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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Fetotoxicity Risk Assessment for Pentachlorophenol and Hexadioxin (PD-2/3, Non-Wood Uses).

FROM: David G. Van Ormer DVO 19/June/84
Toxicology Branch
Hazard Evaluation Division (TS-769)

TO: Lois Rossi, Product Manager
Special Review Branch
Registration Division (TS-768)

THRU: Albin Kocialski, Acting Section Head AK 6/19/84
Toxicology Branch
Hazard Evaluation Division (TS-769)

The rebuttal comments received after the publication of PD 2/3 (Wood Preservative Pesticides, Wood Uses) do not rebut the presumption of fetotoxicity for penta, nor the teratogenicity and fetotoxicity caused by HxCDD.

In the case of penta, the study of Schwetz et al., (1974) showed that either commercial or purified penta, when administered by gavage to rats on gestation days 6 through 15, caused statistically significant increases in fetal resorptions, statistically altered sex ratios, and decreases in fetal body weight and crown-rump length, all at the higher doses tested. Significant increases in fetal anomalies (compared to controls) were observed for skeletal defects of the ribs, sternebrae, and vertebrae, reported at the two highest dose levels of both purified and commercial penta. The lowest dose of purified penta (5 mg/kg/ day) caused an increase in delayed skull ossification. The Agency believes the delayed skull ossification observed at this level is significant.

Due to the lack of an adequate NOEL in the study of Schwetz et al. (1974), the Agency has chosen the one-generation study of Schwetz et al. (1978) for purposes of risk assessment. In this study parental rats were given dietary administration at 3 and 30 mg/kg/day. At the 3 mg/kg/day level the data show a trend toward decreased neonatal weight (consistent with the high dose), which continues as the

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animals age. At a single measurement period, however, this neonatal weight decrease at 3 mg/kg/day is not statistically significant. At the top dose there was "a significant decrease in the percent of pups born alive, as well as significantly decreased survival to days 7, 14, and 21 of lactation." The average litter size after treatment at the top dose also was significantly lower than among controls on days 7, 14, and 21 of lactation. Treatment at the high dose caused a significantly increased number of litters to show variations in lumbar spurs and vertebrae with unfused centra.

The data of Schwetz et al. (1978) are adequate to establish a provisional NOEL for the fetotoxicity of the penta studied.

We may note (as more fully described in the PD-2/3, Wood Uses) that, as a result of penta administration, other toxicity parameters exhibit NOELs near 3 mg/kg/day, or somewhat below. Thus, female rats dosed dietarily with 1.5 mg/kg/day of technical penta (Goldstein et al., 1977) showed a 15-fold increase, over controls, in the activity of aryl hydrocarbon hydroxylase (AHH), and a significant elevation of glucuronyl transferase activity. Although the meaningful toxicity of these elevations is not clear, an elevated AHH activity has been used as a "biochemical correlate" for the presence in biological samples of some of the non-phenolic contaminants of technical penta.

It is also noted in the PD 2/3, (Wood Uses) that at the level of 3 mg/kg/day (or somewhat lower) there exist systemic or organ specific NOELs in rats exposed to chronic or subchronic treatment. Thus, the two-year study of Schwetz et al., (1978) reports body weight and food consumption changes in the adults. For subchronic toxicity Kimbrough and Linder (1978) reported mild histopathologic effects in the liver of rats treated at 1.5 mg/kg/day. The 90-day feeding study of Kociba et al., (1973) reported decreased testes-to-body weight ratios at all doses, including significantly lower ratios at 1.0 mg/kg/day. In the 90-day rat feeding study of Knudsen et al., (1974) the liver-weight increase in females was dose related and significant at 2.5 mg/kg/day. A third 90-day rat feeding study (Johnson et at., 1973) reported a NOEL of 3 mg/kg/day, based on increased liver weight at higher doses. Results of 90-day feeding studies are useful for comparison with fetotoxic effects, which may occur with relatively short exposure duration.

The teratogenicity and fetotoxicity of HxCDD is demonstrated in the gavage study of Schwetz et al. (1973), in which pregnant rats were treated on days 6 through 15 of gestation with two (unspecified) isomers of purified HxCDD. At the upper doses there were significant increases (above control values) in fetal resorptions, dilated renal pelvis, and cleft palate (top dose), as well as decreases in fetal body weight and crown-rump length. Subcutaneous edema was observed at all doses except 0.1 ug/kg/day (low dose), which the Agency had accepted as the fetotoxicity/teratogenicity NOEL for HxCDD.

For risk assessment of the fetotoxic effect of hexachlorobenzene (HCB) the Agency has chosen a NOEL of 1.0 mg/kg/day, based on the four-generation rat reproduction study of Grant et al. (1977). That study showed the effect of higher doses of HCB on neonatal weight gain, relative liver weight, and indices of pregnancy, viability and lactation. At 4.0 mg/kg/day several of the maternal animals died. No gross abnormalities were observed in the young rats.

Immunosuppressive Effect of Hexadioxin

Holsapple et al. (1984) have presented evidence that at least some of the immunosuppressive character of technical penta may reside in its contaminant hexadioxin (HxCDD).

These workers showed that daily exposure (14 days) to technical grade penta at 10, 30, and 100 mg/kg (p.o.) suppressed the peak (day 4) IgM antibody (Ab) response to sheep red blood cells (sRBC) by 44%, 53%, and 72%, respectively. In contrast, similar exposure to pure (dioxin-free) penta had no effect, suggesting that the suppression by technical penta was due to the dibenzodioxins. Similar exposure to 1,2,3,6,7,8-HxCDD at 0.2, 1.0, and 4.0 ug/kg concentrations, corresponding to those found in technical grade penta, indeed suppressed the peak IgM Ab response to sRBC by 30%, 47%, and 62%, respectively. Direct addition of 0.1 ug of either 1,2,3,6,7,8-HxCDD or 1,2,3,7,8,9-HxCDD to spleen-cell suspensions of untreated mice was able to suppress, by greater than 80%, the Ab response to sRBC (with no effect on viability).

An indication that the immunosuppression by the hexadioxins is due to the parent compound follows from the authors' data (Holsapple et al. 1984) showing that preincubation with a crude liver homogenate preparation (which readily activated cyclophosphamide) abolished the activity of the hexadioxins, possibly by a metabolic deactivation process.

Among the dioxin isomers, those chlorinated at the 2,3,7, and 8 positions are recognized as the isomers particularly toxic to several species. Thus, Holsapple et al. (1984) have shown that subchronic (14-day) exposure of their mice to 1,2,3,6, 7,8-HxCDD (the major dioxin in penta) produced significant elevations in liver weight, microsomal protein, cytochrome P450, and in the activity of aryl hydrocarbon hydroxylase (AHH). The induction of AHH is a well-known biochemical response associated with exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), which, for several species, is the most toxic dioxin isomer. Furthermore, the significantly decreased thymus weights among the mice corresponds to the thymic atrophy observed in almost all species exposed to 2,3,7,8-TCDD.

Margins of Safety for Population Sub-Groups

For the fetotoxicity risk assessment of penta and its major contaminants the Agency has calculated individual values of the Margin of Safety (MOS) for the population sub-groups exposed. The MOS value is the ratio of the NOEL for fetotoxicity in animal experiments to the appropriate sub-group exposure value.

For penta and two of its major contaminants the following NOEL values are used for MOS calculation:

Penta: 3 mg/kg/day (Schwetz et al., 1978)

HxCDD: 0.1 ug/kg/day (Schwetz et al., 1973)

HCB: 1.0 mg/kg/day (Grant et al., 1977)

For penta and HxCDD the calculated MOS values, based on the accompanying exposure values are presented in the two tables attached. Exposures to the HCB in penta have been determined by the Agency to range above 3.4×10^{-3} ug/kg/day (H. Day 1984). Thus, the MOS values for the fetotoxic/reproductive effects of HCB, at the various exposure sites, are all above 10000. These MOS values for HCB are not tabulated.

OPP:HED:TOX:D.VANORMER:sb 6/13/84 X73713 Rm 816 TS-769 #1-D17

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Exposures and Margins of Safety for Fetotoxic Effects of Penta

Site	Persons Exposed	Exposure (mg/kg/day) Dermal	Inhalation	MOS (3)
Canning/Sealing	20	2.6	–	1.2
Tanneries				
Soak	35	0.0004	–	7500
Pickle/Tan	700	0.0002	–	>10000
Fat Liquor	160	0.0001	–	>10000
Finish	300	0.0005	–	6000
Application	100	2.6	–	1.2
Marine Paints	(Not used)			
Marine Calking	8	2.8	–	1.1
Use	8650	4.2	–	0.71
Adhesives	20	2.6	–	1.2
Textile/Cordage	15	2.6	–	1.2
Metal Working	(Not used)			
Photo. Solns.	(Not used)			
Pulp/Paper	(Negligible exposure)			
Oil Well Water	(Negligible exposure)			
Condensers	500	15	–	0.20
Cool. Towers	500000	15	–	0.20
Air Washers	10000	15	–	0.20
Mushroom House	500	3	0.3	0.9
Rights-of-way (1)	(Not used)			
Moss Control				
Roofs (2)	?			
Mix 40%	?	34	–	0.09
Mix 28.2%	?	24	–	0.13
Application				
4%	? (brush or spray)	8	0.02 (spray)	0.4
2.1%	? (brush or spray)	4	0.01 (spray)	0.8
Lawns	(Negligible exposure)			
Alfalfa Defol.	(Not used)			

(1) Although active registrations exist, not actively used.
(2) No estimate of number of applicators possible from BUD data. Limited geographically to Pacific Northwest.
(3) NOEL = 3.0 mg/kg/day.

Exposures and Margins of Safety for Fetotoxic Effects of HCDD

Site	Persons Exposed	Exposure (ug/kg/day) Dermal	Inhalation	MOS(3)
Canning/Sealing	20	3.9×10^{-5}	-	2600
Tanneries				
Soak	35	0.0006×10^{-5}	-	>10000
Pickle/Tan	700	0.0003×10^{-5}	-	>10000
Fat Liquor	160	0.00015×10^{-5}	-	>10000
Finish	300	0.00075×10^{-5}	-	>10000
Application	100	3.9×10^{-5}	-	2600
Marine Paints	(Not used)			
Marine Calking	8	4.2×10^{-5}	-	2400
Use	8650	6.3×10^{-5}	-	1600
Adhesivies	20	3.9×10^{-5}	-	2600
Textile/Cordage	15	3.9×10^{-5}	-	2600
Metal Working	(Not used)			
Photo. Solns.	(Not used)			
Pulp/Paper	(Negligible exposure)			
Oil Well Water	(Negligible exposure).			
Condensers	500	22.5×10^{-5}	-	440
Cool. Towers	500000	22.5×10^{-5}	-	440
Air Washers	10000	22.5×10^{-5}	-	440
Mushroom House	500	4.5×10^{-5}	0.45×10^{-5}	2000
Rights-of-way (1)	(Not used)			
Moss Control				
Roofs (2)	?			
Mix 40%	?	51.0×10^{-5}	-	200
Mix 28.2%	?	36.0×10^{-5}	-	280
Application				
4%	? (brush or spray)	12.0×10^{-5}	0.03×10^{-5} (spray)	830
2.1%	? (brush or spray)	6.0×10^{-5}	0.015×10^{-5} (spray)	1700
Lawns	(Negligible exposure)			
Alfalfa Defol.	(Not used)			

(1) Although active registrations exist, not actively used.
(2) No estimate of number of applicators possible from BUD data. Limited geographically to Pacific Northwest.
(3) NOEL = 0.1 ug/kg/day.