CASWELL FILE

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

006351

OCT 7 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANC

MEMORANDUM

SUBJECT: EPA Reg. No. 8340-17 - Triphenyltin hydroxide: Review of a dog chronic feeding study submitted in August, 1987 in response to the data requirement indicated in the Registration Standard.

TOX CHEM No.: 896E
TOX PROJECT No.: 7-0958
Records No.: 201273

FROM: John Doherty 10/2/87
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TO: Lois Rossi
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THRU: Edwin Budd
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Hazard Evaluation Divison (TS-769)

10/2/87
10/7/87

The American Hoechst Co. has submitted a chronic feeding (one year) study with dogs to satisfy the data gap indicated by the Registration Standard for triphenyltin hydroxide (TPTH). Toxicology Branch (TB) has reviewed this study and the following comments apply.

402855-01

Comments

CORE classification of this study is RESERVED. The registrant will have to provide additional information before TB will consider upgrading this study.

1. The certificate of analysis of the test material will have to be provided.

2. The registrant will have to have the nervous system (brain and spinal cord) examined by a specialist in neuropathology. The neuropathologist's report should include a statement that the appropriate stains were used (in either the original pathological examination or any examination made in response to this review by TB) to assess for evidence of neuropathology that might be induced by the organotin family of compounds.

   Since the dogs have been sacrificed many months ago, the neuropathologist must clearly state that the time interval between sacrifice time and subsequent preparation of tissue will not compromise the validity of the assessment.

   It should be noted that when TB reviewed the protocol for this study, it was advised that a specialist in neuropathology assist in the design of the study related to and evaluation of the nervous system. The final report of the study was specifically supposed to include a comprehensive assessment of the pathology of the nervous system.

   The pathologist responsible for the study (Dr. Pappritz) was not indicated as being a specialist in neuropathology or as being familiar with the expected neuropathology related to organotin compounds.

3. The results of the tissue analysis for tin content will have to be provided.

Submission of the above information will not guarantee that this study will be upgraded to CORE MINIMUM or higher. TB has noted that the study does not demonstrate an effect level for any response to TPTH. Chronic feeding studies are expected to show toxic responses in the highest test dose level. Since the highest dose level tested (18 ppm) is in the range of toxic response levels (when converted to mg/kg/day) from other study types with this chemical, it may be desireable to know the LEL for this species to assist in risk assessments and determining the MOS. The decision to require or not to require a study which demonstrates a LEL for the dog will be made at a later time.

Study Reviewed

Study	Results	CORE Classification
Chronic feeding - dogs one year. RCC Itingen Switzerland #047013/047024 June, 1987.	NOEL > 18 ppm Levels tested 0, 2, 6, and 18 ppm. [Average compound consumed for males 0.062, 0.206, and 0.562 mg/kg/day and for females 0.071, 0.213, and 0.624 mg/kg/day for the low, mid and high dose groups.]	[RESERVED]

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Reviewed by: John Doherty
Section II, Tox. Branch (TS-769C)
Secondary reviewer: Edwin Budd
Section II, Tox. Branch (TS-769C)

DATA EVALUATION REPORT

STUDY TYPE: Chronic feeding (1 yr)-dog TOX. CHEM. NO.: 896E

ACCESSION NUMBER: 402855-01 (three volumes) MRID NO.: not provided

TEST MATERIAL: Triphenyltin hydroxide

SYNONYMS: TPTH, fentin hydroxide

STUDY NUMBER(S): 047013/047024

SPONSOR: American Hoechst Corporation

TESTING FACILITY: RCC (Itingen Switzerland)

TITLE OF REPORT: TPTH - Substance Technical (HOE 029664 of ZD97 0004) Chronic Oral Toxicity 52 Week Feeding Study in Beagle Dogs.

AUTHOR(S): K. Sachsse, Th. Frei, H. Luetkemeier, W. Vogel, G. Pappritz and Ch. Terrier.

REPORT ISSUED: June 1987

CONCLUSIONS:

NOEL > 18 ppm (highest dose tested)

Levels tested 0, 2, 6, and 18 ppm.

Classification: CORE-[RESERVED].

Special Review Criteria (40 CFR 154.7)

A. MATERIALS:

1. Test compound: Triphenyltin Hydroxide (TPTH), Description: powder, Batch #02782, Purity 97.2%, contaminants:

The certificate of analysis of the test article was deleted from the report as submitted. The reason for this deletion was stated as being that it "discloses identity of percentage of added inert ingredients".

This reasoning is unacceptable to TB. The test material was stated as being of 97.2% purity indicating that no inerts should have been present. The registrant will have to provide a complete description of the test material and explain fully why the certificate of analysis was deleted so that the identity of the "added inerts" would not be disclosed.

If 97.2% pure TPTH was not tested, the registrant must fully identify the test material. If 97.2% pure TPTH was used, TB would like as complete a description of the contaminants as reasonably possible.

2. Test animals: Species: dog , Strain: beagle, Age: 4-6 months, Weight: males: 5.1 - 11.8 kg, females: 5.4 - 9.6 kg, Source: Kleintierfarm Madoerin AG Switzerland.

B. STUDY DESIGN:

1. Animal assignment

Animals were assigned by computer generated random algorithm to the following test groups:

Test Group	Dose in diet (ppm)	Main Study 52 weeks male	Main Study 52 weeks female	Interim Sac. 4, 13 and 27 weeks male	Interim Sac. 4, 13 and 27 weeks female	Total (each sex)
1 Cont.	0	4	4	2*	2*	10
2 Low (2 ppm)	2	4	4	2	2	10
3 Mid (6 ppm)	6	4	4	2	2	10
4 High(18 ppm)	18	4	4	2	2	10

*two dogs of each sex per dose at each of the three interim sacrifices.

No rationale was provided in the study report for the selection of these dose levels. In a summary of this study prepared July 17, 1987 by Dr. Edward Carmines, an American Hoecsht Co.

toxicologist, it was stated that these dose levels were selected because a previous 2 year study with dogs indicated that the NOEL was considered to be 2.5 ppm. No other rational for the selection of these dose levels was provided.

2. Diet preparation

Diet was prepared twice monthly and stored at -20° C temperature. Samples of treated food were analyzed for concentration homogeneity at every two months.

Results -

The mean concentrations were analytically determined to be 82.6 (+/-12.9%) for the low dose, 79.2 (+/-11.4%) for the mid dose, and 83.1 (+/-3.3%) for the high dose group. The homogeneity of the sample diets was analytically determined to be +/-18% of the mean concentrations.

It was reported that TPTH was stable in dog feed when stored at -20°C for at least 20 days.

TB notes that the feed composition and homogeneity data indicate possible errors in preparation or faulty mixing of the test material in the diet. At least the variations noted in these parameters were considered by TB to be large.

3. Animals received food (Kliba - 335 dog maintainence diet) and water ad libitum.

4. Statistics - The following procedures were utilized in analyzing the numerical data:

Univariate one-way analysis of variance - intergroup differences.

Dunnett-test (many to one t-test) when variables were assumed to follow a normal distribution.

Steel-test (many-one rank test) when variables could not be assumed to follow a normal distribution.

5. Quality assurance:

Nine inspections were made during the inlife phase and nine reports were made (the reports were not submitted with the study). Eight other inspections were apparently made

after the inlife phase and a single report for these inspections was made on June 9, 1987.

C. METHODS AND RESULTS:

1. Observations

Animals were inspected twice daily for signs of toxicity and mortality.

Toxicity/Mortality (survival): No dogs died during the treatment period.

There were no symptoms or reactions to treatment reported.

2. Body weight

Animals were weighed weekly.

No definite effects of the test material on body weight gain were evident.

3. Food consumption and compound intake

Efficiency and compound intake were calculated from the consumption and body weight gain data. The following table illustrates the mean intake of TPTH.

	Males (in mg TPTH/kg bw/day)	Females
2 ppm	0.062	0.071
6 ppm	0.206	0.213
18 ppm	0.562	0.624

[Refer to pages 318 (males) and 323 (females)].

4. Ophthalmalogical examinations

Performed at pretest, and on weeks 4, 13, 26 and 52 weeks on all available animals using the Heine-Bifocal Ophthalmoscope.

No evidence of a test chemical related effect on the eyes was reported.

4A. Hearing tests

Each animal was evaluated at pretest and at weeks 4, 13, 26 and 52 weeks by a "simple noise test" (the exact procedure or method of quantitation was not provided).

No evidence of a test chemical related effect on hearing was reported.

5. Blood was collected before treatment and at weeks 4, 13, 26 and 52 for hematology and clinical analysis from all available animals. The CHECKED (X) parameters were examined.

a. Hematology

X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)*	X	Mean corpuscular HGB conc.(MCHC)
X	Erythrocyte count (RBC)*	X	Mean corpuscular volume (MCV)
X	Platelet count*	X	Reticulocyte count
	Blood Clotting Measurements		
X	(Thromboplastin time)	X	Nucleated erythrocytes
	(Clotting time)	X	Heinz bodies
X	(Thrombin time)	X	Red Cell Morphology
X	(Partial thromboplastin time)		

* Required for subchronic and chronic studies

Results:

There were no parameters which either the testing laboratory or TB determined to be affected by the test material.

There were some indications of increased thrombin time among the mid and high dose female groups which reached statistical significance. Examination of the data revealed that most of the individual data showed increases in thrombin time to be less than 5 seconds (greater than 5 seconds is a criteria considered acceptable for a meaningful difference). TB concurs with the rational provided by the test report which includes that the increases in thrombin time were not truely dose related and supported by other hemostatic and thrombotic disorders and the apparent effect was observed in only a single sex.

NOEL > 18 ppm.

b. Clinical Chemistry

	Electrolytes:		Other:
X	Calcium*		Albumin*
X	Chloride*	X	Blood creatinine*
	Magnesium*	X	Blood urea nitrogen*
X	Phosphorous*	X	Cholesterol*
X	Potassium*		Globulins
X	Sodium*	X	Glucose*
	Enzymes	X	Total Bilirubin* and direct
X	Alkaline phosphatase	X	Total Serum Protein*
	Cholinesterase#		Triglycerides
X	Creatinine phosphokinase*°	X	Serum protein electrophoresis
X	Lactic acid dehydrogenase	X	Uric acid
X	Serum alanine aminotransferase (also SGPT)*		
X	Serum aspartate aminotransferase (also SGOT)*		
X	gamma glutamyl transferase	X	creatinine
	glutamate dehydrogenase		
X	ornithine carbamyl transferase	X	Uric acid
X	Immunoglobulins (IgG, IgA, IgM)		

* Required for subchronic and chronic studies
\# Should be required for OP
° Not required for subchronic studies

The IgG, IgM, and IgA immunoglobulins were assessed by single radial immunodiffusion technique (J. Immunology 94:84, 1965 and Immunochemistry 2:234, 1965). Although there were no indications that TPTH affected the titers of these immunoglobulins, the assay methods used are not considered by TB to be sufficiently quantitative to determine a definite affect of a test chemical on these immunoglobulins. This study does not provide data considered by TB to indicate that TPTH does or does not affect the immune system of dogs.

Results:

There was no evidence of definite effects of TPTH on any of these parameters.

NOEL > 18 ppm.

There were noted some incidences of statistically significant increases in the protein electrophoretic pattern (particularly related to changes in the alpha-1 globulin fraction). This change was considered to be slight and not conclusively related to TPTH administration.

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6. Urinalysis

Urine was collected from fasted animals at pretest and 4, 13, 26 and 52 weeks. The CHECKED (X) parameters were examined.

X	Appearance*	X	Glucose*
	Volume*	X	Ketones*
X	Specific gravity*	X	Bilirubin*
X	pH	X	Blood*
X	Sediment (microscopic)*		Nitrate
X	Protein*	X	Urobilinogen

* Required for chronic studies
° Not required for subchronic studies

Results:

There was no evidence of definite effects of TPTH on any of these parameters.

NOEL > 18 ppm.

7. Sacrifice and Pathology -

All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs in addition were weighed.

X	Digestive system	X	Cardiovasc./Hemat.	X	Neurologic
X	Tongue	X	.Aorta*	XX	.Brain*†
X	.Salivary glands*	XX	.Heart*	X	Periph. nerve*# (sciat
X	.Esophagus*	X	.Bone marrow*	X	Spinal cord (2 levels)
X	.Stomach*	XX	.Lymph nodes* (cerv)	XX	.Pituitary*
X	.Duodenum*	XX	.Spleen*	X	Eyes *#
X	.Jejunum*	XX	.Thymus*		Glandular
X	.Ileum*		Urogenital	XX	.Adrenals*
X	.Cecum*	XX	.Kidneys*†		Lacrimal gland#
X	.Colon*	X	.Urinary bladder*	X	Mammary gland*#
X	.Rectum*	XX	.Testes*†	X	.Parathyroids*††
XX	.Liver*†	X	Epididymides	XX	.Thyroids*††
X	Gall bladder*#	X	Prostate		Other
X	.Pancreas*		Seminal vesicle	X	Bone*# (sternum)
	Respiratory	XX	Ovaries*†	X	Skeletal muscle*#
X	.Trachea*	X	Uterus*	X	Skin*#
X	.Lung*			X	All gross lesions and masses*
	Nose°				
	Pharynx°				
	Larynx°				

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* Required for subchronic and chronic studies
° Required for chronic inhalation
In subchronic studies, examined only if indicated by signs of toxicity or target organ involvement
† Organ weights required in subchronic and chronic studies
†† Organ weight required for non-rodent studies

a. Organ weight
[The organs indicated by XX were weighted.]

The weights of none of the organs showed evidence of effects of TPTH treatment.

NOEL > 18 ppm.

b. Gross pathology

There was no evidence of treatment related gross necropsy observations in any of the organs examined.

NOEL > 18 ppm.

c. Microscopic pathology
[The organs indicated by X were examined microscopically.]

No treatment related pathological findings either non-neoplastic or neoplastic were reported.

NOEL > 18 ppm.

The pathologist responsible for the compilation of the histopathology data was Dr. Guenter Pappritz (Veterinary Pathologist). Pathomorphological examiniation was performed on 32 dogs (16 males and 16 females). The dogs in the interim sacrifice groups were apparently not examined by this pathologist and there is no evidence that they were examined.

The tissues were said to have been fixed in neutral phosphate buffered 10% formalin (except for the eyes). The sections were said to have been cut at the level of 4 micrometers thickness and stained in hematoxylin and eosin.

No evidence that a specialist is neuropathology or one who had a knowledge of the expected neuropathological responses to organotin compounds assisted in the preparation of or the analysis of the slides of the brain or nerve tissue was presented.

D. DISCUSSION:

The testing laboratory reports that the NOEL for the study is > 18 ppm for both sexes or the highest dose level tested. On the basis of the data presented, TB concurs that the NOEL for the study is > 18 ppm. No Least Effective Level (LEL) for potential toxic responses of dogs to TPTH was established.

The CORE classification of this study is RESERVED.

The certificate of analysis for the test material confirming that the test material was 97.2% pure TPTH must be provided. The registrant must also submit an assessment of this study especially prepared by a neuropathologist verifying that the histopathological techniques used were sufficient to determine if the nervous system (particularly the brain and spinal cord) were affected. The neuropathologist must demonstrate that the lesion types typical of those induced by organotin chemicals were looked for in the most appropriate manner.

[Note: the study report states that some tissues were analyzed for tin content and the report on this aspect of the study will be submitted at a later time.]