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

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3-20-99

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Memorandum:

Subject: EPA Id. No.: 083601. Triphenyltin Hydroxide: Toxicology Branch Chapter for the RED.

PC Code: 083601
DP Barcode: DP254359
Submission No.: S558716

From: John Doherty 3/20/99
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To: Angel Chiri
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Through: Steven Knizner
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Health Effects Division 7509C

Attached is the Toxicology Chapter for the RED for triphenyl tin hydroxide. An Electronic copy is available on the LAN.

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Note:

Subject: Triphenyltin Hydroxide: Toxicology Section of the RED Chapter

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PC. No.: 083601

Attached is the Toxicology Section of the RED for triphenyl tin hydroxide. An electronic copy is available for insertion into the RED.

Copies of the HIARC report dated November 13, 1998 and the FQPA Safety Committee report dated December 17, 1998 are also attached.

Also attached is APPENDIX 1. Updated Executive Summaries for Selected Toxicity Studies.

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3.0 HAZARD CHARACTERIZATION

3.1 Hazard Profile

Table 1. Acute Toxicity of Triphenyltin Hydroxide

Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
81-1	Acute Oral-rat	071364 252512	LD_{50} = 165 mg/kg ♂ 156 mg/kg ♀	II
81-2	Acute Dermal-rat	071364	LD_{50} = 1600 mg/kg	II
81-3	Acute Inhalation-rat	071364	LC_{50} = 60.3 μg/L	I
81-4	Primary Eye Irritation	071364	Corrosive	I
81-5	Primary Skin Irritation	071364	PIS = 2.8	III
81-6	Dermal Sensitization	Several Studies	Not a sensitized in the Buehler assay.	Not considered a sensitizer

Table 2. Toxicity Profile of Triphenyltin Hydroxide[1].

Study Type	MRID No.:	Results
21-day dermal - rats (1985)	00142880 258230 (Accession Number)	Systemic: NOAEL > 20 mg/kg/day. No systemic effects at highest dose tested. Systemic: NOAEL < 5 mg/kg/day. Local irritation.
Subchronic feeding - rats (1986)	00157771 261754 (Accession Number)	NOAEL < 0.33 mg/kg/day: decreased IgG antibodies. At 7.63 mg/kg/day: decreased body weight and gain and food consumption.
Subchronic feeding -mouse (1986)	00157952 261753 (Accession Number)	< 0.75 mg/kg/day: decreases in IgA and IgM antibodies. At 3.78 mg/kg/day: decreased adrenal weight and at 19.46 mg/kg/day: decreased ovary weight and increased liver weight.

[1]All studies classified as ACCEPTABLE or otherwise determined to contain useful data.

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Study Type	MRID No.:	Results
Subchronic feeding - guinea pig (1960)	00086467	NOAEL < 2.5 ppm (estimated 0.1 Mg/kg/day): decreased leucocyte counts.
Subchronic feeding -dog		No valid study. Refer to chronic feeding study below.
Subchronic inhalation - rats (1989)	41017701	NOAEL = 0.00034 mg/L. LOAEL = 0.002 mg/L: deaths and lung and respiratory irritation and edema.
Chronic feeding - dog (1987)	40285501	NOAEL and LOAEL > 0.562 ♂ and 0.624 ♀ mg/kg/day. No effects at the highest dose tested.
Chronic feeding - rat (1970)	00080390 099050 (Accession Number)	NOAEL = 0.1 mg/kg/day; LOAEL = 0.25 mg/kg/day: decreased leucocyte counts.
Chronic/carcinogen-city -rat (1989)	41085702	NOAEL < 0.3 in ♂ and 0.4 in ♀ mg/kg/day: deaths in females and decreases in immunoglobulin. **Positive for pituitary and testicular tumors.** Dose levels considered adequate.
Carcinogenicity - mouse (1989)	41087501	NOAEL < 0.85 mg/kg/day based on decreased in immunoglobulins. Particularly IgA and IgM in either males or females. **Positive for hepatocellular adenomas and carcinomas.** Dose levels considered adequate.
Developmental toxicity - (1985) rat representative study, one of several studies	257402 (Accession number)	Maternal toxicity: NOAEL = 1 mg/kg/day; LOAEL = 2.8 mg/kg/day: decreased body weight and food consumption. Developmental toxicity: NOAEL = 2.8 mg/kg/day; LOAEL = 8 mg/kg/day: decreased fetal weight and increased sternebrae unossified. (Typical response) at this dose level. At 8 mg/kg/day may have smaller litter size and less viable fetuses in other studies or poor pup survival.
Developmental toxicity - rabbit/oral (1987)	40104801	Maternal toxicity: NOAEL = 0.1 mg/kg/day; LOAEL = 0.3 mg/kg/day: decreased body weight gain. Developmental toxicity: NOAEL = 0.3 mg/kg/day; LOAEL = 0.9 mg/kg/day: lower fetal body weight and unossified hyoid.

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Study Type	MRID No.:	Results
Developmental toxicity - rabbit/dermal (1993) (dermal)	42909101	Maternal and developmental toxicity: NOAEL and LOAEL > 3 mg/kg/day. No effects at highest dose tested.
Reproductive toxicity - rat (1986)	264667 to 2254676 (Accession number)	Parental toxicity: NOAEL = 0.925 mg/kg/day; LOAEL = 2.5 mg/kg/day decreased body weight. Developmental toxicity: NOAEL = 0.25 mg/kg/day; LOAEL = 0.925 mg/kg/day: decreased litter size, liver and spleen weights.
Gene Mutation-Ames test (1981)	00125264	Not mutagenic in *S. tymphimurium* or *E. Coli* ± metabolic activation.
Mouse lymphoma assay (1985)	00152226	Borderline positive in the presence of S-9 mix but negative in absence of S-9.
Cytogenetics - human chromosome aberrations (1985)	00152223	Positive for inducing chromosome aberrations in ± of S-9. Study demonstrates clastogenic property of TPTH.
Recombinant assay (Convers) (1985)	00155521	Negative in *Sacc. Cerevisiae* ± S-9 metabolic activation.
Bone marrow cells *in vivo* (1987)	40377102	No effect on bone marrow cells.
Micronucleus assay *in vivo* (1985)	00152225	Negative at 140 mg/kg but study did not demonstrate that TPTH went to the bone marrow.
Dominant lethal assay (1978)	00125265	Negative at up to 38 mg/kg/day. At 150 mg/kg/day, high rate of deaths.
Gene mutation (1985)	00152224	Not mutagenic ± metabolic activation in Schizosaccharomyces.
Unscheduled DNA synthesis (1985)	00155522	Negative up to cytotoxic dose levels.

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Study Type	MRID No.:	Results
General metabolism (several studies 1986 to 1989)	41309102 40029406 40029405 40029407 41387201 41309101	Absorption, excretion, tissue retention and identification of metabolites characterized.
Dermal penetration (1986 and 1987)	00156684 40198301 40073001	Understanding of the true potential for TPTH to penetrate the skin and enter the systemic circulation confounded by the adherence of TPTH to the skin.
Special Immunotoxicity (Several studies 1982 to 1990	41518200 40303701 00124218 00124217 00141313	In rats (41518200): NOAEL = 1.82 mg/kg/day; LOAEL = 3.4 mg/kg/day: decreases in IgG. At higher doses: decreased spleen weight and white blood cells and circulating lymphocytes. In mice (41518200): NOAEL = 0.23 mg/kg/day, LOAEL = 1.15 mg/kg/day: decreased spleen weight absolute and relative. At higher doses: decreased IgM, WBC, neutrophils and circulating lymphocytes. Immunosuppression: (40303701): No evidence of increased susceptibility to *trichinella spiralia* at 2.5 mg/kg/day.

3.1 Hazard Profile.

Currently there are data gaps for the following studies:

81-8 (870.6200). Acute Neurotoxicity screen
82-7 (870.6200). Subchronic neurotoxicity screen
83-6 (870.6300). Developmental neurotoxicity with special inclusions for immunotoxicity assessment in the neonates and weanlings.
Special study to assess for hormonal changes.

Quality and completeness of the data base. The available toxicity data base for TPTH is considered to *partially* define the potential toxicity of TPTH. There are questions remaining concerning the potential for immunotoxicity and there are no series 81-8, 82-7 and 83-6 acute, subchronic and developmental neurotoxicity studies. The existing toxicity data base for TPTH has been developing since the 1960's. Nearly all of the earlier studies have been replaced by studies conducted in the mid to late 1980's and have been classified to be acceptable using review criteria in effect in the late 1980s and early 1990s. In general, there is a high degree of confidence in the existing toxicity data base especially for the studies used in assessing developmental toxicity and carcinogenicity. The chronic RfD is based on decreased leucocytes and immunoglobulins which are indicators of immunotoxicity. There is a high degree of confidence that the dose levels selected for the chronic RfD are appropriate in that there would

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not be significant decreases in leucocytes or immunoglobulins at lower doses than 0.1 mg/kg/day. Additional data to define the potential for TPTH to cause true immunotoxicity would be desirable.

Toxicity in rats. The toxicologically significant effects of TPTH *in rats* include decreases in leucocytes and immunoglobulins at dose levels as low as 0.25 or 0.33 mg/kg/day which are considered potential indicators of immunotoxicity. Following chronic feeding deaths result at doses as low as 0.4 mg/kg/day in females that were probably related to pituitary tumors. In subchronic and chronic studies, decreases in body weight and food consumption result at approximately 1.3 to 1.6 mg/kg/day. Other systemic effects include decreased liver weight, bile duct hyperplasia and portal sclerosis as well as increases in serum enzyme activity (ASAT, ALP and ALAT). The pituitary displayed hyperplasia in the pars intermedia and the testis displayed Leydig cell hyperplasia and tubular atrophy and the testis also had increases in Leydig cell tumors.

In several developmental toxicity studies in rats, maternal toxicity consisted of lower body weight and food consumption at approximately 2.8 mg/kg/day and developmental toxicity at approximately 8 mg/kg/day consisted of lower fetal weight, smaller litter size and some decreases in ossification. An initial concern for hydronephrosis and hydroureter observed in an earlier study was removed by subsequent studies that did not demonstrate this effect. There was an indication that the fetuses may be more sensitive than adults in the multi generation reproduction study since at 0.925 mg/kg/day the fetuses were lower in weight and appeared smaller in size and also their liver and spleen weights were decreased. Parental toxicity was noted only at 2.5 mg/kg/day and consisted mainly of a body weight decreases.

Toxicity in dogs. Dogs were assessed at a dose level of 18 ppm (equivalent to approximately 0.562 in males and 0.624 in females mg/kg/day)in a chronic study but there were no systemic effects noted in either sex.

Toxicity in mice. In both the subchronic dose range finding study and the carcinogenicity study, mice showed decreases in immunoglobulins. In the subchronic study, there was slightly increased initial body weight, decreases adrenal and ovary weight in females without pathological changes and increased liver weight. In the carcinogenicity study, there were decreases in kidney weight (without associated pathology), liver weight decreases and at higher doses body weight decreases and deaths. The mouse study was considered positive for liver tumors.

Toxicity in rabbits. In the oral developmental toxicity studies with *rabbits*, TPTH resulted in decreases in body weight at doses as low as 0.3 mg/kg/day. At higher doses such as 2 mg/kg/day, poor general condition and resorptions in the pregnant does result. Developmental toxicity was noted at 0.9 mg/kg/day as lower fetal weight and a slight increase in unossified hyoid. A developmental toxicity study by the dermal route demonstrated a NOAEL and LOAEL of > 3 mg/kg/day for both maternal and developmental toxicity since there were no effects at 3 mg/kg/day the highest dose tested.

Immunotoxicity. Substituted organotins are also known to be immunotoxic and the chronic RfD is set on the basis of decreased leucocytes and the rat studies consistently showed decreases in certain

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antibodies. Decreases in leucocytes were a feature of the guinea pig (at approximately 0.1 mg/kg/day). Decreased immunoglobulins were noted in the mouse study at 0.75 mg/kg/day. Subacute dosing verified that the rat at 3.4 mg/kg/day and mouse at 1.15 mg/kg/day have decreased white blood cells and spleen size. A special Immunotoxicity study with TPTH, however, did not indicate that TPTH is specifically immunotoxic since the rats dosed at 2.5 mg/kg/day for 10 days were not more susceptible to opportunistic infections. In order to further assess for potential immunotoxicity, the rat series 83-6 developmental toxicity study must include in addition to the neurotoxicity parameters special provisions to assess for the function of the immune system in the neonate and weaned offspring. It is strongly advised that the protocol for this study be submitted to the Agency for review prior to initiating the study.

Endocrine disruption. There are several indications that imply that TPTH causes endocrine disruption. In rats, testicular and pituitary tumors were a marked feature in the carcinogenicity study. In the mouse there were changes in adrenal and ovary weights. There were no specific assays for blood levels of hormones in the studies submitted to further assess for possible endocrine disruption. There has been discussion between the registrants and the Agency regarding the design of some special studies to assess the potential for TPTH to affect the hormone levels in an attempt to demonstrate and characterize the possible relationship between TPTH, hormonal effects and the development of pituitary and testicular tumors. These studies have not been submitted to the Agency as of March 1999.

Carcinogenicity. TPTH is classified as a B2: probable human carcinogen based on evidence of carcinogenicity in mice (liver tumors) and rats (pituitary and testicular tumors) at dose levels that were adequate for assessment of carcinogenicity. The low dose linear approach (Q1*) was used for human characterization and was based on the pituitary tumors observed in rats. The Q1* is 1.83 mg/kg/day.

Mutagenicity. TPTH is not considered to have a mutagenicity/genetic toxicity concern. Most studies are negative for mutagenic/genetic toxicity effects. Although there were some apparent positive responses, other tests, particularly *in vivo*, conducted to verify the significance of the apparent positive studies *in vitro*. were negative.

General metabolism. There are several studies which define the metabolism of TPTH using wither ^{14}C or ^{113}Sn labelled TPTH. The contributions form 6 studies combine to meet the general metabolism requirement for TPTH. The ^{14}C studies are confounded by the fact that the labelled phenyl groups split off and the fate of the parent compound is not followed. Thus, the labelled phenyl may be excreted inthe urine but this does not represent the excretion on intact TPTH. The ^{113}Sn labelled TPTH studies follow the fate of the tin although this may be as triphenyl, diphenyl or monophenyl or tin itself. The biliary route is important in excretion of ^{113}Sn. Most of the label (80-100% in several studies) is recovered in the feces. Little remains in the tissues (for example, 0.5%). After 24 hours, the kidneys, liver, epididymis and brain had the most label. After 7 days very little label remained in the tissues.

Metabolites. There are no known special toxicity problems or issues associated with the metabolites of TPTH. It appears that all plant metabolites are also animal metabolites. TPTH is serially metabolized to diphenyl and monophenyl tin and excreted. The need to regulate the tolerance to include

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the metabolites of TPTH,

Dermal absorption. There are several studies to assess for dermal absorption. However, the high affinity that TPTH has for the skin confounds assessing for the potential for TPTH to be absorbed dermally. A dermal absorption factor of 10% was extrapolated based on the comparison of the LOAELs of the oral and dermal developmental toxicity studies in rats.

3.2. FQPA Considerations.

3.2.a. *Neurotoxicity.* TPTH belongs to a class of chemicals called substituted organotins. This class includes trimethyl and triethyl tin which are noted for their neurotoxic effects and serve as positive controls in neurotoxicity studies. TPTH did not demonstrate obvious neurotoxicity in either the rat, rabbit or dog studies. This may be because the larger and bulkier phenyl groups prevent TPTH from reaching the nervous tissue at sufficiently high concentrations. Neurotoxicity assessment, however, is not considered complete for TPTH and the series 81-8, 82-7 and 83-6 acute, subchronic and developmental neurotoxicity studies are being requested. The series 83-6 developmental toxicity study will require a special protocol (refer to paragraph on immunotoxicity below.

3.2.b. *Increased susceptibility.* There were no indications of increased susceptibility in either the rat or rabbit prenatal developmental toxicity studies. The rat multigeneration reproduction study, however, did indicate toxicity increased susceptibility (based on decreases in liver and spleen weight and a decease in live litter size in offspring) at a dose (0.9 mg/kg/day) lower than the dose causing parental toxicity (2.5 mg/kg/day).

3.2.c. *Data gaps for assessment of potential hazard to infants and children.* The HIARC determined that developmental immunotoxicity assessment or assessment if potential immunotoxicity in neonatal rats is necessary. There is no series 83-6 developmental neurotoxicity study. The developmental neurotoxicity study will require the inclusion of the standard battery of tests to assess for developmental neurotoxicity and also special inclusions to assess for immunotoxicity in the neonate and weanling rat. It is recommended that the protocol for this study be submitted to OPP prior to initiating the study.

3.2.d. *Status of the 10 x FQPA safety factor.* TPTH was discussed by the FQPA Safety Factor Committee on November 30, 1998 and the committee recommended two different factors: a 3 x for acute and a 10 X for chronic dietary risk assessments. There are no registered residential uses at the present time.

3.2.e. *Application of the 10 x safety factor.* The following is an excerpt for the FQPA Safety Committee report dated December 17, 1998.

1. FQPA Safety Factor Recommendation

The Committee recommended two different FQPA Safety Factors: 3x for acute dietary risk

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assessments and 10x for chronic dietary assessments.

2. Rationale for the FQPA Safety Factor

The Committee made these recommendations for the FQPA Safety Factor for TPTH because:

1. There was evidence of increased susceptibility to the offspring following pre- and/or postnatal exposure in the two-generation reproduction study in rats. Offspring toxicity was observed at a dose lower than parental systemic toxicity.

2. TPTH is considered to affect the endocrine system and there is concern for the possible relationship between TPTH, hormonal effects, and the development of pituitary and testicular tumors.

3. TPTH is considered as an agent that may cause immunotoxicity. The chronic dietary RfD is based on decreases in white blood cells and both the rat and mouse chronic feeding and/or oncogenicity studies indicate decreases in immunoglobulins.

4. HIARC required a developmental toxicity study that evaluates immunotoxicity, a potential toxic effect of TPTH to which fetuses and neonates may be specially susceptible, in place of a developmental neurotoxicity study.

3. Population Subgroups for Application of the Safety Factor

Acute Dietary Assessment: The Committee determined that the FQPA Safety Factor can be **reduced to 3x** for acute dietary risk assessment for **All Populations which include Infants and Children** because the increased susceptibility was seen only in the offspring of parental animals receiving repeated oral exposures (two-generation reproduction toxicity study) and not seen following *in utero* exposures (developmental studies). Thus the increased susceptibility concern was for chronic dietary exposure. The application of the 3x safety factor to the acute dietary exposure assessment is based on the concern for the potential immunotoxic effects which resulted in the requirement for a developmental immunotoxicity study (data gap).

Chronic Dietary Assessment: The Committee determined that the FQPA Safety Factor should be **retained (10x)** for chronic dietary risk assessment for **All Populations which include Infants and Children** because increased susceptibility to the offspring was seen following repeated oral exposures in the two generation reproduction study in rats.

Residential Assessment: There are no registered residential uses at the present time.

3.3. Dose Response Assessment

Table 3. Summary of Toxicological Endpoints for Use in Human Risk.

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EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	NOAEL= 0.3 mg/kg/day (100 UF)	Increased hyoid arches in rabbit fetuses.	Oral Developmental toxicity -Rabbit (MRID No.: 40104801)
Chronic Dietary	NOAEL= 0.1 mg/kg/day (300 UF)	Decreased white blood cells.	Chronic feeding study -Rat (Accession No.: 099050)
Carcinogenicity (oral/dermal/ inhalational)	Oral Q1* 1.83 $Mg/kg/day^{-1}$	TPTH is classified as a B2 Carcinogen -probable human carcinogen based on pituitary and testicular tumors in rats and liver tumors in mice. A dermal absorption of 10% should be used for this risk assessment.	
Short-Term (Dermal)	Dermal NOAEL= 3 mg/kg/day	No effects a the highest dose tested.	Dermal Developmental toxicity - Rabbit (MRID No.: 42909101)
Intermediate-Term (Dermal)	Dermal NOAEL = 3 mg/kg/day	No effects a the highest dose tested.	Dermal Developmental toxicity - Rabbit (MRID No.: 42909101)
Long-Term Non-cancer (Dermal)	None	Use pattern does not indicate exposure will be for this interval.	
Inhalation (Any Time Period)	0.00034 mg/L (100 UF)	Deaths following lung lesions.	Subchronic inhalation toxicity -Rat (MRID No.: 41017701)

The endpoints selected for the acute dietary, chronic dietary, short, intermediate and long term exposure scenarios are listed in Table 3 above. A more detailed discussion of the selection of these endpoints can be found in the HIARC report dated. December 17, 1998.

The slope of the doses selected for these exposure endpoints is considered steep. The oral developmental toxicity study in rabbits assessed doses as close as 0.1, 0.3, 0.9 and 1, 2, 4, and 8 mg/kg/day. At doses above 1 mg/kg/day, the general condition of the rabbits and the incidence of resorptions changed dramatically with an increase in dose over this narrow dose range. In the chronic study in rats., the dose levels varied from 5 to 80 ppm and there were marked increases in deaths over this narrow range of doses.

HED DOC. NO. 012972

DATE: **November 13, 1998**

MEMORANDUM

SUBJECT: ***TRIPHENYLTIN HYDROXIDE (TPTH)*** - Report of the Hazard Identification Assessment Review Committee.

FROM: John Doherty
Registration Action Branch 3
Health Effects Division (7509C)
and
Jess Rowland
Executive Secretary
Hazard Identification Assessment Review Committee.
Health Effects Division (7509C)

THROUGH: K. Clark Swentzel, Chairman
Hazard Identification Assessment Review Committee.
Health Effects Division (7509C)

TO: Christina Scheltema, Risk Assessor
Registration Action Branch 3
Health Effects Division (7509C)

PC Code: 083601

On October 20, 1998 Health Effects Division's Hazard Identification Assessment Review Committee evaluated the toxicology data base of **Triphenyltin Hydroxide (TPTH),** re-assessed the Reference Dose (RfD) set in 1992 and selected the toxicological endpoints for acute dietary as well as occupational exposure risk assessments. The HIARC also addressed the potential increased susceptibility of infants and children from exposure to TPTH as required by the Food Quality Protection Act (FQPA) of 1996. The Committee's conclusions are presented in this report.

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Committee Members in Attendance

Members present were: David Anderson (for Susan Makris), Karl Baetcke, William Burnam, Robert Fricke, Melba Morrow, John Redden, Jess Rowland and Clark Swentzel.

HED staff present at the meeting: Virginia Dobozy, Pat Gaunt, Mike Ioannou, Nicole Paquette, P.V. Shah, and Pauline Wagner.

Data Presentation:
and
Report Presentation

_____
John Doherty, Ph.D., D.A.B.T.
Toxicologist

Report Concurrence:

_____
Jess Rowland
Executive Secretary

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I. INTRODUCTION

On October 20, 1998 Health Effects Division's Hazard Identification Assessment Review Committee evaluated the toxicology data base of **Triphenyltin Hydroxide (TPTH),** re-assessed the Reference Dose (RfD) set in 1992 and selected the toxicological endpoints for acute dietary as well as occupational exposure risk assessments. The HIARC also addressed the potential increased susceptibility of infants and children from exposure to triphenyltin as required by the Food Quality Protection Act (FQPA) of 1996.

II. HAZARD IDENTIFICATION

A. 1. Acute Reference Dose (RfD) Subpopulation: Females 13 +

Study Selected: Oral Developmental Toxicity Study in Rabbits. Series 83-3.

MRID No.: 40104801

Executive Summary: In a rabbit oral developmental toxicity study, four groups of 22 assumed pregnant New Zealand White rabbits were dosed as control, 0.1, 0.3 or 0.9 mg/kg/day of triphenyltin hydroxide (TPTH in 1% aqueous carboxymethyl cellulose) on days 6 through 18 of gestation. The does were sacrificed on day 29 and their uterine contents evaluated. At 0.3 mg/kg/day, **body weight gain** was reduced (59% for the entire gestation period). At 0.9 mg/kg/day, body weight gain was reduced 79% and the effect was greatest during the dosing period. There was a rebound in body weight following cessation of dosing. **The maternal toxicity LOAEL is 0.3 mg/kg/day based on decreased body weight gain. The NOAEL is 0.1 mg/kg/day.** At 0.9 mg/kg/day, there was a slight decrease (-11%, not significant) in mean fetal weight (possibly related to the decrease in maternal body weight) and there were six incidents of "hyoid body and/or arches unossified" vs. none in the control but one each in the low and mid dose groups. **The developmental toxicity LOAEL is 0.9 mg/kg/day based on lower fetal body weight and unossified hyoid. The NOAEL is 0.3 mg/kg/day.**

Dose and Endpoint for Risk Assessment: Developmental NOAEL= 0.3 mg/kg/day based increased incidents of "hyoid body and/or arches unossified" at 0.9 mg/kg/day (LOAEL).

Comments about Study/Endpoint: The fetal malformations are presumed to occur following a single exposure (dose) and therefore, was considered to be appropriate for this risk assessment. Since this is an *in utero* effect, this endpoint is applicable to the subpopulation Females 13 + only.

Uncertainty Factor (UF): 100 which includes 10x for inter-species extrapolation and 10x for intra-species variation.

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$$\text{Acute RfD} = \frac{\text{0.3 mg/kg (NOAEL)}}{\text{100 (UF)}} = \text{0.003 mg/kg}$$

This Risk Assessment is required for the subpopulation Females 13 + only .

A. 2. Acute RfD General Population including Infants and Children

A dose and endpoint was not selected for this population because there were no effects attributable to a single does (exposure) observed in oral toxicology studies including maternal toxicity in the rat and rabbit developmental toxicity studies that are appropriate for extrapolation.

This Risk Assessment is NOT required for this population.

B. Chronic RfD

Study Selected: 2-year chronic feeding study with rats. Series 82-1 (1970 study, supported by the 1989 study)

MRID No.: (Accession No.: 099050)

Executive Summary: In a chronic feeding study, triphenyltin hydroxide (TPTH) was administered in the diets of Wistar strain rats (25/sex/dose group) at dose levels of 0, 0.5, 1, 2, 5 or 10 ppm corresponding to approximately 0, 0.025, 0.05, 0.10 or 0.25 or 0.5 mg/kg/day) for a period of 104 weeks. They were newly weaned or about 21 days old at study initiation. At 5 ppm and above there were decreases in leucocyte counts (14-24%) in males in the first year of the study. At 10 ppm there were deaths among the females at termination and an increase in body weight (females 7-10% and males 3-4%). **The LOAEL is 5 ppm (0.25 mg/kg/day in males) based on decreased leucocyte counts. The NOAEL is 2 ppm (0.1 mg/kg/day).**

Dose and Endpoint for Establishing RfD: NOAEL = 0.1 mg/kg/day based on decreased leucocytes counts in males at 0.25 mg/kg/day (LOAEL).

Uncertainty Factor(s): 300 which includes 10x for inter-species extrapolation and 10x for intra-species variation and an extra 3 fold for instability of the test material in the diet and potential for increased mortality near the LOAEL for a total of 300.

$$\text{Chronic RfD} = \frac{\text{0.1 mg/kg/day (NOAEL)}}{\text{300 (UF)}} = \text{0.0003 mg/kg/day}$$

Comments about Study/Endpoint/Uncertainty Factor: This 1970 study was classified as supplementary due to reporting deficiencies, lack of certain individual animal data and individual animal pathology (HED Doc. No. 008480). To address these concerns the Registrant conducted another chronic toxicity/carcinogenicity study in rats in 1989

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(MRID No.: 41085702). In that study, however, a NOAEL was not established. The LOAEL was 0.4 mg/kg/day based on *increased mortality*, decreases in immunoglobulins (IgG1, IG2a, IG2c and IgA), and behavioral reactions in females probably associated with tumors of the pituitary glands (HED Doc. No. 007501). The results of these two studies are taken together to establish the NOAEL of 0.1 mg/kg/day.

In 1992, the RfD/Peer Review Committee applied an additional UF of 3 due to lack of information on the analysis of the test diets used in the critical study (1970) and due to variations from the nominal dose levels in the test diets from the 1989 study. In the 1989 study, mean concentration ranged from 79.6 to 115.7%, homogeneity was from -14% to +17%; and on one occasion the value ranged from -29% to +52%. The HIARC concurred with the previous recommendations that the application of the additional UF is appropriate for the reasons stated above and because the 1989 study indicates potential mortality at the LOAEL, a dose level near the NOAEL selected for the RfD.

C. Occupational/Residential Exposure

1. Dermal Absorption

Dermal Absorption Factor: A **dermal absorption factor of 10%** was extrapolated from comparing the LOAELs of an oral and a dermal developmental toxicity study in rabbits.

In the oral developmental toxicity study in rabbits, the maternal LOAEL was 0.3 mg/kg/day based on decreased body weight gain (MRID No. 40104801).

In the dermal developmental toxicity study in rabbits, the maternal LOAEL was >3 mg/kg/day (MRID No.: 42909101).

A dermal penetration factor of 10% was calculated as follows:

$$\frac{\text{LOAEL for oral toxicity}}{\text{LOAEL for dermal toxicity}} = \frac{0.3 \text{ mg/kg/day}}{3.0 \text{ mg/kg/day}} \times 100 = 10\%$$

Although there are studies which attempt to assess the dermal penetration of TPTH, these studies result in demonstrating that labeled TPTH adheres to the skin thus confounding the estimation of the actual amount that enters the systemic circulation to be potentially toxic. This approach to deriving a dermal penetration factor is further described in the document "Revised Occupational Risk Assessment for the Use of TPTH" prepared by Paul Lewis and dated March 6, 1997.

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2. Short-Term Dermal - (1-7 days)

Study Selected: Special dermal developmental toxicity study in rabbits. 83-3.

MRID No.: 42909101

Executive Summary: In a developmental toxicity study conducted to assess the potential maternal and developmental toxicity following *dermal* exposure, four groups of 25 assumed pregnant New Zealand White rabbits does were dosed dermally with triphenyltin hydroxide (TPTH in 1% carboxymethyl cellulose)) as control, 1.5, 2.25 or 3.0 mg/kg/day on days 7 through 19 of gestation. The applications were made to a series of four quadrants on the shaved backs of each doe with each daily dose being applied on a rotating basis to each site in turn in order to minimize dermal irritation. The does were sacrificed on day 29 of gestation. The only reactions to treatment were local irritation which was expected because of the corrosive nature of TPTH. There were no maternal or developmental toxicity noted. **The LOAEL and NOAEL for both maternal and developmental toxicity is ≥ 3.0 mg/kg/day.**

Dose and Endpoint for Risk Assessment: >3.0 mg/kg/day based on lack of maternal or developmental toxicities.

Comments about Study/Endpoint:. This study was specifically requested because the oral developmental toxicity studies (both pilot and definitive) demonstrated unacceptable risks when coupled with dermal penetration factors based on attempts to assess dermal penetration by means of radiolabeled TPTH. The interpretation of these studies with radio-labeled TPTH to assess for dermal penetration/absorption was confounded because much of the label adhered to the skin without actually being systemically absorbed. The lack of systemic toxicity noted in the dermal developmental toxicity study is considered to be consistent with poor dermal penetration and absorption of TPTH or with the label adhering to the skin and not actually penetrating into the systemic circulation.

Also, no systemic toxicity was seen in a 21-day dermal toxicity study in *rats* following repeated dermal applications of TPTH at 0, 5, 10 or 20 mg/kg/day, 6 hours/day, 5 days/week for a total of 15 applications over a 21-day period. The NOAEL for systemic effects was >20 mg/kg/day, the highest dose tested. The rabbit, however, is considered the more sensitive species and the special rabbit developmental toxicity study is being used for this endpoint.

This risk assessment is required.

3. Intermediate-Term Dermal (7 Days to Several Months)

Study Selected: Special dermal developmental toxicity study in rabbits. 83-3.

MRID No.: 42909101

Executive Summary: See Short-Term

Dose and Endpoint for Risk Assessment: >3.0 mg/kg/day based on lack of maternal or developmental toxicities.

Comments on Study and Endpoint. This study was considered to be appropriate for this exposure period because: 1) no maternal or developmental toxicity was seen via the dermal route in the rabbit dermal developmental toxicity study; 2) no systemic toxicity was seen in the 21-day dermal toxicity study in a second species (rats) at doses up to 20 mg/kg/day; 3) when the oral LOAEL of 0.3 mg/kg/day established in a 90-day feeding study in rats (Accession No.: 261754) based on marginal changes in the immunoglobulins is used in conjunction with a dermal absorption rate of 10%, the resultant dermal equivalent dose is 3 mg/kg/day (0.3 mg/kg/day ÷ 0.1 = 3 mg/kg/day) which is the same as the dermal dose that did not induced maternal or developmental toxicity in the rabbit. Since the effect on immunoglobulins was considered *minimal* even though it was also noted in the rat chronic feeding study at a similar dose, it was not considered an appropriate endpoint for this exposure period.

This risk assessment is required.

4. Long-Term Non-Cancer Dermal (Several Months to Life-Time)

Study Selected: None

MRID No.: None

Executive Summary: None

Dose and Endpoint for Risk Assessment: Not applicable

Comments about Study and Endpoint. The use pattern (1-3 application/year with a maximum of 6 applications) dose not indicate potential long-term dermal exposure. Therefore, a dose and endpoint was not identified for non-cancer dermal risk assessment..

This risk assessment is NOT required for non-cancer risk.

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5. Dermal CANCER

Since TPTH is classified as a B2 carcinogen with a Q_1*(1.83 mg/kg/day $^{-1}$), dermal cancer risk assessment is required and a dermal absorption factor of 10% should be used for this risk assessment.

This risk (Cancer) assessment is required.

6. Inhalation Exposure (Short and Intermediate Term).

Study Selected: § 82-4. Subchronic inhalation toxicity study in rats.

MRID No.: 41017701

Executive Summary: In a study (MRID No.: 41017701), four groups of 20/sex Wistar strain rats were exposed to atmospheres containing 0, 0.014 ± 0.007, 0.34 ± 0.054 or 2..0 ± 0.334 mg/m^3 for a period of 90 days with exposures on 5 days per week for 6 hours per day. 10 rats/sex/group were sacrificed on day 90 and the remaining 10 were sacrificed following a 28 day recovery period. The test atmosphere was generated as a dust by means of RBG-1000 aerosol generator. The particle size of the test atmosphere was assessed using a Mercer 7 stage cascade impactor and it was determined that 100% of the particles were < 4.6 μm in diameter and that 60.8% and 38.6% Of the particles were < 1.06 μm in diameter in the mid and high dose test groups, respectively. The MMAD was not reported.

At 2.0 mg/m^3 there were deaths (11/20 males and 2/20 females). Clinical signs in this group included labored respiration and rales and transitory signs of "somnolence, apathy, hunched posture and ruffed fur". Lung weight was increased in males (32.5%) and this increase only slowly regressed through the recovery period. Females were not definitely effected. Spleen weights in males were *decreased* (25%) at exposure termination but were *elevated* 23% following the recovery period. Pathology revealed lesions in the nasal cavity, trachea and lungs all indicative corrosive and irritant nature of TPTH and the rats are believed to have died as a result of these lung lesions. Possible effects on white blood cells were apparent but considered equivocal at all doses since dose responses were not clear. Special assessments for Immunoglobulins were included but the changes noted reflected *increases* rather than *decreases.* **The LOAEL is 0.002 mg/L based on deaths. The NOAEL is 0.00034 mg/L.**

Dose/Endpoint for Risk Assessment: NOAEL= 0.00034 mg/L based on clinical signs (labored breathing, rales) and inflammatory lesions in the lungs and deaths at 0.002 mg/L (LOAEL).

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Comments about Study/Endpoint:. Since this is the only study available, it will be used for Short-and Intermediate-term inhalation exposure risk assessments. Based on the use pattern, a Long-term inhalation risk assessment is not required..

This risk assessment is required

D. Recommendation for Aggregate (Food, Water and Dermal) Exposure Risk Assessments

For **acute** aggregate exposure risk assessment, combine the high end exposure values from Food + Water and compare it to the acute RfD.

There are no residential homeowner uses at the present time. Therefore, aggregate exposure risk assessment is NOT required for short, intermediate or long-term dermal and inhalation exposure.

E. Margins of Exposures for Occupational/Residential Exposure Risk Assessments

There are no registered residential homeowner uses at the present time. A Margin of Exposure of 100 is adequate for occupational exposure risk assessment.

III. CLASSIFICATION OF CARCINOGENIC POTENTIAL

1. Combined Chronic Toxicity/Carcinogenicity Study in Rats

MRID No. 41085702 (two volumes)

Executive Summary In a combined chronic feeding and carcinogenicity study (MRID No.: 41085702), four groups of 60/sex Wistar strain rats were dosed with triphenyltin hydroxide (TPTH ~97% purity) as control, 5, 20 or 80 ppm for two years. These dose levels correspond to 0, 0.3, 1.3 or 6.2 mg/kg/day for males and 0, 0.4, 1.6 or 6.2 mg/kg/day for females. A satellite group of 10 rats/sex were sacrificed after one year.

At 5 ppm there were increased **deaths and clinical signs** in females that were apparently related to increased pituitary tumors as well as decreases in **immunoglobulin**. At 20 ppm, there were decreases in **body weight**, cystoid changes in males and nodules in females in the pituitary which compressed the brain, bile duct proliferation and portal sclerosis. At 80 ppm there were deceases in food consumption, increases in serum enzyme levels for SAT, ALP, and ALA and pituitary *pars intermedia* hyperplasia in males and Leydig cell hyperplasia and testicular atrophy as well as liver eosinophilic focuses in females. **The LOAEL < 5 ppm (0.3 mg/kg/day in males 0.4 mg/kg/day in females) based on deaths in females and deceases in immunoglobulins. The NOAEL was not established.**

TPTH was determined to have compound related increases in **pituitary** tumors in females

and **testicular** tumors.

Discussion of Tumor Data The **pituitary** in females and the **testis** have been identified as carcinogenic target organs for TPTH in the rat.

Adequacy of the Dose Levels Tested The Peer review Committee determined that the "highest adequate dose is considered to have been attained". Meaning that the dose levels did not exceed a maximum tolerated dose.

2. Carcinogenicity Study in Mice

MRID No.: 41085701.

Executive Summary. Triphenyltin hydroxide (TPTH, purity 97.2%) was assessed in a mouse Oncogenicity study (MRID No.: 41085701) at dose levels of 0, 5, 20 and 80 ppm for 80 weeks using NMRI KDF-HAN strain mice. These dose levels corresponded to 0, 0.85, 3.50 and 15.24 mg/kg/day in males and 0, 1.36, 4.56 and 20.16 mg/kg/day in females.

Systemic effects noted included.: At 5 ppm and above there were decreases in **immunoglobulins** (i.e. IgA was decreased 31% in males and 23% in females). At 20 ppm there were increases in **body weight** in females (6-9%); absolute (-7.3%, $p < 0.05$) and relative to brain weight (-9.3%) kidney weights were decreased (without accompanying pathology). At 80 ppm, there was an increase in spontaneous **deaths** ($p <$).05) among females after week 50; **liver** weight was increased in both males (24.9%, $p < 0.01$) and females (9.9%, but not significant) and **heart** weight was increased (14% males and 22% females, both $p < 0.01$). Since this study is not a chronic feeding study, no NOEL and LOEL are being set.

Hepatocellular adenomas were statistically significantly increased for both males ($p <$ 0.01) and females ($p < 0.001$) in the 80 ppm dose group. **Hepatocellular carcinomas** were present in the high dose females (3/50) but not in the control or low or mid dose groups.

Discussion of Tumor Data The **liver** was demonstrated as a target organ for the carcinogenic effects of TPTH at 80 ppm.

Adequacy of the Dose Levels Tested The Carcinogenicity Peel Review Committee indicated that the "highest adequate dose was considered to have been attained".

3. Classification of Carcinogenic Potential As per the HED Carcinogenicity Peer Review Committee report (dated May 24, 1990), TPTH is classified as a group B2-Probable Human Carcinogen. This conclusion was reviewed by the SAP and its recommendations considered. HED retained its original classification and currently a Q1* of 1.83 mg/kg/day $^{-1}$ is recommended for carcinogenicity risk assessments with

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TPTH (refer to the memo from Fisher and Pettigrew, 1996).

IV. MUTAGENICITY

The carcinogenicity Peer review Committee determined that the weight-of-the-evidence suggests that there is little support for a mutagenicity concern. There was one positive finding in the *cultured* human lymphocyte assay. However, the *in vivo* data from other studies do not indicate a concern.

V. FQPA CONSIDERATIONS

1. Neurotoxicity:

There are no series 81-8, 82-7 or 83-6 acute, subchronic or developmental neurotoxicity studies available nor have these studies been requested by HED as of November 1998. The available studies in the conventional guideline toxicity data base do not indicate *specific* neurotoxicity with TPTH. TPTH, however, is related to a chemical class that is known to cause neurotoxicity. In particular, trimethyl and triethyl tin are known neurotoxins and are used as positive controls in neurotoxicity studies. The neurotoxicity of the alkyl and aryl substituted tin derivatives is apparently influenced by the size of the substitutes. As the chain length increases or gets bulkier (substitution of an aryl group in place of the alkyl), the propensity of the chemical to cause neurotoxicity diminishes. For example, tributyltin does not share the marked neurotoxicity that trimethyl and triethyl tin derivatives do. The rat and dog subchronic and chronic studies and the rat multi generation reproduction study nor do other studies with TPTH indicate obvious neurotoxicity. See also item 6 below.

2. Developmental Toxicity:

TPTH has been extensively studied for potential developmental toxicity (refer to the Developmental Toxicity Peer Review report dated January 9, 1991). These studies indicate that the rabbit is a more sensitive species compared with the rat or hamster with regard to the maternal and developmental effects of TPTH. There was nearly total fetal lose at a dose level of 2 mg/kg/day and above due to resorptions and maternal deaths in rabbit does. The rat was extensively studied for possible effects on hydrocephalus and hydronephrosis and the results varied from study to study but the maternal toxicity effects were demonstrated at or below the same dose level. Subsequent studies with rabbits using the dermal route of administration did not result in maternal or developmental toxicity at a dose level of 3 mg/kg/day. Frank developmental malformations are not considered a response to TPTH treatment.

The Executive Summary for the best representative rat developmental toxicity study is presented below. There are several developmental toxicity studies with rats but the

following study is being presented because it is considered to best represent the potential developmental toxicity in rats.

In a rat developmental toxicity study (MRID No.: 257402 - accession number), five groups of 45 mated Sprague-Dawley rats were dosed as control, 0.35, 1, 2.8 or 8 mg/kg/day of triphenyltin hydroxide in corn oil on days 6-15 of gestation. Of the original 45 dams, there were 41, 39, 40, 38 and 31 dams which had viable fetuses when sacrificed on day 20 for examination of their uterine contents.

Maternal toxicity was evident at 2.8 mg/kg/day which included decreased **body weight** and food consumption (10-22%). The dams were described as being in poor general condition (emaciated, lethargic, hair loss, yellow staining red vaginal discharge and dried red matting in the anogenital area). At 8 mg/kg/day, body weight decreased to 6-12% and food consumption decreased to about 50%. **The LOAEL for maternal toxicity is 2.8 mg/kg/day based mainly on body weight and food consumption decreases. The NOAEL is 1 mg/kg/day.**

There were 570, 549 (-4%), 557 (-2%), 514 (-10%) and 399 (-30%) viable pups for the control, low, low mid, high mid and high dose groups. Thus, indicating a definite decrease in pups in the high dose group which was associated with increases in early resorptions and implantation loss. The pups in the high dose group also had an 11% decrease in mean weight. The 10% decrease in pups noted in the mid high dose group was not statistically significant and was not associated lower birth weight or other signs of toxicity in the dams and overall was not considered a definite response to treatment. At 8 mg/kg/day there was noted a statistically significant ($p < 0.5$) increase in litters with "sternebra(e) #5 and/or #6 unossified". Hydrocephaly was seen at the high dose group in 2 pups and 2 litters compared with the control (1 pup in 1 litter). **The LOAEL for developmental toxicity is 8 mg/kg/day based mainly on decreased number of viable pups, decreased fetal weight and sternebrae unossified. The NOAEL is 2.8 mg/kg/day.**

This study is classified as Acceptable/Guideline and satisfies the requirement for a series 83-3 developmental toxicity study in rats. It is noted that since this study had nearly 40 gravid dams/dose, twice as many as the required 20, it is considered the best representative assessment for developmental toxicity in the rat.

The oral developmental toxicity study in rabbits is discussed in Section II. Acute RfD. For maternal toxicity, the NOAEL was 0.1 mg/kg/day and the LOAEL was 0.3 mg/kg/day based on decreases in body weight. For developmental toxicity, the NOAEL was 0.3. mg/kg/day and the LOAEL was 0.9 mg/kg/day based on .lower fetal body weight and unossified hyoid.

The dermal developmental toxicity study in rabbits is discussed in Section II. C. Short-Term Dermal. No maternal or developmental toxicity was seen at the highest dose tested;

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NOAEL = >3.0 mg/kg/day.

3. Reproductive Toxicity:

In a multi generation reproduction study (MRID No.: 264667 to 264676), an initial set of 30/sex Wistar strain rats (Fo) were dosed as control, 5, 18.5 or 50 ppm of triphenyltin hydroxide (TPTH) for 70 days and bred (one to one) to produce the F1 generation. The F1 generation was also dosed and bred to produce the F2 generation. These dose levels corresponded to approximately 0, 0.25, 0.925 and 2.5 mg/kg/day for both sexes.

Parental systemic effects were limited to decreases in body weight gains in the Fo, F1 and F2 generations at 50 ppm (as much as 20% lower in males and 14% lower in females). Decreases of up to 5% were noted at 18.5 ppm but were not consistent and not considered treatment related. **The LOAEL for parental effects is 2.5 mg/kg/day based on body weight decreases. The NOAEL is 0.925 mg/kg/day.**

Offspring toxicity was evident at 18.5 ppm as indicated by decreases in **live litter size** (11.9% for the F2 generation), decreases in **liver weight** (i.e. 11.6% for relative to brain **weight** for the F2 weanlings, $p < 0.05$ and 8% not significant for the F1 weanlings). **Spleen** weight was decreased 17% for males and 18% for females for the F2 generation weanlings (relative to brain weight and both $p < 0.05$). Thymus weight was decreased ~16% for males. At 50 ppm mean fetal weight was decreased 12% for males and 16% for females for the F1 generation and 30% for both sexes for the F2 generation. Testis weight was decreased in both the F1 and F2 weanlings (17-21% relative to brain weight for both generations). Other organ weight changes in the ovaries, kidneys, heart, lung, pituitary and adrenal gland were all considered to be related to the weight decreases and not direct effects. There was no supporting pathology in any of the organs showing weight changes. **The LOAEL for offspring toxicity is 0.925 mg/kg/day based on decreased live litter size, liver and spleen weights. The NOAEL is 0.25 mg/kg/day.**

4. Additional Information from the Literature:

Several literature reports were available and considered based on literature surveys made in approximately 1990 and again in October 1998. The indications of toxicity noted in these reports were considered addressed in the studies submitted to OPP by the registrant.

5.Determination of Susceptibility:

In the prenatal developmental toxicity study in rats, evidence of possible developmental toxicity was seen only in the presence of definite maternal toxicity. In the prenatal developmental toxicity study in rabbits, developmental toxicity was seen at the higher dose than that caused maternal toxicity.. However, increased susceptibility was

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demonstrated in the two-generation reproduction study in rats in which effects in the offspring were observed at a dose that did not cause parental/systemic toxicity .

6. Recommendation for a Developmental Neurotoxicity Study:

The HIARC determined that a developmental neurotoxicity study in rats is NOT required based on the following factors:

A. Immunotoxicity is considered a more significant effect of concern for TPTH than neurotoxicity and the developmental *neurotoxicity* study is not designed to evaluate immunotoxicity.

B. In the two-generation reproduction study which demonstrated increased susceptibility, the target organ was the liver and spleen and not the nervous system.

C. No evidence of alterations to the fetal nervous system were seen in the prenatal developmental toxicity studies in rats and rabbits or in the multi generation reproduction study in rats. Initial studies showing possible hydrocephalus were not verified in subsequent studies.

D. No neuropathology or alterations in brain weights were seen in adult animals in mice, rats, and dogs in subchronic or chronic studies.

7. Determination of the FQPA Safety Factor:

Based solely on the hazard assessment for TPTH, the HIARC recommends to the FQPA Safety Committee, that the 10x FQPA safety factor for the protection of infants and children *should be retained* because:

A. Increased susceptibility to the fetuses was seen in the two-generation reproduction toxicity

B. The toxicology database is not complete; data gaps exists for acute and subchronic neurotoxicity studies in rats.

C. Need a developmental toxicity study that evaluates immunotoxicity, a potential toxic effect of TPTH that fetuses and neonates may be especially susceptible too.

The final recommendation on the FQPA Safety Factor, however, will be made during risk characterization by the FQPA Safety Factor Committee.

VI. HAZARD CHARACTERIZATION

Carcinogenicity. TPTH is considered a B2 carcinogen based on positive findings in rats (pituitary and testicular tumors) and mice (liver tumors). The registrations of TPTH require supporting carcinogenicity risk assessments.

Immunotoxicity. TPTH is considered as an agent that may cause immunotoxicity. The chronic dietary RfD is based on decreases in white blood cells and both the rat and mouse chronic feeding and/or oncogenicity studies indicate decreases in immunoglobulins. Specially designed studies failed to indicate that rats or mice dosed with TPTH were more susceptible to opportunist infections.

Endocrine disruption. TPTH is considered to affect the endocrine system and there was discussion between the registrants and EPA regarding the design of some special studies to assess the potential for TPTH to affect the hormone levels. These studies were a part of an attempt to demonstrate the possible relationship between TPTH, hormonal effects and the development of pituitary and testicular tumors but have not been completed or submitted to the Agency.

VII. DATA GAPS

Series 81-8. Acute Neurotoxicity Screen
Series 82-7. Subchronic Neurotoxicity Screen
Special Study. Developmental Immunotoxicity screen (consult with Agency on protocol).

VIII. ACUTE TOXICITY

Acute Toxicity of Triphenyltin Hydroxide

Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
81-1	Acute Oral-rat	071364 252512	LD_{50} = 165 mg/kg ♂ 156 mg/kg ♀	II
81-2	Acute Dermal-rat	071364	LD_{50} = 1600 mg/kg	II
81-3	Acute Inhalation-rat	071364	LC_{50} = 60.3 μg/L	I
81-4	Primary Eye Irritation	071364	Corrosive	I
81-5	Primary Skin Irritation	071364	PIS = 2.8	III
81-6	Dermal Sensitization	Several Studies	Not a sensitized in the Buehler assay.	Not considered a sensitizer

IX. TOXICOLOGY ENDPOINT SELECTION.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	NOAEL= 0.3 mg/kg/day (100 UF)	Increased hyoid arches in rabbit fetuses.	Oral Developmental toxicity -Rabbit (MRID No.: 40104801)
Chronic Dietary	NOAEL= 0.1 mg/kg/day (300 UF)	Decreased white blood cells.	Chronic feeding study -Rat (Accession No.: 099050)
Short-Term (Dermal)	Dermal NOAEL= 3 mg/kg/day	No effects a the highest dose tested.	Dermal Developmental toxicity - Rabbit (MRID No.: 42909101)
Intermediate-Term (Dermal)	Dermal NOAEL = 3 mg/kg/day	No effects a the highest dose tested.	Dermal Developmental toxicity - Rabbit (MRID No.: 42909101)
Long-Term Non-cancer (Dermal)	None	Use pattern does not indicate exposure will be for this interval.	
Cancer-Dermal	Oral Q_1* 1.83 mg/kg/day $^{-1}$	TPTH is classified as a B2 Carciongen -probable human carcinogen based on pituitary and testicular tumors in rats and liver tumors in mice. A dermal absorption of 10% should be used for this risk assessment.	
Inhalation (Any Time Period)	0.00034 mg/L (100 UF)	Deaths following lung lesions.	Subchronic inhalation toxicity -Rat (MRID No.: 41017701)

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HED DOC. NO. 013030

17-DEC-1998

MEMORANDUM

SUBJECT: ***TRIPHENYLTIN HYDROXIDE (TPTH)*** - Report of the FQPA Safety Factor Committee.

FROM: Brenda Tarplee, Executive Secretary
FQPA Safety Factor Committee
Health Effects Division (7509C)

THROUGH: Ed Zager, Chairman
FQPA Safety Factor Committee
Health Effects Division (7509C)

TO: Sarah Law, Risk Assessor
Reregistration Action Branch 3
Health Effects Division (7509C)

PC Code: 083601

The Health Effects Division (HED) FQPA Safety Factor Committee met on November 30, 1998 to evaluate the hazard and exposure data for TPTH and made two separate recommendations. The Committee recommended that the FQPA safety factor (as required by Food Quality Protection Act of August 3, 1996) be **retained in chronic dietary risk assessments** and **reduced (to 3x) in acute dietary risk assessments** for this pesticide.

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I. HAZARD ASSESSMENT

1. Determination of Susceptibility

(I) Developmental Toxicity

The Hazard Identification Assessment Review Committee (HIARC) determined that the available Agency Guideline studies indicated no increased susceptibility of rats or rabbits, quantitatively or qualitatively, to *in utero* exposure to TPTH. In the prenatal developmental toxicity study in rats, no evidence of developmental toxicity was seen even in the presence of maternal toxicity. In the prenatal developmental toxicity study in rabbits, developmental toxicity was seen at a higher dose than that causing maternal toxicity (*Memorandum:* J. Doherty to C. Scheltema dated November 13, 1998).

(ii) Reproductive Toxicity

There was evidence of increased susceptibility to the offspring following pre-/postnatal exposure in the two-generation reproduction study in rats. In this study, offspring toxicity was manifested as decreased live litter size; decreased liver and spleen weights at a dose lower than that which caused parental systemic toxicity characterized as decreased body weight.

(iii) Immunotoxicity.

TPTH is considered as an agent that may cause immunotoxicity. The toxicity endpoint for deriving the chronic dietary RfD is based on decreases in white blood cells. Additionally, decreases in immunoglobulin levels were observed in long-term feeding studies with rats and mice.

(iv) Evidence of Endocrine Disruption

TPTH is considered to affect the endocrine system. There has been discussion between the registrants and the Agency regarding the design of some special studies to assess the potential for TPTH to affect the hormone levels in an attempt to demonstrate and characterize the possible relationship between TPTH, hormonal effects, and the development of pituitary and testicular tumors.

2. Adequacy of Toxicity Database

The toxicity data base for TPTH is lacking acute and subchronic neurotoxicity studies in rats, however, these studies are not critical for hazard characterization for FQPA since the available guideline studies do not indicate *specific* neurotoxicity with TPTH (subchronic and chronic studies in rats and dogs, multi-generation reproduction study in rats, and other studies with TPTH do not indicate obvious neurotoxicity). Although TPTH is related to a chemical class that

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is known to cause neurotoxicity (trimethyl and triethyl tin are known neurotoxins and are used as positive controls in neurotoxicity studies), the neurotoxicity of the alkyl and aryl substituted tin derivatives is apparently influenced by the size of the substitutes. As the chain length increases or gets bulkier (substitution of an aryl group in place of the alkyl), the propensity of the chemical to cause neurotoxicity diminishes (as is the case of TPTH).

The HIARC required a developmental immunotoxicity study which will evaluate immunotoxicity, a potential toxic effect of TPTH to which fetuses and neonates may be specially susceptible, in place of a developmental neurotoxicity study.

II. EXPOSURE ASSESSMENT

1. Dietary (Food) Exposure Considerations

Tolerances for residues of the fungicide, TPTH, are established at 0.05 ppm in/ on raw agricultural commodities including pecans, potatoes, sugar beet roots, milk, and meat [40 CFR 180.236]. Parent TPTH, and metabolites, DPTH (diphenyltin hydroxide) and MPTH (monophenyltin hydroxide), are excluded in Codex MRLs.

Typically, TPTH can be applied to potatoes at a maximum rate of 3 oz. ai/A, 4-6 times a year (depending upon the rate); To sugar beets at a maximum rate of 4 oz. ai/A, 3-6 times per year (depending upon the rate; submission proposes increase to at 5 applications at 4 oz. ai/A); and to pecans at a maximum rate of 6 oz. ai/A, 10 times per year.

Residues do transfer to meat/milk (sugar beet tops) and tolerances are currently established at 0.05ppm. These tolerances, however, will need to be adjusted to higher levels (0.1 ppm for milk fat and 2.0 ppm for liver).

There are no PDP or FDA monitoring data for TPTH. There is information available from BEAD on % crop treated. The source of the information for TPTH is quantitative usage analysis (QUA). Percent crop treated is approximately 50% for pecans, 25% for potatoes, and 30% for sugar beets.

The HED Dietary Risk Evaluation System (DRES) was used to assess the risk from acute and chronic dietary exposure to TPTH residues in food. The chronic analysis was performed using percent crop treated (%CT) information and anticipated residues (ARs). The acute analysis assumed 100 %CT and tolerance level residues.

2. Dietary (Drinking Water) Exposure Considerations

A comprehensive fate review of TPTH was not complete at the time of this meeting. A preliminary review of the existing data indicates that TPTH is relatively non-persistent to

moderately persistent in soil. TPTH is not susceptible to hydrolysis or photolysis and is relatively insoluble in water. Microbial degradation appears to be the dominant route of dissipation. An accurate determination of K_d or K_{oc} via a batch adsorption experiment is not available for TPTH. This information is essential for estimating the leaching potential of the compound. There is sufficient information to estimate a K_{oc}, however estimations of this nature should be used with caution. Based on the estimated K_{oc}, TPTH is not expected to leach to groundwater. However, in soils were TPTH does not rapidly degrade there is potential for transport of TPTH bound to soil via runoff due to irrigation or rain events.

There are no monitoring data available for TPTH, therefor Tier I Estimated Environmental Concentrations (EECs) are calculated using GENEEC (surface water) and SCI-GROW (ground water) based on the maximum application rate for TPTH of 0.375 lb ai × 10 applications per year on pecans.

3. Residential Exposure Considerations

There are currently no registered residential uses for TPTH, therefore, this type of exposure to infants and children is not expected.

III. SAFETY FACTOR RECOMMENDATION AND RATIONALE

1. FQPA Safety Factor Recommendation

The Committee recommended two different FQPA Safety Factors: 3x for acute dietary risk assessments and 10x for chronic dietary assessments.

2. Rationale for the FQPA Safety Factor

The Committee made these recommendations for the FQPA Safety Factor for TPTH because:

3. There was evidence of increased susceptibility to the offspring following pre- and/or postnatal exposure in the two-generation reproduction study in rats. Offspring toxicity was observed at a dose lower than parental systemic toxicity.

4. TPTH is considered to affect the endocrine system and there is concern for the possible relationship between TPTH, hormonal effects, and the development of pituitary and testicular tumors.

3. TPTH is considered as an agent that may cause immunotoxicity. The chronic dietary RfD is based on decreases in white blood cells and both the rat and mouse chronic feeding and/or oncogenicity studies indicate decreases in immunoglobulins.

4. HIARC required a developmental toxicity study that evaluates immunotoxicity, a potential toxic effect of TPTH to which fetuses and neonates may be specially susceptible, in place of a developmental neurotoxicity study.

3. Population Subgroups for Application of the Safety Factor

Acute Dietary Assessment: The Committee determined that the FQPA Safety Factor can be **reduced to 3x** for acute dietary risk assessment for **All Populations which include Infants and Children** because the increased susceptibility was seen only in the offspring of parental animals receiving repeated oral exposures (two-generation reproduction toxicity study) and not seen following *in utero* exposures (developmental studies). Thus the increased susceptibility concern was for chronic dietary exposure. The application of the 3x safety factor to the acute dietary exposure assessment is based on the concern for the potential immunotoxic effects which resulted in the requirement for a developmental immunotoxicity study (data gap).

Chronic Dietary Assessment: The Committee determined that the FQPA Safety Factor should be **retained (10x)** for chronic dietary risk assessment for **All Populations which include Infants and Children** because increased susceptibility to the offspring was seen following repeated oral exposures in the two generation reproduction study in rats.

Updated Executive Summaries for TPTH.

The following studies were considered in the selection of toxicity endpoints for TPTH. The original reviews were written in the late 1980's and early 1990's. The DERs generally are consistent with current standards but the executive summaries needed to be prepared in the current format.

List of Studies and MRID (or ACCESSION) No.:

82-1 (870.3100). Rat Subchronic Feeding Study (Accession No.: 261754)
82-1 (870.3100). Mouse Subchronic Feeding Study (Accession No.: 261753)
82-1 (870.3100). Hamster Subchronic Feeding Study (Accession No.: 00086467)
82-2 (870.3200). 21-day Rat Dermal Toxicity Study (Accession No.: 258230)
82-4 (870.3465). Rat subchronic Inhalation Study (MRID No.: 4107701)
83-1 (870.4100). Rat Chronic Feeding Study (1970) (Accession No.: 099050)
83-1 (870.4100). Dog Chronic Feeding Study (MRID No.: 402855701)
83-2 (870.4200). Mouse Carcinogenicity Study (MRID No.: 41085701)
83-3 (870.3700). Rabbit Dermal Developmental Toxicity Study (MRID No.: 42909101)
83-3 (870.3700). Rabbit Oral Developmental Toxicity Study - definitive and pilot studies. (MRID No.: 40104801)
83-3 (870.3700). Rat Developmental Toxicity Study (MRID No.: 257402)
83-4 (870.3800). Rat Multi Generation Reproduction Study (Accession No.: 264667 to 26476)
83-5 (870.4300). Rat Combined Chronic Feeding and Carcinogenicity (MRID No.: 41085702)

Executive Summaries.

82-1 (870.3100). Rat subchronic Provides support for potential for TPTH to disrupt the immune system.

Triphenyltin hydroxide (TPTH, 97.2%) was assessed in a 90-day feeding study (Accession No.: 261754) classified as **ACCEPTABLE (82-1)** in the Wistar strain rat at dose levels of o, 4, 20 or 100 ppm for 90 days. These dose levels corresponded to 0, 0.3, 1.56 or 7.41 mg/kg/day for males and 0.35, 1.72 or 7.85 mg/kg/day for females.

Immunoglobulins were reduced (i.e., IgM was reduced 41% at 4 ppm in females) in all dose levels. At 100 ppm, there were decreases in body weight gain and food consumption in both sexes and possible increases in ASAT. **The LOAEL is < 4 ppm (0.33 mg/kg/day in females) based on decreases in IgM immunoglobulins. No NOAEL was established.**

This study is classified as ACCEPTABLE/GUIDELINE and satisfies the requirement for a series 82-1 subchronic feeding study in rats.

33740

82-1 (870.3100). Mouse Subchronic. Provides additional support that TPTH affects the immune system.

Triphenyltin hydroxide (TPTH 97.2% purity) was assessed in a 90-day pilot study (Accession No.: 261753) that was classified as **USEABLE** for selecting the dose levels for the definitive study at dose levels of 0, 4, 20 or 80 ppm for 90 days in 10 NMRI mice/sex/dose. These dose levels correspond to 0, 0.62, 3.44 or 18.28 mg/kg/day in males and 0, 0.88, 4.12 or 20.64 mg/kg/day in females.

Immunoglobulins were decreased at all dose levels (i.e., IgA was reduced 26% in males and 28% in females at 4 ppm). At 20 ppm the adrenal weight was decreased in females and at 100 ppm ovary weight was decreased while liver weight was increased in both sexes. No NOAEL or LOAEL is being assigned for this study since it is not a formal chronic feeding study. The study does provide data useful for selecting the dose levels for the definitive study

This study is classified as ACCEPTABLE/NON-GUIDELINE and but serves as a dose range finding study for the definitive carcinogenicity study in mice.

82-1. (870.3100). Hamster Subchronic Study Provides additional support for the potential for TPTH to affect the immune system or the white blood cells.

In an earlier study (MRID No.: 00086467, dated 1960) in guinea pigs (10/sex/dose) that was classified as UNACCEPTABLE because there is a paucity of data to validate toxicity data from guinea pigs, triphenyltin hydroxide (TPTH, purity not stated) was assessed at 0, 2.5, 5, 10 or 50 ppm for 90 days. These doses correspond to approximately 0, 0.1, 0.2, 0.4 or 2 mg/kg/day based on a conversion factor of 25 mg/kg/day per 1 ppm in the diet.

At 2.5 ppm **lymphocytes** (-25%, $p < 0.05$) and **leukocytes** (-24%, $p < 05$) were decreased in females and the percent decrease was greater at the higher doses. At 10 ppm lymphocytes (23%, $p < 0.05$) and leukocytes (16%, not significant) were decreased in males. The liver (increased 19% males, $p < 0.01$), kidneys (increased 10% males and 11% females), spleen (decreased 12% males and 29% females) relative organ weights were affected. At 20 ppm these organs showed larger differences to indicate an actual effect and the brain (36% males and 185 females both $p < 0.01$) and heart (16% males and 13% females, both $p < 0.05$) and uterus (decreased 31%, $p < 0.05$) and testis (decreased 35%, $p < 0.05$) were also affected. This study suggests that the guinea pig is a more sensitive species than the rat.

This study is classified as UNACCEPTABLE/NON-GUIDELINE but is considered to contain data useful in confirming that TPTH affects the leucocytes and lymphocytes.

34340

82-2 (87.3200). Rat 21-day dermal toxicity study. Study not selected for an endpoint but provides some justification for low dermal penetration absorption and low systemic toxicity following dermal application. .

Rats (Crl:CD (SD)BR strain, 10/sex) were assessed for potential systemic toxicity of triphenyltin hydroxide (TPTH, 97.1% purity applied in distilled water) in a 21 day study (Accession No.: 258230) that was classified as **ACCEPTABLE (82-2).**. The test animals were prepared by shaving but not abrading ~10% of their backs and the test material was applied five days per week for three weeks for a total of 15 applications at dose levels of 0, 5, 10 or 20 mg/kg/day and was kept in place for 6 hours.

Local dermal reactions including erythema, edema, scabbing, atonia, fissuring and/or blanching were noted at *all* doses except controls. There were no systemic effects at any dose. **The LOAEL and NOAEL are ≥ 20 mg/kg/day for systemic effects.**

This study is classified as ACCEPTABLE/GUIDELINE and satisfies the requirement for a series 82-2 21-day dermal toxicity study in rats.

82-4 (870.3465). Subchronic Inhalation Toxicity Study

In a study (MRID No.: 41017701) classified as **ACCEPTABLE (82-4)** designed to assess the subchronic inhalation toxicity of triphenyltin hydroxide (TPTH, 96.2% purity), four groups of 20/sex Wistar strain rats were exposed to atmospheres containing 0, 0.014 ± 0.007, 0.34 ± 0.054 or 2.0 ± 0.334 mg/m^3 for a period of 90 days with exposures on 5 days per week for 6 hours per day. 10 rats/sex/group were sacrificed on day 90 and the remaining 10 were sacrificed following a 28 day recovery period. The test atmosphere was generated as a dust by means of RBG-1000 aerosol generator. The particle size of the test atmosphere was assessed using a Mercer 7 stage cascade impactor and it was determined that 100% of the particles were < 4.6 μm in diameter and that 60.8% and 38.6% of the particles were < 1.06 μm in diameter in the mid and high dose test groups, respectively. The MMAD was not reported.

At 2.0 mg/m^3 there were **deaths** (11/20 males and 2/20 female). Clinical signs in this group included labored respiration and rales and transitory signs of "somnolence, apathy, hunched posture and ruffed fur." **Lung weight** was increased in males (32.5%) and this increase only slowly regressed through the recovery period. Females were not definitely effected. **Spleen weights** in males were *decreased* (25%) at exposure termination but were *elevated* 23% following the recovery period. Pathology revealed lesions in the **nasal cavity**, **trachea** and **lungs** all indicative corrosive and irritant nature of TPTH and the rats are believed to have died as a result of these lung lesions. Possible effects on white blood cells were apparent but considered equivocal at all doses since dose responses were not clear. Special assessments for Immunoglobulins were included but the changes noted reflected *increases* rather than *decreases.* **The LOAEL is 0.002 mg/L based on deaths. The NOAEL is 0.00034 mg/L.**

This study is classified as ACCEPTABLE/GUIDELINE and satisfies the requirement for a series 82-4 subchronic inhalation toxicity study in rats.

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83-1 (870.4100). Rat Chronic Feeding Study (1970). This study is being recommended for the chronic dietary RfD.

In a chronic feeding study (Accession No.: 099050) classified as USEABLE for risk assessment purposes, Triphenyltin hydroxides (TPTH) was administered in the diets of Wistar strain rats (a 25/sex/dose group) at dose levels of 0, 0.5, 1, 2, 5 or 10 ppm corresponding to approximately 0, 0.025, 0.05, 0.10 or 0.25 or 0.5 mg/kg/day for a period of 104 weeks. They were newly weaned or about 21 days old at study initiation.

At 5 ppm and above there were decreases in **leucocyte counts** (14-24%) in males in the first year of the study. At 10 ppm there were **deaths** among the females at termination and an increase in body weight (females 7-10% and males 3-4%). **The LOAEL is 5 ppm (0.25 mg/kg/day in males) based on decreased leucocyte counts. The NOAEL is 2 ppm (0.1 mg/kg/day).**

This chronic feeding study in rats was classified as ACCEPTABLE/NONGUIDELINE and does not satisfy the requirement for a series 83-1 chronic feeding toxicity study in rats. The series 83-5 chronic feeding study was satisfied by a later study (MRID No.: 41085702).

83-1 (870.4100). Dog Chronic Feeding Study.

In a chronic feeding study (MRID No.: 40285501) classified as **ACCEPTABLE (83-1),** four groups of 10/sex beagle dogs were dosed with triphenyltin hydroxide (TPTH, 97.2% purity) at dose levels of 0, 2, 6 or 18 ppm. 2 dogs/sex were sacrificed at weeks 4, 13, and 27 and the remaining 4/sex were sacrificed at 52 weeks. These dose levels corresponded to 0, 0.062, 0.206 and 0.562 mg/kg/day in males and 0.071, 0.213 and 0.624 mg/kg/day in females.

No effects of treatment of any kind were noted. **The LOAEL and NOAEL are $\geq$ 18 ppm (0.562 mg/kg/day in males and 0.624 mg/kg/day in females).**

This study is classified as ACCEPTABLE/GUIDELINE and satisfies the requirement for a series 83-1 chronic feeding study in dogs.

83-2 (870.4200). Mouse Onco Study

Triphenyltin hydroxide (TPTH, purity 97.2%) was assessed in a mouse Oncogenicity study (MRID No.: 41085701) that was classified as **ACCEPTABLE (83-2)** at dose levels of 0, 5, 20 and 80 ppm for 80 weeks using NMRI KDF-HAN strain mice. These dose levels corresponded to 0, 0.85, 3.50 and 15.24 mg/kg/day in males and 0, 1.36, 4.56 and 20.16 mg/kg/day in females.

Systemic effects noted included.: At 5 ppm and above there were decreases in **immunoglobulins** (i.e. IgA was decreased 31% in males and 23% in females). At 20 ppm there were increases in **body weight** in females (6-9%); absolute (-7.3%, $p < 0.05$) and relative to brain weight (-9.3%) kidney weights were decreased (without accompanying pathology). At 80 ppm, there was an

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increase in spontaneous **deaths** ($p < .05$) among females after week 50; **liver** weight was increased in both males (24.9%, $p < 0.01$) and females (9.9%, but not significant) and **heart** weight was increased (14% males and 22% females, both $p < 0.01$). Since this study is not a chronic feeding study, no NOAEL and LOAEL are being set.

Hepatocellular adenomas were statistically significantly increased for both males ($p < 0.01$) and females ($p < 0.001$) in the 80 ppm dose group. **Hepatocellular carcinomas** were present in the high dose females (3/50) but not in the control or low or mid dose groups.

This study is classified as ACCEPTABLE/GUIDELINES and satisfies the requirement for a series 83-2 carcinogenicity study in mice.

83-3 (870.3700). Rat developmental toxicity study. This study was selected as the best representative of the several developmental toxicity studies in rats.

A. In a rat developmental toxicity study (MRID No.: 257402 - accession number), five groups of 45 mated Sprague-Dawley rats were dosed as control, 0.35, 1, 2.8 or 8 mg/kg/day of triphenyltin hydroxide in corn oil on days 6-15 of gestation. Of the original 45 dams, there were 41, 39, 40, 38 and 31 dams which had viable fetuses when sacrificed on day 20 for examination of their uterine contents.

Maternal toxicity was evident at 2.8 mg/kg/day which included decreased **body weight** and food consumption (10-22%). The dams were described as in poor general condition (emaciated, lethargic, hair loss, yellow staining red vaginal discharge and dried red matting in the anogenital area). At 8 mg/kg/day, body weight decreased to 6-12% and food consumption decreased to about 50%. **The LOAEL for maternal toxicity is 2.8 mg/kg/day based mainly on body weight and food consumption decreases. The NOAEL is 1 mg/kg/day.**

There were 570, 549 (-4%), 557 (-2%), 514 (-10%) and 399 (-30%) viable pups for the control, low, low mid, high mid and high dose groups. Thus, indicating a definite decrease in pups in the high dose group which was associated with increases in early resorptions and implantation loss. The pups in the high dose group also had an 11% decrease in mean weight. The 10% decrease noted in the mid high dose group was not statistically significant and was not associated lower birth weight or other signs of toxicity in the dams and overall was not considered a definite response to treatment. At 8 mg/kg/day there was noted a statistically significant ($p < 0.5$) increase in litters with "sternebra(e) #5 and/or #6 unossified". Hydrocephaly was slightly elevated in the high dose group (2 pups and 2 litters vs 1 pup in 1 litter in the control). **The LOAEL for developmental toxicity is 8 mg/kg/day based mainly on decreased number of viable pups, decreased fetal weight and sternebrae unossified. The NOAEL is 2.8 mg/kg/day.**

This study is classified as ACCEPTABLE/GUIDELINES and satisfies the requirement for a series 83-3 developmental toxicity study in rats. It is noted that since this study had nearly 40 gravid dams/dose, twice as many as the required 20, it is considered the best representative assessment for developmental toxicity in the rat.

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83.3 (870.3700). Rabbit Oral Developmental Toxicity (Dose Range Finding and Definitive Studies). Studies were recommended for the acute dietary RfD.

A. Definitive Study

In a rabbit oral developmental toxicity study (MRID No.: 40104801) classified as **ACCEPTABLE (83-3)**, four groups of 22 assumed pregnant New Zealand White rabbits were dosed as control, 0.1, 0.3 or 0.9 mg/kg/day of triphenyltin hydroxide (TPTH in 1% aqueous carboxymethyl cellulose) on days 6 through 18 of gestation. The does were sacrificed on day 29 and their uterine contents evaluated.

At 0.3 mg/kg/day, **body weight gain** was reduced (59% for the entire gestation period). At 0.9 mg/kg/day, body weight gain was reduced 79% and the effect was greatest during the dosing period. There was a rebound in body weight following cessation of dosing. **The maternal toxicity LOAEL is 0.3 mg/kg/day based on decreased body weight gain. The NOAEL is 0.1 mg/kg/day.**

At 0.9 mg/kg/day, there was a slight decrease (-11%, not significant) in mean fetal weight (possibly related to the decrease in maternal body weight) and there were six incidents of "hyoid body and/or arches unossified" vs. none in the control but one each in the low and mid dose groups. **The developmental toxicity LOAEL is 0.9 mg/kg/day based on lower fetal body weight and unossified hyoid. The NOAEL is 0.3 mg/kg/day.**

This study is classified as ACCEPTABLE/GUIDELINE. The study satisfies the requirement for a series 83-3 oral developmental toxicity study in the rabbit.

B. Pilot Study

In a pilot developmental toxicity study (MRID No.: 40104801) classified as USEABLE for dose range finding purposes, six groups of New Zealand White rabbits were dosed as control, 0.1, 1, 2, 4, 6 or 8 mg/kg/day of triphenyltin hydroxide (TPTH in 1% carboxymethyl-cellulose) on days 6 to 18 of gestation. The does were sacrificed on day 29 of gestation.

At 1 mg/kg/day (-6%) with progressively greater losses at higher doses, mean body weight was decreased and the symptoms consisted of lethargy, emaciation, respiratory rales and decreased defecation . At 6 mg/kg/day, 3 of the 6 does died and at 8 mg/kg/day all of the does died. Only one of the six does had viable fetuses in the 2 mg/kg/day dose group and these fetuses had severely reduced weight. There was **total resorption** in the rest of the does in the 2 mg/kg/day group and in the 4 and 6 mg/kg/day dose groups. Uterine data for the 0.1 and 1 mg/kg/day dose group could not be meaningfully evaluated. There was an insufficient number of viable fetuses to evaluate for developmental toxicity effects on the fetuses. **NO NOAEL or LOAEL is being established for this study. This study demonstrates that TPTH is severely toxic to the rabbit does at 1 mg/kg/day and above.**

This study is classified as ACCEPTABLE/NON-GUIDELINE. The study does not satisfy the requirement for a series 83-3 developmental toxicity study in rabbits. The data series 83-3 requirement has been satisfied by the definitive study. This study provides very important information on the toxicity of TPTH in rabbit does and justifies the acceptability of the definitive study.

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83.3. (870.3700). Rabbit Dermal Developmental Toxicity Study is being recommended for short, intermediate and chronic occupational and residential exposure.

In a developmental toxicity study (MRID No.: 42909101) classified as **ACCEPTABLE** (83-3) especially conducted to assess the potential maternal and developmental toxicity following dermal exposure, four groups 25 assumed pregnant New Zealand White rabbits does were dosed dermally with triphenyltin hydroxide (TPTH in 1% carboxymethyl cellulose) as control, 1.5, 2.25 or 3.0 mg/kg/day on days 7 through 19 of gestation. The applications were made to a series of four quadrants on the shaved backs of each doe with each daily dose being applied on a rotating basis to each site in turn in order to minimize dermal irritation. The does were sacrificed on day 29 of gestation.

The only reactions to treatment were local irritation which was expected because of the corrosive nature of TPTH. There were no systemic reactions noted. **The LOAEL and NOAEL for both maternal and developmental toxicity is ≥ 3.0 mg/kg/day.**

This study is classified as ACCEPTABLE/GUIDELINE. The study satisfies the requirement for a series 83-3 oral developmental toxicity study in the rabbit.

83-4. (870.3800). Multi-generation reproduction study

In a multi generation reproduction study (MRID No.: 264667 to 264676), an initial set of 30/sex Wistar strain rats (Fo) were dosed as control, 5, 18.5 or 50 ppm of triphenyltin hydroxide (TPTH) for 70 days and bred (one to one) to produce the F1 generation. The F1 generation was also dosed and bred to produce the F2 generation. These dose levels corresponded to approximately 0, 0.25, 0.925 and 2.5 mg/kg/day for both sexes.

Parental systemic effects were limited to decreases in body weight gains in the Fo, F1 and F2 generations at 50 ppm (as much as 20% lower in males and 14% lower in females). Decreases of up to 5% were noted at 18.5 ppm but were not consistent and not considered treatment related. Organ weight changes in adults were noted in **The LOAEL for parental effects is 2.5 mg/kg/day based on body weight decreases. The NOAEL is 0.925 mg/kg/day.**

Developmental toxicity was evident at 18.5 ppm as indicated by decreases in **live litter size** (11.9% for the F2 generation), decreases in **liver weight** (i.e., 11.6% for relative to brain **weight** for the F2 weanlings, $p < 0.05$ and 8% not significant for the F1 weanlings). **Spleen** weight was decreased 17% for males and 18% for females for the F2 generation weanlings (relative to brain weight and both $p < 0.05$). Thymus weight was decreased ~16% for males. At 50 ppm mean fetal weight was decreased 12% for males and 16% for females for the F1 generation and 30% for both sexes for the F2 generation. Testis weight was decreased in both the F1 and F2 weanlings (17-21% relative to brain weight for both generations). Other organ weight changes in the ovaries, kidneys, heart, lung, pituitary and adrenal gland were all considered to be related to the weight decreases and not direct effects. There was no supporting pathology in any of the organs showing weight changes. **The LOAEL for developmental toxicity is 0.925 mg/kg/day based on decreased live litter size, liver and spleen weights. The NOAEL is 0.25 mg/kg/day.**

This study is classified as ACCEPTABLE/GUIDELINE and satisfies the requirement for a series 83-4 multi generation reproduction study in rats.

83-5 (870.4300). Rat Chronic Feeding/Onco Study.

In a combined chronic feeding and carcinogenicity study (MRID No.: 41085702) classified as **ACCEPTABLE (83-5)** four groups of 60/sex Wistar strain rats were dosed with triphenyltin hydroxide (TPTH ~97% purity) as control, 5, 20 or 80 ppm for two years. These dose levels correspond to 0, 0.3, 1.3 or 6.2 mg/kg/day for males and 0, 0.4, 1.6 or 6.2 mg/kg/day for females. A satellite group of 10 rats/sex were sacrificed after one year.

At 5 ppm there were increased **deaths and clinical signs** in females that were apparently related to increased pituitary tumors as well as decreases in **immunoglobulin**. At 20 ppm, there were decreases in **body weight**, cystoid changes in males and nodules in females in the pituitary which compressed the brain, bile duct proliferation and portal sclerosis. At 80 ppm there were decreases in food consumption, increases in serum enzyme levels for SAT, ALP, and ALA and pituitary *pars intermedia* hyperplasia in males and Leydig cell hyperplasia and testicular atrophy as well as liver eosinophilic focuses in females. **The LOAEL is < 5 ppm (0.3 mg/kg/day in males 0.4 mg/kg/day in females) based on deaths in females and decreases in immunoglobulins. The NOAEL was not established.**

TPTH was determined to have compound related increases in **pituitary** tumors in females and **testicular** tumors.

This study is classified as ACCEPTABLE/GUIDELINE and to satisfy the requirement for a series 83-5 combined chronic feeding/carcinogenicity study in rats.