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

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

MEMORANDUM

June 25, 2004

Subject: Triphenyltin hydroxide: Review of the acute neurotoxicity screen study (2000, MRID No.: 45299901).

TXR # 0052373
DP Barcode No.: D272193
Submission No.: Not provided.
PC Code: 083601

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Through: Danette Drew
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Conclusions:

ReRegistration Branch III has reviewed the series 870.6200a acute neurotoxicity screen study (2000, MRID No.: 45299901) and has determined that the study is classified as ACCEPTABLE/Guideline and satisfies the guideline requirement for an acute neurotoxicity screen study in rats. A copy of the DER is attached. The study is further identified and the Executive Summary of the study are presented in the accompanying table.

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Table. Study reviewed.

Study Identification	Executive Summary
870.6200a. Acute neurotoxicity screen - rats. WIL Research Laboratories, Inc., Laboratory report No.: WIL-399002, December 19, 2000. MRID 45299901.	In an acute neurotoxicity study (2000, MRID 45299901), groups of non-fasted, 44-47 day-old Crl:CD®(SD)IGS BR rats (10/sex/dose) were given a single oral dose (5 mL/kg) of fentin hydroxide (TPTH; 97.5% a.i.; Lot # ZVRAM.928K) in aqueous 0.5% (w/v) methylcellulose at doses of 0, 5, 25, or 75 mg/kg bw and observed for 14 days. Neurobehavioral assessments (functional observational battery and motor activity testing) were performed on 10 animals/sex/group pretest, 4 hours after dosing on Day 0 and on Days 7 and 14. On Day 15, all surviving animals/sex/group were euthanized and perfused *in situ* for neuropathological examination. Following perfusion, brain weights and dimensions were recorded for all animals, and 5 animals/sex from the control and 75 mg/kg groups were subjected to histopathological evaluations of the central and peripheral nervous system tissues. Clinical signs were noted to develop a few *days* following treatment and occurred sporadically so that they were not also seen in the FOB assessments at set time intervals. At 5 mg/kg and above, excessive grooming, increased activity upon handling, and piloerection were observed in both sexes. Gait abnormalities (rocks, sways, or lurches as it proceeds forward), decreased defecation, and decreased urination were noted in the 25 mg/kg and above groups. At 75 mg/kg, the following additional signs were observed: repetitive movement of the mouth and jaws upon handling (both sexes) and following dosing (females); feces absent (both sexes); gasping (males); soft stools (males); and hunched appearance (females). At 75 mg/kg, one male was found dead on Day 2, and one female was killed *in extremis* on Day 3. These animals displayed gasping (both animals), gait alterations (female only), and piloerection (female only). Body weights were decreased in the males on Day 7, while body weight gains and food consumption were decreased in both sexes on Days 0-7. Body weights in this group returned to control levels by Day 14, and overall (Day 0-14) body weight gains were similar to controls. No effects of treatment were observed on FOB parameters, motor activity, gross pathology, brain weight, brain measurement, or neuropathology. **The LOAEL is 5 mg/kg, based on clinical signs of toxicity (excessive grooming, increased activity on handling, and piloerection) in both sexes. The systemic NOAEL was not established.** This study is classified as **Acceptable/Guideline** and satisfies the Guideline requirements (870.6200a; OECD 424) for an acute neurotoxicity screening battery in rats.

B

DATA EVALUATION RECORD

FENTIN HYDROXIDE (TPTH)

Study Type: §81-8a; Neurotoxicity Screening Battery in Rats

Work Assignment No. 1-01-23 A (MRID 45299901)

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Disclaimer

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

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Registration Action Branch 3, Health Effects Division (7509C) **Date** 6/18/04
Template version 11/01

DATA EVALUATION RECORD

STUDY TYPE: Acute Neurotoxicity - Rats OPPTS 870.6200a [§81-8]; OECD 424.

PC CODE: 083601 **DP BARCODE:** D272193
TXR#: 0052373 **SUBMISSION NO.:** None

TEST MATERIAL (PURITY): Fentin Hydroxide (TPTH; 97.5% a.i.)

SYNONYMS: Triphenyltin hydroxide

CITATION: Nemec, M. (2000) An oral acute neurotoxicity study of TPTH in rats. WIL Research Laboratories, Inc., Ashland, OH. Laboratory report No.: WIL-399002, December 19, 2000. MRID 45299901. Unpublished.

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

EXECUTIVE SUMMARY: In an acute neurotoxicity study (2000, MRID 45299901), groups of non-fasted, 44-47 day-old Crl:CD®(SD)IGS BR rats (10/sex/dose) were given a single oral dose (5 mL/kg) of fentin hydroxide (TPTH; 97.5% a.i.; Lot # ZVRAM.928K) in aqueous 0.5% (w/v) methylcellulose at doses of 0, 5, 25, or 75 mg/kg bw and observed for 14 days. Neurobehavioral assessments (functional observational battery and motor activity testing) were performed on 10 animals/sex/group pretest, 4 hours after dosing on Day 0 and on Days 7 and 14. On Day 15, all surviving animals/sex/group were euthanized and perfused *in situ* for neuropathological examination. Following perfusion, brain weights and dimensions were recorded for all animals, and 5 animals/sex from the control and 75 mg/kg groups were subjected to histopathological evaluations of the central and peripheral nervous system tissues.

Clinical signs were noted to develop a few *days* following treatment and occurred sporadically so that they were not also seen in the FOB assessments at set time intervals. At 5 mg/kg and above, excessive grooming, increased activity upon handling, and piloerection were observed in both sexes. Gait abnormalities (rocks, sways, or lurches as it proceeds forward), decreased defecation, and decreased urination were noted in the 25 mg/kg and above groups. At 75 mg/kg, the following additional signs were observed: repetitive movement of the mouth and jaws upon handling (both sexes) and following dosing (females); feces absent (both sexes); gasping (males); soft stools (males); and hunched appearance (females). At 75 mg/kg, one male was found dead on Day 2, and one female was killed *in extremis* on Day 3. These animals displayed gasping (both animals), gait alterations (female only), and piloerection (female only).

Body weights were decreased in the males on Day 7, while body weight gains and food consumption were decreased in both sexes on Days 0-7. Body weights in this group returned to control levels by Day 14, and overall (Day 0-14) body weight gains were similar to controls. No effects of treatment were observed on FOB parameters, motor activity, gross pathology, brain weight, brain measurement, or neuropathology. **The LOAEL is 5 mg/kg, based on clinical signs of toxicity (excessive grooming, increased activity on handling, and piloerection) in both sexes. The systemic NOAEL was not established.**

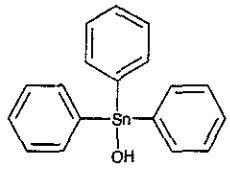
This study is classified as **Acceptable/Guideline** and satisfies the Guideline requirements (870.6200a; OECD 424) for an acute neurotoxicity screening battery in rats.

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

I. MATERIALS AND METHODS

A. MATERIALS

1. **Test material:** Fentin hydroxide (TPTH)

Description:	Fine white powder
Lot/Batch #:	ZVRAM.928K
Purity (w/w):	97.5 % a.i.
Stability of compound	Stable in the vehicle for at least 10 days at ambient temperature
CAS # of TGAI:	76-87-9
Structure	

2. **Vehicle and/or positive control:** 0.5% (w/v) aqueous methylcellulose

3. **Test animals:**

Species:	Rat	
Strain:	CD (Crl:CD®(SD)IGS BR)	
Age/weight range at initiation of dosing:	44-47 days/187-238 g males; 150-186 g females	
Source:	Charles River Laboratories (Raleigh, NC)	
Housing:	3/cage/sex for approximately 3 days following receipt, individually thereafter in suspended, stainless steel wire-mesh cages	
Diet:	Certified Rodent LabDiet® 5002 (PMI Nutrition International, Inc.) *ad libitum*; except during behavioral testing	
Water:	Tap water *ad libitum*	
Environmental conditions:	**Temperature:**	22.1-22.6°C
	Humidity:	46.6-68.5%
	Air changes:	Not provided
	Photoperiod:	12 hrs light/12 hrs dark
Acclimation period:	At least 12 days	

B. STUDY DESIGN:

1. **In life dates:** Start: July 17, 2000 End: August 4, 2000

2. **Animal assignment and treatment:** Animals were randomly assigned (stratified by body weight) to the test groups noted in Table 1.

Table 1. Study design[a]

Experimental Parameter	Dose Group (mg/kg)			
	0	5	25	75
Total # of Animals (M/F)	10/10	10/10	10/10	10/10
Behavioral Testing (Functional Observational Battery (FOB), Motor Activity)	10/10	10/10	10/10	10/10
Neuropathology	5/5	5/5	5/5	5/5

a Data were obtained from pages 23-26 of the study report.

Dosing was staggered over 4 consecutive days to facilitate neurobehavioral observations.

3. **Dose selection rationale:** It was stated that the dose levels presented in Table 1 were based on the results of an acute oral range-finding toxicity study (WIL-399001, 2001, MRID No.: 45350301). In this study, animals were given a single 10, 50, 75, or 125 mg/kg dose of TPTH. One 125 mg/kg female was killed *in extremis* on Study Day 7. Treatment-related clinical signs of toxicity noted *on the day of dosing* were twitching in the males and/or females in the 10, 75, and 125 mg/kg groups, Low arousal was noted in the 75 and 125 mg/kg dose groups. One animal in the high dose group had abnormal gait and tremors. One rat in the high dose group had reduced body temperature within one hour of dosing. Additional signs after the first day included piloerection. rocking, lurching or swaying while ambulating and urogenital staining. There were occasions of lacrimation, impaired use of one or more limbs, repetitive movement of the mouth/jaws, vocalization, hyperactivity and tremors as well as abnormal defecation. Hunched appearance, and hypoactivity and dropping eyelids were also reported and the dropping eyelids were first noted after day 3. Dose-dependent body weight losses were also observed.

It was estimated that on the first day, the reactions to treatment occurred in the 4 to six hours postdosing. The secondary effects occurred after the first day but some were not first observed until a few days later.

4. **Test substance preparation, administration, and analysis:** Dose formulations were prepared once by mixing the appropriate amounts of TPTH with 0.5% aqueous methylcellulose at approximately 70% of the final volume. The formulations were stirred with a magnetic stirrer and then homogenized with an electronic homogenizer until uniform suspensions were obtained. The formulations were brought up to final volume with vehicle and stirred throughout the sampling and dosing procedures. Non-fasted rats were given a single dose of TPTH at a dosing volume of 5 mL/kg. Samples from the bulk preparations of each formulation were analyzed for homogeneity (top, middle, bottom) and concentration at the beginning of the study. Resuspensions of these samples (top, bottom) were analyzed on the first day of dosing and 10 days later. Stability was also determined from the samples taken 10 days after preparation and stored at room temperature.

Results: **Homogeneity Analysis** (range % RSD): 0.19-6.3%

Stability Analysis (% of concentration on first day of dosing): 98.6-104%

Concentration Analysis (% of nominal): 84.2-100%

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the animals was acceptable.

5. Statistics: All statistical tests were two-sided. Significance was denoted at $p \leq 0.05$ and $p \leq 0.01$. The data were analyzed using the following statistical methods.

Parameter	Statistical Method
Body weight, body weight gain, food consumption, continuous FOB data, locomotor activity data, brain weights, and brain measurements	One-way ANOVA, followed by Dunnett's Test if significant
Scalar or descriptive FOB data	Fisher's Exact Test

It was not stated if the data were tested for normal distribution or homogeneity of variance. Tests for these assumptions should be performed prior to the analyses listed above. The analyses used were considered appropriate.

C. METHODS / OBSERVATIONS

1. Mortality and clinical observations: Animals were observed twice daily (morning and afternoon) for mortality and morbidity. Detailed clinical observations were recorded daily for all animals. On Day 0, clinical observations were recorded prior to dosing, immediately following dosing, and approximately 1-2 hours after dosing. On Days 7 and 14, no additional clinical observations were performed beyond those conducted as part of the FOB.

2. Body weight: All animals were weighed prior to the start of treatment (Day -7), and on Days 0, 7, 14, and at sacrifice.

3. Food consumption: Individual food consumption (g/animal/day) was recorded weekly, beginning one week prior to initiation of treatment.

4. Cholinesterase determination: Cholinesterase assessment was not determined and is not necessary for TPTH.

5. Neurobehavioral assessment

a. Functional observational battery (FOB): All animals were subjected to an FOB pretest, on Day 0 at 4 hours post-dosing (time of peak effect), and on Days 7 and 14. Testing was performed by the same technicians whenever possible, without knowledge of the animal group assignment. Testing was performed in a soundproofed room equipped with a white noise generator operating at 70±10 dB; however, home cage observations were recorded in the animal room. Open field

observations were recorded over a 2 minute period. The scoring criteria for the FOB were presented on pages 786-800 of the study report.

The following CHECKED (X) parameters were examined.

	HOME CAGE OBSERVATIONS		HANDLING OBSERVATIONS		OPEN FIELD OBSERVATIONS
X	Posture*	X	Reactivity*	X	Mobility
X	Biting	X	Lacrimation* / chromodacryorrhea	X	Rearing+
X	Convulsions*	X	Salivation*	X	Arousal/ general activity level*
X	Tremors*	X	Piloerection*	X	Convulsions*
	Abnormal Movements*	X	Fur appearance	X	Tremors*
X	Palpebral closure*	X	Palpebral closure*		Abnormal movements*
X	Feces consistency	X	Respiratory rate+	X	Urination / defecation*
		X	Red/crusty deposits*	X	Grooming
	SENSORY OBSERVATIONS	X	Mucous membranes /eye /skin color	X	Gait abnormalities / posture*
X	Approach response+	X	Eye prominence*	X	Gait score*
X	Touch response+	X	Muscle tone*	X	Bizarre / stereotypic behavior*
X	Startle response*			X	Backing
X	Pain response*			X	Time to first step
X	Pupil response*				
X	Eyeblink response		PHYSIOLOGICAL OBSERVATIONS		NEUROMUSCULAR OBSERVATIONS
X	Forelimb extension	X	Body weight*	X	Hindlimb extensor strength
X	Hindlimb extension	X	Body temperature+	X	Forelimb grip strength*
X	Air righting reflex+	X	Catalepsy	X	Hindlimb grip strength*
X	Olfactory orientation			X	Landing foot splay*
				X	Rotarod performance

* Required parameters; + Recommended parameters

b. Locomotor activity: Following FOB testing, animals were individually placed in an automated photobeam activity monitoring device (Photobeam Activity System, San Diego Instruments Inc., San Diego, CA) for 60 minutes. Testing was conducted in a soundproofed room with a white noise generator operating at approximately 70 dB. Data for ambulatory and total motor activity were recorded; total motor activity was defined as a combination of fine motor skills (interruption of one photobeam) and ambulatory motor activity (interruption of 2 or more consecutive photo beams). Data were collected in 5 minute epochs.

6. Sacrifice and pathology: A complete necropsy was performed on all animals found dead or killed *in extremis*; however, no tissue samples were preserved. All surviving animals were euthanized by an intraperitoneal injection of sodium pentobarbital and perfused *in situ* with a buffered 4.0% paraformaldehyde/1.4% gluteraldehyde solution. The central and peripheral nervous systems were then dissected and preserved. Fixed brain weight (excluding the olfactory bulbs) and brain length and width were recorded, along with any observable gross alteration, abnormal coloration, or lesion of the brain and spinal cord. Five animals/sex from the control and 75 mg/kg groups were selected for a qualitative histopathological examination. Central nervous system tissues and eyes were embedded in paraffin; peripheral nervous system tissues were embedded in plastic. All tissues were sectioned and stained with hematoxylin and eosin.

The following CHECKED (X) tissues were evaluated microscopically.

	CENTRAL NERVOUS SYSTEM		PERIPHERAL NERVOUS SYSTEM
	BRAIN		**SCIATIC NERVE**
X	Forebrain	X	Mid-thigh
X	Center of cerebrum	X	Sciatic Notch
X	Midbrain		
X	Cerebellum		**OTHER**
X	Pons	X	Sural Nerve
X	Medulla oblongata	X	Tibial Nerve
	SPINAL CORD	X	Peroneal Nerve
X	Cervical swelling	X	Lumbar dorsal root ganglion
X	Lumbar swelling	X	Lumbar dorsal root fibers
	Thoracic swelling	X	Lumbar ventral root fibers
	OTHER	X	Cervical dorsal root ganglion
X	Gasserian Ganglion	X	Cervical dorsal root fibers
X	Trigeminal nerves	X	Cervical ventral root fibers
X	Optic nerve		
X	Eyes		
	Gastrocnemius muscle		

7. **Positive controls:** Summaries of four studies (WIL-99032, WIL-99034, WIL-99035, and WIL-99149) performed to generate positive control data and validate the procedures and observers of the performing lab to conduct the FOB and to assess motor activity, neurotoxicity and behavioral effects were provided in the current study. Exposure to **3,3-Iminodipropionitrile** (IDPN, 2000 mg/kg, single gavage dose) induced the following in both sexes: (i) decreased body weight; (ii) FOB effects (eg. decreased mobility, impaired gait, retropulsion, and circling); (iii) decreased fore- and hindlimb grip strength in males; (iv) decreased startle response; and (v) impaired air righting reflex. Inter-observer reliability was also demonstrated, as all observers detected the FOB effects from IDPN. **Acrylamide** (10 or 20 mg/kg, daily gavage doses 5 days/week for 4 weeks) induced the following effects in both sexes during the FOB at 14, 21, and 28 days after initial dosing: (i) alterations in muscle tone; (ii) alterations in startle and tail pinch responses and air righting reflex; (iii) decreased hindlimb extensor strength and fore- and hindlimb grip strength; (iv) reduced rotarod performance; (v) increased hindlimb foot splay; and (vi) decreased body weight and body temperature. Additionally, the following histopathological lesions were noted at 20 mg/kg: axonal degeneration, digestion chambers, swollen axon cylinders or demyelination in the trigeminal nerve, lumbar dorsal and ventral root fibers, cervical dorsal root fibers, sciatic, sural, tibial, and peroneal nerves, lumbar root (females only), and cervical ventral root fibers (females only). **Trimethyltin chloride** (7.5 mg/kg, single i.p. dose) induced neuronal loss in the dentate gyrus and chromatolysis in the gasserian ganglion neurons in the males. **Carbaryl** (10 or 50 mg/kg, single i.p. dose) induced the following FOB effects: (i) altered posture, palpebral closure, and convulsions/tremors during home cage observations; (ii) altered ease of removal and handling, salivation, fur appearance, and eye prominence during

handling; (iii) increased time to first step, alterations in mobility, gait, gait score, arousal, convulsions/tremors, and number of rears during open-field observations; (iv) alterations in approach, touch, startle, tail pinch, and pupil responses, olfactory orientation, and air righting reflex; (v) alterations in hindlimb extensor strength, grip strength, and rotarod performance; and (vi) alterations in catalepsy time and body temperature. Additionally, total and locomotor activity were decreased. Total and locomotor activity were increased with **d-Amphetamine sulfate** (2 or 4 mg/kg, single i.p. dose) and decreased with **Chlorpromazine hydrochloride** (5 or 10 mg/kg, single i.p. dose).

Historical control data were also provided.

II. RESULTS

A. OBSERVATIONS

1. **Clinical signs:** Clinical signs of toxicity are presented in Tables 2a and b. At ≥5 mg/kg, excessive grooming, increased activity upon handling, and piloerection were observed in both sexes. Gait abnormalities (rocks, sways, or lurches as it proceeds forward), decreased defecation, and decreased urination were noted in the ≥25 mg/kg groups. At 75 mg/kg, the following additional signs were observed: repetitive movement of the mouth and jaws upon handling (both sexes) and following dosing (females); feces absent (both sexes); gasping (males); soft stools (males); and hunched appearance (females).

In general, these signs developed after day one and the piloerection was noted on day 5 or later. The pattern of signs indicates a slow acting nature of TPTH possibly indicating structure damage to some internal organs.

Table 2a. Clinical observations (total occurrences/# of animals) in male rats treated with TPTH[a]

Observation	Dose Level (mg/kg)			
	0	5	25	75
Excessive grooming (within the first few days)	4/3	14/7	28/9	22/9
Increased activity upon handling (day 5 or later)	13/7	58/10	44/9	43/8
Piloerection (day 5 or later)	11/8	70/10	74/10	80/9
Rocks, lurches, or sways as it walks	0/0	0/0	0/0	3/2
Repetitive movement of mouth and jaws upon handling	0/0	0/0	0/0	5/4
Rocks, sways, or lurches as it proceeds forward	0/0	0/0	6/4	29/9
Decreased defecation	4/4	4/4	11/8	29/10
Soft stool	0/0	0/0	1/1	3/3
Feces absent	0/0	0/0	0/0	3/3
Decreased urination	3/3	6/5	8/6	23/9
Gasping	0/0	0/0	0/0	3/2

a Data were obtained from pages 44-47 of the study report.

Table 2b. Clinical observations (total occurrences/# of animals) in female rats treated with TPTH[a]

Observation	Dose Level (mg/kg)			
	0	5	25	75
Excessive grooming	6/4	29/9	30/9	19/9
Increased activity upon handling	25/6	50/10	52/10	50/9
Piloerection	5/4	69/10	83/10	78/10
Rocks, lurches, or sways as it walks	0/0	1/1	1/1	3/3
Repetitive movement of mouth and jaws following dosing	0/0	0/0	0/0	4/3
Repetitive movement of mouth and jaws upon handling	0/0	1/1	0/0	6/6
Rocks, sways, lurches as it proceeds forward	0/0	0/0	2/2	23/9
Hunched appearance	0/0	0/0	0/0	3/2
Decreased defecation	14/7	8/5	21/10	33/10
Decreased urination	12/8	6/5	21/10	30/10
Feces absent	0/0	0/0	0/0	3/3

a Data were obtained from pages 48-51 of the study report.

2. Mortality: At 75 mg/kg, one male (# 47178) was found dead 2 days after dosing, and one female (# 47212) was killed *in extremis* 3 days after dosing. These animals displayed gasping (both animals), gait alterations (female only), and piloerection (female only). All other animals survived to scheduled sacrifice.

B. BODY WEIGHT AND BODY WEIGHT GAIN: At 75 mg/kg, body weights were decreased ($p \leq 0.01$) by 13% in the males on Day 7 (Table 3), while body weight gains were decreased ($p \leq 0.05$) by 39-67% in both sexes on Days 0-7. Body weights in this group returned to control levels by Day 14, and overall (Day 0-14) body weight gains were similar to controls. No treatment-related effects on body weight or body weight gains were observed at 5 or 25 mg/kg.

Table 3. Mean (±SD) body weights and body weight gains (g) in rats treated with TPTH once by gavage.[a]

Study Day	Dose Level (mg/kg)			
	0	5	25	75
Males				
0	208±14.2	208±12.8	210±21.3	208±12.2
7	260±12.4	262±17.4	252±25.6	226±15.4** (↓13)
14	290±45.1	306±17.4	303±26.8	282±14.7
Gain Days 0-7	52±10.0	54±5.8	42±8.3	17±14.8** (↓67)
Gain Days 7-14	31±43.6	44±6.6	51±9.1	56±8.9
Overall gain (Days 0-14)[b]	82	98	93	74
Females				
0	169±7.0	165±9.6	166±9.7	167±10.4
7	192±11.9	190±10.9	188±10.5	181±10.2
14	214±10.1	209±12.6	204±13.9	206±8.4
Gain Days 0-7	23±8.5	25±5.4	21±6.8	14±4.8* (↓39)
Gain Days 7-14	22±5.0	19±5.8	16±7.4	25±6.7
Overall gain (Days 0-14)[b]	45	44	38	39

a Data were obtained from pages 56-59 of the study report. Percent differences from controls, calculated by reviewers, are included in parentheses.
b Calculated by reviewers from data presented in this table.
* Significantly different from controls; $p \leq 0.05$
** Significantly different from controls; $p \leq 0.051$

C. FOOD CONSUMPTION: At 75 mg/kg, food consumption was decreased ($p \leq 0.01$) by 27-31% on Days 0-7 (Table 4), corresponding with the observed decreases in body weight and body weight gains. No effect of treatment was observed on food consumption at 5 or 25 mg/kg.

Table 4. Mean (±SD) food consumption (g/animal/day) in rats treated with TPTH once by gavage.[a]

Study period	Dose Level (mg/kg)			
	0	5	25	75
Males				
Days 0-7	22±2.1	23±1.7	21±2.8	16±3.0** (↓27)
Days 7-14	22±7.1	24±2.0	25±3.2	24±1.9
Females				
Days 0-7	16±1.3	16±1.2	15±1.3	11±1.4** (↓31)
Days 7-14	16±1.4	17±1.7	16±1.7	18±1.2

a Data were obtained from pages 60-61 of the study report. Percent differences from controls, calculated by reviewers, are included in parentheses.

** Significantly different from controls; $p \leq 0.01$

D. NEUROBEHAVIORAL RESULTS

1. FOB findings: No treatment-related differences were observed in any FOB parameter. In the 25 mg/kg females, an increase ($p \leq 0.05$) in the number of animals asleep, lying on their side, or curled up was noted on Day 14. Also in this group, the number of alert animals was decreased ($p \leq 0.05$). Since dose dependency was not observed, these findings were considered unrelated to treatment. Body temperature was nearly always above 38 degrees C for all measurements except for the males and females in the mid and high dose groups when they were 37.6 (males and females mid dose), 37.8 (males high dose) and 37.2 (females, high dose) during the first (time of peak effect) FOB assessment. A decrease in body temperature might be expected from TPTH treatment but since the effect is slight and there are no statistical differences (the standard deviation was high for the mid and high dose groups), there is no definite relationship with treatment.

2. Motor activity: No treatment-related effects were observed on motor activity in either total activity or ambulatory counts. Habituation was unaffected by treatment.

Table 5a. Mean (±SD) session locomotor activity (total activity counts) in rats treated with TPTH once by gavage.[a]

Interval	Dose Level (mg/kg)			
	0	5	25	75
Males				
Pre-test	871±295.7	1127±301.3	850±448.5	835±255.4
Day 0 (peak effect)	497±202.3	613±355.0	388±220.7	587±306.9
Day 7	883±244.0	986±343.2	852±341.2	830±224.5
Day 14	904±260.7	996±220.8	828±193.0	957±233.4
Females				
Pre-test	1179±626.6	954±471.4	1102±461.1	1039±262.1
Day 0 (peak effect)	829±299.6	625±277.7	707±309.6	649±327.6
Day 7	1199±339.1	987±234.0	1070±306.6	887±387.9
Day 14	1040±277.6	1094±303.1	1179±329.7	1121±384.1

a Data were obtained from pages 214-215 of the study report.

Table 5b. Mean (±SD) session locomotor activity (ambulatory counts) in rats treated with TPTH once by gavage.[a]

Interval	Dose Level (mg/bw)			
	0	5	25	75
Males				
Pre-test	251±107.2	348±112.5	259±154.2	258±92.8
Day 0 (peak effect)	137±69.8	177±93.1	100±71.8	166±103.1
Day 7	277±99.6	329±119.7	258±143.4	246±89.0
Day 14	265±97.5	327±84.2	256±76.7	292±98.6
Females				
Pre-test	415±240.8	311±200.5	360±190.3	333±109.0
Day 0 (peak effect)	301±132.8	201±109.3	237±119.5	202±123.3
Day 7	420±155.3	346±109.9	374±134.9	312±144.4
Day 14	373±123.6	362±102.4	406±148.3	403±176.6

a Data were obtained from pages 214-215 of the study report.

F. SACRIFICE AND PATHOLOGY

1. **Gross pathology:** No treatment-related findings were observed.

2. **Brain weights and brain measurements:** No findings related to treatment were observed on brain weights or brain measurements (Table 6).

Table 6. Mean (±SD) brain weights and brain measurements in rats treated with TPTH once by gavage.[a]

Parameter	Dose Level (mg/bw)			
	0	5	25	75
Males				
Brain weight (g)	1.81±0.073	1.79±0.053	1.79±0.112	1.80±0.098
Brain length (mm)	19.8±0.78	19.9±0.53	19.9±0.63	20.0±0.54
Brain width (mm)	15.0±0.37	14.8±0.56	15.0±0.55	15.2±0.62
Females				
Brain weight (g)	1.73±0.057	1.67±0.051	1.74±0.081	1.72±0.076
Brain length (mm)	19.6±0.46	19.5±0.61	19.6±0.80	19.8±0.55
Brain width (mm)	14.4±0.59	14.6±0.52	14.7±0.62	14.6±0.67

a Data were obtained from pages 216-217 of the study report.

3. Neuropathology: Minimal, focal or multifocal axonal degenerations in the sciatic nerve or lumbar dorsal root fibers (characterized by dilated myelin sheaths containing centrally located eosinophilic globular debris) were observed in the controls (1 male, 1 female) and the 75 mg/kg group (2 males, 2 females). However, this finding was considered incidental, as axonal degeneration is a common spontaneous finding in rats and there were no corroborating findings in the more distal nerves.

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS: Based on the results of the study, the NOAEL for neurotoxicity was 75 mg/kg. The NOAEL for systemic toxicity was less than 5 mg/kg. Clinical signs of systemic toxicity were observed at all dose levels of TPTH. In addition, two deaths and transient decreases in body weight gain and food consumption during the first week were observed at 75 mg/kg.

B. REVIEWER COMMENTS: At ≥5 mg/kg, excessive grooming, increased activity upon handling, and piloerection were observed in both sexes. Gait abnormalities (rocks, sways, or lurches as it proceeds forward), decreased defecation, and decreased urination were noted in the ≥25 mg/kg groups. At 75 mg/kg, the following signs were also observed: repetitive movement of the mouth and jaws upon handling (both sexes) and following dosing (females); feces absent (both sexes); gasping (males); soft stools (males); and hunched appearance (females).

At 75 mg/kg, one male was found dead on Day 2, and one female was killed *in extremis* on Day 3. These animals displayed gasping (both animals), gait alterations (female only), and piloerection (female only). Additionally at 75 mg/kg, body weights were decreased ($p \leq 0.01$) in the males on Day 7 (↓13%), while body weight gains were decreased ($p \leq 0.05$) in both sexes on Days 0-7 (↓39-67%). Body weights in this group returned to control levels by Day 14, and overall (Day 0-14) body weight gains were similar to controls. Food consumption was decreased ($p \leq 0.01$) on Days 0-7 (↓27-31%).

The LOAEL is 5 mg/kg, based on clinical signs of toxicity (excessive grooming, increased activity on handling, and piloerection) in both sexes. The NOAEL was not established.

The submitted study is classified as **Acceptable/Guideline** and satisfies the Guideline requirements (870.6200a; OECD 424) for an acute neurotoxicity screening battery in rats.

In this definitive study, triphenyltin hydroxide did not result in signs of toxicity during the time selected for peak effect since there were no reactions to treatment reported in the FOB assessment on Day 1. TPTH toxicity appears to develop after the first day of treatment and was mostly seen in the first week. Similar observations of clinical signs in the first week following treatment were noted in the pilot dose range finding study (2001, MRID No.: 45350301). However, the pilot study reported signs of low arousal, twitches to suggest a time to peak effect of approximately 4 hours. These same reactions were not seen in the main study with more animals. Since selecting a higher dose may result in fatalities, and considering the slow response time to develop responses to treatment, this study is considered acceptable and to satisfy the guideline requirement even though there were no neurotoxic reactions noted at the time to peak effect.

C. STUDY DEFICIENCIES: The following minor deficiency was noted, but does not affect the conclusions of this report:

- Positive control studies were conducted during 1990-1991. More recent studies should be conducted for validation.
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DATA FOR ENTRY INTO ISIS

Acute Neurotoxicity Study - rats (870.6200a)

PC code	MRID #	Study type	Species	Duration	Route	Dosing method	Dose range mg/kg/day	Doses tested mg/kg/day	NOAEL mg/kg/day	LOAEL mg/kg/day	Target organ(s)	Comments
083601	45299901	acute neurotox	rats	14 days	oral	gavage	5-75	0, 5, 25, 75	Not established	5	Clinical signs	Systemic
083601	45299901	acute neurotox	rats	14 days	oral	gavage	5-75	0, 5, 25, 75	75	Not observed		Neurotoxicity

13544

R101374

Chemical:	**Fentin hydroxide**
PC Code:	**083601**
HED File Code	**13000 Tox Reviews**
Memo Date:	**06/25/2004**
File ID:	***TX0052373***
Accession Number:	**412-05-1000**

HED Records Reference Center
09/07/2004