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FOOD AND
DRUG ADMINISTRATION
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DATA EVALUATION REPORT
(Summary of Journal Article)

Study Type: Teratogenicity With Subchronic Feeding

TOX Chem No.: 641 and 638 F
MRID No.: N/A

Test Material: Pentachlorophenol; Pentachloroanisole (both purified)

Synonyms: PCP, Penta; PCA

Testing Facility: Food and Drug Administration, Washington, DC

Title of Article: Teratogenic Potential of Purified Pentachlorophenol and Pentachloroanisole in Subchronically Exposed Sprague-Dawley Rats.

Authors: J.J. Welsh, T.F.X. Collins, et al.

Journal: Food Chemistry and Toxicology 25(2), 163-172 (1987)

Conclusions:

1. Pentachlorophenol

NOEL, maternal toxicity = 4 mg/kg/day (LDT).

LEL, maternal toxicity = 13 mg/kg/day (increased resorptions).

Maternal effects at top dose (43 mg/kg/day): reduced body weight (adjusted).

NOEL, developmental toxicity: reserved pending availability of individual fetal data.

Developmental effects at mid-dose (13 mg/kg/day): reduced fetal body weight, reduced crown-rump length, increased incidence of misshapen centra, increased overall skeletal variations.

Developmental effects at top dose (43 mg/kg/day): markedly reduced number of viable fetuses.

2. Pentachloroanisole

NOEL, maternal toxicity = 12 mg/kg/day (mid dose).

LEL, maternal toxicity = 41 mg/kg/day (HDT): increased resorptions, reduced body weight gain (adjusted), fewer corpora lutea.

NOEL, developmental toxicity = less than 4 mg/kg/day (LDT).

LEL, developmental toxicity = 4 mg/kg/day: decreased fetal weight and crown-rump length in males (also at top dose).

Other effects at top dose (44 mg/kg/day): markedly reduced number of viable fetuses, increased sternebral and other skeletal variations.

Before recording a developmental NOEL from this study for penta, HED requests availability of the individual data for fetal body weights. The data of this study, however, do not appear to give concern regarding the current penta NOEL (developmental toxicity) at 3 mg/kg/day.

The 6-month treatment period is much longer than for a standard teratogenicity study. The classification of Supplementary reflects the ancillary value of the present study as either a teratogenicity or subchronic feeding study.

Classification: Supplementary

Purified pentachlorophenol (penta) and purified pentachloroanisole (PCA; a penta metabolite in some biological systems) were separately administered to male and female Sprague-Dawley rats for 181 days, through mating and pregnancy. The analysis of penta showed octachlorodibenzodioxin (1.25 ppb) as the only detected impurity. The daily dietary intakes of penta were 0, 4, 13, or 43 mg/kg, and of PCA were 0, 4, 12, or 41 mg/kg. Each dose group contained 20 rats of each sex (32 to 34 days old), except the control group, which contained 40 rats of each sex.

Neither of the chemicals produced adult mortality. Signs present in the high-dose penta dams: 50 percent showed "ringed eye" and 25 percent showed vaginal bleeding.

Food consumption was generally elevated (relative to controls) in all penta treatment groups throughout pregnancy. Food consumption showed little change in the PCA groups.

At the end of pregnancy, the female body-weight gain (unadjusted) was slightly elevated at penta low and mid doses, but markedly reduced at top dose. When adjusted for gravid uterus weight, the patterns of body weight gains for either the penta or PCA dams were similar to the pattern of unadjusted weight gains for penta. Pregnancy rate (as affected by either compound) was slightly reduced at low dose and slightly elevated at the top two doses.

The number of corpora lutea was significantly reduced at top dose of the PCA animals only. The number of viable fetuses was significantly and markedly reduced at top dose for either compound, and also somewhat reduced at the PCA mid dose. Either compound at top dose showed marked embryoletality, with the lower dose levels unaffected. For penta at top dose, 16/17 litters were totally resorbed (15/18 for PCA). The penta mid dose showed 81.25 percent of litters with two or more resorptions (control, 41.94 percent).

Penta produced a dose-related decrease in fetal body weight, significant at mid dose and also reduced at low dose in either sex.

<u>Dose Penta</u> (mg/kg)	<u>Mean Body Weight (g)</u>	
	<u>Male</u>	<u>Female</u>
0	4.25	3.98
4 (60 ppm)	4.06	3.87
13 (200 ppm)	3.81*	3.65*
43 (600 ppm)	2.70**	----

*p < 0.05

**Not analyzed statistically due to small sample size.

Crown-rump length was reduced at mid dose in either sex of the penta animals. When treated with PCA, either low-dose or top-dose male fetuses exhibited significant reductions in fetal weight and crown-rump length.

For either compound, the dietary exposure was unrelated to specific external or sternebral variations. At mid dose, the fetuses exposed to penta showed an increase in misshapen centra, the only specific skeletal variation significantly increased over controls. With regard to overall skeletal variations among penta fetuses, there were significant increases at mid dose for mean fetuses per litter having at least one or (separately) two skeletal variations, and for percent litters with fetuses having at least two skeletal variations.

There were neither specific nor overall changes in soft tissue variations that could be related to either penta or PCA treatment.

The extreme embryoletality at top dose prevented inclusion of results at that level in the statistical analysis (except for implantation, survival, and resorption data).