10-29-93

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

Expedite

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA File No.: 083601. Triphenyltin Hydroxide: Review of a series 83-3 special dermal developmental toxicity study in rabbits.

TOX CHEM No.: 896E
PC No.: 083601
Barcode No.: D195095
Submission No.: S448205

FROM: John Doherty 10/20/93
Section IV, Toxicology Branch I
Health Effects Division (7509C)

TO: Margaret Rice
Product Manager #62
Special Review and Reregistration Division (7508W)

THROUGH: Marion Copley, DVM, Section Head Marion Copley 10/20/93
Section IV, Toxicology Branch I
Health Effects Division (7509C)
Karl Baetcke 10/29/93

I. CONCLUSION

The special dermal developmental toxicity study with triphenyltin hydroxide (TPTH) with rabbits was reviewed and determined to be CORE GUIDELINE. The study was determined to support a NOEL of $\geq$ 3 mg/kg/day (highest dose tested) for both maternal systemic effects and developmental toxicity for dermal exposure. Equivocal findings of external malformations noted in the study report were not considered by Toxicology Branch to be sufficient to be conclusively attributed to the test material.

No additional developmental toxicity study data are required at this time,

II. Action Requested

The Elf Atochem Co. has submitted a special dermal developmental toxicity study (WIL Research Laboratories # WIL-160012, August 27, 1993, MRID No.: 429091-01) in order to provide

a study that will allow a direct determination of risk assessment for dermal exposure for maternal and developmental toxicity rather than extrapolating from an oral developmental toxicity study. The study submitted was reviewed and a copy of the DER is attached. The following comments apply.

III. Toxicology Branch Comments

1. The study was determined to be CORE GUIDELINE and to support a LEL > 3 mg/kg/day for both maternal and developmental toxicity.

Local site of application dermal irritation was present in all groups dosed with TPTH with the higher dose levels showing more severe reactions. This local irritation due to TPTH indicates that the test material affected the skin and was available for absorption but it does not affect the interpretation of the dermal developmental toxicity aspects of the study.

2. The study report concluded that certain malformations noted at external examination in the high dose test group were equivocal with regard to being related to test material administration. Toxicology Branch I (TB-I) has concluded that these malformations should be noted but that they are not considered to be conclusively related to compound administration. The justification for TB-I's position is indicated as follows:

i. There was no effect on fetal body weight. Decreased fetal body weight was determined to be the most sensitive indicator of developmental toxicity in three species (rat, rabbit and hamster, refer to the TPTH Developmental Toxicity Peer Review packages for the Peer Review meetings dated April 5, 1990 and June 13, 1990)) following oral administration. The lack of an effect on body weight suggests that TPTH never actually reached the fetuses in utero.

ii. Malformations of the same description were not also noted in the oral rabbit developmental toxicity study (refer to HED Document No.: 005917, MRID No.: 401048-01) which showed evidence of maternal toxicity (decreased gestational weight gain) and developmental toxicity (decreased pup weight and possible decreased ossification of the hyoid). The presence of maternal toxicity and developmental toxicity in the oral study indicated absorption of the test material. The dermal study did not indicate any decreased ossification of the hyoid.

iii. The external malformations do not reach statistical significance.

iv. The dose levels are very close together and TB-I considers that a test chemical effect noted at the high dose group of 3.0 mg/kg/day should also have at least some effect at the next lower dose of 2.25 mg/kg/day. Based on the similarity of the dermal reactions to treatment, TB-I considers that there is no meaningful pharmacological difference between the dose levels 2.25 and 3.0 when applied dermally.

v. The variety of the external malformations noted in the high dose group do not suggest a common target organ or pattern of developmental toxicity. On the contrary here, it is noted that of the six fetuses in the

high dose group that had the external malformations involving the skeletal system (confirmed or otherwise) all were males indicating that the male fetus is a common target. This fact is noted but does not convince TB-I that the effect is test chemical related.

vi. The total of pups/litters noted to have skeletal, soft tissue and external malformations was about equal in all test groups being 10/4, 6/4, 9/5, and 11/8 in the control, low, mid and high dose groups respectively. For example, although the high dose group had more incidents of pups with external malformations (8) than the control (1), the high dose group (2) had less skeletal malformations than the control group (10). On a litter basis, although there were more litters affected in the high dose group (8) than in the control (4), some of these litters had only a single pup with a malformation.

Although these justifications, when considered individually, may not be sufficient to dismiss the findings, TB-I considers that these justifications taken all together are the basis for concluding that the malformations are unlikely related to the test article administration. These incidents are noted and discussed as above but should not be included in the conclusions for definite effects of TPTH in this dermal developmental toxicity study.

IV. Studies Reviewed

Study Identification	Material	MRID No.:	Results	Classification
83-3. Special dermal developmental toxicity study - rabbits. WIL Research Laboratories, Study No.: WIL-160012, August 27, 1993	Technical TPTH lot No.: GFRAM911K	429091-01	LEL (maternal and developmental toxicity) > 3.00 mg/kg/day. Equivocal findings for certain external malformations noted at 3.0 mg/kg/day are not considered sufficient to conclude a definite relationship to the test material. Strain: New Zealand White Rabbit. Dose levels tested: 0, 1.5, 2.25 or 3.0 mg/kg/day in 1% carboxymethylcellulose.	GUIDELINE