(6)

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

September 28, 2005

MEMORANDUM

Subject: EPA Id No.: 083601. Triphenyltin hydroxide: Review of the non-guideline special study (2003, MRID No.: 45890101) on milk secretion.

TXR No.: 0051781
PC Code: 083601
DP Barcode No.: D289372

From: John Doherty 10/26/05
ReRegistration Branch III
Health Effects Division 7509C

To: Susan Bartow
Special Review and ReRegistration Division 7507C

Through: Catherine Eiden
Branch Chief
ReRegistration Branch III
Health Effects Division 7509C

Conclusion

ReRegistration Branch III (RRBIII) has reviewed the special non-guideline study 2003, MRID No.: 45890101) designed to assess the lactational transfer of triphenyltin hydroxide (TPTH). The study was classified as acceptable/non-guideline and determined achieve its objectives. The study demonstrated that very little TPTH either as intact parent TPTH or its metabolites was transferred to the rats milk. Only as much as 0.10 μg/ml of total TPTH was present in the milk after daily doses of 4 mg/kg/day six hours after the last dose. The study is further identified together with the Executive Summary in the accompanying table. A copy of the DER is attached.

Study Identification	Executive Summary
Non-Guideline milk secretion study - rats. Huntingdon Laboratory, LDA/036, March 14, 2003, MRID No.: 45890101.	In a non-guideline study (2003, MRID 45890101), groups of lactating Sprague-Dawley [Crl:CD(SD)IGS BR] rats were exposed to Fentin hydroxide (TPTH; 99.4% a.i.; Lot/Batch #: AZH 01-00) in corn oil by gavage. In one group, fifteen rats were given a single 4 mg/kg dose and milk samples were collected from 3 rats/time point at 0.5, 1, 3, 6, or 24 hours post-dosing. In a second group, twelve rats were given daily 4 mg/kg doses for 10 days and milk samples were collected on Days 5 or 10 from 6 rats/time point at 6 or 24 hours post-dosing, or on Day 15 (5 days after the final dose) from all 12 rats. It was stated that milk samples were also taken from control groups of 4 lactating rats on 3 separate occasions. *Systemic effects.* No effects of treatment were observed on clinical signs of toxicity, mortality, or body weight. *Transfer to milk.* No detectible residue was found in samples from lactating rats dosed with a single 4 mg/kg oral dose of TPTH. On Study Day 5 at 6 hours post-dosing, the mean concentration of parent TPTH was 0.05 µg/mL, while total TPTH (TPTH plus metabolites) was 0.06 µg/mL. By 24 hours post-dosing, parent TPTH concentration was below the limit of detection (LOD; <0.02 µg/mL), while total TPTH concentration was <=0.03 µg/mL. On Study Day 10 at 6 hours post-dosing, the mean concentration of parent TPTH was 0.09 µg/mL, while total TPTH concentration was 0.10 µg/mL. By 24 hours post-dosing, parent TPTH concentration was below the LOD, while total TPTH concentration was 0.03 µg/mL. On day 15, there was no TPTH or its metabolites in the milk. The data indicate that TPTH will be transferred to the milk of lactating dams at the low level of approximately 0.09 µg/mL achieved following multiple oral doses of 4 mg/kg/day for 10 days. This study is classified as **acceptable/non-guideline**.

DATA EVALUATION RECORD

FENTIN HYDROXIDE (TPTH)

Study Type: Non-guideline Study; Milk Secretion of TPTH in Rats

Work Assignment No. 1-01-20 Amended; (MRID 45890101)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by
Pesticide Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
Rockville, MD 20850-3268

Primary Reviewer:
Michael E. Viana, Ph.D.

Signature: Michael E Viana
Date: 4/5/04

Secondary Reviewer:
John W. Allran, M.S.

Signature: John W. Allran
Date: 4/5/04

Program Manager:
Mary L. Menetrez, Ph.D.

Signature: Mary L Menetrez
Date: 4/6/04

Quality Assurance:
Steven Brecher, Ph.D.

Signature: Steven Brecher
Date: 4/6/04

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

2

FENTIN HYDROXIDE (TPTH)/083601 Non-guideline

EPA Reviewer: John Doherty **Signature:** John Doherty
Toxicology Branch, Health Effects Division (7509C) **Date** 6/2/04
Work Assignment Manager: Ghazi Dannan, Ph.D. **Signature:** Ghazi Dannan
Registration Action Branch 3, Health Effects Division (7509C) **Date** 9/29/05

Template version 11/01

DATA EVALUATION RECORD

STUDY TYPE: Non-guideline Study; Milk Secretion of TPTH - Rats

PC CODE: 083601 **DP BARCODE:** D289372
TXR#: 0051781 **SUBMISSION NO.:** None

TEST MATERIAL (PURITY): Fentin hydroxide (TPTH; 99.4% a.i.)

SYNONYM: Triphenyltin hydroxide; AE F029664

CITATION: Taylor, L., Hackett, A., Cordon, C., *et al.* (2003) Triphenyltin hydroxide (TPTH): milk secretion following single and repeated oral doses to the rat. Huntingdon Life Sciences, Ltd., Alconbury, Huntingdon, Cambridgeshire, England. Laboratory Project ID. No.: LDA/036, March 14, 2003. MRID 45890101. Unpublished.

SPONSOR: TPTH Task Force, c/o Landis International, Inc., 3185 Madison Highway, Valdosta, GA

EXECUTIVE SUMMARY: In a non-guideline study (2003, MRID 45890101), groups of lactating Sprague-Dawley [Crl:CD(SD)IGS BR] rats were exposed to Fentin hydroxide (TPTH; 99.4% a.i.; Lot/Batch #: AZH 01-00) in corn oil by gavage. In one group, fifteen rats were given a single 4 mg/kg dose and milk samples were collected from 3 rats/time point at 0.5, 1, 3, 6, or 24 hours post-dosing. In a second group, twelve rats were given daily 4 mg/kg doses for 10 days and milk samples were collected on Days 5 or 10 from 6 rats/time point at 6 or 24 hours post-dosing, or on Day 15 (5 days after the final dose) from all 12 rats. It was stated that milk samples were also taken from control groups of 4 lactating rats on 3 separate occasions.

Systemic effects. No effects of treatment were observed on clinical signs of toxicity, mortality, or body weight.

Transfer to milk. No detectible residue was found in samples from lactating rats dosed with a single 4 mg/kg oral dose of TPTH.

On Study Day 5 at 6 hours post-dosing, the mean concentration of parent TPTH was 0.05 µg/mL, while total TPTH (TPTH plus metabolites) was 0.06 µg/mL. By 24 hours post-dosing, parent TPTH concentration was below the limit of detection (LOD; <0.02 µg/mL), while total TPTH concentration was <=0.03 µg/mL. On Study Day 10 at 6 hours post-dosing, the mean concentration of parent TPTH was 0.09 µg/mL, while total TPTH concentration was 0.10 µg/mL.

4

By 24 hours post-dosing, parent TPTH concentration was below the LOD, while total TPTH concentration was 0.03 µg/mL. On day 15, there was no TPTH or its metabolites in the milk. The data indicate that TPTH will be transferred to the milk of lactating dams at the low level of a maximum of 0.09 µg/mL achieved following multiple oral doses of 4 mg/kg/day for 10 days.

This study is classified as **acceptable/non-guideline**.

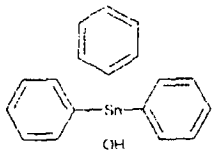
COMPLIANCE - Signed and dated Data Confidentiality, GLP, and Quality Assurance statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test material: Fentin hydroxide (TPTH)

Description:	White powder
Lot/Batch #:	AZH 01-00
Purity (w/w):	99.4% a.i.
Stability of compound:	Not provided
CAS #:	76-87-9
Structure:	



2. Vehicle: Corn oil

3. Test animals

Species:	Rat (female)
Strain:	Sprague-Dawley [Crl:CD(SD)IGS BR]
Age and body weight range at study initiation:	Approximately 10-15 weeks; 317-371 g single dose group; 281-375 g repeated dose group
Source:	Charles River UK, Ltd. (Margate, Kent, England)
Housing:	Individually, in standard polypropylene cages with solid floors
Diet:	Pelleted VRF1C diet (Using d'Alimentation Rationelle), *ad libitum* (assumed)
Water:	Tap water, *ad libitum*
Environmental conditions	
Temperature:	19-23°C
Humidity:	40-70%
Air changes:	Not provided
Photoperiod:	12 hrs light/12 hrs dark
Acclimation period:	At least 5 days

B. STUDY DESIGN

1. In life dates: Start: 09/04/01 End: 09/28/01

2. Objective: The objective of this study was to determine the concentration of TPTH secreted into milk by lactating female rats following single or repeated oral doses to demonstrate possible exposure to pups during postnatal studies.

3. **Mating**: Four lactating females and their litters were received from the breeding laboratory. An additional 34 animals were mated by the breeding laboratory and supplied as "time-mated females." Further details on mating were not provided.

4. **Animal assignment/dose levels**: The animals were assigned to the test groups shown in Table 1.

Table 1. Study design[a]

Study Group	Dose (mg/kg)	# of Animals
Control[b]	0	8
Single Dose[c]	4	15
Repeated Dose[d]	4	12

a Data were obtained from pages 15, 27-28, and 104-109 of the study report.
b Milk from control group was used to validate the method of analysis.
c Single dose animals received one 4 mg/kg dose of test compound.
d Repeated dose animals received 4 mg/kg doses of test compound for 10 days.

5. **Dose-selection rationale**: A dose rationale was not provided.

6. **Dose formulation and analysis**: The frequency and storage conditions of dose formulations were not provided. Dose formulations were prepared by mixing a weighed amount of the test substance with a small volume of corn oil in a mortar until a smooth paste was formed. Additional corn oil was added to form a pourable suspension, which was brought up to a final concentration of 1 mg/mL with corn oil. It was stated in a developmental neurotoxicity study submitted concurrently (MRID 46055701) that homogeneity and stability of the test compound at concentrations of 0.002 and 2 mg/mL in corn oil vehicle were determined previously (data not reported). The test compound was shown to be stable in corn oil for 2 days at room temperature and 15 days refrigerated. It was stated that concentration analyses were performed in duplicate on samples taken after dosing; however, no data were provided.

7. **Dosage administration**: Dose suspensions were administered by gavage at a volume of 5 mL/kg body weight, and were adjusted using the most recent body weight. Animals receiving a single oral dose were treated on lactation days (LD) 11or 12. Animals receiving repeated oral doses were treated daily from LD 4-14 and then were allowed to recover for 5 days (LD 19).

8. **Statistics**: No statistical analyses were performed.

C. METHODS

1. **Observations**: Animals were observed for clinical signs of toxicity immediately after dosing, within 2 hours following dosing, and on at least one other occasion towards the end of the working day. Animals were observed at least once daily during the recovery period.

2. **Body weight:** All animals were weighed prior to administration of each dose.

3. **Milk sampling:** Milk samples (approximately 0.5-0.7 g each) were collected by gentle manual pressure on the nipple from lactating rats. Pups were removed from the dams approximately 3 hours prior to the scheduled time of collection. Oxytocin (1 U/kg) was administered intraperitoneally to dams approximately 15 minutes before sampling to stimulate milk production. All samples were stored at -20°C until analysis.

a. Controls - Milk samples were collected from control groups of 4 rats on 3 separate occasions. After sampling, dams were killed by cervical dislocation under anesthesia and discarded.

b. Single dose group - Milk samples were collected from groups of 3 rats at 0.5, 1, 3, 6, or 24 hours post-dosing. After sampling, dams were exsanguinated by cardiac puncture under anesthesia, killed by cervical dislocation, and discarded.

c. Repeated dose group - Study Days 5 and 10 milk samples were collected from groups of 6 rats at 6 or 24 hours post-dosing. Pups were returned to dams immediately after sampling. Five days after the final dose (Study Day 15), milk samples were collected from all rats. After final sampling, dams were killed by cervical dislocation under anesthesia and discarded.

7. **Measurement of test substance in milk:** Milk samples were extracted with acidified methanol and partitioned into toluene. The toluene was evaporated to dryness, and the residue was either butylated with a Grignard reagent (single dose samples), or partitioned between hexane and acetonitrile, and then butylated with a Grignard reagent (repeated dose samples). The excess Grignard reagent was hydrolyzed and the butylated analytes were extracted into hexane and purified by column chromatography. TPTH and its metabolites (diphenyltin and monophenyltin) were then quantitated by gas chromatography using a flame photometric detector with a tin (610 nm) filter. The limit of quantitation of TPTH by this method was determined to be 0.02 µg/mL. The method was validated by analysis of control milk samples spiked with butyltriphenyltin, dibutyldiphenyltin, or tributylphenyltin. Milk from single dose samples were analyzed individually, while repeated dose samples were pooled in pairs to yield 3 samples per time point and then analyzed. The Sponsor stated that the method used for analysis of the single dose samples was not sufficiently sensitive; therefore, a hexane/acetonitrile partitioning clean up step was added. However, this resulted in reduced recoveries that were lower than would normally be acceptable. For the purposes of this study, this method was found acceptable for use.

II. RESULTS

A. OBSERVATIONS

1. **Clinical signs of toxicity:** No clinical signs of toxicity were reported.

2. **Mortality:** All animals survived to sacrifice.

8

B. BODY WEIGHT: Body weights were comparable between the single dose and repeated dose groups (Table 2). A slight decrease in body weight was noted on Study Day 2, but dams recovered and continued to gain weight throughout the remainder of the Study period.

Table 2. Mean (± SD) body weights (g) of lactating female rats treated with single or repeated 4 mg/kg doses of TPTH by gavage[a]

Study Day	Mean	Standard Deviation
Single Dose (n=15)		
0	338	16
Repeated Dose (n=12)		
1	305	16
2	303	17
3	313	16
4	319	18
5	321	19
6	328	20
7	332	19
8	337	18
9	337	17
10	339	18

a Values were calculated by reviewers from data obtained from Appendix 3 on pages 104-109 of the study report.

C. MILK RESIDUES:

1. Single dose: No detectible residue was found in any sample at any time point for either parent TPTH or total TPTH (TPTH plus metabolites).

2. Repeated dose: The concentrations of parent and total TPTH in repeated dose group samples are presented in Table 3. On Study Day 5, the mean concentration of total TPTH was 0.06 µg/mL at 6 hours post-dosing, falling to ≤0.03 µg/mL by 24 hours. On Study Day 10, the mean concentration of total TPTH was 0.10 µg/mL post-dosing, falling to 0.03 µg/mL by 24 hours. On Study Day 5, the mean concentration of parent TPTH was 0.05 µg/mL at 6 hours post-dosing, falling below the limit of detection (0.02 µg/mL) by 24 hours. On Study Day 10, the mean concentration of parent TPTH was 0.09 µg/mL at 6 hours post-dosing, falling to ≤0.02 µg/mL by 24 hours. TPTH plus metabolites and parent TPTH were below the limit of detection on Study Day 15, 5 days after administration of the final dose.

9

Table 3. Concentrations (µg/mL) of TPTH in the milk of lactating female rats treated by gavage with 4 mg/kg daily doses of TPTH for up to 10 days[a]

Hours post-treatment	Study Day	
	5	10
TPTH plus metabolites		
6	0.08	0.07
	0.03	0.11
	0.07	0.13
Mean±SD[b]	0.06±0.03	0.10±0.03
24	<0.02	0.03
	0.02	0.03
	0.03	0.03
Mean±SD[b]	—	0.03±0.00
Parent TPTH		
6	0.06	0.06
	0.02	0.09
	0.06	0.11
Mean±SD[b]	0.05±0.02	0.09±0.03
24	<0.02	<0.02
	<0.02	<0.02
	<0.02	0.02
Mean±SD[b]	—	—

a Data were obtained from pages 23 and 28 of the study report.
b Calculated by reviewers from data presented in this table.
— Not applicable

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS: TPTH residues were detectable in rat milk following 5 days of daily oral dosing. There was some "accumulation" of TPTH in rat milk following 10 days of daily oral dosing. The data also indicated that the TPTH residues in milk disappeared on cessation of treatment.

B. REVIEWER COMMENTS: No effects of treatment were observed on clinical signs of toxicity, mortality, or body weight.

No detectible residue was found in samples from lactating rats dosed with a single 4 mg/kg oral dose of TPTH.

On Study Day 5, the mean concentration of total TPTH was 0.06 µg/mL at 6 hours post-dosing, falling to ≤0.03 µg/mL by 24 hours. On Study Day 10, the mean concentration of total TPTH was 0.10 µg/mL post-dosing, falling to 0.03 µg/mL by 24 hours. On Study Day 5, the mean concentration of parent TPTH was 0.05 µg/mL at 6 hours post-dosing, falling below the limit of detection (0.02 µg/mL) by 24 hours. On Study Day 10, the mean concentration of TPTH was 0.09 µg/mL at 6 hours post-dosing, falling to ≤0.02 µg/mL by 24 hours. These data indicate that TPTH does accumulate in rat milk with increasing time of dosing. Lactating female rats are able to reduce the levels of TPTH in milk below the limit of detection within 5 days of cessation of treatment.

The submitted study is classified as **acceptable/non-guideline**.

C. **STUDY DEFICIENCIES:** Concentration analyses were not reported for the dose formulations. This deficiency does not alter the conclusions of this review.