Occupational Studies of Workers in Pentachlorophenol Production

James J. Collins, PhD
The Dow Chemical Company
Published Epidemiology Studies of Workers Manufacturing Pentachlorophenol

- Dow (Midland, Michigan)
  - Collins et al. 2007; Ramlow et al. 1996
  - Ruder & Lin 2011
- Middle Volga Chemical (Chapaevsk, Russia)
  - Revich et al., 2001
- Monsanto (Krummerich in Sauget, Illinois)
  - Hryhorczuk et al. 1998
  - O’Malley et al. 1990
  - Ruder & Lin 2011
- Monsanto (Newport, South Wales)
  - Baxter, 1984
- Phillips (Amsterdam, The Netherlands)
  - Boers et al. 2010; Bueno de Mesquita et al. 1993
- Reichhold (Tacoma, Washington)
  - Ruder & Lin 2011
- Spolana (Czech Republic)
  - Jirasek et al. 1976
- Tianjin Chemical (Tianjin, China)
  - Cheng et al. 1993
- Vulcan (Wichita, Kansas)
  - Ruder & Lin 2011
Exposures in PCP Manufacture

• Exposures thought to be highest in PCP manufacture compared to wood treating, pulp & paper, and sawmill
  – Most cases of chloracne reported in PCP manufacture
  – Supported by Limited serum dioxin evaluations

• Chloracne has rarely occurred in wood treating industry
  – Case study (Cole et al. 1986)
    • Dermal exposure from poor work practices

• Case control studies have relatively low dioxin levels and often no difference in dioxin levels between cases and controls (Hardell et al., 2001)

Sources: Williams 1982; Schecter et al. 1994; Collins et al. 2007; McLean et al. 2009
Percentage of PCP Manufacturing Workers Who Developed Chloracne

Days of Exposure

- Sauget (1938-78 production)
- NIOSH Dioxin Registry PCP
- Midland (1937-80 production)
- Chapaevsk (operation)
- Newport (operation)
- Ufa (accidents & operations)
- Tianjin (1974 outbreak)

Percentage

0 20 40 60 80 100
Lipid adjusted serum dioxin and furan levels

Source: Schecter et al. 1994; Collins et al. 2007; McLean et al. 2009
Two Methods of Making PCP

1. Chlorination of phenol
   a. Mostly widely used (all US production)
   b. Contaminants include polychlorinated phenols (tetra-, tri-), hexachlorobenzene, dioxins (HXDD, HPDD, OCDD), and some furans

2. Hydrolysis of hexachlorobenzene
   a. Used sometimes in Europe and China
   b. Contaminants include polychlorinated phenols (tetra-, tri-), hexachlorobenzene, dioxins (TCDD, HXDD, HPDD, OCDD), and some furans

Sources: Plimmer 1973; Fisher 1991; IARC 1997; ATSDR 2001
## Estimated Half-Life in Human Body

<table>
<thead>
<tr>
<th>Substance</th>
<th>Half-life</th>
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<tbody>
<tr>
<td>Pentachlorophenol</td>
<td>30-50 hours</td>
</tr>
<tr>
<td>Tetrachlorophenol</td>
<td>30-50 hours</td>
</tr>
<tr>
<td>Trichlorophenol</td>
<td>30-50 hours</td>
</tr>
<tr>
<td>Hexachlorobenzene</td>
<td>2.5-3.0 years</td>
</tr>
<tr>
<td>2378-TCDD</td>
<td>6.5 years</td>
</tr>
<tr>
<td>123478-HXDD</td>
<td>7.0 years</td>
</tr>
<tr>
<td>123678-HxDD</td>
<td>9.0 years</td>
</tr>
<tr>
<td>123789-HXDD</td>
<td>6.3 years</td>
</tr>
<tr>
<td>1234678-HPDD</td>
<td>6.7 years</td>
</tr>
<tr>
<td>OCDD</td>
<td>7.3 years</td>
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</tbody>
</table>

Sources: Plimmer 1973; ATSDR 2001; Aylward et al. 2013
Lipid adjusted serum dioxin and furan levels

Source: Collins et al. 2007
US Pentachlorophenol  Dioxin Profile

Octachlorodibenzodioxin

Heptachlorodibenzodioxin

Hexachlorodibenzodioxin (1,2,3,4,7,8), (1,2,3,6,7,8), and (1,2,3,7,8,9) Isomers
Biomonitoring

• Chlorophenols disappear rapidly in the body
  – difficult to access past exposure from biomonitoring

• Dioxins are long-lived in the body
  – could be used as indicators of past exposure to not only dioxins, but also to commercial PCP
    • assumes level of contaminants constant
Other Exposures

- PCP was often made in plants making other pesticides including 2,4,5 trichlorophenol (TCP) and 2,4,5 trichlorophenoxyacetic acid (2,4,5-T)
- Many other potential exposures depending on site
Lipid adjusted serum dioxin levels

Source: de Mesquita et al. 1993; Boers et al., 2010
OCDD Levels

Source: Collins et al., 2007
Treatment of Mixtures

• Occupational exposures are always mixtures of exposures
• Approaches for mixtures in epidemiology
  1. **Independent** – each exposure produces separate exposure response
     • Focus on one chemical and ignore others (most common)
  2. **Additive** – two or more chemicals have additive effect on exposure response
     • TEQ for dioxins
  3. **Synergistic** – total effect is greater than the sum of the effects
     • Smoking, asbestos and lung cancer
     • Smoking, arsenic and lung cancer
  4. **Antagonist** – Some chemicals interfere with the toxic impact of other chemicals
     • Selenium and mercury in diet
Methods of Exposure Assessment

1. Four dimensions of exposure
   a. Identity
      • PCP and contaminants
        – Dioxin’s Toxic Equivalents
   b. Form
      • Distilled, solution (oil or aqueous), flakes, prills, blocks
        – Dermal, inhaled, ingested
   c. Concentration
      • Expert opinion
      • Industrial hygiene monitoring
      • Biomonitoring
   d. Time
      • Work history
Exposure Modeling Issues

• If disease risk is thought to be proportional to dose then a cumulative exposure model may be appropriate
• Induction time analyses may be necessary to study cancer risk
• Internal versus external comparisons
  – Internal comparisons
    • usually reduce the healthy worker effect (selection bias)
    • allow direct comparison of relative risk across strata.
  – External comparisons
    • based on regional rates can adjust for geographic variability in social, cultural, and economic factors in relation to disease (Doll, 1985)
    • generally very stable.
Modeling of Pentachlorophenol Exposures
Modeling of Dioxin Exposures

- **Workplace Exposure**
- **Background Exposure**

- End of Exposure
- Time of Measurement

**Dioxin, ng/kg**

**Age**

**Thursday, April 10, 2013**
Exposure Estimation Approaches

1. Exposed/Unexposed
   – PCP w/contaminants (Cheng et al., 1993)

2. Duration of exposure
   – PCP w/contaminants (Hryhorczuk et al., 1998) (Ruder & Yin, 2011)
   – Dioxins (Kogevinas et al., 1997)*

3. Estimation using expert opinion and industrial hygiene monitoring
   – PCP & dioxins (Ramlow et al. 1996)

4. Modeling from biomonitoring
   – Dioxins (Flesch-Janys et al. 1998; Boers et al. 2010)* (Collins et al. 2009)

* Combines PCP and TCP workers
Summary

• Few studies have examined cancer risk in PCP production workers
  – Exposure characterization is mostly crude

• Few studies have examined serum dioxin levels in PCP exposed workers
  – While there has been several studies which examined TCDD, few studies even tried to measure the higher chlorinated dioxins
Only 3 PCP Industrial Workers Studies Examined Cancer Rates

- Cheng et al. 1993
- Collins et al., 2009 & Ramlow et al., 1996
- Ruder & Yin 2011

Number of Workers

<table>
<thead>
<tr>
<th>Study</th>
<th>Number</th>
</tr>
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<tbody>
<tr>
<td>Cheng et al. 1993</td>
<td>0</td>
</tr>
<tr>
<td>Collins et al., 2009 &amp;</td>
<td>800</td>
</tr>
<tr>
<td>Ramlow et al., 1996</td>
<td>0</td>
</tr>
<tr>
<td>Ruder &amp; Yin 2011</td>
<td>2000</td>
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PCP STUDY RESULTS – MIDLAND, MICHIGAN (DOW)
Relative Risk & 95% Confidence Interval of Cancer Among Dow’s **Pentachlorophenol** Workers using IARC Cancers of Concern

Source: Collins et al. 2009
Relative Risk & 95% Confidence Interval for Non-Hodgkin Lymphoma

Relative Risk

ppt-years

Background 0.01-0.69 0.70-3.99 4.00-113.37
Dow PCP Worker Studies

- Dioxin exposures among Dow PCP workers were well above background
  - Chloracne present in 20% of PCP workers
  - Extensive serum dioxin evaluations including serial serum samples
- Detailed work histories for all workers
- Long follow-up (1940-2003) and low loss during follow-up
- Our findings are consistent with other studies of highly exposed persons
Conclusions

• “Other than possibly an increased risk of non-Hodgkin lymphoma, we find no other causes of death related to the mixture of dioxin contaminants found in PCP.”

• All cancers combined and lung cancer at expected levels

• For NHL
  – No trend with exposure
  – NHL risk greatest in highest exposure category (only 4 deaths)
  – Other studies have not consistently found increase in NHL