

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

Comments on Behalf of Pentachlorophenol Task Force

**Robert Golden, Ph.D.
ToxLogic LC
Gaithersburg, MD
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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
 - Kogevinas et al. (1995), Hardell et al. (1994, 1999, 2002)

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 biological 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

NTP/OHAT (2013) Approach For Systematic Review & Evidence Integration

- 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

Study/Type	Potential PCP causation confounders
Ruder & Yiin 2011 Cohort	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.)
Collins et al. 2009 Cohort	773 PCP workers at 1 plant; 577 with presumed minimal TCDD exposure; 196 potentially exposed to TCDD through work in TCP operations
Demers et al. 2006 Cohort	27,464 Canadian saw-mill workers; PCP exposed sub-cohort; all with presumed minimal TCDD exposure
Kogevinas et al. 1995 Nested Case-control	32 NHL cases and 158 controls among 21,183 workers exposed to phenoxy herbicides, chlorophenols and dioxins (including TCDD)
Hardell et al. 1994 Case-control	105 NHL cases and 335 controls; possible exposure to phenoxyacetic acids, TCDD and other chemicals
Hardell et al. 1999 Case-control	442 NHL cases and 741 controls; possible exposure to phenoxyacetic acids, TCDD and other chemicals

Strength & Consistency of Association with NHL

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

a = TCDD/dioxin/furan contaminant; OR, odds ratio

Exposure-Response for NHL

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

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 → tumor formation
 - Cytotoxicity-induced events → tumor formation

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

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 hexachloro dioxins (NCI 1980)*
 - No evidence of carcinogenicity in male or female mice
- With TEFs of 0.1, 0.01 and 0.0003 for hexa, hepta, & octadioxins, no basis to suspect hepta- or octa-compounds of carcinogenic activity

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.***