9-6-91

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

008554

SEP 6 1991

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: EPA Id. #8340-17. Triphenyltin hydroxide: Registrants response to the review of the rat chronic feeding/oncogenicity study dated September 27, 1989 regarding skeletal muscle atrophy and degenerative neuropathy in the sciatic nerve and results of analysis of tissues for total tin in both the rat and dog chronic feeding studies.

TOX CHEM No.: 896E
PC No.: 83601
TOX PROJECT No.: 0-0268
Record No.: 255798

FROM: John Doherty, Ph.D. 8/15/91
Section IV, Toxicology Branch I
Health Effects Division (H7509C)

TO: Cynthia Giles-Parker
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THROUGH: Marion Copley, DVM 8/19/91
Section Head
Section IV, Toxicology Branch I
Health Effects Division (H7509C)

CONCLUSIONS

1. Rat Study (RCC # 046980, April 18, 1989, MRID # 410857-01 and -02, Document # 007501). New submissions MRID #s 412975-01 and 02). Refer to DER attached.

TB-I determined that insufficient data were provided by the registrant on the lesion skeletal muscle atrophy to dismiss the possibility that this lesion is directly or indirectly related to dietary TPTH in male rats. The NOEL/LEL for this lesion is regarded as 5/20 ppm.

The historical control information provided for the

lesion described as degenerative neuropathy in the sciatic nerve indicated that there is a wide range of occurrence for this lesion. Thus, TB-I does not regard the apparent trend for this condition in males as a definite response to dietary TPTH.

The data on the analysis of the rat tissue samples for total tin content from the chronic feeding study satisfied the Agency's request for these data. In general, the data indicate that TPTH does not appreciably accumulate in the liver, kidney, brain and blood.

No additional data for the rat chronic feeding/ carcinogenicity study are required at this time. The information provided does not alter the LEL setting for this study (< 5 ppm).

The CORE classification of the chronic feeding aspects of this study is being reclassified as MINIMUM for reasons unrelated to the new data provided (see item 4 under comments below).

2. Dog Chronic Feeding Study (RCC #047013/047024, June 1987, MRID # 402855-01, Document No.s: 006351 and 006915). New submission MRID # is 412975-03. Refer to DER attached.

The data on the analysis of the dog tissue samples for total tin content satisfies the Agency's request for these data.

The CORE classification of the dog chronic feeding study is still SUPPLEMENTARY pending verification of the test material used for the study (refer to point 5 below for additional details).

Background

Toxicology Branch I (TB-I) previously reviewed a chronic feeding/oncogenicity study in rats (refer to review by J. Doherty dated September 27, 1989 for RCC Laboratory study #046980, dated April 18, 1989) with triphenyltin hydroxide (TPTH). The review of this study indicated that there were apparent dose related increases in lesions described as skeletal muscle atrophy and degenerative neuropathy in the sciatic nerve. TB-I could not at the time of the original review make a more definite conclusion with regard to these lesions being a result of TPTH intoxication and requested that historical control data for these lesions be provided by the registrant. The registrant has provided the data as requested.

The registrant has also provided the results of the analysis of the various tissues/organs for total tin content for both the above mentioned rat chronic feeding/oncogenicity and dog (RCC Laboratory, #047013/047024, dated June 1987) chronic feeding

studies.

The information regarding the lesions in the rat study and analytical data provided by the registrant have been reviewed by TB-I and the following comments apply. DERs for analytical reports for the rat and dog chronic feeding studies are attached.

Toxicology Branch Comments.

1. Skeletal muscle atrophy in rats.

Historical control data provided by the RCC Laboratories indicated that the range in percentage for this lesion type in 18 studies of from 104 to 130 weeks duration was from 0 to 56%. There were 13 studies in which the lesions was not reported, and one study each with a reported incidence of 2, 4 26, 55 or 56%. The registrant provided comments on this lesion by Dr. K.-H. Leist who implied that the high incidence of skeletal muscle atrophy in muscle taken from the thigh especially when detected in aging animals could result from demobilization.

TB-I has considered both the historical control data and the comments by Dr. Leist but does not consider that a acceptable explanation for the apparent dose related increase (1.7, 8.5, 15 and 23.3% for the control, low, mid and high dose male groups respectively, with the mid and high dose groups being statistically significant) has been provided by the registrant.

Thus, on the basis of available information, the lesion skeletal muscle atrophy is considered a possible consequence of TPTH dosing, either direct or indirect. The NOEL and LEL for this lesion are 5 and 20 ppm. Since the NOEL for the study is already considered < 5 ppm based on other aspects of TPTH toxicity, the characterization of this lesion as a toxic response to TPTH does not alter the previous conclusion for assigning the NOEL for this study.

2. Degenerative neuropathy in the sciatic nerve in rats.

Historical control data provided by the RCC company indicated that in 18 long tern studies (104 to 130 weeks) the incidence of degenerative neuropathy in the sciatic nerve was from 0 to 98 percent. There were 10 studies in which the incidence was 0 and one study each in which the incidence was 2, 6, 10, 12, 29, 33, 40 or 98%. Comments provided by the registrant's toxicologist Dr. K.-H. Leist attempted to explain that this lesion is a consequence of demobilization of old rats in cages.

In the study with TPTH the incidence of this lesion was, in males, 33.3, 33.9, 55.9 and 51.7% and, in females,

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16.7, 15, 6.9 and 24.1% for the controls, low, mid and high dose test groups respectively. Only the data for a trend in males showed statistical significance for this lesion type.

TB-I has reconsidered the information available for this lesion type and does not considered that there is sufficient data to conclusively link the increase noted with a definite correlation with TPTH dosing. The NOEL for this study is already set at a dose level below the level at which increases in degenerative neuropathy might possibly occur.

3. Analysis of rat and dog tissues/organs for total tin content.

This information provided was determined to be ACCEPTABLE and to satisfy the Agency's request. Refer to DERs attached. Data were generated which demonstrated that neither rats or dogs progressively accumulate total tin in the liver, kidney, brain, thymus (dogs only) or blood. The total tin in these organs (except blood which remains consistently low of about 0.1 ppm in rats and 0.03 ppm in dogs), rises to maximum within a year and may progressively decline afterwards in rats. In the one year dog study, there was roughly a two fold increase in total tin content between 4 weeks and 52 weeks. The liver in dogs (9.5 to 12 ppm) and kidney in rats (about 10 ppm, but with a value of up to 25 ppm also reported) showed the highest levels. There was a tendency for female rats but not dogs to have higher residues than males. More definite conclusions regarding the time course of accumulation and sex differences were precluded because only a limited number of sampling repetitions were made.

4. CORE Classification of the Chronic Feeding Aspect of the Rat Chronic Feeding/oncogenicity Study.

The HED RfD Peer Review panel met to discuss the RfD for TPTH on June 6, 1991 (refer to memo dated June 27, 1991 from R. Engler to K. Baetcke, attached). The committee noted that since the rat chronic feeding study (RCC # 046980, April 18, 1989, MRID # 410857-02) did not define a NOEL for deaths, the study should not be classified as CORE GUIDELINE. Thus in response to the RfD committee's recommendation, this study is reclassified as CORE MINIMUM.

5. CORE Classification of the dog chronic feeding study.

The CORE classification of the dog study was originally assigned as RESERVED and the registrant requested to provide additional information on:

i. certificate of analysis of the test material,

ii. nervous system (brain and spinal cord) pathology,

iii. tissue analysis for tin.

The registrant previously satisfied TB's request for additional information on the nervous system (refer to J. Doherty review dated November 3, 1988 for EPA Reg. No.: 8340-17). This current submission has satisfied TB's request for the analysis of the tissues for tin.

The registrant, however, has not yet properly identified the test material used for the dog chronic feeding study. TB cannot upgrade the study until the certificate of analysis of the test material is provided. Proper identification of the test material is a prerequisite for determining the acceptability of a study submitted to meet a CORE study data gap.

6. Other Considerations.

The information provided in this submission is considered ACCEPTABLE and the "one liners" for the rat and dog chronic feeding studies should be updated to include this memorandum. In particular, the CORE classification for the chronic feeding aspects of the rat chronic feeding/oncogenicity study should be changed to MINIMUM.

7. Materials Submitted.

Study	TB-I Comments
83-5. Chronic Feeding/Oncogenicity - rats (Supplementary report - Company response to inquiries concerning skeletal muscle atrophy and sciatic nerve degeneration). K.-H. Leist, Hoechst Celanese Co. for study RCC Study #46980 Report dated 11/6/89 MRID # 412975-01.	Historical control data presented. NOEL/LEL for skeletal muscle atrophy retained as 5/20 ppm. Status of sciatic nerve degeneration changed from effect to an equivocal response.

83-5. Chronic Feeding/Oncogenicity - rats (Supplementary report on analysis of tissue for total tin content. For RCC study #46980 (2 years) and 56575 (13 weeks). E. Dorn and H.-J. Werner report # AG CR077/88, 9/10/89. MRID #412975-02.	In general, tin levels in the three organs (except blood) appear to reach a maximum at 52 weeks and decline thereafter. Maximum total tin level was in the kidney of females at 52 weeks and was reported as 8-25 ppm. At 104 weeks female kidneys had about 9 ppm. The small number of repetitions assayed preclude more definite conclusions.
83-1. Chronic feeding - dog (Supplementary report on analysis of tissue for total tin content. For RCC study #047013/047024. E. Dorn and H.-J. Werner report AGCR076/88 6/23/89. MRID # 412975-03.	In general, the tin levels in the four organs (except blood) reach an apparent steady state after four weeks and over the next 52 weeks the tissue level gradually reaches a level only about twice as high as at four weeks. The liver had the highest concentration being 10-12 ppm after 52 weeks. The limited number of repetitions per condition preclude more definite conclusions.

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Reviewed by: John Doherty John Doherty 8/15/91
Section IV, Toxicology Branch I (H7509C)
Secondary reviewer: Marion Copley, DVM Marion Copley 8/19/91
Section IV, Toxicology Branch I (H7509C)

DATA EVALUATION REPORT-Supplement
Original DER Document No.: 007501

STUDY TYPE: 83-5. Chronic feeding/Oncogenicity -rats. Supplement: Analysis of tissues for test material and registrant's response to TB inquiries concerning skeletal muscle atrophy and degenerative neuropathy.

MRID NO.: 412975-01 and -02 TOX. CHEM. NO.: 896E

TEST MATERIAL: Triphenyltin hydroxide, TPTH

TEST ANIMALS: Wistar rats, KFM-Han, outbred.

STUDY NUMBER(S): Hoechst AG CR077/88, RCC 046980 (52 and 104 weeks and 056575 (13 weeks).

SPONSOR: Hoechst Celanese Corporation.

TESTING FACILITY: Hoechst AG Analytisches Laboratorium, Germany

TITLE OF REPORT: "Triphenyltinhydroxide (HOE 029664 of ZD97 0007) Determination of Residues in Organs, Tissues and Blood of Rats after Chronic Feeding (104 weeks)". (412975-02)
and
"Response to EPA's Toxicology Branch Review dated September 27, 1989 regarding the Rat Chronic Feeding/ Oncogenicity Study". (412975-01).

AUTHOR(S): Dr. E. Dorn and H.-J. Werner (analytical report)
K.-H. Leist (response report)

REPORTS ISSUED: September 10, 1989 (analytical report).
November 6, 1989 (response report).

CONCLUSIONS: Revised "one liner":

The NOEL < 5 ppm (deaths and behavioral reactions in females), At 20 ppm: decreased body weight gain, decreased liver weight, "cystoid change" (males), pituitary nodules and compression of brain (females), bile duct proliferation and portal sclerosis, and skeletal muscle atrophy (males). At 80 ppm: decreased food consumption, increases in serum enzyme activity (ASAT, ALP, and ALAT). pituitary pars intermedia hyperplasia (males) Leydig cell hyperplasia and testicular atrophy, and liver eosinophilic focus (females). Equivocal: degenerative neuropathy (males).

Study classification - core minimum (Down graded from guidline due To lack of a Nor. at request of RED committee)

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The analytical data presented illustrate the tissue content at weeks 13, 52 and 104 of total tin (for kidney, liver, brain and blood) in the rat chronic feeding study. In general, tin levels in the three organs (except blood) appear to reach a maximum at 52 weeks and decline thereafter. Maximum total tin level was in the kidney of females at 52 weeks and was reported as 8-25 ppm. At 104 weeks female kidneys had about 9 ppm. The small number of repetitions assayed preclude more definite conclusions.

The company response was insufficient to dismiss the finding of skeletal muscle atrophy as a possible lesion resulting from TPTH administration at 20 and 80 ppm. The historical control data provided indicate that degenerative neuropathy can vary widely in this strain of rat and thus the trend for this lesion is considered a less definite (equivocal) response.

Classification of newly submitted data: ACCEPTABLE (analytical report). The registrant's response is not subject to CORE classification.

Quality Assurance Statement: A signed statement (signature illegible) attested that three inspections were made and three reports prepared. No comments on the conduct of the study were provided in the Quality Assurance Statement.

REVIEW

[Note: The DER for the rat chronic feeding/oncogenicity study was prepared previously and is dated Sept. 27, 1989.]

Part A. Analytical Report

In this special analytical phase of the rat chronic feeding/oncogenicity study, the liver, kidney, brain and blood of selected male and female rats was assessed for total tin at weeks 13, 52 and 104. Total tin was assessed for following mineralization of the sample with nitric and sulfuric acids. The tin was separated as tin hydride by reduction with sodium borohydride in a nitrogen stream and determined by atomic absorption spectral photometry. The efficiency of the analytical procedure was validated by spiking samples of kidney and liver with a low (0.0529 for kidney and 0.212 mg/kg of total tin for liver) and a high (2.12 for kidney and 5.28 mg/kg of total tin for liver) TPTH sample. The efficiency of the extraction was reported as being 108 and 123% for the low and high spiking levels for the kidney and 104 and 76% for the low and high spiking levels for the liver. The organs from three animals from each group were combined to make a single sample for analysis.

The control and high dose groups were analyzed at 13 and 52 weeks, but all four dose levels were analyzed for the 104 week interval.

Results

1. Selective accumulation.

The tissue with the highest level of total tin was the kidney. Table I below illustrates the disposition of total tin in selected organs from rats after 104 weeks.

Table I. Disposition of total tin after 104 weeks.

		Dose Group[1]			
Organ	Sex	Control	5 ppm	20 ppm	80 ppm
Kidney	M	<0.005/<0.005	0.85/0.67	1.8/2.6	3.45/3.9
	F	0.062/0.062	1.8/1.5	3.8/4.2	10.5/8.5
Liver	M	<0.005/<0.005	1.2/0.96	0.78/1.45	2.0/2.4
	F	0.067/0.085	1.2/1.1	2.05/1.7	3.1/2.5
Brain	M	<0.005/<0.005	0.32/0.32	1.0/0.97	3.0/2.3
	F	0.019/0.009	0.48/0.46	1.15/1.25	3.0/3.4
Blood	M	0.006/<0.005	0.005/0.008	0.024/0.028	0.075/0.062
	F	0.005/0.006	0.007/0.006	0.031/0.033	0.090/0.11

[1] Data are mg total tin/kg of tissue or ppm.
The numerator is for one set of data from three rats, the denominator is for a second set of data from three rats.

After the kidney, the liver and brain have similar concentrations and the blood has the lowest level.

2. Dose level.

The above table also illustrates that in general each organ has a higher level of total tin although a true dose dependent manner is not apparent in that there is not a four and sixteen fold increase in tissue residues with a four and sixteen fold increase in dose level.

3. Time course of accumulation.

The time course for the accumulation of tin in the kidney, liver and brain for the high dose test group are illustrated in Table II:

Table II. Time course for accumulation of total tin in selected tissues.

		Total Tin (mg/kg)		
Interval	Sex	Kidney	Liver	Brain
13 weeks	M	2.7	1.4	1.4
	F	4.7	1.0	1.35
52 weeks	M	8.0	3.55	2.8
	F	25.0	9.5	6.7
104 weeks	M	3.45/3.9	2.0/2.4	3.0/2.3
	F	10.5/8.5	3.1/2.5	3.0/3.4

The total tin level in the kidney and liver seems to reach a maximum at 52 weeks and the level at 104 weeks is lower than at 52 weeks but still higher than at 13 weeks. This same pattern was also apparent in the brain. More definite conclusions regarding a peak at 52 weeks followed by a decline cannot be made in the absence of more determinations at each time interval. The blood levels were constant (about 0.048 to 0.11 mg/kg) at all intervals.

4. Sex

Females consistently (at all time intervals, see above table) had higher total tin levels in the kidney but not the liver or brain. It is noted, however, that at week 52 the total tin content was higher for females than for males in the brain and liver.

CONCLUSION. This report is ACCEPTABLE. The data presented illustrate the tissue content (for kidney, liver, brain and blood) in the rat chronic feeding study. In general tin levels in the three organs (except blood) appear to reach a maximum at 52 weeks and decline thereafter. Maximum total tin level was in the kidney of females at 52 weeks and was reported as 8-25 ppm. At 104 weeks female kidneys had about 9 ppm. The small number of repetitions assayed preclude more definite conclusions.

Part B. Registrants Response to TB-I's Inquiries Concerning Skeletal Muscle Atrophy and Degenerative Neuropathy.

Attached are historical control data submitted by the registrants from 18 sets of control groups which illustrate the frequency of rats with degenerative neuropathy in the sciatic nerve and skeletal muscle atrophy.

1. Skeletal muscle atrophy in rats.

Historical control data provided by the RCC Laboratories indicated that the range in percentage for this lesion type in 18 studies of from 104 to 130 weeks duration was from 0 to 56%. There were 13 studies in which the lesions was not reported, and one study each with a reported incidence of 2, 4 26, 55 or 56%. The registrant provided comments on this lesion by Dr. K.-H. Leist who implied that the high incidence of skeletal muscle atrophy in muscle taken from the thigh especially when detected in aging animals could result from demobilization.

TB-I has considered both the historical control data and the comments by Dr. Leist but does not consider that a acceptable explanation for the apparent dose related increase (1.7, 8.5, 15 and 23.3% for the control, low, mid and high dose male groups respectively, with the mid and high dose groups being statistically significant) has been provided by the registrant.

Thus, on the basis of available information, the lesion skeletal muscle atrophy is considered a possible consequence of TPTH dosing, either direct or indirect. The NOEL and LEL for this lesion are 5 and 20 ppm. Since the NOEL for the study is already considered < 5 ppm based on other aspects of TPTH toxicity, the characterization of this lesion as a toxic response to TPTH does not alter the previous conclusion for assigning the NOEL for this study.

2. Degenerative neuropathy in the sciatic nerve in rats.

Historical control data provided by the RCC company indicated that in 18 long tern studies (104 to 130 weeks) the incidence of degenerative neuropathy in the sciatic nerve was from 0 to 98 percent. There were 10 studies in which the incidence was 0 and one study each in which the incidence was 2, 6, 10, 12, 29, 33, 40 or 98%. Comments provided by the registrant's toxicologist Dr. K.-H. Leist attempted to explain that this lesion is a consequence of demobilization of old rats in cages.

In the study with TPTH the incidence of this lesion was, in males, 33.3, 33.9, 55.9 and 51.7% and, in females,

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16.7, 15, 6.9 and 24.1% for the controls, low, mid and high dose test groups respectively. Only the data for a trend in males showed statistical significance for this lesion type.

TB-I has reconsidered the information available for this lesion type and does not considered that there is sufficient data to conclusively link the increase noted with a definite correlation with TPTH dosing. The NOEL for this study is already set at a dose level below the level at which increases in degenerative neuropathy might possibly occur.

Note: Data are not subject to CORE Classification since they are a resposne to an inquirey from TB.

TPTH

Page _____ is not included in this copy.

Pages 13 through 14 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 quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

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_____ The product confidential statement of formula.

_____ Information about a pending registration action.

X FIFRA registration data.

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_____ 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: John Doherty 8/15/91 008554
Section IV, Toxicology Branch I (H7509C)
Secondary reviewer: Marion Copley, DVM 8/19/91
Section IV, Toxicology Branch I (H7509C)

DATA EVALUATION REPORT-Supplement
Original DER Document No.: 006351

STUDY TYPE: 83-2. Chronic feeding - dog. Supplement: Analysis of tissues and organs for total tin.

MRID NO.: 412975-03 TOX. CHEM. NO.: 896E

TEST MATERIAL: Triphenyltinhydroxide (TPTH)

TEST ANIMALS: beagle dogs

STUDY NUMBER(S): Hoechst AG CR076/88, RCC 047024/047013

SPONSOR: Hoechst Celanese Corporation

TESTING FACILITY: Hoechst AG Analytisches Laboratorium, Germany

TITLE OF REPORT: Triphenyltin hydroxide (HOE 029664 of ZD97 0007) Determination of Residues in Organs, Tissues and Blood of dogs after Chronic Feeding (52 weeks).

AUTHOR(S): Dr. E. Dorn and H.-J. Werner

REPORT ISSUED: June 23, 1989

CONCLUSIONS:

The NOEL for the study remains as > 18 ppm (HDT or 0.6 mg/kg/day).

The data presented illustrate the tissue content for total tin following administration of TPTH in the dog chronic feeding study. In general, the tin levels in the four organs (except blood) reach an apparent steady state after four weeks and over the next 52 weeks the tissue level gradually reaches a level only about twice as high as at four weeks. The liver had the highest concentration being 10-12 ppm after 52 weeks. The limited number of repetitions per condition preclude more definite conclusions.

Classification of new data submitted: SUPPLEMENTARY. These data do not change the classification of the study from SUPPLEMENTARY. Additional information on the exact identity of the test material must be submitted.

Quality Assurance Statement: A signed statement (signature illegible) attested that three inspections and three reports were made. No comments on the conduction of the study were provided by the Quality Assurance.

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REVIEW

[Note: The DER for the dog chronic feeding study was prepared previously and is dated October 2, 1987 and is Document No.: 006351.

In this special analytical phase of the dog chronic feeding study, the liver, kidney, brain, blood and thymus were assessed for total tin residues at 4, 13, 27 and 52 weeks of dosing. Total tin was assessed for following mineralization of the sample with nitric and sulfuric acids. The tin is separated as tin hydride by reduction with sodium borohydride in a nitrogen stream and determined by atomic absorption spectral photometry (wavelength 286.3 m). The method was validate by spiking samples of liver and kidney with TPTH. No efforts were made to characterize the tin residues as parent TPTH or is di and mono tin metabolites. The tissues from one dog of each sex per dose group for the control, low and mid dose groups and two dogs of each sex for the high dose group were obtained at the 52 week interval. At weeks 4, 13 and 27 weeks, a single control dog and two high dose group dogs were analyzed.

Results

1. Selective accumulation.

The tissue with the highest level of total tin (9.5 to 12 mg/kg) was the liver. Table 1 below illustrates the disposition of total tin after 52 weeks.

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Table 1. Disposition of total tin in selected dog tissues after 52 weeks.

Organ	Sex	Dose Group: Control	2 ppm	6 ppm	18 ppm
Liver	M	0.06	0.75	1.5	12/11[1]
	F	0.04	2.7	1.5	11/9.5
Kidney	M	<0.005	0.42	1.1	1.5/2.9
	F	<0.005	0.36	1.7	1.4/3.25
Brain	M	<0.005	0.082	0.26	0.66/0.59
	F	<0.005	0.11	0.27	0.93/0.73
/mus	M	<0.005	0.071	0.19	0.73/0.50
	F	0.100	0.090	0.34	0.62/0.45
Blood	M	<0.005	<0.005	0.008	0.026/0.027
	F	<0.005	0.007	0.009	0.024/0.020

[1] Data entries are for the analysis of one animal for the control, low and mid dose group. For the high dose group, the numerator and denominator each represent the result for one animal. Some entries are the means for multiple injections from one animal.

As indicated above, the kidney, brain and thymus (about equal) and blood had lower amounts of total tin.

2. Dose level

The above table also illustrates that in general each of the organs has a higher level of total tin in a dose dependent manner although there was not a 3 and 9 fold increase in residues with a 3 and 9 fold increase in dose. The low dose female liver data is not in the true dose response but this is probably related to there being only one sample for analysis.

3. Time Course of Accumulation.

The time course for accumulation of tin in the liver is illustrated in table 2 below.

Table 2. Time course of disposition of total tin in selected tissues from dogs.

Interval	Sex	Tin mg/kg
4 weeks	M	4.5/4.8
	F	7.1/4.2
13 weeks	M	6.0/8.2
	F	7.7/9.4
27 weeks	M	8.0/9.8
	F	8.5/11
52 weeks	M	12/11
	F	11/9.5

There is roughly only a two fold increase in total tin content between the 4 week and 52 week time periods. Thus, there is only minor accumulation of tin following repeated dosing.

The kidney, brain and thymus showed less than a two fold increase in total tin content over the experimental period. The blood had similar values at each time tested.

4. Sex.

No real or consistent differences in the disposition of total tin in males and females were noted.

CONCLUSION. This report is SUPPLEMENTARY. The data presented illustrate the tissue content for total tin in the dog chronic feeding study. In general the tin levels in the four organs (except blood) reach an apparent steady state after four weeks and over the next 52 weeks the tissue level gradually reaches a level only about twice as high as at four weeks. The limited number of repetitions per condition preclude more definite conclusions.

These data do not, however, change the classification of the study from SUPPLEMENTARY. Additional information on the exact identity of the test material must be submitted.