CASWELL FILE

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

MAR 31 1986

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Reg. NO. 8340-17. Triphenyltin Hydroxide: Review of revised protocols for analyses of dog and rat tissue samples for triphenyltin hydroxide and its metabolites.

TOX CHEM No. 896E
TOX Project No. 1500

FROM: John Doherty 3/27/86
Acting Section Head
Toxicology Branch
Hazard Evaluation Division (TS-769)

TO: Henry Jacoby
Product Manager #21
Registration Division (TS-767)

3/27/86

3/31/86

Background

In a previous memo (refer to J. Doherty memo for EPA Reg. No. 8340-17 dated June 18, 1985) Toxicology Branch (TB) reviewed protocols for proposed dog and rat chronic toxicity and rat reproduction studies. The comments made by TB for these protocols included that the tissue samples be analyzed for triphenyltin hydroxide (TPTH) and its diphenyl and monophenyl tin metabolites.

In a subsequent meeting with the registrants (refer to notes of the meeting prepared by J. Doherty and dated December 31, 1986) the representatives informed EPA that to analyze for all of the samples as requested by TB would require an estimated expense of $670,000 and two years labor. The registrants thus requested and TB agreed to allow the registrants to submit a revised protocol for analyses of the tissues from the dogs and rats on the the chronic feeding studies with TPTH.

The registrants have submitted a revised protocol as attached.

TB Comments

The revised protocol consists mainly of analyzing the dog tissue samples at 3, 6 and 12 months and the rat tissue samples at 3 and 12 months and ~~four~~ Five tissue types (including the blood) plus the excreta will be analyzed. Only the control and high dose test groups will be assessed. TB also understands that the tissue samples will be analyzed for TPTH and its metabolites.

TB concurs with the revised protocol for analyzing the reduced number of tissue samples for the dog and rat chronic feeding studies. It is, however, strongly recommended that the tissue samples which are not analyzed for TPTH and its metabolites be preserved (frozen) for possible future analyis.

It should also be noted that additional tissue types may have to be analyzed pending receipt and review of the general metabolism studies with TPTH.

TB also agrees that tissue samples from the rat two generation reproduction study need not be analyzed. TB, however, strongly recommends that data be generated to describe the placental transfer of TPTH.

American Hoechst Corporation
Route 202-206 North • Somerville, New Jersey 08876
Telex 833-449 • Cable Hoechstus, Somerville, N.J.
Telephone (201) 231-2000

Hoechst

Direct dial number: (201) 231-2367

January 22, 1986

Mr. Henry M. Jacoby
Product Manager (21)
Fungicide-Herbicide Branch
Registration Division (TS-767C)
U. S. Environmental Protection Agency
Crystal Mall Building #2, Room 227
1921 Jefferson Davis Highway
Arlington, VA 22202

Dear Mr. Jacoby:

Subject: TPTH
EPA Registration No. 8340-17
Review of Protocols Requesting
Organ Analysis for Tin

This letter refers to our December 12th meeting with the Agency, represented by P. Hunderman, B. Shackleford, E. Budd, J. Doherty, R. Zendzian. Mr. D. J. Lawatsch of American Hoechst handed out a status report which included Table 1 (Attachment 1). This table exhibits the analysis work originally requested by the Agency. Based on this list, we discussed the scientific significance of each of the four outlined studies and the need for regulatory actions. It was agreed that the extent of those investigations (13,380 analyses in total, two chemists work for two years, estimated costs of $670,000) is far to large. The Agency suggested that we reduce this project and resubmit it for their approval. Therefore, we are submitting the modified list Table 2 (Attachment 2).

Basically, we propose to evaluate the liver, kidney, brain, fat, blood, urine and feces for residues of Mono-, Di-, and Tri-PTH from the high dose and control animals in the chronic dog and rat study. (See Table 2)

In the 1-year dog study we will analyze the 3, 6 and 12 month sacrifices.

In the 2 year rat study we will evaluate the 3 and 12 month samples so that the carcinogenicity study will not be held up waiting for the analysis of the two year samples and will be submitted to the Agency on time. Otherwise, we would need to delay the report at least one year or even more to include this information. The three and six month samples, as well as, intermediate dose groups have already been collected and will be kept frozen.

Because of the sample size of the different tissues/organs in rats, we are planning to combine the individual samples so that we have two samples per sex, per group. This will enable us to carry out proper analyses for each metabolite.

We do not plan to analyze the samples from the two generation rat study, which is due on September 7, 1986, or the placenta transfer study. We do not feel that the data obtained would give us any additional information which would help or affect the interpretation of the reproductive hazards associated with TPTH.

Please review these proposals with your scientists and advise us of your decision so that we can proceed with the analysis which will enable us to submit the reports on time.

Very truly yours,

Dr. Berthold Volger
Manager, Hoechst AG Products
Registration & Projects Coordination

BV:Ad

TABLE 1 (Attachment 1)

Number of Tissue Samples for Analysis

Dog Studies

	Liver	Kidney	Brain	Fat	Blood	Urine	Feces	Total
3 Month Sacrifice (2/sex/gp)	16	16	16	16	16	16	16	112
6 Month Sacrifice (2/sex/gp)	16	16	16	16	16	16	16	112
12 Month Sacrifice	48	48	48	48	48	48	48	336
							Subtotal =	560

Rat Studies

	Liver	Kidney	Brain	Fat	Blood	Urine	Feces	Total
3 Month Rat (10/sex/gp)	80	80	80	80	80	80	80	560
1 Year Rat (10/sex/gp)	80	80	80	80	80	80	80	560
2 Year Rat (10/sex/gp)	80	80	80	80	80	80	80	560
							Subtotal =	1680

2 Generation Rat

	Liver	Kidney	Brain	Fat	Blood	Urine	Feces	Total
F_1 Day 4 (30/sex/gp)	10	10	10	10	10	10	10	50
F_1 Weanlings	20	20	20	20	20	20	20	100
F_2 Day 4	10	10	10	10	10	10	10	50
F_2 Weanlings	20	20	20	20	20	20	20	100
							Subtotal =	300

Placental Transfer	Maternal Blood	Amniotic Fluid	Placenta	Membrane	Fetuses	Uterus
	40	40	600	600	600	40
						Subtotal = 1920

All tissues will be analyzed for Triphenyltin, Diphenyltin and Monophenyltin Hydroxide. Some tissues may be combined to aid in processing.

(Attachment 2)

TABLE 2

Number of Tissue Samples for Analysis

Dog Studies

	Liver	Kidney	Brain	Fat	Blood	Urine	Feces	Total
3 Month Sacrifice (2/sex/gp) (High Dose & Control)	8	8	8	8	8	8	8	56
6 Month Sacrifice (2/sex/gp) (High Dose & Control)	8	8	8	8	8	8	8	56
12 Month Sacrifice	24	24	24	24	24	24	24	168
						Subtotal	=	280

Rat Studies

	Liver	Kidney	Brain	Fat	Blood	Urine	Feces	Total
3 Month Rat (2/sex/gp) High Dose & Control)	8	8	8	8	8	8	8	56
1 Year Rat (2/sex/gp) High Dose & Control)	8	8	8	8	8	8	8	56
						Subtotal	=	112