Report on Carcinogens (RoC) Concept: Pentachlorophenol

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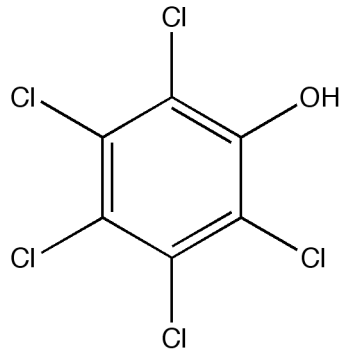

1. Rationale

Pentachlorophenol (PCP) and its sodium salts are chlorinated aromatic compounds that are primarily used as wood preservatives in the United States. They have been selected as candidate substances[1] for the RoC review based on widespread past use and current U.S. exposure and a database of studies in humans and animals specific for PCP that are adequate for evaluating its potential carcinogenicity. People have been and are currently exposed to PCP from its production and use in lumber treatment, and in other lumber-related occupations; they were exposed in the past from its broad use as a pesticide. PCP is a ubiquitous environmental contaminant and ranked fifty-third in the 2011 National Priorities List of Hazardous Substances (ATSDR 2011). Although its use as a wood-preservative has been limited to non-residential and non-agricultural applications since 1984, there is still potential for occupational and environmental exposure in the United States (ATSDR 2001). It was detected in ambient air of a community of residents near a wood treatment facility, in indoor air, in food, and in the urine from children and adults (Wilson *et al.* 2007).

In 1991, the International Agency for Research on Cancer classified PCP as possibly carcinogenic to humans (IARC 1991). More recently, the U.S. EPA completed a hazard assessment pertaining to chronic exposure to PCP and concluded that PCP was "likely to be carcinogenic to humans" by all exposure routes (EPA 2010).

[1]The scientific evaluation of pentachlorophenol will be captured in the draft RoC monograph, which consists of a cancer evaluation component and draft substance profile (for more details see *http://ntp.niehs.nih.gov/go/rocprocess*). The proposed approach, delineated in this concept document, for preparing the cancer evaluation of the draft monograph is tailored to the nature, extent, and complexity of the scientific information on this chemical. This concept document also discusses information supporting the rationale and the proposed approach including (1) data on human exposure, (2) an overview of the nature and extent of the scientific information for evaluating carcinogenicity in humans and/or animals, (3) scientific issues and questions relevant to the evaluation of pentachlorophenol carcinogenicity, (4) the proposed approach for conducting the cancer evaluation, including the literature search strategy, the scope and focus of the monograph, and the approaches for obtaining scientific and public input to address the key scientific questions and issues.

In January 2012, the NTP solicited information on PCP and other nominated substances (77FR2728, see *http://ntp.niehs.nih.gov/go/rocnom* for comments). One public comment on PCP was received containing two reports (see *http://ntp.niehs.nih.gov/go/37663*). Both reports disagreed with the U.S. EPA IRIS conclusions on PCP. One report focused on the human cancer studies and concluded the data do not meet the criteria for *reasonably anticipated to be a human carcinogen*, and noted that potential confounding by dioxins was a concern in some of the epidemiologic studies. The other report primarily addressed risk assessment questions based on studies in experimental animals and noted that the liver tumors in experimental animals could be due to contaminants and not PCP alone.

The ORoC presented the draft concept document for pentachlorophenol to the NTP Board of Scientific Counselors (BSC) at the June 21-22, 2012 meeting[2] which provided an opportunity for written and oral public comments. No public comments were received. The NTP Director approved pentachlorophenol as a candidate substance and this concept was finalized based on review of the BSC's comments. The concept may be revised again if new information on pentachlorophenol would lead to a change in the proposed approach for conducting the cancer evaluation.

2. Overview of Data Related to Human Exposure

PCP and its sodium salt have primarily been used as wood preservatives to protect wood from fungal decay and wood boring insects (IARC 1991). It was also previously used as an herbicide, bactericide, insecticide, molluscicide, and algaecide. Because of its past use as a broad-spectrum pesticide, it was a high production volume chemical (estimated world usage at 30,000 tonnes (66 million pounds) per year (WHO 1987)). PCP's use in the United States was restricted to wood preservation in 1984, and it can no longer be used on wood in residential or agricultural buildings. Use in the United States is restricted primarily to the treatment of utility poles and cross arms, and PCP is also used in the treatment of railroad ties and wharf pilings. Current use in Canada includes bridge decking, fence posts, exterior laminated timbers, piles, and wood poles.

PCP was detected in more than half of the samples of indoor air, hand wipes, solid food, liquid food, and urine collected in the U.S. EPA Children's Total Exposure to Persistent Pesticides and Other Persistent Organic Pollutants (CTEPP) study of 257 preschool children and their primary adult caregivers in North Carolina and Ohio in 2000-2001 (Wilson *et al.* 2007). Possible evidence of U.S. exposure to PCP comes from National Health and Nutrition Examination Survey (NHANES) data, which found PCP in urine (also a metabolite of several organochlorine insecticides) from adults and children for the 2003–2004 survey period of 3.44 µg/L (creatinine corrected, 95th percentile; N = 2352) (CDC 2012).

2.1. Environmental exposure

Contamination of the environment can occur with releases from production facilities, treated wood in service (e.g., treated lumber and utility poles), contaminated sites, and unsealed log homes; disposing of PCP-contaminated wood in landfills poses additional health risks (vander Zande 2010). Thirty-two U.S. companies reported releases of 370,662 pounds of PCP into the environment in 2010 (TRI 2012). PCP was detected in air samples at concentrations ranging from non-detectable to 29 µg/m^3 in a community of residents near a

[2]Information on the NTP BSC June 21-22, 2012 meeting is available at *http://ntp.niehs.nih.gov/go/9741*.

U.S. wood treatment facility fence line in 2004; the highest PCP level measured near a residence within 1 mile of this facility was 8.1 μg/m^3 (ATSDR 2007). Airborne PCP concentrations ranging from non-detectable to 0.38 μg/m^3 have been measured in PCP-treated log homes (CDC 1980).

2.2. Occupational exposure

Workers may be exposed to PCP in production facilities, wood treatment facilities, direct contact with treated lumber and utility poles, and waste handling. Primary routes of occupational exposure are inhalation of mist and dermal absorption. Nine U.S. companies reported using PCP to treat wood products and one U.S. company, which produces and markets PCP to the United States, Canada, and Mexico as a wood preservative, estimated production was 7,257 tonnes (16 million pounds) in 2009 (vander Zande 2010). Historical occupational exposure data identified from NIOSH reports published between 1975 and 1986 indicate that airborne PCP concentrations at a PCP-production facility ranged from non-detectable to 1.65 mg/m^3 and those at wood-treatment facilities from non-detectable to 1.33 mg/m^3 (NIOSHTIC-2 2012). Serum PCP concentrations for workers building PCP-treated log homes ranged from 72 to 94 ppb (mean = 83 ppb) and those for telephone line maintenance workers ranged from 26 to 260 ppb (mean = 110 ppb) (Cline 1989).

2.3. Production methods

Technical grade and commercial grade PCP are approximately 90% PCP plus contaminants (such as tetrachlorophenols, and predominantly higher chlorinated congeners of dibenzo-*p*-dioxins, and dibenzofurans) formed during production. Suppliers of PCP in the United States and Canada are required to limit hexachlorodibenzo-*p*-dioxin content to less than 4 ppm (mg/kg) and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD) content to non-detectable (< 0.001 ppm [mg/kg]) (reviewed by IARC 1991). All PCP manufactured in the United States is produced by direct chlorination of phenol in the presence of a catalyst and is not contaminated with 2,3,7,8-TCDD. An alternative production method used in other countries is the hydrolysis of hexachlorobenzene, which can form 2,3,7,8-TCDD (reviewed by IARC 1991).

3. Overview of the Scientific Information Regarding Carcinogenicity

3.1. Human cancer studies

The human cancer studies available to IARC in 1991 (IARC 1991) were considered inadequate to evaluate the potential carcinogenicity from exposure to PCP. In general, earlier studies (mostly prior to 1990) evaluated cancer risks among broad occupational groups or for exposure to mixtures of chlorophenols or phenoxy herbicides and were not informative for exposures specific to PCP. More recent studies have attempted to evaluate cancer effects from exposures specific for PCP. From an initial review of the peer-reviewed literature, the available studies include: (1) several case-control studies (primarily of hematopoietic cancer) reporting risk estimates for job titles associated with PCP exposure or exposure to chlorophenols with limited information on exposure specific for PCP (reviewed by EPA 2010), (2) several case-control studies (including a nested case-control study among PCP production workers) of non-Hodgkin's lymphoma (Hardell *et al*. 1981, 1994; Kogevinas *et al.* 1995; Hardell and Eriksson 1999), a case-control study of childhood leukemia (Ward *et al*. 2009), and a meta-analysis of soft tissue sarcoma (Hardell *et al.* 1995) reporting risk estimates specific for PCP and (3) three cohort studies of PCP production workers or users, one of which evaluated exposure-response relationships (Demers *et al.*

2006). The cohort studies include two cancer mortality studies on PCP production workers, including a study of workers at a large manufacturing plant in Michigan, United States (Ramlow *et al.* 1996, followed up by Collins *et al.* 2009) and a large cancer mortality and incidence study of sawmill workers in Canada (Demers *et al.* 2006). The Michigan plant studied by Ramlow and Collins is one of the four U.S. plants in the National Institute for Occupational Safety and Health Dioxin Registry study (Ramlow *et al.* 1996; Collins *et al.* 2008, 2009; and Ruder and Yiin 2011). The major cancer sites of interest are lymphomas, soft-tissue sarcoma, and liver.

As discussed above, contamination of PCP with polychlorodibenzo-*p*-dioxins and polychlorodibenzofurans can occur during its production. Serum levels of dioxin and dioxin-like contaminants have been measured (20 years after production had ceased) among a subset of former PCP workers in the Michigan manufacturing plant (Collins *et al*. 2007), and a mortality study evaluating cancer risks from exposure to dioxins in these PCP workers has been published (Collins *et al.* 2009). Former PCP workers had higher serum levels of hexa-, hepta-, and octa-chlorodioxins than a non-exposed comparison group but did not have higher levels of polychlorinated dibenzo-*p*-dioxins including 2,3,7,8-TCDD, and polychlorinated dibenzofurans. In Europe and New Zealand, contamination of PCP with 2,3,7,8-TCDD may occur during the manufacturing process, and thus it may be more of a concern in several of the case-control studies (Ruder and Yiin 2011). Among end users of PCP (such as sawmill workers), the major contaminants are hexachlorinated dibenzodioxins, dibenzofuran, and other chlorophenols (especially tetrachlorophenol) (Cooper and Jones 2008). The cohort study of sawmill workers (Demers *et al.* 2006) also evaluated cancer risk from exposure to tetrachlorophenol.

3.2. Cancer studies in experimental animals

Several experimental animal studies in mice and rats were identified from an initial search of the peer-reviewed literature and are listed in Table 1. These include studies using (1) technical grade PCP, (2) commercial grade PCP, and (3) 99% PCP. No cancer studies in mice using 99% PCP were located and no cancer studies by inhalation or dermal routes of exposure using any form of PCP were located. Potential target tissue cancer sites identified from studies in mice were adrenal gland, liver, and vascular system; in rats, the sites were nasal cavity and peritoneal cavity.

Table 1. Cancer Studies in Experimental Animals

Substance	Reported Primary Impurities	Strain/Species Tested	Reference/Study
Technical grade 90.4% PCP	3.8% tetrachlorophenol, 0.17% chlorinated dibenzo-*p*-dioxins	B6C3F_1 mice (m, f)[a]	NTP 1989/2-yr feed
Dowicide EC-7 91% PCP	9.4% tetrachlorophenol	B6C3F_1 mice (m, f)	NTP 1989/2-yr feed
Dowicide EC-7 % PCP not reported	Not reported	(C57BL/6xC3H/Anf)F_1 mice (m, f) (C57BL/6xAKR)F_1	Innes *et al.* 1969/1.5-yr feed[b]

Substance	Reported Primary Impurities	Strain/Species Tested	Reference/Study
		mice (m, f)	
Dowicide EC-7 90.4% PCP	10.4% tetrachlorophenol	Sprague-Dawley rats (m, f)	Schwetz *et al.* 1978/2-yr feed
99% PCP	1% tetrachlorophenol	F344/N rats (m, f)	NTP 1999/2-yr feed
99% PCP	1% tetrachlorophenol	F344/N rats (m, f)	NTP 1999/2-yr feed with stop exposure to PCP at 1 yr

[a]m, f = males, females.
[b]Gavage dosing post-natal days 7–28 followed by feed dosing to necropsy at 18 months of age.

PCP has also been tested in the diet for tumor initiation and promoting activity in mice. Phenobarbital was administered as the promoter when the initiating activity of PCP was assessed and diethylnitrosamine was given as the initiator when the promoting activity of PCP was assessed. In another study, PCP and a metabolite (tetrachlorohydroquinone) were topically tested for tumor promoting activity after dermal administration of DMBA (reviewed by EPA 2010).

3.3. Mechanistic and other relevant data

PCP can be oxidatively dechlorinated to tetrachlorohydroquinone, and tetrachlorohydroquinone and PCP have been identified in the urine of rats and mice exposed to PCP (reviewed by EPA 2010). PCP is metabolized *in vitro* by human liver microsomes to tri- and tetrachlorohydroquinone (reviewed by EPA 2010) and PCP-glucuronide (reviewed by IARC 1991).

Tetrachlorohydroquinone can be oxidized to quinones through semiquinone (free radical) intermediates, which in turn react with macromolecules to form protein and DNA adducts. PCP or quinone metabolites have been tested *in vivo* for induction of oxidative stress and albumin and hemoglobin protein adducts. PCP-exposed workers have been tested for chromosome damage (reviewed by EPA 2010). PCP and metabolites have been tested in numerous genotoxicity assays, primarily *in vitro* (reviewed by IARC 1991).

4. Key Scientific Questions and Issues Relevant for the Cancer Evaluation

The key scientific questions concern the evaluation of the human cancer studies, cancer studies in experimental animals, and mechanistic data. These are as follows:

- 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 or co-exposures 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 mechanistic data support findings in experimental animals or humans?

5. Proposed Approach for Conducting the Cancer Evaluation

5.1. Scope and focus of the draft RoC monograph

The ORoC will prepare the draft RoC monograph on PCP, which will consist of two parts, the cancer evaluation component and the substance profile. The cancer evaluation component of the draft monograph will review and assess the scientific literature, provide a discussion of scientific issues, and assess and integrate the relevant scientific evidence, applying the listing criteria to reach a preliminary RoC listing recommendation[3]. The substance profile of the draft monograph will give the NTP's preliminary listing recommendation and a summary of the key supportive evidence. Details on the methods for writing the draft RoC monograph and topics typically covered in the monograph are outlined in the NTP process for the preparation of the RoC (*http://ntp.niehs.nih.gov/go/rocprocess*). Details of the preliminary literature search strategy including data sources and literature search terms that are consistent with this approach are discussed in Appendix 1.

5.2. Proposed approach for obtaining scientific and public input

Public comments on scientific issues are requested on PCP at several times prior to the development of the draft RoC monograph including the request for information on the nomination,[4] and the request for comment on the draft concept in conjunction with the NTP Board of Scientific Counselors meeting. The ORoC will consider this information and experts suggested by the public in drafting the cancer evaluation component of the draft monograph. The Office of the RoC (ORoC) will create a webpage for the candidate substances currently under review. The webpage will typically include the following: (1) RoC documents related to the review of the substance (e.g., concept document, draft RoC monograph), (2) citations for references identified from literature searches, (3) public comments, (4) an input box for the public to provide information (such as new literature) or comments (such as the identification of additional scientific issues), and (5) information on public meetings or listening sessions. The NTP will communicate when new information is added or updated (such as updated literature searches) to the website via the NTP list serve.[5] Additional scientific issues may be identified during preparation of the monograph. Future forums (such as a listening session) for receiving public comment on any additional scientific issues may be considered depending on public interest; these would be announced via a *Federal Register* notice, NTP list serve and the RoC website.

ORoC will receive input on issues related to the evaluation of human cancer studies, such as distinguishing the effect of pentachlorophenol from that of its contaminants, by convening a web-based scientific symposium with presentations by invited speakers. The symposium and a request for speakers will be announced via a *Federal Register* notice and other NTP

[3]A listing recommendation can be not to list, to list as *reasonably anticipated to be a human carcinogen*, or to list as *known to be a human carcinogen*.

[4]Federal Register notice and public comments are available at *http://ntp.niehs.nih.gov/go/rocnom*.

[5]Persons can subscribe to the NTP list serve free-of-charge at *http://ntp.niehs.nih.gov/go/getnews*.

media (see above). Speakers may be from stakeholder groups, environmental groups, government scientists, and/or external scientists, and approximately 2 to 4 speakers will present their views on the human cancer studies. Substance-specific government or non-government technical advisors with knowledge of epidemiology or occupational hygiene will also be invited to provide their expertise to the ORoC, promote discussion of the issues, and provide critical comment on the human cancer studies section of the draft monograph. All experts may be identified from the peer-reviewed literature databases, membership databases in relevant professional societies, and from recommendations from other scientists or the public. The goal of this symposium will be to inform the assessment of the human cancer studies in the draft RoC monograph.

A second issue is whether PCP contaminants have contributed to the results of some cancer studies in experimental animals. NTP will convene an information group[6] of approximately 2 to 4 scientists with substance-specific expertise to independently review animal data, discuss, and inform ORoC of potential effects from these contaminants. These experts may be identified from the peer-reviewed literature databases, membership databases in relevant professional societies, and from recommendations from other scientists or the public. Toxicological or cancer data in experimental animals on the contaminants will be provided. Input on the animal cancer data will be used by ORoC staff in drafting a synthesis of findings in the experimental animal section of the draft monograph.

6. Public Release and Peer Review of the Draft Monograph

Once completed, the draft RoC monograph will undergo interagency review, and the NTP will release the draft monograph for public comment and public peer review. The NTP will convene an external peer-review scientific panel[7] to review the draft RoC monograph on PCP in a public forum (*http://ntp.niehs.nih.gov/go/rocprocess*). The panel will consist of members with expertise in disciplines related to the cancer evaluation of PCP such as epidemiology, exposure assessment, metabolism of polychlorophenols and other contaminants of commercial PCP, genotoxicity, and mechanisms of carcinogenesis. The NTP will also set aside time at the peer-review meeting for a discussion of scientific issues raised in the public comments.

[6]An information group is a group assembled for the purpose of exchanging facts or information and is not covered by the Federal Advisory Committee Act. Members provide input on an individual basis and not from the group as a whole.

[7]NTP panels are federally chartered technical and scientific advisory groups convened as needed to provide advice on specific scientific issues and peer review. Members of NTP panels are scientists with relevant expertise and knowledge from the public and private sectors. The final selection of membership is based upon providing a balanced and unbiased group of highly qualified individuals and is made in accordance with Federal Advisory Committee Act and HHS implementing guidelines; *http://ntp.niehs.nih.gov/go/166*.

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Appendix 1

Preliminary Literature Search Strategy: Pentachlorophenol

This document identifies the data sources, search terms and preliminary search strategies for identifying literature for the draft monograph on pentachlorophenol. The literature search will be updated approximately every three months, and prior to submitting the draft monograph for interagency review. Additional literature searches will be conducted as needed to identify information to address scientific issues that arise during the review. Citations retrieved from literature searches will be uploaded to web-based systematic review software and screened using inclusion and exclusion criteria. Multi-level reviews of the literature are conducted, with initial reviews based on titles and abstracts only, and later reviews based on full-text.

1. Data Sources

Identification of synonyms and metabolites for pentachlorophenol (CASRN 87-86-5); chemical class = chlorophenols, chlorinated phenols, polychlorinated phenols

- *Synonyms*- IARC (1991) and National Library of Medicine databases (e.g., ChemIDplus, Hazardous Substances Data Bank)
- *Metabolites*- EPA (2010), NTP (1999), IARC (1991)

Citation databases (searches for titles, abstracts, and key words)

- PubMed
- Web of Science
- Scopus

Additional data sources:

- Authoritative reviews or general sources for exposure and other information (e.g., Toxnet; U.S. Government agencies websites, publications and databases; International Agency for Research on Cancer)
- Citations in authoritative reviews or in primary references located by literature search
- QUOSA library of occupational case-control studies (full text search for pentachlorophenol)

2. Preliminary Literature Searches

Literature searches in the three databases (see Data Sources, Section 1) are conducted using search terms specific for pentachlorophenol (synonyms, chemical class, metabolites, and exposure scenario) and for the topics covered by the monograph (See Table 1).

The specific literature searches are constructed to answer the key questions of the monograph, as a result, not all topic-specific searches will include all the different types of substance-specific search terms; for example, searches for exposure information will only be combined with search terms for pentachlorophenol synonyms since information on exposure to pentachlorophenol metabolites is beyond the scope of this document.

Searches for human cancer studies are somewhat unique because they involve the identification of search terms for exposure scenarios in which people may be exposed to pentachlorophenol in addition to search terms specific for pentachlorophenol. For

pentachlorophenol, these include terms related to its use as a wood preservative, and in wood-related industries such as sawmills, fencing, and lumber. Because pentachlorophenol was a major pesticide, searches using either pentachlorophenol synonyms or the chemical class should pick up any potential epidemiological studies in the pesticide industry.

In addition to the human cancer studies identified from the above searches, a full-text search for pentachlorophenol is conducted using a QUOSA library of occupational case-control studies.

Table 1. Preliminary literature search approach for pentachlorophenol (PCP)

Substance	Search terms	Topics (combined with)[a]
Penta-chlorophenol synonyms	Pentachlorophenol, 87-86-5 (CASRN), hydroxypentachlorobenzene, pentachlorobenzene, pentachlorophenate, Dowicide EC-7, Dowicide 7	Human Exposure Toxicokinetics Human Cancer Studies Cancer Studies in Experimental Animals Genotoxicity Toxicity Mechanism
Chemical class	chlorophenols/chlorinated phenols/polychlorinated phenols	Human Cancer Studies Cancer Studies in Experimental Animals (for the mechanistic section) Genotoxicity Toxicity Mechanism
Penta-chlorophenol metabolites	tetrachlorophydroquinone (TCHQ), tetrachloro-1,2-hydroquinone (TCoHQ), tetrachlorocatechol (TCpCAT), tetrachloro-*p*-benzoquinone (TCpBQ), tetrachloro-1,4-benzosemiquinone (TCpSQ), tetrachloro-1,2-benzosemiquinone (TCoSQ), tetrachlorophenol, and trichlorophenol	Cancer Studies in Experimental Animals (for the mechanistic section) Genotoxicity Toxicity Mechanism
Exposure scenario	(wood and preserv*) OR lumber OR sawmill OR fenc* or lumber	Human Cancer Studies Toxicity (restricted to human studies) Genotoxicity (restricted to human studies)

[a]Search terms for each of these topics have been developed in consultation with an information specialist.