Draft RoC Monograph on Pentachlorophenol and By-Products on its Synthesis

National Institute of Environmental Health Sciences

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Human cancer studies
Cancer studies in humans

• Key Questions
  – What is the level of evidence of carcinogenicity from studies in humans?
    • What are the potential confounders?
    • Can any observed association between pentachlorophenol and cancer be explained by chance, bias or confounding?

• Methods: Protocol posted on the RoC website
  – Literature search strategy (3.1)
  – Description of studies (3.2)
  – Evaluation of study quality (3.3)
  – Cancer assessment: individual studies, integration of evidence across studies (3.4, 3.5)
  – Preliminary level of evidence conclusion (3.6)
Identification and selection of literature

- Literature search strategy (Appendix A, protocol)
- Excluded studies
  - Studies of mixed chlorophenols/pesticides/jobs (no specific information on PCP)
  - No risk estimates for PCP
  - Not externally peer reviewed
# Studies identified from literature search

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Industry/exposure</th>
<th>Endpoints</th>
</tr>
</thead>
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<tr>
<td>Studies specific for PCP</td>
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<tr>
<td>Historical cohort</td>
<td>US producers (2)</td>
<td>Multiple</td>
</tr>
<tr>
<td></td>
<td>Canadian sawmill workers (1)</td>
<td></td>
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<tr>
<td>Nested case-control</td>
<td>Dioxin exposures (IARC registry) (1)</td>
<td>NHL, STS</td>
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<tr>
<td>Population based case-control studies</td>
<td>Occupational: Swedish series (3)</td>
<td>NHL, STS, Glioma</td>
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<td></td>
<td>Occupational: US (1)</td>
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<tr>
<td></td>
<td>Environmental: US (1)</td>
<td>Childhood ALL</td>
</tr>
<tr>
<td>Ecological</td>
<td>Environment (1)</td>
<td>Multiple</td>
</tr>
<tr>
<td>Studies with limited information on PCP</td>
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<tr>
<td>Nested case-control</td>
<td>Occupational (parental): sawmill (1)</td>
<td>Childhood cancer</td>
</tr>
<tr>
<td>Population-based case-control</td>
<td>Occupational: New Zealand series (3)</td>
<td>NHL, MM, STS</td>
</tr>
<tr>
<td></td>
<td>Occupational: Australian study (1)</td>
<td>Lymphoma, STS</td>
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</table>

Cancer endpoints of concern: non-Hodgkin lymphoma (NHL), multiple myeloma (MM), soft tissue sarcoma (STS), kidney cancer, liver cancer, lung cancer, and all cancers combined

PCP = pentachlorophenol; ALL = acute lymphocytic leukemia
Methods for evaluating study quality: Potential for biases, confounding and utility of studies

- Questions and guidelines in protocol used to reach conclusions for the potential (both differential, non-differential) for selection and information bias (Section 3.3.1/Appendix C)
  - Potential for a bias does not always mean the study was biased
  - Consideration of whether there was information to determine the direction of the bias
- Adequacy of statistical methods, statistical power and other factors also evaluated
- When possible, guidelines are specific for endpoint
- Evaluation of methods (or other information) for potential confounding (Section 3.3.2)
- Identification of most informative studies (Section 3.3.3)
  - Inadequate: Chinese ecological study (Zheng et al. 2013)
  - Less informative: Studies with limited information on PCP exposure
Non-Hodgkin lymphoma

• Incidence data more informative than mortality
  – High survival
  – ICD codes have changed over time

• Potential (limited evidence) occupational risk factors for NHL
  – Co-exposures in PCP studies: 2,3,7,8-TCDD, phenoxy herbicides, mixed polychlorinated phenols, styrene (Cogliano 2011, NTP 2011)
  – Other substances: benzene, tetrachloroethylene, trichloroethylene, ionizing radiation

• Potential (limited evidence or suspected) non-occupational risk factors for NHL
  – Radiation, immunosuppressive disorders and drugs, chemotherapy drugs, viral infections
  – No clear evidence that tobacco smoking is a risk factor
Non-Hodgkin lymphoma: Most informative studies
Human studies

<table>
<thead>
<tr>
<th>Study (number of subjects or cases/controls)</th>
<th>Exposure assessment</th>
<th>Analysis and treatment of confounders</th>
</tr>
</thead>
</table>
| Canadian sawmill workers (> 27,000) (Demers 2006) | Work history, industrial hygiene data
Estimated cumulative dermal exposure to PCP and TeCP
Validation of dermal exposure based on urine analysis, expert assessment, work history | Mortality/incidence:
SMR, SIR, RR by lagged and unlagged exposure
Separate RR analyses for TeCP
Adjusted for age and time period |
| PCP MI producers (770;773) (Ramlow 1996, Collins 2009a) | Industrial hygiene data (including quantitative data), work history
Some workers co-exposed to TCP
Cumulative exposure to PCP, PCP dioxin byproducts and total TEQ dioxins | Mortality:
SMR, RR by lagged and unlagged cumulative exposure and dioxin congeners
Separate SMR analysis for PCP+TCP-exposed workers
Adjusted for age, hire year, birth year |

TCP = trichlorophenol, TeCP = tetrachlorophenol
## Non-Hodgkin lymphoma: Other human studies

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<th>Study (# of subjects or cases/controls)</th>
<th>Exposure assessment</th>
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| PCP NIOSH producers (2122) (Ruder and Yiin 2011) | 4 plants with work history, industrial hygiene  
Duration of employment in PCP dept.  
Includes MI PCP-exposed workers; different assessment of combined PCP and TCP exposure | Mortality:  
SMR, SRR by duration  
Separate SMR analysis for PCP+TCP-exposed workers  
Adjusted for age, sex, calendar year |
| Nested (IARC registry) case-control study (32/153) (Kogevinas 1995) | Individual exposure assessment  
Cumulative exposure | Mortality:  
OR by ever, low, med, high exposure  
No control for potential confounders except for age, sex, and county of residence  
PCP production plant did not make other herbicides/pesticides |
| Swedish case-control studies (105/335; 515/1141) (Hardell 1994, 2002) | Questionnaire/work history | Incidence:  
2002: OR by time since first exposure  
1994: adjusted for occupational co-exposures, age, vital status |

TCP = trichlorophenol
| Michigan PCP producers and NHL: Comparison between Collins (2009a) and Ruder and Yiin (2011) |
|---------------------------------------------------|---------------------------------------------------|---------------------------------------------------|
| **Total PCP Workers** (PCP ± TCP workers)          | **Collins et al. 2009a**                           | **Ruder and Yiin 2011**                            |
|                                                   | SMR = 2.4 (1.0 to 4.7); 8                          | SMR = 2.18 (0.94-4.30); 8                         |
| PCP, no TCP                                       | 577                                                | 110                                               |
|                                                   | SMR = 2.8 (1.1 to 5.7)                              | SMR = not reported                                 |
|                                                   | Serum profile: Elevated levels of higher chlorinated dioxins |                                                   |
| PCP + TCP                                         | 196                                                | 675                                               |
|                                                   | Serum profile: Elevated levels of higher chlorinated dioxins and 2,3,7,8-TCDD |                                                   |
| TCP exposure characterization                     | Workers who worked in both TCP departments & PCP departments; did not consider any dept. to have exposure to both TCP & PCP* | Working directly in TCP process and/or in buildings where TCP processes were co-located* |

*Personal communication, study authors*
Strongest evidence of an association with exposure to pentachlorophenol is for NHL

• Increased risks of NHL found in all studies; however, strength of findings varies across studies
  – Strongest evidence from Canadian sawmill worker cohort (Demers 2006)
  – Supported by MI pentachlorophenol producers cohort study (Ramlow 1996, Collins 2009a)
  – Evidence from other studies is more limited but as a group support the findings from the more informative studies

• Exposure-response relationship in most informative study
  – No exposure-response observed in PCP producer studies

• Highest risk observed among PCP producers with the highest level of PCP by-products of synthesis (Collins et al. 2009a)
Increased risk of NHL across studies

Ever vs. never exposed

- All sawmill workers
- MI PCP producers cohort mortality
- NIOSH PCP producers cohort mortality
- IARC registry nested case-control study
- Swedish 1994 case-control study
- Swedish 2002 pooled case-control study

Highest exposure to PCP

- PCP exposure
- OCDD

SIR and RR for Canadian sawmill cohort; SMR for PCP producers; OR for nested case-control and 2 Swedish case-control studies

= cohort or nested case-control study;  = case-control study
Positive exposure-response relationship with PCP exposure and NHL: Canadian sawmill worker cohort

- Follow-up 20+ years
- 92 cases/49 deaths NHL
- Cumulative dermal exposure assessment
- Exposure-response analysis for PCP (unlagged, lagged):

<table>
<thead>
<tr>
<th>Endpoint/lag (yr)</th>
<th>$P_{trend}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality/0</td>
<td>0.06</td>
</tr>
<tr>
<td>Incidence/0</td>
<td>0.03</td>
</tr>
<tr>
<td>Incidence/10</td>
<td>0.03</td>
</tr>
<tr>
<td>Incidence/20</td>
<td>0.02</td>
</tr>
</tbody>
</table>

- Little evidence of exposure-response relationship for tetrachlorophenol

NHL by continuous cumulative PCP exposure (20-yr lag) (Friesen et al. 2007)
NHL risk is increased among PCP production workers with the highest levels of PCP by-products of synthesis

<table>
<thead>
<tr>
<th>PCP by-product (dioxin congener)</th>
<th>Cumulative level of congener</th>
<th>SMR (95% CI); # of exposed deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
<td>Medium</td>
</tr>
<tr>
<td>HxCDD</td>
<td>2.5 (0.5-7.4); 3</td>
<td>0.0 (0.0-3.1); 0</td>
</tr>
<tr>
<td>HpCDD</td>
<td>1.8 (0.2-6.4); 2</td>
<td>1.5 (0.2-5.25); 2</td>
</tr>
<tr>
<td>OCDD</td>
<td>1.7 (0.2-6.2); 2</td>
<td>1.6 (0.2-5.6); 2</td>
</tr>
</tbody>
</table>

Ref: Collins 2009a

- Highest risk (4-5-fold) observed for highest PCP dioxin by-product (HxCDD, HpCDD, OCDD) exposure category
  - No monotonic exposure-response relationship was observed in this analysis; however, there was potential potential misclassification of exposure in lower exposure groups (low and medium) due to dioxin modeling
  - Highest exposure group is a reasonable surrogate for past exposure to PCP
  - Internal analyses not conducted for PCP by-products

- No exposure-response relationship observed in internal or external analysis for total toxic equivalent (TEQ), which included 2,3,7,8-TCDD

- “Dioxin-like” activity of PCP by-products may contribute to increased risk
Can biases or potential confounding explain observed associations between pentachlorophenol and NHL?

Potential for biases:

- Associations unlikely to be explained by selection or information bias in cohort or nested case-control studies
  - industrial hygiene and work histories used
- Potential for non-differential misclassification in case-control studies, but detailed questionnaire or expert assessment helps to mitigate concern

Potential for confounding: non-occupational risk factors

- No evidence that smoking is associated with NHL in the case-control studies or that there are more smokers in the Canadian sawmill workers cohort study than the general population
- Smoking is not considered to be an established risk factor for NHL
- Other NHL risk factors unlikely to be related to exposure to pentachlorophenol
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Can occupational co-exposures explain the association between exposure to pentachlorophenol and NHL?

• Sawmill workers
  – No clear exposure-response for NHL and TeCP; no independent evidence to evaluate TeCP carcinogenicity
  – Creosote and copper chromate arsenate were not used regularly in the sawmills in this study
  – Other potential co-exposures (e.g., wood dust) are not known risk factors for NHL

• PCP producers
  – No association was observed between cumulative exposure to 2,3,7,8-TCDD and NHL among all TCP workers in the MI plant (Collins et al. 2009b)
  – Other exposures present but unknown whether they correlated with PCP exposure; no known risk factors for NHL

• Potential confounding possible in case-control studies
• Co-exposures vary across studies
Other Cancers

- Multiple myeloma and kidney cancer (some evidence)
  - Significant exposure-response relationships observed among Canadian sawmill workers for both cancers (Demers et al. 2006)
  - Elevated SMRs (statistically non-significant) from other cohort studies (Collins et al. 2009a – kidney cancer; Ruder and Yiin 2011 – multiple myeloma)

- Soft tissue sarcoma (conflicting evidence)
  - Increased risk in pooled case-control study (Hardell et al. 1995)
  - No evidence of association in Canadian sawmill workers (Demers et al. 2006)

- Liver and lung cancer (little to no evidence)
  - No evidence of an association for lung cancer in any cohort study.
  - Elevated SMR of liver cancer in the NIOSH study but co-exposure to other animal liver carcinogens; no evidence of an association in the other cohort studies

- All cancers combined
  - Elevated risks in the NIOSH study; no exposure-response analysis was conducted in the Canadian sawmill study
Preliminary level of evidence conclusion: Vote

Sufficient evidence for the carcinogenicity of pentachlorophenol and by-products of its synthesis from studies in humans, based on:

- Consistent evidence of an association between PCP and its by-products of synthesis and non-Hodgkin lymphoma across studies
  - Different populations, geographical areas and study designs
  - Strength of the association varied across studies
- High risk among those with the highest exposure
  - Exposure response relationship observed with cumulative dermal exposure in most informative study
  - Higher risk observed among PCP producers with the highest level of PCP by-products
- Not reasonably explained by chance, bias or confounding
- “Dioxin-like activity” of PCP by-products of synthesis may contribute to the carcinogenicity