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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**

**Date:** February 18, 2009

**SUBJECT:** Fentin Hydroxide; Review and generation of a Data Evaluation Record.

**PC Code: 083601**
**Decision No.: NA**
**Petition No.: NA**
**Risk Assessment Type: NA**
**TXR No.: 0054718**
**MRID No.: 45350301**

**DP Barcode: D 273507**
**Registration No.: NA**
**Regulatory Action: NA**
**Case No.: NA**
**CAS No.: NA**
**40 CFR: NA**

Ver.Apr.08

**FROM:** Anwar Y Dunbar, Ph.D.
Toxicologist, Risk Assessment Branch 1
Health Effects Division (HED) (7509P)

**THROUGH:** Dana Vogel,
Chief, Risk Assessment Branch 1
Health Effects Division (HED) (7509P)
And

Robert Mitkus, Ph.D.
Toxicology Team Leader, Risk Assessment Branch 1
Health Effects Division (HED) (7509P)

**TO:**
Robert McNally, Risk Manager
Registration Division (7505P)

I. Conclusions

RAB1 has reviewed this Oral Range-Finding study in rats and it is an acceptable/non-guideline Oral Range-Finding toxicity study in rats.

II. Action Requested

Please review Oral Range-Finding toxicity study in rodents.



Received in PC 3/4/2009

# DATA EVALUATION RECORD

FENTIN HYDROXIDE (TPTH)

Study Type: Non-guideline; Oral Range-Finding Acute Neurotoxicity Study in Rats

Work Assignment No. 5-1-204 (MRID 45350301)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
2777 South Crystal Drive
Arlington, VA 22202

Prepared by
Pesticides Health Effects Group
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Dynamac Corporation
1910 Sedwick Road, Bldg 100, Ste B.
Durham, NC 27713

| | |
|---|---|
| Primary Reviewer:<br>Michael E. Viana, Ph.D., D.A.B.T. | Signature: Michael E Viana<br>Date: 2/4/09 |
| Secondary Reviewer:<br>David A. McEwen, B.S. | Signature: David A. McEwen<br>Date: 2/4/09 |
| Program Manager:<br>Michael E. Viana, Ph.D., D.A.B.T. | Signature: Michael E Viana<br>Date: 2/4/09 |
| Quality Assurance:<br>Steven Brecher, Ph.D., D.A.B.T. | Signature: Steven Brecher<br>Date: 2/4/09 |

Disclaimer

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

**EPA Reviewer:** Anwar Dunbar, Ph.D. **Signature:**
**Registration Action Branch 1, Health Effects Division (7509P)** **Date:** 02-24-09
**EPA Work Assignment Manager:** Myron Ottley, Ph.D. **Signature:**
**Registration Action Branch 3, Health Effects Division (7509P)** **Date:** 2/26/2009

Template version 02/06

## DATA EVALUATION RECORD

**STUDY TYPE:** Non-guideline; Oral Range-Finding Acute Neurotoxicity Study in Rats.

**PC CODE:** 083601 **DP BARCODE:** D273507
**TXR #:** 0054718

**TEST MATERIALS (PURITY):** Fentin hydroxide (TPTH; 96% a.i.)

**SYNONYMS:** Triphenyltin hydroxide; triphenylstannylium hydroxide

**CITATION:** Nemec, M. D. (2001) An oral range-finding acute study of TPTH in rats. WIL Research Laboratories, Inc., Ashland, OH. Laboratory Study No.: WIL-399001, February 14, 2001. MRID 45350301. Unpublished.

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

**EXECUTIVE SUMMARY:** The objectives of this oral range-finding acute toxicity study (MRID 45350301) were to establish test article dose levels and to estimate the approximate time of peak effect for a definitive acute neurotoxicity study in rats. Therefore, groups of five Sprague Dawley (Crl:CD®(SD)IGS BR) rats/sex/dose level were administered a single dose of fentin hydroxide (TPTH; 96% a.i.; Lot No. ZVRAM.928K) in aqueous 0.5% methylcellulose by oral gavage (5 mL/kg) at dose levels of 10, 50, 75, or 125 mg/kg bw. Home cage and open field arena clinical examinations were performed prior to dosing and at 1, 2, 3, 4, 5, and 6 h post-dosing. The rats were also weighed and given additional detailed clinical examinations daily until scheduled euthanasia on Study Day 8 or 9.

One 125 mg/kg female (# 44817) was euthanized *in extremis* on Day 7. This animal was observed with severe body weight loss (-66 g) from Day 0 to 7, and was noted to have impaired use of the hindlimbs on the day of death, and other clinical signs similar to those detailed below. At necropsy, this animal was observed with enlarged, dark red adrenal glands, reddened gastric mucosa, yellow matting on various body areas, red matting around the eyes, and was emaciated with no abdominal adipose tissue present.

The most frequently observed clinical signs on the day of dosing were palpebral closure and piloerection, which were observed in all groups. Other frequently observed clinical signs were low arousal in the 75 and 125 mg/kg groups, and twitches in the 10, 50, and 125 mg/kg groups. The highest incidence of these signs was noted in the 125 mg/kg group. Additionally at 125 mg/kg, single observations of abnormal gait (body drag) and tremors were seen, and group mean

body temperature was reduced one hour after administration in the males (34.82°C 1 h post-dosing vs. 35.96°C prior to dosing). Based on the incidences of the treatment-related clinical signs observed in each treatment group, the approximate times of peak effect were as follows: 4 h at 10 mg/kg; 4-6 h at 50 mg/kg; 4-6 h at 75 mg/kg; and 4-5 h at 125 mg/kg.

After the day of administration, the most common treatment-related findings in the males were piloerection, rocking, lurching, and swaying when walking, decreased urination and defecation, and dried red material around nose in all dose groups; the most common findings in the females were decreased urination and defecation, rocking, lurching, and swaying when walking, and dried red material around the nose in all dose groups. Additional treatment-related findings included: wet yellow matting of the urogenital area, dried brown material at the base of the tail, dried yellow matting of the urogenitial area, dried red material around both the right and left eye, absent feces, hunched appearance, hypoactivity, eyelids slightly drooping, soft stool, and lacrimation of both the right and left eye. These findings were observed with the greatest frequency in the 125 mg/kg group, and most occurred in a dose-dependent manner.

A group mean body weight loss was observed in all dose groups on Days 0-1. The 10 mg/kg animals began to gain weight on Days 1-2 and continued to gain weight for the remainder of the study, while the 50, 75, and 125 mg/kg groups lost weight on Days 1-3, 1-4, and 1-6, respectively. Overall (Days 0-8) mean body weight gains were decreased in the 50 mg/kg group and 75 mg/kg females compared to the 10 mg/kg group, while the 75 mg/kg day males and 125 mg/kg group lost weight overall.

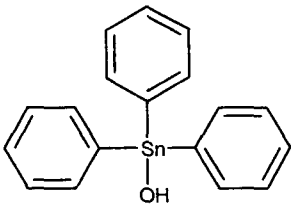
This study is classified as **acceptable/non-guideline** and provided valuable data for the determination of a time of peak effect for the proposed definitive acute neurotoxicity study.

**COMPLIANCE:** Signed and dated Data Confidentiality and Compliance statements were provided. It was stated that this was a non-GLP study that was conducted in compliance with the standard operating procedures of the performing laboratory. A Quality Assurance statement was not provided, and it was stated that neither the data nor the report were reviewed by the Quality Assurance Unit of the performing laboratory.

# I. MATERIALS AND METHODS

## A. MATERIALS

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

| | |
|---|---|
| **Description:** | Fine white powder |
| **Lot No.:** | ZVRAM.928K |
| **Purity:** | 96% a.i. |
| **Compound stability:** | Stable in the vehicle for up to 48 h at room temperature or up to 15 days refrigerated |
| **CAS # of TGAI:** | 76-87-9 |
| **Structure:** |  |



2. **Vehicle:** Aqueous 0.5% methylcellulose

3. **Test animals**

| | |
|---|---|
| **Species:** | Rat |
| **Strain:** | Crl:CD®(SD)IGS BR |
| **Age/mean weight at dosing:** | At least 8 weeks; 246-447 g males, 199-286 g females |
| **Source:** | Charles River Laboratories, Inc. (Raleigh, NC) |
| **Housing:** | On arrival, rats were housed 3/cage (by sex) for three days, then individually in wire-mesh cages suspended over cage-board |
| **Diet:** | Certified Rodent LabDiet® #5002 (PMI Nutrition International, St. Louis, MO); *ad libitum* |
| **Water:** | Reverse osmosis treated tap water ; *ad libitum* |
| **Environmental conditions:** | **Temperature:** 21.8-22.2°C<br>**Humidity:** 44.8-66.5%<br>**Air changes:** Not provided<br>**Photoperiod:** 12 hrs dark/12 hrs light |
| **Acclimation period:** | Minimum of six days |

## B. STUDY DESIGN

1. **Study objectives:** The objectives of this study were to establish test article dose levels and to estimate the approximate time of peak effect for a definitive acute neurotoxicity study in rats.

2. **In-life dates:** Start: June 8, 2000 End: June 30, 2000

3. **Animal Assignment:** The animals were randomly assigned to the dose groups shown in Table 1 based on body weight stratification in a block design.

| TABLE 1: Study design [a] | | | |
|---|---|---|---|
| Group # | Dose group (mg/kg/day) | Dose volume (mL/kg) | Concentration (mg/mL) |
| 1 | 10 | 5 | 2 |
| 2 | 50 | 5 | 10 |
| 3 | 75 | 5 | 15 |
| 4 | 125 | 5 | 25 |

a Data were obtained from page 19 of the study report.

4. **Dose preparation, administration, and analysis:** For each dose level, a weighed amount of the test material was homogenized in 0.5% aqueous methyl cellulose (approximately 70% of the final volume). The resulting suspension was then adjusted to the final volume to achieve the desired concentration. All dose formulations were prepared on the day of administration, and were administered as a single dose via oral gavage to non-fasted animals at a dose volume of 5 mL/kg. Individual doses were calculated based upon body weights recorded prior to administration. The dose formulations were constantly stirred during the administration procedure. On the day of study initiation, two formulations that bracketed the range of concentrations used in the study (0.2 and 40 mg/mL) were prepared for determination of homogeneity and stability of the test substance in the vehicle; these formulations were divided into two aliquots each, with one set stored at room temperature while the other was stored refrigerated. Duplicate samples were collected from the top, middle, and bottom zones of each concentration at 0, 1, 2, and 48 h for the room temperature aliquots and at 48 h, 8 days, and 15 days from the refrigerated aliquots for concentration, homogeneity and stability analyses.

**Results**

**Homogeneity (%CV):** 2.78-7.04%

**Stability (% initial):** 88.6-96.7% for 48 h at room temperature
91.5-103% for 15 days refrigerated

**Concentration (% nominal)** 97.3-106.5%

The reviewers note that the actual dose formulations were not analyzed for concentration; however, the concentrations of the formulations tested bracketed the concentrations used in the study and were sufficiently accurate to assure the reviewers that the actual dose formulations were acceptably close to the stated nominal concentrations. The analytical data indicated that the mixing procedure was adequate.

5. **Statistics:** Statistical analyses were limited to calculation of means and standard deviations for body weights and body weight gains. Considering the objectives of this study and noting that a concurrent control group was not included, the reviewers consider this level of analysis to be appropriate.

## C. METHODS

1. **Clinical observations and mortality:** The animals were observed twice daily for mortality and moribundity. Detailed clinical observations (a modified functional observational battery) were performed on the day of dosing prior to administration, approximately 1, 2, 3, 4, 5, and 6 h post-dosing, and then daily for seven or eight days and just prior to termination on Day 8 or 9. Animals were observed in their home cages and then in an open field arena for approximately two minutes. The technicians were blind as to the treatment group assignment of the animals. The CHECKED (X) parameters were examined.

| | HOME CAGE OBSERVATIONS | | HANDLING OBSERVATIONS | | OPEN FIELD OBSERVATIONS |
|---|---|---|---|---|---|
| X | Posture | X | Ease of removal | X | Convulsions |
| X | Convulsions (tonic and clonic) | X | Salivation | X | Tremors |
| X | Tremors | X | Lacrimation | X | Twitches |
| X | Twitches | X | Piloerection | X | Palpebral closure |
| X | Spontaneous vocalization | X | Ease of handling | X | Arousal |
| X | Palpebral closure | X | Exophthalmus | X | Posture |
| | | X | Vocalization | X | Gait |
| | | | **PHYSIOLOGICAL OBSERVATIONS** | X | Backing |
| | | X | Body weight | X | Rearing |
| | | X | Body temperature | X | Grooming |
| | | | | X | Urination |
| | | | | X | Defecation |

Data were obtained from pages 23-24 of the study report.

2. **Body weight:** Individual body weights were recorded daily on Study Day -1, and then on Days 0 through 8 or 9. Mean body weight gains were calculated for each weighing period and cumulatively from Day 0.

3. **Sacrifice and pathology:** A complete necropsy was performed on one animal that was killed *in extremis*. All other animals were euthanized by carbon dioxide asphyxiation on Day 8 or 9 and discarded.

## II. RESULTS

A. **CLINICAL OBSERVATIONS AND MORTALITY:** One 125 mg/kg female (# 44817) was euthanized *in extremis* on Day 7. This animal was observed with severe body weight loss (-66 g) from Day 0 to 7, and was noted to have impaired use of the hindlimbs on the day of death, and other clinical signs similar to those detailed below. All other rats survived to scheduled termination.

The most frequently observed clinical signs on the day of dosing were palpebral closure and piloerection, which were observed in all groups. Other frequently observed clinical signs were low arousal in the 75 and 125 mg/kg groups, and twitches in the 10, 50, and 125 mg/kg groups. The highest incidence of these signs was noted in the 125 mg/kg group. Additionally at 125 mg/kg, single observations of abnormal gait (body drag) and tremors were seen, and group mean body temperature was reduced one hour after administration in the males (34.82°C 1 h post-dosing vs. 35.96°C prior to dosing). Based on the incidences of the treatment-related clinical signs observed in each treatment group, the approximate times of peak effect were as follows: 4 h at 10 mg/kg; 4-6 h at 50 mg/kg; 4-6 h at 75 mg/kg; and 4-5 h at 125 mg/kg.

After the day of administration, the most common treatment-related findings (Table 2) in the males were piloerection, rocking, lurching, and swaying when walking, decreased urination and defecation, and dried red material around nose in all dose groups; the most common findings in the females were decreased urination and defecation, rocking, lurching, and swaying when walking, and dried red material around the nose in all dose groups. Additional treatment-related findings included: wet yellow matting of the urogenital area, dried brown material at the base of the tail, dried yellow matting of the urogenitial area, dried red material around both the right and left eye, absent feces, hunched appearance, hypoactivity, eyelids slightly drooping, soft stool, and lacrimation of both the right and left eye. These findings were observed with the greatest frequency in the 125 mg/kg group, and most occurred in a dose-dependent manner.

**TABLE 2.** Selected clinical observations (total occurrence/# of rats) in rats administered a single dose of fentin hydroxide by oral gavage.[a]

| Clinical observation | Dose (mg/kg) | | | |
|---|---|---|---|---|
| | 10 | 50 | 75 | 125 |
| **Males** | | | | |
| Piloerection | 34/5 | 37/5 | 36/5 | 23/5 |
| Rocks, lurches, or sways when walking | 2/2 | 27/5 | 28/5 | 30/5 |
| Decreased urination | 10/4 | 17/5 | 25/5 | 22/5 |
| Decreased defecation | 14/5 | 17/5 | 22/5 | 13/5 |
| Dried red material around nose | 3/2 | 4/3 | 11/3 | 12/5 |
| Wet yellow matting urogenital area | 0/0 | 5/3 | 3/2 | 16/5 |
| Dried brown material at base of tail | 0/0 | 7/3 | 18/4 | 16/4 |
| Dried yellow matting urogenital area | 0/0 | 5/3 | 8/3 | 13/5 |
| Dried red material around right eye | 0/0 | 4/3 | 12/4 | 14/5 |
| Dried red material around left eye | 0/0 | 2/2 | 12/3 | 14/5 |
| Feces absent | 0/0 | 2/1 | 3/2 | 7/4 |
| Hunched appearance | 0/0 | 0/0 | 5/3 | 4/3 |
| Hypoactive | 0/0 | 0/0 | 0/0 | 5/4 |
| Eyelids slightly drooping | 0/0 | 0/0 | 0/0 | 5/3 |
| Soft stool | 0/0 | 0/0 | 0/0 | 2/2 |
| **Females** | | | | |
| Decreased urination | 14/5 | 18/5 | 21/5 | 31/5 |
| Decreased defecation | 15/5 | 16/5 | 26/5 | 22/5 |
| Rocks, lurches, or sways when walking | 3/3 | 14/5 | 16/5 | 24/5 |
| Dried red material around nose | 1/1 | 4/3 | 12/3 | 7/2 |
| Dried red material around right eye | 0/0 | 5/3 | 7/4 | 20/5 |
| Dried red material around left eye | 0/0 | 5/3 | 10/5 | 18/5 |
| Wet yellow matting urogenital area | 0/0 | 5/3 | 6/4 | 17/4 |
| Dried yellow matting urogenital area | 0/0 | 7/4 | 14/4 | 10/4 |
| Piloerection | 0/0 | 8/5 | 14/5 | 4/4 |
| Feces absent | 0/0 | 3/3 | 4/3 | 8/4 |
| Dried brown material at base of tail | 0/0 | 1/1 | 3/2 | 8/3 |
| Dried red material left forelimb | 0/0 | 1/1 | 4/2 | 6/4 |
| Dried red material right forelimb | 0/0 | 1/1 | 5/3 | 5/3 |
| Hunched appearance | 0/0 | 0/0 | 3/2 | 8/4 |
| Eyelids slightly drooping | 0/0 | 0/0 | 0/0 | 7/4 |
| Hypoactive | 0/0 | 0/0 | 0/0 | 4/3 |
| Lacrimation left eye | 0/0 | 0/0 | 0/0 | 3/2 |
| Lacrimation right eye | 0/0 | 0/0 | 0/0 | 2/1 |

a Data were obtained from Table 1D on pages 240-245 of the study report.

**B. <u>BODY WEIGHT AND BODY WEIGHT GAINS</u>:** Body weight and body weight gain data are presented in Table 3. A group mean body weight loss was observed in all dose groups on Days 0-1. The 10 mg/kg animals began to gain weight on Days 1-2 and continued to gain weight for the remainder of the study, while the 50, 75, and 125 mg/kg groups lost weight on Days 1-3, 1-4, and 1-6, respectively. Overall (Days 0-8) mean body weight gains were decreased in the 50 mg/kg group and 75 mg/kg females compared to the 10 mg/kg group, while the 75 mg/kg day males and 125 mg/kg group lost weight overall.

**TABLE 3.** Selected mean (±SD) body weights and body weight gains (g) in rats administered a single dose of fentin hydroxide by oral gavage.[a]

| Study day | | Dose (mg/kg) | | | |
|---|---|---|---|---|---|
| | | 10 | 50 | 75 | 125 |
| **Males** | | | | | |
| Body weight | Day 0 | 312±78.0 | 320±64.4 | 328±16.1 | 283±4.6 |
| | Day 8 | 350±75.5 | 325±55.4 | 325±19.3 | 254±18.0 |
| Body weight gain | Days 0-8 | 38±11.7 | 4±14.3 | -3±6.1 | -29±20.2 |
| **Females** | | | | | |
| Body weight | Day 0 | 231±33.7 | 236±28.2 | 224±18.0 | 215±7.8 |
| | Day 8 | 242±29.5 | 238±25.2 | 227±15.9 | 188±32.3 |
| Body weight gain | Days 0-8 | 10±7.9 | 2±4.0 | 2±6.4 | -28±36.1 |

a Data were obtained from Tables 3D and 5D on pages 248-251, 257, and 259.

C. **NECROPSY:** The only animal necropsied was the 125 mg/kg female (# 44817) that was killed on Day 7. This animal was observed with enlarged, dark red adrenal glands, reddened gastric mucosa, yellow matting on various body areas, red matting around the eyes, and was emaciated with no abdominal adipose tissue present. These findings were considered to be a result of treatment.

## III. DISCUSSION AND CONCLUSIONS

A. **INVESTIGATORS CONCLUSIONS:** Due to the single mortality, extensive clinical signs of toxicity, and body weight losses observed at 125 mg/kg, this dose was considered too high to be a benchmark dose for an acute neurotoxicity study. At 75 mg/kg, clear test article-related effects were observed on clinical condition and body weight, but there was no effect on survival and the animals in this group appeared to be progressing towards full recovery at the end of the observation period. Thus, 75 mg/kg was selected as the benchmark dose, with an estimated time of peak effect of four hours after dosing.

B. **REVIEWER COMMENTS:** One 125 mg/kg female (# 44817) was euthanized *in extremis* on Day 7. This animal was observed with severe body weight loss (-66 g) from Day 0 to 7, and was noted to have impaired use of the hindlimbs on the day of death, and other clinical signs similar to those detailed below. At necropsy, this animal was observed with enlarged, dark red adrenal glands, reddened gastric mucosa, yellow matting on various body areas, red matting around the eyes, and was emaciated with no abdominal adipose tissue present.

The most frequently observed clinical signs on the day of dosing were palpebral closure and piloerection, which were observed in all groups. Other frequently observed clinical signs were low arousal in the 75 and 125 mg/kg groups, and twitches in the 10, 50, and 125 mg/kg groups. The highest incidence of these signs was noted in the 125 mg/kg group. Additionally at 125 mg/kg, single observations of abnormal gait (body drag) and tremors were seen, and group mean body temperature was reduced one hour after administration in the males (34.82°C 1 h post-dosing vs. 35.96°C prior to dosing). Based on the incidences of the treatment-related clinical signs observed in each treatment group, the approximate times of peak effect were as follows: 4 h at 10 mg/kg; 4-6 h at 50 mg/kg; 4-6 h at 75 mg/kg; and 4-5 h at 125 mg/kg.

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After the day of administration, the most common treatment-related findings in the males were piloerection, rocking, lurching, and swaying when walking, decreased urination and defecation, and dried red material around nose in all dose groups; the most common findings in the females were decreased urination and defecation, rocking, lurching, and swaying when walking, and dried red material around the nose in all dose groups. Additional treatment-related findings included: wet yellow matting of the urogenital area, dried brown material at the base of the tail, dried yellow matting of the urogenitial area, dried red material around both the right and left eye, absent feces, hunched appearance, hypoactivity, eyelids slightly drooping, soft stool, and lacrimation of both the right and left eye. These findings were observed with the greatest frequency in the 125 mg/kg group, and most occurred in a dose-dependent manner.

A group mean body weight loss was observed in all dose groups on Days 0-1. The 10 mg/kg animals began to gain weight on Days 1-2 and continued to gain weight for the remainder of the study, while the 50, 75, and 125 mg/kg groups lost weight on Days 1-3, 1-4, and 1-6, respectively. Overall (Days 0-8) mean body weight gains were decreased in the 50 mg/kg group and 75 mg/kg females compared to the 10 mg/kg group, while the 75 mg/kg day males and 125 mg/kg group lost weight overall.

Based on the results of this study, dosage levels of 5,25 and 75 mg/kg per day were selected for an acute neurotoxicity study of triphenyltin hydroxide (TPTH), with an estimated peak effect of four hours.

This study is classified as **acceptable/non-guideline** and provided valuable data for the determination of a time of peak effect for the proposed definitive acute neurotoxicity study.

C. **STUDY DEFICIENCIES:** The following minor deficiencies were noted but do not alter the conclusions of this review:

- The actual dose formulations were not analyzed for concentration; however, the concentrations of the formulations tested bracketed the concentrations used in the study and were sufficiently accurate to assure the reviewers that the actual dose formulations should be acceptably close to the nominal concentrations.
- A Quality Assurance statement was not provided, and it was stated that neither the data nor the report were reviewed by the Quality Assurance Unit of the performing laboratory.
- There was no control group included in these experiments.

13544

# R167440

**Chemical Name:** Fentin hydroxide

**PC Code:** 083601
**HED File Code:** 13000 Tox Reviews
**Memo Date:** 2/18/2009
**File ID:** TX0054718
**Accession #:** 000-00-0127

HED Records Reference Center
3/10/2009