Draft Report on Carcinogens Monographs for Pentachlorophenol and By-Products of Its Synthesis

Comments on Behalf of Pentachlorophenol Task Force

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Conclusions in RoC PCP Listing Document

• PCP & by-products of its synthesis should be considered as “known” to cause cancer in humans (i.e., specifically non-Hodgkin’s lymphoma; NHL).
• “…by-products of..synthesis..from biomonitoring studies
  – hexachlorodibenzo-p-dioxin
  – heptachlorodibenzo-p-dioxin
  – octachlorodibenzo-p-dioxin
  – not TCDD, which is not a by-product of PCP synthetic process used in the United States.
PCP & Synthesis By-Products

- Potential confounding from TCDD a concern for studies from Europe, New Zealand & U.S.*
- TCDD listed in 12th RoC as *Known Human Carcinogen* for all cancer with emphasis on NHL
- TCDD listed by IARC as *Known Human Carcinogen* for all cancer with emphasis on NHL
- Logic of RoC PCP listing when potential contaminant *Known* to have similar effects already listed?

*Collins, Ruder, Kogevinas, Hardell*
PCP & Synthesis By-Products

- NHL major cancer site of interest
  - Other sites: multiple myeloma, soft-tissue sarcoma
- Human studies on NHL
  - Cohort studies
    - Demers et al. (2006), Collins et al. (2009), Ruder & Liin (2011)
  - Case-control studies
NTP/RoC Listing Criteria

• Known To Be a Human Carcinogen
  – **Sufficient evidence** of carcinogenicity in humans which indicates a **causal relationship** between exposure to the agent...and human cancer

• What constitutes “**sufficient evidence**” or a “**causal relationship**”?
  – 1 study? 2 studies? Corroboration/consistency?
  – Findings statistically significant?
  – Is dose-response a consideration?
  – Is biologically plausibility a consideration?
NTP/RoC Listing Criteria

-Reasonably Anticipated to be Human Carcinogen
  - Limited evidence of carcinogenicity from human studies.. which indicates causal interpretation is credible but alternative explanations such as chance, bias or confounding could not be adequately excluded

-What constitutes “limited evidence,” “causal interpretation” or “adequately excluded”? 
  - Inadequate a synonym for limited?
  - Does “causal interpretation” = causal relationship?
  - If not, what are criteria for “causal interpretation”?
  - How are chance, bias or confounding “adequately excluded?”
NTP/RoC Listing Criteria

• “Listing Criteria” silent on how a body of data should be explicitly & transparently evaluated
• Numerous RoC chemicals *Reasonably Anticipated Human Carcinogens* based solely on positive animal data
• Multiple human studies should be primary basis for assessing potential PCP carcinogenicity
• Lacking any cogent guidance recent NTP/OHAT* Guidelines provide only relevant causal framework

*Office of Health Assessment and Translation (OHAT) Draft OHAT Approach For Systematic Review And Evidence Integration For Literature-Based Health Assessments (2013)
NTP/OHAT (2013) Approach For Systematic Review & Evidence Integration

• Preferred basis for evaluation of PCP & synthesis by-products for potential carcinogenicity

• Explicitly embrace established evidence-based causation criteria

• Contrary to current RoC *ad hoc* criteria, i.e., “sufficient evidence,” “reasonably anticipated” or “limited evidence”

• Similar (but improved) to EPA (2005) Cancer Risk Assessment Guidelines
Levels of confidence in the body of evidence

- High
- Moderate
- Low
- Very low

“Conclusions developed in.. subsequent steps of the approach are based on the evidence with the highest confidence.”
NTP/OHAT (2013) Approach For Systematic Review & Evidence Integration

• “Unexplained inconsistency: Inconsistency, or large variability in the magnitude or direction of estimates of effect, that cannot be explained, reduces confidence in the body of evidence.”

• Upgrade confidence rating
  – large magnitude of effect
  – dose-response
  – all plausible confounding
  – cross-species/population/study consistency
NTP/OHAT (2013) Approach For Systematic Review & Evidence Integration

• “Aspects of the Hill considerations on causality within the OHAT Approach”
  – Strength of association
  – Consistency of association
  – Temporality
  – Biological gradient (i.e., exposure-response)
  – Biological plausibility
  – Experimental evidence

• Levels of Evidence for Health Effects Descriptors
  – High
  – Moderate
  – Low
NTP/OHAT (2013) Approach For Systematic Review & Evidence Integration

• *Four hazard identification conclusion categories are*:  
  – Known to be a hazard to humans  
  – Presumed to be a hazard to humans  
  – Suspected to be a hazard to humans  
  – Not classifiable or not identified to be a hazard to humans  

• If human evidence conclusion high, hazard ID conclusion “known” based on the human data alone.

• If human evidence conclusion moderate, hazard ID depends on strength of non-human animal evidence.
## Overview of Key Studies on NHL

<table>
<thead>
<tr>
<th>Study/Type</th>
<th>Potential PCP causation confounders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruder &amp; Yiin 2011 Cohort</td>
<td>2122 U.S. PCP production workers (788 from plant studied by Collins et al. 2009); 1402 with presumed minimal TCDD exposure; 720 potentially exposed to TCDD through work in TCP operations (675 from plant studied by Collins et al.)</td>
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<tr>
<td>Collins et al. 2009 Cohort</td>
<td>773 PCP workers at 1 plant; 577 with presumed minimal TCDD exposure; 196 potentially exposed to TCDD through work in TCP operations</td>
</tr>
<tr>
<td>Demers et al. 2006 Cohort</td>
<td>27,464 Canadian saw-mill workers; PCP exposed sub-cohort; all with presumed minimal TCDD exposure</td>
</tr>
<tr>
<td>Kogevinas et al. 1995 Nested Case-control</td>
<td>32 NHL cases and 158 controls among 21,183 workers exposed to phenoxy herbicides, chlorophenols and dioxins (including TCDD)</td>
</tr>
<tr>
<td>Hardell et al. 1994 Case-control</td>
<td>105 NHL cases and 335 controls; possible exposure to phenoxyacetic acids, TCDD and other chemicals</td>
</tr>
<tr>
<td>Hardell et al. 1999 Case-control</td>
<td>442 NHL cases and 741 controls; possible exposure to phenoxyacetic acids, TCDD and other chemicals</td>
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</table>
## Strength & Consistency of Association with NHL

<table>
<thead>
<tr>
<th>Study</th>
<th>SMR</th>
<th>95% CI</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruder and Yiin</td>
<td>1.41</td>
<td>0.64-2.67</td>
<td>9 observed and 6.4 expected NHL deaths among 1402 workers not exposed to TCP (presumably, most NHL deaths included in Collins et al.)</td>
</tr>
<tr>
<td>Collins et al.</td>
<td>2.8</td>
<td>1.1-5.7</td>
<td>7 observed and 2.5 expected NHL deaths among 577 workers not exposed to TCP</td>
</tr>
<tr>
<td>Demers et al.</td>
<td>1.02</td>
<td>0.75-1.34</td>
<td>49 observed and 48 expected NHL deaths</td>
</tr>
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<td></td>
<td>0.99</td>
<td>0.81-1.21</td>
<td>92 observed and 93 expected NHL cases</td>
</tr>
<tr>
<td>Kogevinas et al. a</td>
<td>2.75 (OR)</td>
<td>0.45-17.0</td>
<td>3 (9.4%) NHL cases and 9 (5.7%) controls exposed</td>
</tr>
<tr>
<td>Hardell et al. a 1994</td>
<td>8.8 (OR)</td>
<td>3.4-24</td>
<td>15 (14.3%) NHL cases and 9 (2.7%) controls with &quot;high&quot; exposure (&gt;1 week of continuous exposure or &gt;1 month of total exposure to PCP)</td>
</tr>
<tr>
<td>Hardell &amp; Eriksson a</td>
<td>1.2 (OR)</td>
<td>0.7-1.8</td>
<td>55 (13.6%) NHL cases and 87 (11.7%) controls exposed; any exposure</td>
</tr>
</tbody>
</table>

a = TCDD/dioxin/furan contaminant; OR, odds ratio
# Exposure-Response for NHL

<table>
<thead>
<tr>
<th>Study</th>
<th>SMR/SRR/RR/OR (95% confidence interval)</th>
<th>Trend p or slope</th>
<th>Exposure variable &amp; comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruder &amp; Yiin</td>
<td>SMR: 2.45 (0.90-5.34), 1.56 (0.42-3.99), 1.63 (0.45-4.18), 1.42 (0.29-4.14)</td>
<td>Not reported</td>
<td>Days worked in PCP departments (≤57, 58-&lt;182, 182-&lt;650, ≥650); total cohort; no trend</td>
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<td></td>
<td>SRR: 1.0 (referent), 0.55 (0.15-1.97), 0.63 (0.18-2.28), 0.62 (0.15-2.55)</td>
<td>Slope (se): -3.744e-8 (9.095e-8)</td>
<td></td>
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<tr>
<td>Collins et al.</td>
<td>SMR: 2.4 (0.5-7.1), 0.8 (0.0-4.7), 4.5 (1.2-11.5)</td>
<td>p=0.61</td>
<td>Categories of toxic equivalent summary dioxin cumulative exposure; total cohort; no trend</td>
</tr>
<tr>
<td>Demers et al., 20-year lag</td>
<td>RR (incidence) : 1.0 (referent), 1.83 (0.95-3.50), 2.05 (1.14-3.68), 1.98 (0.97-4.06)</td>
<td>p=0.02</td>
<td>Exposure-years (&lt;1, 1-2, 2-5, 5+); trend, but not monotonic: statistical significance reflects unexplained difference between lowest exposure group and all higher exposure groups</td>
</tr>
<tr>
<td></td>
<td>[mortality results not reported]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kogevinas et al.</td>
<td>OR: 1.0 (referent), 4.19 (0.59-29.59)</td>
<td>Not reported</td>
<td>High cumulative exposure score compared to medium, low and no exposure, combined; trend not able to be evaluated due to sparse data</td>
</tr>
<tr>
<td>Hardell et al.</td>
<td>Not Analyzed</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Hardell &amp; Eriksson</td>
<td>OR: 1.0 (0.3-2.9), 2.0 (0.7-5.3), 1.1 (0.7-1.8)</td>
<td>Not reported</td>
<td>Years from first exposure (&gt;10-20, &gt;20-30, &gt;30); no apparent trend</td>
</tr>
</tbody>
</table>
Biological Plausibility

• ...causality tends to be strengthened by consistency with data...demonstrating plausible biological mechanisms.*
• ...consideration of both exposure-related factors & toxicological evidence relevant to identification of potential modes of action (MOAs)*, e.g.,
  – Early mutation $\rightarrow$ tumor formation
  – Cytotoxicity-induced events $\rightarrow$ tumor formation

*EPA 2005. Guidelines for Carcinogen Risk Assessment
Biological Plausibility

• Little *in vivo* evidence of PCP-induced mutagenicity/genotoxicity
  – “...standard mutagenicity assays have produced weak or equivocal evidence for PCP”*

• High dose PCP cytotoxicity-induced events likely involved in animal carcinogenesis*
  – Oxidative stress (ROS)
  – ROS-induced DNA damage/mutation
  – GJIC inhibition
  – Chronic inflammation

*EPA 2009. IRIS  Assessment of Pentachlorophenol
Biological Plausibility

• 2-Year rat study with >99% PCP most relevant for potential effects in humans
  – No PCP-related tumors in males or females in full study at any dose

• 2-Year dermal exposure study with hexachlorodioxins (NCI 1980)*
  – No evidence of carcinogenicity in male or female mice

• With TEFs of 0.1, 0.01 and 0.0003 for hexa, hepta, & octa-dioxins, no basis to suspect hepta- or octa-compounds of carcinogenic activity

*Not cited/discussed in Draft NTP Listing Document
Final Conclusions

• No significant finding in any study corroborated in a different study
• Neither of RoC Listing Criteria, i.e., *Known or Reasonably Anticipated to be a Human Carcinogen* satisfied by available human & animal data for PCP
• Based on *Key Scientific Questions Relevant for Cancer Evaluation* the level of evidence from human studies for the carcinogenicity of PCP is *limited*
• Based on NTP/OHAT Approach for Systematic Review & Evidence Integration the totality of evidence from human & animal studies for PCP carcinogenicity is *Suspected of Carcinogenic Potential*. 