3-27-84

007915

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Submission of the Toxicology Branch Chapter of the Registration Standard for Triphenyltin Hydroxide

Tox. Chem. No. 896E

TO: Tom Johnston
Project Manager for Triphenyltin Hydroxide
Fungicide-Herbicide Branch
Registration Division (TS-767)

THRU: Edwin R. Budd, Acting Deputy Branch Chief
Toxicology Branch
Hazard Evaluation Division (TS-769)

and

William L. Burnam, Branch Chief
Toxicology Branch
Hazard Evaluation Division (TS-769)

Enclosed is the Toxicology Branch (TB) chapter for the registration standard for triphenyltin hydroxide (TPTH) including the following three subparts.

1. Triphenyltin Hydroxide Policy Discussion.

2. Table A: Generic Data Requirements for Triphenyltin Hydroxide.

3. Summary of the Evaluated Data ("one-liners" and detailed reviews).

John Doherty 3/27/84
John D. Doherty, Ph.D.
Toxicology Branch
Hazard Evaluation Division (TS-769)

1 of 64

007915

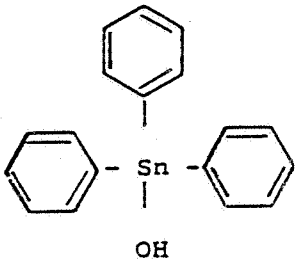
Triphenyltin Hydroxide Policy Discussion

A. Use Summary:

Triphenyltin hydroxide (see structure below) which is also known as fentin hydroxide and TPTH is sold under the names of DuTer, Flo-Tin, and Vancide-KS. TPTH is used as a fungicide on sugarbeets, potatoes, peanuts, carrots and pecans. TPTH is also registered for use as a spider mite suppressant on peanuts and as an industrial preservative. According to the Triphenyltin Hydroxide Qualitative Use Assessment (see G.J. Weidemann, Ph.D., memorandum dated June 14, 1982), "At present, there are 7 Federally-registered products containing TPTH as a sole active ingredient, 23 state registrations, and two intrastate registrations. Formulations include a 50% wettable powder, 19.7 and 40% flowable, and a 95% technical solid for industrial use. Overall application rates range from 1.5-12 oz. active ingredient per acre using ground, aerial, or sprinkler irrigation equipment."

As of February 1984 there are petitions pending regarding establishing tolerances on rice and soybeans. TPTH was developed for use in agriculture by the Thompson-Hayward Agriculture and Nutrition Co. but this company no longer has an interest in this chemical. The American Hoechst and the Uniroyal Companies currently are seeking the rice and/or soybean tolerances.

No information was provided to Toxicology Branch regarding the production and use (in pounds of active ingredient) per year.



Structure of triphenyltin hydroxide.

2

B. Data Summary:

1. One Liners

Attached

2. Policy Discussions

Triphenyltin hydroxide causes several types of toxic effects and/or lesions which are of serious concern to Toxicology Branch. These and other Toxicology Branch concerns are listed as follows:

a. Immunotoxicity - Toxicology Branch could not concur with the registrant or the testing laboratory in assigning a NOEL for immunotoxic effects in mice. Additional information has been requested from the company. As of February 1984, this information has not been provided.

Triphenyltin hydroxide was also shown to be immunotoxic to the guinea pig and the lowest dose tested (2.5 ppm) showed effects. The immunotoxic effects in mice and guinea pigs will have to be taken into consideration when the ADI is determined.

b. Reproductive effects - The multi-generation reproduction study, reviewed in 1980, indicated reduction in testicular weights for the pups. Based on available information, a NOEL of 0.5 ppm and a LEL of 1.0 ppm were assigned for this lesion. This study was determined to be INVALID because it was submitted in a summary form only without supporting data. The registrant was not able to provide the original data and has advised EPA that they will conduct a second study. The range finding study for dose selection for this second study has been reviewed by Toxicology Branch.

c. Teratology - A study with rats indicated that triphenyltin hydroxide was associated with the development of hydronephrosis and hydrocephalus in rat pups and that the study did not show a NOEL for these lesions. The registrant was asked to conduct additional studies and later submitted teratology studies with rats and hamsters. There were no teratological effects noted in the hamster study. The rat study, however, again indicated that the pups were affected with hydroureter. Toxicology

Branch did not concur with the registrant regarding the NOEL for this second study in rats.

The registrant agreed to provide additional data and analysis defending their position that the study shows a NOEL. As of February 1984, no response has been provided.

d. Oncogenicity testing - There is no acceptable oncogenic study with rats.

Review of a mouse oncogenicity study showed that the female mice developed "endometrial hyperplasia." This lesion was listed in the table of oncogenic findings by the authors. Normally hyperplasias are not considered neoplastic by Toxicology Branch but there was no explanation provided by the testing laboratory for inclusion of this lesion among the neoplasms. Toxicology Branch has requested the registrant to clarify the classification of this lesion. As of February 1984, the registrant has not provided a response.

Possible classification of this lesion as nonneoplastic will not eliminate a serious toxicity problem for this chemical because this effect was noted at the lowest test dose (7 ppm). There is, therefore, no NOEL for this lesion in this study.

e. Inhalation toxicity - Technical triphenyltin hydroxide has an acute inhalation LC_{50} of 60.3 ug/l and is classified as toxicity category I by the inhalation route. A subacute inhalation study (90 days) also indicated that inhalation toxicity may be a serious hazard. Depending on the pattern of application and exposure to applicators, special precautions for the use of this chemical may be required to protect against its inhalation hazard.

f. A dog chronic feeding study and metabolism studies are considered data gaps for this chemical. The available rat chronic feeding study is considered by Toxicology Branch to be CORE MINIMUM data. The registrant should be advised, however, that in conducting the required rat oncogenicity study a chronic feeding study should also be included. Including the chronic feeding study in the oncogenicity study will be to the registrant's own advantage and aid in establishing more firmly the NOEL in the rat.

4

g. The following mutagenesis studies should be submitted:

i. Primary DNA damage test (i.e., sister chromatid exchange or unscheduled DNA synthesis).
ii. A mammalian in vitro cytogenetics test.

C. Risk Assessment/Tolerance Reassessment:

1. Risk assessment. The clarification of the status of the lesions found in the uterus in the mouse oncogenicity study is currently (as of February 1984) being evaluated. Risk assessment may or may not be required pending the resolution of the status of "endometrial hyperplasia" as being oncogenic or otherwise.

2. Tolerance reassessment. Tolerances of 0.05 to 0.10 ppm were established several years ago for residues of triphenyltin hydroxide on several human food items. See 40 CFR 180.236 (attached).

The Acceptable Daily Intake (ADI) for triphenyltin hydroxide was previously set using the rat chronic feeding study for which at that time a NOEL of 10 ppm was considered appropriate. The data base for triphenyltin hydroxide was later re-reviewed as a part of a petition to establish tolerances on soybeans (see J. Doherty review dated July 25, 1980 for PP #0F2282 and FAP #0H5242). This re-review indicated that additional tolerances should not be established until certain problems related to the chronic feeding, teratology, reproductive and oncogenicity studies were resolved and additional data were submitted. An appropriate NOEL could not be determined from the available (in 1980) data base.

Refer to part B above for discussion of the deficiencies in the chronic feeding, reproductive, teratology and oncogenicity testing for triphenyltin hydroxide.

The current (February 1984) status of triphenyltin hydroxide in Toxicology Branch is that tolerances should not be granted until the problems in the above studies are resolved or acceptable studies are submitted and reviewed.

5

D. Use Classification

Technical TPTH is Toxicity Category I based on acute inhalation toxicity, acute dermal toxicity (when the TPTH is dissolved in starch), and primary eye irritation.

Because of the acute toxicity of this chemical and because of potential effects of subchronic and/or chronic exposure, Toxicology Branch recommends that all formulations of TPTH be considered for restricted use classification.

Commodities	Parts per million
Cattle, fat	0.02(N)
Cattle, meat	0.02(N)
Cattle, mbyp	0.02(N)
Cucumbers (residues expressed as naled)	0.5
Eggs	0.05(N)
Figs	0.1
Goats, fat	0.02(N)
Goats, meat	0.02(N)
Goats, mbyp	0.02(N)
Horses, fat	0.02(N)
Horses, meat	0.02(N)
Horses, mbyp	0.02(N)
Lettuce (residues expressed as naled)	1
Milk	0.02(N)
Mushrooms (residues expressed as naled)	0.5
Poultry, fat	0.05(N)
Poultry, meat	0.05(N)
Poultry, mbyp	0.05(N)
Raisins	0.5
Raw agricultural commodities, nonperishable, bulk stored regardless of fat content (post-H)	0.5
Raw agricultural commodities, nonperishable, packaged or bagged, containing 6 percent fat or less (post-H)	0.5
Raw agricultural commodities, nonperishable packaged or bagged, containing more than 6 percent fat (post-H)	2
Sheep, fat	0.02(N)
Sheep, meat	0.02(N)
Sheep, mbyp	0.02(N)
Tomatoes (pre- and post-H) (residues expressed as naled)	0.05

(b) The tolerance of 0.1 part per million prescribed by 21 CFR 561.180 for negligible residues of 2,2-dichlorovinyl dimethyl phosphate in the edible tissue of swine covers both its use as an anthelmintic in swine feed and as an insecticide applied directly to swine.

(Sec. 408(d)(2), 68 Stat. 512 (21 U.S.C. 346a(d)(2)))

[47 FR 55223, Dec. 8, 1982]

§ 180.236 Triphenyltin hydroxide; tolerances for residues.

Tolerances are established for residues of the fungicide triphenyltin hydroxide in or on raw agricultural commodities as follows:

0.4 part per million in or on peanut hulls.

0.1 part per million (negligible residue) in or on carrots and sugar beet roots.

0.05 part per million (negligible residue) in or on pecans, peanuts, and potatoes.

0.05 part per million (negligible residue) in the kidney and liver of cattle, goats, hogs, horses, and sheep.

[36 FR 22540, Nov. 25, 1971, as amended at 38 FR 3045, Feb. 1, 1973]

§ 180.237 4 - (Methylsulfonyl) - 2, 6-dinitro-*N,N*-dipropylaniline; tolerances for residues.

Tolerances are established for negligible residues of the herbicide 4-(methylsulfonyl) - 2,6 - dinitro - *N,N*-dipropylaniline in or on the raw agricultural commodities almonds, almond hulls, broccoli, brussels sprouts, cabbage, cauliflower, cottonseed, cucurbits, forage legumes, fruiting vegetables, grapes, peanuts, pome fruits, safflower seed, seed and pod vegetables, soybeans (dry form), and stone fruits at 0.1 part per million.

[37 FR 13619, July 12, 1972]

§ 180.238 *S*-Propylbutylethylthiocarbamate; tolerances for residues.

Tolerances are established for negligible residues of the herbicide *S*-propylbutylethylthiocarbamate in or on the raw agricultural commodities sugar beets (roots and tops) and tomatoes at 0.1 part per million.

§ 180.239 Phosphamidon; tolerances for residues.

Tolerances (expressed as phosphamidon) for residues of the insecticide phosphamidon (2-chloro-2-diethylcarbamoyl-1-methylvinyl dimethyl phosphate) including all of its related cholinesterase-inhibiting compounds in or on raw agricultural commodities are established as follows:

1 part per million in or on apples.

0.75 part per million in or on grapefruit, lemons, oranges, tangerines.

0.5 part per million in or on broccoli, cauliflower, cucumbers, peppers.

0.25 part per million in or on cantaloups, watermelons.

0.1 part per million in or on cottonseed, potatoes, sugarcane, tomatoes and walnuts.

§ 180.240 *S*-Propyl dipropylthiocarbamate; tolerances for residues.

Tolerances are established for the herbicide *S* Propyl dipropylthiocarbamate in or on the following raw agricultural commodities:

CFR 180.236 Triphenyltin Hydroxide 6/19/79

File Last updated 6/19/79

ACCEPTABLE DAILY INTAKE DATA

RAT, Older mg/kg	NOEL ppm	S.F.	ADI mg/kg/day	MPI mg/day/60kg
0.500	10.00	100	0.0050	0.3000

Published Tolerances

CROP	Tolerance	Food Factor	mg/day/1.5kg
Carrots (24)	0.100	0.48	0.00072
Sugar, cane & beet (154)	0.100	3.64	0.00546
Pecans (118)	0.050	0.03	0.00002
Peanuts (115)	0.050	0.36	0.00027
Potatoes (127)	0.050	5.43	0.00407
Kidney (203)	0.050	0.03	0.00002
Liver (211)	0.050	0.03	0.00002

MPI	TMRC	%ADI
0.3000 mg/day/60kg	0.0106 mg/day/1.5kg	3.53

4

Table A
Generic Data Requirements for Triphenyltin Hydroxide

Data Requirement	Composition	Use Patterns	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)?	MRID No.	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)?
§158.135 Toxicology					
Acute Testing:					
81-1 Oral LD_{50}-Rat	TGAI	All	Yes	00083557	No
81-2 Dermal LD_{50}	TGAI	All	Yes	00083560	No
81-3 Inhalation LC_{50}-Rat	TGAI	All	Yes	00088562	No
81-7 Acute Delayed Neurotoxicity-Hen	Not Required	-	--		--
81-6 Sensitization Study-g.p.	TGAI	All	Partially	Not available	Yes
Subchronic Testing:					
82-1 90-Day Feeding-rodent	TGAI	A	Partially	00086514,00045837 & 00086548	Yes[1]
-nonrodent (dog)	TGAI	A	Partially	00065167 and 00045831	Yes[2]
-nonrodent (guinea pig)	TGAI	A	Yes	00086467	No
82-2 21-Day Dermal	TGAI	A,IP	No		Yes
82-3 90-Day Dermal	Not Required	-	-		-
82-4 90-Day Inhalation	TGAI	A,IP (see footnote 6)	Yes	Not Available	Yes[3]
82-5 90-Day Neurotoxicity-Hen	Not Required	-	--		--
Chronic Testing:					
83-1 Chronic Toxicity-rat	TGAI	A	Partially	00046016 and 00080390	Yes
-dog	TGAI	A	Partially	00080391	Yes

Table A (Continued)
Generic Data Requirements for Triphenyltin Hydroxide

Data Requirement	Composition	Use Patterns	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)?	MRID No.	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)?
83-2 Oncogenicity-rat	TGAI	A	Partially	00046016 and 00080390	Yes
-mouse	TGAI	A	Partially	Not Available	Yes
83-3 Teratology-1st species (rat)	TGAI	A,IP	Yes	00086547 and 00094903	Yes[4]
2nd species (hamster)	TGAI	A,IP	Yes	00094904	No
83-4 Reproduction-2 generations	TGAI	A	Partially	00086548, 00086549	Yes
Mutagenicity Testing:					
84-2 Gene Mutation	TGAI	All	Yes	00086551	No
84-2 Chromosome Abberation	TGAI	All	No		Yes
84-2 Other Mechanism of Mutagenesis (Dominant Lethal)	TGAI	All	Yes	05016869	Yes[5]
Special Testing:					
General Metabolism	PAI or PAIRA	A	No		Yes

Composition: TGAI=technical grade of the active ingredient: PAI = pure active ingredient; PAIRA = pure active ingredient, radio-labeled.
The use patterns are coded as follows: A=Terrestrial, food crop; B=Terrestrial, non food; C=Aquatic, food crop; D=Aquatic, non-food; E=Greenhouse, food crop; F=Greenhouse, non-food; H=Domestic, outdoor; I=Indoor; IP = Industrial preservative.

See next page for footnotes 1-6.

1-Submission of an acceptable chronic feeding study with rodents will eliminate this requirement.
2-The dog 100-day study was by IBT and has not been validated. Submission of an acceptable chronic feeding study with dogs will eliminate the requirement for a 90-day study with dogs.
3-Additional information related to the 90 day inhalation study was requested of the registrant. No reply has been provided as of February 1984.
4-TB is waiting for the registrant to provide an acceptable defense for establishing a NOEL for teratogenic/fetotoxic effects in rat fetuses.
5-See discussion of mutagenicity concerns under Policy Discussion.
6-The requirement for a 90-day inhalation study relates to the acute inhalation toxicity of this chemical.

0079

Study/Lab/Study #/Date	Test Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Acute Oral LD_{50} - Rat Hoechst Akt. #182/81 April 22, 1981	Technical TPTH	071364	LD_{50} = 165 (113-230) mg/kg - males Toxicity develops slowly, deaths 5-13 days after initial dose.	II	Minimum 003116
Acute Oral LD_{50} - Rat Hoechst Akt. #183/81 April 22, 1981	Technical TPTH	071364	LD_{50} = 156 (115-208) mg/kg - females Toxicity develops slowly, deaths 5-9 days later.	II	Minimum 003116
Acute Oral LD_{50} - Rat Cannon Labs study # Not provided January 31, 1978 MRID #00083557	Technical TPTH		LD_{50}'s 313 (232-422) mg/kg-males 345 (138-862) mg/kg-females	II	Minimum
Acute Oral LD_{50} - Dog Hoechst Akt. #462/81 August 13, 1981	Technical TPTH	071364	LD_{50} not determined, dogs vomited doses in excess of 25.0 mg/kg.	-	Supplementary 003116
Acute Dermal LD_{50} - Rabbit Hoechst Akt. #229/81 May 6, 1981	Technical TPTH	071364	LD_{50} = 127 (79.6-223) mg/kg-males only, deaths occurred 3-8 days post dosing.	I	Minimum 003116
Acute Dermal LD_{50} - Rat Hoechst Akt. #A21453 April 22, 1981	Technical TPTH	071364	LD_{50} = 1600 mg/kg (females)	II	Supplementary 003116
Acute Dermal LD_{50} - Rabbit Cannon Labs# Not provided February 15, 1978 MRID #00083560	Technical TPTH		LD_{50} = 3000(1820-4950) mg/kg	III	Guidelines

-6-

00 7915

Study/Lab/Study #/Date	Test Material	EPA Accessic No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Acute Inhalation LC_{50} - Rat Hoechst Akt. #355/81 June 22, 1981	Technical TPTH	071364	LC_{50} = 60.3 (46.5-79.5) mg/m^3 or ug/L. Deaths may be delayed in onset. (Note: 4 hr. exposure time)	I	Guidelines 003116
Acute Inhalation LC_{50} - Rat Cannon Labs # Not provided February 22, 1978 MRID #00088562	Technical TPTH		LC_{50} = 0.21 mg/l (0.18-0.25) for males = 0.24 mg/l (0.22-0.26) for females	I or II	Supplementary
Primary Dermal Irritation - Rabbit Hoechst Akt. #104/81 March 10, 1981	Technical TPTH	071364	PIS = 2.8	III	Minimum 003116
Primary Eye Irritation - Rabbit Hoechst Akt. #104/81 March 10, 1981	Technical TPTH	071364	CORROSIVE! Only 3 days were allowed for reversal of opacity.	I	Minimum 003116
Primary Eye Irritation - Rabbit Cannon Labs # Not Provided October 19, 1977 MRID #00088622	Technical TPTH		CORROSIVE	I	Guidelines
Sensitization (Buehler) - Guinea Pig Hoechst Akt. #724/81 December 30, 1981	Technical TPTH	071364	Not a sensitizer. Severe dermal irritation may have obscured an effect.	-	Supplementary 003116

Study/Lab/Study #/Date	Test Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
90-Day Feeding - Rat National Institute of Public Health Utrecht, November 19, 1962 MRID #00086514	Technical TPTH		Depressed leukocyte counts at all dose levels (5 ppm LDT). Increased adrenal weight, decreased thyroid and prostate weights.	-	Supplementary
90-Day Subacute Feeding - Rat IBT #B4634 December 29, 1966 MRID #00045837	Technical TPTH		Decreased lymphocytes noted but poor dose response relationship.	-	Invalid
90-Day Subacute Feeding - Rat Central Institut Voor Voedingoenderzock August 1967 MRID # 00086549	Technical TPTH		Changes in organ weights-kidney, spleen and testicle (see review).	-	Invalid
90-Day Feeding - Guinea Pig National Institute of Public Health Utrecht May 30, 1960 MRID #00086467	Technical TPTH	099050	LEL < 2.5 ppm (lowest level tested). Decreased leukocyte count.	-	Minimum 001492
90-Day Feeding - Dog Industrial Biotest # IBT-C3964 March 7, 1966 MRID #00065167	Technical TPTH		NOEL = 25 ppm LEL = 37 ppm Body weight loss, irregular pigment deposition in Kupfer cells in liver, Depressed hematocrit and erythrocyte count.	-	001493 INVALID (as assigned February 1984)

Study/Lab/Study #/Date	Test Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
100-Day Feeding - Dog IBT #C-4343 December 2, 1966 MRID #00045831	Technical TPTH		NOEL = 10 ppm LEL = 25 ppm Tin found in livers.	-	001494 INVALID (as assigned February 1984)
90-Day Inhalation - Rat Cannon Labs #7E-8305 April 12, 1979	Technical TPTH	071366	Histopathology report incomplete. Conclusions not finalized as of February, 1984. Effects noted at 0.0011 mg/liter (LDT), see review.	-	RESERVED - pending submission of complete histopathology report. 003116
One-Generation Reproduction - Rat (Range Finding Study) Battelle #N0723-0400 July 22, 1982	Technical TPTH	071368	Adverse effects (pup deaths and decreased pup body weight) and kidney effects in parents at 100 and 200 ppm. Doses selected for definitive study were 0, 5, 15.8 and 50 ppm. See Review for more effects.	-	Supplementary 003116
3-Generation Reproduction - Rat Central Institut Voor Voedingoenderzock August 1967 MRID #00086548	Technical TPTH	099052	NOEL for effects on testes and spleen weights = 0.5 ppm. Effects not verified.	-	INVALID 001492
Testicular Development - Rat Central Institut Voor Voedingoenderzock February 1968 MRID #00086549	Technical TPTH		NOEL = 25 ppm (Highest level tested)	-	Supplementary 001492

Study/Lab/Study #/Date	Test Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
19-Day Feeding - Rat Histology of Testis Clemson Univ. 1968 MRID # Not available	Triphenyltin acetate and Triphenyltin chloride		LEL $\leq$ 20 ppm (Only level tested). Decreased number of cell layers per seminiferous tubule, decreased tubular diameter, decrease in overall testicular size, depletion of more advanced cell forms from the tubules and closing of tubule lamina.	-	001492 SUPPLEMENTARY (as assigned February 1984)
Teratology - Rat Cannon Labs # Not provided October 12, 1976 MRID #00086547	Technical TPTH	099051	Teratogenic LEL $\leq$ 1.25 mg/kg (lowest level tested) Hydrocephalus & hydronephrosis. Maternal NOEL = 5 mg/kg Maternal LEL = 8.75 mg/kg Abortions Decreased body weight gain. Decreased % live fetuses. Decreased fetal weight. Increased resorptions.	-	Minimum 001492
Teratology - Rat Battelle Columbus #NO 723-0200 June 25, 1981 MRID #00094903	Technical TPTH	070696	Teratogenic LEL $\leq$ 1.0 mg/kg (lowest level tested) for hydroureta. Maternal NOEL = 2.8 mg/kg Maternal LEL = 8.0 mg/kg Mortality ↓body weights ↓pregnancy rate ↓uterine weights ↓live fetuses/litter ↓fetal weights	-	Minimum 001782

Study/Lab/Study #/Date	Test Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Teratology - Hamster Battelle Columbus #NO 723-0100 February 10, 1982 MRID #00094904	Technical TPTH	070697	Teratogenic NOEL $\geq$ 12.0 mg/kg (HDT) Fetotoxic at 12.0 mg/kg (NOEL = 5.08 mg/kg) Maternal toxicity NOEL = 5.08 mg/kg	-	Guidelines 001782
Teratology - rat Univ. of Milano (No study no.) 1980 (in Bull Environm. Contam. Toxicol. 24:936-939 (1980)	Triphenyltin acetate	070695	Hydroureter at 15 mg/kg (13.8% vs. 0% in controls)	-	Supplementary
2-Year Feeding - Rat Central Institut Voor Voedingoenderzock #R-3138 August 1970 MRID #00046016 and 00080390	Technical TPTH	099050	NOEL = 2 ppm LEL = 5 ppm Decreased WBC	-	Minimum-As a Chronic feeding study Supplementary as an oncogenic study 001492 001495
Carcinogenicity - Rat NCI 78-1394 Litton Bionetics	Technical TPTH	099050	No evidence of oncogenic effects up to and including 75 ppm (HDT)	-	Supplementary 001492
2-Year Feeding - Dog Central Institut Voor Voedingoenderzock #R-2717 July 1968 MRID #00080391	Technical TPTH	099050	NOEL = 2.5 ppm LEL = 5 ppm Rapid hair growth, decreased thyroid weights, increased water content of the brain. Study poorly done: Animals crowded, steroid and sulfa drugs used to treat dermatoses.	-	Supplementary 001492 001495

Study/Lab/Study #/Date	Test Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
18-Month Oncogenicity - Mice Cannon Labs #6E-725 August 28, 1978 and April 18, 1979 (revised)	Technical TPTH	071367	Endometrial hyperplasia of the uterus observed in all TPTH-treated female groups. The nature of this lesion must be clarified. Levels tested - 0, 7, 28 and 52 ppm. Conclusions not finalized as of February 1984.	-	RESERVED - pending submission of additional information and tables. 003116
Carcinogenicity - Mouse NCI 78-1394 Litton Bionetics	Technical TPTH	099050	No evidence of oncogenic effects up to and including 75 ppm (HDT)	-	Supplementary 001492
10-Day Immunotoxicity- Immature Male Rat, Hoechst Akt. #637/81 November 2, 1981	Technical TPTH	071364	No immunotoxicity noted as indicated by changes in the thymus or spleen weights. Only dose tested was 2.5 mg/kg for 10 days.	-	N/A 0003116
14-Day Immunotoxicity - Male Mice Quintox #QU/THAN 104 May 17, 1982	Technical TPTH	071365	Toxicology Branch's conclusions = Effects on spleen weight and IgM AFC spleen cells and on spleen cell response to mitogens at 2.5 mg/kg/day. (LTD) - i.e., study does not demonstrate a NOEL for immuno-toxicological effects. Decreased leukocyte counts also observed at most dosage levels (including LDT).	-	N/A 003116

Study/Lab/Study #/Date	Test Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Mutagenicity - Ames Test Huntingdon Res. Ctr., #450/81A July 23, 1981	Technical TPTH	071368	Not mutagenic to E. coli (WP2-UVRA) or S. typhimurium (TA-1535, 1537, 1538, 98 and 100), with and without metabolic activation.	-	N/A 003116
Mutagenicity - dominant lethal - Rat Cannon Labs, #7E-8306 April 23 [redacted] 1978	Technical TPTH	071368	Negative at doses up to and including 38 mg/kg/day. At 150 mg/kg/day, high rate of deaths obscure possibly positive results.	-	N/A 003116
Mutagenicity - Ames Test Lab not identified Report date = April 4, 1976 MRID #00086551	Technical TPTH		Not a mutagen	-	N/A 001492

The Acute Oral Toxicity of Technical TPTH in Rats

Cannon Laboratories, Inc., January 31, 1978
MRID #00083557

Five groups of ten rats (5 male and 5 female) were dosed with 0, 100, 200, 300, 400 and 500 mg/kg of "Technical TPTH" in corn oil.

Results: Animals dosed with the test chemical displayed piloerection, decreased locomotor activity, oily or wet ventral surfaces, nasal hemorrhaging, ptosis, alopecia, diarrhea, decreased food consumption, and body weight gain.

Acute oral LD_{50}'s of -

313 (422-232) mg/kg for males

345 (862-138) mg/kg for females

Autopsy of all test animals revealed irregular thickening of the tissue separating the pylorus and cardia and thickening of the cardiac muscosa.

This test is CORE MINIMUM. No autopsy report is presented, the pathological findings are statements only. The autopsy report should be presented in order to appraise the extent of lesions described as irregular thickening of various tissues. Toxicity Category II.

Acute Oral Toxicity of HOE 29664 Active Principle in Male and Female Rats

Hoechst Aktiengesellschaft Drug Research Toxicology, #182/81 (males) and 183/81 (females), April 22, 1981, EPA Acc. No. 071364, Tabs C-1 (males) and C-2 (females).

Four groups of 10 male and 10 female rats were fasted and dosed with either 80, 160, 315 or 630 mg/kg of technical TPTH and observed for 19 days.

LD_{50}'s of 165 (113-230) mg/kg for males, and
156 (115-208) mg/kg for females

were determined. The rats which died, died 5-9 days after treatment (females) and 5-13 days after treatment (males). Toxic signs developed 2 days after treatment and included "passivity", equilibrium disturbances and reddening of the skin; still later symptoms of squatting, ataxia, piloerection, blood encrusted, adhering eyelid margins, diminished respiratory rate, mucous stool and poor general condition. Body weight

was decreased. Autopsy of the rats which died showed generalized changes in the liver (discoloration), GI tract (reddening), lungs (reddening). Autopsy of the survivors was reported as unremarkable.

These two studies together are CORE MINIMUM. The symptoms of poisoning and autopsy are listed in narrative form without tables showing intensity and duration. Sufficient data are presented to assign Tox Cat. II. This chemical produces toxic symptoms that are slow in onset and may persist for several days if the product is swallowed. Death may result several days after ingestion.

Acute Oral Toxicity of Fentin-Hydroxide, Active Ingredient, to the Male and Female Beagle Dog

Hoechst Aktiengesellschaft, #462/81, August 13, 1981. EPA Acc. No. 071364, Tab. C-3.

Four groups of two dogs (1 male and 1 female) were dosed with either 12.5, 25.0, 50.0 or 100 mg/kg of TPTH in gelatin capsules and observed for 14 days.

No dogs died. The dogs receiving 12.5 mg/kg did not show adverse effects of the test chemical. Dogs receiving the higher doses (except the bitch receiving 25.0 mg/kg) vomited the test material. In some cases the vomitus was bloody.

This study is CORE SUPPLEMENTARY. The study demonstrates primarily that the dogs will not tolerate doses 25.0 mg/kg or higher. No LD_{50} was determined.

The Acute Dermal LD_{50} of Technical TPTH on New Zealand Albino Rabbits

Cannon Laboratories, February 15, 1978
MRID #00083560

Four groups of four rabbits (2 of each sex) were prepared and dosed dermally with 3, 4, 5 or 6 gm/kg body weight of technical TPTH.

These rabbits exhibited edema, erythema, decreased locomotor activity, loss of righting reflex and mortality. All dose levels exhibited a decrease in body weight and food consumption. Necropsy revealed "injected blood vessels" in the intestines.

The acute dermal LD_{50} was 3.00 (1.82 to 4.95) gm/kg.

This test is CORE GUIDELINES. Toxicity Category III. Following the dermal route of exposure, a persistent lesion develops.

Acute Dermal Toxicity of HOE 29664 (TPTH) Active Principle Code = HOE 29664 OFAT201 in Female Rats

Hoechst Aktiengesellschaft, #A21459, April 22, 1981.
EPA Acc. No. 071364, Tab C-6.

Four groups of female Wistar rats were prepared (clipped but not abraded) and dosed with 1,000, 1,600, 2,000 or 2,500 mg/kg of TPTH suspension. Contact was made for 24 hours. The rats were observed for 21 days.

The LD_{50} was determined to be about 1,600 mg/kg. Symptoms similar to those noted in the male rabbits (see below) were noted.

This study is CORE SUPPLEMENTARY. The product is Tox Cat. II by the dermal route to rats. No males were included and rats are not the usual species for acute dermal LD_{50} testing and no justification for the use of rats was presented.

Acute Dermal Toxicity of HOE 29664 Active Principle in Male Rabbits (Report #229/81).

Hoechst Aktiengesellschaft, #229/81, May 6, 1981.
EPA Acc. No. 071364, Tab C-5.

Three groups of 6 male rabbits were prepared by clipping and abrading and dosed with 50, 100, or 200 mg/kg of TPTH (as a 20% suspension in 2% starch syrup). After 6 hours, the test material was washed off. The rabbits were observed for reactions for 21 days.

An LD_{50} of 127 mg/kg with confidence interval of 79.6-223 mg/kg was determined. Deaths occurred between 3-8 days after dosing. The signs of toxicity which developed after the first day of treatment were passivity, squatting, ataxia, erythema, sedation, lying on the abdomen and side, slow intermittent breathing, abnormal breathing sounds, paresis of the rear extremities, diminished reflexes, coma and hypothermia. The treated areas of the skin became dry, cracked, scaly, hard and bulging and eventually peeled. At 21 days the skin of the survivors showed signs of healing. Body weights were reduced. Autopsy revealed in the rabbits which died "tautly distended bladders, gastrointestinal tract empty, and plethora of the lungs." Autopsy of the survivors was reported as being unremarkable.

This study is CORE MINIMUM. The data for reactions and necropsy are as statements only without giving the onset, intensity or duration of the symptoms. TPTH is shown to be a slow acting poison with deaths and toxicity resulting a few days after contact. The test data support a Tox Cat. I

22.

classification. Because of the Tox Cat. I classification, an additional study in female rabbits is not required. The chemical was in contact with the skin for only 6 hours.

Acute LC_{50} Inhalation Study of Technical TPTH

Cannon Laboratories, Inc., February 22, 1978.
MRID #00088562

Groups of 10 (5 male and 5 female) rats were exposed to atmospheric concentrations of 0.18 to 0.32 mg/l for single four hour periods. The exposure chamber was a 40 liter glass housing. The atmosphere was generated as a dust using a 3-neck, roundbottom, 250 ml Pyrex flask. The dust was introduced into the chamber by blowing across the surface of the test material. The atmospheric concentration was monitored by glass fiber filters. The particle sizes were monitored by a cascade impactor.

Results: The mean particle size was determined to be 1.25 to 2.67 u. During exposure the rats exhibited marked inactivity, reddened ears, decreased respiration, lacrimation and gasping inactivity and death. A variety of symptoms were noted during the 14-day post-exposure period.

The LC_{50} was determined to be 0.21 mg/l (0.25-0.18) for males; for females: 0.24 (mg/l) (0.26-0.22). This is Toxicity Category II criteria.

This test is CORE SUPPLEMENTARY. The large std. errors obtained in determining the mean concentrations indicate that this chemical may be more toxic than this test determines and belongs in Toxicity Category I. This test indicates that this chemical may be more hazardous by the inhalation route than by the dermal or oral exposure. Even at the lower doses, some of the toxic signs persist after 14 days in the survivors. These included red ears, puffy eyes, loss of hair and moribund appearance.

Dust Inhalation of HOE 29664-Active Ingredient in the Male and Female SPF-Wistar Rat - 4-Hour LC_{50}

Hoechst Aktiengesellschaft, #355/81, June 22, 1981
EPA Acc. No. 071364, Tab C4.

1. The test substance was triphenyltin hydroxide (TPTH) and was stated as being 97.0% pure with code numbers HOE 29664 OF AT201 and was described as being a pure white powder.

2. The test substance was introduced into the exposure chamber by means of a Wright Dust Feed Mechanism. The chamber was defined as a glass/steel cylinder which contained the test rats in such a way that only the noses of the test rats were exposed to the atmosphere containing TPTH.

3. The test rats used were Wistar-derived SPF. Six males and six females per dose group were tested. The exposure time was for 4 hours. There was a 21-day post-exposure observation period.

4. The atmospheric chamber concentrations were determined gravimetrically by trapping the dust on membrane filter paper. The chamber concentrations were determined to be 27.2, 42.0, 74.5, 132 and 369 mg/m^3 of air. This corresponds to ug/l of air.

5. Particle sizes of the dust in the chamber were monitored by a "particle-size counter, model 225, manufactured by Kratel GK, Gerlingen." It was determined that >90% of the particles were <3.00 um in diameter. [Note: it is not known if the apparatus was a Cascade type impactor or otherwise.]

6. The LC_{50} of 60.3 (46.5-79.5) mg/m^3 was determined for 4 hours of exposure. No deaths were noted in the lowest dose level group. There were 4 deaths (of 12 rats) in the group dosed with 42 ug/l. Most of the rats in the higher dose groups died. Deaths were usually at 24-29 hours after exposure but some rats died as late as 13 days later.

7. The signs of exposure included "blepharophimoses, irregular, noisy and jerky respiration, spasmodic respiration, bristled hair, passiveness, disequilibrium, squatting, abdominal position, trembling, hyporeflexia, reduced reflexes, ears with marked supply of blood, encrusted ears, alopecia at the orbital margins." Some of these signs persisted until day 13.

8. Necropsy of the rats which died revealed dark red foci of the lungs. Some of the survivors displayed "muddy grey-rose pink lungs of soiled consistency."

CONCLUSION: This study is CORE GUIDELINES. The LC_{50} is 60.3 ug/l or Tox Cat. I. This chemical must be considered dangerous by the inhalation route. Inhalation may result in a persistent lung irritation.

Skin and Mucous Membrane Tolerance of HOE 29664 Active Principle in Rabbits

Hoechst Aktiengesellschaft, #104/81, March 10, 1981
EPA Acc. No. 971364, Tab C-7

Part I. Skin Tolerance (Patch Test).

2X500 mg of test material (TPTH, HOE 29664 OF AT201, a beige powder) was applied to the prepared backs of six rabbits. The rabbits were prepared by clipping and abrading and 500 mg was applied to an abraded area and a nonabraded area of each rabbit. The test material was first made into a mixture with 0.9% NaCl prior to application and was kept in place for 24 hours with plaster strips.

A PII of 2.8 was determined. One of the rabbits died as a result of the exposure. The treated area of some of the rabbits was reported as "dry and rough, superficially cracked and bulging."

This study is CORE MINIMUM. The product may be classified as Tox Cat. III as a primary dermal irritant.

Part II. Mucous Membrane Tolerance.

100 mg of powdered test material mixed with saline (same as Part I above) was applied to the conjunctival sac of the left eye of each of 9 rabbits. Three of the rabbits were washed with 200 ml of physiological salt solution. The eyes were examined for 3 days afterward.

After 72 hours, corneal opacity was present in all rabbits (except 1 washed rabbit).

This study is CORE MINIMUM. The technical TPTH is considered CORROSIVE to the eyes. The study used only a 3-day observation period and thus not enough time for possible reversal of opacity was allowed.

The Effects of Technical TPTH (Lot No. pp. 523A, -94.8%) on the Eye Mucosa of New Zealand Albino Rabbits

Cannon Laboratories, Inc., October 19, 1977
MRID #00088622

Nine New Zealand albino rabbits were dosed with 50 mg of technical TPTH by instillation into the right eye. Three of these rabbits were further treated by rinsing the eye 30 seconds after instillation.

Corneal opacity that did not reverse within 7 days developed in all 9 rabbits. Washing reduced the severity but the opacity persisted to 7 days in these rabbits.

This test is CORE GUIDELINES. Toxicity Category I. The Technical TPTH is CORROSIVE.

Test for Sensitizing Properties of Fentin Hydroxide - Technical in Guinea Pig (According to Buehler)

Hoechst Aktiengesellschaft, #724/81, December 30, 1981
EPA Acc. No. 071364, TAB C-9

This study is in summary form only. No data are presented to confirm the procedures and support the conclusions.

The study consisted of two preliminary trials to assess primary irritancy of technical triphenyltin hydroxide. Doses as low as 0.5% proved to be irritating to the skin when applied by epicutaneous injection. Thus, a dose of 0.1% was used for the main test. The main test consisted of making 9 epicutaneous applications of 0.5 ml each of TPTH in 0.9% saline. The exposure was for 6 hours. The 9 applications were made over a three-week period. 16 days after the last application, challenge applications were made by applying 0.5 ml of a 0.10% solution of TPTH. A second challenge was made 3 more days after the first. Skin reactions were evaluated 6, 24 and 48 hours after the challenge applications.

The skin of the treated guinea pigs became hardened and cracked after 7 days of treatment. The challenged guinea pigs did not produce evidence that TPTH caused sensitization.

This study is CORE SUPPLEMENTARY. No positive control was included. The primary irritancy of the test material may have obscured a sensitization reaction.

90-Day Semi-chronic Investigation as to the Toxicity of Triphenyltin Hydroxide in Guinea Pigs

National Institute of Public Health - Utrecht, May 30, 1960
MRID #00086467

Five groups of guinea pigs were grouped as control (20 males and 20 females), or test groups that were dosed with 2.5, 5, 10, 20, or 50 ppm of triphenyltin hydroxide (10 males and 10 females). The test groups receiving 50 ppm were not reported in complete form in this report.

Results:

1. Depressions in weight gain were noted in both males and females in the 20 ppm test groups only.

2. Composition of the blood.

White blood cells were adversely affected.

Dose (ppm)	Lymphocytes M	Lymphocytes F	Leukocytes M	Leukocytes F
		(% less than control)		
0	0	0	0	0
2.5	11	25*	9	24*
5	2	29**	6	25*
10	23*	44**	16	32**
20	32**	49**	25*	44**

Data are in % less than the corresponding control.
* = p of <0.05; ** = p of <.01.

This table indicates that there is an adverse effect at the lowest dose tested in females.

3. Organ weights and organ to body weight ratios: The following differences were noted.

Organ		2.5	5.0	10.0	20.0
Liver	M	-	-	19**	25**
	F	-	-	-	16**
Kidneys	M	-	-	10**	32**
	F	-	-	11*	21**
Spleen	M	-	-	-12*	16
	F	-	-	-29**	-24
Heart	M	-	-	-	16*
	F	-	-	-	13*
Brain	M	-	-	-	36**
	F	-	-	7	18**

Organ		2.5	5.0	10.0	20.0
Pancreas	M	15*	16*	7	15
	F	8	11	19**	19**
Uterus	F	-	-	-14	-31*
Testis	M	-	-	-	-35*

These data are expressed in % less than (-) or greater than the corresponding controls and are for relative weights. In summary, the NOEL for adverse efects on the weights of organs is 5 ppm.

When these data were recalculated and expressed in relative heart weight, the thymus at the highest dose level for both males and females shows an indication of a loss in weight (29% for males and 31% for females, laboratory calculations).

4. Water content of brain and spinal cord (stated as being determined as quickly as possible after death). No differences reported. There was noted an 18-36% increase in relative brain weight for the high dose males and females.

5. Protein content in the urine - none reported as being detected.

6. Histopathology - There was noted an apparent dose dependent atrophy of lymphoid tissue (at 20 and 50 ppm) and a lesion described as mesenteric lymph nodes with mycotic inflammatory process (50 ppm).

Conclusion:

The most sensitive criterion for the evaluation of triphenyltin compounds appears to be inhibition of lymphopoiesis. [See Verschieuren et al. Fd. Cosmet Toxicol 4:35-45 (1966)].

This test is CORE MINIMUM. A NOEL for effects of TPTH on blood elements was not established. Only 10 animals of each sex per test dose were used. Not all criteria were determined to qualify this test for a 90-day feeding study.

This study gives very valuable information relating to the effects of triphenyltin hydroxide on the white blood cells.

The observation that several relative organ weights were adversely affected at 10 ppm indicates that the guinea pig is a more sensitive species than the rat. Compare, for example, to the rat two-year feeding study.

24

90-Day Semi-chronic Investigation as to the Toxicity of Triphenyltin Hydroxide in Rats

National Institute of Public Health - Utrecht, November 19, 1962
MRID #00086514

4 groups of 20 rats (10 male and 10 female) were dosed with 0, 5, 10 and 25 ppm of triphenlytin hydroxide. (The 10 ppm group actually consisted of 9 females and 11 males and were fed for 12 weeks).

Results:

1. Food intake: in the later weeks females were said to consume more.

2. The data on weight gain are impossible to interpret.

3. Composition of the blood - Females exhibited a lower number of leukocytes at all doses (27% to 36%).

4. Content of the spinal fluid - No dose dependent differences noted.

5. Organ weights - In females: the adrenals were higher at both 10 and 25 ppm. The thyroid and hypophysis were lower at 25 ppm.

   In males: the thyroid and prostate were lower (29% and 22%) at the highest dose level.

   [No summary of pathology and histopathology accompanies this report.]

Conclusion:

SUPPLEMENTARY: Only 10 rats/sex/dose. May be upgraded if the pathology and histopathology reports are submitted for review. No NOEL for depression of blood elements was established by this test.

90-day Subacute Oral Toxicity of Triphenyltin Hydroxide - Albino Rats

Industrial Biotest (B4634), December 29, 1966
MRID #00045837

6 groups of 20 rats (10 males and 10 females) were dosed with triphenytin hydroxide at levels of 0, 1.0, 3.1, 10.0, 31.0 and 5.0 ppm in their diet for 90 days.

Results:

1. Weight gain - No observable adverse effects, females were lower but not progressively lower with dose. Food consumption was also not affected.

2. No untoward reactions or compound related deaths occurred.

3. Hematologic studies - No consistent statistically significant dose related adverse effects are noted on lymphocytes. However, there were statistically significant depressions in lymphocytes reported.

4. Urine analysis - No differences.

5. Pathogenic studies - No gross pathologic changes noted (no raw data presented).

6. Organ weight and ratio data - Only random deviations were noted.

7. Histopathological findings - No significant differences noted - raw data not presented, control and 31 ppm group only examined.

Discussion:

The testing laboratory asserts a NOEL of 31 ppm.

Conclusion:

INVALID: IBT data, no raw data, summaries only, only 10 rats of each sex per dose level were tested, not all determinations were made to qualify this study for a 90-day feeding study. It is unlikely the study will be upgraded higher than SUPPLEMENTARY, therefore auditing is probably not worthwhile.

90-day Subacute Oral Toxicity of Triphenyltin Hydroxide in Rats

[Supplemental to the reproduction study]

Central Institut Voor Voedingoenderzock, August 1967

Rats were prepared for a 3-generation reproduction study at diet levels at 0, 0.5, 1.0, 2.0 and 5.0 ppm of technical triphenyltin hydroxide. 10 males and 10 females were selected from the F_1b and F_2b generations and continued on the diets for 90 days.

Results:

1. (Data are in summary tables only.) There was no compound related mortality. There were no evident adverse effects on growth, food consumption or utilization.

2. No differences in white blood cells or other elements of the blood were reported. The rats were analyzed after 14 weeks on the diet.

3. Organ weights - The kidney was higher in F_1b males only at all levels, but did not exhibit a dose dependent response. F_2b males were equivalent to controls. Spleen weights were higher in males (F_1b, high dose) and females (F_2b, two highest doses). Testicle weights were lower in the F_2b high dose group only.

4. Gross Pathology - There were reported increased incidences of proteinaceous droplets in the kidneys of the F_1b generation males only. These rats were also higher in kidney weight than others.

This test is CORE INVALID. Not all tests were conducted, data are in summary tables only. No raw data are presented.

Subchronic Dog Feeding (Tech) (90 days)
IBT #C3964, March 7, 1966
MRID #00065167.

Groups of 3 male and 3 female purebred Beagle dogs were fed the test material for 90 days at the following dose levels: 0, 10, 25, and 37 ppm. The dogs were examined daily for clinical signs indicative of toxic effects. Complete hematologic and clinical blood chemistry studies, urine analyses, and liver function tests were conducted upon each dog from the control group and all test groups prior to the inception of the test and just prior to its conclusion. The same determinations were conducted upon dogs from the control group and upon animals from the highest test group after 45 days of testing. Dogs which succumbed and sacrificed survivors underwent gross and histopathologic examinations. Organ weights and ratios were determined.

Results:

4 of the 6 animals at the 37 ppm level showed body weight losses. 1 male animal at the 10 ppm level also showed a body weight loss. Upon autopsy these animals were found to have pneumonia. A depressed food intake was noted among the female animals at the highest level during the last week of testing. 4 deaths were recorded: 1 male dog at the 25 ppm level and 1 male and 2 female dogs at the 37 ppm level. These deaths were attributed to a combination of pneumonia and a weakened condition caused by ingestion of the test material. Lethargy and a darkening of the hair color were the only reactions that occurred among test animals. Results of the 45 and 85 day determinations showed somewhat depressed hematocrit and erythrocyte count values in female dogs being fed at the 37 ppm level. The only significant histopathologic finding related to the ingestion of the test material was the irregular pigment deposition in Kupfer cells in the livers of female animals at the 37 ppm level. Organ body weight ratios revealed somewhat elevated liver ratios among all test dogs. However, these elevations were not dose related. Therefore the no effect level for the test material when fed to Beagle dogs for 90 days is 25 ppm.

Note: As reviewed by R.E. Pittman, July 11, 1969.

Note added February 17, 1984: This study is INVALID IBT data. See also the references made to this study in the following review of another subchronic dog study.

One hundred day subacute oral toxicity of triphenyltin hydroxide, beagle dogs.

Lab. Report IBT No. C4343
Dec. 2, 1966
MRID #00045831

Groups of purebred beagle dogs, 3 of each sex, were fed 0, 10, 25 and 37 ppm of TPTH diets for 100 days.

Observations included:

1. Weekly body weights.
2. Food consumption.
3. Daily examination for clinical signs.
4. Hemograms including hemoglobin, hematocrits, erythrocyte counts, total and differential leucocyte counts and bone marrow smears (terminal), at 0, 45, 85 and 100 days.
5. Blood chemistry including BUN, blood glucose, SAP, SGPT, and SGOT at 0, 45 and 85 days of control and 37 ppm group dogs and at 0 and 85 days for the 10 and 25 ppm group dogs.
6. Urinary function tests including glucose, albumin, pH, and sediment examination at 0, 45 and 85 days for the control and 37 ppm group dogs and at 0 and 85 days for the 10 and 25 ppm group dogs.
7. Sulphobromophthalein liver function tests of the control and 37 ppm group dogs at 0, 45 and 85 days and at 0 and 85 days for the 10 and 25 ppm group dogs.
8. Necropsy at termination.
   a. Examination for compound related organ and tissue effects.
   b. Weight of livers, kidneys, spleens, hearts, lungs, brains, gonads, adrenals, thyroids, thymuses and pituitaries.
9. Microscopic examination of tissue and organs included heart, aorta, trachae, lung, liver, gall bladder, pancreas, GI tract, spleen, lymph node, thymus, tonsil, genitourinary system, pituitary, thyroid, adrenal, parathyroid, salivary gland, skeletal muscle, skin, bone marrow, sciatic nerve, spinal cord, and brain.
10. Tin residues in livers.

Results: Observations were negative with the following exceptions:

1. Lethargy was a reaction observed in the 37 ppm group.
2. Hair darkening.
3. Tin (above amount in controls) in the livers of 5 of the 6 dogs in the 37 ppm group; in the livers of 2 of the dogs in the 25 ppm group.

DISCUSSION:

A 90 day dog study submitted for this petition and evaluated in a memorandum dated April 6, 1966 failed to demonstrate no effect levels with diets of 10, 25 and 37 ppm. The dogs used in this study were apparently ill from an infectious disease during the feeding period. Part of the observed reactions were related to this infection rather than to compound ingestion. Lethargy was observed in all compound ingesting groups in the first study but only in the 37 ppm group in this second study.

The significance of the hair coloration is questionable. Hair coloration has not been reported in albino rats consuming 31 ppm TPTH diets for 90 days nor in another rat study at diet levels of 10 ppm for as long as one year. Related to the absence of influence in all other observations in the dogs consuming 10 and 25 ppm diets and the evidence of not more than traces, if any, of TPTH residues in the human food stuffs resulting from the proposed use, the hair coloration is judged toxicologically insignificant.

The increased tin residues in the livers of the dogs consuming 25 and 37 ppm tin diets were an expected finding since storage occurs from the ingestion of ordinary available dietary tin.

[As reviewed by H. Blumenthal PP#6F0496 dated 6/6/67]

Note added February 17, 1984: This study is INVALID IBT data.

A. 90-day inhalation toxicity study of technical TPTH.

Cannon Laboratories, 7E-8305, April 12, 1979
EPA Acc. No. 071366, Tab. C12.

B. The test material was defined as "Technical TPTH" (triphenyltin hydroxide) and was described as a fine white powder. The lot # and purity of the material were not provided.

C. The test material was generated into the atmosphere using a Wright Dust Generator. The exposure chamber was a 500 liter stainless steel chamber which held several rats in individual wire mesh cages.

D. The test animals used were Sprague-Dawley rats (150-200 gm). They were grouped into 4 groups of 15 males and 15 females and were exposed to the atmospheres containing TPTH for six hours per day, five days a week for 13 weeks (90 days). There were thus 65 days of actual exposure.

E. The atmospheric concentration of TPTH was determined gravimetrically using glass fiber filters and analyzing for the concentration of TPTH found on the filter after allowing measured volumes of air to pass through the filters. Nominal concentrations were also determined. The following table summarizes the atmospheric concentrations.

	TPTH (mg/l)	
	Analytical	Nominal
Control	0	0
Low	.0011 ± .0006*	.012 ± .004
Mid	.0023 ± .0011	.018 ± .010
High	.0032 ± .0019	.036 ± .031

*± - Standard deviation.

These low levels correspond to 1.1 to 3.2 mg/m^3 and 1.1 to 3.2 ug/l as determined by the analytical method of determination. The above data are the average of 65 exposures.

F. Particle size of the atmosphere was determined using a Cascade impactor. The analysis showed that the mean particle size was 1.21 to 1.31 um.

G. Survival and behavioral reactions. There were 7 deaths among the female high dose test group. All other groups had only 0, 1 or 2 incidences. Thus it is apparent that survival in the high dose group females was affected by the test chemical.

The clinical observations in all rats dosed with TPTH included dose-dependent alopecia, brownish red material in the nasal area, nasal discharge, red ears, ptosis and piloerection and the high dose test group only had their "eyes sealed shut by discharge."

H. Body weight gain (weighed weekly). No consistent dose related progressive loss in body weight gain was reported. The high dose test group did appear to be lower in weight at the end of the study (90 days) for males (-13%). Terminal female weights were equal in spite of the fact that the high dose test group was 19% lower at the initiation of the study.

For parts I and J below, blood samples were collected from three male and three females from each group by orbital sinus puncture at 0 (before exposure), day 45 and after the last exposure on day 90 (on day 90 additional blood was collected via heart puncture). The clinical chemistry, analysis and hematology assays were contracted to the Berks Clinical Laboratory for analysis.

I. Clinical chemistry included evaluations made on blood sugar, BUN, total serum protein, cholesterol, uric acid, creatinine, Ca^{++}, serum albumin, Na^{+}, K^{+}, CO_2, Cl^{-}, alkaline phosphatase, serum glutamic pyruvic transaminase, gamma-glutamyl transpeptidase and protein (including electrophoresis). Note: samples for some of these were taken on day 90 only.

No consistent dose related changes were noted due to the presence of TPTH in the atmosphere.

J. Hematology included evaluations made on total leukocyte count, erythrocyte count, hemoglobin, hematocrit, and differential leukocyte count (polynucleates, lymphocytes, monucleates, eosinophiles).

No consistent dose related changes were noted due to the presence of TPTH in the atmosphere.

K. Urinalysis consisted of evaluation of the specific gravity, pH, total protein, ketones, bilirubin and microscopic examination of sediment.

No consistent dose related changes were noted.

L. Organ Weights:

Among the males, the relative brain weight was increased for the low level (+10%), mid level (+17%) and high level (+34%); only the high dose level was statistically significantly higher. TB recognizes that a trend toward higher brain relative weight is noted at the lowest test dose level.

The relative spleen weight was increased for the mid level (+23%), and high level (+49%).

Among the females, the relative brain (+35%), lungs (+18%), heart (+32%), liver (+15%), spleen (+17%, not significant), and kidneys (+12%) were all otherwise statistically significantly higher.

A firm NOEL for changes in organ weights is set at 0.0023 mg/l (the mid dose level). At the higher level (0.0032 mg/l) several organ appears to be increased in relative weight. These changes in weight may reflect non-specific toxicity rather than specific target organ toxicity.

It should be recognized that brain and spleen weight may have been affected at the lower levels of exposure.

M. Gross necropsy: The external surface of the test rats was shown to be affected by the test chemical in all dose groups. The adverse findings included alopeica, piloerection, brownish crusted material around nasal area. Other organs (internal) were not clearly affected by the exposure.

N. Histopathology was conducted mostly for the control and high dose exposure groups. Some 26 or more tissue types were routinely examined or preserved for future examination.

The histopathology report was incomplete. Data for the controls and only some of the low dose group III were presented (according to the description in the Appendix J). The summary of the study states that "epithelial hyperplasia of the skin showed an apparent dose response relationship." This observation could not be evaluated by TB because the individual animal data were not presented. Possible adverse effects in other organs could not be evaluated except for the summary table.

CONCLUSION: CORE Classification of this study is RESERVED pending receipt of a complete histopathology report describing microscopic findings.

Reproduction Study with Triphenyltin Hydroxide in Three Generations of Rats.

Central Instituut Voor Voedingoenderzock, August 1967.
MRID #00086548

37.

5 groups of Wistar derived rats (10 males and 20 females in each group) were dosed with diets containing 0, 0.5, 1.0, 2.0 and 5.0 ppm. These rats were mated within their groups at 12 and 20 weeks after being started on the diet to produce F_1a and F_2b generations. The F_1b litters were culled to produce F_2a and F_2b generations. F_2b litters subsequently produced F_3a and F_3b generations. Some special attention was devoted to examining the testicles and spleens of the male rats.

In a special aspect of this experiment, 10 males and 10 females were selected from the F_1b and F_2b generation litters for 90-day feeding studies.

Results:

1. Health and mortality were reported as not being affected.

2. No adverse effects of triphenyltin hydroxide were reported for various aspects of fertility including number of females which cast a litter, average birth weight of the young, and average body weight of the young. All males were reported as being fertile.

3. Spleen weights of the F_1b and F_2b generation rats were significantly increased (see Table below).

4. Testicle weights of the F_2b generation were lower (14%) than controls at 1.0 ppm and above. These weight differences were not accompanied by pathological lesions, but decreased maturation of the testicle was noted. The weight differences were statistically significant (see Table below).

Average relative testicle and spleen weight of P, F_1b and F_2b generation male rats, at week 28, 24 and 28 respectively

ppm TPTH in the ration	organ weights in g per 100 g rat					
	P-generation		F_1b-generation		F_2b-generation	
	testicle	spleen	testicle	spleen	testicle	spleen
0.0	0.75	____ 1)	0.78	0.140	0.86	0.134
0.5	0.80	____	0.80	0.156	0.78	0.148
1.0	0.74	____	0.79	0.158**	0.74*	0.158**
2.0	0.76	____	0.78	0.155*	0.81	0.147*
5.0	0.77	____	0.77	0.153*	0.73**	0.177**

1) not determined

* significantly different from controls according to the test of Wilcoxon, $0.01 < P < 0.05$

** idem, $0.001 < P < 0.01$

*** idem, $P < 0.001$

Inspection of this Table calls into question whether or not adverse effects on the spleen are not also present at the 0.5 ppm level. For example, for the F_1b generation at the 0.5 ppm level, a figure is given that is higher than the figure given for 2.0 or 5.0 ppm. However, the figures for 2.0 and 5 ppm are statistically significant. An independent statistical analysis of the data could not be performed by Toxicology Branch because no raw data were presented.

CONCLUSION: This test is INVALID (provisionally). No raw data were presented and Toxicology Branch was unable to concur with the result that suggested a NOEL of 0.5 ppm for adverse effects on spleen development.

Discussion: Triphenyltin derivatives have been reported elsewhere to have adverse effects in testis in rats [see B. D. Pate and R. L. Hays, J. Econ. Entomol. 61:32-34 (1968)].

The adverse effects on spleen development cannot be ignored because other studies with triphenyltin hydroxide have demonstrated decreases in white blood cells and the lymphopietic system has been suggested as the most sensitive index of toxic action of triphenyltin compounds.

Observations on a Possible Effect of TPTH on Testicular Development in Rats.

Central Institute Voor Voedingoenderzock, February, 1968.
MRID #00086549

This study was designed to follow-up the observations noted in the three generation rat reproduction study where a NOEL of 0.5 ppm was noted relative to apparent adverse effects on testicles and maturation of this organ.

Three successive experiments were carried out. Newly weaned rats were dosed with 0, 0.5, 1.0, 5.0 or 25.0 ppm of TPTH in groups of 10 or 20 male rats. In the first experiment, the rats were sacrificed after two weeks of feeding. In the second and third experiments, the rats were sacrificed at either 2 or 4 weeks after weaning. The weights of the testicles (relative to total body weight) were recorded. Following necropsy, the testicles were stained and examined microscopically.

Results:

1. There were no consistent dose dependent changes in relative testicle weight reported.

2. Testicular descent (relative to the body weight at descent) was not consistently affected.

3. No effects were noted in microscopic examination of the testicles.

Conclusion:

SUPPLEMENTARY DATA: This test does not resolve if TPTH can cause adverse effects on testicular development as was reported in the previous experiment. If TPTH is given while the pup is in utero or during suckling the effect may be realized.

Histological Studies of Testis in Rats Treated with Certain Insect Chemosterilants

B. D. Pate and R. L. Hays
J. Econ. Entom. 61:32-34 (1968)

Dept. of Zoology and Entomology, Clemson University, Clemson, S.C.

The compounds triphenyltin acetate and triphenyltin chloride produced several degenerative changes in testicular tissue at doses of 20 mg/kg/day for 19 days. These lesions were described as decreases in the number of cell layers per seminiferous tubule, decrease in tubule diameter, and overall testicular size, depletion of the more advanced cell forms from the tubules and a closing of tubule lamina.

Range-Finding Study for the Evaluation of Reproductive Effects of Triphenyltin Hydroxide (TPTH) in Wistar Rats.

Battelle, #N0723-0400, July 22, 1982.
EPA Acc. No. 071368, Tab C-17.

Substance tested: Triphenyltin hydroxide (TPTH, lot. No. 75414) obtained from the Thompson Hayward Co. The test rats used were Wistar strain obtained from the Charles River Breeding Co. This preliminary study consisted of dosing 6 groups of rats (10 males and 10 females per group) with 0, 12.5, 25, 50, 100 or 200 ppm of TPTH in their diet for 59 days, breeding the rats and allowing the pups to be delivered. All animals were sacrificed and examined at 1 day after parturition. The following summarizes the results.

a. Toxic signs were noted chiefly in the group dosed with 200 ppm. These signs included rough coat, hunched back, lethargy, nasal discharge, alopecia and a lower pregnancy rate. One male was sacrificed in extremis. Some of these signs were reported in the rats dosed at the lower levels.

b. Body weight was depressed in the group receiving 200 ppm.

c. Pregnancy rate was depressed in the high dose test group (200 ppm). There were only 4 out of 10 rats pregnant in the high dose group. The other groups were 80-100% pregnant.

d. Litter data. The control group had 99.2% live pups (120 live pups); the lowest dose test group had 77.2% live pups (78 live pups) but the next highest dose had 95% live pups (95 live pups), thus no definite effect at the lowest test dose level was noted. A more definite effect on the litters was noted at the 100 and 200 ppm groups, there were only 56.9% and 0% live pups for these groups. Pup weights were decreased for the 100 ppm dose group. No gross abnormalities were noted among the treated rat pups.

e. Necropsy. The rat which died in extremis displayed a thymus which was small, pale liver, the testes and the meninges of the brain appeared reddened. Other gross necropsy observations were not attributable to the test material.

f. No meaningful weight differences in the spleen, gonads, thymus, liver, kidneys, heart, adrenals, brain or pituitary were noted or reported. The lot size of N=10 may have obscured some weight differences.

g. Hematology (WBC and RBC counts). Total WBC count was stat. sign. decreased in the high dose test group females. This was accompanied by a relative and absolute marked neutropenia with a relative lymphocytosis and a moderate absolute lymphopenia. RBCs were elevated in males at 12.5 and 25 ppm but not above. The apparent RBC affect is not considered definitely related to the test material.

h. Histopathology. (For controls and rats dosed with 100 ppm). The kidney appeared to be affected with "minimal to mild chronic nephrosis." Mineralization (mineral deposits) were found in the highest dosed animals. This was considered to have led to a "life-threatening" secondary hydronephrosis. Thus, the kidney appears to be a target organ for TPTH.

CONCLUSION: SUPPLEMENTARY DATA: Based on this study, the dose levels chosen for the definitive reproduction study were 0, 5, 15.8 and 50 ppm. It should be noted that at 100 ppm and above adverse effects on reproduction are evident.

Investigation of Teratogenic and Toxic Potential of Technical Triphenyltin Hydroxide (in Rats).

Cannon Laboratories, Inc., October 12, 1976 MRID #00086547

5 groups of Sprague-Dawley rats were dosed with 0, 1.25, 5.0, 8.75 or 12.5 mg/kg b.w. of triphenyltin hydroxide on days 6

through 15 of gestation. Each group, except the 5.0 mg/kg group, consisted of 20 pregnant rats. The 5.0 mg/kg group consisted of 19 pregnant rats.

Results:

A. Maternal effects. There was one abortion in the 8.75 mg/kg dose group and 3 abortions in the 12.5 mg/kg dose group. These abortions were considered to be test chemically related. Body weight gain in the two highest dose groups was lowered (31% and 47%). At the two highest doses the % live fetuses, % dead fetuses, resorptions, and mean fetal weight were all adversely affected.

B. Fetal examination.

1. External - No dose dependent abnormalities were noted (all pups reported as being examined).

2. Visceral examination (1/3 of pups) (Wilson technique). Increases in hydrocephalus and hydronephrosis were realized as indicated in the following table.

Dose Level mg/kg	Hydrocephalus %	Hydronephrosis %
0	1.06% (1/94)	2.1% (2/94)
1.25	20% (15/75)	6.7% (5/75)
5.0	10.9% (8/73)	16.4% (12/73)
8.75	14.9% (7/47)	34% (16/47)
12.5	30% (6/20)	30% (6/20)

3. Skeletal observation (2/3 of pups), Alizarin technique. No truly dose dependent abnormalities were reported.

CONCLUSION:

No NOEL for the fetotoxic/teratogenic effects of hydrocephalus and hydronephrosis was obtained. This test is CORE MINIMUM - no concurrent positive control was included.

Evaluation of the Teratogenicity of Triphenyltin Hydroxide (TPTH) in the Sprague-Dawley Rat

Battelle Columbus Laboratories, #N0723-0200, June 25, 1981.
EPA Accession No. 070696.
MRID #00094903

Four groups of 26 female Sprague-Dawley rats were mated and dosed with 0, 1.0, 2.8 or 8.0 mg/kg triphenyltin hydroxide (TPTH) (Lot TS414K, 97.3% purity) in 1 ml of corn oil/200 gm body weight on days 5 thru 19 of gestation.

On the 20th day, 20 pregnant rats were culled and sacrificed and hysterectomy was performed. No positive control group was included in this study.

Results:

A. Maternal Effects

1. Two rats in the high dose test group died. All of the rats in this dose group showed some abnormal signs which included rough coat and oral/nasal discharge, alopecia, diarrhea, ocular discharge, lethargy, vaginal discharge, hemorrhage from the vaginal area and thinness. Three rats in the 2.8 mg/kg group demonstrated at least some of these symptoms. Only one rat in the 1.0 mg/kg dose group showed a single possible sign; slight red discharge from the nose and mouth on day 19 (the last day of dosing). The solvent control group did not show symptoms other than alopecia.

2. The pregnancy rate was lower for the high dose group (80% vs 100% for all other groups) and it could not be determined if this was due to fertilization or a toxic response resulting from administering the TPTH on day 5.

3. Maternal body weight gain throughout pregnancy was adversely affected for the high dose test group only. For example, this group gained only 82 $\pm$ 28 gm, whereas the other three groups gained >130 gm $\pm$ 24 gm. Uterine weight was also significantly decreased in the high dose test group.

4. Hysterectomy data indicated no differences in the average number of implantations per litter, and the average number of implantation sites/number of corpora lutea.

The average number of live fetuses/litter was slightly lower (-15%) and the average live fetal weight was lower (-22%) for the high dose test group when compared to the controls. The average % dead and resorbed fetuses/litter was also affected in the high dose test group (12% vs 3% for the control). There was no difference in the sex ratio due to the test chemical.

A NOEL for maternal toxicity is 2.8 mg/kg.

B. Fetal Effects:

There were 262, 244, 257, and 200 fetuses from the control, low, mid and high dose test groups respectively. Approximately one half from each group were culled and prepared for skeletal

examination. The other half was prepared for soft tissue examination following free hand sectioning in Bouin's solution.

1. Soft tissue analysis revealed 11, 11, 13 and 12 abnormal fetuses or 8, 9, 11 and 13% for the control, low, mid and high dose test groups. There was no hydrocephalus noted in any group dosed with TPTH. Hydroureter were present in the order of 1 (1%), 7 (6%), 7 (6%) and 12 (12%) for the control, low, mid and high dose test groups. Hydronephrosis was present in 2% to 4% of the fetuses. Hydroureter and hydronephrosis are related lesions and the following table prepared by Toxicology Branch illustrates the frequency of occurrence of these lesions:

HYDROURETER AND HYDRONEPHROSIS

	At Worst*	At Best**
Control	3/131 (2.3%)	2/131 (1.5%)
Low (1.0 mg/kg)	12/118 (10.1%)	7/118 (5.9%)
Mid (2.8 mg/kg)	10/123 (8.1%)	8/123 (6.5%)
High (8.0 mg/kg)	16/96 (16.7%)	13/96 (13.5%)

(% of animals with lesions)

* At worst refers to no fetuses having both hydroureter and hydronephrosis.

** At best refers to all fetuses having hydronephrosis also having hydroureter.

It is necessary to prepare "at worst" and "at best" figures because the individual fetus data were not submitted.

2. Skeletal analysis indicated that there were 26 (20%), 24 (19%), 26 (20%) and 18 (17%) total number of fetuses with skeletal malformations in the control, low, mid and high dose test groups. No single skeletal malformation type showed consistent increases in excess of the control group. Thus no indication of a teratogenic effect on the skeletal system is evident from these data.

Conclusion:

This study is Core Minimum. A NOEL of 2.8 mg/kg/day is assigned for toxic effects to the dam. The development of hydroureter in pups occurred at all test dose levels but at only a very low frequency among the controls. Historical control data confirmed that this strain of rat has a low

spontaneous rate of hydroureter in the fetuses. This experiment confirms the previous rat study which demonstrated that triphenyltin hydroxide causes lesions related to hydronephrosis in rats. Other symptoms of fetotoxicity also occured in the high dose test group (8.0 mg/kg/day), these include deaths and fetal body weight decreases.

The Evaluation of the Teratogenicity of Triphenyltin Hydroxide (TPTH) in the Syrian Golden Hamster

Battelle Columbus Laboratories, # N0723-0100, February 10, 1982. EPA Accession No. 070697.
MRID #00094904

A. Preliminary Range Finding Study:

A series of preliminary range finding studies indicated that the hamsters developed problems that were attributed to either corn oil alone or a synergistic effect between corn oil and TPTH. The data related to this effect were not presented and it was not established if there was an effect between corn oil and TPTH. Testing TPTH in corn oil in hamsters resulted in deaths due to hemorrhage (unspecified location), prolapse and intussusception. Because of a possible corn oil effect, the solvent was changed to Klucel® (0.3 percent hydroxypropyl cellulose in saline) and it was determined that 12.0 mg/kg of TPTH would be a reasonable maximal tolerated dose level. Hamsters tested at 15.7 mg/kg died as a result of the TPTH.

B. Teratology Study:

Five groups of 25 female hamsters were mated and assigned to dosing groups as control, 2.15 mg/kg, 5.08 mg/kg, 12.0 mg/kg of TPTH and positive control (250,000 IU of Vitamin A/kg). The TPTH used was from lot No TS414K. Analysis of the test material as prepared for dosing indicated that the TPTH animals were dosed with 1.97 $\pm$ .12 mg/kg, 4.91 $\pm$ .24 mg/kg, and 10.94 $\pm$ .52 mg/kg or 92%, 97% and 91% of the expected dose level. The test chemicals were administered by gavage on days 5 through 14 of pregnancy with 1 ml/100 gm of body weight. Twenty females from each group were sacrificed on day 15 and their uterine contents examined.

Results:

A. Effects on the Dams:

Pregnancy rate was 80-100% and there was no indication of a compound related effect. Four of the 25 hamsters in the high dose group died and 18 showed toxic responses which included oral/nasal discharge and diarrhea and rough coats, rectal discharge, weakness/lethargy, weight loss, and vaginal hemorrhage. Toxic responses in the low and mid dose groups showed some signs of diarrhea (2 animals in the mid dose group), a single animal in the low dose group showed a bloody discharge from the vagina.

The dams in the high dose test group did not gain weight as well as the controls and low and mid dose test animals. They gained only 11 gm compared with 24-27 gm for the other groups. The weight of the uterus was only slightly lower (13%) than the control group.

The mean number of implantation sites per litter, the pre-implantation loss rate as judged by the corpora lutea implantation ratio, or the mean number and percent of dead or resorbed fetuses were not shown to be statistically significantly affected by TPTH treatment. But the high dose group and the positive control group showed more than twice as many average percent dead/resorbed fetuses per litter. The average number of live fetuses was lower (-20%) than the control group and this depression was significant ($p < 0.001$) for the 12 mg/kg test dose group.

B. Effects on the Fetuses:

There were 242, 252, 258, 193 and 207 fetuses for the control, low, mid and high and positive control test groups available for analysis. The average live fetal weight for the high dose test and positive control was lower than the control group (-10% for both groups). Approximately one half of all fetuses per dose group were saved for skeletal analysis.

1. Soft tissue analysis (performed by free hand sectioning of the fetuses preserved in Bouin's solution). Only one fetus among the controls was affected (with mottled liver). No low dose group fetuses were affected. Three mid dose group fetuses were affected with hydronephrosis. Three high dose group fetuses were affected: one with hydrocephaly, one with mottled liver and one with hematoma. The positive control group had high incidences of hydronephrosis (32) and hydroureter (25) as well as several other abnormalities including palate malformations and renal dysplasia.

The development of 3 incidences of hydronephrosis in the mid dose group (2%) of the fetuses is disturbing because the other test groups and control (except the positive control group) did not develop this lesion. However, a dose relationship is not evident.

2. Skeletal effects: The high dose test group showed a higher incidence of "poorly ossified, missing metatarsals" (26 incidences, 27%) than the control group (14 incidences, 12%). There was also a single incident of a fetus with "absent cranial vault" in the high dose test group and the only other group showing this was the positive control group (14 incidences). There was also noted a 14% increase in the total number of abnormalities when the high dose test group is compared with the control group.

3. Gross necropsy revealed a higher incidence of anemia among the high dose test group. Hematomas were present only in the test group fetuses with the following frequencies 0/242, 5/252, 4/258, 5/193 and 2/207. The development of hematomas is considered by Toxicology Branch to be possibly but not conclusively related to the test chemical.

Conclusion

This study is Core Guidelines. No teratogenic effects of TPTH at dose levels up to and including 12 mg/kg were noted. The high dose level (12 mg/kg) developed signs of fetotoxicity which included anemia and showed some signs of delayed development of the metatarsals. The development of hematoma was only in treated animals and at best is only possibly related to TPTH. A lack of a dose response or supporting data from other studies prevents the conclusion that the hematoma was more definitely related to ingestion of TPTH.

3. Effect of Triphenyltin Acetate on Pregnancy in the Rat

University of Milano, Milano, Italy, as published in Bull. Environm. Contam. Toxicol. 24:936-939 (1980). EPA Accession No. 070695.

The following table shows that hydroureter resulted in fetuses whose mothers were treated with triphenyltin acetate during gestation (days 6-15).

Group	Hydroureter Incidences/Fetuses Examined
Control	0/52
5 mg/kg Triphenyltin acetate	0/52
10 mg/kg Triphenyltin acetate	0/65
15 mg/kg Triphenyltin acetate	4/29 (13.8%)

This study is Supplementary.

Chronic (Two-Year) Toxicity Study with Triphenyltin Hydroxide (TPTH) in Beagle Dogs.

Central Institute Voor Voedingoenderzock, July, 1968. (#R-2717)

MRID # 00080391

Thirty-four beagle dogs were used in this test. They were grouped as controls (5 males and 5 females) and four test groups (3 males and 3 females). All dogs were started in the experiment within 3 months of each other, and were fed the test diet for 2 years. Hematological, biochemical, and urinalysis tests were determined at weeks 13, 26, 52, 78, and 102. Other tests were conducted at termination. Four weeks were allowed from the last test dose diet day to sacrifice. Dose levels were 0, 0.5, 2.5, 5 and 10 ppm.

1. General appearance and behavior. - There were no consistent dose dependent abnormalities noted.

2. Growth and food consumption. There were no dose dependent effects noted.

3. Clinical and biochemical observations and urine analysis. No differences in hematological (blood cell count), biochemical values (BUN, blood sugar, SAP, SGPT, and SGOT) or urine analysis were reported.

4. Liver function test. (sulphobromophthalein method) at week 103 and kidney function test (phenol red excretion method) at week 103 did not indicate a dose dependent effect.

5. Hair color - Indicated a more rapid hair growth in dogs in test levels of 5 and 10 ppm than in controls and 0.5 and 2.5 ppm.

6. Organ weights - Possibly some effects at 5 and 10 ppm. Thyroids were lower at all levels, but dose response is questionable.

7. Water content of the brain. The laboratory report states that the water content of the cerebrum, frontal and parietal lobe was slightly higher in the two highest dose groups than in the other groups.

8. Pathology - Gross examination. No consistent pathological lesions reported.

9. Histopathology - No consistent pathological lesions reported.

Note: Because there were only 3 dogs per sex per test group, pathology and histopathology are of limited value.

CONCLUSION:

This test is CORE SUPPLEMENTARY, only three dogs of each sex at each dose level. Organ weight differences are not interpretable. The four week "recovery period" should not have been allowed because the nature of this chemical suggests transitional edema of internal organs. A NOEL of 2.5 pm is assigned.

Chronic Toxicity Study with Triphenyltin Hydroxide in Rats for Two Years.

Central Instituut Voor Voedingcenderzock, August, 1970, #R-3138
MRID #00046016 and #00080390

Six groups of 50 Wistar rats (25 males and 25 females) were segregated and fed diets containing 0, 0.5, 1.0, 2.0, 5.0 and 10.0 ppm of TPTH for 2 years.

Results:

1. From 10-15 of the 25 males survived the 2-year dosing. Females appeared to survive better, from 15-21 were alive after 2 years. There was no consistent dose related mortality. General health is described as not being adversely affected.

2. No adverse effects on weight gain or food consumption were noted.

3. Hematology - There were statistically significant depressions of WBC (at 6, 13, 26 weeks for males at 5 and 10 ppm and on week 26 at 2 ppm). Other variations were considered incidental.

4. Blood sugar and urea nitrogen showed only incidental variations.

5. Urine analysis - (sampled at weeks 32, 76, and 102). No changes noted.

6. Serum enzymes (SGPT, SGOT, SAP) gave essentially equivalent activity for all dose levels.

7. Body weight and organ weights - (determined on survivors). No differences are reported for heart, kidney, liver, brain, ovary, eye pituitary, and adrenal. This reviewer notes that the spleens were 18% (females) and 15% (males) lower than controls for the high dose groups. The thyroids for the females were 12% lower and 9% lower for males.

8. No gross pathologic lesions were noted.

9. Histopathology (TAB 18) was conducted on the controls and 10 ppm test group only. 25 males and females from the control group and 24 males and females from the test group were examined. No chemically related lesions were noted. [This reviewer notes that there were 9 incidences of atrophy of the thymus in the high test group vs. 3 incidences in the control group (males).]

   This test is CORE MINIMUM for a chronic feeding study. A NOEL for a 2-year chronic feeding study is 2 ppm. At 5 and 10 ppm there was noted a decrease in white blood cell formation. This test is CORE SUPPLEMENTARY and does not qualify as an oncogensis study because only 25 rats of each sex were used and an even lesser number endured the two-year feeding. Most of the data are in summary tables only, without supporting individual animal data.

Bioassay of Triphenyltin Hydroxide for Possible Carcinogenicity (in Rats and Mice).

National Cancer Institute. [Contracted to Litton Bionetics, Inc. Bethesda, Maryland.]

DHEW Publication No. (NIH) 78-1394.

Part A - Rats (Fischer 344)

Three groups of rats were dosed with 0, 37.5 or 75 ppm triphenyltin hydroxide for 78 weeks and allowed 26 weeks to recover. Controls consisted of 20 males and 20 females. Test groups consisted of 50 males and 50 females.

Results:

1. Survival was always greater than 75% for both males and females.

2. There were no dose related incidences of tumor pathology reported.

SUPPLEMENTARY DATA for oncogenesis. Not acceptable as a chronic feeding study.

Part B - Mice (B6 C3F1) - Same protocol as with rats.

1. No abnormal clinical signs were reported: Body weight was not adversely affected. Male survival rate was 95% (controls), 74% (low dose group) and 66% (high dose group). A dose dependent increase in mortality that was statistically significant resulted. Female mortality was equivalent in all test groups.

2. There was no dose dependent increase in tumors noted.

SUPPLEMENTARY Data for oncogenesis. It is noted that allowing 26 weeks for "recovery" following the last day on the test diet might have obscured transient but serious lesions induced by this chemical.

Note: These studies were classified as CORE SUPPLEMENTARY for the following reasons.

i. Individual pathology reports for both gross and histological examinations were not included. The data were in summary form only.

ii. The rats used in these experiments were not kept on their diets for their life span (or at least 24 months). They were fed the test chemical for only 17 months. In addition they were allowed to live for 6 months after cessation of feeding the test chemical.

iii. Organ weight data were neither collected nor reported, or at least not reported if collected.

iv. There are no signed reports for the various aspects of these studies. Thus, it is not possible to determine the individuals responsible for the observations and conclusions.

v. Other individual animal data are not reported (body weight, death, etc.).

vi. These studies may be upgraded if the above information is provided and the studies when reviewed in their entirety are found to be acceptable to Toxicology Branch.

A. 18-month Carcinogenicity Study of Technical TPTH 96.3% (lot no. SWRAM-1K) in CD_1 Mice.

Cannon Labs. #6E-725, August 28, 1978 and revised April 18, 1979, EPA Acc. No. 071367, TAB C13.

B. The test material was triphenyltin hydroxide (TPTH), and was stated as being 96.3% pure and was from lot no. SWRAM-1K.

C. 4 groups of CD-1 strain mice (obtained from Charles River, Wilmington, Mass.), about 6 weeks old, were used in this assay. Each group comprised 60 males and 60 females. The test material was mixed into the diet (NIH-07) at the levels of 0, 7, 28 and 52 ppm. These levels correspond to roughly 1 mg/kg/day, 4 mg/kg/day and 7.4 mg/kg/day (using 1 mg/kg = 7 ppm). The highest dose level tested was about 1/17 of the acute oral LD_{50} of 125 mg/kg. The mice were dosed for 18 months (78 weeks).

D. The protocol provided that the test diets were prepared at weekly intervals. Samples of the diet were taken for analysis twice during the first month and "quarterly" for the remainder of the study.

The results of the analysis of the diet were not presented in the report.

E. Survival and clinical/behavioral reactions. The following table indicates that the male survival was apparently affected by the test chemical. Female survival appears unaffected.

18-Month Survival Rate

	n	Males	Females
Control	60	42 (70%)*	35 (58%)
7 ppm	60	33 (55%)	33 (55%)
28 ppm	60	25 (42%)	43 (72%)
52 ppm	60	25 (42%)	32 (53%)

*Survivors (as percent of 60 starters).

A table occupying 82 pages presented data on the pharmacotoxic signs of the mice in the study. No summary table was presented. The laboratory report states that the frequency of aggression (fighting), alopecia, irritation, laceration and scabs increased with each higher dose level. Inspection of the table indicates increased

57

incidences of these parameters at the 28 and 52 ppm dose levels. These observations are of interest, but TB declines from making judgments as to the assessment of TPTH as a behavioral toxin in mice based on these data.

F. Body weight and food consumption. Individual animal body weights were not determined. The average body weight/mouse/cage was determined (5 animals per cage). No consistent dose related effects on body weight were noted. Similarly, no really meaningful consistent differences in food consumption were reported.

G. No hematology assays were made.

H. No clinical biochemical assays were made.

I. No urinalysis was determined.

J. Gross pathology. [No individual animal pathology data sheets were presented.]

i. 23 mice developed observable masses during the in-life phase of the study but no dose response relationship was evident.

ii. The gross necropsy results are presented in a table occupying 73 pages, but no table summarizing the results was presented. Thus, determining whether or not grossly observable lesions were followed up microscopically requires considerable time and effort on the part of the reviewer.

iii. Organ weights were <u>not</u> determined.

K. Histopathology: The protocol provided that microscopic examination be performed in all tissues listed (for example: adrenals, brain, eye, heart, small intestine, large intestine, kidneys, liver, spleen, pancreas, prostate or uterus, sternum (bone marrow), skin, stomach, testis or ovary, thyroid, urinary bladder (and lung) for the control and high dose test groups. The low and mid dose test animals were subjected to microscopic examination only in response to significant gross pathological findings. It should be noted that current guidelines for oncogenicity testing list 34 tissue types that should be examined microscopically.

Oncogenic response (based on data presented in the April 18, 1979 revised report). The following table indicates the overall neoplastic findings for this study.

(Refer to Table VII of the report):

53

	MALES*			FEMALES*		
	Mice with tumors	Mice with malignancies	Total Number of tumors	Mice with tumors	Mice with malignancies	Total Number of tumors
ontrol	15	9	16	23	15	27/27**
ow 7 ppm)	9	5	11	13	5	16/11
id 28 ppm)	7	5	7	26	7	42/19
igh 52 ppm)	9	2	12	33	2	41/9

* Based on 60 mice per dose group.

** Total number/not including uterine endometrial hyperplasias. This table shows that there is no obvious neoplastic response in males or a increase in malignancy in either males or females. However, there appears to be an increase in the mid and high dose levels for females when the total number of tumors is counted, but not when pathology of the uterus is not included. Individual organs are discussed as follows for both neoplastic and non-neoplastic findings:

1. The uterus was shown to be a target organ for a neoplastic or other effect of TPTH in this study with mice. The following table illustrates the response for mice having "endometrial hyperplasia" and "endometrial hyperplasia with cysts."

	Total
Control	0
Low (7 ppm)	5
Mid (28 ppm)	23*
High (52 ppm)	32

(Note: 60 rats per group, refer to Table IX in study report)

*Includes one mouse (#308) with mononuclear hyperplasia.

54

Toxicology Branch has not made the final conclusion that these data indicate a definite oncogenic response. Further description of this lesion must be provided by the pathologist responsible for the diagnosis. For example, "hyperplasia" is not normally considered a neoplastic response. However, the pathologist clearly listed this lesion in the table of tumor findings (refer to Table VII and Table IX of the study report). The summary of this study (pages 3 and 9) did not conclude that these data represented an oncogenic finding, but rather dismissed these data as not being of biological significance (see p. 3 of the Summary of the report). To further complicate the classification of this lesion, Table XVIII lists the uterine hyperplasia with other nonneoplastic lesions. Whether or not the eventual conclusion for the diagnosis of this hyperplasia is neoplastic or otherwise, the development of a test chemical related change in a reproductive organ is considered a serious and adverse response to the test chemical. In this case with TPTH, because of the low doses involved (lowest dose = 7 ppm), these data will have to be given due consideration in the overall assessment of TPTH toxicity.

2. Other organs/tissues will be further evaluated pending receipt and review of the additional information requested for this study (See below).

CONCLUSIONS: Core classification of this study is RESERVED pending receipt and review of additional tables and information. The registrant is asked to prepare and submit for review:

1. Complete description of the lesion(s) described as "endometrial hyperplasia" and "endometrial hyperplasia with cysts" in the uterus. In addition, it should be clearly stated by the examining pathologist that these lesions are or are not considered by him to be neoplastic.

2. Individual animal pathology sheets which show on the same page (two or more pages for some animals may be necessary) both the gross and microscopic findings. The time of death (and cause if known) must also be included on these individual animal data sheets.

3. A revised summary table which shows the neoplastic and nonneoplastic findings from all of the mice examined for each group. (Note: Tables XV - XVIII include only those mice surviving the 18-month dosing period.)

4. A summary table tabulating the behavioral reactions during the in-life phase of the study.

5. A summary table tabulating the gross necropsy findings.

6. Results of the diet analyses performed twice during the first month and "quarterly" thereafter.

Repeated-Dose (10 day) Study for the Immuno-suppresive Effect of Fentin Hydroxide Technical in Immature Rats.

Hoechst Aktiengesellschaft, #637/81, November 2, 1981, EPA Acc. No. 071364, Tab. C10. Translation from German. Study # A22434.

A. The test material for this study was fentin hydroxide, technical grade (code: HOE 29664 OF AT201). The positive control was di-n-octyltindichloride (DOTC).

B. The test animals were 27-29 day old male rats of the Wistar strain (no females were included). They were obtained from the Hoechst company's breeding farm.

C. Treatment of the test rats consisted of making 10 consecutive intubations by stomach tube of the test materials dissolved in peanut oil. The dose levels studied were 0 (peanut oil vehicle control), 2.5 mg/kg of TPTH, and 25.0 and 125.0 mg/kg of DOTC (positive controls). 24 hours after the last dosing, the rats were sacrificed by pentobarbital.

D. Survival and Behavioral Reactions. Although a single rat receiving TPTH died, its death was not due to TPTH, but to improper intubation. No changes in behavioral patterns were noted in any of the other rats dosed with TPTH. 3 positive control rats died.

E. The rats dosed with TPTH were reported as not showing differences in body weight, food consumption, or water consumption. The positive control rats showed some effects in these parameters.

F. Organ weights: The liver, spleen and thymus only were weighed after sacrifice. The following table shows that the positive control rats but not the rats dosed with TPTH had thymus weights affected by the test chemical.

Determination of the weights of the spleen and thymus were the only indexes used for determining an effect on the immunosystem.

RELATIVE WEIGHT

	Liver	Spleen	Thymus
CONTROL	4.519	0.339	0.367
DOTC 25 mg/kg	4.531	0.325	0.115 (-69%)
DOTC 125 mg/kg	4.573	0.313 (-8%)*	0.062 (-83%)
TPTH 2.5 mg/kg	4.821	0.334	0.366

*(% decrease)

G. No definite lesions related to intubation of TPTH were noted at gross necropsy. The DOTC treated rats had noticeably reduced thymus size.

CONCLUSION. Only a single dose of the TPTH was made. This dose level did not produce any toxic respose and it does not adequately define if TPTH can affect the thymus. The study does provide useful information in that no adverse effects were noted at 2.5 mg/kg/day for 10 days.

Subchronic Fourteen-Day Immunotoxicological Study of Triphenyltin Hydroxide in B_6 C_3 F_1 Male Mice

Quintox Incorporated, Richmond, VA #QU/THAN 104, May 17, 1982. EPA Acc. No. 071365, TAB C-11.

This study was designed to define and evaluate and to determine a no observed effect level for immunotoxic effects of triphenyltin hydroxide (TPTH) on the immune system in B_6 C_3 F_1 strain male mice. The study consisted of a dosing (by gavage) phase of 14 days with 6 groups of male mice: a vehicle control group (90 mice), four TPTH treatment groups of 40 mice receiving either 2.5, 5, 10, or 20 mg/kg of TPTH; and a positive control group of 40 mice receiving 30 mg/kg of cyclophosphamide (CTX). Following 14 daily doses, the mice were sacrificed and assessed for reference toxicity (general reactions to treatment); mitogen proliferation response; IgM antibody forming cell response; or the delayed hypersensitivity response. There were 10 mice from each treatment group originally allocated for each assessment.

A preliminary experiment indicated that 20 mg/kg of TPTH was an appropriate high dose level. Mice dosed with higher levels died as a result of treatment.

57

Results

Part 1. General responses.

Survival: 7 of the 40 mice treated with 20 mg/kg of TPTH died. A single mouse treated with CTX died. All other mice survived the treatment.

Body weight: The mice treated with 20 mg/kg of TPTH lost weight. The weights of the mice dosed with 10 mg/kg of TPTH were only slightly less than the controls.

Organ weights: The weights of the brain (+27% relative weight) in the high dose group and liver (+18% relative) for both the mid and high dose (10 and 20 mg/kg) were increased and this was said to be consequent to the loss in body weight. The kidney weight was decreased (33% absolute, 15% relative) in the high dose group and the relative weight was reduced (-8%) for the 10 mg/kg dose group.

The organs associated with immunology, the spleen and thymus were also affected by TPTH: mean spleen weight was decreased 41% in the high dose test group, the mid dose group was unaffected. The relative thymus weights were reduced in the 10 (-15%) and 20 mg/kg (-58%) dose groups, and a trend was evident for the 5 mg/kg dose group.

Hematology: (Blood was collected by cardiac puncture and analyzed for hemoglobin, hematocrit, and leukocyte count and differential). The leucocyte counts were reduced at all doses (except 10 mg/kg) but a pronounced dose response was not obtained although the 20 mg/kg dose level had the greatest reduction (50%). The leukocyte differentials were not reported as being different among the treated groups and the control.

Part 2. Spleen IgM Antibody Forming cell Response. This aspect of the study assesses for effects on antibody producing cells or the B lymphocytes. This study was conducted by immunizing the mice (10 per group per dose) on day 9 and day 10 of the exposure period by administering an intraperitoneal dose of 5×10^8 sheep erythrocytes. On the day of the assay, one day after the last treatment with TPTH, the spleens were removed and prepared and then incubated with sheep erythrocytes and guinea pig complement. The principle of this assay is that the complement reacts with the antigen (sheep erythrocytes) antibody (mouse B lymphocytes) and causes hemolysis. A failure to show hemolysis is an indication of the test chemical to interfere with the production of B lymphocytes. For this study, both 4-day and 5-day responses were determined. The conclusion by the laboratory is that "the spleen cell response to T dependent antigen was shown to be reduced at the high dose level with a trend towards dose dependency." This is related in the following table.

58

Dose Level	IgM AFC 10^6 spleen cells		IgM AFC / spleen		Spleen Cell Number X 10		Spleen Weight (mg)	
	4[1]	5[2]	4	5	4	5	4	5
0	1146	812	190042	151335	5.57	6.26	115	125
2.5 mg/kg TPTH	1972*	939	284700	147240	5.00[T]	5.31*	108[T]	107*
5 mg/kg TPTH	1110	1288*	159030[T]	196200*	4.81[T]	5.18*	89*	105*
10 mg/kg TPTH	847[T]	899	116100*	114240	4.75*	4.26*	87*	85*
20 mg/kg TPTH	587*	501	76300*	50800*	4.30*	3.05*	78*	62*
30 mg/kg CTX	2**	3*	180*	167*	2.60*	1.64*	74*	54*

T = Trend
* = $p < .05$
** = $p < .01$

[1] day 4 response
[2] day 5 response

TB notes that the reduction in spleen weight was obvious even at the lowest dose level - i.e., stat. sig. for the day 5 data (-14%). This depression was stated by the laboratory to be related to the spleen undergoing proliferation due to antigenic stimulation and under this condition the spleen "may be slightly more sensitive to TPTH." The spleen cell number was also shown to be statistically significantly lower (-15%) for the mice dosed with 2.5 mg/kg/day.

In the opinion of this reviewer, TPTH has at least some effects (adverse or otherwise) on the spleenic immunosystem at 2.5 mg/kg, the lowest dose level tested. These are indicated by decrease in spleen weight, increase in IgM AFC/10^6 spleen cells and IgM AFC/spleen. These increases were noted both at day 4 and day 5 and they are followed at higher doses by decreases. The significance of these increases were not discussed by the laboratory. Because the increases were noted at both day 4 and day 5, TB considers the response to be due to the presence of TPTH. The spleen cell number and spleen weight were statistically significantly lower for the mice dosed with 2.5 mg/kg/day.

Part 3. Delayed hypersensitivity response.

This study consisted of sensitizing the mice (10 males per group) with keyhole limpet hemocyanin (100 ug) on days 2 and 8 of the 14-day treatment with TPTH. On the 13th day of

treatment the mice were administered a pulse dose of ^{125} Iododeoxyuridine to label mononuclear cell precursors. The mice were also injected with fluorodeoxyuridine to inhibit de novo synthesis of thymidine. A group of mice not sensitized with the keyhole limpet hemocyanin were included as a control group. 24 hours after being dosed with the ^{125} Iododeoxyuridine, all mice were challenged with 30 ug of keyhole limpet hemocyanin which was injected (20 ul) into the central part of the pinna of the left ear. After allowing 24 hours for reaction, the mice were sacrificed and the injected and uninjected ears were removed. Sections from each ear (5 mm in diameter) were removed and counted for ^{125}I. The stimulation index (S.I.) was calculated for each sensitized mouse according to the equation:

$$S.I. = \frac{(\text{cpm left ear})}{(\text{cpm right ear})}_{\text{Sensitized group}} - \frac{(\text{cpm left ear})}{(\text{cpm right ear})}_{\text{Mean of the unsensitized group}}$$

The S.I. obtained for this study is shown in the following table.

	TPTH (mg/kg)					CTX
	0	2.5	5.0	10.0	20.0	30.0
S.I.	5.67 ±0.42*	5.37 ±.82	5.88 ±.90	5.66 ±.78	3.54 ±1.27	1.16 ±.30

*Data are ± the standard error.

These data show that the group dosed with 20 mg/kg of TPTH caused a 38% decrease in the stimulation index which was not significant and the data showed a large standard error. In contrast, the positive control showed a statistically significant decrease of about 80%.

The test laboratory concluded that TPTH caused an effect at the highest dose level only (20 mg/kg) and assigned a NOEL of 10 mg/kg for induction of delayed hypersensitivity response.

Part 3. Spleen cell response to mitogens.

For this aspect of the study, the mice were sacrificed one day after the last treatment with TPTH and their spleens were removed and coincubated with murine T cell mitogens (concanavalin A and phytohemagglutinin) and a B cell mitogen

60

(bacterial lipopolysaccharide). These mitogens are considered to be nonspecific inducers of lymphocyte proliferation, and the test was designed to assess the effects of TPTH to inhibit this lymphocyte proliferation. After allowing 48 hours for the mitogens to coincubate with the spleens, H^3-thymidine was added and allowed to associate with the cells, the cells were harvested and counted. Two vehicle control groups were prepared, but the first group was considered compromised because of clumping among the cells (attibuted to an artifact of centrifugation temperature).

The laboratory reported that there were no consistent dose related responses to the mitogens caused by the treatment with TPTH.

TB notes that there are many instances of depression in the response to the mitogens even at the dose level of 2.5 mg/kg. Because of the many instances of depression relative to the control group, TB does not consider this study to sufficiently define a lack of an effect of TPTH on the spleen cell response to mitogens. Because the immune system is prone to results which do not show a dose response, TB interprets the data presented here as indicating a possible effect of TPTH at all doses tested. Tables 9 and 10 from the study report are attached to show the many instances of depressions in response due to TPTH.

Overall conclusions.

As an assessment of the effects of TPTH on the immune system, this study does not demonstrate a definite NOEL for TPTH. There is noted at the lowest test dose level (2.5 mg/kg/day for 14 days) a decrease in spleen weight (at least under the conditions of the spleen antibody forming cell assay). This study also shows a consistent (day 4 and day 5 <u>increase</u> in response to T dependent antigen. The study designed to show spleen cell responses to peak mitogen (concentration) gave rather consistent decreases at the low dose level to each of 3 mitogens. Although the mitogen response is not dose dependent, the data allow the interpretation of showing an effect of TPTH because of the known character of the immune system to not always follow dose response relationships. In addition, decreased leukocyte counts were observed at all dosage levels of TPTH (except at 10 mg/kg).

61

[Xeroxed from the Study report]

Table 9

Spleen Cell Response to Peak Mitogen of Male $B_6C_3F_1$ Mice

Treated with Triphenyltin Hydroxide For 14 Days

Mitogen	H/NH	Triphenyltin Hydroxide Dose (mg/kg) 0	2.5	5	.10	20	CTX-30 mg/kg 30
Media	NH	3981 ±634	1696 ±449	2843 ±278	4249 ±1060	3438 ±1170	1852 ±471
Con A (5 ug/mg)	H	138930 ±13330	87659** ±12536	96147 ±9130	101980 ±12868	123380 ±13942	54379** ±10841
PHA (1 ug/mg)	H	157163 +8748	113450* ±13882	130250 ±9620	122429 ±12253	148348 ±7381	53396** ±11328
LPS (100 ug/mg)	NH	29994 ±3740	12944** ±1697	21374 ±2719	23146 ±3979	20652 ±4683	4351** ±846

$B_6C_3F_1$ male mice were administered triphenyltin hydroxide daily for 14 days by gavage. Cyclophosphamide (CTX), the positive control, was administered at 30 mg/kg daily for 14 days by the intraperitoneal route. Twenty-two-26 hours after the last treatment, the mice were sacrificed, spleens removed, single cell suspensions prepared and response to mitogens determined. The numbers represent the mean ± S.E. derived from the number of mice indicated in parenthesis. **=p <.01 and * = P <.05, respectively as compared to the vehicle (0) control. (NH) = non-homogeneous and (H) = homogeneous by the Bartlett's test for homogeneity. If the data were homogeneous a Dunnett's multiple range test was used for testing significance. If the data were non-homogeneous, the Wilcoxon rank test was used for testing significance.

87

[Xeroxed from study report]

Table 10

Spleen Cell Response To Various Concentrations of Mitogens of Male $B_6C_3F_1$ Treated with Triphenyltin Hydroxide Daily For 14 Days

		Triphenyltin Hydroxide (mg/kg)						CTX mg/kg
	H/NH	VH[1] (10)	VH[2] (10)	2.5 (10)	5.0 (10)	10.0 (10)	20.0 (10)	30.0 (10)
Spleen Cell Number x 10^7	NH	7.1* ±0.9	5.4 ±0.4	4.6 ±0.4	7.0 ±0.4	6.7 ±0.3	2.1* ±0.4	2.1* ±0.3
Spleen Weight (mg)								
Media	NH	1586* ±317	3981 ±634	1696* ±449	2843 ±278	4249 ±1060	3438 ±1170	1852* 471
Mitogen Concentration (ug/mg)								
Con A 0.5	NH	1019* ±339	9828 +2448	1668* ±945	6436 ±946	5771 ±1992	6828* +2541	1631* +491
Con A 1.0	NH	6171* ±2184	41125 ±9167	7538* +2411	30046 ±3945	30803 ±9391	24465* ±8501	2430* ±819
Con A 5.0	H	59106** ±12142	138930 ±13330	87659* ±12536	96147 ±9130	101980 ±12868	123380 ±13942	54379** ±10841
Con A 10.0	H	33444* ±6167	76970 +11695	46295 ±7970	42961 ±7318	56005 ±11338	56351 ±16608	52224 +11796
PHA 0.5	H	47106** ±11833	137685 ±13470	67091** +12699	102780 ±8114	85589* ±14195	91213 ±19066	19091** ±4321

[Xeroxed from study report]

Table 10 (Continued)

Mitogen Concentration (ug/mg)	H/NH	Triphenyltin Hydroxide (mg/kg) VH[1]	VH[2]	2.5	5.0	10.0	20.0	CTX mg/kg 30.0
PHA 1.0	H	101916** ±15340	157163 ±8748	113450* ±12882	130250* ±9620	122429 ±12253	148343 ±7381	53396** ±11328*
PHA 5.0	H	64142** ±12275	122757 ±13087	87794 ±11471	54075** ±10833	63775** ±8887	96880 ±15861	67284** ±11081
PHA 10.0	NH	10298* ±2947	42867 ±10837	15238* ±6877	6771* ±1963	9545* ±2188	17534* ±10635	20116* ±4750
LPS 10	NH	13169* ±2431	28180 ±3985	10192* ±1703	21210 ±2982	23691 ±4603	19880* ±5741	3975* ±851
LPS 100	NH	15837* ±2703	29994 ±3740	12994* ±1697	21374 ±2719	23146 ±3979	20652 ±4683	4351* ±846
LPS 500	NH	8313* ±1512	24062 ±4531	7306* ±1395	16421 ±2376	17442 ±3385	20759 ±6533	3136* ±705

$B_6C_3F_1$ male mice were administered triphenyltin hydroxide daily for 14 day by gavage. Cyclophosamide (CTX), the positive control, was administered at 30 mg/kg daily for 14 days by the intraperitoneal route. Twenty-two-26 hours after the last treatment, the mice were sacrificed, spleens removed, single cell suspensions prepared and response to mitogens determined. The numbers represent the mean ± S.E. derived from the number of mice indicated in parenthesis. **=P<.01 and *=P<.05, respectively as compared to the vehicle (0) control. (NH)=non-homogeneous and (H)=homogeneous by the Bartlett's test for homogeneity. There were two vehicle groups VH^1 and VH^2. The control group used for comparison is the VH^2 group because of cell clumping in the VH^1 group. If the data were homogeneous a Dunnett's multiple range test was used for testing significance. If the data were non-homogeneous, the Wilcoxon rank test was used for testing significance.

Screening Triphenyltin Hydroxide (Alfa 717) in the Ames Salmonella Typhimurium Mutagenicity Assay.

By H. E. Bryant, report dated October 4, 1976 (The name and location of this laboratory is not stated). MRID #00086551

This report states that triphenyltin hydroxide was tested in the Salmonella typhimurium assay system as described by Ames et al. [Mutation Research 31: 347-367 (1975)]. The strains used were TA-98, -100, -1535, -1538, and -1978. Both activation (S-9 liver supernatant) and non-activation assays were run. Acetylaminofluorene was used as a positive control. Both a spot test and a test where TPTH was suspended in the nutrient were run.

The results indicated that TPTH was extremely toxic to the bacteria (1.0 ug/plate was found to be working range). In no case was there evidence that TPTH was a mutagen in this system.

CONCLUSION:

No CORE assignment.

Ames Metabolic Activation Test to Assess the Potential Mutagenic Effect of HOE 29664 OF AT 201

Huntingdon Research Center, #450/81A
July 23, 1981
EPA Acc. No. 071368, Tab C-18.

Triphenyltin hydroxide (TPTH, HOE 29664 OF AT 201) was tested for mutagenic effects in five strains of S. typhimurium and in one strain of E. Coli (WP2UVRA). Preliminary range finding studies with TPTH (tested over the range of 5, 50, 500 and 5000 ug/plate) indicated that TPTH was very toxic to S. typhimurium and that 5 ug/plate was the highest dose level for the definitive study. TPTH was not as toxic to E. Coli and 5000 ug/plate could be assayed. Assays were run with and without metabolic activation (S9 mixture from rat liver from rats treated with Aroclor 1254).

The results did not show signs of mutation due to TPTH when tested over the range of 312.5 to 5000 ug/plate for E. Coli (The positive controls 2-aminoanthracene and N-ethyl-N'-nitro-N-nitroso-guanidine produced the expected positive results). It should be noted that the TPTH precipitated in the plates.

No positive mutation response was noted for TPTH for the S. typhimurium strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100 with or without metabolic activation. The positive controls when used produced the expected positive results. At least three plates were run per condition. TPTH was tested over the range of 0.3125 to 5.0 ug/plate.

65

This study provides a demonstration that TPTH does not produce mutations in E. coli or S. typhimurium under the conditions used.

The Dominant Lethal Assay of Technical TPTH (Triphenyltin Hydroxide) in Sprague-Dawley Rats

Cannon Labs. #7E8306, April 23, 1978.
EPA Acc. No. 071368, Tab C-19.

This study consisted of a total of 7 test groups of male Sprague-Dawley rats which were dosed as either solvent control (corn oil), 3, 20, 38 or 150 mg/kg of TPTH (lot PP523 A, and 94.8%) in corn oil and two positive control groups dosed by gavage with triethylene-melamine in corn oil. There were two positive control groups because the first group, dosed i.p. at 0.35 mg/kg, had a high rate of death. A second positive control group was dosed with 0.25 mg/kg and consisted of 4 males. There were 10 males per group in the other groups.

Dosing was made on a daily basis for five consecutive doses. One day after the last dose, each male was allowed to mate with two females. Each succeeding week for 10 weeks, the mating procedure was followed with two new virgin females. The female rats were sacrificed 12 days after mating and their uterine contents were examined.

Results

1. Reactions in the treated males. 8 of the high dose test group males (150 mg/kg/day) died as a result of TPTH. Some of the rats in the group dosed with 38 mg/kg/day had loose hair but other symptoms were not reported. No other clinical investigations were made on the males with regard to their physical appearance or condition (i.e., body weights were not determined).

2. The fertility index was depressed for the 20, 38 and 150 mg/kg/day dose groups for week 1 and for week 2 for the high dose test group. For week one the fertility index was 35% for the group dosed with 20.0 mg/kg and was 20% for the group dosed with 38 mg/kg. The lowest level noted for any control week was 75%. The depression in the fertility index was claimed by the laboratory to be due to the poor overall health of the rats.

3. On some occasions there were both lower and higher group mean weekly total number of implantations sites for each of the groups treated with TPTH, but no consistant effect was evident. However, at weeks 2, 5 and 7, the high dose test group was considerably lower than the control groups.

164

4. Evaluations were also made on the preimplanation losses, early dead implants, late dead implants, proportion of female rats with one or more dead implants, proportion of female rats with two or more dead implants and dead implants/total implants.

Of these parameters, the most important in evaluating a positive dominant lethal effect are an "increase in preimplantation losses and/or an increase in dead implants." In this study the high dose test group (150 mg/kg/day of TPTH) showed some evidence of there being increases in preimplantation losses at weeks 2, 3, 4, 5, 6, 7 and 8. The mid dose group was also elevated at week 3. The highest mean weekly data for the solvent control group was "1.4" and the highest for the mid dose group (38.0 mg/kg) was 2.5. No meaningful differences in early or late dead implants were noted for the females mated with rats treated with TPTH when compared with the solvent treated controls.

CONCLUSION: Toxicology Branch concludes that this study is negative for dominant lethal effects at doses up to and including 38 mg/kg/day. At 150 mg/kg/day, a possible positive effect is obscured by the high rate of deaths and poor overall health in this test group.

Note: See also Epstein, S., Arnold, E., Andrea, J., Bass, W. and Bishop, V. (1972). Detection of Chemical Mutagens by the Dominant Lethal Assay in the Mouse. Toxicol. Appl. Pharmacol. 23: 288-325 (1972).

J.Doherty:DCR-44868:Part II of II:bje:2/1/84:
REVISED:DCR-44873:J.Doherty:efs:Raven:557-2226:CLIENT'S DISKETTE:2/15/84