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

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

**DATE:** **November 13, 1998**

**MEMORANDUM**

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

**FROM:** John Doherty 11/17/98
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 11/17/98
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

11/17/98
John Doherty, Ph.D., D.A.B.T.
Toxicologist

Report Concurrence:

11/18/98
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.

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



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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 (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.

**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.**



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**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 $\mu$m in diameter and that 60.8% and 38.6% Of the particles were < 1.06 $\mu$m 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.



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



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## 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.



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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; NOAEL = >3.0 mg/kg/day.



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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 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 .



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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.



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## 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<br>252512 | $LD_{50}$ = 165 mg/kg ♂<br>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 |



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## 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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