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

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OCT 21 1991

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: EPA ID #8340-17. Triphenyltin hydroxide: Review of rat metabolism studies following oral administration and utilizing ^{113}Sn and ^{14}C labelled material and rats with bile duct fistulas. Summary of metabolism studies following oral administration.

TOX CHEM No.: 896E
TOX PROJECT Nos: 0-0362 and 0-0760
Record Nos: 256547 and 260061

FROM: John Doherty, Ph.D. John Doherty 10/15/91
Section IV, Toxicology Branch I
Health Effects Division (H7509C)

TO: Cynthia Giles-Parker
Product Manager #22
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THROUGH: Marion Copley, DVM Marion Copley 10/15/91
Section Head
Section IV, Toxicology Branch I
Health Effects Division (H7509C)

CONCLUSION

Two studies with rats especially fitted with bile duct fistulas demonstrated the significance of the biliary route in the excretion of either ^{14}C phenyl or ^{113}Sn labelled TPTH. This route is the major route of excretion of labelled tin following absorption of TPTH or its tin metabolites. ^{14}C phenyl groups liberated from TPTH can be absorbed but are mostly conjugated and excreted in the urine.

Several individual metabolism studies all have SUPPLEMENTARY/ACCEPTABLE classifications. Refer to Appendix 1 of this memo for list of studies. When these several metabolism studies are taken together, however, they meet MINIMUM requirements for satisfying the Agency's requirement for a general metabolism study with TPTH (low and high single doses and

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low dose repeated doses. No additional oral metabolism studies with TPTH are required at this time.

Action Requested

The Hoechst Celanese Co. has submitted rat metabolism studies (three studies) with triphenyltin hydroxide (TPTH) radiolabelled as ^{113}Sn (two studies) or phenyl ^{14}C. Two of these studies (one with each isotope) utilized rats with bile duct fistulas and were designed to assess the enterohepatic (biliary) route for its relative importance in the excretion of labelled TPTH following oral administration. These studies were designed to supplement previously generated data and to resolve questions on the metabolism and distribution of TPTH in rats already obtained with ^{14}C phenyl labelled TPTH. These studies were reviewed by Toxicology Branch I (TB-I) and the Data Evaluation Records (DERs) are attached. The following comments apply to the studies themselves and to the overall problem of the data requirement for a metabolism study with TPTH.

Toxicology Branch Comments

1. ^{14}C Labelled TPTH Study.

The study with ^{14}C TPTH (Hoechst # A 36680 and (B) 97/87. December 7, 1987 MRID # 413872-01) was determined to be SUPPLEMENTARY/ACCEPTBALE . Only three male rats (no females) were used thus limiting the scope of the study with regard to number of animals and sexes tested.

The data presented, however, were considered useful and indicate that only 2.8 ± 1.4% of the total of the administered ^{14}C was excreted in the bile following a single oral dose of 2 mg/kg. There was a higher amount (11.03 ± 9.01%) excreted in the urine. Indicating that the urinary route is of considerably more importance than the biliary route for the excretion of ^{14}C following oral administration of labelled TPTH.

Attempts were made using TLC and HPLC to identify the structure of the metabolites in the bile but definite characterizations were not made. There was however apparently no intact TPTH in the bile.

2. ^{113}Sn Labelled TPTH.

Both studies were determined to be SUPPLEMENTARY/ACCEPTABLE. Neither study conforms to GUIDELINE procedures.

In spite of the SUPPLEMENTARY classification, these studies

were considered by TB-I to be well executed and to provide useful data for assessing the uptake, distribution and excretion of the tin in TPTH.

These studies show that following oral administration (Hoechst Study # CM086/87 and A 41407, May 30, 1989 MRID # 413091-01) most (96-100%) of the ^{113}Sn is excreted in the feces. Less than 1.5% was found in the urine. The study with the bile duct fistula (Hoechst Study # CM079 and A 41409, May 29, 1989 MRID # 413091-02) indicated 6.21% (males) and 2.78% (females) of the total labelled material was excreted in the bile. Since the study with ^{14}C indicated more labelled material in the urine, the discrepancy relates to the fact that split off phenyl groups are eliminated in the urine. The biliary route, however, is the major route of excretion once TPTH or its tin metabolites are absorbed from the gastrointestinal tract.

3. An appendix to this memo entitled "Overview of the metabolism of TPTH in rats following oral administration" which summarizes the available data on the absorption distribution and excretion of TPTH in rats is attached. In conclusion, when all of the available metabolism studies with orally administered TPTH are considered the data when taken together meet MINIMUM standards are no additional metabolism studies with oral administraion are required at this time.

Studies Reviewed

Study	Results
85-1. Metabolism - rats with ^{113}Sn modified to include bile fistula. Hoechst Study # CM079 and A 41409, May 29, 1989 MRID # 413091-02 SUPPLEMENTARY/ACCEPTABLE	Study demonstrates that the biliary route is the major route of excretion of the tin metabolites and of TPTH. TPTH may be absorbed from the gastro-intestinal tract but is metabolized to diphenyl, monophenyl and inorganic tin.
85-1. Metabolism - rats with ^{113}Sn. Hoechst Study # CM086/87 and A 41407, May 30, 1989 MRID # 413091-01 SUPPLEMENTARY/ACCEPTABLE	Most (96-100%) TPTH is excreted in the feces. Fecal excretion is biphasic indicating a probable role of biliary excretion of absorbed material. After 24 hours, the kidneys, liver, brain and heart contained the most radioactivity. The mucosal lining of the stomach and small intestine also transiently retained some isotope. The epididymis retained about twice as much radioactivity as the testis. Seven days after administration, most of the radioactivity was eliminated with only traces remaining.
85-1. Metabolism - rats with ^{14}C phenyl U modified to include bile fistula. Hoechst # A 36680 and (B) 97/87. December 7, 1987 MRID # 413872-01 SUPPLEMENTARY/ACCEPTABLE	Data were generated to demonstrate that 2.8 $\pm$ 1.4% radioactivity resulting from orally administered ^{14}C TPTH is excreted in the bile. The biliary products were mostly polar (possibly containing mono and diphenyl tin) but intact TPTH was not conclusively present. There was a higher amount (11.03 $\pm$ 9.01%) excreted in the urine.

Appendix-1.

Overview of the metabolism of TPTH in rats following oral administration. [Prepared by TB-I October 1991.]

Note: The letter in parenthesis identifies the studies which best represent the data cited. These references are listed below. Refer to DERs for quantitative details.

Absorption. Based on the studies with ^{113}Sn (D,E) approximately 27% in males and 12% in females of TPTH label (as either intact TPTH or its tin metabolites) administered by gavage can be absorbed from the gastrointestinal tract. Males apparently absorb more than females.

Based on studies with ^{14}C labelled TPTH (A,B and F) it appears that 10 to 26% (based on the amount found in the urine) is absorbed from the gastro-intestinal tract. The absorbed material may be either intact TPTH or its tin metabolites or phenyl groups split off from intact TPTH in the intestine.

Excretion. Based on both tin (D, 96-100%) and ^{14}C (A,B, estimated 54 to 77%) labelled TPTH studies, most of the labelled material is excreted in the feces. Urinary excretion is important in the excretion of conjugated (sulfate) phenyl groups spilt off from parent TPTH.

Little (between 0.07 and 0.44% of the administered dose) labelled material was found in the expired air (A). In addition, the registrant referenced a study which evaluated the respiratory route for the excretion of TPTH in rats (Report Biev-V-32.044-05 from the Battelle Institute, 1987). This study, however, has not been submitted to HED for review.

The biliary route was demonstrated to be the probable route of excretion of absorbed TPTH and its tin metabolites based on the study with ^{113}Sn (D,E) and supported by studies with ^{14}C labelled TPTH (F).

Retention. The kidneys (0.26 and 0.37 ug equivalents/gm for males and females respectively), liver (0.15 and 0.30), and brain (0.09 and 0.11) were the organs that retained the highest concentrations as indicated by the analysis of tissues following administration of ^{113}Sn (D). Multiple dosing (7 daily doses) with ^{113Sn} labelled tin resulted in there being higher levels (i.e kidney levels were 1.55 and 2.48) radioactivity in these same organs (D). Seven days after the last administration of the

labelled material, the tissue residues decreased to only trace levels. The stomach lining and gastrointestinal wall transiently retains some of the labeled material but not a major portion.

Analysis of selected tissues from the rat (G) and dog (H) chronic feeding studies for total tin content confirmed that tin is not accumulated over the course of two years for rats and one year for dogs.

Metabolism. TPTH is metabolized to yield diphenyl and monophenyl tin and inorganic tin (A,B,D). The degradation of TPTH to mono and diphenyl tin may occur to some extent in the gastrointestinal system prior to absorption. Since the amount of label apparently absorbed from both the ^{113}Sn and ^{14}C experiments was nearly equal and since TB does not consider that a sufficient number of animals were used TB does not consider that there is sufficient data to determine the actual sites of degradation of TPTH to its metabolites. About 14% intact TPTH has been detected as the total % of isotope in the bile (E,F) implying that intact TPTH may be absorbed from the gastrointestinal tract or once absorbed is rapidly metabolized. The phenyl groups split off are conjugated and excreted.

References:

A. "Kinetics in the Rat Following Single and Repeated Administration of 2 mg/kg and Single Administration of 10 mg/kg Body Weight". MRID # 400294-07. Hoechst Aktiengesellschaft, # 111/1-111/5; 112/12; 111/12.1 and Report # 01-L42-0489-86, dated September 30, 1986. Refer to DER prepared by J. Doherty Document #006236.

B. "Metabolism in rats After Single and Repeated Oral Administration at the Two Dosage Levels 2 and 10 mg/kg Body Weight". MRID # 400294-06. Hoechst Aktiengesellschaft, # CM011/85, dated October 29, 1986. Refer to review By J. Doherty Document No.: 006236

C. "Degradation of triphenyltin chloride on sugar beets and in rats" (no MRID #) as published in Pesticide Science 5:731-739 (1974). Refer to review by J. Doherty in Registration Standard.

D. "HOE 029664 (TPTH) - ^{113}Sn Accumulation Study Kinetics and Metabolism in the Rat after Single and Repeated Oral Administration of 2 mg/kg Body Weight". MRID #413091-01. Hoechst Pharma Forschung, #CM086/87, May 30, 1989. Refer to Review by J. Doherty attached.

E. "HOE 029664 (TPTH) - ^{113}Sn Absorption Studies in Rats with Bile Fistula after a Single Oral Dcse of 2 mg/kg Body Weight" MRID # 413091-02. Hoechst AG Radiochemisches Laboratorium, #

CM079 and AG# A 41409, dated May 29, 1989. Refer to review by J. Doherty attached.

F. "HOE 029664 (TPTH) -^{14}C Excretion Study in Rats with Bile Fistula Following Oral Administration of 2 mg a.i./kg Body Weight". MRID # 413872-01. Hoechst Aktiengesellschaft, # A 36680. December 7, 1987. Refer to review prepared by J. Doherty attached.

G. Supplementary report to the rat chronic feeding/carcinogenicity study (Study RCC Laboratory #046980, April 18, 1989 and supplementary report dated September 10, 1989 under MRID # 412975-02). Refer to DER prepared by J. Doherty Document No.: 008554.

H. Supplementary report to the dog chronic feeding study (RCC Laboratory #0470113, June 1987 and Supplementary report dated June 23, 1989 under MRID #412975-03). Refer to DER prepared by J. Doherty Document No.: 008554.

008721

Reviewed by: John Doherty John Doherty 10/9/91
Section IV, Toxicology Branch I (H7509C)
Secondary reviewer: Marion Copley
Section IV, Toxicology Branch I (H7509C) Marion Copley 10/15/91

DATA EVALUATION REPORT

STUDY TYPE: 85-1. Metabolism - rats (modified to include bile fistula)

MRID NO.: 413091-02 TOX. CHEM. NO.: 896E

TEST MATERIAL: ^{113}Sn labelled triphenyltin hydroxide (HOE 029664 00 ZE99 0005, batch #7321, specific activity 1420.0 MBq/g, about 99% radiochemical purity) and unlabelled triphenyltin hydroxide (HOE 029664 00 ZB99 0006 from batch 7321 of 99% chemical purity).

TEST ANIMALS/SYSTEM: SPF Wistar rats, strain WISKf (SPF71) from Hoechst, AG. The males were about 70 days old and the females were stated as being ">150 days".

STUDY NUMBER(S): Laboratory Project # CM079 Hoechst AG # A 41409.

SPONSOR: Submitted by Hoechst Celanese Corporation.

TESTING FACILITY: Hoechst AG Radiochemisches Laboratorium, Germany

TITLE OF REPORT: "HOE 029664 (TPTH) - ^{113}Sn Absorption Studies in Rats with Bile Fistula after a Single Oral Dose of 2 mg/kg Body Weight"

AUTHOR(S): W.L. Burkle, H.G. Eckert and H.-N. Kellner

REPORT ISSUED: May 29, 1989

CONCLUSIONS:

Study demonstrates that the biliary route is the major route of excretion for absorbed TPTH and its tin containing metabolites. TPTH may be absorbed from the gastro-intestinal tract but is metabolized to diphenyl, monophenyl, and inorganic tin.

Classification: CORE-SUPPLEMENTARY/ACCEPTABLE by itself, MINIMUM with other studies (see Appendix V for list of studies). of cover memo

Quality Assurance Statement: A signed statement (signature illegible) by the Quality Assurance Department attested that three inspections were made and that three reports were prepared. The QAS did not indicate deficiencies in the conduction of the study.

REVIEW

The purpose of this study was to compliment the existing data on the metabolism of TPTH already generated using ^{14}C phenyl labelled material. The studies with ^{14}C labelled TPTH did not assess the potential for organotin chemicals to be absorbed via the gastro-intestinal system. Since most of the ^{14}C was found in the feces, additional data were considered desirable to assess the role of the biliary route in the excretion of TPTH.

The basic design of this study consisted of a single group of 7 rats (4 males and 3 females) which were surgically fitted with bile duct cannula (near the hilus of the liver). A second catheter was placed in the duodenum. Bile was drained from the duodenum and bile which had been collected from the rats prior to administration of the test material as perfused via peristaltic or infusion pump into the bile duct cannula. The rats were kept warm during the study by exposure to an infrared lamp.

The rats were dosed by gavage with a dose of a mixture of labelled and unlabelled TPTH in ethanol (70%) and water (30%) such that they received 2 mg/kg of body weight. Following dosing the urine and bile and cage washings (presumably including the feces) were collected. After 30 hours the rats were sacrificed by carbon dioxide overdose. The distribution (excreta and carcass) of radioactivity was determined and attempts were made to characterize the chemical structure of the metabolites.

RESULTS

1. Distribution of radioactivity.

The following table illustrates the distribution of radioactivity after 30 hours (data are as percent of the original dose).

	Males	Females
Bile	6.21 ± 4.76	2.78 ± 2.01
Urine	0.01 ± 0.03	0.07 ± 0.08
Cage Washings	[Not detectable in 5 of 7 cages]	
Carcass*	21.59 ± 7.21	8.86 ± 3.09
Amount absorbed	27.81 ±12.48	11.77 ± 1.70

*The carcass included the whole body minus the gastro-intestinal

tract. The study report did not specify how the whole body radioactivity was determined other than that the "carcass was placed in a glass beaker and directly measured without any sample preparation". It is assumed that the remainder of the radioactivity after 30 hours was in the gastro-intestinal tract being prepared for excretion as feces or entwined in the gastro-intestinal tract walls.

Based on the above data and inspection of the individual animal findings it appears that the males absorb as much as 10.84 to 43.02% of the original dose . The female rats appear to absorb on average about one half as much as the males. [Note: The difference may possibly be related to the age differences in the male and female rats in this study. See under test animals on page 1 of DER.]

2. Identification of the metabolites.

The bile was extracted with sodium diethyldithiocarbamate (DDT-Na, chelating agent) and the extract further characterized by TLC. This procedure indicated that tri-(9%), di-(60%) and monophenyl (31%) tin were present in the extractable portion. Additional data indicated that the nonextractable (with the chelating agent) material was triphenyl tin and inorganic tin. Overall the distribution of the radiolabel among the metabolites is estimated as "inorganic tin" $\leq$ 25%, monophenyl tin 21%, diphenyl tin 40% and unmetabolized triphenyltin 14%.

CONCLUSION. This study is SUPPLEMENTARY. An insufficient number of rats were used, only a single time was studied and no attempts were made to study the distribution of the labelled material among the various organs.

The study, however, provides some very important data which indicate that the biliary route is the major route of excretion of tin metabolites of TPTH following oral administration. Most of the absorbed material was characterized as TPTH metabolites but at least some portion of the absorbed material is intact TPTH. Males were shown to absorb from 10-43% (27% average for 4 rats) of the original dose but females absorbed about 9-14% (11% average for 3 rats).

TPT H (376 F)
Hoechst Labs # CM079/87
A 47469
May 29, 1989
HLW # 113-91-02

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85-1 Metabolism Studies

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

1. V — **Analytically pure grade of the active ingredient.**
2. V — **Isotopically labeled in the core of the molecule and/or significant portions thereof.**

-OR-

3. ___ **Analytical procedures sufficiently specific and sensitive to identify the test substance.**
4. A — **Young adult rats. Other mammalian species may be used for specific purposes.**
5. B — **Five male and five female rats for each dose, 4 if following OECD protocol.**
6. NO — **Two doses, the low to be without effect and the high to produce toxic or pharmacological signs but not severe effects or mortality.** Single dose only
7. * NO — **Dosing group A, single low dose by intravenous route (not required if insoluble in water or normal saline).**
8. V — **Dosing group B, single low dose by oral route.**
9. NO — **Dosing group C, 14 consecutive daily low dose of the unlabeled test material by oral route followed by a single low dose of the labeled test material.**
10. NC — **Dosing group D, single high dose by oral route.**
11. NO — **Collect individually all urine, feces and expired air for 7 days after labeled dose or until 90+ percent of the dose is excreted (whichever occurs first). Expired air not required if a pilot study shows no excretion in 24 hours.** Urine/bile only at 30 hours
12. NO — **For dosing groups B, C and D, quantity of label in the following tissues and organs;**

NONE

___ bone	___ liver
___ brain	___ lung
___ fat	___ blood
___ testes	___ muscle
___ heart	___ spleen
___ kidney	___ residual carcass

___ **tissues showing pathology in this or prior studies**

For all dosing groups:

13. NO — **Quantities of label in urine, feces and expired air (if detected in preliminary study) at appropriate intervals (e.g. 4, 8, 12 and 24 hours, 1.5, 2, 3, 4, 5, 6 and 7 days.** NO NO — 30 hours only
14. NO — **Qualitative analysis of urine and feces to detect metabolism and identify metabolites (pooled urine and feces by dosing group may be used).** bile only

NOTE **The metabolism data requirement may be filled in part. For example performing the analysis on a single dose group can satisfy the requirement for that dose.**

Criteria marked with a * are supplemental and may not be required for every study.

A - females were probably mature (i.e. > 150 days)
B - 4 males and 3 females

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Reviewed by: John Doherty 10/9/91
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Secondary reviewer: Marion Copley, DVM
Section IV, Toxicology Branch I (H7509C) Marion Copley 10/15/91

DATA EVALUATION REPORT

STUDY TYPE: 85-1. Metabolism (rats)

MRID NO.: 413091-01 TOX. CHEM. NO.: 896E

TEST MATERIAL: ^{113}Sn labelled triphenyltin hydroxide. Stated as being about 99% radiochemical and chemical purity. Code No. HOE 029664 00 ZE99 0005 for the radioactive substance and HOE 029664 00 ZB99 0006 for the nonradioactive substance.

TEST ANIMALS: Young adult male (6-7 weeks) and female (7-10 weeks) SPF Wistar rats strain WISKf, from Hoechst AG.

STUDY NUMBER(S): Lab No. CM086/87 and Hoechst AG Project No. A 41407.

SPONSOR: Hoechst AG. Study submitted by Hoechst Celanese Corporation. Somerville, NJ.

TESTING FACILITY: Hoechst AG Pharma Forschung GB-L Radiochemisches Laboratories and Hoechst AG Produktenwicklung-Okologie.

TITLE OF REPORT: "HOE 029664 (TPTH)-^{113}Sn Accumulation Study Kinetics and Metabolism in the Rat after Single and Repeated Oral Administration of 2 mg/kg Body Weight".

AUTHOR(S): Dr. W.L. Burkle, Dr. H.G. Eckert and Dr. H.-M. Kellner.

REPORT ISSUED: May 30, 1989.

CONCLUSIONS:

Most (96-100%) TPTH is excreted in the feces. Fecal excretion is biphasic indicating a probable role of biliary excretion of absorbed material. After 24 hours, the kidneys, liver, brain and heart contained the most radioactivity. The mucosal lining of the stomach and small intestine also transiently retained some isotope. The epididymis contained about twice as much radioactivity as the testis. Seven days after administration, most of the radioactivity was eliminated with only traces remaining.

Classification: SUPPLEMENTARY/ACCEPTABLE by itself, MINIMUM with other studies (see Appendix V of Cover memo for list of studies).

Quality Assurance Statement: A statement signed by the Quality Assurance Department officer (signature illegible) attested that five inspections (over the time span of Jan.18, 1988 to August 15, 1989) were made and five reports were made to the study director. The QAS did not indicate deficiencies in the conduct of the study.

REVIEW

The objectives of this study were to assess the extent to which organotin compounds could be absorbed from the gastro-intestinal tract following oral administration of TPTH. Previously submitted studies with ^{14}C phenyl labelled TPTH indicated that most of the administered material was eliminated via the feces. Since the labelled phenyl groups are hydrolyzed from the parent molecule, the studies with phenyl labelled material obscure the pathway for the metabolism and fate of tin. This present study utilizes ^{113}Sn labelled TPTH to help to clarify certain questions regarding the metabolism and excretion of TPTH including the distribution of labelled material among the internal organs.

The basic design of this study consisted of dosing two groups of rats (5 males and 5 females per dose group) with either a single dose of 2 mg/kg of labelled TPTH or 7 daily doses of 2 mg/kg/day of labelled TPTH disolved in sesame oil. These rats were placed in metabolism cages and their urine and feces were collected. Collection continued for seven days following the last dosing with the radiolabelled material. At this time the rats were sacrificed with carbon dioxide and the organs/tissues prepared for analysis.

Separate male and female groups (4) of rats were also dosed with radiolabelled TPTH and were sacrificed 24 hours (2 of each sex) and 7 days (2 of each sex) following dosing and were frozen together with embedding medium to a solid block by immersion in liquid nitrogen. These rats were subjected to whole body radiography. They were sectioned in a cryomicrotome at -20°C to a thickness of 30 microns prior to preparation for isotope analysis.

RESULTS

1. Kinetics of excretion of radiolabelled material.

For both the single and multiple doses the feces contained the greater amount of radioactivity. No attempts were made to quantify radioactivity in the expired air. TB-I does not consider this necessary since essentially all of the radio-activity was accounted for. Excretion of the radiolabelled

material in the feces was biphasic. Table 1 below illustrates the findings.

Table 1. Recovery and half life of TPTH.

		Males	Females
Recovery percentage (%)			
Urine	single	0.66 ± 0.17	0.87 ± 0.33
	multiple	1.36 ± 0.21	1.42 ± 0.35
Feces	single	96.17 ± 4.87	100.80 ± 4.32
	multiple	97.76 ± 0.64	96.80 ± 0.75
Total	single	96.82 ± 4.70	101.70 ± 4.13
	multiple	99.12 ± 0.53	98.22 ± 0.51
Half Life (hours)			
Urine	single	55.7 ± 15.3	41.5 ± 1.5
	multiple	41.9 ± 2.2	41.4 ± 3.4
Feces*	single	9.6 ± 1.0	8.2 ± 1.8
		57.0 ± 9.9	49.1 ± 11.3
	multiple	9.1 ± 1.2	7.9 ± 0.7
		51.2 ± 4.9	53.2 ± 5.9

*The half life for fecal elimination was biphasic. The first phase (shorter half life) is entered first, the second phase is entered second.

2. Residual concentrations and retention of labelled material.

Samples of the spleen, kidneys, gonads, liver, heart, lungs, skeletal muscle, subcutaneous fat, retroperitoneal fat, brain, bones, bone marrow, carcass, blood, stomach/intestine thymus and stomach intestinal contents were assessed for radioactivity.

Seven days following a single oral dose the amount of radioactivity in the spleen, lungs, fat, bone, bone marrow, blood and thymus were below the detection limit. The kidneys (0.26 and 0.37), liver (0.15 and 0.30), brain (0.09 and 0.11) and heart (0.07 and 0.10) were demonstrated to contain radioactivity (in ug equivalents/gm for males and females respectively).

Seven days following multiple dosing, all of the

tissue/organs except the ovaries were reported to have detectable levels of radioactivity. The kidneys (1.55 and 2.48), liver (0.81 and 1.82), and brain (0.68 and 0.71) had the highest concentrations (in ug equivalents/gm for males and females respectively. Concentrations ranging from 0.2 to 0.57 were reported in the skeletal muscle, heart, "carcass", spleen, testis, and bones. The other organs/ tissues were reported as having less than 0.2 ug equivalents/gm.

In general the residues in the tissues in the multiple dosed animals were several times higher than in the single dosed animals. Females usually retained more material than males. The amount of radioactivity remaining in the tissue (including the carcass) was estimated to be 2.8 to 3.2 % of the original administered dose level (refer to "Table 23" and "Table 24" xeroxed from the study report and attached).

3. Whole Body Autoradiography.

Four sets of data were obtained from radioanalyses made at:

i. 24 hours following a single oral dose.

ii. 7 days following a single oral dose.

iii. 24 hours following seven multiple doses.

iv. 7 days following seven multiple doses.

[The reproductions of the diagrams attempting to show the distribution of radioactivity were not considered useful by TB-I. The narrative of the study results as provided by the study report provides the basis for evaluation of this aspect of the study.]

In summary, 24 hours after administration of a single dose, most of the label was in the distal parts of the gut (i.e. in the fecal pellets in the large intestine). Radioactivity was also found in the glandular mucosa of the stomach. Most other organs/tissues also showed "low" levels of radioactivity. The kidneys (zona medullaris), and liver had the highest concentrations. Harder's gland, salivary gland, central nervous system (brain) and myocardium had lower counts. The lung, blood and eye lens were reported as showing background level.

Seven days after administration of a single dose only "very low concentrations were determined in the kidney and also traces in liver and skin".

Twenty-four hours after the last multi dose application

the distribution of radioactivity was found to be similar to that after the single application except that higher levels were found per tissue. Of particular note was that the epididymis showed higher concentrations than the testis. There was no radioactivity evident in the walls of the large intestine although the stomach glandular mucosa and small intestine contained radioactivity.

Seven days after multiple dosing the radioactivity concentrations decreased throughout the body and the distribution patterns were similar to that at 24 hours. Again the epididymis displayed a higher concentration than the testis. Only trace amounts of radioactivity were detectable in the liver, brain/spinal cord, adrenals, spleen and skeletal musculature. There were still residues of radioactivity in the kidney, urethra and penis but the gastro intestinal tract including the gut walls did not demonstrate radioactivity.

4. Characterization of the residues.

The radioactive residues in the walls of the gastrointestinal tract were extracted and characterized chromatographically. It was demonstrated that these residues contained 30% TPTH, 6% polar compounds (inorganic tin and monophenyltin) and 51% non-extractable, bound tin residues (not identified). Diphenyltin compounds were not reported as being identified. The study report asserts that 86.4% of the radiolabelled material was characterized but 51% of this material was described as "non-extractable, bound tin residues". Thus, only about 36% was actually characterized.

CONCLUSION: This study is classified as SUPPLEMENTARY. There was no high dose included and the protocol did not follow the prescribed procedure of dosing the animals for multiple doses with unlabelled test material followed by a dose of labelled test material. The study, however, is considered to provide some very useful information regarding the metabolism and pharmacokinetics of TPTH. The following "one liner" has been provided for this study:

Most (96-100%) TPTH is excreted in the feces. Fecal excretion is biphasic indicating a probable role of biliary excretion of absorbed material. After 24 hours, the kidneys, liver, brain and heart contained the most radioactivity. The mucosal lining of the stomach and small intestine also transiently retained some isotope. The epididymis contained about twice as much radioactivity as the testis. Seven days after administration, most of the radioactivity was eliminated with only traces remaining.

TPTH (E96E)

Hoechst Ge: CHO86/87 and A 41407

= May 30, 1989

Acc # 413371-01

008721

85-1 Metabolism Studies

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

1. ✓ Analytically pure grade of the active ingredient.
2. ✓ Isotopically labeled in the core of the molecule and/or significant portions thereof.

-OR-

3. ✓ Analytical procedures sufficiently specific and sensitive to identify the test substance.
4. ✓ Young adult rats. Other mammalian species may be used for specific purposes.
5. ✓ Five male and five female rats for each dose, 4 if following OECD protocol.
6. NO A Two doses, the low to be without effect and the high to produce toxic or pharmacological signs but not severe effects or mortality.
7. NO Dosing group A, single low dose by intravenous route (not required if insoluble in water or normal saline).
8. ✓ Dosing group B, single low dose by oral route.
9. NO A Dosing group C, 14 consecutive daily low dose of the unlabeled test material by oral route followed by a single low dose of the labeled test material.
10. NO C Dosing group D, single high dose by oral route.
11. ✓ Collect individually all urine, feces and expired air for 7 days after labeled dose or until 90+ percent of the dose is excreted (whichever occurs first). Expired air not required if a pilot study shows no excretion in 24 hours.
12. ___ For dosing groups B, C and D, quantity of label in the following tissues and organs;

✓ bone (and bone marrow)	✓ liver
✓ brain	✓ lung
✓ fat	✓ blood
✓ testes	✓ muscle
✓ heart	✓ spleen
✓ kidney	✓ residual carcass
✓ tissues showing pathology in this or prior studies (thymus)	

whole body autoradiography.

✓ stomach / intestine

For all dosing groups:

13. ✓ Quantitate of label in urine, feces and expired air (if detected in preliminary study) at appropriate intervals (e.g. 4, 8, 12 and 24 hours, 1.5, 2, 3, 4, 5, 6 and 7 days.
14. ✓ Qualitative analysis of urine and feces to detect metabolism and identify metabolites (pooled urine and feces by dosing group may be used).

NOTE The metabolism data requirement may be filled in part. For example performing the analysis on a single dose group can satisfy the requirement for that dose.

Criteria marked with a * are supplemental and may not be required for every study.

A Single dose only

B 7 daily doses of radiolabelled material

C. No high dose group.

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Table 23: Hoe 029664-^{113}Sn

Distribution in tissues after single oral administration of approx. 0.41 mg (2 mg/kg body weight) to female rats (% of the administered radioactivity)

Rat	R 222	R 223	R 224	R 225	R 226	$\bar{x}$	SD
Dose [mg]	.4279	.4051	.4141	.3986	.4165	.4124	
Spleen	< DL	< DL	< DL	< DL	< DL	-	-
Kidneys	.1370	.1555	.0995	.1354	.1381	.1331	.0205
Gonads	< DL	< DL	< DL	< DL	< DL	-	-
Liver	.7830	.7607	.6142	.4530	.6450	.6512	.1323
Heart	.0156	.0186	< DL	< DL	.0197	.0108	-
Lungs	< DL	< DL	< DL	< DL	< DL	-	-
Skeletal muscle	.0610	.0810	.1004	.0708	.0637	.0754	.0160
Subcutaneous fat	< DL	< DL	< DL	< DL	< DL	-	-
Retroperiton. fat	< DL	< DL	< DL	< DL	< DL	-	-
Brain	.0504	.0660	.0374	.0230	.0581	.0470	.0171
Bones	< DL	< DL	< DL	< DL	< DL	-	-
Bone marrow	< DL	< DL	< DL	< DL	< DL	-	-
Carcass	2.510	2.770	1.725	1.332	2.406	2.149	.5978
Blood	< DL	< DL	< DL	< DL	< DL	-	-
Stomach/Intest.	.0550	.0678	.0441	.0284	.0569	.0504	.0149
Thymus	< DL	< DL	< DL	< DL	< DL	-	-
Stom./Intest.cont.[1]	.1219	.1724	.1109	.0702	.1301	.1211	.0368
Total	3.734	4.092	2.732	2.113	3.518	3.238	.8025

Time of killing: 168 hrs p. appl.
1) Content of stomach and intestines

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Table 24: Hoe 029664-^{113}Sn
Distribution in tissues after seven daily oral administrations of approx. 0.41 mg (2 mg/kg body weight) to male rats
(% of the administered radioactivity)

Rat	R 181	R 182	R 183	R 184	R 185	$\bar{x}$	SD
Dose [mg]	2.955	2.917	2.901	2.910	2.901	2.917	
Soleen	.0041	.0037	.0043	.0059	.0028	.0042	.0011
Kidneys	.0826	.0796	.1156	.0841	.0739	.0872	.0164
Gonads	.0295	.0268	.0335	.0075	.0225	.0240	.0100
Liver	.3244	.2662	.3646	.2862	.2871	.3057	.0391
Heart	.0082	.0082	.0113	.0109	.0079	.0093	.0017
Lungs	.0066	.0056	.0074	.0061	.0041	.0060	.0012
Skeletal muscle	.0398	.0387	.1494	.1244	.0470	.0799	.0529
Subcutaneous fat	< DL	< DL	.0035	.0034	< DL	.0014	-
Retroperiton. fat	< DL	< DL	.0028	< DL	< DL	.0006	-
Brain	.0439	.0454	.0470	.0462	.0351	.0435	.0048
Bones	.0040	.0049	.0053	.0053	.0038	.0047	.0007
Bone marrow	< DL	< DL	< DL	< DL	< DL	-	-
Carcass	1.892	2.038	2.358	2.314	1.843	2.089	.237
Blood	.0034	.0029	.0045	.0047	.0043	.0040	.0008
Stomach/Intest.	.0315	.0323	.0423	.0374	.0267	.0340	.0060
Thymus	< DL	< DL	.0027	.0026	< DL	.0011	-
Ston./Intest.cont.[1]	.0804	.0862	.0974	.0965	.0543	.0830	.0175
Total	2.550	2.639	3.250	3.035	2.413	2.777	.351

Time of killing: 168 hrs p. appl. 7
1) Content of stomach and intestines

008721

Reviewed by: John Doherty 10/9/91
Section IV, Toxicology Branch I (H7509C)
Secondary reviewer: Marion Copley, DVM 10/15/91
Section IV, Toxicology Branch I (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: 85-1. Metabolism - rats (modified to include bile fistula)

MRID NO.: 413872-01 TOX. CHEM. NO.: 896E

TEST MATERIAL: Triphenyltin hydroxide (TPTH) with phenyl-u-^{14}C with a specific radioactivity reported as 10.8 Ci/gm and 97% radiochemical purity. The sample was from lot #15101 V and obtained from the Hoechst Aktingesllschaft, Frankfurt Germany.

TEST ANIMALS/SYSTEM: Male Wistar rats from the WISKf (SPF 71) strain obtained from the Hoechsst AG breeding facility.

STUDY NUMBER(S): Hoechst AG Project # A 36680 and Laboratory Id # (B) 97/87.

SPONSOR: Hoechst Celanese Corporation, Somerville, New Jersey.

TESTING FACILITY: Hoechst Aktiengesellschaft and Analytisches-Laboratorium/Radiochemisches Laboratorium. Frankfurt, Germany.

TITLE OF REPORT: "HOE 029664 (TPTH) -^{14}C Excretion Study in Rats with Bile Fistula Following Oral Administration of 2 mg a.i./kg Body Weight".

AUTHOR(S): W.L. Burkle and H.-M. Kellner

REPORT ISSUED: December 7, 1987

CONCLUSIONS: Data were generated to demonstrate that 2.8 ± 1.4% radioactivity resulting from orally administered ^{14}C TPTH is excreted in the bile. The biliary products were mostly polar (possibly containing mono and diphenyl tin) but intact TPTH was not conclusively present. A larger amount or 11.03 ± 9.01% of the administered dose was recovered in the urine and was considered to be conjugated phenyl metabolites (no tin). The results of this study must be compared with other metabolism studies with TPTH to more fully assess the absorption and excretion of TPTH.

Classification: SUPPLEMENTARY/ACCEPTABLE by itself, MINIMUM with other studies (see Appendix for list of studies).

of current memo

Quality Assurance Statement: A statement attesting that four inspections and reports to the facility management were made. The signature of the signee is not intelligible.

REVIEW

The purpose of this study was to help clarify the relative importance of the biliary route as a means of excretion of orally administered TPTH. In this study a single group of only three male rats were surgically fitted with a bile duct fistula in the common bile duct one day prior to test article administration. The catheter (fistula) was placed in the hilus of the liver in order to collect pure bile, not contaminated with pancreatic secretions. These rats were also fitted with a second catheter which opened into the duodenum in order to substitute (with taurocholic acid) for the bile which was drained off. During the administration of the test material, the rats were allowed free access to food and water.

The test article was administered to the rats via gavage as an aqueous suspension in 70% ethanol at a dose level of 2 mg/kg (actual doses were 1.8 for 2 rats and 2.14 for the third rat). Following administration, urine, feces and bile were collected and frozen (-10° C) for a 0-30 hour period. Following the 30th hour, the rats were sacrificed and the cages washed and the wash collected. The urine, feces and bile were assessed for radioactivity by liquid scintillation counting. Attempts were made to identify the metabolites in the bile by means of thin layer and high performance liquid chromatography.

Results.

1. Distribution of Radioactivity.

Table 1 below illustrates the distribution of radioactivity after 30 hours (data are as percent of the original dose).

Table 1. Distribution of ^{14}C in rats 30 hours following an oral dose.

	Mean % ± SD
Bile	2.76 ± 1.38
Urine	11.03 ± 9.01
Cage Washings	0.41 ± 0.27
Sum	14.20 ± 10.51
Carcass (remaining)	about 86%

Based on the above data it appears that in the 30 hour interval allowed for absorption, the rats absorb and excrete about 14% of the administered dose level. The distribution within the rat of the 86% remaining in the carcass was not investigated. A substantial amount may still be in the gastro-intestinal system and a smaller amount may be in the circulatory system of the rat.

2. Identification of Metabolites.

a. Thin Layer Chromatography.

Samples of the bile (apparently without any concentration or other preparation) were assessed by spotting on thin layer plates (silica gel, Merck 60), developed in toluene (30 ml), ethyl acetate (60 ml), water (0.5 ml) and glacial acetic acid (1 ml) and analyzed for radioactivity by means of a TLC-Linear-Analyzer. The biliary metabolites cochromatographed with polar compounds (Rf 0.0 - 0.1, 1.8% and 66%) which also contained monophenyltin and diphenyltin (Rf 0.1 - 0.2, 0.7% and 26%) and a third metabolite (Rf 0.5 - 0.6, 0.2% and 5%). Note: the percentages in () are percent of the administered dose and percent of the bile radioactivity respectively. The third metabolite did not precisely cochromatograph with the TPTH reference standard (Rf 0.4 -0.5). The third metabolite was not further identified.

b. HPLC

Additional aliquots of the bile were subjected to analysis by HPLC (Spectra Physics Gmbh Model SP8700, stationary

phase RF18, mobil phase methyl cyanate, water (Ph 2 with H_2SO_4)). Both UV and ^{14}C detectors were used to monitor the eluate.

Analysis of the untreated bile was reported as resulting in two areas, the first with a retention time of 2-3.5 minutes (66% of bile fraction) and the second with a retention time of 3.5-5 (34% of bile fraction) minutes. These areas represent relatively polar compounds although the compounds were not specifically identified.

The bile was subjected to hydrolysis via reaction with an equal volume of concentrated HCl acid for refluxing (4 hours) and agitation (overnight). The resulting mixture was subjected to HPLC as above. This treatment resulted in a mixture four peaks or areas to indicate that products of lesser polarity resulted from hydrolysis. For example the four peaks consisted of the two original peaks (consisting of 9 and 14% of the original bile fraction and two new ones or peaks with retention times of 20.5 to 22 minutes (65% of the bile fraction) and 35.5 - 26.4 minutes (12% of the bile fraction). Neither of the peaks corresponded to the reference standards of phenol (retention time 18-19.5 minutes) or phenylmercapturic acid (retention time 29.5-31.5 minutes). Thus the biliary metabolites were not conclusively identified.

DISCUSSION. The authors maintain that, based on the low level of ^{14}C in the bile, the enterohepatic cycling of orally administered TPTH residues is "negligible". Attempts were made to compare the results of this study with a previous study in which both oral and intravenous administrations of TPTH were made. This comparison led the authors to conclude that the compound injected into the blood (TPTH) is not the same as the compounds being absorbed from the gastrointestinal tract (i.e. mostly if not all of the absorbed material phenyl and mono and diphenyl tin). The intravenous study does not then give a representative example of the pharmacokinetics of TPTH absorption sand excretion.

CONCLUSION. This study is SUPPLEMENTARY. Data were generated to demonstrate that 2-3% radioactivity resulting from orally administered ^{14}C TPTH is excreted in the bile. The biliary products were mostly polar (possible containing mono and diphenyl tin) but intact TPTH was not conclusively present. A larger amount or 11.03 ± 9.01% of the administered dose was recovered in the urine and were considered to be conjugated phenyl metabolites (no tin). The results of this study must be compared with other metabolism studies with TPTH to more fully assess the absorption and excretion of TPTH.

TPTH
Hoechst Aktiengesellschaft
A 36680
Dec. 7, 1987
HRID # 413972-01
SUPPLEMENTARY

008721

85-1 Metabolism Studies

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

1. V — Analytically pure grade of the active ingredient.
2. V — Isotopically labeled in the core of the molecule and/or significant portions thereof.

-OR-

3. ___ Analytical procedures sufficiently specific and sensitive to identify the test substance.
4. V — Young adult rats. Other mammalian species may be used for specific purposes.
5. A — Five male and five female rats for each dose, 4 if following OECD protocol.
6. B — Two doses, the low to be without effect and the high to produce toxic or pharmacological signs but not severe effects or mortality.
7. •N/A — Dosing group A, single low dose by intravenous route (not required if insoluble in water or normal saline).
8. N/A — Dosing group B, single low dose by oral route.
9. N/A — Dosing group C, 14 consecutive daily low dose of the unlabeled test material by oral route followed by a single low dose of the labeled test material.
10. N/A — Dosing group D, single high dose by oral route.
11. ~~7~~ 30 hours — Collect individually all urine, feces and expired air for 7 days after labeled dose or until 90+ percent of the dose is excreted (whichever occurs first). Expired air not required if a pilot study shows no excretion in 24 hours.
12. N/A — For dosing groups B, C and D, quantity of label in the following tissues and organs;

NONE

___ bone	___ liver
___ brain	___ lung
___ fat	___ blood
___ testes	___ muscle
___ heart	___ spleen
___ kidney	___ residual carcass
___ tissues showing pathology in this or prior studies	

For all dosing groups:

13. NO — Quantities of label in urine, feces and expired air (if detected in preliminary study) at appropriate intervals (e.g. 4, 8, 12 and 24 hours, 1.5, 2, 3, 4, 5, 6 and 7 days.
14. NO — Qualitative analysis of urine and feces to detect metabolism and identify metabolites (pooled urine and feces by dosing group may be used). Bile only.

NOTE The metabolism data requirement may be filled in part. For example performing the analysis on a single dose group can satisfy the requirement for that dose.

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Criteria marked with a • are supplemental and may not be required for every study.

A. Males only were used. Only three rats were used.
B. A single dose was used