Key issues for discussion

• PCP versus PCP and byproducts of its synthesis
• Exposure-response relationships
• External versus internal analyses
• Confounding by TCDD in the studies?
• Does the NIOSH study argue against the findings?
  – Confounding, exposure-response
• Summary of issues/evidence across cohort studies
PCP versus PCP and byproducts of its synthesis

- The database does not allow us to separate any health effects of PCP from those due to its byproducts
  - Workers in all studies were most likely exposed to PCP byproducts
- Most people exposed to PCP are exposed to its byproducts
- Byproducts have dioxin like activity, thus it is biologically plausible that they could contribute to cancer risk
Exposure response relationships: Monotonic, exposure metric

- Demers study: cumulative dermal exposure
  - Strong exposure-response relationships: mortality and incidence, lagged and unlagged analysis
  - Concerns that categorical analysis does not appear to be monotonic
    - Authors state that continuous analysis are “roughly monotonic” (not clear from publication figure)
    - Graph in presentation plotted modeled rather than actual data
    - Categorical exposure relationships are often non-monotonic in occupational studies, which is thought to be due to measurement error

- Ruder and Yinn: employment duration
  - No association; duration may not be best surrogate for exposure level
  - Small numbers of cases, healthy worker survival effect, non-informative rather than negative evidence

- Collins: PCP dioxin byproducts
  - Highest risk in individuals with highest exposure; potential exposure misclassification in other categories
External analysis and Demers study

• No association found in external analysis for either mortality or incidence for any cancer (except kidney mortality) in Demers study
  – SIR/SMR is for all sawmill workers and is not specific for PCP exposure
  – Healthy worker effect for NHL has been observed for other carcinogens (e.g., benzene)
  – Lack of an association in external analyses doesn’t weaken the Demers study’s findings
Serum dioxins and PCP, TCP, PCP+ TCP classification among PCP production workers in MI plant

Serum profiles support their exposure classification

PCP±TCP relevant to both Collins and NIOSH

*TCP subchort (workers not included in Collins 2009a or Ruder and Yiin analyses)

Lipid adjusted dioxins measured in TCP, PCP workers 20 years after exposure (Collins et al. 2008)
Potential confounding of TCDD among PCP producers

- Although NIOSH and Collins differ in how they classified TCP exposure, the serum profiles conducted by Collins may be relevant to the NIOSH cohort for evaluating potential exposure to TCDD
  - PCP + TCP: NIOSH 675 vs. 196 Collins
  - 675 workers probably include the 196 workers classified by Collins, which have potential exposure to TCDD, the remaining PCP + TCP workers have little exposure to TCDD (e.g., PCP serum profile)
  - Most (~77%) of the PCP+ TCP workers in the entire NIOSH study are from the MI plant, ~23% are from the IL plant. Thus the MI PCP + TCP workers may contribute to the SMR for PCP + TCP (2.50, 95% CI =1.08-4.93); 8 cases
  - Argues against confounding by TCDD
  - NIOSH study probably doesn’t contradict findings of Collins
<table>
<thead>
<tr>
<th>Study</th>
<th>Association Magnitude</th>
<th>Number of cases/deaths</th>
<th>Exposure response</th>
<th>Confounding TCDD?</th>
<th>Confounding Others?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demers</td>
<td>Elevated risks (incidence &amp; mortality) for all exposure groups ~2 fold</td>
<td>92 cases/49 deaths</td>
<td>Strong based on trends Shape of exposure-response curve?</td>
<td>No</td>
<td>None, TeCP not associated with NHL, no others identified</td>
</tr>
<tr>
<td>Collins/ramlow</td>
<td>Elevated risks for PCP, no TCP, cumulative PCP*, PCP byproducts ~2 fold</td>
<td>8 deaths, 7 PCP no TCP</td>
<td>Highest risk in highest PCP byproduct exposure group</td>
<td>No</td>
<td>No association of TCDD with NHL among TCP exposed workers</td>
</tr>
<tr>
<td>Ruder</td>
<td>Elevated risk for PCP + TCP, weak for PCP, no TCP ~2-fold, 1.4</td>
<td>17 deaths, 9 PCP no TCP</td>
<td>Not for employment duration</td>
<td>Probably no</td>
<td>Possible</td>
</tr>
<tr>
<td>Kogevinas</td>
<td>Statistically non-sign. elevated risk ~3</td>
<td>3 deaths</td>
<td>All 3 cases in highest exposure category</td>
<td>Probably no</td>
<td>Possible</td>
</tr>
</tbody>
</table>

Demers study has more cases than sum of other studies
Summary: association between NHL and PCP and its byproducts of production

- Demers study provides strong evidence of an association
- Collins study supports findings in a different occupational group, using a different exposure metric
- NIOSH study does not contradict evidence