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

001782

MEMORANDUM

4/20/82

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

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

SUBJECT: PP 0F2282. Teratogenic Evaluation of Triphenyltin Hydroxide.

TOX Chem. No. 896E

Background:

A previous review of the chemical triphenyltin hydroxide (see J. Doherty memo dated July 20, 1980, PP 0F2282 and 0H5242; Reg. No. 148-689 and 148-1195) indicated that the rat teratology study demonstrated a teratogenic or fetotoxic effect (hydrocephalus and hydronephrosis). The registrant was asked to submit additional studies on two different species to clarify a NOEL for this lesion. Teratology studies in rats and hamsters were submitted and are reviewed as follows.

Conclusions:

1. The rat study does not demonstrate a NOEL for hydroureter. Thus, this study confirms that triphenyltin hydroxide causes hydronephrosis related lesions in the fetuses when administered to the dams.

A study from the published literature sent by the registrant concerning the teratogenic effects of triphenyltin acetate also indicated that the triphenyltin compounds can cause hydroureter (Bull Environ. Contam. Toxicol. 24: 936-939 [1980], see EPA Accession No. 070695).

An additional study will have to be conducted which clearly demonstrates a NOEL for hydronephrosis related lesions in rats and must be submitted and found to be acceptable by Toxicology Branch.

2. The teratology study with hamsters did not show development of hydroureter in hamsters treated with triphenyltin hydroxide (TPTH). There were three incidences of hydronephrosis in the mid dose group fetuses but none in the high dose test group or other groups (except the positive controls) were reported.

The hamster study demonstrated that triphenyltin hydroxide was not teratogenic at doses up to and including 12 mg/kg. The NOEL for fetotoxic effects in hamsters was 5 mg/kg.

REVIEW OF STUDIES

1. Evaluation of the Teratogenicity of Triphenyltin Hydroxide (TPTH) in the Sprague-Dawley Rat

Battelle Columbus Laboratories, #N0723-0200, June 25, 1981
EPA Accession No. 070696

Four groups of 26 female Sprague-Dawley rats were mated and dosed with 0, 1.0, 2.8 or 8.0 mg/kg triphenyltin hydroxide (TPTH) (Lot TS414K, 97.3% purity) in 1 ml of corn oil/200 gm body weight on days 5 thru 19 of gestation. On the 20th day, 20 pregnant rats were culled and sacrificed and hysterotomy was performed. No positive control group was included in this study.

Results:

A. Maternal Effects:

1. Two rats in the high dose test group died. All of the rats in this dose group showed some abnormal signs which included rough coat and oral/nasal discharge, alopecia, diarrhea, ocular discharge, lethargy, vaginal discharge, hemorrhage from the vaginal area and thinness. Three rats in the 2.8 mg/kg group demonstrated at least some of these symptoms. Only one rat in the 1.0 mg/kg dose group showed a single possible sign; slight red discharge from the nose and mouth on day 19 (the last day of dosing). The solvent control group did not show symptoms other than alopecia.

2. The pregnancy rate was lower for the high dose group (80% vs 100% for all other groups) and it could not be determined if this was due to fertilization or a toxic response resulting from administering the TPTH on day 5.

3. Maternal body weight gain throughout pregnancy was adversely affected for the high dose test group only. For example, this group gained only 82 $\pm$ 28 gm, whereas the other three groups gained > 130 gm $\pm$ 24 gm. Uterine weight was also significantly decreased in the high dose test group.

4. Hystertomy data indicated no differences in the average number of implantations per litter, and the average number of implantation sites/number of corpora lutea.

The average number of live fetuses/litter was slightly lower (-15%) and the average live fetal weight was lower (-22%) for the high dose test group when compared to the controls. The average % dead and resorbed fetuses /litter was also affected in the high dose test group (12% vs 3% for the control). There was no difference in the sex ratio due to the test chemical.

A NOEL for maternal toxicity is 2.8 mg/kg.

B. Fetal Effects:

There were 262, 244,257, and 200 fetuses from the control, low, mid and high dose test groups respectively. Approximately one half from each group were culled and prepared for skeletal examination. The other half was prepared for soft tissue examination following free hand sectioning in Bouin solution.

1. Soft tissue analysis revealed 11, 11, 13 and 12 abnormal fetuses or 8, 9, 11 and 13% for the control, low, mid and high dose test groups. There was no hydrocephalus noted in any group dosed with TPTH. Hydroureter were present in the order of 1 (1%), 7 (6%), 7(6%) and 12 (12%) for the control, low, mid and high dose test groups. Hydronephrosis was present in 2% to 4% of the fetuses. Hydroureter and hydronephrosis are related lesions and the following table prepared by Toxicology Branch illustrates the frequency of occurrence of these lesions:

HYDROURETER AND HYDRONEPHROSIS

	At Worst*	At Best**
Control	3/131 (2.3%)	2/131 (1.5%)
Low (1.0 mg/kg)	12/118 (10.1%)	7/118 (5.9%)
Mid (2.8 mg/kg)	10/123 (8.1%)	8/123 (6.5%)
High (8.0 mg/kg)	16/96 (16.7%)	13/96 (13.5%)

(% of animals with lesions)

* At worst refers to no fetuses having both hydroureter or hydronephrosis.

** At best refers to all fetuses having hydronephrosis also having hydroureter.

It is necessary to prepare "at worst" and "at best" figures because the individual fetus data were not submitted.

3. Skeletal analysis indicated that there were 26 (20%), 24 (19%), 26 (20%) and 18 (17%) total number of fetuses with skeletal malformations in the control, low, mid and high dose test groups. No single skeletal malformation type showed consistent increases in excess of the control group. Thus no indication of a teratogenic effect on the skeletal system is evident from these data.

Conclusion:

This study is Core Minimum. A NOEL of ~~2.0~~ 1.8 mg/kg/day is assigned for toxic effects to the dam. The development of hydroureter occurred at all test dose levels but at only a very low frequency among the controls. Historical control data confirmed that this strain of rat has a low spontaneous rate of hydroureter in the fetuses and that xenobiotics increased the frequency of occurrence of this abnormality in development. This experiment confirms the previous rat study which demonstrated that triphenyltin hydroxide causes lesions related to hydronephrosis in rats. Other symptoms of fetotoxicity occur in the high dose test group (8.0 mg/kg/day), these include deaths and fetal body weight decreases.

2. The Evaluation of the Teratogenicity of Triphenyltin Hydroxide (TPTH) in the Syrian Golden Hamster

Battelle Columbus Laboratories, # N0723-0100, February 10, 1982
EPA Accession No. 070697

A. Preliminary Range Finding Study:

A series of preliminary range finding studies indicated that the hamsters developed problems that were attributed to either corn oil alone or a synergistic effect between corn oil and TPTH. The data related to this effect were not presented and it was not established if there was an effect between corn oil and TPTH. Testing TPTH in corn oil in hamsters resulted in deaths due to hemorrhage (unspecified location), prolapse and intussusception. Because of a possible corn oil effect, the solvent was changed Klucel® (0.3 percent hydroxypropyl cellulose in saline) and it was determined that 12.0 mg/kg of TPTH would be a reasonable maximal tolerated dose level. Hamsters tested at 15.7 mg/kg died as a result of the TPTH.

B. Teratology Study:

Five groups of 25 female hamsters were mated and assigned to dosing groups as control, 2.15 mg/kg, 5.08 mg/kg, 12.0 mg/kg of TPTH and positive control (250,000 IU of Vitamin A/kg. The TPTH used was from lot No TS414K. Analysis of the test material as prepared for dosing

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indicated that the TPTH animals were dosed with 1.97 ± .12 mg/kg, 4.91 ± .24 mg/kg, and 10.94 ± .52 mg/kg or 92%, 97% and 91% of the expected dose level. The test chemicals were administered by gavage on days 5 through 14 of pregnancy with 1 ml/100 gm of body weight. Twenty females from each group were sacrificed on day 15 and their uterine contents examined.

Results:

A. Effects on the Dams:

Pregnancy rate was 80-100% and there was no indication of a compound related effect. Four of the 25 hamsters in the high dose group died and 18 showed toxic responses which included oral/nasal discharge and diarrhea and rough coats, rectal discharge, weakness/lethargy, weight loss, and vaginal hermorrhage. Toxic responses in the low and mid dose groups showed some signs of diarrhea (2 animals in the mid dose group), a single animal in the low dose group showed a bloody discharge from the vagina.

The dams in the high dose test group did not gain weight as well as the controls and low and mid dose test animals. They gained only 11 gm compared with 24-27 gm for the other groups. The weight of the uterus was only slightly lower (13%) than the control group.

The mean number of implantation sites per litter, the pre implantation loss rate as judged by the corpora lutea implantation ratio, or the mean number and percent of dead or resorbed fetuses were not shown to be statistically significantly affected by TPTH treatment. But the high dose group and the positive control group showed more than twice as many average percent dead/resorbed fetuses per litter. The average number of live fetuses was lower (-20%) than the control group and this depressionn was significant ($p < 0.001$) for the 12 mg/kg test dose group.

B. Effects on the Fetuses:

There were 242, 252, 258, 193 and 207 fetuses for the control, low, mid and high and positive control test groups available for analysis. The

average live fetal weight for the high dose test and positive control was lower than the control group (-10% for both groups). Approximately one half of all fetuses per dose group were saved for skeletal analysis.

1) Soft tissue analysis (performed by free hand sectioning of the fetuses preserved in Bouin's solution). Only one fetus among the controls was affected (with mottled liver). No low dose group fetuses were affected. Three mid dose group fetuses were affected with hydronephrosis. Three high dose group fetuses were affected: one with hydrocephaly, one with mottled liver and one with hematoma. The positive control group had high incidences of hydronephrosis (32) and hydroureter (25) as well as several other abnormalities including palate malformations and renal dysplasia.

The development of 3 incidences of hydronephrosis in the mid dose group (2%) of the fetuses is disturbing because the other test groups and control (except the positive control group) do not develop this lesion. However, a dose relationship is not evident.

2) Skeletal effects: The high dose test group showed a higher incidence of "poorly ossified, missing metatarsels" (26 incidences, 27%) than the control group (14 incidences, 12%). There was also a single incident of a fetus with "absent cranial vault" in the high dose test group and the only other group showing this was the positive control group (14 incidences). There was also noted a 14% increase in the total number of abnormalities when the high dose test group is compared with the control group.

3) Gross necropsy revealed a higher incidence of anemia among the high dose test group. Hematomas were present only in the test group fetuses with the following frequencies 0/242, 5/252, 4/258, 5/193 and 2/207. The development of hematomas is considered by Toxicology Branch to be possibly but not conclusively related to the test chemical.

Conclusion

This study is Core Guidelines. No teratogenic effects of TPTH at dose levels up to and including 12 mg/kg were noted. The high dose level (12 mg/kg) developed signs of fetotoxicity which included anemia and showed some signs of delayed development of the metatarsels. The development of hematoma was only in treated animals and at best is only possibly related to TPTH. A lack of a dose response or supporting data from other studies prevents the conclusion that the hematoma was more definitly related to ingestion of TPTH.

3. Effect of Triphenyltin Acetate on Pregnancy in the Rat

University of Milano, Milano, Italy, as published in Bull. Environm. Contam. Toxicol. 24: 936-939 (1980) EPA Accession No. 0706985.

The following table shows that hydroureter resulted in fetuses whose mothers were treated with triphenyltin acetate during gestation (days 6-15).

Group		Incidences/Fetuses Examined
Control	Triphenyltin acetate	0/52
5 mg/kg	Triphenyltin acetate	0/52
10 mg/kg	Triphenyltin acetate	0/65
15 mg/kg	Triphenyltin acetate	4/29 (13.8%)

This study is Supplementary.

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