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WASHINGTON, D.C. 20460

008480

JUL 30 1991

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OFFICE OF  
PESTICIDES AND TOXIC  
SUBSTANCES

MEMORANDUM

SUBJECT: Triphenyltin Hydroxide: Request for an updated DER for the rat two-year chronic feeding study conducted at the Centraal Instituut voor Voedingsonderzoek in 1970 and reclassification of 1989 rat chronic feeding study conducted at RRC Laboratory.

TOX CHEM No.: 896E  
TOX PROJECT No.: INTRA-0201  
Record No.: none

FROM: John Doherty *John Doherty 7/25/91*  
Section IV, Toxicology Branch I  
Health Effects Division (H7509C)

TO: Reto Engler  
Chief, Science Analysis and Coordination Branch  
Health Effects Division (H7509C)

THROUGH: Marion Copley, DVM, Section Head *Marion Copley 7/26/91*  
Section IV, Toxicology Branch I  
Health Effects Division (H7509C)

CONCLUSION

The 2-year chronic feeding study with triphenyltin hydroxide (TPTH) conducted at the Centraal Instituut voor Voedingsonderzoek in 1970 (Study # R 3138 and Pathology Report # 56645/19/70) was rereviewed. The study was reclassified as SUPPLEMENTARY. The NOEL of 2 ppm (0.1 mg/kg/day) based on decreases in white blood cell counts in males was retained. In addition to an effect on white blood cells, TB has determined that the study demonstrates an effect on body weight gain and survival in females at 10 ppm (0.5 mg/kg/day).

The data from this study taken together with the more recent chronic feeding/oncogenicity study (RCC #046980, April 18, 1989, MRID #410857-02, DER in document #007501) are considered useful in helping to set the NOEL for chronic feeding in rats RfD for TPTH.

*12/12*

ACTION REQUESTED

The HED RfD/Peer Review committee met on June 6, 1991 to discuss the reference dose (RfD) for triphenyltin hydroxide (TPTH). The committee agreed that the 1970 rat study was co-critical in setting the RfD. The DER for this study was first prepared in approximately 1980 and was not up to current standards. In a memo from Dr. Engler, Chief Science Analysis and Coordination Branch to Dr. Karl Baetcke, Chief, Toxicology Branch I, it was requested that the study be rereviewed and a new DER be generated.

Dr. Engler's June 6, 1991 memo also recommended that the more recent chronic feeding study (RCC # 046980, April 18, 1989, MRID #410857-02, DER Document # 007501) be reclassified as MINIMUM because this study did not demonstrate a NOEL for systemic toxicity.

TB-I has rereviewed the 1970 study and the new DER is attached. The following comments apply.

Toxicology Branch Comments

1. The study was reclassified as SUPPLEMENTARY. There were noted deficiencies in data reporting, not all individual animal data were reported and the individual animal pathology sheets were not provided.
2. The NOEL of 2 ppm (0.1 mg/kg/day) was assigned based on decreases in white blood cell counts in the first year of the study. This NOEL is the same as originally assigned. In addition to the effect on white blood cells, the new DER indicates that the high dose group (10 ppm, 0.5 mg/kg/day) is associated with decreased survival in females and increased body weight gains.  

The effect on survival was not considered an effect in the original review because of the small difference between the control and the high dose group and the statistically significance noted was only transitory. However, the more recent chronic feeding study demonstrated quite clearly that death results at 5 ppm and above and the conclusions of the previous review of the 1970 study were reconsidered.
3. Although the 1970 study was classified as SUPPLEMENTARY, the data from the 1970 study when taken together with the more recent 1989 chronic feeding/oncogenicity study is considered useful in setting the RfD for TPTH.
4. The 1970 study was reevaluated in terms of what was noted in the 1989 chronic feeding/oncogenicity study but none of the lesions in the pituitary, testis or other structures were noted

in the 1970 study. This is considered reasonable because the dose levels tested in the 1970 study were 0, 0.5, 1, 2, 5 and 10 ppm. The dose levels in the 1989 study were 0, 5, 20 and 80 ppm. Thus, the higher dose levels in the later study would be expected to result in different lesions.

5. The classification of the RCC 1989 rat chronic feeding study was discussed separately in TOX PROJECT No.:1-0268. The classification of this study was changed to MINIMUM. The date of this review is pending.

Study	Study Reviewed	Results
82-1 Chronic Feeding-rat Centraal Instituut voor Voedingsonderzoek, Study # R 3138, Pathology report # 56645/19/70 August 1970 Accession # 099050 SUPPLEMENTARY*	NOEL = 2 ppm. LEL = 5 ppm: De- creased <u>leucocyte</u> counts in males. AT 10 ppm: Decreased leucocyte counts in females and increased <u>deaths</u> in females and increased <u>body weight</u> in females and to a lesser extent in males.	Dose levels tested: 0, 0.5, 1, 2, 5, and 10 ppm (0, 0.025, 0.05, 0.10, 0.25 and 0.5 mg/kg/day).
*When combined with a later chronic feeding study (RCC #046980, April 18, 1989) these data are considered MINIMUM.		

cc: Lew Kerestesy, Special Review Branch (H7508W)  
 Cynthia Giles-Parker, Registration Division (H7509c)  
 Toxicology Branch Files

Reviewed by: John Doherty *John Doherty* 7/23/91  
Section IV, Toxicology Branch I (H7509C)  
Secondary reviewer: Marion Copley, DVM *Marion Copley* 7/25/91  
Section IV, Toxicology Branch I (H7509C)

008480

DATA EVALUATION REPORT

STUDY TYPE: 83-1. Chronic feeding-rat

Accession No.: 099050 TOX. CHEM. NO.: 896E

TEST MATERIAL: Triphenyltin hydroxide (TPTH). Presumed to be 100% purity. Infrared spectrum of test material provided.

STUDY NUMBER(S): Main Study Number R 3138. Pathology Report Addendum: Report # 56645/19/70

SPONSOR: Philips Duphar

TESTING FACILITY: Centraal Instituut voor Voedingsonderzoek

TITLE OF REPORT: "Chronic toxicity study with Triphenyltinhydroxide in rats for two years"

AUTHOR(S): Drs. H.P. Til, V.J. Peron and A.P. de Groot

REPORT ISSUED: August 1970. Pathology Report July 1970.

STUDY DATES: Not provided

CONCLUSIONS:

NOEL = 2 ppm. LEL = 5 ppm: Decreased leucocyte counts in males. At 10 ppm: Decreased leucocyte counts in females and increased deaths in females and increased body weight in females and to a lesser extent in males.

Dose levels tested: 0, 0.5, 1, 2, 5, and 10 ppm. Approximately 0, 0.025, 0.05, 0.10 and 0.25 mg/kg/day.

Classification: SUPPLEMENTARY\*. Reporting deficiencies, lack of certain individual animal data and individual animal pathology sheets and not all endpoints in current guidelines investigated. NOTE: The registrant has already provided a replacement study (RCC #046980, April 18, 1989, MRID # 410857-02, DER in document #007501). \*This study when taken together with the RCC study is considered MINIMUM.

Quality Assurance Statement: None provided. Study is circa 1969. Good Laboratory Practice Statement: None provided.

## REVIEW

Basic Study Design and Study Constants.

Test Animals. Wistar strain rats were obtained from the testing laboratory's colony. They were reported as being newly weaned (42-59 gms) at the start of the study. They were housed five per cage.

The basic design of this study consisted of dosing six groups of 25 male and 25 female rats with diets containing either 0, 0.5, 1.0, 2.0, 5.0 or 10 ppm of TPTH.

No data were provided on the analysis of the test diets for homogeneity, stability or verification of the dose level.

Results.

## 1. Clinical Reactions and Survival.

The study report maintains that no compound related effects on general health or mortality were noted. No data on clinical signs were presented. A table (Table 1 of the study report) on the cumulative mortality over the two year experiment was presented. Inspection of the study report table confirms that there was no apparent compound related deaths among the males. For example there were 15, 11, 10, 13, 9, and 14 deaths for the control to high dose groups respectively.

The cumulative mortality among the females is illustrated in Table I below:

Table I. Cumulative deaths among female rats dosed with TPTH.

Interval	Dose level <sup>1</sup>					
	Control	0.5	1.0	2.0	5.0	10.0
48	0	0	0	0	0	1
60	0	0	0	0	0	1
72	0	0	0	0	0	2
84	1	2	2	1	1	5
96	1	3	5	3	3	9**
104	4	4	7	6	6	10

\* Reported as being statistically significantly different from controls  $.001 < p < 0.1$ . The test method used by the study report was not defined.

<sup>1</sup> There were 25 rats at the initiation of the study.

The above table shows that the first death (at week 48) occurred in the high dose female group and that by week 96 this group reaches statistical significance. The statistical significance, however, disappears by week 104 because there were 3 deaths in the control group but only a single death in the high dose group. There were no comments in the study report on the cause of death. TB concludes that deaths in the high dose female group were related to the test material. This conclusion is based partly on the similar finding in the more recent chronic feeding study with TPTH (RCC Study #046980, April 18, 1989, MRID # 410857-02, review in Document #007501) in which no NOEL could be established for females (LEL = 5 ppm).

CONCLUSION (survival). NOEL = 5 ppm. LEL = 10 ppm. Deaths in females.

2. Body Weight and Food Consumption. The rats were reported as being weighted weekly for the first three months and thereafter every four weeks.

Body weight and food consumption for the controls and treated rats were reported as being comparable throughout the study. The weights of the high dose female group, however, reached statistical significance of  $p < 0.01$  (i.e. about 7% increased) for the weeks 4 to 52. The males high dose group was also slightly higher (i.e. usually about 3-4%) but statistical significance was only attained at week 96 (10.8% increased).

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The increase in body weight was not paralleled by obvious increases in food consumption.

CONCLUSION (body weight). NOEL = 5 ppm. LEL = 10 ppm. Body weight increase in females and to a lesser extent in males.

3. Hematology. Blood was collected (specifics of collection not reported) from 8 males and 6 females on week 6 and 10 males and 10 females on weeks 13, 26, 52, 78 and 100. The following parameters were reported as being investigated: haemoglobin, packed cell volume, red blood cell counts, and total and differential white blood cell counts.

Table 4 (entitled "Average figures of blood analyses of rats fed TPTH at different levels in diets for two years", three pages) xeroxed from the study report is attached. This table illustrates that white blood cell count (WBC x  $10^3$ /mm<sup>3</sup>) is statistically significantly decreased for males and females at the following intervals (note in some cases the percent difference from the control is also shown although statistical significance was not attained):

week 6:	males	5 ppm:	-18.8%	p < 0.05 <sup>1</sup>
		10 ppm	-20%	p < 0.05
	females	10 ppm	-23%	p < 0.05
week 13:	males	5 ppm	-14%	ns
	males	10 ppm	-16%	p < 0.05
	females	10 ppm	-24%	p < 0.01
week 26:	males	2 ppm	-14%	p < 0.05
		5 ppm	-9%	p < 0.05
		10 ppm	-14%	p < 0.05
week 52:	males	10 ppm	+4%	ns
	females	10 ppm	-20%	p < 0.05
week 78:	males	10 ppm	-9%	ns
	females	10 ppm	+6%	ns
week 100	males	10 ppm	-7%	ns
	females	10 ppm	-5%	ns

<sup>1</sup> Statistical significance according to the study report. The statistical test was not described. ns = not reported to be statistically different from control.

The study report (page 6) asserts that "the no-toxic effect level could safely be placed at 1 ppm. However, if the slight and transitory effect on leukocytes is considered to be toxicologically unimportant, the no-toxic effect level could be placed at 5 ppm". In the original review of this study the NOEL was set at 2 ppm because the leucocyte count especially in males was decreased consistently at 5 and 10 ppm at weeks 6, 13 and 26. The decrease at week 26 for the group dosed with 2 ppm was not noted at other intervals. Therefore is not considered biologically significant.

CONCLUSION (hematology): NOEL = 2 ppm. LEL = 5 ppm: Decreases in leucocyte counts in the first year of dosing.

4. Clinical Chemistry. Blood sugar and urea nitrogen were assessed at weeks 81 and 102. Serum glutamic-pyruvic transaminase (SGPT), serum glutamic-oxalacetic transaminase (SGOT) and serum alkaline phosphatase (SAP) were determined on 10 males and 10 females at termination.

A summary table was presented with these data and no apparent dose related increase or decrease was noted. The mean values only were presented without the standard deviations. The high dose group females were about 26% ( $p < 0.05$ ) decreased relative to the control at week 81 but were essentially the same as the control at week 102. Thus, no effects on these parameters were evident.

There were no elevations in the levels of SGOT, SGPT or SAP noted. Some decreases were noted but these are not considered toxicologically significant.

CONCLUSION (clinical chemistry). NOEL > 10 ppm.

5. Urinalysis. Urine was sampled from 5 male and 5 female rats at weeks 32, 76, and 102. The parameters investigated were pH, glucose, protein, occult blood and acetone using Hemacombistix and Ketostix techniques.

There were no compound related changes in the composition of the urine reported.

CONCLUSION (urine analysis): NOEL > 10 ppm.

6. Organ weights. After termination of the study the rats were sacrificed by decapitation and necropsied. The following organs from the survivors were weighted: heart, kidney, liver, spleen, brain, testicles or ovary, eye, pituitary, thyroid and adrenals. Data on the relative organ weights were summarized.

Only the thyroid from the high dose (10 ppm) females (-11%,  $p < 0.05$ , study report statistics, method not provided) was reported as being statistically significantly different from the control. The female group dosed with 5 ppm was also slightly lower than the control (-5%, not significant). The high dose male group did not reach statistical significance but was 9% less than the control but the low dose group was about 20% higher than the control.

7. Pathology. The microscopic pathology report was presented as an addendum to the study report. It is report # 56645/19/70 from the Department of Toxicology Philips-Dupar and dated July 1970.

[Note: The main report refers to necropsy and states that the animals were subjected to autopsy. The report also concludes that based on gross examination no treated-related pathological changes were detected.]

The tissues from all animals in the control groups (male and female) and all animals (except one male and one female which died and were too autolyzed for analysis) were evaluated histologically. In addition, it was stated that if effects were observed in any organ in the high dose group, the low middle dose groups were to be prepared and evaluated. The tissues were cut into 5 u sections and stained with haematoxylin-eosin "according to standard procedures".

The report stated that the following tissues had lesions or that no lesions were found in these tissues.

Digestive system group: "gastro-intestinal tract", trachea, liver, urinary bladder, salivary gland, pancreas and kidney.  
Cardiovascular/pulmonary group (including blood and lymph): heart, lung, bone marrow (and bone), spleen, thymus, and lymph glands.  
Neuro/muscular group: "peripheral central nervous system", eye, cerebrum, cerebellum and muscle.  
Endocrine group: thyroid, adrenal, pituitary, mammary gland and parathyroid gland.  
Reproductive group: testicle, epididymides, prostate, seminal vesicle, uterus and ovary.

The study report author (Dr. H.M. van der Linde, resident pathologist of Philips Duphar), concluded that the test material "did not evoke pathological changes in rats when fed 10 ppm of TPTH in the diet during a period of two years". No data were reported on observations in the low and mid dose groups.

Inspection of the pathology report and data tables indicates that in only a few instances were there more of a specified lesion type in the high dose group than in the controls. When there were more in the high dose group, the

lesions were commonly occurring and no definite effect of TPTH treatment was obvious. The report did not indicate if any statistical tests were used to compare the data, thus no statistically significant increases in a lesion type were noted.

There was only a single pituitary tumor (adenoma) reported, this was in a high dose female. The incidence of non-neoplastic lesions in the pituitary were infrequent (only 1 or 2 incidents) and no evidence of increased hyperplasia was evident.

TB notes that the thymus of males had 9 incidents of "slight atrophy" whereas the control group had only three. This may have been a response to the chemical because the thymus is considered a likely target for TPTH possible related to the immunotoxicity of TPTH. Since the rats were two years old, thymus pathology data are considered of limited usefulness in the absence of other supporting data.

CONCLUSION (pathology) = NOEL > 10 ppm.

CONCLUSION (Study). This study is classified as SUPPLEMENTARY. Reporting deficiencies (such as not all individual animal data or individual animal pathology sheets provided), not all clinical chemistry or blood parameters in current guidelines investigated.

NOEL = 2 ppm. LEL = 5 ppm: Decreased leucocyte counts in males. At 10 ppm: Decreased leucocyte counts in females and increased deaths in females and increased body weight in females and to a lesser extent in males.

TPTH

Centraal Instituut voor Veehygiëne en Diergeneeskunde

# R3138

August 1970

Acc # 099050

008480

DRAFT  
Subdivision F  
Guideline Ref. No. 83-1  
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83-1 Chronic Feeding in the Rodent and Nonrodent

SUPPLEMENTARY ACCEPTANCE CRITERIA

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Does your study meet the following acceptance criteria?:

1.  Technical form of the active ingredient tested.
2.  At least 20 rodents or 4 nonrodents/sex/group ( 3 test groups and control group).
3.  Dosing duration in rodents minimum 12 month nonfood use, 24 months food use; in nonrodents minimum 12 months<sup>1</sup>.
4.  Doses tested include signs of toxicity at high dose but no lethality in nonrodents or a limit dose if nontoxic (1,000 mg/kg). *Signs were indefinite*
5.  Doses tested include a NOEL.
6.  ~~NO~~ Analysis for test material stability, homogeneity and concentration in dosing medium
7.  ~~NO~~ Individual daily observations.
8.  ~~NO~~ Individual body weights. *summary table*
9.  ~~NO~~ Individual or cage food consumption. *summary table*
10.  ~~NO~~ Ophthalmoscopic examination (at least per test and at term) control and high dose.
11.  ~~NO~~ Clinical pathology data for all nonrodents and at least 10 rodents/group consisting of 12, 13 & 14.
13.  Hematology at 6 month intervals consisting of at least:
 

<input checked="" type="checkbox"/> Erythrocyte count	<input checked="" type="checkbox"/> Leucocyte count
<input checked="" type="checkbox"/> Hemoglobin	<input type="checkbox"/> Differential count
<input type="checkbox"/> Hematocrit	<input type="checkbox"/> Platelet count (or clotting measure)
14.  Clinical chemistry at 6 month intervals consisting of at least:
 

<input checked="" type="checkbox"/> Alkaline phosphatase	<input type="checkbox"/> Total Protein
<input type="checkbox"/> Aspartate aminotransferase	<input type="checkbox"/> Albumin
<input type="checkbox"/> Creatinine kinase	<input type="checkbox"/> Urea (as BUN)
<input type="checkbox"/> Lactic dehydrogenase	<input type="checkbox"/> Inorganic phosphate
<input checked="" type="checkbox"/> Glucose	<input type="checkbox"/> Calcium
<input type="checkbox"/> Bilirubin	<input type="checkbox"/> Potassium
<input type="checkbox"/> Cholesterol	<input type="checkbox"/> Sodium
<input type="checkbox"/> Creatinine	<input type="checkbox"/> Chloride
15.  Urinalysis at 6 month intervals consisting of at least:
 

<input checked="" type="checkbox"/> Bilis	<input type="checkbox"/> Total bilirubin
<input checked="" type="checkbox"/> Protein	<input type="checkbox"/> Urobilirubin
<input checked="" type="checkbox"/> Ketone bodies	<input type="checkbox"/> Sediment
<input checked="" type="checkbox"/> Appearance	<input type="checkbox"/> Specific gravity (osmolality)
<input checked="" type="checkbox"/> Glucose	<input type="checkbox"/> Volume
16.  ~~NO~~ \* Individual necropsy of all animals. *No report*
17.  ~~NO~~ Histopathology of the following tissues performed on all nonrodents and rodents, all control and high dose animals, all animals that died or were killed on study, all gross lesions on all animals, target organs on all animals and lungs, liver and kidneys on all other animals.

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

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- |   |   |  |
|---|---|--|
| <input checked="" type="checkbox"/> eyes      | <input checked="" type="checkbox"/> bone marrow   | <input checked="" type="checkbox"/> kidneys†               |
| <input checked="" type="checkbox"/> caecum    | <input checked="" type="checkbox"/> liver†        | <input type="checkbox"/> esophagus not mentioned           |
| <input checked="" type="checkbox"/> colon     | <input checked="" type="checkbox"/> lung†         | <input checked="" type="checkbox"/> ovaries†               |
| <input checked="" type="checkbox"/> duodenum  | <input checked="" type="checkbox"/> lymph nodes   | <input type="checkbox"/> oviduct not mentioned             |
| <input checked="" type="checkbox"/> brain†    | <input checked="" type="checkbox"/> stomach       | <input checked="" type="checkbox"/> pancreas               |
| <input checked="" type="checkbox"/> skin      | <input checked="" type="checkbox"/> mammary gland | <input checked="" type="checkbox"/> rectum                 |
| <input checked="" type="checkbox"/> heart†    | <input checked="" type="checkbox"/> spleen†       | <input checked="" type="checkbox"/> spinal cord (3x)       |
| <input checked="" type="checkbox"/> testes†   | <input checked="" type="checkbox"/> musculature   | <input checked="" type="checkbox"/> thyroid / parathyroids |
| <input checked="" type="checkbox"/> pituitary | <input checked="" type="checkbox"/> epididymis    | <input type="checkbox"/> salivary glands                   |
| <input checked="" type="checkbox"/> ileum     | <input checked="" type="checkbox"/> adrenals†     | <input checked="" type="checkbox"/> thymus                 |
| <input checked="" type="checkbox"/> trachea   | <input checked="" type="checkbox"/> uterus        | <input checked="" type="checkbox"/> urinary bladder        |
|   |   | <input checked="" type="checkbox"/> prostate               |
|   |   | <input checked="" type="checkbox"/> seminal vesicle        |
|   |   | <input checked="" type="checkbox"/> salivary gland         |
|   |   | <input checked="" type="checkbox"/> bone                   |

† organs to be weighed

~~Some of the criteria may be acceptable. (?)~~

\* Necropsy was said to be done on all animals and the report states that there were no compound related pathological changes detected. No summary table was presented.

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

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