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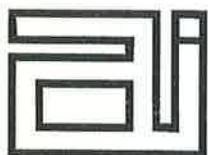
# Adverse effects of Pentachlorophenol on fertility and reproduction

A literature study

Conducted at the request of the Directorate General of Labour by:  
the TNO-CIVO Toxicology and Nutrition Institute;  
in cooperation with:  
the Coronel Laboratory of Occupational and Environmental Health,  
Faculty of Medicine, University of Amsterdam

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Directoraat-Generaal van de Arbeid



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## ADVERSE EFFECTS OF PENTACHLOROPHENOL ON FERTILITY AND REPRODUCTION

### 1. Introduction

Pentachlorophenol which is mainly used as microbiocide and preservative is available as a pure compound (purity > 99%), or as a technical product (purity ranging from 84.6% to 98%). The most common impurities are phenols, dibenzop-dioxins, dibenzofurans and hexachlorobenzene. For the treatment of wood in private homes it is used in an uncontrolled way, which has led to cases of intoxication. The MAC-value in the Netherlands is 0.5 mg/m<sup>3</sup> (0.045 ppm).

To study the placental transfer of pentachlorophenol in rats, 14C-pentachlorophenol was orally administered to pregnant rats on day 15 of gestation. The dose was 60 mg/kg body weight. The level of specific radioactivity in maternal blood serum was highest at 8 hour being about 1.1% of the administered dose per gram tissue. The levels in the placenta and fetus never exceeded 0.3% or 0.1%, respectively. Thus, the amount of pentachlorophenol that crosses the placental barrier is very low (Larsen et al., 1975).

### 2. Animal data

#### 2.1 Risks of exposure of female animals with respect to gonads, endocrine system and fertility

Welsh et al. (1987) exposed rats (20 males and 20 females per dose group) to dietary levels of 0, 60, 200 or 600 ppm purified pentachlorophenol for 181 days, through mating and pregnancy. The diets were supplied ad lib. The daily intakes of pentachlorophenol were 0, 4, 13 or 43 mg/kg body weight. After completing the subchronic phase (181 days) the animals were mated, and on day 20 of gestation (see 2.7), dams were examined externally for gross abnormalities and then killed. In the high-dose group ringed eyes were seen in 50% of the dams (P=0.002) and vaginal haemorrhages were found in 25% of the dams (P=0.013). According to the authors, the former observation may have been the result of a toxic effect, and the latter could have been normal bleeding that occurs occasionally during pregnancy. The 60 ppm group consumed significantly (P<0.05) more food than the control group from day 0-7. The 200 ppm group ate

significantly more throughout gestation (days 0-20). The 600 ppm group ate significantly more than the control group during days 0-7 ( $P < 0.01$ ) and 7-14 ( $P < 0.05$ ), but less ( $P < 0.01$ ) was consumed during days 14-20. Mean maternal weight gain in the 60 ppm group was significantly ( $P < 0.05$ ) greater than in the controls on days 0-7. There was no effect on body weight gain at the 200 ppm group. Initial body weights of the 600 ppm group were significantly ( $P < 0.01$ ) less than control weights. Probably related to the reduced weight gain during gestation was the observed embryoletality (see 2.7). No compound-related effects on fertility were found. Gravid uterus weight was lower in the 600 ppm group than in the control group, but according to the authors, the difference was less obvious when adjustments for initial body weight were made in the ANCOVA procedure.

## 2.2 Risks of exposure of female animals with respect to gestation and prenatal development

Hinkle (1973, abstract) administered to Syrian golden hamsters oral doses varying from 1.25 to 20.0 mg pentachlorophenol/kg daily from day 5 to 10 of gestation. Fetal deaths and/or resorptions were observed in 3 out of 6 test groups (detailed information not available).

Schwetz et al. (1974) administered pentachlorophenol in corn oil by gavage to groups of 20-40 rats on days 6-15 of gestation. Two samples were used, a purified compound (compound A) and a commercial grade compound (compound B, purity?). The doses were 0, 5, 15, 30 and 50 mg/kg of compound A and 0, 5.8, 15, 34.7 or 50 mg/kg/day of compound B. The rats were weighed on days 6, 13 and 21 of gestation and autopsied on day 21. A statistically significant ( $P < 0.05$ ) decrease in maternal weight gain (during days 6 through 21 of gestation) was seen in the two high dose groups of each of the both samples. Apart from decreased weight gain, no signs of maternal toxicity was observed. Treatment with 15, 34.7, 50 mg/kg compound B or 40 or 50 mg/kg compound A caused a significant ( $P < 0.05$ ) increase in the incidence of resorptions both among the fetal population (when the foetus was used as a unit for calculation) and among the litters (when the litter was used as a unit for calculation). At 50 mg/kg/day of compound A all implantations were resorbed. The majority of the offspring of dams receiving 50 mg of compound B or 30 mg of compound A were males. Administration of 5.8 mg of compound B and 5 or 15 mg of compound A/kg/day had no effect on the incidence of resorptions.

Treatment of rats with 34.7 or 50 mg of compound B or 30 mg of compound A /kg/day caused a statistically significant ( $P < 0.05$ ) decrease in fetal body weight. With compound A (30 mg) there was also a significant ( $P < 0.05$ ) decrease in crown-rump length.

Examination of the data suggests that the incidence of various anomalies such as subcutaneous edema, dilatation of the ureter, and anomalies of the skull (delayed ossification), ribs, vertebrae and sternbrae increased with an increasing dose of pentachlorophenol in both samples. Only at a level of 5 mg compound B /kg/day no detectable effect on the incidence of fetal anomalies was noticed.

In the same study additional groups of rats were treated with 0 or 34.7 mg of compound B or 30 mg of compound A /kg/day on days 8-11 or 12-15 of gestation. The administration of both samples separately on days 8 through 11 of gestation caused a significant decrease in maternal weight gain during gestation, while administration on days 12 through 15 had no effect. Both samples caused a significant increase ( $P < 0.05$ ) in the incidence of resorptions among the fetal population and among the litters, when administered on days 8 through 11, but not on days 12-15. Neither compound A nor compound B significantly altered the sex ratio of the offspring at any exposure. Both samples when administered separately on days 8 through 11 of gestation caused a significant decrease in fetal body weight and in crown-rump length. This effect also was found with compound A when administered on days 12 through 15 of gestation. When the two samples were administered on days 8 through 11 of gestation a significant increased incidence of subcutaneous edema and variations in the development of the ribs, vertebrae and sternbrae were observed.

Administration of compound A on days 12 through 15 of gestation caused a significantly ( $P < 0.05$ ) increased incidence of subcutaneous edema as well as an increased incidence of variations in sternbral development.

Larsen et al. (1975) administered a single dose of 0 or 60 mg/kg pentachlorophenol (purity > 99%) orally to rats ( $N=66$ ) at various points of time during days 8-13 of gestation. On the day of treatment deep rectal temperatures were taken just prior to dosing and then every 2 hr for 8 hr.

The animals were killed on day 20 of gestation. A significant increase of deep rectal temperature (the increase ranged from about 0.5 to 0.8 degree), were observed in animals receiving pentachlorophenol on days 8, 9 and 10 of gestation. The weight of the fetuses of the treated animals was significantly ( $P < 0.05$ ) lower than that of the controls, but only after treatment on days 9 and 10. The average reduction in weight after treatment on days 9 and 10 was

about 20 and 13%, respectively. The incidence of resorptions was not significantly higher than in controls. Of 46 fetuses prenatally treated on day 8 one dwarf of one-fourth the size of a normal fetus was observed. Three fetuses with malformations (exencephaly, macrophthalmia, and taillessness) were observed in three different litters (with a total number of 51 fetuses) prenatally treated on day 9. No malformations were observed in any of the fetuses from the control animals. The authors concluded that there is a slight teratogenic effect of pentachlorophenol. These findings were, however, considered by the authors to be an indirect effect ascribed to maternal toxicity (elevation of the body temperature), since it is known, that maternal hyperthermia induces teratogenic effects in rats (Edwards 1968). Hyperthermia is a common outcome of exposure to large, single doses of pentachlorophenol. Courtney et al. (1976) administered 0 or 75 mg/kg pentachlorophenol orally to rats on gestational days 7-18 (N=7). The animals were sacrificed 1 or 2 days before parturition. The only effect observed was a slight but significant decrease in fetal body weight.

### 2.3 Risks of exposure of female animals with respect to the offspring

Exon et al. (1982) exposed rats to 0, 55, 550 or 5500 mg/m<sup>3</sup> pentachlorophenol. The study was designed to produce progeny that were exposed to pentachlorophenol both prenatally and postnatally. Female rats were weaned at 21 days and placed on dietary regimens containing pentachlorophenol in the feed. The rats were bred at 90 days of age, and the dams were terminated at weaning. Effects on reproduction was observed as indicated by decreased litter size in the 5500 mg/m<sup>3</sup> group (P<0.10). There were no significant differences in mean weight gain of dams, in birth weight, percent of stillborn pups, weaning weight, or survival to weaning (%)

### 2.4 Risks of exposure of male animals with respect to gonads, endocrine system and fertility

No data available.

### 2.5 Risks of exposure of male animals with respect to gestation of the partner

No data available.



2.6 Risks of exposure of male animals with respect to the offspring

No data available.

2.7 Risks of exposure of both male and female animals (mating partners)  
with respect to gestation

Welsh et al. (1987) exposed rats (20 males and 20 females per dose group) to dietary levels of 0, 60, 200 or 600 ppm purified pentachlorophenol for 181 days, throughout mating and pregnancy (for details of the study see 2.1). Pentachlorophenol exposure had no effect on the number of corpora lutea, the implantation efficiency, and the number of implants per female. In the 600 ppm group a significant ( $P < 0.01$ ) increase in the mean number of early deaths per litter, and consequently a lower proportion of viable fetuses per female was observed. In the 200 ppm and 600 ppm group a significant increase in the numbers of females with two or more resorptions was observed. The 600 ppm group was not included in further analysis, since there was only one (male) fetus. Pentachlorophenol treatment resulted in a dose-related decrease in the body weight of the fetuses ( $P < 0.05$  in the 200 ppm group). Crown-rump length for females fetuses in the 200 ppm group was significantly ( $P < 0.01$ ) less than that of controls. Pentachlorophenol exposure had no effect on the incidence of runts at any of the dose levels.

In the 200 ppm group vertebral body anomalies were the only skeletal variation that was significantly ( $P < 0.01$ ) increased when compared with controls. The average number of fetuses with skeletal variations was increased in the 200 ppm group.

This group also showed a significant increase in the number of fetuses with at least one and in those with at least two skeletal variations as well as in the litter incidence of fetuses with at least two variations.

2.8 Risks of exposure of both male and female animals (mating partners)  
with respect to the offspring

Fielder (1982) summarized the results of another reproductive toxicity study of Schwetz et al. (1978). Rats (10 male and 20 female animals per group) were treated with 0, 3 or 30 mg/kg pentachlorophenol (compound A7 or compound B7) in their diet for 62 days prior to mating, and during the 15 days when the

animals were allowed to mate. The male animals were then separated from the females, but both were exposed to pentachlorophenol for the duration of the pregnancy and lactation period. The adult animals and the offspring were killed after the 21-day lactation period. Signs of toxicity noted in the parental animals during the exposure period were limited to reduced weight gain in the female rats given 30 mg/kg. A slightly lower proportion of viable offspring was noted at the higher dose level (P=7), with 91% (188/206), 96% (195/204) and 97% (174/180) in the 30 mg/kg, 3 mg/kg, and control group respectively. Mean body weight of the live offspring was reduced at 30 mg/kg but not at 3 mg/kg. Reduced weight gain and increased mortality was noted over the 21-day lactation period in the offspring from the 30 mg/kg group but no effects were noted in offspring from the 3 mg/kg group. At autopsy a significant (P=7) increase in the incidence of skeletal defects (lumbar spurs, vertebrae with unfused centra) was noted in the offspring from the 30 mg/kg group. No other effects were noted. The no-effect level in this study was 3 mg/kg.

#### 2.9 Conclusions on the animal data

With respect to the embryotoxicity and teratogenicity there are only two detailed studies available (Schwetz et al. 1974; Welsh et al. 1987) with purified and commercial grade pentachlorophenol. Both samples induced embryotoxic/embryo-lethal and/or teratogenic effects, and the purified pentachlorophenol appeared to be slightly more toxic and teratogenic than the commercial grade sample. Adverse effects were observed on maternal weight gain, fetal resorptions, fetal body length and fetal anomalies. Treatment on days 12 through 15 (late organogenesis) only had very little adverse effect on embryonal and fetal development, while treatment on days 8 through 11 caused a degree of toxicity comparable to treatment throughout organogenesis, days 6 through 15 of gestation. The no-effect level of the commercial grade of pentachlorophenol was 5 mg/kg/day, and the NAEL of purified pentachlorophenol was less than 5 mg/kg/day. One study (the no-effect level in this study was 3 mg/kg) which was mentioned in a review paper is available, that deals with a reproductive toxicity study. However, sufficient data are lacking to draw a well-documented conclusion about the effect of pentachlorophenol on fertility and reproduction in laboratory animals. Therefore, a reliable NAEL could not be assessed.

According to the WHO (1985) it is possible that the enhanced fetotoxicity of purified pentachlorophenol relative to the technical material, if not an artifact, is a result of the presence of microcontaminants, like polychlorodibenzodioxins and polychlorodibenzofurans, in the technical material.

### 3. Human data

#### 3.1 Risk of exposure of women with respect to the reproductive organs, the endocrine system and fertility

No data available.

#### 3.2 Risk of exposure of women with respect to pregnancy and offspring

No data available.

#### 3.3 Risk of exposure of women with respect to infant through lactation

No data available.

#### 3.4 Risk of exposure to the male reproductive organs, the endocrine system, and fertility

Dougherty et al. (1980) and Kuehl & Dougherty (1980) investigated toxic substances in human seminal plasma because of the apparent decrease in sperm density in US males of the last 30 years. Among other xenobiotic chemicals, they also observed that PCP is selectively concentrated by the cellular material. The authors expressed their concern because of mildly mutagenic properties of PCP.

#### 3.5 Risks of exposure of males with respect to pregnancy of the partner and offspring

Corddry (1981) investigated the pregnancy outcome in women married to sawmill workers in Canada. Although there was a slight trend towards more adverse pregnancy outcomes in the exposed group, this trend disappeared when the alcohol consumption was considered as a confounding factor. Analysis of data on 43 women with a total of 100 pregnancies did not reveal any significant differences in the pregnancy outcome between the exposed and the unexposed group.

### 3.6 Risk of exposure to pregnancy and offspring; environmental studies

No data available.

### 3.7 Discussion and conclusion of human data

Human data with respect to the reproduction are too limited to draw any valid conclusions.

## 4. Conclusion and evaluation

According to the study in animals described by Schwetz et al. (1974), pentachlorophenol induces embryotoxic and teratogenic effects whereas Welsh et al. (1987) reported embryo-lethal effects. Further, any animal and human data with respect to endocrine system, gonads and fertility are lacking. Data on offspring are inadequate for evaluation. It is therefore concluded that a NAEL could not be assessed and that further studies are necessary. The present MAC is 0.5 mg/m<sup>3</sup>; in exposure for 8 h. Without dermal resorption, the maximum (overestimated) respiratory intake is equal to the NAEL of 5 mg/m<sup>3</sup>. However, this neglects possible species differences in sensitivity for toxic effects. Moreover, in practice dermal absorption is likely. Therefore, there is reason to reassess the MAC.

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