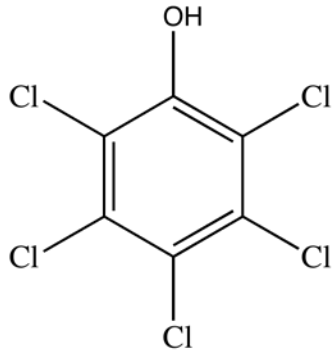
NTP
National Toxicology Program

Report on Carcinogens Pentachlorophenol Concept Review

Gloria D. Jahnke, DVM, DABT
National Toxicology Program
National Institute of Environmental Health Sciences
Board of Scientific Counselors Meeting
June 21, 2012

Pentachlorophenol (PCP)



- PCP and its sodium salt are polychlorinated phenols, primarily used as wood preservatives.
- Restricted use pesticide (1984), primary use is in treatment of utility poles, cross-arms, and also railroad ties, wharf pilings.
- Proposed as a candidate substance for the RoC: 1) widespread past and current U.S. exposure, 2) an adequate database of studies in humans and animals for evaluation of its potential carcinogenicity.

Pentachlorophenol – U.S. Exposure

Environmental

- Releases from wood treatment facilities, treated wood in service (e.g., treated lumber, utility poles), contaminated sites, waste handling, and unsealed log homes.
- Evidence of exposure (indoor air, handwipes, food, urine) in preschool children and adult caregivers.
- NHANES (urine) adults and children (1.30 μg/L 95th percentile). [PCP is also a metabolite of other pesticides.]
- Contaminant of concern for soil, groundwater, rivers. Listed on ATSDR Substance Priorities List for Hazardous Substances.

Occupational

- Wood treatment facilities and contact with treated lumber and utility poles and waste handling.
- Past exposure from use and production as a pesticide, and in lumber treatment and other lumber-related occupations.

Pentachlorophenol – Production

- One U.S. company, estimated production 3 million pounds (2009). Marketed to U.S., Canada, and Mexico as a wood preservative.
- Technical grade and commercial grade PCP is approx. 90% PCP plus contaminants (such as tetrachlorophenols, and primarily higher chlorinated congeners of dibenzo-*p*-dioxins and dibenzofurans) formed during production.
- All PCP produced in the U.S. by catalytic chlorination of phenol; no 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD) produced. However, other countries may use hydrolysis of hexachlorobenzene which can form 2,3,7,8-TCDD.
- Suppliers to U.S. and Canada must limit hexchlorodibenzo-*p*-dioxin content in PCP to < 4 ppm (mg/kg) and 2,3,7,8-TCDD to none detectable (<0.001 ppm (mg/kg)).

Pentachlorophenol

- Authoritative reviews on pentachlorophenol
  - IARC (1991) Possibly carcinogenic to humans (Group 2B)
  - U.S. EPA IRIS (2010) Hazard and dose-response assessment of chronic PCP exposure: ‘Likely to be carcinogenic in humans’ by all exposure routes.
- Public Comment- Disagreement with IRIS conclusions
  - Human studies - Data did not meet criteria for carcinogenicity.
    - Potential confounding by dioxins was one of several concerns.
  - Animal studies - Primarily addressed risk assessment
    - Liver tumors in mice could be due to contaminants.

Human Cancer Studies

- Tumor sites of interest are non-Hodgkin's lymphoma and soft tissue sarcoma.
- Early studies evaluated cancer among broad occupational groups or for exposure to chlorophenols in general and were not specific for exposure to PCP.
- More recent studies have focused on PCP exposure.
  - Cohort studies (mortality or incidence) of PCP production or sawmill workers in North America; two of which provide estimates of cumulative exposure to PCP, and one which evaluated exposure-response relationships.
  - Several case-control studies (including a nested case-control among PCP production workers) of non-Hodgkin's lymphoma and meta-analysis of soft tissue sarcoma reporting risk estimates for PCP.
  - Several case-control studies (primarily of hematopoietic cancers) reporting risk estimates for exposure to chlorophenols with limited information on exposure specific for PCP or job titles associated with PCP exposure.

Human Cancer Studies – Potential Coexposures

- PCP production workers
  - Contamination of PCP with dioxins occurs during the production process.
  - Biomonitoring data are available for a sample of former PCP production workers from one of the cohort studies.
    - Higher serum levels of dioxin (mainly hexa-, hepta-, and octa-chlorodibenzo-*p*-dioxins) but not 2,3,7,8-TCDD were found in exposed workers compared to non-exposed workers.
- PCP users such as sawmill workers
  - 2,3,7,8-TCDD was not a contaminant in commercial or technical grade.
  - Potential confounding from other chlorophenols (primarily tetrachlorophenol), dibenzodioxins, and dibenzofurans.
- Potential confounding from exposure to 2,3,7,8 TCDD may be a concern for case-control studies conducted in Europe and New Zealand.

Experimental Animal Studies

Substance	Impurities Reported	Species Tested	Study/ Reference
Technical grade 90.4% PCP	3.8% tetrachlorophenol, 0.17% chlorinated dibenzo-*p*-dioxins (major impurities)	B6C3F$_1$ Mice (m, f)[a]	2-yr feed/ NTP 1989
Dowicide EC-7 91% PCP	9.4% tetrachlorophenol (major impurity)	B6C3F$_1$ Mice (m, f)	2-yr feed/ NTP 1989
Dowicide EC-7	Not reported	(C57BL/6 x C3H/Anf) F$_1$ (C57BL/6 x AKR) F$_1$ Mice (m, f)	1.5-yr feed[b]/ Innes *et al.* 1969
Dowicide EC-7 90.4% PCP	10.4% tetrachlorophenol	Sprague-Dawley Rats (m, f)	2-yr feed/Schwetz *et al.* 1978

[a] m, f = males, females

[b] Gavage dosing post-natal days 7-28, followed by feed dosing to necropsy at 18 months of age

Experimental Animal Studies (continued)

Substance	Impurities Reported	Strain/Species Tested	Study/ Reference
PCP (approx. 99% pure)	1.4% tetrachlorophenol	F344/N Rats (m, f)[a]	2-yr feed/ NTP 1999
PCP (approx. 99% pure)	1.4% tetrachlorophenol	F344/N Rats (m, f)	2-yr feed study with stop exposure to PCP at 1 yr/ NTP 1999
[a] m, f = males, females			

Potential target tissue cancer sites: adrenal gland, liver, vascular system (mice); Nasal cavity and peritoneal cavity (rats).

PCP has also been tested for tumor initiation and promoting activity in mice.

Metabolism and Mechanistic Data

- Metabolism in laboratory animals is expected to be similar to that in humans
  - Tetrachlorohydroquinone (TCHQ) and PCP glucuronide have been identified in urine of exposed workers and TCHQ and PCP have been detected in the urine of exposed rats and mice.
- PCP can be oxidatively dechlorinated to quinones through semiquinone intermediates which can form cross-links with protein and DNA.
- Quinone metabolites and PCP have been studied *in vitro* and *in vivo* in numerous genotoxicity assays.
- PCP and quinone metabolites have been tested *in vivo* for induction of oxidative stress and for albumin and hemoglobin adducts.
- There are studies measuring DNA damage to PCP-exposed workers.

Key Scientific Questions Relevant for Cancer Evaluation

- What is the level of evidence (inadequate, sufficient, or limited) of carcinogenicity from human studies? What are the tissue sites?
  - Can possible effects of contaminants be separated from possible effects of PCP?
- What is the level of evidence (sufficient or not sufficient) of carcinogenicity from animal studies? What are the tissue sites?
  - Can exposure to contaminants be ruled out as potential contributors to reported effects?
- What are the potential modes of action by which PCP may cause cancer? Does the mechanistic data support findings in experimental animals or humans?

Proposed Approaches for Obtaining Public Input

- Public comments requested on the nomination and draft concept.
- RoC webpage for candidate substances under review.
  - Communicate status and relevant documents related to the monograph preparation.
  - Provide information on public meetings.
  - Mechanism to receive public input.
  - All experts may be identified from the peer-reviewed literature databases, membership in relevant professional societies, and recommendations from other scientists or the public.

Proposed Approach

- Human Studies
  - ORoC will convene a web-based public symposium to receive public and scientific input on relevant issues such as distinguishing the effects of PCP from its contaminants.
  - Speakers will present their views on human cancer studies; speakers may be from stakeholder groups, environmental groups, government or non-government scientists.
  - Invited substance-specific technical advisors will provide expertise and promote discussion of the issues.
  - Future forums may be convened to address any additional scientific issues.

Proposed Approach

- Experimental Animal Studies
  - *Informational group* of scientists will review animal data on PCP and any toxicological data on the contaminants and will discuss and inform ORoC of potential effects from these contaminants.
  - *Informational group* is assembled for the purpose of exchanging facts or information and is not covered by Federal Advisory Committee Act (FACA). Members provide input on an individual basis and not from the group as a whole.
  - Additional meetings may be convened to address any additional scientific issues.

Next Steps

- The draft RoC monograph will undergo interagency review and be released for public comment.
- NTP will convene a peer-review panel to review the monograph on pentachlorophenol.
- The panel will consist of members with expertise related to the cancer hazard evaluation such as: epidemiology, exposure assessment, metabolism of polychlorophenols and other contaminants of commercial PCP, genotoxicity, mechanisms of carcinogenesis.
- Time will be set aside at the peer-review meeting for a discussion of scientific issues raised in public comments.

Specific Charge Questions

1. Comment on whether the cited information suggests that exposures to the substance in the US are “significant” and whether the extent and nature of the scientific information on the carcinogenicity of the nominated substance are clearly described and adequate (studies in humans, animals, and/or mechanistic information) to support a RoC evaluation.

2. Advise as to whether the relevant scientific issues are identified. Are you aware of any other scientific issues that need to be considered during the evaluation?

3. Comment on the proposed scope and focus for the cancer evaluation component of the draft RoC monograph.

4. Comment on the proposed approach for obtaining scientific and public input in development of the evaluation.

5. Rate the overall significance and public health impact of this evaluation as low, moderate, or high. NTP will use this rating in assessing the relative priority of evaluations of RoC candidate substances.

6. Provide any other comments you feel staff should consider in developing this evaluation.