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

Comments on Behalf of Pentachlorophenol Task Force

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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
- Validity of basing RoC NHL listing for PCP when a contaminant *Known* to have similar effects already listed?

*Collins et al. (2009)

PCP & Synthesis By-Products

- NHL major cancer site of interest
  - Other sites of interest: 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 biologically 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 of 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 *p* 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.	RR (incidence) : **1.0** (referent), **1.83** (0.95-3.50), **2.05** (1.14-3.68), **1.98** (0.97-4.06)	p=0.02	Exposure-years (<1, 1-2, 2-5, 5+), 20-yr lag; **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**
Hardel 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

*EPA 2005. Guidelines for Carcinogen Risk Assessment

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

*EPA 2009. IRIS Assessment of Pentachlorophenol

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

*Not cited/discussed in Draft NTP Listing Document

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***.