

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

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# **Draft RoC monograph on pentachlorophenol and by-products of its synthesis**

## **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*

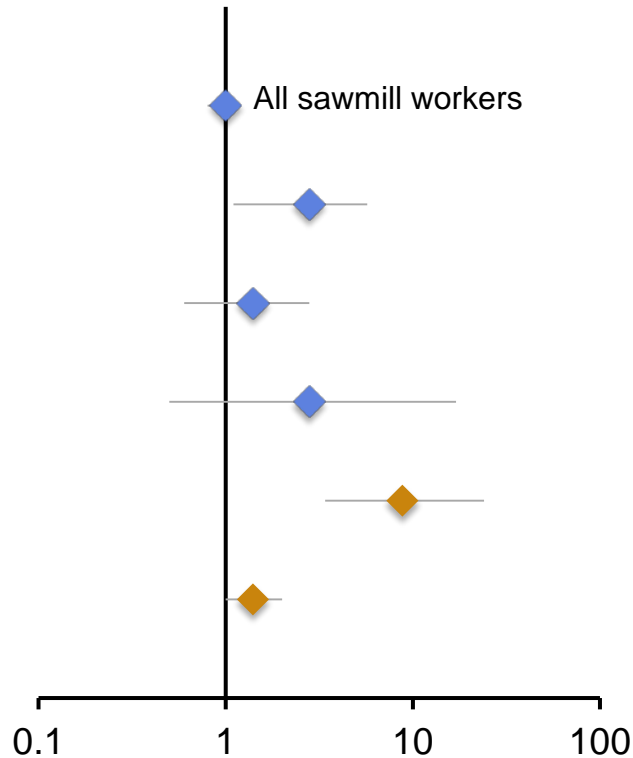
\*Personal communication, study authors

## 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)

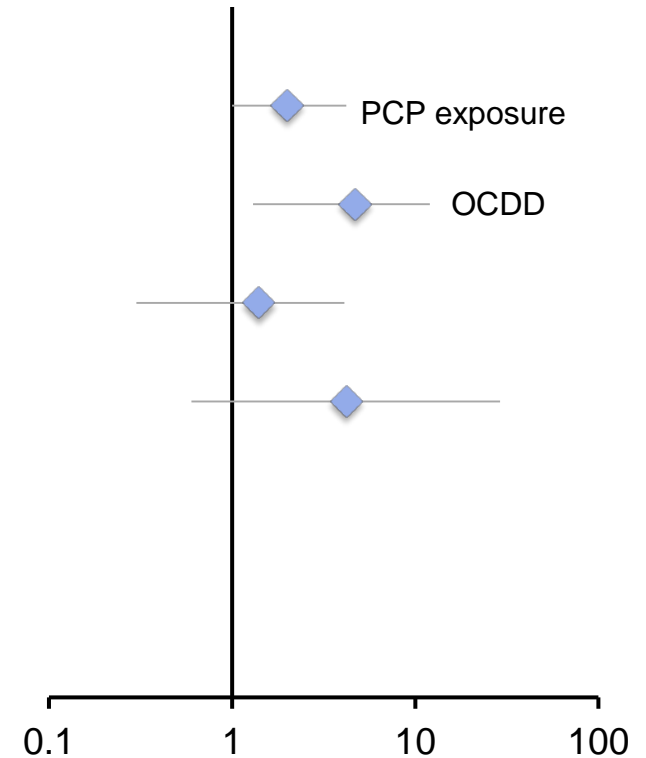
# Increased risk of NHL across studies

Ever vs. never exposed



Highest exposure to PCP

Sawmill workers cohort incidence  
 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



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

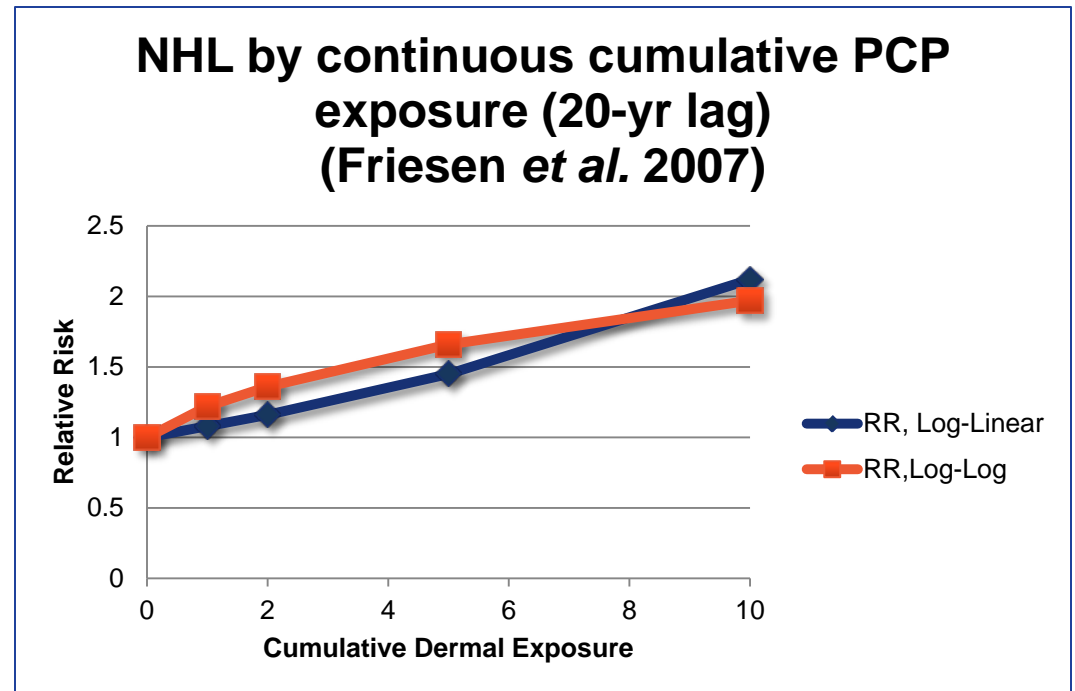
◆ = cohort or nested case-control study; ◆ = case-control study

# 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 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