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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: EPA Reg. No. 8340-15: Triphenyltin hydroxide (TPTH) additional data submitted related to the rat and hamster teratology studies conducted at the Battelle Research Laboratories.

Tox Chem No. 896E

FROM: John Doherty John Doherty 7/15/85
Toxicology Branch
Hazard Evaluation Division (TS-769)

TO: H.A. Jacoby
Product Manager #21
Registration Division (TS-767)

THRU: Edwin R. Budd Budd 7/15/85
Section Head
Toxicology Branch
Hazard Evaluation Division (TS-769)

Background:

A previous review from Toxicology Branch (TB) (refer to J. Doherty memo dated July 25, 1980, EPA Reg. No. 148-689 and 148-1195 and PP #0F2282 and FAP # 0H5242) of a rat teratology study indicated that triphenyltin hydroxide (TPTH) was associated with higher incidences of hydronephrosis and hydrocephalus in the pups. Since the then available study did not demonstrate a NOEL level and to further assess the potential of TPTH to cause these types of lesions in rat pups, the registrant was requested to conduct additional teratology studies.

The registrant responded by conducting and submitting additional teratology studies using the rat and hamster as the test species. These studies were reviewed (see J. Doherty memo dated April 19,

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1982, PP #0F2282). The hamster study did not indicate teratogenic or fetotoxic effects at dose levels up to and including 12 mg/kg/day. The rat study, however, showed possible compound related increased incidences of hydroureter and again no NOEL could be satisfactorily established. The registrant was requested to conduct an additional study to establish the NOEL.

On April 28, 1982, the registrants together with representatives from the Battelle laboratory visited EPA to discuss the possible teratoganic effects of TPTH. During this meeting it was agreed that the individual pup data and other data would be submitted to the agency in order to assist the agency in making an independent statistical evaluation using either the incidences of hydroureter alone or combined with the incidences of hydronephrosis. A paper from the scientific literature (unspecified) which discusses the significance of hydroureter/hydronephrosis was also to be included in the submission.

This additional data as previously requested was finally submitted to the Agency on May 7, 1985. Comments on the information submitted are below.

In the meanwhile (between 1982 and 1985) a third teratology with rats study was submitted by the registrants and TB requested that the Health Effects Research Laboratory of the Office of Research and Development of EPA conduct an independent teratology study with rats. Reviews of these studies were completed recently and neither the study submitted by the registrants (see J. Doherty review dated April 25, 1985, EPA Reg. No. 8340-15) or the study conducted at EPA's facilities (see E. Budd review dated May 2, 1985 memo to H. Jacoby) indicated that TPTH was associated with increased incidences of hydroureter or hydronephrosis.

Response:

TB acknowledges receipt of the individual animal data (refer to EPA Acc. No. 257882). Inspection of the data confirms that there were indeed more rat pups affected with hydroureter in the rats dosed with TPTH and a dose response relationship is evident. The following table summarizes the response:

Group	n*	Litters Affected	Pups Affected	Pups with hydroureter	Pups with hydronephrosis
Control	131	2	2(1.5%)	1(<1%)	2(1.5%)
1.0 mg/kg	118	4	7(5.9%)	7(5.9%)	6(5.1%)
2.8 mg/kg	123	3	9(7.3%)	8(6.5%)	2(1.6%)
8.0 mg/kg	96	5	12(12.5%)	12(12.5%)	4(4.2%)

n* = number of pups examined - obtained from the April 19, 1982 review.

Many of the pups had both hydroureter and hydronephrosis with only 2 pups having hydronephrosis in the absence of hydroureter.

Although these data show indications of a possible test chemical effect, the subsequent studies (see above) do not indicate a similar response. The "hydro" condition of the kidney and its associated structures (i.e. ureter) is often related to the time differences in delivery (by caesarian section). The study conducted at EPA facilities included sets of rat pups which were allowed to develop to weanling stage before being sacrificed and assessed for the condition of their kidneys and ureters. This special group of pups did not show indications of malformations in these structures (see Budd review indicated above).

Because of the inconsistencies of the responses among the different studies designed to assess the effects of TPTH for this condition, the available data do not consistently directly relate TPTH with causing hydroureter or hydronephrosis. If TPTH is related to the slightly higher incidences of this condition noted in rat pups examined at the time of delivery (i.e. see the table above), the data from EPA's study indicate that this effect is transitory.

2. For edification purposes only, TB requests that the reference from the published scientific literature which discusses the significance of hydroureter/hydronephrosis in teratology studies be submitted.