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

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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

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

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

Study (# of subjects or cases/controls)	Exposure assessment	Analysis and treatment of confounders
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

Study (# of subjects or cases/controls)	Exposure assessment	Analysis and treatment of confounders
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)

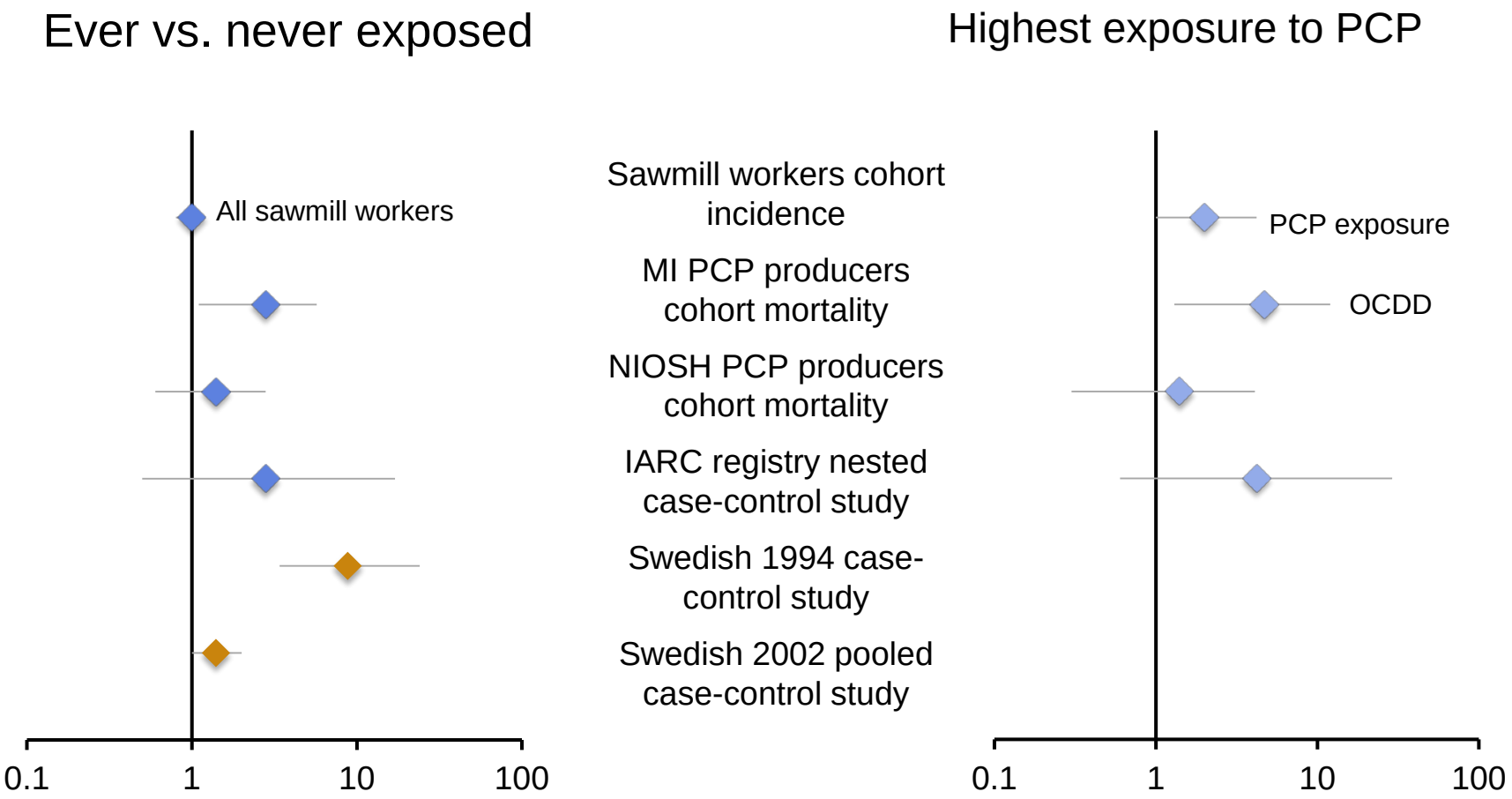
	Collins et al. 2009a	Ruder and Yiin 2011
Total PCP Workers (PCP ± TCP workers)	773 (1937-1980) SMR = 2.4 (1.0 to 4.7); 8	788 (1936-1980) SMR = 2.18 (0.94-4.30); 8
PCP, no TCP	577 SMR = 2.8 (1.1 to 5.7) Serum profile: Elevated levels of higher chlorinated dioxins	110 SMR = not reported
PCP + TCP	196 Serum profile: Elevated levels of higher chlorinated dioxins and 2,3,7,8-TCDD	675
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



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

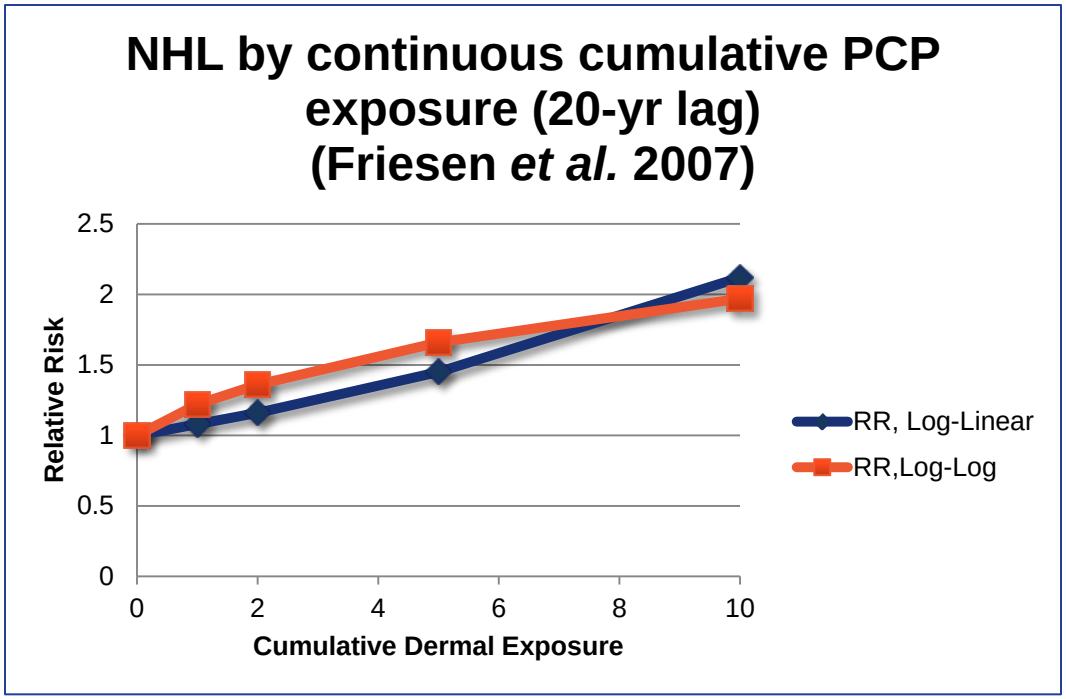
◆ = cohort or nested case-control study; ◆ = case-control study

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):

Endpoint/lag (yr)	P_{trend}
Mortality/0	0.06
Incidence/0	0.03
Incidence/10	0.03
Incidence/20	0.02

- Little evidence of exposure-response relationship for tetrachlorophenol



NHL risk is increased among PCP production workers with the highest levels of PCP by-products of synthesis

PCP by-product (dioxin congener)	Cumulative level of congener SMR (95% CI); # of exposed deaths)		
	Low	Medium	High exposure
HxCDD	2.5 (0.5-7.4); 3	0.0 (0.0-3.1); 0	5.3 (1.7–12.4); 5
HpCDD	1.8 (0.2-6.4); 2	1.5 (0.2-5.25); 2	4.6 (1.3–11.8); 4
OCDD	1.7 (0.2-6.2); 2	1.6 (0.2-5.6); 2	4.7 (1.3–12.0); 4

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 mitigates 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