

Chlorinated Dibenzodioxins and Pentachlorophenol

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Introduction

Pentachlorophenol is a registered antimicrobial agent whose principal use is for the preservation of wood. Typical commercial pentachlorophenol contains a variety of substances which are considered to be "inactive" from the aspect of antimicrobial efficacy. Consequently, pentachlorophenol is sold as an antimicrobial agent with 95% active ingredients and 5% "inert" ingredients. Analysis of acceptable commercial pentachlorophenol is shown in Table 1.

The "caustic insolubles," sometimes referred to as the "nonphenolic or neutral impurities," include chlorinated dibenzo-*p*-dioxins and chlorinated dibenzofurans (1). Recently developed analytical technology has allowed quantitation of hexachlorodibenzo-*p*-dioxins and octachlorodibenzo-*p*-dioxin in pentachlorophenol. Portrayed in Table 2 are concentration ranges for these two chlorodibenzo-*p*-dioxins in samples of currently available commercial grade pentachlorophenol. Techniques capable of detecting 0.05 ppm showed no 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in any sample of pentachlorophenol examined by us. The absence of this compound in pentachlorophenol is not surprising, because the appropriate precursors for its formation are not present.

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Table 1. Commercial pentachlorophenol composition.

	Content %
Pentachlorophenol	85-90
Tetrachlorophenol	4-8
Trichlorophenol	<0.1
Higher chlorophenols	2-6
Caustic insolubles (maximum)	1

Table 2. Concentration ranges of some chlorinated dioxins in commercial pentachlorophenol.

Chlorinated dibenzo- <i>p</i> -dioxin	Concentration range, ppm
2,3,7,8-Tetrachlorodibenzo- <i>p</i> -dioxin	None
Hexachlorodibenzo- <i>p</i> -dioxins	9-27
Octachlorodibenzo- <i>p</i> -dioxin	575-2510

Heptachlorodibenzo-*p*-dioxin and hexa-, hepta- and octachlorodibenzofurans have been qualitatively detected in commercial pentachlorophenol. However, the lack of appropriate standards for these materials does not allow their quantitation.

Severe toxicological responses have been attributed to certain chlorodibenzo-*p*-dioxins (2). For example, the LD₅₀ of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin ranges from 0.6 μg/kg in male guinea pigs to 115 μg/kg in rabbits of mixed sexes. A benzene solution of this agent containing as little as 0.04 μg/ml produces acne in the rabbit ear bioassay. Very high embryotoxicity and the production of edema in chicks are other properties of this material. The no-effect

dose levels for these latter activities are 0.03 and 0.1 $\mu\text{g}/\text{kg}\text{-day}$, respectively. Although pertinent for perspective, it is re-emphasized that this agent is not a contaminant of pentachlorophenol.

Limited lethality data are available on hexachlorodibenzo-*p*-dioxins and octachlorodibenzo-*p*-dioxin. The former material killed 1 of 2 and 0 of 2 male rats given overdoses of 100 and 10 mg/kg, respectively. Doses of 1 g/kg and 4 g/kg of octachlorodibenzo-*p*-dioxin failed to kill female rats and male mice, respectively.

With regard to acneogenic activity, chloroform solutions containing 10 to 50 $\mu\text{g}/\text{ml}$ hexachlorodibenzo-*p*-dioxin are active while preparations of octachlorodibenzo-*p*-dioxin are inactive.

Hexachlorodibenzo-*p*-dioxin administered to pregnant rats at a dose of 100 $\mu\text{g}/\text{kg}\text{-day}$ has been found teratogenic, while doses of 1 or 10 $\mu\text{g}/\text{kg}\text{-day}$ produced only subcutaneous edema. A dose of 0.1 $\mu\text{g}/\text{kg}/\text{day}$ was not associated with untoward effects in embryos or fetuses. Studies to date have revealed that octachlorodibenzo-*p*-dioxin is essentially devoid of untoward activity in the embryo and fetus.

Daily doses of 10 and 100 $\mu\text{g}/\text{kg}$ hexachlorodibenzo-*p*-dioxin produce a positive response in the chick edema bioassay, while doses of 0.1 and 1.0 $\mu\text{g}/\text{kg}$ are negative. As with the other untoward effects previously referred to, octachlorodibenzo-*p*-dioxin appears to be devoid of this activity.

Although the principal chlorodibenzo-*p*-dioxin contaminant of pentachlorophenol, octachlorodibenzo-*p*-dioxin, in the amounts normally present does not appear to present a significant hazard, the presence of hexachlorodibenzo-*p*-dioxin as well as the other contaminants in pentachlorophenol previously mentioned give rise to concern. In at least one instance, the product literature warns that frequent skin contact may result in an acneform dermatitis (3). However, documentation of such occurrences is unavailable. In addition, it has been stated that contamination of fat used in the diet of

chickens with pentachlorophenol may be responsible for the "toxic fat" syndrome.

In response to the concern about the toxicological significance of the nonphenolics in pentachlorophenol, we conducted studies to determine whether their presence in the product may contribute to its toxicological properties. After finding that the toxicological properties of the nonphenolics could, indeed, be detected by toxicological evaluations, acneogenic response, chick edema assay, and 90-day dietary feeding studies in rats, we set out to develop a product which was a "toxicological mimic" of pure pentachlorophenol. Before presenting the results of our toxicity studies, it should be emphasized that pentachlorophenol is an economic poison, and although we believe we have developed the capability to produce a product in which the contaminants do not contribute to its potential hazard, it remains an economic poison.

Experimental

The rabbit ear bioassay test was conducted according to published procedures (2, 4). The chick edema bioassay test was conducted according to the procedure described in the official methods of analysis of the Association of Official Agricultural Chemists (5). The feeding studies utilized the Spartan strain of Sprague Dawley rats which were maintained on diets formulated to supply the various dose levels for 90 days. Parameters monitored in these feeding studies included the following: body weights, food consumption, appearance and demeanor of the rats, routine hematologic and urinary parameters, routine serum enzymes, terminal organ weights and gross and histopathologic examination of tissues.

Results

The concentration, of hexa- and octachlorodibenzo-*p*-dioxin in the commercial pentachlorophenol sample utilized in the toxicological studies reported herein are given in Table 3. Table 4 is a compilation of the toxicological data on this sample of

commercial pentachlorophenol. A positive response was noted in both chick edema and rabbit ear bioassays. In the 90-day rat feeding study, untoward effects were noted in a majority of the parameters monitored. Hematological examination revealed a depression of erythrocytes, hemoglobin, and packed cell volumes at a dose level of 30 mg/kg-day pentachlorophenol. Clinical chemistry alterations included an elevation of serum alkaline phosphatase at 30, 10, or 3 mg/kg-day and a depression of serum albumin at 30 or 10 mg/kg-day. The weights of liver and kidneys were increased at 30, 10, or 3 mg/kg-day. Pathologic examination revealed minimal focal hepatocellular degeneration and necrosis at 30 mg/kg-day. Thus, it is evident that commercial pentachlorophenol induced untoward effects in each of the three toxicological tests.

Table 3. Concentrations of chlorinated dioxin "indicators" in commercial pentachlorophenol utilized in toxicological evaluations.

Chlorinated dioxin	Concentration, ppm
Octachlorodibenzo- <i>p</i> -dioxin	1980
Hexachlorodibenzo- <i>p</i> -dioxins	19

A chemically pure pentachlorophenol having no detectable concentrations of any chlorinated dioxins was subjected to the same toxicological tests. The toxicological data on this chemically pure pentachlorophenol, summarized in Table 5, include negative responses in both the chick edema and rabbit ear bioassays. In the 90-day rat feeding study, the only changes noted were increased liver weights at 30 or 10 mg/kg-day and increased kidney weights at 30 mg/kg-day. However, in contrast to commercial pentachlorophenol, gross and histopathological alterations did not accompany these increases in organ weights. Thus, by utilizing the results of these three tests, it may be concluded that the presence of the contaminants in commercial pentachlorophenol may be detected by toxicological evaluation.

An analysis of a sample of pentachloro-

Table 4. Toxicological data on sample of commercial pentachlorophenol.

Study	Result ^a
Chick edema bioassay	+
Rabbit ear bioassay	+
Rat feeding study	
Food consumption	-
Body weight	-
Hematology	
30 mg/kg-day	+
10 mg/kg-day	-
3 mg/kg-day	-
Urinalysis	-
Clinical chemistry	
30 mg/kg-day	+
10 mg/kg-day	+
3 mg/kg-day	+
Liver weight	
30 mg/kg-day	+
10 mg/kg-day	+
3 mg/kg-day	+
Kidney weight	
30 mg/kg-day	+
10 mg/kg-day	+
3 mg/kg-day	+
Pathology	
30 mg/kg-day	+
10 mg/kg-day	-
3 mg/kg-day	-

^a + denotes effect; - denotes no effect.

phenol representative of that which we are capable of producing is shown in Table 6.

The toxicological data on this sample of pentachlorophenol are summarized in Table 7. Both the chick edema and rabbit ear bioassays gave negative responses. In the 90-day rat feeding study, the only unequivocal changes were increased liver weights at 30 or 10 mg/kg-day and increased kidney weights at 30 mg/kg-day. There were no gross or histopathological alterations noted.

To reiterate the toxicological findings on these three samples of pentachlorophenol, a comparison is provided in Table 8.

Commercial pentachlorophenol gave positive responses in both the chick edema and rabbit ear bioassays; in contrast, the chemically pure pentachlorophenol and the improved pentachlorophenol both gave negative responses in these bioassays.

In the rat feeding studies, commercial pentachlorophenol was associated with hema-

Table 5. Toxicological data on sample of chemically pure pentachlorophenol.

Study	Results *
Chick edema bioassay	—
Rabbit ear bioassay	—
Rat feeding study	
Food consumption	—
Body weights	—
Hematology	—
Urinalysis	—
Clinical chemistry	—
Liver weight	
30 mg/kg-day	+
10 mg/kg-day	+
3 mg/kg-day	—
Kidney weight	
30 mg/kg-day	+
10 mg/kg-day	—
3 mg/kg-day	—
Pathology	—

* + denotes effect; — denotes no effect.

Table 6. Concentrations of chlorinated dioxin "indicators" in improved pentachlorophenol utilized in toxicological evaluations.

Chlorinated dioxin	Concentration, ppm
Octachlorodibenzo- <i>p</i> -dioxin	26
Hexachlorodibenzo- <i>p</i> -dioxins	1 ± 0.1

Table 7. Toxicological data on sample of improved pentachlorophenol.

Study	Results *
Chick edema bioassay	—
Rabbit ear bioassay	—
Rat feeding study	
Food consumption	—
Body weights	—
Hematology	—
Urinalysis	—
Clinical chemistry	—
Liver weights	
30 mg/kg-day	+
10 mg/kg-day	+
3 mg/kg-day	—
1 mg/kg-day	—
Kidney weights	
30 mg/kg-day	+
10 mg/kg-day	—
3 mg/kg-day	—
1 mg/kg-day	—
Pathology	—

* + denotes effect; — denotes no effect.

toxic changes, clinical chemistry alterations, liver damage, plus liver and kidney weight increases at dose levels of 30, 10, or 3 mg/kg-day.

The results of the feeding studies with improved pentachlorophenol gave results which closely paralleled the results obtained with the chemically pure pentachlorophenol, wherein changes were limited to increased liver and kidney weights at the higher dose levels.

Table 8. Comparative evaluation of toxicological data obtained on pentachlorophenol (PCP) samples.*

Study	Commercial PCP	Chemically pure PCP	Improved PCP
Chick edema bioassay	+	—	—
Rabbit ear bioassay	+	—	—
Rat feeding study			
Hematologic depression	+	—	—
Clinical chemistry alterations	+	—	—
Liver damage (histopathology)	+	—	—
Liver weight increase			
30 mg/kg-day	+	+	+
10 mg/kg-day	+	+	+
3 mg/kg-day	+	—	—
Kidney weight increase			
30 mg/kg-day	+	+	+
10 mg/kg-day	+	—	—
3 mg/kg-day	+	—	—

* + denotes effect; — denotes no effect.

Discussion and Summary

The toxicological data have enabled us to conclude that a commercial pentachlorophenol conforming to the "improved" pentachlorophenol would not elicit chick edema and chloracne. In addition, the histopathological effects resulting from the impurities in commercial pentachlorophenol would be eliminated.

The toxicological findings discussed in this paper have been utilized as part of an application for registration of new pentachlorophenol. This application has been approved by the Environmental Protection Agency in accordance with the requirements of the Federal Insecticide, Fungicide and

Rodenticide Act. The composition specifications for this new commercial pentachlorophenol are cited in Table 9.

In conclusion, it is feasible to produce a pentachlorophenol in commercial quantities which by comparative evaluations mimics pure pentachlorophenol in toxicological responses.

Table 9. Composition and specifications of improved pentachlorophenol.

	Content
Pentachlorophenol	88-93%
Tetrachlorophenol	12- 7%
Trichlorophenol	<0.1%
Higher chlorophenols	0.1%
Chlorinated dioxins	
Octachlorodibenzo- <i>p</i> -dioxin	30 ppm (max.)
Hexachlorodibenzo- <i>p</i> -dioxins	1.0 ppm (max.)

REFERENCES

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