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

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MAY 2 1985

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Triphenyltin Hydroxide (TPTH). Review of Developmental Toxicology Study, Performed and Reported by Robert Kavlock, Ph.D. (EPA, Health Effects Research Laboratory, Research Triangle Park), Dated March 28, 1985.

Tox. Chem. No. 896E

FROM: Edwin R. Budd, Section Head
Section 2, Toxicology Branch
Hazard Evaluation Division (TS-769)

Budd 4/17/85

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

THRU: Theodore M. Farber, Chief
Toxicology Branch
Hazard Evaluation Division (TS-769)

Theodore M. Farber 4/28/85

Background:

To further assess the potential of TPTH to induce hydrocephaly, hydronephrosis and/or hydroureter in rat fetuses, and the reversibility of these effects, if any, in rat weanlings, the Office of Pesticide Programs requested Neil Chernoff, Ph.D. and Robert Kavlock, Ph.D. of the Health Effects Research Laboratory in Research Triangle Park, North Carolina to design, perform and report the results of a special experimental investigation. The report for that investigation was received on April 1, 1985 and is reviewed in this memorandum.

Summary of Study:

Technical grade TPTH or vehicle was administered to pregnant Sprague-Dawley strain rats during the period of organogenesis. Offspring from these rats were examined for morphological status of cerebral ventricles (hydrocephaly) just prior to birth and for urinary tract morphology (hydronephrosis and hydroureter) just prior to birth and at the time of weaning. Renal function tests were also performed on neonates.

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The corn oil vehicle or test material was administered by gastric intubation on days 7 through 20 of gestation at a constant dosage volume of 5 ml/kg. The volume actually administered was adjusted daily based on body weight determinations. On day 21 of gestation, the dams were sacrificed. Uteri were removed, weighed and examined. Extra-uterine body weight gains during pregnancy were calculated. Live fetuses were weighed (as a litter), counted, examined for gross external anomalies and then fixed for later necropsy. Necropsies were limited to assessing the morphological status of the cerebral ventricles, the kidneys and the ureters. A special "developmental grading system" was devised and used to assess the morphological status of these three organs.

Phase II (Prenatal Group B and Postnatal Group)

On day 4 of gestation, pregnant rats were weighed and then divided into treatment groups as follows:

Treatment Group	No. of Pregnant Rats
Vehicle Control (corn oil)	40
TPTH, 4 mg/kg/day	42

The corn oil vehicle or test material was administered by gastric intubation on days 7 through 20 of gestation at a constant dosage volume of 5 ml/kg. The volume actually administered was adjusted daily based on body weight determinations. On day 21 of gestation, approximately 1/3 of the dams in each group were sacrificed and the dams and fetuses examined as in Phase I except that only the kidneys and ureters of fetuses were examined, since no evidence of treatment related lesions outside the urogenital tract was observed in Phase I fetuses (Prenatal Group B). The remaining 2/3 of the dams were permitted to deliver and the pups were observed through weaning (Postnatal Group).

On postnatal days 1, 2 and 3, pups were counted and weighed. In addition, renal function tests were performed on all surviving pups as follows.

1. a renal concentrating test (see below) - on postnatal day 7, 8, 9 or 10, and

2. serum and urine chemistries (sodium, potassuim, glucose, urea, creatinine, chloride, osmolality) - on postnatal day 22 or 23.

At 22-23 days after delivery, the weanlings were sacrificed and examined for morphological abnormalities of the kidneys and ureters. At 24 days after delivery, the dams were sacrificed and the number of implantation scars were counted.

Mean prenatal mortality was 8.8%, 9.7% and 30.0% (significantly increased) for the control, 4 mg/kg/day and 8 mg/kg/day groups, respectively. Mean fetal body weights were 4.3 gm, 4.1 gm and 2.9 gm (significantly decreased), respectively. Prenatal mortality was clearly increased and fetal body weights clearly decreased at 8 mg/kg/day. Gross abnormalities observed in fetuses were dextrocardia (1 fetus), edema (2 fetuses), clubbed foot (2 fetuses) and runting (2 fetuses). These abnormalities occurred randomly and none were considered to be treatment related.

Morphological Status of Cerebral Ventricles of Prenatal Groups

The "developmental grading system" for cerebral ventricles is presented below.

Grade 1 - no gap exists in lateral ventricles
Grade 2 - slight gap present in ventricles
Grade 3 - moderate gap present in ventricles
Grade 4 - extreme dilation of ventricles, little cortex present

Grades of 3 or 4 were considered to represent significant deviations from the normal pattern of development.

Phase I (Prenatal Group A)

The distribution of developmental grades is shown below for each Phase I group (in % of fetuses examined).

	Cerebral Ventricles		
	Control	4 mg/kg/day	8 mg/kg/day
No. of litters exam.	17	18	7
No. of fetuses exam.	191	198	89
Grade 1	0%	0%	0%
Grade 2	97.9	97.5	93.3
Grade 3	1.6	2.5	6.7
Grade 4	0.5	0	0
Mean Score	2.03	2.03	2.04

The percentages of fetuses with grade 3 or 4 (combined) were 2.1%, 2.5% and 6.7% for the control, 4 mg/kg/day and 8 mg/kg/day groups, respectively. Although a small increase was observed at 8 mg/kg/day, the increase was not considered to be of biological concern because of the considerable maternal and fetal toxicity which was also observed at this same dosage level.

animals were clearly demonstrated in this Phase I group with respect to development of the kidneys.

Phase II (Prenatal Group B)

The distribution of developmental grades is shown below for each Phase II group (in % of fetuses examined).

	Kidneys			
	Control		4 mg/kg/day	
No. of litters examined	12		13	
No. of fetuses examined	141		149	
	right kidney	left kidney	right kidney	left kidney
Grade 1	20%	25%	9%	9%
Grade 2	79	72	88	88
Grade 3	1	3	3	3
Grade 4	0	1	0	0
Mean Score	1.81	1.79	1.93	1.93

No apparent differences in percentages of fetuses with grade 3 or 4 (combined) were observed when 4 mg/kg/day fetuses were compared to control fetuses. Mean scores were slightly higher in 4 mg/kg/day fetuses for right and left kidney than in control fetuses. This was due to a higher percentage of 4 mg/kg/day fetuses being classified as Grade 2 as compared to the control group. This shift was regarded by Toxicology Branch as being of little concern since both Grades 1 and 2 are considered to be within the normal pattern of development. No biologically meaningful differences between control and TPTH treated animals were observed in this Phase II group with respect to development of the kidneys.

Morphological Status of the Ureters of Prenatal Groups

The "developmental grading system" for ureters is presented below.

Grade 1 - ureters very thin, path to bladder is straight
Grade 2 - ureter somewhat dilated, path to bladder is straight or mildly tortuous
Grade 3 - ureters very dilated, path to bladder is often tortuous

	right ureter	left ureter	right ureter	left ureter
Grade 1	58%	40%	41%	22%
Grade 2	42	58	59	75
Grade 3	0	2	0	3
Mean Score	1.42	1.62	1.59	1.81

The percentages of fetuses with Grade 3 were quite similar in the control and 4 mg/kg/day groups. As was observed in Phase I fetuses, the left ureter was again generally affected more than the right ureter. The somewhat higher mean scores for the 4 mg/kg/day group, as compared to the control group, are again equivocal.

Reproductive Parameters and Selected Gross Fetal Data for Postnatal Group

Phase II (Postnatal Group)

In Phase II, 22 control and 22 4 mg/kg/day dams were allowed to deliver normally (Postnatal Group). One 4 mg/kg/day dam delivered a non-viable litter and another delivered only 1 viable pup at birth. The pup died 2 days later. Mean implantation sites, determined 24 days after delivery, were equivalent in both groups. Mean litter sizes, although about 10% less in the 4 mg/kg/day group than in the control group, were not statistically different. At post-delivery day 1, mean pup weights for TPTH treated animals (6.1 gm) were significantly lower than for control animals (6.6 gm). At post-delivery days 2 and 3, mean pup weights for TPTH treated animals were still lower than control animals, but the decrease was no longer statistically significant. The mean numbers of pups weaned per litter and the mean perinatal loss per litter (number of implantation sites minus number of pups surviving 22-23 days) were equivalent in control and TPTH treated groups.

Renal Concentrating Test for Postnatal Group

The renal concentrating ability test was performed on 231 control and 205 neonates at 7, 8, 9 or 10 days after delivery. No biologically meaningful differences were observed between the control and the TPTH treated groups.

Serum and Urine Chemistries for Postnatal Group

Serum chemistries were performed on 230 control and 205 4 mg/kg/day neonates at 22 or 23 days after delivery. No biologically meaningful differences in serum potassium, sodium or

Increased incidences of renal and/or ureteric dilations were not observed in TPTH treated postnatal weanlings as compared with the control group. The equivocal findings observed in the ureters of prenatal fetuses were not observed in postnatal weanlings.

cc: Betty Shackleford (RD)
Tom Johnston (RD)
Anne Barton (HED)
Amy Rispin (HED)
Judy Heckman (HED)
John Jordan (EAB)
John Doherty (TB)
Marion Copley (TB)
Robert Kavlock (HERL)

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April 17, 1985

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To Whom It May Concern:

I would like to express my great appreciation and thankfulness to Neil Chernoff, Ph.D. and Robert Kavlock, Ph.D. of the EPA Health Effects Research Laboratory, Research Triangle Park, for their very timely response and excellent report on the potential developmental effects of triphenyltin hydroxide (TPTH) on young rats.

To assist in regulatory decisions regarding this chemical for the coming growing season, the Office of Pesticide Programs (OPP), Washington, DC, with no forewarning, requested Neil Chernoff and Robert Kavlock in November, 1984, to design, execute and report the results of a large-scale laboratory experiment on TPTH as soon as possible. Their response to this request was superb in all respects.

Their immediate and full commitment to this project was most extraordinary -- and gratifying. Subsequent discussions with them during the early planning phases of the experiment were also quite reassuring for it was evident that they were quite knowledgeable and highly competent in the subject matter. As the experiment progressed, frequent status reports were most helpful. The final report of the experiment, authored by Robert Kavlock, was received by OPP prior to April 1, 1985, the scheduled due date. The report was complete, well-written and highly satisfactory in all respects.

I would particularly like to emphasize the magnitude of this experiment. Over 150 pregnant rats were used to generate over 1700 offspring, all of which were carefully examined for urinary tract morphology at various times! In addition, tests of renal functional competence were performed on a large percentage of the neonates. It is especially noteworthy that these functional tests were only possible because the experimental methodology had been previously developed by Robert Kavlock. These functional tests, which were directly applicable and extremely valuable in assessing the renal competence of the neonates, probably would not have been performed in any other laboratory in this country.

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