CASWELL FILE

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

006236

AUG 27 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Reg. No. 8340-17 - Triphenyltin Hydroxide: Review of subchronic inhalation and metabolism studies in rats submitted in response to data requirements listed in the Registration Standard.

TOX CHEM. No.: 896E
TOX PROJECT No.: 7-0362
Record No.: 187934

FROM: John Doherty John Doherty 8/18/87
Toxicology Branch
Hazard Evaluation Division (TS-769)

TO: Lois Rossi
Product Manager #21
Registration Division (TS-767)

THRU: Edwin Budd
Section Head
Toxicology Branch
Hazard Evaluation Division (TS-769) 8/19/87 8/27/87

The American Hoechst Corporation has submitted inhalation and metabolism studies in rats with triphenyltin hydroxide (TPTH) to fulfill data requirements indicated in the Toxicology Branch (TB) chapter for the Registration Standard for this chemical. The studies were reviewed and the Data Evaluation Records (DERs) are attached. The following comments apply.

40029401
02
40029403
40029404

-06
-07

Toxicology Branch Comments.

1. Inhalation studies.

The study designed to be the definitive subchronic inhalation study (RCC Project No. 046157) was determined to be INVALID.

Based on the results of the preliminary range finding study with TPTH (RCC Project No. 048756), it was indicated that this chemical caused 60% deaths after 2 exposures to an atmospheric concentration of 10 ug (of TPTH)/l. In the definitive study where the highest dose level tested was supposedly 5 ug (of TPTH) /l for 64 exposures, there were few or very limited definite toxicity responses (aside from some signs of behavioral responses) in the test animals. Based on expectations from the preliminary study, considerable more toxicity should have been observed in this study. Thus, the potential inhalational toxicity of TPTH was not considered by Toxicology Branch (TB) to have been defined by this study.

The probable reason for the apparent discrepancies between the studies was that in the study designed to be the definitive subchronic study, TPTH was mixed with a carrier (talcum powder) so that it could be easily generated into the atmosphere. In the pilot study TPTH was generated into the test chamber without a carrier. TB recognizes three major problems with the procedure of using talcum powder as a carrier which contributed to rendering the the study INVALID as follows:

i. There were discrepancies and/or inconsistencies in the reporting of the particle sizes of the talcum powder particles. The pilot study with talcum powder alone (RCC Study No. 052942) reported that 100% of the particles were > 7 micrometers. The pilot study with TPTH carried into the atmosphere with talcum powder (RCC Study No. 051390) and the definitive study (RCC Study No. 046157) reported that the particle sizes were < 7 micrometers for 33% of the atmospheric particles. Particle sizes of 7 micrometers or less are considered to be respirable by the rat. Since probably at least 67% of the particles were > 7 micrometers (although the pilot study with talcum powder alone indicated that all particles were > 7) most of the particles were considered too large to be respirable for this species.

ii. Although particle size and atmospheric concentrations of TPTH were determined, there is no way to determine what the weight/weight ratio of TPTH per se to talcum powder was for those particles which were of respireable size. It is

quite possible that the respired particles contained a concentration of TPTH that was substantially lower than the atmospheric concentration as determined. Overall it is not possible based on available information to determine the concentration of TPTH that the rats were actually exposed to.

iii. The rats in the definitive study developed "foreign body pneumonia" apparently due to the talcum powder since the rats in the talcum powder control group but not the air control group developed this condition. This condition may have both obscured an effect of TPTH in the lung and/or it may have interfered with the absorption of TPTH. Thus, talcum powder is clearly not an innocuous vehicle (or carrier) and its use confounded interpretation of the study results to an unacceptable degree.

Thus, a satisfactory subchronic inhalation study which clearly demonstrates a NOEL for toxicity responses has not yet been provided to the Agency and this requirement remains unfulfilled.

2. Metabolism Studies.

The metabolism studies submitted when taken together were determined to be SUPPLEMENTARY and the requirement for a metabolism study is not fully satisfied. An additional study is required using either ^{113}Sn or ^{119}Sn - TPTH as the test material. This future study with radioactive tin should clarify the amount of organotin compounds and tin that are absorbed from the gastro-intestinal tract. The study should also clarify if the male gonad selectively accumulates labelled material and should carefully assess the remains of the gastro-intestinal wall for residual label.

STUDIES REVIEWED

Study	Result	CORE Classification
Subchronic inhalation-rats Pilot study - 3 days using technical TPTH without a carrier.	Exposure to 10 ug/l for 3 days resulted in 60% deaths and at 100 ug/l 90% deaths.	SUPPLEMENTARY
Subchronic inhalation-rats Pilot study - 5 days using talcum powder only without TPTH.	Exposure to 100 ug/l for 6 hours per day did not affect the rats. 100% of particles reported as being > 7 micrometers in size.	SUPPLEMENTARY
Subchronic inhalation-rats Pilot study - 9 days using TPTH mixed with talcum powder	Possible decreases in liver, heart, and kidney weight especially in males at 1 and 5 ug/l and body weight decreases of 5-8% at 5 ug/l and moderate rales.	SUPPLEMENTARY
Subchronic inhalation-rats Definitive study - 90 days (64-6 hour-exposures) using TPTH and talcum powder as carrier.	Use of talcum powder compromises interpretation of the study. Rats develop "foreign body pneumonia" due to talcum powder but show few signs of definite TPTH toxicity except for behavioral signs (rales and sedation etc.)	INVALID
Metabolism-rats Excretion and principle metabolites	Most ^{14}C excreted in the feces. ^{14}C in urine results from benzene metabolism and conjugation. Very little intact TPTH absorbed.	See summary below.
Metabolism-rats Kinetics and tissue retention	Excretion is biphasic, first phase with half-life of about 10 hours, second phase half-life > 50 hours. Residues in tissues < 1 ug equivalent/gm, but females appear to retain more than males.	See summary below.

Metabolism-rats Summary	Resummarizes the results of the above two studies and compares with previously published studies.	SUPPLEMENTARY (two studies taken together).
Metabolism-rats Absorption of ^{113}Sn triphenyltin chloride.	Most ^{113}Sn found in the feces (>80%), little found in the urine (about 3%). Organs retain only about 0.5% and indicate that the testis may accumulate a disproportionally higher amount. Study does not define the extent of gastro-intestinal absorption.	SUPPLEMENTARY

Reviewed By: J.D. Doherty
Section II, Toxicology Branch (TS-769C)
Secondary Reviewer: E.R. Budd
Section II, Toxicology Branch (TS-769C)

006236

DATA EVALUATION REPORT

Study Type: 82-4 (Pilot) Subchronic Inhalation

Tox. Chem. No. 896E
MRID No.: N/A

Accession No.: 400294-01

Test Material: Triphenyltin Hydroxide (Technical Powder)

Synonyms: TPTH

Study No.(s): 048756

Sponsor: American Hoechst Corporation

Testing Facility: Research and Consulting Co. (RCC), Switzerland

Title of Report: 3-Day Inhalation Toxicity (Range-Finding) Study with TPTH - Technical Powder in the Rat

Author(s): L. Ullmann

Report Issued: December 11, 1985

Conclusions:

Study terminated at day 3 of scheduled 5 day study because of excess deaths (60 percent in group exposed to 10 mg/m^3 and 90 percent in the group exposed to 100 mg/m^3). Author maintains that generating system would not generate a lower concentration of TPTH and that future studies would have to use TPTH dispersed in talcum powder.

Classification: Core-Supplementary.

Special Review Criteria (40 CFR 154.7): N/A.

Review:

The purpose of this study was to serve as a range-finding study to determine the dose levels, method of atmosphere generation, and other conditions to test TPTH in a definitive subchronic inhalation study.

Three groups of Wister rats (five males and five females) were exposed to atmospheres containing either 0, a low dose (est. 10 mg/m^3) and a high dose (est. 100 mg/m^3). The dosing was scheduled to be for 6 hours per day for 5 days.

The aerosol was reported as being generated by a nozzle. In particular, the powdered TPTH (97.2% purity) was supplied to the nozzle by a Grafix Exaktomat Injector into a high velocity air stream which discharged into the chamber. The air flow was set at 1000 L/hour. Within the chamber, the rats were positioned radially around the exposure chamber with their snouts and nostrils exposed to the aerosols.

Samples for analysis of the atmospheric concentrations were taken from the regions of the animals' snouts. Samples were taken using selection filters (pore size 0.2 micrometers and 50 mm in diameter). The sample air concentration was determined gravimetrically. Aerosol particle size determinations were also performed twice daily using a 4-stage Cascade Impactor.

Using these methods, the atmospheric concentrations for the low and high dose exposure groups were gravimetrically determined to be 10.5 mg/m^3 and 103 mg/m^3. The particle size studies showed that 30 to 85 percent of the particles were < 7 micrometers in diameter for most of the determinations made.

Nine of the rats in the high dose group died at day 3, four males and two females died by day 3 in the low dose group. None of the rats in the control group died. The experiment was terminated at day 3 because of excess mortality.

The symptoms which appeared in the rats dosed with TPTH included moderate to severe sedation, severe dyspnea, ruffled fur and crying with rales. The experiment was considered of too short a duration for body weight and food consumption data to be interpretable.

Pathology revealed discoloration (partly focal) of the lungs as the principal macroscopic finding. Meteorism (gas) of the small intestine was also reported in the high-dose test group.

Conclusion:

This study is SUPPLEMENTARY. The data indicate that TPTH is highly toxic via the inhalational route of exposure. The LC_{50} for 2 to 3 days of exposure for 6 hours per day would be estimated to be < 10 mg/m^3. The study report maintains that lower atmospheric dose levels of TPTH could not be generated using this method.

Reviewed By: J.D. Donerty
Section II, Toxicology Branch (TS-769C)
Secondary Reviewer: E.R. Budd
Section II, Toxicology Branch (TS-769C)

006236

DATA EVALUATION REPORT

Study Type: 82-4 (Pilot) Subchronic Inhalation

Tox. Chem. No.: 896B
MRID No.: N/A

Accession No.: 400294-02

Test Material: Talcum powder

Synonyms:

Study No.(s): 052942

Sponsor: American Hoechst Corporation

Testing Facility: Research and Consulting Company (RCC), Switzerland

Title of Report: 5-Day Inhalation Toxicity (Range-Finding) Study with Talcum Powder in the Rat

Author(s): L. Ullmann

Report Issued: January 8, 1986

Conclusions:

No effects noted in rats exposed to 100 mg/m^3 talcum powder for 5 days, 6 hours per day. Particle size of talcum powder was > 7 micrometers for 100% of the particles.

Classification: Core-Supplementary.

Special Review Criteria (40 CFR 154.7): N/A.

Review:

The purpose of this study was to assess the inhalation toxicity of talcum powder because future studies will assess the inhalational toxicity of TPTH dispersed in talcum powder.

In this study a single group of five male and five female Wistar rats were exposed to an atmosphere 100 mg/m^3 of talcum powder for a total of 5 consecutive days at 6 hours per day.

The test material was administered to the chamber by generation through a nozzle by injection with a Grafix Exaktomat Injector.

The atmospheric concentration was determined by a gravimetric technique which sampled the air twice daily. Particle size was determined using a 4-stage Cascade Impactor. Analyses determined that the atmospheric concentration was 104 +/-5.4 mg/m^3 (92 to 113 range). The particle size was, however, > 7 micrometers for 100% of the particles.

No deaths, signs of local or systemic symptoms were noted. No changes in food consumption or body weight gain or in organ weights at necropsy were reported.

Conclusion:

This study is SUPPLEMENTARY. Data were generated which demonstrated that talcum powder at an atmospheric concentration of 100 mg/m^3 does not affect the rats.

The study, however, also showed that the particle size of the talcum powder was > 7 micrometers and thus may not have been respirable. For example, the particle size was described as being > 7 micrometers for 100% of the particles.

Reviewed By: J.D. Doherty
Section II, Toxicology Branch (TS-769C)
Secondary Reviewer: E.R. Budd
Section II, Toxicology Branch (TS-769C)

006236

DATA EVALUATION REPORT

Study Type: 82-4 (Pilot) Subchronic Inhalation

Tox. Chem. No. 896E
MRID No.: N/A

Accession No.: 400294-03

Test Material: Triphenyltin Hydroxide (in Talcum Powder)

Synonyms: TPTH

Study No.(s): 051390

Sponsor: American Hoechst Corporation

Testing Facility: Research and Consulting Co. (RCC), Switzerland

Title of Report: 9-Day Inhalation Toxicity (Range-Finding) Study with TPTH Technical Powder Dispersed in Talcum Powder in the Rat

Author(s): L. Ullmann

Report Issued: December 13, 1985

Conclusions:

Range-finding study indicates that dose levels for the definitive study should be 0, 0.1, 1, and 5 mg/m^3 of TPTH in talcum powder. Dose levels of 1 and 5 mg/m^3 result in "rales," and possibly decreases in liver, heart, and kidney weight especially in males. At 5 mg/m^3 body weight decreases of 5 to 8 percent.

Classification: Core-Supplementary.

Special Review Criteria (40 CFR 154.7): N/A.

11

Review:

The purpose of this study was to serve as a dose range-finding study to determine the dose levels and other parameters to be used in the definitive 90-day inhalation study.

In this study, three groups of Wistar rats (five males and five females per group) were exposed to atmospheres containing either 0.1 mg, 1 mg, or 5 mg of TPTH for 6 hours daily for 9 exposure days (5 days per week). The TPTH (97.2% purity) was dispersed into talcum powder and each dose level received an atmosphere containing about 100 mg/m^3 of talcum powder containing either 0.1 percent, 1.0 percent, or 5 percent TPTH.

The TPTH (dispersed in talcum powder) was generated into the chambers via a nozzle and a Grafix Exaktomat Injector. Atmospheric concentrations were determined gravimetrically and shown to be 101 to 105 mg/m^3 of talcum powder. The atmospheres were apparently not specifically analyzed for TPTH. Particle size of the atmosphere was determined by a 4-stage Cascade Impactor. The report stated that the mean particle sizes were between 1 and 7 micrometers for 38 percent of the low dose, 17 percent of the mid dose, and 59 percent of the high-dose test groups. The remainder were > 7 micrometers.

Note: In the preceding study (#052942) with talcum powder, 100% of the particles were > 7 micrometers. This is inconsistent with the results in this study where the range of the mean for particles > 7 microns was 41-83%. It is apparent that from exposure to exposure and from study to study, the percent of particles in the respireable range (< 7 micrometers) is highly variable and does not appear to be related to dose level. Furthermore, for the particles that were in the respireable range, there was no reason to assume that the percent TPTH on a weight/weight basis was exactly the same as for the larger particles in the chamber. Thus, the percent composition of the respireable particles (with respect to TPTH and talcum powder was unknown. Therefore, it was not possible to determine the concentration or amount of respireable TPTH *per se* the animals were actually exposed to.

The exposure chamber provided that the rats were positioned radially such that their snouts and nostrils were exposed to the aerosol.

None of the rats died as a result of exposure. No symptoms were reported in the rats in the low-dose group. In the mid-dose group, both the males and the females developed "slight rales." The high-dose group developed "moderate rales" and at an earlier time (day 4 vs. day 9). In addition, the rats in the high-dose group developed slight to moderate reddened eyes and rhinorrhea.

Food consumption was reported as being decreased in the high-dose group relative to the control group for both males and females. Body weight decreases were also reported for the high-dose group and described as slight (-5% males and -8% females).

No macroscopic organ changes were reported. The lungs apparently were within normal appearing limits.

The heart, liver, and kidney weights, particularly among males, were decreased as indicated in the following table.

	Males		Females	
	Mid	High	Mid	High
Heart	-6%NS (-9%**)	-10%** (-6%NS)	-8%NS (-6%NS)	-14%* (-6%NS)
Liver	-8%NS (11%*)	-17%** (-13%**)	-- --	-6%NS (+2%)
Kidneys	-7% (-32%**)	-13%** (-31%**)	-5%NS --	-8%NS --

** $p < .01$, * $p < .05$ when compared to the low dose group.
( ) Data are for relative weight.
-- Essentially the same as the low-dose group.

Before TB concludes that the above organ weight changes are a result of TPTH exposure, TB will determine if similar changes are also evident in the definitive study.

Conclusion:

This study is SUPPLEMENTARY. The study author concluded that based on the range-finding data generated, the atmospheric dose levels for the definitive 90-day study should be 0.1, 1.0, and 5.0 mg TPTH-technical powder/m^3 of air. The study should also include a negative control of 0 mg/m^3 and a talcum powder control group with "5 mg/m^3." This statement apparently should have read "100 mg/m^3" for the talcum powder control.

It is also noted that the method of generation does not produce atmospheres of consistent particle size composition. In many individual cases the particles were essentially all greater than 7 micrometers and may not have been respirable. For reasons presented in the preceding note (page R-7), it was not possible to determine the concentration or amount of respirable TPTH per se the rats were actually exposed to.

Reviewed By: J.D. Doherty
Section II, Toxicology Branch (TS-769C)
Secondary Reviewer: E.R. Budd
Section II, Toxicology Branch (TS-769C)

006236

DATA EVALUATION REPORT

Study Type: 82-4: Subchronic Inhalation

Tox. Chem. No. 896E
MRID No.: N/A

Accession No.: 400294-04

Test Material: Triphenyltin Hydroxide

Synonyms: TPTH

Study No.(s): 046157

Sponsor: American Hoechst Corporation

Testing Facility: Research and Consulting Co. (RCC), Switzerland

Title of Report: Subchronic (90-Day) Inhalation Toxicity with Fentinhydroxide-Technical Grade in the Rat

Author(s): L. Ullmann

Report Issued: November 14, 1986

Conclusions:

Study is compromised by "foreign body pneumonia" due to the presence of talcum powder used in generating the atmosphere. TB has also determined that the concentration or total amount of respirable TPTH per se the rats were actually exposed to cannot be determined. Study did not define the potential subchronic inhalation toxicity as indicated by preliminary pilot studies and a previous subchronic inhalation study.

Classification: Core-INVALID.

Special Review Criteria (40 CFR 154.7): N/A.

Experimental:

Five groups of 15 male and 15 female Wister rats were exposed to atmospheres containing either air only, talcum powder, or 0.1, 1.0, or 5.0 mg/m^3 of TPTH (97.2% purity) dispersed in talcum powder. The atmospheric concentration of talcum powder was 100 mg/m^3 for each of the groups except the air control group. These rats were exposed for a total of 64 exposures over a 90 day period which consisted of exposure for 5 days per week. Each exposure was for 6 hours daily. At the end of the exposure period 10 males and 10 females from each group were sacrificed and the remaining 5 of each sex were allowed 4 weeks to recover from any exposure related effects.

The exposure chamber consisted of a 100 liter polyvinyl chloride nose-only chambers, thus only their snouts and nostrils were exposed to the atmospheres containing TPTH.

The TPTH was generated into the test chamber by means of a Grafix Exaktomat Injector which calibrated the amount of talcum powder (containing the TPTH at a specified concentration) into an air stream which went into the chamber. The chambers were sampled periodically by drawing the atmosphere from a region near the snouts of the rats through Selectron filters. The trapped material was chemically analyzed for TPTH content. The results of the analyses revealed that the atmospheric concentrations were 0.09 $\pm$ 0.02, 0.94 $\pm$ 0.17, and 4.05 $\pm$ 0.72 mg/m^3 for the low-, mid-dose, and high-dose test groups in the proximity of the snouts. These values are 80 to 90 percent of nominal concentrations of TPTH given. The talcum powder was determined to be 100 to 101 mg/m^3 (+/-8 or 9%) or within the expected range for the low-, mid-, and high-dose test groups and the talcum powder control group.

Particle size of the atmosphere was determined by a 4-stage Cascade Impactor. Analyses revealed that the particles were greater than 7 micrometers for 50 percent of the particles for each of the test dose groups. On average the particle size was less than 7 micrometers for 32 to 34 percent of the particles.

Note: Here again there is an inconsistancy in the reporting of the particle size which was first indicated as being > 7 micrometers for 100% of the talcum powder particles in the first study (#052942) with talcum powder. Although particle sizes and atmospheric concentrations were provided, no evidence was presented that all of the particles were of consistent TPTH composition on a weight/weight basis (TPTH/talcum powder). Thus the amount of TPTH which the rats were actually exposed to (particles < 7 micrometers) could not be assessed.

Results:

No rats died as a result of exposure. The following exposure-related symptoms were reported in the groups receiving 1 or 5 mg/m^3 of TPTH.

The only symptom reported in the mid-dose group (1 mg/m^3) was "rales" and this was evident only in the later 45 days of the study and during recovery.

Rales, sedation, dyspnea, ruffled fur, and alopecia were reported in the high dose males and females with some of the symptoms starting as early as day 8. The laboratory report states that "rales" were a consequence of the presence of talcum powder in the test atmosphere. TB does not concur with this conclusion. For example, two other test groups in this study and one in the 9-day pilot study did not develop "rales" and in this study and in the pilot study both the mid (1 mg/m^3) and high (5 mg/m^3) dose test groups developed "rales". Thus, the rales are apparently a dose related consequence of exposure to TPTH.

Food consumption was decreased between days 1 to 15 in the high-dose group males but in females there was only noted a decrease in food consumption on days 8 to 15.

Body weight gain in the high-dose group males was reported as being slightly decreased (not significantly). Female body weight did not show indications of a decrease.

Opthalmoscopic examinations performed at pretest and at termination were reported as being unremarkable.

Extensive hematological, clinical biochemistry and urinalysis were carried out at weeks 4, 13 and 17.

Hematological analyses consisted of quantitation of RBCs, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count, reticulocyte count, nucleated erythrocytes, normoblasts, Heinz bodies, total leukocyte count, differential leukocyte count, red cell morphology, coagulation (thromboplastin time and partial thromboplastin time). The following possible (but indefinite) effects were noted:

1. Decrease in mean corpuscular hemoglobin (< 5%, no dose response) and mean corpuscular hemoglobin concentration (about 2%), no dose response among the males.

2. Increase in coagulation time in the females (about 6%).

Clinical chemistry assessment consisted of determination

86

of blood glucose, urea, creatinine, bilirubin (total and direct), cholesterol, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, creatine kinase, alkaline phosphatase, gamma-glutamyl transferase, ornithine carbamyl transferase, calcium, phosphorous, sodium, potassium, chloride, protein (total and electrophoresis), and immunoglobulin IgG.

Slight increases in aspartate (+22%) and alanine (+29%) aminotransferase in the high-dose group were reported at the end of 13 weeks but these enzyme levels were equivalent to the control groups after the recovery period. Increases in the levels of these enzymes together with slight increases in other enzymes indicate a possible reversible liver or lung damage.

No consistent test chemical related increases or decreases in the levels of I_gG were noted when measured by a single radial immunodiffusion technique.

Urinalysis (most parameters assessed by Chem-Stix) included assessment of volume, specific gravity, pH, protein, glucose, ketone, bilirubin, blood, urobilinogen, and sediment. No test chemical related effects were noted on these parameters.

Organ weight data. The liver, thymus, kidneys, adrenals, and testes were weighed after 90 days and for the group which was allowed to recover.

No consistent differences in the weights of these organs were evident for either absolute weight or relative weight. The indications of possible effects (weight decreases) in the heart, liver, and kidney as indicated in the pilot study were not confirmed in this study.

A serious omission from this study is that the lungs were not weighted. The pathological evaluation of the lungs indicated that the test mixture (with and without TPTH) caused a "foreign body pneumonia." It is possible that such a pneumonia prevented absorption of TPTH. Also, spleens and thyroid glands were not weighted and these organs are important in indicating possible immunotoxic effects.

Pathology

No dose-related gross pathology lesions were reported.

Dr. Burkhard Schlotke, Veterinary Pathologist, was the pathologist responisble for evaluating the tissue slides. Complete histologic examination was performed on all animals in the control (air), talcum powder control, and the high dose test groups. Only lungs, nasal cavity, nasopharynx, turbinates, spleen, thymus, and gross lesions were examined histologically for the remaining dose

groups (low and mid dose test groups).

All of the rats treated with either talcum powder alone or talcum powder mixed with TPTH were reported as developing chronic "foreign body pneumonia" which was characterized by the presence of "alveolar macrophages" ladened with "birefringent particles." More severe cases were associated with alveolar cell hyperplasia and lymphoid cell infiltration. No relationship between severity of the "foreign body pneumonia" and content of TPTH in the talcum powder was reported. This "foreign body pneumonia" did not reverse during the 4 week recovery period. All other microscopic findings were considered to be spontaneous in nature.

Conclusion:

This study is INVALID. This study fails to define or describe the potential subchronic inhalation toxicity of TPTH. The use of talcum powder seriously compromises the study to justify the INVALID classification. Exposure to talcum powder resulted in the rats developing "foreign body pneumonia" which was apparently so severe that the rats did not recover during the 4 week recovery period. Such treatment may have affected the lung such that TPTH was not absorbed. The use of talcum powder also resulted in much less than one-half of the TPTH particle being less than the 7 microns meaning that much more than half were not considered to be of a respirable size in this species. It was not possible to determine the concentrations or amount of respirable TPTH per se that rats were actually exposed to.

The study did not demonstrate toxicity which would be expected for the levels of TPTH tested based on a preliminary pilot study (#048756) and a previously submitted subchronic inhalation study (conducted by Cannon Laboratories). These studies were conducted without talcum powder and one of these, a preliminary study reviewed previously in this memo, indicated that 60% of the rats died when exposed to TPTH at 10 mg/m^3. 90% deaths were obtained when the rats were exposed to 100 mg/m^3. The definitive study should have indicated signs of serious (potentially life threatening) toxicity at the dose level of 5 mg/m^3. The symptoms noted at this level were considered by TB to be too vague to be definite.

Reviewed By: J.D. Doherty
Section II, Toxicology Branch (TS-769C)
Secondary Reviewer: E.R. Budd
Section II, Toxicology Branch (TS-769C)

006236

DATA EVALUATION REPORT

Study Type: 85-1 Metabolism (Rats)

Tox. Chem. No. 896E
MRID No.: N/A

Accession No.: 400294-06

Test Material: Triphenyltin Hydroxide (^{14}C-phenyl labeled)

Synonyms: TPTH

Study No.(s): CM011/85

Sponsor: Hoechst

Testing Facility: Hoechst Aktiengesellschaft, West Germany

Title of Report: Metabolism in Rats After Single and Repeated Oral Administration at the Two Dosage Levels 2 and 10 mg/kg body weight.

Author(s): W.L. Burkle

Report Issued: October 29, 1986

Conclusions:

Most of the ^{14}C-(phenyl) TPTH was found in feces. Urinary metabolites represent split off benzene which was metabolized, conjugated, and excreted. No organotin compounds found in the urine.

Classification: Refer to Metabolism Summary Review

Special Review Criteria (40 CFR 154.7): N/A.

Review:

In this study the following parameters were investigated:

1. Rate and degree of excretion.

2. Potential enzymatic induction after repeated applications.

3. Nature and amount of important metabolites.

To study these parameters, groups of 5 or 10 male and female rats (Wister, 7 to 14 weeks of age) were dosed by stomach tube with one of the following schedules.

a. A single dose of 2 mg/kg of ^{14}C TPTH.
b. A single dose of 10 mg/kg of ^{14}C TPTH.
c. 14 daily doses of 2 mg/kg of unlabeled TPTH followed on the 15th day by a single 2 mg/kg dose of ^{14}C TPTH.

The ^{14}C labeled TPTH was phenyl-U-^{14}C labeled such that the probability that each of the three phenyl groups was labeled with ^{14}C was equal.

Following administration, extensive efforts to determine the absorption, excretion, and identification of the urinary and fecal metabolites were made. For the studies designed to identify the metabolites, the samples were pooled from each group. Technical procedures used to assist in identification of the metabolites included TLC, HPLC, gas chromatography/mass spectrometry, enzyme treatment (beta-glucuronidase and arylsulfatase) as well as other techniques to quantitate the material which volatized from the feces.

Results:

Table 1 (zeroxed from the study report) attached depicts and compares the urinary and fecal excretion of labeled ^{14}C TPTH following each of the three different administration protocols. There was little difference in the groups receiving 2 or 10 mg/kg but the group receiving 2 mg/kg/day for 14 days appeared to excrete more in the urine. In all cases, most of the material was excreted within 48 hours and the labeled material was largely in the feces.

Analysis of the feces indicated that most (63.93% as reported) of the radioactivity was unchanged parent compound for all groups. Diphenyltin was identified as 2 to 24 percent of the starting material and 1 to 11 percent was believed to be monophenyl tin compounds.

Since less than 100 percent (75.8 to 91.2%) of the administered

doses could be collected in the total urine and feces samples, attempts were made to analyze the feces for volatile radioactivity. This analysis revealed that ^{14}C benzene volatized from the feces at the approximate rate of 3 percent per 24 hours.

All of the urinary metabolites were reported as being polar. Using enzyme and acid hydrolysis, the radioactive components of the urine were identified as "mainly phenol" with lesser amounts of hydroquinone, catechol, and resorcinol. They were excreted as conjugates with sulfuric acid, and phenol was conjugated with mercapturic acid. No organotin metabolites were detected in the urine.

The proposed metabolic scheme based on these study results is depicted in Figure 8 zeroxed from the study report attached.

Conclusion:

The study reports that the metabolism of TPTH is mostly in the stomach and/or intestine such that organotin compounds are not eliminated in the urine. There could still be some passage of organotin compounds from the gut to inside the body but they would be hydrolyzed to benzene before excretion. Indeed, the pattern of urinary excretion of radiolabeled TPTH in the urine is the same as for benzene. For example, the benzene split off of TPTH becomes oxidized, conjugated, and excreted.

The study does provide useful information on the principle route of excretion, the rate of excretion (half-life for elimination) as well as identification of metabolites. No data were presented which firmly established enzyme induction after repeated applications although there was a higher rate of excretion of radiolabelled products in the urine following repeated dosing.

Additional comments on the metabolism of ^{14}C-TPTH are in the following review.

Attachments.

TPTH toxicology review

Page _____ is not included in this copy.

Pages 22 through 23 are not included in this copy.

The material not included contains the following type of information:

___ Identity of product inert ingredients

___ Identity of product impurities

___ Description of the product manufacturing process

___ Description of product quality control procedures

___ Identity of the source of product ingredients

___ Sales or other commercial/financial information

___ A draft product label

___ The product confidential statement of formula

___ Information about a pending registration action

X FIFRA registration data

___ The document is a duplicate of page(s) _____

___ The document is not responsive to the request

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Reviewed By: J.D. Doherty
Section II, Toxicology Branch (TS-769C)
Secondary Reviewer: E.R. Budd
Section II, Toxicology Branch (TS-769C)

006236

DATA EVALUATION REPORT

Study Type: 85-1 Metabolism (Rat)

Tox. Chem. No. 896E
MRID No.: N/A

Accession No.: 400294-07

Test Material: Triphenyltin Hydroxide (^{14}C-phenyl labeled)

Synonyms: TPTH

Study No.(s): TEP No. 111/1-111/5; 111/12; 111/13.1 and Report No. 01-L42-0489-86)

Sponsor: Hoechst

Testing Facility: Hoechst Aktiengesellschaft

Title of Report: Kinetics in the Rat Following Single and Repeated Administration of 2 mg/kg and Single Administration of 10 mg/kg Body Weight.

Author(s): H.M. Kellner and H.G. Eckert

Report Issued: September 30, 1986

Conclusions:

Excretion of ^{14}C following ^{14}C TPTH was biphasic with half-lives of $\sim$10 hours for the first phase and > 50 hours or longer for the second phase. Residues in tissue were higher in females than males and the liver had the highest level (< 1 ug/eq/g).

Classification: Refer to Metabolism Summary Review

Special Review Criteria (40 CFR 154.7): N/A.

Review:

This study was conducted in conjunction with the previous study to assess the overall metabolism, tissue retention and pharmacokinetics of TPTH in rats. The particular objectives of this study were to examine the following parameters.

- Distribution of the test substance in the organs, tissues, and fluid compartments following single or repeated admnistration of various dosages.

- The rate and extent of excretion.

- Possible bioaccumulation after repeated administration.

To study these parameters, TPTH was administered in the radioactive form to both male and female rats by gavage using sesame oil to disperse the test material. Treatment consisted of dosing groups of rats with either 2 or 10 mg/kg in a single dose (with ^{14}C TPTH) or 2 mg/kg/day of unlabeled TPTH followed on the 15th day with 2 mg/kg of ^{14}C labeled TPTH. A group of rats were also dosed with 2 mg/kg/day intravenously.

For these studies, the Wistar rat (10 to 16 weeks of age) was used and following dosing the treated rats were placed into animal metabolism cages so that their urine, feces and (in some cases) their expired air could be collected. The followed summarizes the significant findings from this study.

1. Metabolites in Expired Air. Excretion via this route following a single dose of 11.02 mg/kg was considered to be "slight" and between 0.07 and 0.44 percent of the administered dose. Maximum excretion via this route was between 24 and 48 hours posttreatment. In this type of study, when the connecting tubes for the collection apparatus were made of glass, more radioisotope was recovered in the trapping medium. In these studies only a total of 36 to 51 percent of the administered dose was recovered with most of the material (22 and 36%) being found in the feces. Another 10 and 15 percent was uncovered in the urine and at 72 hours only 1.5 percent remained in the body. Refer to Table 2 attached.

2. Single Dose Study Major Route of Excretion. Following a single dose of 2 mg/kg/day most of the radiolabeled material was recovered in the feces (39.10% males and 32.41% females) vs. a lesser amount in the urine (9.902% in the males and 13.13% in the females). In both sexes < 50 percent of the administered dose was recovered in the excreta. Refer to Tables 5 and 6 attached.

The radioactivity was eliminated from the rats in a biphasic fashion with, there being a rapid Phase I (7 to 11 hours) and a slower Phase II (45 to 70 hours) for both sexes.

After 7 days there were residues of ^{14}C remaining in the carcass and body organs as shown in Table 8 (reproduced from the study report). In males the liver (0.1356 u equivalent/g) had the highest content, followed by the carcass and kidneys (0.0228 u eq/g). In females (Table 9 attached), the residues were slightly higher with liver having the highest concentration (0.1612 ug/eq/g).

Overall < 50 percent of the administered doses were accounted for.

3. Intravenous Dosing. Following an intravenous dose of 2 mg/kg the excretion was biphasic with half-lives of 9 to 10 hours and 60 to 71 hours for renal elimination and slightly longer (11 hours and 69 or 81 hours) for intestinal elimination.

The bilary route is important in eliminating TPTH because 44.03 percent in the males and 37.75 percent in the females of the administered dose was found in the feces. The urine had an average 31.36 percent in the males and 28.89 percent in the females. The overall recovery was 75.37 $\pm$ 2.77 percent in the males and 66.64 $\pm$ 10.45 percent in the females.

Excretion in the urine implies that the blood or internal organs can metabolize TPTH to split off benzene which in turn is then conjugated and eliminated. No specific attempts, however, were made to identify the urinary metabolites following intravenous injection to determine for the presence of organotin compounds.

4. Single Dose of 10 mg/kg. This aspect of the study assessed the blood levels of radioactivity and the half-lives for the excretion of ^{14}C. The maximum blood levels in males were 0.146 or 0.194 ug/mL but females were higher 0.245 and 0.297 ug/mL. The highest levels were 2 (for males but 4 for females) to 8 hours after treatment and the halflives for elimination from the blood were biphasic with the ranges being 11.9 to 17.6 hours for the first phase and 155.7 to 291.1 hours for the second elimination phase. The second elimination phase may have been slightly faster in females.

Excretion of this dose was mostly in the feces (42.3 ± 4.3 percent for the males and 46.97 ± 0.90 percent for the females). Renal elimination was higher for this dose level than for the 2 mg/kg dose level with there being 17.95 ± 3.57 percent of the administered dose in the urine of the males and 22.14 ± 7.02 percent in the females. The half-lives for elimination were again biphasic with the initial phase being 8 to 11 hours and the slower phase being 55 to 71 hours.

Total recovery rates were 62.03+/-6.91% for the males and 71.75% +/-6.36% for the females meaning that approximately 28 to 38% of the original dose was unaccounted for.

Dosing with 10 mg/kg resulted in there being higher levels of ^{14}C retained by the tissues (refer to Tables 17 and 18 from the study attached). Again the liver had the highest concentrations of radiolabel.

5. Repeated Administration. (14 days of unlabeled TPTH followed by 2 mg/kg of ^{14}TPTH on the 15th day). For example, excretion via the feces was 49.48 ± 4.63 percent in the males and 53.37 ± 2.39 percent in the females together with 20.08 ± 7.06 percent in the males and 27.74 ± 4.63 percent in the female excreted in the urine. Elimination was biphasic.

   Seven days following the ^{14}TPTH administration, the radiolabel was distributed over the body with the highest level again in the liver. Refer to Tables 23 and 24 attached.

Conclusion:

The study provides useful data with respect to the absorption, excretion, and retention of ^{14}C following administration of ^{14}-labeled phenyl TPTH. The study data suffers because of the poor overall recovery of administered dose. The explanation provided by the testing laboratory (that much of the label is lost following elimination in the feces and subsequent breaking off of the ^{14}C-benzene which volatizes from the feces) was not sufficiently supported by a quantitative proof.

Overall, the study demonstrates that little intact TPTH is absorbed from the gut with most the label that is absorbed and excreted being ^{14}C-benzene (or a benzene metabolite). Once absorbed, the benzene is conjugated and excreted in the urine. Most of the absorbed radiolabel was eliminated in the feces

following an intravenous dose indicating that the bilary route may be important in excretion of intact TPTH.

Attachments

TPTH toxicology review

Page _____ is not included in this copy.

Pages 29 through 39 are not included in this copy.

The material not included contains the following type of information:

___ Identity of product inert ingredients

___ Identity of product impurities

___ Description of the product manufacturing process

___ Description of product quality control procedures

___ Identity of the source of product ingredients

___ Sales or other commercial/financial information

___ A draft product label

___ The product confidential statement of formula

___ Information about a pending registration action

X FIFRA registration data

___ The document is a duplicate of page(s) _____

___ The document is not responsive to the request

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Reviewed by: J.D. Doherty
Section II, Tox. Branch (TS-769C)
Secondary Reviewer: E.R. Budd
Section II, Tox. Branch (TS-769C)

DATA EVALUATION REPORT

STUDY TYPE: Metabolism-rats TOX CHEM No.: 896E

ACCESSION NO.: None MRID NO.: N/A

TEST MATERIAL: ^{113}Sn - triphenyltin chloride

SYNONYMS:

STUDY NUMBER(S): None (Journal article)

SPONSOR: None (Journal article)

TESTING FACILITY: University of Mainz

TITLE OF REPORT: Degradation of triphenyltin chloride on sugar beets and in rats.

AUTHOR(S): K.-D. Freitag and R. Bock

REPORT ISSUED: Pesticide Science 5:731-739 (1974)

CONCLUSIONS:

Most of the ^{113}Sn was found in the feces (>80%) and a much lesser amount was found in the urine (about 3%). Internal body organs retained only about 0.5%. Study does not define the extent of gastrointestinal absorption. Organ retention data indicate that the testis may accumulate a disproportional amount of labelled tin.

Classification: SUPPLEMENTARY

SPECIAL REVIEW CRITERIA (40 CFR 154.7) N/A.

REVIEW

This study utilized triphenyltin chloride radiolabelled with ^{113}Sn in a series of metabolism experiments which should give some generalizations for the metabolic fate in rats of triphenyltin hydroxide (TPTH). In these experiments rats were dosed orally with both single and multiple (five consecutive daily doses) at 3 mg/rat of ^{113}Sn triphenyltin chloride and the excretion rate and chemical composition of the excreted phenyltin or other compounds investigated. For the single dose experiment 11 rats per sex were used, for the multiple dosing experiment, 10 rats per sex

were used.

In summary the results showed:

1. About 3% of the radioactivity was in the urine and 88% was in the feces after 7 days following a single dose.

2. About 2.3% of the radioactivity was in the urine and 81.5% in the feces after 7 days following the last dose in the multi-dosing experiments. This left approximately 15% unaccounted for.

3. In a study designed to determine the distribution of ^{113}Sn (irrespective of the molecular structure) it was determined that 0.5% of the material remained in the carcass. Refer to Table 4 (zeroxed from the study report attached). This table indicates that in both sexes the liver had the highest concentration. The male gonads had the second highest concentration among the male organs.

4. Attempts were made to identify the metabolites in the urine and feces.

   In urine, there were about equal amounts (17-33%) of tri-, di-, and monophenyl and inorganic tin present. Only 0.6-5% of the radioactivity was not extracted.

   In feces, in general on the first day 81% of the labelled material was as triphenyltin, but at day 7 only 31% was as this species. Over the course of the seven day period, as the triphenyltin species declined, the concentrations of diphenyl and inorganic tin increased. Monophenyltin also increased but appeared to be more rapidly converted to inorganic tin. There was also some evidence that an "oxine" which was probably a monophenyltin compound was present.

CONCLUSION:

TB considers this information to be SUPPLEMENTARY. Although the study provides some useful information regarding the fate of tin labelled triphenyltin compounds the more important question concerning how much material is actually absorbed was not resolved. For example, significant quantities of organotins may have been absorbed from the gastro-intestinal tract and eliminated in the feces. Thus the urinary excretion data as provided by this study may misrepresent the amount that is absorbed and excreted. The importance of the feces as the route of excretion following subcutaneous administration is emphasized in the paper by Nagamatsu et. al. (Japanese Journal of Hygiene 33:486-496 (1978).

TABLE 4. Distribution of the remaining activity in the organs of rats

Organ	Total amount (g)		Percentage of the activity given	
	Males	Females	Males	Females
Stomach and intestines	43.67	40.14	0.079	0.077
Kidneys	7.43	6.61	0.055	0.097
Gonads	12.36	0.89	0.117	0.002
Liver	34.02	29.30	0.164	0.212
Heart	3.28	3.02	0.008	0.010
Muscles	23.71	18.68	0.045	0.018
Fat (skin)	5.83	6.96	0.004	0.004
Fat (kidneys)	3.75	4.08	0.003	0.005
Brain	7.25	7.16	0.025	0.030
Total:	141.30	116.84	0.50	0.46
=	18% of the total weight	16.7%		

3.4.3. *Results*

The results of these tests show that after a single application of triphenyltin chloride (3 mg) on the average, 88% of the radioactive tin is excreted in the faeces within 7 days, 3% in the urine and 0.5% was detected in the organs at the end of the test. The deficit of about 7.5% is explained by errors in counting the activity, errors in measuring the viscous oil, losses arising from collecting and processing the test material, and also because of residues in parts of the animals not examined. No significant differences in excretion between male and female animals were observed. As was to be expected the percentage of radioactive tin excreted was less after prolonged application for 5 days, but the difference in comparison to the test series with a single application was surprisingly small (83.8% and 91%, respectively).

3.5. Identification of excreted tin compounds

3.5.1. *Urine*

The tin compounds were extracted from the urine in succession as described above. The results of several analyses are given in Table 5. To confirm these results, the R_F

TABLE 5. Concentration of tin compounds in rat urine (percentage of the total radioactivity)

Compound	Percentage of the radioactivity
$(C_6H_5)_3Sn^+$	25
$(C_6H_5)_2Sn^{2+}$	17–19
$(C_6H_5)Sn^{3+}$	20–29
Inorganic tin (IV)	29–33
Not extracted from the aqueous solution	0.6–5