease in live litter size.

at 50 ppm — Decreased body weight gains (F_0 and F_1 parents), decreases in testes, thymus, and ovary weights of pups and other organ weights. Decreases in body weights at birth and in adults. Organ weight changes were not accompanied by pathological findings.

Classification: Core-Guidelines

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

1. Basic Design

The study consisted of dosing five groups of male and female Wistar (Crls(WI)BR COBS) rats as either controls (two separate groups), 5 ppm, 18.5 ppm, or 50 ppm TPTH. Each group consisted of 30 males and 30 females. The F_0 animals were obtained from the supplier, grouped, numbered, and assessed for any obvious defects and initiated on their respective diets for 70 days and then mated (one male to one female) to produce the F_1 generation.

The dosing regimen was continued through the F_1 generation and 30 males and 30 females from each dose group were dosed for 70 days before being mated (1:1) to produce the F_2 generation. At each step, adults and pups and/or weanlings were selected for necropsy, organ weight determinations, and microscopy.

Overall, there were <u>two</u> matings total, or <u>one</u> for each generation.

2. The <u>test material</u> (Triphenyltin hydroxide, TPTH or Fentinhydroxid Substanz Tech. HOE 029664 OF ZD97 0004) was described as a white powder and was stated as being of 97.2% purity. The diets were prepared by directly adding the powdered material to basal laboratory diet (Purina® Certified Rodent Meal® 5002). Diets were prepared each 5 to 7 days and blended with a Hobart mixer.

Appendix BB of the study report (in Volume 10) presents information on the diet analyses and assessment for homogeneity and stability of TPTH in the diet. In these studies, TPTH was quantitated by HPLC following extraction from the feed using 95% toluene/5% glacial acetic acid.

The tests for homogeneity (samples from top, middle, and bottom) indicated that each layer contained 94 to 103 percent of the expected concentration.

In an experiment to determine the stability of TPTH in the diet, samples were taken on the day of mixing, day 5 and day 7 following mixing. On the day of mixing, the samples were 98 to 104 percent of the expected concentration range. On day 5 the samples were 81 to 87 percent of the expected concentrations and on day 7 they were 70 to 81 percent of the expected concentrations. <u>This information indicates that TPTH decomposes in the test diet over the course of 1 week.</u> The study report states that (page 2786) storage of the test diets in plastic bags was not appropriate as losses of TPTH could be induced by the plastic bags. Storage in glass containers showed "improved analytical values."

Overall, the study reports that the low-dose group (5 ppm) received 92 to 112.6 percent, the mid-dose group (18.5 ppm) received 84.2 to 114.6 percent, and the high-dose group (50 ppm) received 83.2 to 113.1 percent of the theoretical levels of TPTH.

3. Results: Clinical observations and body weight gains (general)

There were no consistent behavioral or clinical signs reported for either the F_o or F_1 parental or F_1 or F_2 pups or weanlings. Some signs of "soft stool and wet, brown anogenital staining" were reported to be "slightly" increased in the males at dose levels of 18.5 and 50 ppm and in the females dosed at 50 ppm. These signs were also present in the control rats and not definitly shown to be a consequence of TPTH dietary administration.

In general, body weight gain for the F_o and F_1 parental groups for the rats receiving 50 ppm showed signs of decreased gain. The effects were most noticeable in the F_2 parental groups (males as much as 20% and females as much as 14% lower). There were some occasions when the mid dose group also showed decreased body weight gain (about 5%). The study report did not consider the minor and occasional decreases noted in the mid dose group to be biologically meaningful.

4. Results: Reproductive parameters (specific):

No adverse effects were noted on male or female fertility, precoital time, gestation length, or parturition for either the F_0 or F_1 parental groups.

4. Results: Litter data (quantitative) size and weights):

Live litter size was decreased for the F_1 and F_2 groups receiving 50 ppm (16% and 19%) and for the F_2 group receiving 18.5 ppm (13%) as shown in the following table.

	F_1			F_2		
Group	No. Dead	Live Litter Size	Mean	No. Dead	Live Litter Size	Mean
1 (0)[1]	1	374/29[2]	12.9	6	387/27	14.3
2 (0)	15**	358/27	13.3	1	439/30	14.6
3 (5)	2	387/29	13.3	20**	354/27	13.1
4(18.5)	3	374/30	12.5	2	341/27	12.6*
5 (50)	7	307/28	11.0*	7	338/29	11.7**

1. Number in () is dose level. 2. Numerator is number of pups, denominator is number of litters. *, $p<.05$, **, $p<.01$.

On the basis of this parameter, the NOEL for this study would be 5 ppm and the LEL would be 18.5 ppm.

Pup weight was decreased for the F_1 50 ppm dose group at lactation days 14 (-10%) and 21 (-18%). The high dose group was also lower in weight for the F_2 pups at days 7 (-12%), 14 (-23%), and 21 (-28%). Pup weights for the groups receiving 18.5 ppm were equivalent to the controls or showed only slight weight reductions.

5. Litter Data (Necropsy, organ weights, and microscopy):

There were no macroscopic lesions reported which were indicative of a test chemical effect for either the F_0 or F_1 adults or the F_1 or F_2 weanlings.

A. There were several organ weight changes noted, particularly in the 50 ppm dose groups but also in the groups receiving 18.5 ppm. These are as follows:

Weanlings:

[Note: The F_1 males (-12%) and females (-16%) and the F_2 males (-30%) and females (-30%) groups receiving 50 ppm were lower in weight than the control groups. The other dose groups (5 and 18.5 ppm) also showed slight weight decreases but were not statistically significant. Because the high-dose group was decreased in weight, organ weights would also be expected to be decreased at this dose level. Absolute organ weights and organ/brain weight ratios were determined.]

Individual organ weight deviations are discussed as follows:

a. Testes: (The testes were described as being a possible target organ and weight reduction was one of the symptoms based on the review of the earlier 3 generation reproduction study.)

The F_1 weanlings' testes weights were 17 to 23 percent lower than the control based on absolute weight, 7 to 12 percent decreased based on relative to body weight, and 17 to 21 percent decreased based on relative to brain weight in the group receiving 50 ppm. The other groups were equivalent to the controls.

The F_2 weanlings' had absolute decrease of -22 percent, but the relative to body weight ratio was slightly higher (+2 to +9%) when compared to the controls. The testes weight ratio relative to brain weight was decreased (-19 to -21%) in the group receiving 50 ppm.

No consistent increase or decrease in testes weights were evident for the F_0 or F_1 adults.

The NOEL for effects on weight of the testis is set at 18.5 ppm. The LEL is 50 ppm.

b. The spleen. The spleen was also identified in the earlier reproduction study as having a lower weight than controls.

In this study, the spleen weights of the weanlings were decreased in the mid-dose and high-dose test groups as indicated in the following table.

		Males		Females	
		Mid	High	Mid	High
F_1	Absolute	-17*	-22**	NS	-29**
	Rel. to Body	NS	NS	NS	NS
	Rel. to Brain	-17**	-21**	NS	-27**
F_2	Absolute	NS	-45**	-17*	-48**
	Rel. to Body	NS	-21**	NS	-26**
	Rel. to Brain	-17*	-40**	-18*	-44**

[Note: Data are the percent decrease in spleen weight when compared to the control for those values showing statistical significance [either $p < .05$(*)or $p < .01$(**)]. The symbol NS means that, although a decrease in weight may have been evident, there was no statistical difference noted for the group when compared to the control.]

There were no consistent decreases in spleen weights for the F_0 or F_1 adults.

Because both male and female pups show significant depressions in spleen weight for at least some of the comparisons made above including rats in the mid dose level group, the NOEL for effects on the weight of the spleen may be set at 5 ppm.

c. The thymus. TPTH is suspected as being immunotoxic; thus, organs involved with the immunity system should be carefully examined in studies with TPTH.

In this study the thymus weight was decreased in both the F_1 and F_2 weanlings but not in either the F_0 or F_1 adults. On one occasion the thymus weights for the mid-dose group males (relative to brain weight) were statistically significantly depressed (-16%). Other times the mid-dose group was depressed but not

significantly. The groups receiving 50 ppm of TPTH were depressed as much as 39 percent (absolute weight males) and 43 percent (absolute weight females).

d. The liver. The liver weight was decreased for both the mid-dose and high-dose study groups for the F_2 weanlings (both males and females), and for the F_1 adult females. The liver weight was also reduced for the high-dose group F_1 weanling females. The following table shows the liver weight deviations.

		Males		Females	
		Mid	High	Mid	High
F_0 Adults	Absolute	+6	+8.4*	--	--
	Rel. to Body	+4.6*	+6.0**	--	--
	Rel. to Brain	+5	+7	--	--
F_1 Weanlings	Absolute	-8	-9	-9	-18.2**
	Rel. to Body	--	--	--	--
	Rel. to Brain	-9	-8	-8	-15.7**
F_1 Adults	Absolute	-4	-9.3**	-8.6**	-11.8**
	Rel. to Body	--	--	-5.9**	-5.6*
	Rel. to Brain	-5	-9.2**	-8.4**	-10.5**
F_2 Weanlings	Absolute	-8	-29**	-11.5*	-27.6**
	Rel. to Body	--	--	--	--
	Rel. to Brain	-8.9*	-24.2**	-11.6*	-22.3**

[Note: Data are the percent difference from the control. The statistical differences are from the study report (*, $p < .05$; **, $p < .01$). The percentage differences shown are based on the reviewer's calculations using both the control values. --, data are very close to control and there was no statistical difference noted for the group when compared to the control.]

In particular, the F_1 adult females and the F_2 weanlings (females) and to a lesser degree, the F_2 weanlings (males) provide evidence for a liver weight effect in the group receiving 18.5 ppm.

e. The ovaries. The F_1 female weanlings had reduced absolute ovary weights for the low (-15), mid (-23), and high (-42) dose groups and the relative weights were reduced for the mid and/or higher dose groups. The ovaries for the F_2 weanlings were decreased for the high-dose group (-12% absolute weight) only. The F_0 adult females also had reduced relative ovary weights (-12%).

Because of the lack of consistency between the F_1 and F_2 weanling data with regard to ovary weight changes, no effect of TPTH on ovary weight at dose levels below 50 ppm is recognized.

f. Other organs showing decreases in weight were the kidneys, heart, lung, pituitary, and adrenal gland. The brain and adrenal gland also occasionally showed increases in weight.

Overall, based on recurring decreases in liver and spleen weight TB assigns a NOEL of 5 ppm and an LEL of 18.5 ppm. This conclusion differs from the study report conclusion which assigns a NOEL of 18.5 ppm.

TB also notes that testes weight is decreased at 50 ppm (NOEL = 18.5 ppm).

TB considers, in concurrence with the study report, that the differences in kidney, heart, lung, pituitary, and adrenal gland were related to the decrease in body weights and not specific responses to TPTH.

B. There were no microscopic findings indicative of TPTH toxicity in any of the organs for which weight differences were reported or for other organs for either the weanlings or the adults.

Conclusion:

This study is CORE GUIDELINES and fulfills the data requirement for a multigeneration reproduction study. The following "one-liner" pertains.

NOEL = 5 ppm.

at 18.5 ppm, decreases in liver and spleen weight of pups, decrease in live litter size.

at 50 ppm decreased body weight gains (F_0 and F_1 parents), decrease in testes, thymus and ovary- and other organ weights concurrent with decreases in body weight of pups. Organ weight changes were not accompanied by microscopic or macroscopic pathological changes.