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

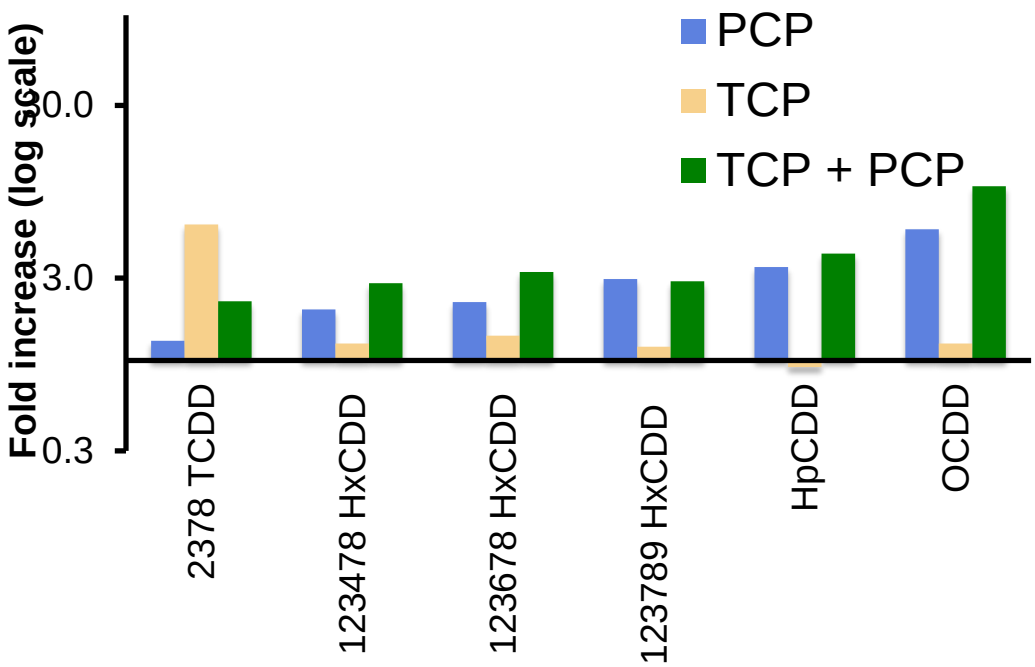
Exposure response relationships: Monotonic, exposure metric

- 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

Study	Association Magnitude	Number of cases/deaths	Exposure response	Confounding TCDD?	Confounding Others?
Demers	Elevated risks (incidence & mortality) for all exposure groups ~2 fold	92 cases/49 deaths Exposed cases: 54, 53, 46	Strong based on trends Shape of exposure-response curve?	No No evidence of exposure	None, TeCP not associated with NHL, no others identified
Collins/raml ow	Elevated risks for PCP, no TCP, cumulative PCP*, PCP byproducts ~2 fold	8 deaths, 7 PCP no TCP	Highest risk in highest PCP byproduct exposure group	No No association of TCDD with NHL among TCP exposed workers	Not likely
Ruder	Elevated risk for PCP + TCP, weak for PCP, no TCP ~2-fold, 1.4	17 deaths, 9 PCP no TCP	Not for employment duration	Probably no	Possible
Kogevinas	Statistically non-sign. elevated risk ~3	3 deaths	All 3 cases in highest exposure category	Probably no	Possible

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