



**National Toxicology Program**

U.S. Department of Health and Human Services

**Peer-Review Draft:  
Report on Carcinogens  
Monograph on Pentachlorophenol  
and By-Products of Its Synthesis**

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Office of the Report on Carcinogens  
Division of the National Toxicology Program  
National Institute of Environmental Health Sciences  
U.S. Department of Health and Human Services

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## FOREWORD

The National Toxicology Program (NTP) is an interagency program within the Public Health Service (PHS) of the Department of Health and Human Services (HHS) and is headquartered at the National Institute of Environmental Health Sciences of the National Institutes of Health (NIEHS/NIH). Three agencies contribute resources to the program: NIEHS/NIH, the National Institute for Occupational Safety and Health of the Centers for Disease Control and Prevention (NIOSH/CDC), and the National Center for Toxicological Research of the Food and Drug Administration (NCTR/FDA). Established in 1978, the NTP is charged with coordinating toxicological testing activities, strengthening the science base in toxicology, developing and validating improved testing methods, and providing information about potentially toxic substances to health regulatory and research agencies, scientific and medical communities, and the public.

The Report on Carcinogens (RoC) is prepared in response to Section 301 of the Public Health Service Act as amended. The RoC contains a list of identified substances (i) that either are *known to be human carcinogens* or are *reasonably anticipated to be human carcinogens* and (ii) to which a significant number of persons residing in the United States are exposed. The Secretary, Department of HHS, has delegated responsibility for preparation of the RoC to the NTP, which prepares the report with assistance from other Federal health and regulatory agencies and nongovernmental institutions. The most recent RoC, the 12th Edition (2011), is available at <http://ntp.niehs.nih.gov/go/roc12>.

Nominations for (1) listing a new substance, (2) reclassifying the listing status for a substance already listed, or (3) removing a substance already listed in the RoC are evaluated in a scientific review process (<http://ntp.niehs.nih.gov/go/rocprocess>) with multiple opportunities for scientific and public input and using established listing criteria (<http://ntp.niehs.nih.gov/go/15209>). A list of candidate substances under consideration for listing in (or delisting from) the RoC can be obtained by accessing <http://ntp.niehs.nih.gov/go/37893>.

## INTRODUCTION

Pentachlorophenol (PCP, CASRN 87-86-5) is a chlorinated aromatic compound whose current uses in the United States are limited to the treatment of utility poles, cross arms, railroad ties, wooden pilings (e.g., wharf pilings), fence posts, and lumber or timbers for construction. In the past, pentachlorophenol also was used as a biocide and was found in ropes, paints, adhesives, leather, canvas, insulation, and brick walls. Pentachlorophenol has been selected as a candidate substance for review for possible listing in the RoC based on current or past U.S. exposure and an adequate database of cancer studies in both animals and humans.

### Monograph contents

This RoC draft monograph on pentachlorophenol consists of the following components: (Part 1) the cancer evaluation component that reviews the relevant scientific information and assesses its quality, applies the RoC listing criteria to the scientific information, and recommends an RoC listing status for pentachlorophenol, and (Part 2) the draft substance profile containing the NTP's preliminary listing recommendation, a summary of the scientific evidence considered key to reaching that recommendation, and data on properties, use, production, exposure, and Federal regulations and guidelines to reduce exposure to pentachlorophenol.

The cancer evaluation component for pentachlorophenol provides information on the following topics: human exposure and chemical properties (Section 1), disposition and toxicokinetics (Section 2), cancer studies in humans (Section 3), cancer studies in experimental animals (Section 4), and mechanistic data and other related effects (Section 5), including studies of relevant toxicological effects, genetic toxicology, and potential mechanisms of carcinogenicity. The information in Section 6 is a synthesis of Sections 2 through 5.

The information reviewed in Sections 2 through 5 must come from publicly available, peer-reviewed sources. Information in Section 1, including chemical and physical properties, analytical methods, production, use, occurrence, and exposure, may come from publicly available, peer-reviewed or non-peer-reviewed sources.

The cancer evaluation for pentachlorophenol focuses on the evaluation of the human cancer studies, animal tumor studies, and mechanistic data.

### Process for preparation of the cancer evaluation component

The process for preparing the cancer evaluation component of the monograph included approaches for obtaining public and scientific input and using systematic methods (e.g., standardized methods for identifying the literature (see [Appendix A](#)), inclusion/exclusion criteria, extraction of data and evaluation of study quality using specific guidelines, and assessment of the level of evidence for carcinogenicity using established criteria).

The Office of the Report on Carcinogens (ORoC) followed the approaches outlined in the concept document, which discusses the scientific issues and questions relevant to the evaluation of pentachlorophenol carcinogenicity, the scope and focus of the monograph, and the approaches to obtain scientific and public input to address the key scientific questions and issues for preparing the cancer evaluation component of the draft monograph. The ORoC presented the draft concept document for pentachlorophenol to the NTP Board of Scientific Counselors (BSC) at the June 21-22, 2012 meeting that provided opportunity for written and oral public comments and is available on the RoC website (<http://ntp.niehs.nih.gov/go/37897>), after which the concept was finalized and pentachlorophenol was approved by the NTP Director as a candidate substance for review.

### ***Key scientific questions and issues relevant for the cancer evaluation***

The key scientific issues concern the evaluation of cancer studies in humans and experimental animals, and mechanistic data. They are as follows:

- What is the level of evidence (sufficient, limited, or inadequate) for the carcinogenicity of pentachlorophenol from studies in humans? What are the tissue sites?
  - What are the major potential confounders for evaluating pentachlorophenol cancer risk in these studies?
  - Can an association between any cancer site and exposure to pentachlorophenol be explained by exposure to these co-exposures or other risk factors for cancer?
- What is the level of evidence (sufficient or not sufficient) for the carcinogenicity of pentachlorophenol from studies in experimental animals? What are the tissue sites? What are the tumor sites that contribute to the sufficient evidence in experimental animals?
- What are the potential mechanisms by which pentachlorophenol may cause cancer?
- Is there evidence that these mechanisms occur in humans? If so, what is the level of the evidence (strong, moderate, or weak)?

### ***Approach for obtaining scientific and public input***

Additional scientific input was obtained for exposure, human cancer studies, and disposition and toxicokinetics of pentachlorophenol. Technical advisors are identified on the “CONTRIBUTORS” page.

One of the key issues identified in the concept document concerns differentiating effects of pentachlorophenol from its contaminants in both the cancer studies in humans and experimental animals. In order to receive public and scientific input on this matter, the ORoC held a webinar titled, “Human cancer studies on exposure to pentachlorophenol (PCP): Differentiating potential cancer effects of PCP exposure from effects due to occupational co-exposures or PCP contaminants” on April 11, 2013. The ORoC also convened an information group consisting of several scientists within and outside of NTP with substance-specific expertise to independently review the experimental animal data.

Based on this input, the NTP has defined the candidate substance as ‘pentachlorophenol and by-products of its synthesis.’

Public comments on scientific issues were requested at several times prior to the development of the draft RoC monograph, including the request for information on the nomination, and the request for comment on the draft concept document, which outlined the rationale and approach for conducting the scientific review. In addition, the NTP posted its protocol for reviewing the human cancer studies and studies in experimental animals for public input on the OROc webpage for pentachlorophenol (available at <http://ntp.niehs.nih.gov/go/37897>) prior to the release of the draft monograph. One public comment on pentachlorophenol was received from the public as of the date on this document (<http://ntp.niehs.nih.gov/go/37663>).

### ***Methods for writing the cancer evaluation component of the monograph***

The procedures by which relevant literature was identified, data were systematically extracted and summarized, and the draft monograph was written, together with the processes for scientific review, quality assurance, and assessment and synthesis of data, are described below.

The preparation of the RoC monograph for pentachlorophenol began with development of a literature search strategy to obtain information relevant to the topics listed above for Sections 1 through 5 using search terms developed in collaboration with a reference librarian (see [Appendix A](#)) for a detailed description of the literature search strategy). The citations (N = 3,980) identified from these searches were uploaded to a web-based systematic review software for evaluation by two separate reviewers using inclusion/exclusion criteria, and 408 references were selected for final inclusion in the draft monograph using these criteria. Studies identified from the literature searches but excluded from the review include publications on chemicals other than pentachlorophenol (or relevant structurally related compounds such as pentachlorophenol metabolites and analogues or by-products of synthesis of pentachlorophenol), and studies involving exposure to pentachlorophenol that reported results for topics not covered in this monograph (see ‘Monograph contents’).

Information for the exposure, relevant cancer, and mechanistic sections was systematically extracted in tabular format and/or summarized in the text, following specific procedures developed by OROc, from studies selected for inclusion in the monograph. All sections of the monograph underwent scientific review and quality assurance (QA) (i.e., assuring that all the relevant data and factual information extracted from the publications have been reported accurately) by a separate reviewer. Any discrepancies between the writer and the reviewer were resolved by mutual discussion in reference to the original data source.

Strengths, weaknesses, and study quality of the cancer studies for pentachlorophenol in humans (see [Appendix C](#)) or experimental animals (see [Appendix D](#)) were assessed based on a series of *a priori* questions. For the cancer studies in humans and experimental animals, these questions and the guidelines for answering the questions were available in the protocols (available at <http://ntp.niehs.nih.gov/go/37897>). Relevant genotoxicity and mechanistic studies were also assessed for their strengths and weaknesses.

Human exposure information was assessed to determine whether the evidence indicates that a significant number of persons residing in the United States are exposed to pentachlorophenol (see Foreword for information regarding the congressional mandate for the RoC). However, for many substances, this information is not available, and typically, U.S. exposure can be inferred from data on use, production volume, occupational monitoring, environmental occurrence, estimated daily intake, and biomonitoring. Because cancer has a long latency period, past exposure is also considered in the assessment.

RoC listing criteria (see text box) were applied to the available database of carcinogenicity data to assess the level of evidence (sufficient, limited, or inadequate) for the carcinogenicity of pentachlorophenol from studies in humans and the level of evidence (sufficient, not sufficient) from studies in experimental animals. The approach for synthesizing the evidence across studies and reaching a level of evidence conclusion was outlined in the protocol. The initial conclusions do not integrate the conclusions from the human cancer studies, or

#### RoC Listing Criteria

##### **Known To Be Human Carcinogen:**

There is sufficient evidence of carcinogenicity from studies in humans\*, which indicates a causal relationship between exposure to the agent, substance, or mixture, and human cancer.

##### **Reasonably Anticipated To Be Human Carcinogen:**

There is limited evidence of carcinogenicity from studies in humans\*, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded, OR

there is sufficient evidence of carcinogenicity from studies in experimental animals, which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site, or type of tumor, or age at onset, OR

there is less than sufficient evidence of carcinogenicity in humans or laboratory animals; however, the agent, substance, or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous Report on Carcinogens as either known to be a human carcinogen or reasonably anticipated to be a human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to, dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub-populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals, but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

\*This evidence can include traditional cancer epidemiology studies, data from clinical studies, and/or data derived from the study of tissues or cells from humans exposed to the substance in question that can be useful for evaluating whether a relevant cancer mechanism is operating in people.

experimental animal cancer studies with the mechanistic data. The evaluation of the mechanistic data included a complete discussion and assessment of the strength of evidence for potential modes of action for pentachlorophenol-induced neoplasia, including metabolic activation, cytotoxicity, genetic-related effects, and epigenetic effects. The RoC listing criteria were then applied to the body of knowledge (cancer studies in humans and experimental animals and mechanistic data) for pentachlorophenol to reach a listing recommendation.

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# Part 1

## **Draft RoC Cancer Evaluation**

**Properties and Human Exposure**

**Disposition (ADME) and Toxicokinetics**

**Human Cancer**

**Studies in Experimental Animals**

**Mechanistic Data and Other Relevant Effects**

**Overall Cancer Evaluation**

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# 1 Properties and Human Exposure

The candidate substance being reviewed in this monograph is ‘Pentachlorophenol and By-products of Its Synthesis.’ During synthesis of pentachlorophenol, several additional chlorinated molecules are formed as by-products because of the elevated temperatures and pressures used in the production processes (see Section 1.3, below). The concentrations of these by-products can be altered somewhat by changing the conditions of the manufacturing process, but all commercial forms of pentachlorophenol contain by-products of its synthesis in detectable amounts.

Evidence that exposure to pentachlorophenol includes exposure to by-products of its synthesis comes from biomonitoring studies. The pentachlorophenol by-products most commonly found in serum samples are 1,2,3,6,7,8-hexachlorodibenzo-*p*-dioxin, 1,2,3,4,6,7,8-heptachlorodibenzo-*p*-dioxin, and octachlorodibenzo-*p*-dioxin, but not 2,3,7,8-TCDD, which is not a by-product of the pentachlorophenol synthetic process used in the United States. These specific by-products consistently have been found in serum samples from people exposed to pentachlorophenol in multiple occupational settings and in the environment near active and former wood treatment facilities, e.g., in dust collected from houses. The by-products have been observed to persist in serum of workers for decades after exposure ceased in sawmill workers and pentachlorophenol manufacturers. Further, these same by-products also have been found in environmental samples from different geographical areas where pentachlorophenol had been used including the United States, China, and New Zealand and in adipose tissue, beef, and milk from cows exposed to pentachlorophenol-treated wood. Thus, people who are exposed to pentachlorophenol or pentachlorophenol-containing products are always exposed to the combination of pentachlorophenol and its by-products. [Note that throughout the rest of this monograph, when the term “pentachlorophenol” is used, it denotes exposure to ‘pentachlorophenol and by-products of its synthesis.’]

This section describes the chemical identification and properties of pentachlorophenol (Section 1.1), use and production data (Section 1.2), synthesis of pentachlorophenol and its by-products (Section 1.3), characterization of exposure in the workplace (Section 1.4), and exposure of people to pentachlorophenol (Section 1.5). The material in Sections 1.1 through 1.5 is summarized in Section 1.6.

## 1.1 Chemical identification and properties

Pentachlorophenol (Figure 1-1) (CASRN 87-86-5) is a chlorinated aromatic compound. Pure pentachlorophenol exists as light tan to white needle-like crystals at room temperature. Also known as PCP, chlorophen, penchlorol, and penta, the compound is relatively volatile, practically insoluble in water at the pH generated by its dissociation ( $pK_a = 4.7$ ), and soluble in most organic solvents (NTP 1989, WHO 1987). Salts of pentachlorophenol, such as sodium pentachlorophenate, are readily soluble in water. Technical grade pentachlorophenol consists of brown flakes; technical grade sodium pentachlorophenate consists of cream-colored beads. Regarding production and use, pentachlorophenol and its salt, sodium pentachlorophenate, are considered the most important forms of pentachlorophenol. Table 1-1 contains some chemical identification

information for pentachlorophenol. Table 1-2 lists some physical and chemical properties of pentachlorophenol.

**Table 1-1. Chemical identification of pentachlorophenol**

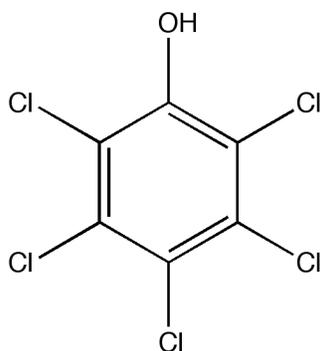
Characteristic	Information
Chemical Abstracts index name	Pentachlorophenol <sup>a</sup>
CAS Registry number	87-86-5 <sup>b</sup>
Molecular formula	C <sub>6</sub> HCl <sub>5</sub> O <sup>b</sup>
Synonyms	Chlorophen; PCP; penchlorol; penta; pentachlorophenol; 2,3,4,5,6-pentachlorophenol <sup>c</sup>

Sources: <sup>a</sup> IARC 1999, <sup>b</sup> Akron 2010, <sup>c</sup> NTP 1989.

**Table 1-2. Physical and chemical properties of pentachlorophenol**

Property	Information
Molecular weight	266.3 <sup>a</sup>
Melting point	188°C <sup>a</sup>
Boiling point	310°C <sup>a</sup>
Vapor pressure (mm Hg)	0.0003 at 25°C <sup>a</sup>
Vapor density (air = 1)	1.98 <sup>a</sup>
Density	1.978 g/cm <sup>3</sup> at 22°C <sup>a</sup>
Solubility in water	14 mg/L at 25°C <sup>b</sup>
Octanol/water partition coefficient (pK <sub>ow</sub> )	5.12 <sup>a</sup>
Henry's law constant	2.45 × 10 <sup>-8</sup> atm·m <sup>3</sup> /mole at 22°C <sup>b</sup>
Conversion factors (pentachlorophenol in air) parts per million (ppm) to µg/m <sup>3</sup> µg/m <sup>3</sup> to parts per million (ppm)	µg/m <sup>3</sup> = 10,900 × (ppm) <sup>c</sup> ppm = 9 × 10 <sup>-5</sup> × (µg/m <sup>3</sup> ) <sup>c</sup>

Sources: <sup>a</sup> Akron 2010, <sup>b</sup> ChemIDplus 2013, <sup>c</sup> SMARTe.org 2008.



**Figure 1-1. Chemical structure of pentachlorophenol (C<sub>6</sub>HCl<sub>5</sub>O)**

## 1.2 Pentachlorophenol use and production data

Current pentachlorophenol use is limited to the treatment of utility poles, cross arms, railroad ties, wooden pilings (e.g., wharf pilings), fence posts, and lumber or timbers for construction. In the United States, pentachlorophenol-containing products remain registered for wood preservation, and utility poles and cross arms represent about 92% of all uses of pentachlorophenol-treated lumber (ATSDR 2001, EPA 2010).

Pentachlorophenol was first used in the United States in 1936 as a wood preservative to prevent decay from fungal organisms and damage from insects. Pentachlorophenol also was used as a biocide and was found in ropes, paints, adhesives, leather, canvas, insulation, and brick walls. In 1984 indoor uses were cancelled. In 1987 non-wood preservative uses were cancelled and restricted. Prior to 1987, pentachlorophenol was one of the most widely used biocides in the United States (EPA 2008a). Pentachlorophenol has also been used in the laboratory as a competitive inhibitor of sulfotransferase (Mulder and Scholtens 1977), but this use would involve very small quantities of the substance.

Pentachlorophenol is a high-production-volume chemical in the United States based on data submitted to EPA under the Chemical Data Reporting rule for 2011 of > 1 million to 10 million pounds annually. In 2012, manufacture of pentachlorophenol was reported for at least 6 companies worldwide, including at least 1 company in the United States (SRI 2012). Although no companies currently report production activities in the United States, one company in North America reports producing pentachlorophenol at a plant in Mexico. This company also operates a formulation facility in the United States (Dunn 2013). Table 1-3 presents production data for pentachlorophenol.

**Table 1-3. Production data for pentachlorophenol**

Category	Years covered	Quantity in pounds <sup>a</sup>
U.S. EPA CDR rule <sup>b</sup>	2011	> 1 million to 10 million
U.S. imports (recent) <sup>c</sup>	2012	14.6 million
U.S. imports (historical) <sup>c</sup>	2007	0
U.S. exports (recent) <sup>c</sup>	2012	99,000
U.S. exports (historical) <sup>c</sup>	2007	697,000

Sources: EPA 2013, USITC 2013.

<sup>a</sup>From 3/2013 Internet searches; data subject to change.

<sup>b</sup>CDR = Chemical Data Reporting Rule, formerly called Inventory Update Rule.

<sup>c</sup>Reported as “pure pentachlorophenol (not pentachlorophenol preparation) other than put up for retail sale.”

## 1.3 Synthesis of pentachlorophenol and its by-products

Synthesis of pentachlorophenol requires a combination of high temperatures and pressure that results in formation of other chlorinated aromatic molecules, particularly chlorinated dibenzo-*p*-dioxins and dibenzofurans (see below). Pentachlorophenol has only been produced by direct chlorination of phenol in the United States (ATSDR 2001, Ruder and Yiin 2011, Williams 1982), but alkaline hydrolysis of hexachlorobenzene (HCB) might have been used in some instances in other countries (e.g., in Europe or China) (Collins 2013, Dunn 2013).

Direct chlorination of phenol to pentachlorophenol uses heat (> 75°C), pressure, and a catalyst to replace the hydrogen atoms on the benzene ring of phenol with chloride atoms (Dunn 2013, Ruder and Yiin 2011, Williams 1982), and the alkaline hydrolysis of hexachlorobenzene to pentachlorophenol also uses high temperatures (approximately 125°C to 275°C) in the presence of caustic soda and solvents (WHO 1987, Williams 1982).

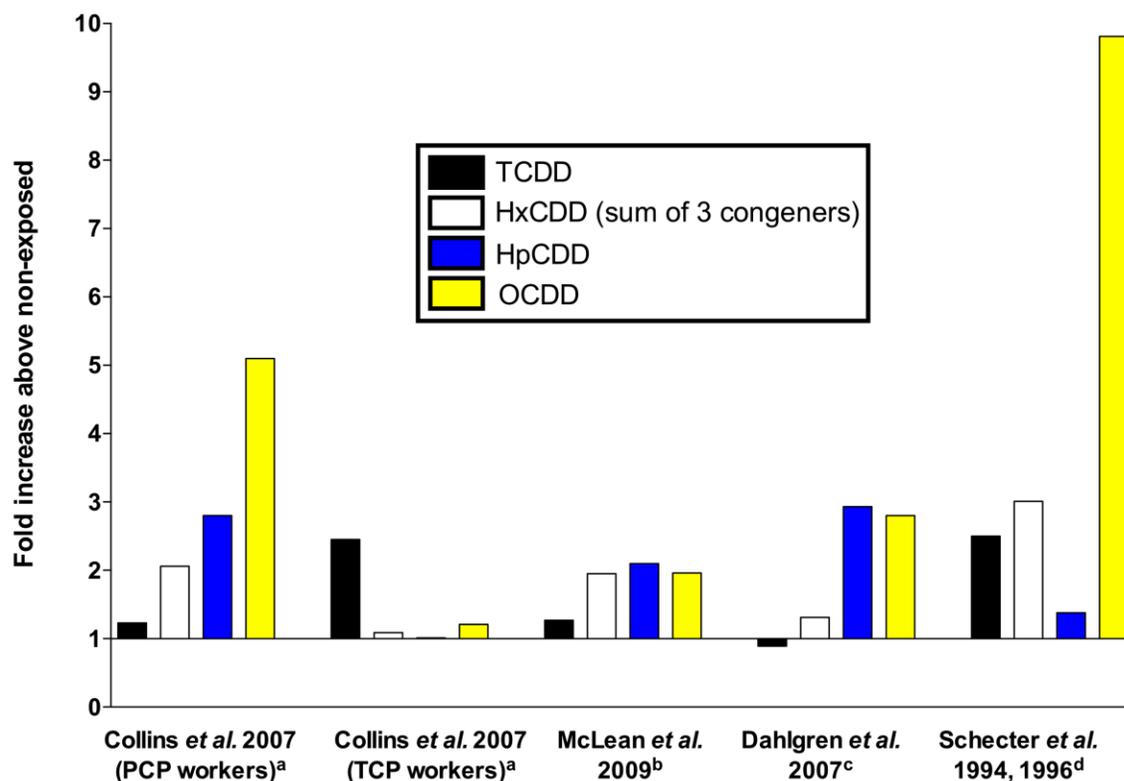
Once pentachlorophenol is manufactured, the solid product is prepared for shipping to end users. It may be converted to flakes by pumping molten pentachlorophenol into a pan, crystallizing it by rolling a water-cooled drum through it, then shaving off the product with a knife and bagging it, to prills by spraying it as a liquid into a tower, forming sleet-like pellets, which collect at the bottom of the tower as beads or pellets or to blocks by pouring molten pentachlorophenol into one or two-ton molds and allowing them to harden before wrapping for shipping.

### 1.3.1 Synthesis of pentachlorophenol by-products

An inherent result of the elevated temperatures and pressure required for the direct chlorination of phenol to pentachlorophenol and for the alkaline hydrolysis of HCB to pentachlorophenol is the generation of side reactions that produce other chemicals (i.e., by-products of its synthesis) in addition to the final pentachlorophenol product (ATSDR 2001, EPA 1999, WHO 1987, Williams 1982). As these chemicals are always produced when pentachlorophenol is synthesized, these intrinsic impurities of manufacture are herein referred to as ‘by-products of synthesis.’ Commonly found by-products of both synthetic processes are polychlorinated phenols (tri- and tetra-); HCB; hexa-, hepta-, and octachlorodibenzo-*p*-dioxins (HxCDD, HpCDD, and OCDD); and hexa-, hepta-, and octachlorodibenzofurans (Collins 2013, Dunn 2013). The alkaline hydrolysis of HCB to pentachlorophenol also results in formation of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). However, 2,3,7,8-TCDD has rarely been detected in commercial preparations of pentachlorophenol (WHO 1987), thus the presence of this molecule in a pentachlorophenol preparation is considered to be a contaminant rather than a by-product of its synthesis. As discussed below, synthesis of both pentachlorophenol and trichlorophenol, whose manufacture produces 2,3,7,8-TCDD as a by-product, in the same plant could result in exposure of workers to 2,3,7,8-TCDD.

### 1.3.2 Pentachlorophenol by-products: biomonitoring data

The pentachlorophenol by-products most commonly found in serum samples are the dioxin congeners 1,2,3,6,7,8-HxCDD, 1,2,3,4,6,7,8-HpCDD, and OCDD (Collins *et al.* 2006, McLean *et al.* 2009a), which reflect the spectrum of by-products found in the PCP from its manufacture and indicate exposure to pentachlorophenol, including past exposure. The pattern of these congeners has been proposed by some authors as distinct “fingerprints” for exposure to pentachlorophenol when individuals have little or no increase in 2,3,7,8-TCDD above the non-exposed reference population level (Collins *et al.* 2008) (see Figure 1-2). Collins *et al.* were able to distinguish between workers exposed to pentachlorophenol and those exposed to 2,4,5-trichlorophenol (TCP), which was manufactured in the same plant; an increase in TCDD levels was seen only in the workers exposed to trichlorophenol.



**Figure 1-2. Relative increase (or decrease) in serum levels of dioxin congeners compared with reference populations for each study**

Serum levels for dioxin congeners of exposed workers were divided by the values from the reference group of unexposed individuals from each study. The horizontal line at “1” indicates equivalence with the reference group. The bar for Dahlgren *et al.* that extends below the line indicates a lower value for the exposed compared with the reference group.

<sup>a</sup>Values shown are for PCP-only workers and TCP-only workers as defined by Collins *et al.* Samples were collected 26 to 62 years after occupational exposure. Values were divided by means for worker referents (N = 37): TCDD, 6.5, HxCDD, 90.8, HpCDD, 68.7, OCDD, 509 pg/g lipid.

<sup>b</sup>Values were divided by means for non-exposed former sawmill workers (N = 23): TCDD, 1.48, HxCDD, 18.53, HpCDD, 13.58, OCDD, 157.83 pg/g lipid.

<sup>c</sup>Values were divided by means for controls (Dallas residents) (N = 200): TCDD, 3.8, HxCDD, 54.5, HpCDD, 45.1, OCDD, 374 pg/g lipid.

<sup>d</sup>Values were divided by means for the general Chinese population > 40 years old (N = 50): TCDD, 1.2, HxCDD, 11.3, HpCDD, 17.5, OCDD, 117 pg/g lipid.

By-products of pentachlorophenol synthesis have consistently been found in serum samples from people occupationally exposed to pentachlorophenol in multiple settings including pentachlorophenol manufacturers the United States (Michigan) (Collins *et al.* 2007, Collins *et al.* 2006) and in Germany (Päpke *et al.* 1992), sawmill workers in New Zealand (McLean *et al.* 2009a, Smith and Lopipero 2001), wood treatment workers and people living near active and former wood treatment facilities in the United States (Florida [Karouna-Renier *et al.* 2007], Texas [Dahlgren *et al.* 2003], and Mississippi [Dahlgren *et al.* 2007]), and pesticide handlers and people living in areas sprayed for control of snail-borne schistosomiasis in China (Schecter *et al.* 1994). Further, these same

by-products have been observed to persist in serum of workers for decades after exposure ceased in sawmill workers (McLean *et al.* 2009a) and in pentachlorophenol manufacturing workers (Collins *et al.* 2007). Levels from studies reporting mean values for exposed populations compared with non-exposed individuals are illustrated in Figure 1-2.

Exposure to pentachlorophenol results in markedly higher levels of HxCDD, HpCDD, and OCDD compared with those in reference groups while 2,3,7,8-TCDD levels increase only slightly, if at all (Collins *et al.* 2008). In contrast, workers exposed to dioxins during manufacture (Päpke *et al.* 1992) or disposal of phenoxy herbicides (Littorin *et al.* 1994) or manufacture of trichlorophenol (Collins *et al.* 2008) show elevations of tetrachlorodioxin that are similar to or greater than those for the hexa-, hepta-, and octachlorodioxins (Littorin *et al.* 1994, Päpke *et al.* 1992). Data from one study of pentachlorophenol sprayers in China indicate that levels of 2,3,7,8-TCDD were higher than those seen for U.S. and New Zealand workers exposed to pentachlorophenol (see below); however, these workers may also have been exposed to other pesticides containing 2,3,7,8-TCDD).

Other evidence supporting the usefulness of these dioxin congener fingerprints to demonstrate current or past pentachlorophenol exposures include measurement of attic dust from houses near treatment facilities. Significantly elevated levels of pentachlorophenol by-products, primarily OCDD and HpCDD, also have been detected in samples of household dust collected from homes in the vicinity (i.e., within a 1- to 2-mile radius) of pentachlorophenol wood treatment plants that also showed significantly elevated OCDD and HpCDD levels relative to local general population control groups (e.g., Dallas, TX unexposed controls) (Dahlgren *et al.* 2007). Elevated levels of dioxins in attic dust, expressed as toxic equivalents (TEQs), were also reported for sampling locations 1 to 2 miles from active wood treatment facilities in Mississippi, Alabama, and Louisiana (2 facilities) (Feng *et al.* 2011) and a former wood treatment facility in Alabama (Hensley *et al.* 2007).

Increased dioxin congeners have also been detected in tissues and milk from cows and pigs exposed to pentachlorophenol-treated wood. A pattern of polychlorinated dibenzo-*p*-dioxins and dibenzofurans (i.e., high amounts of 1,2,3,6,7,8-HxCDD, 1,2,3,4,6,7,8-HpCDD, and OCDD but little or no tetra- or penta-congeners) was found in adipose tissue collected from cattle at agricultural research facilities in the United States where pentachlorophenol-treated wood was present (Huwe *et al.* 2004). According to the authors, the residue pattern “somewhat resembled” the by-products present in pentachlorophenol that would have been used to treat the wood. Residues of dioxins and furans were also detected in beef and milk from cows exposed to pentachlorophenol-treated wood (Fries *et al.* 2002, Fries *et al.* 1999). Ryan (1983) reported levels of HxCDD, HpCDD, and OCDD for tissues and milk from piglets that showed high mortality after being raised on a pentachlorophenol-treated wooden floor.

#### 1.4 Characterization of exposure in the workplace

Occupational exposure to pentachlorophenol still occurs in the United States for workers who treat lumber or come in contact with treated lumber in their work activities even

though no production of pentachlorophenol currently takes place in the United States. This exposure has been documented by measurements of pentachlorophenol in workplace air, work surface wipes, and the blood and urine of exposed workers, including exposure information gathered from a group of NIOSH Hazard Evaluation and Technical Assistance (HETA) surveys. Human exposure to pentachlorophenol occurs in occupational settings through dermal contact with the substance or with treated wood products and via inhalation of affected workplace air. Sources of exposure to workers in the past have included (1) production plants, (2) wood treatment facilities, including sawmills, and (3) contact during the use or disposal of the treated wood. Other uses are possible in other industries (e.g., as an algaecide, fungicide, or bactericide), such as leather tanning and paint or glue manufacturing, but no exposure data for these uses were identified. Comparisons of exposures across different processes are not possible in all instances; for example, exposure data for manufacturing are limited to air levels while data for other uses include blood and urine levels in some instances.

Pentachlorophenol absorbed in the human body is excreted primarily in the urine, largely unchanged (ATSDR 2001), and elimination half-lives of pentachlorophenol between 4 and 72 days have been observed (McLean *et al.* 2009a). By-products of pentachlorophenol synthesis, however, are believed to have elimination half-lives of up to 10 years (Collins 2013, McLean *et al.* 2009a). As such, pentachlorophenol measurements in urine or blood can provide estimates of current exposure, and blood measurements of by-products of pentachlorophenol synthesis (e.g., serum dioxin measurements) may provide estimates of past exposure (see Section 1.3).

#### 1.4.1 Pentachlorophenol manufacturing

The most important route of exposure for workers in pentachlorophenol manufacturing is through inhalation. Air sample measurements taken at U.S. manufacturing plants between 1971 and 1983 as part of the NIOSH Dioxin Registry indicate that workers involved in the various stages of production of pentachlorophenol are exposed to the chemical in workplace air (see Appendix B, [Table B-1](#)). Based on the air samples, both area and personal, taken at the factories over several years, exposure varied by work area. Although there was some indication that specific areas had higher airborne levels, results varied for each site and for different years. As described by Marlow *et al.* (1991), the “chlorination area,” i.e., the factory site where phenol is directly chlorinated, had airborne pentachlorophenol levels as high as 4.5 mg/m<sup>3</sup> in 1976, but maximum levels for samples from other years were 0.14 and 0.333 mg/m<sup>3</sup>. A related area tagged “chlorination area, torch burning” reported a single unusually high level of 68.69 mg/m<sup>3</sup>. Workers handling the chemical “blocks” near the end of production or in the packaging area could also be exposed to appreciable levels, up to 14 or 17 mg/m<sup>3</sup>, respectively, while levels in the warehouse were consistently low.

#### 1.4.2 Workers processing or using pentachlorophenol to treat wood products

Very high levels of exposure to pentachlorophenol have been reported for some workers handling the product in preparation for its use as a wood preservative or other end uses. Pentachlorophenol is most commonly used as a solution in petroleum-based products or as its salt sodium pentachlorophenate in a water-based solution. In either case, exposure can occur to workers who process the original product to formulate solutions for end

users. The processing step can be carried out by the same company that produces pentachlorophenol as blocks, flakes, or prills at either the same location or at another facility (KMG 2011), by intermediate processors, or by the end user at a sawmill or wood-treatment facility where solutions are prepared onsite from solid pentachlorophenol. In all instances of use of pentachlorophenol, dermal exposure is much more likely than during manufacture, where inhalation is the more important route.

[Table B-2](#) (Appendix B) lists blood and urine pentachlorophenol levels for workers exposed in various processing and wood treating steps. Wood preservations workers were reported by Cline *et al.* (1989) to have mean serum pentachlorophenol levels of 0.49 ppm. Only urine levels were available for sawmill and wood treatment workers in other studies, but the highest mean value (2.8 ppm) was reported for mixers of concentrated pentachlorophenol at a sawmill in New Zealand (McLean *et al.* 2009b).

The major route of exposure for workers using pentachlorophenol to treat wood is dermal (as much as 95% of total exposure based on urinary chlorophenol levels for sawmill workers exposed dermally) to the solutions used to treat a variety of wood products, such as fence posts, telephone poles, and railroad ties (Demers 2013, Fenske *et al.* 1987). The wood products are treated with solutions of pentachlorophenol in oil or sodium pentachlorophenate in water. The dermal exposure of these workers occurs due to the manner in which pentachlorophenol is used and because of its low vapor pressure, which limits inhalation exposure in these settings mainly to mist from the pentachlorophenol solutions (Demers *et al.* 2006, Santodonato 1986, as cited in ATSDR 2001). Dermal exposure can occur during both pressure and non-pressure treating processes (Williams 1982). Exposure to wood preservatives can occur in a variety of ways, including during mixing and handling of the chemicals, entering pressure-treatment cylinders, preservative spraying or dipping, handling freshly treated wood, cleaning or repairing equipment, or disposing of wastes (Thomasson *et al.* 2006). Wearing of protective equipment (e.g., gloves and aprons) in areas where pentachlorophenol is sprayed or where basic joinery occurs (i.e., construction of roof trusses, pallets, etc.) can help mitigate these exposures (Jones *et al.* 1986).

Inhalation can also occur in these occupational setting during pressure treating of wood; inhalation exposure can occur when the door to the pressure chamber is opened. The greatest inhalation exposure to workers during the wood treatment process occurred during the manual handling of bagged pentachlorophenol in an industrial facility that reported lower, but detectable, levels in the air for other tasks. Measurements in personal workplace air ranged up to 2.00 mg/m<sup>3</sup> with area levels to 3.83 mg/m<sup>3</sup>.

#### 1.4.3 Handlers and users of pentachlorophenol-treated wood

Exposure in workers who have contact with wood that has been treated with pentachlorophenol has been assessed for several groups, including those working at plywood mills and paper mills, as well as fence installers and electrical utility linemen. Levels of urinary pentachlorophenol were elevated for wood preservation workers (handlers) who had a mean value of 0.49 ppm and for employees in a log museum with pentachlorophenol-treated logs (mean of 0.45 ppm) (see Appendix B, [Tables B-2](#) and [B-3](#)).

## 1.5 Non-occupational exposure of people to pentachlorophenol

Exposure to pentachlorophenol is widespread for people living in the United States because of its presence in the environment, and this exposure has been documented by measurements during the last decade or so of levels of pentachlorophenol in blood and urine that reflect current exposure (see Section 1.5.1) and levels in tissues such as liver, brain, kidneys, spleen, and body fat (see Section 2.1.1) that likely reflect more long-term exposure. Dioxin congeners making up the “fingerprint” pattern for current and/or past exposure also have been demonstrated in samples collected in the last 10 years. In addition to this documentation for current or recent exposure of the U.S. general population to pentachlorophenol, the evidence for past exposure, i.e., the 1990s and earlier, is very extensive and indicates levels of exposure more than 10-fold higher than recent exposures. The decrease in exposure from the period 30 to 40 years or more ago to the present is consistent with actions taken by EPA to restrict pentachlorophenol use as a heavy duty preservative, cancelling and restricting non-wood uses in the 1984 and finalizing that in the 1987 Registration Eligibility Decision.

Studies of current or recent exposure are discussed in Section 1.5.1, past exposures in Section 1.5.2, sources of exposure to pentachlorophenol in Section 1.5.3, and occurrences in environmental media in Section 1.5.4. Exposure data tables and regulations are provided at the end of [Appendix B](#).

### 1.5.1 Current or recent exposures and biomonitoring

Data for releases to the environment through the continued use of pentachlorophenol for treatment of wood in limited settings indicate continuing exposure to nearby residents. Direct release of pentachlorophenol into the atmosphere occurs via volatilization from pentachlorophenol-treated wood (ATSDR 2001). Pentachlorophenol also can be released to the atmosphere from incineration of chlorine-containing wastes and from pyrolysis of polyvinyl chlorides. Historically, atmospheric releases of pentachlorophenol (used as a slimicide) from cooling tower waters also has occurred, but pentachlorophenol and its salt are no longer commonly used for this purpose since its use restriction in 1984.

Data for air, dust, urine, and blood measurements for individuals living in the vicinity of active wood treatment facilities in the United States reflect release of pentachlorophenol from these facilities into the environment. Individuals living near sites where pentachlorophenol is used, such as wood-treatment facilities are more likely to be exposed than other members of the general public. Exposure of the general population to pentachlorophenol is most likely to result from inhalation of air or from dietary or non-dietary ingestion. Dermal exposure could occur, but it would not be expected to represent a large part of exposure as it does for workers using pentachlorophenol in wood-treatment facilities. Exposure to individuals is most commonly monitored by collection and analysis of urine samples, which can be analyzed for pentachlorophenol, and by collection and analysis of blood samples for both pentachlorophenol and the dioxin congeners that are by-products of its synthesis. Potential environmental sources of exposure are monitored by measurements of pentachlorophenol in indoor and outdoor air, household dust from floors and other surfaces, and soil outside houses.

Evidence for exposure to pentachlorophenol in the United States after use was restricted comes primarily from samples taken from people and homes near wood treatment facilities, from samples taken from preschool children and from their homes and day care centers, and from the results of the most recent data from the National Health and Nutrition Examination Survey (NHANES).

Dahlgren and coworkers (Dahlgren *et al.* 2007) collected blood samples from 29 residents of a neighborhood adjacent to a wood-treatment plant in a small town in Mississippi where a plant had treated railroad cross ties with creosote and pentachlorophenol from 1904 until the time of the report. Blood levels of dioxin congeners from this study and from 200 controls from the general population of Dallas, Texas are listed in Table 1-4 showing the “fingerprint” pattern of increases in the higher chlorinated dioxins for these studies. The authors also calculated mean levels for attic dust, soil, and sediment samples combined for the area near the facility and compared them with Mississippi Department of Environmental Quality (MDEQ) Soil Cleanup Target Levels. The authors were not able to explain the large TEQ values for these samples other than by the presence of the wood-treatment facility. They also noted that the current blood levels of dioxin congeners could reflect current exposure, prior exposure, or a combination of both.

**Table 1-4. Dioxin congeners in blood of residents near wood-treatment facilities in Mississippi**

Dioxin congener, ppt (lipid based)	Blood levels		Soil levels	
	Near wood treatment, N = 29	General population (Dallas, TX), N = 200	Homes near wood treatment, N = 10	MDEQ soil cleanup targets
TCDD	3.4	3.8	3.068	4.26
HxCDD	71.3	54.5	1669.238	248.60
HpCDD	132.0	45.1	34,788.292	426.00
OCDD	1049	374	271,366.694	4260.00

Source: Dahlgren *et al.* 2007.

Evidence for recent exposure to pentachlorophenol was also reported in a series of studies of preschool children (Wilson *et al.* 2003, 2007) that detected pentachlorophenol in indoor and outdoor air, floor or house dust collected at daycare centers or the children’s homes, and urine from the children living in North Carolina and Ohio. Pentachlorophenol was detectable in these environmental media, and the children in both studies had detectable levels in their urine (Table 1-5) (Wilson *et al.* 2003, Wilson *et al.* 2007).

**Table 1-5. Environmental samples from daycare centers and homes of preschool children**

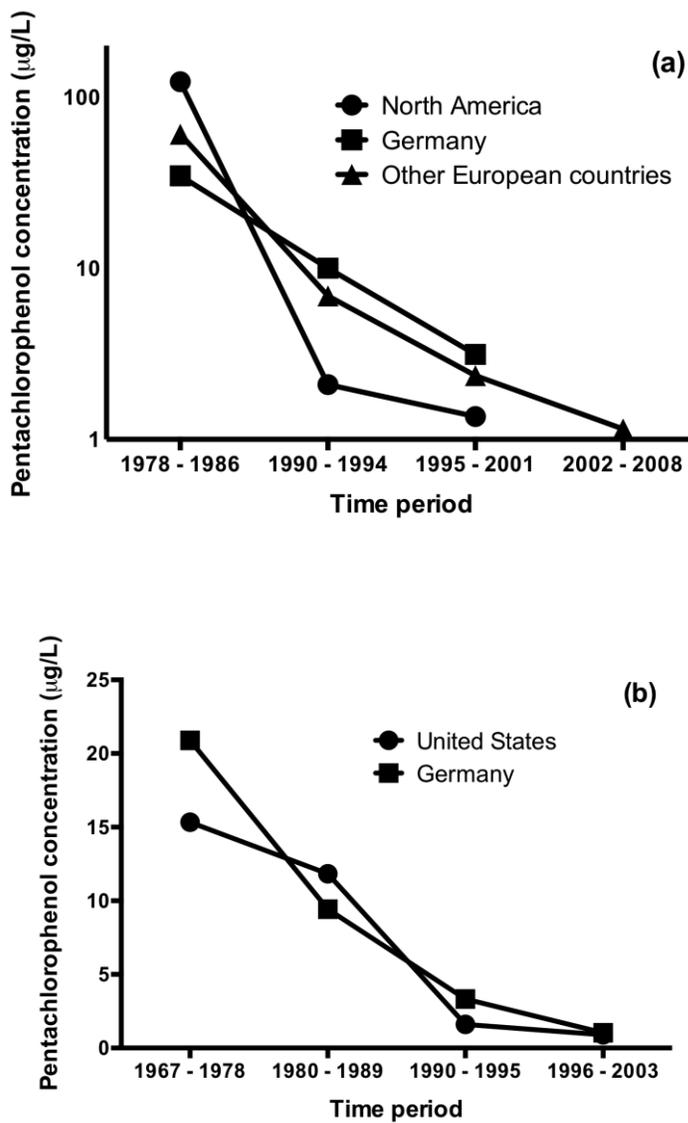
Analyte	Wilson <i>et al.</i> (2003)		Wilson <i>et al.</i> (2007)	
	Day care	Home	Day care NC, OH	Home NC, OH
Indoor air, ng/m <sup>3</sup>	0.918	9.11 <sup>a</sup>	1.16, 1.32	1.50, 2.14
Outdoor air, ng/m <sup>3</sup>	0.480	0.244	0.770, 0.220	0.910, 0.430
House or floor dust, ng/g	0.050	0.135	81.3, 35.6	59.8, 59.8
Urine (48 hr) ng/mL	0.329 ng/mL (0.175–0.666) <sup>a</sup>		0.433–0.993 ng/mL <sup>b</sup>	

<sup>a</sup>Mean (range) for 9 children (25 yrs old). The authors noted that creatinine-adjusted values were not included because of the uncertainty of the applicability of this adjustment to data for young children.

<sup>b</sup>Geometric means for 254 children (120 daycare, 134 home care).

Urinary pentachlorophenol measurement in the most recent NHANES dataset (2003 to 2004) showed levels at the 95<sup>th</sup> percentile of 4.58 µg/L for men and 3.20 µg/L for women and at the 75<sup>th</sup> percentile of 1.32 µg/L for men and 0.880 µg/L for women, but the proportions of results below the limit of detection (0.5 µg/L) were too high (~66%) to allow for calculation of valid geometric means. However, exposure to even 34% of the U.S. population equates to more than 100 million individuals. These results show a decrease in pentachlorophenol levels in the general public compared with results of earlier NHANES studies. Results from NHANES II (1976 to 1980) showed that pentachlorophenol was detectable in 71.6% of the general population, and geometric means for males were 6.7 ng/mL (µg/L) while those for females tended to be lower at 5.9 ng/mL (µg/L) (Kutz *et al.* 1992).

Thus, the evidence of exposure from these recent studies is consistent with continuing exposure to pentachlorophenol for many individuals in the United States based on environmental levels and urinary excretion that are easily measurable. However, the levels of these exposures are generally lower than those from 3 or 4 decades ago due to the greater past uses of pentachlorophenol. Zheng *et al.* (2011) conducted a meta-regression analysis of 80 studies with data from 21 countries published between 1967 and 2010. The trends for urine and blood levels are illustrated in Figure 1-3.



**Figure 1-3. (a) Trends in blood levels for North America, Germany, and other European countries and (b) trends in urinary levels for the United States and Germany**

The data shown in Figure 1-3 illustrate several important points for exposure to pentachlorophenol.

- 1) They indicate that levels of approximately  $1 \mu\text{g/L}$  pentachlorophenol have been reported in blood and urine for samples collected in studies in North America and Europe during the last 10 to 15 years, and these are slightly higher than levels reported recently for children in the United States by Wilson *et al.* (2003, 2007).
- 2) They clearly demonstrate the decrease in levels of exposure over time. Blood levels for North America, Germany, and other European countries (Figure 1-3a) decreased with a global half-life of 3.6 years, while the decrease in urinary levels for the United States and Germany (Figure 1-3b) had a half-life of 5.7 years.

(Zheng *et al.* 2011). The half-lives differed between the two countries with 3.4 years for Germany compared with 8.1 years for the United States.

- 3) The patterns of exposure show considerable similarity for the United States (and North America) compared with European countries. This is reasonable since the United States and most European countries took actions to restrict use of pentachlorophenol in the 1980s and use of pentachlorophenol declined in these areas since that time.

Although no significant gender difference was found for blood levels in the United States (Cline *et al.* 1989), statistically significantly ( $P < 0.019$ ) higher levels were reported for children (ages 2 to 7 years) compared with individuals over 15 years among Canadian Inuit (Sandau *et al.* 2000). Other data indicated that serum pentachlorophenol in children of all ages was approximately twice as high as in their parents. In contrast, mean pentachlorophenol levels in urine have been reported to be higher in adults than in children (Zheng *et al.* 2011).

Recent estimates for potential exposure were calculated by Wilson *et al.* (2007, 2010) based on diet, inhalation, and non-dietary ingestion. Estimates of aggregate potential dose for two groups of children were 7.26 and 8.83 ng/kg/day with approximately half the total exposure resulting from inhalation. Wilson *et al.* estimated potential doses for children in two households for dietary ingestion (37% or 51%), inhalation (54% or 43%), and non-dietary, indirect ingestion (9% or 6%).

#### 1.5.2 Past exposures (more than 15 years ago)

As noted above, more extensive exposure to pentachlorophenol occurred in the past because of its more widespread use as a pesticide for many uses besides treating wood. Pentachlorophenol levels in blood and urine (see Appendix B, [Table B-4](#)) in the range of 10s to 100s of  $\mu\text{g/L}$  for blood and generally around 10  $\mu\text{g/L}$  for urine (see also Figure 1-3 for U.S. and European data) were reported for people living in the United States in studies published from the late 1960s through the 1980s.

Potential sources of exposure to pentachlorophenol in the past are discussed below along with information on environmental occurrence (i.e., air, dust, water, and soil levels) that resulted from those exposures.

#### 1.5.3 Sources of exposure to pentachlorophenol

Current or past exposure to pentachlorophenol is primarily attributable to its release during production and particularly during its processing and use, which result in both occupational exposure to workers and exposure to the general public. Exposures to the general population have been modeled based on exposure from ingestion of food, inhalation of air, and other potential sources. The main routes of exposure to the general public are through inhalation of air and ingestion of food. Releases of pentachlorophenol can result from the presence of treated wood in the environment as well as from the releases that occur during production, processing, and use in treating wood products. Several studies have also reported high levels of exposure to people living in log homes

or other houses treated with pentachlorophenol. Exposure for the general public to pentachlorophenol from food, water, and dust has also been identified.

#### *Modeling studies of exposure to the general population*

A number of modeling studies were carried out using exposure data from the 1980s, when environmental exposure to pentachlorophenol would likely have been higher than for more recent time periods. The estimated daily intakes of pentachlorophenol for adults in the United States was 16 µg/day in a model published by Hattemer-Frey and Travis (1989), which estimated levels in food from environmental distribution of pentachlorophenol and uptake into plants and animals. The range of estimates from Canada (2.6 µg/day), the United Kingdom (4.53 µg/day), and Germany (19.4 µg/day) as well as from the United States might be explained by differences in modeling assumptions as well as from geography and time period of data collection since uses of pentachlorophenol were changing in the late 1980s due to restrictions on use.

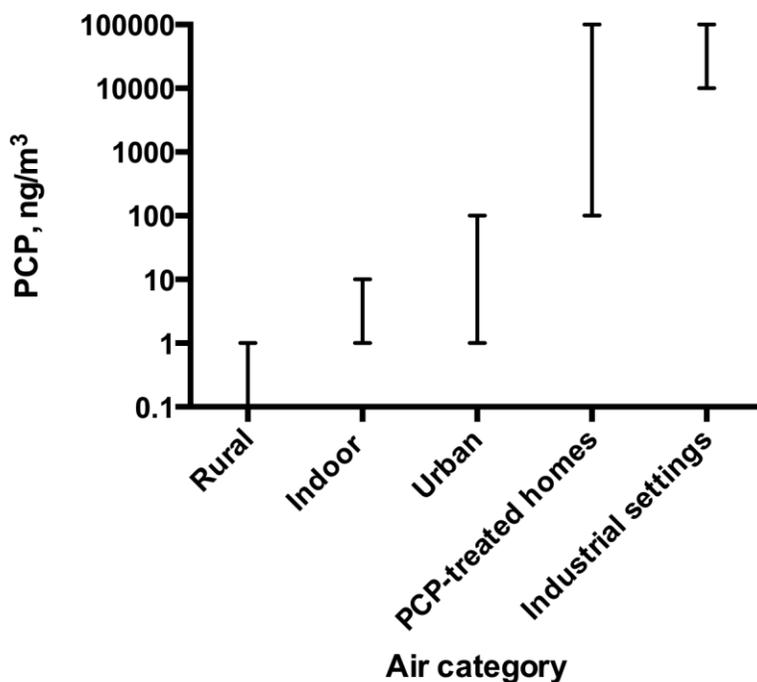
#### *Releases from production, processing, and use to treat wood*

Pentachlorophenol has been widely used throughout the United States historically as a pesticide and currently as a heavy-duty wood preservative. Thus, based on releases of pentachlorophenol at wood treatment facilities in the United States and the widespread distribution of Superfund sites where pentachlorophenol is listed as a site contaminant, dispersion modeling data support likely widespread exposure of the general population to pentachlorophenol. Pentachlorophenol is not currently produced within the United States, but a production plant belonging to a U.S. company operates just across the border from Brownsville, Texas in Matamoros, Mexico, and pentachlorophenol released to the air during production there could travel hundreds of mile into the United States. This is supported by pentachlorophenol emission transport calculations from Hungarian and United Kingdom emission sources and multimedia modeling estimates that indicate pentachlorophenol can be transported over substantial distances (1,500 to 3,000 km [930 to 1,860 mi]) with a half-life in the environment of approximately 1.5 months (Berdowski *et al.* 1997, Duchak *et al.* 2002, and Shatalov *et al.* 2002, as cited in Borysiewicz 2008). The European dispersion modeling data also support possible widespread exposure of the general population to pentachlorophenol from its current use as a wood preservative or because of its past widespread use historically as a pesticide and continuing presence in the environment.

Evidence that pentachlorophenol is currently released to the environment in the United States comes from the U.S. Environmental Protection Agency's (EPA) Toxics Release Inventory (TRI), the National Priorities List (NPL), and the National Response Center (NRC). TRI lists the total reported on- and off-site release of pentachlorophenol as slightly over 96,000 lb from approximately 30 facilities in 2011 (TRI 2013). Releases to land (RCRA Subtitle C landfills) accounted for 92.9% of total releases, off-site disposal for 6.3%, releases to water for 0.5%, and releases to air for 0.3%. Sites with reported on-site releases are concentrated in the southeastern and northwestern United States, with the highest reported release (89,200 lb) by a hazardous waste treatment and disposal facility operating a hazardous waste landfill on the border between Oregon and Washington State. In addition to these sites, 220 Superfund sites on the National Priorities List at

which pentachlorophenol was listed as a site contaminant appear to be distributed throughout the United States and Alaska, but more commonly in the eastern half of the nation (<http://toxmap.nlm.nih.gov/toxmap/main/index.jsp>; enter “pentachlorophenol” in the Chemical Name search box to access a map showing both TRI and NPL sites). Based on a review of spill report data from the National Response Center (NRC 2013) covering the period from January 1, 1990 to the present, 100 chemical spill incidences were reported involving “pentachlorophenol” (N = 97) or “sodium pentachlorophenate” (N = 3).

Although the pentachlorophenol released during production, processing, and use could become a contaminant in any environmental medium (i.e., air, water, soil, and dust), pentachlorophenol in air is likely to result from those releases and to cause exposure to workers and the general public. Pentachlorophenol is detectable in air samples from multiple sources (see Appendix B, [Tables B-5](#) and [B-6](#) and Figure 1-4) ranging from < 1 ng/m<sup>3</sup> in air from rural settings to approximately five orders of magnitude higher in industrial settings where pentachlorophenol is manufactured or used, in homes near sites of use of pentachlorophenol, (e.g., wood treatment facilities, or in log homes treated with pentachlorophenol, as discussed in the section below) (WHO 1987, Zheng *et al.* 2011).



**Figure 1-4. Comparison of pentachlorophenol concentration ranges in air from different sources**

Other evidence for the presence of pentachlorophenol in the environment comes from measurements of household dust and of soil. Sampling of household dust in homes in the vicinity (i.e., within a 1 to 2-mile radius) of pentachlorophenol wood treatment plants has shown significantly elevated levels of pentachlorophenol by-products (Dahlgren *et al.* 2007) (see Section 1.5.1). The highest levels of pentachlorophenol in soil (200,000 and

45,600 µg/kg soil) were collected immediately beneath production sites for pentachlorophenol. Other onsite samples exceeded 10,000 µg/kg; however, levels in soil sampled in the vicinity of pentachlorophenol production facilities were in the range of only 12 to 184 µg/kg.

#### *Exposure from log homes and other treated wood products*

The general population can be exposed to pentachlorophenol released from treated wood, especially if that wood is used for building houses such as log homes. Several publications reported much higher levels of exposure for people living in pentachlorophenol-treated log homes (Hernandez *et al.* 1980, Cline *et al.* 1989) with some blood levels exceeding 1000 µg/L. Similar exposure was reported for workers in the log museum at Fort Stanwix National Monument in Rome, NY (see Appendix B, [Table B-7](#)), but washing the surfaces of the logs with ethyl alcohol to remove crystals of pentachlorophenol greatly reduced exposure for those workers. Some of the highest levels of pentachlorophenol in indoor air (as much as five orders of magnitude higher than ambient levels) (see Figure 1-4) have been associated with log homes treated with pentachlorophenol (WHO 1987, Zheng *et al.* 2011). Concentrations of pentachlorophenol have also been measured in dust sampled from the houses of residents in Germany using wood preservatives at a median value of 13.3 µg/g (N = 65) versus 0.008 µg/g (N = 41) for controls (Krause *et al.* 1989).

Because wood products treated with pentachlorophenol (e.g., utility poles) often are in contact with soil, this provides another potential route of exposure to pentachlorophenol. Exposure of the general population to pentachlorophenol from the soil is less likely than for inhalation of contaminated air, but ATSDR (2001) noted that small children have a tendency to eat soil and to put their hands or foreign objects in their mouths, which could expose them to pentachlorophenol present in the soil or on the objects. Pentachlorophenol can be released to soil via leaching from treated wood products (e.g., utility poles) that results from downward movement within the pole due to movement of the solvent as a result of gravity (ATSDR 2001). In a study of 180 in-use utility poles, surface soil samples generally showed higher levels of pentachlorophenol than subsurface soil samples, and pentachlorophenol soil concentrations decreased exponentially with distance from the pole (EPA 1999) (see Appendix B, [Table B-8](#)).

#### *Exposure from food, water, and dust*

While pentachlorophenol in food was found to be an important source of exposure in the models for environmental exposure, the available data indicate that pentachlorophenol was found at higher levels more frequently in foods from time periods before its restricted use, but that low levels of pentachlorophenol continued to be found in food in the time period after its restricted use (1991 to 3 and 2003). In the period of 1965 to 1970, pentachlorophenol had as much as a 3.3% average positive incidence in food composites in the United States (Duggan and Corneliussen 1972, as cited in WHO 1987). In comparison, in the April 1982 to April 1984 time period, pentachlorophenol was detected in 15% of the foods from 8 United States market basket surveys (Gundersen 1988 as cited in ATSDR 2001). Based on analytical results for U.S. Food and Drug Administration Total Diet Study market baskets 1991 to 1993 through 2003 to 2004

collected between September 1991 and October 2003, pentachlorophenol was found at levels ranging from 0.01 to 0.02 ppm in only 1 out of 44 samples in two food categories: (1) ham, cured (not canned), baked and (2) chicken breast, oven-roasted (skin removed) (FDA 2006). Although both of the earlier samples reported more frequent detection of pentachlorophenol in foods compared with the period after 1990, it is not clear why the earliest period (1965 to 1970) had a lower percentage than the period from 1982 to 1984.

Pentachlorophenol was also reported in a wide variety of foods such as meats, fish, dairy products, grains and vegetables (see Appendix B, [Table B-9](#)) in studies from Canada, the United Kingdom, and Germany from the 1980's. Levels of pentachlorophenol in food varied in the different studies and no clear patterns were observed for specific types of food or geographical areas. In a more recent report, no pentachlorophenol was detected in 1995 to 1996 in a Danish National Pesticide Monitoring Program that sampled fruits, vegetables, dairy foods, meats, and other foods (ATSDR 2001).

Pentachlorophenol has been detected in drinking water supplies as well as in groundwater and surface water. The data reported here are for measurements made before restrictions were placed on the use of pentachlorophenol and are reported from several secondary sources; no recent reports of levels in water were identified. Pentachlorophenol concentrations in drinking water have been reported to range from < 1 to 50 µg/L (WHO 1987, ATSDR 2001), which can result in part from synthesis of pentachlorophenol due to chlorination of phenolic compounds during water treatment (Detrick 1977, Smith *et al.* 1976, as cited in ATSDR 2001) (see Appendix B, [Table B-10](#)). Pentachlorophenol has been detected in groundwater at levels ranging from 0.6 to 19,000 µg/L (ATSDR 2001, WHO 1987). Higher levels were reported for groundwater near industrial areas such as wood preserving facilities. Pentachlorophenol levels in surface water have been reported to range from non-detectable to 10,500 µg/L (WHO 1987, Zheng *et al.* 2011).

Releases of pentachlorophenol to surface water can occur through direct discharge and entry from nonpoint sources such as treated wood. Additionally, wet deposition from the atmosphere and runoff and leaching from soil also can transport pentachlorophenol to surface water (ATSDR 2001).

Pentachlorophenol has been detected on household dust, as noted above, but Liebl *et al.* (1996, as cited by Schnelle-Kreis *et al.* 2000) did not find a correlation between pentachlorophenol dust concentrations and pentachlorophenol in blood plasma. Ingestion of non-dietary pentachlorophenol, such as that associated with dust, has been considered a minor contributor to exposure (Wilson *et al.* 2007, 2010), but it might be more of a factor for small children because of their contact with dust on floors.

#### *Other sources of exposure*

Pentachlorophenol has been detected in commercial samples (9 of 65 samples at concentrations ranging from 100 to 2,700 mg/kg) of paints used on children's toys in the United States in a study from the 1970's (van Langeveld 1975, as cited in WHO 1987) and at low levels in clothing samples (concentrations ranging from 0.015 to 0.96 mg/kg) from Switzerland (Siegwart 1983, as cited in WHO 1987).

A potential source of pentachlorophenol exposure to people that was not taken into account in the models described above is the metabolic transformation of other chlorinated compounds within the body (WHO 1987). The chlorinated compounds that can give rise to pentachlorophenol include hexachlorobenzene, pentachlorobenzene, pentachloronitrobenzene,  $\gamma$ -2,3,4,5,6-pentachlorocyclohexene, lindane, and other hexachlorocyclohexanes. WHO suggested that this source of endogenous production of pentachlorophenol, particularly from hexachlorobenzene, could explain the low level of pentachlorophenol excretion from people with no apparent exposure to pentachlorophenol; however, the extent to which this occurs has not been established.

## 1.6 Synthesis and summary

U.S. exposure to pentachlorophenol and by-products of its synthesis is significant based on available biomonitoring data, its widespread past use as a pesticide, and current use in treated-wood products. Exposures have decreased by at least an order of magnitude in recent years (e.g., the last 10 to 15 years) compared with exposures prior to restrictions on use of pentachlorophenol to treat certain wood products in the 1980s. People living near wood treatment facilities that use pentachlorophenol may be exposed through the air or through soil contamination. Modeling studies of pentachlorophenol intake by humans in the United States indicate that human exposure in the 1980s or before occurred primarily from the food chain (i.e., fruits, grains, and vegetables), but more current data indicate that this source has declined in importance.

Synthesis of pentachlorophenol involves conditions of high temperatures and pressure that result in formation of additional chlorinated aromatic molecules, particularly dibenzo-*p*-dioxins and dibenzofurans, as by-products of its synthesis. Human exposure to pentachlorophenol and its by-products occurs in occupational settings via inhalation of affected workplace air and dermal contact with the substance or with treated wood products. Occupational exposure has been documented by measurements of pentachlorophenol in workplace air, on work surface wipes, and in the blood and urine of exposed workers. Individuals exposed to pentachlorophenol occupationally also have a pattern of increased by-products, particularly the hexa-, hepta-, and octachlorodioxin congeners, that reflect their long-term exposure.

Pentachlorophenol was ubiquitously distributed in the environment in the past as evidenced by measured levels reported for surface water, groundwater, drinking water, ambient and indoor air, soil, sediment, and food from several countries and time periods. Current exposures are generally lower than those in the past, but exposures to workers using pentachlorophenol and to the general public still occur for a significant number of people living in the United States. Levels of pentachlorophenol in indoor air in industrial settings can be as much as five orders of magnitude higher than ambient levels. The by-products of pentachlorophenol manufacture have been detected in people exposed to pentachlorophenol occupationally in the past or from exposures of the general public to air and dust, particularly at sites near production or use of pentachlorophenol.

## 2 Disposition and Toxicokinetics

Disposition and toxicokinetics discuss how a xenobiotic chemical can enter and leave the body, what happens to it once it is in the body, and the rates of these processes. Section 2.1 discusses the absorption, distribution, and excretion of pentachlorophenol.

Metabolism is discussed in Section 2.2. Toxicokinetic models were described in humans and laboratory animals in several studies and are reviewed in Section 2.3. These data are important because they help identify the various factors that affect the toxicity of a chemical. These factors include routes and rates of absorption, tissue concentrations and their temporal changes, reactive metabolites, metabolic activation and detoxification reactions, routes of elimination, and gender and/or species differences in these factors. The mechanistic implications of these data are discussed in Section 5.

### 2.1 Absorption, distribution, and excretion

Several studies were available that described the absorption, distribution, and excretion of pentachlorophenol in humans and experimental animals and are reviewed below. The data are generally consistent across studies and show that pentachlorophenol is well absorbed, widely distributed, and excreted primarily in the urine.

#### 2.1.1 Human studies

Humans are exposed to pentachlorophenol from a variety of sources (see Section 1) and by different routes. Pentachlorophenol and other chlorophenols are well absorbed from all routes of exposure (ingestion, inhalation, and dermal). The dermal route is the most important for sawmill or other timber-processing workers who handle treated wood (Demers *et al.* 2006, Fenske *et al.* 1987, Kauppinen and Lindroos 1985). The inhalation route may be more important for pentachlorophenol producers or residents living in treated homes (IARC 1991, Ruder and Yiin 2011, Wilson *et al.* 2007).

Pentachlorophenol has been detected in blood and/or urine samples collected from the general population or from people living in log homes (Cline *et al.* 1989, Gerhard *et al.* 1999, Gomez-Catalan *et al.* 1987, Hosenfeld 1986, Peper *et al.* 1999, Reigner *et al.* 1992a, Thompson and Treble 1994, 1996, To-Figueras *et al.* 1997, Treble and Thompson 1996, Wilson *et al.* 2007), as well as from accidental (Gray *et al.* 1985, Smith *et al.* 1996), or occupational exposures (Demers *et al.* 2006, Fenske *et al.* 1987, Hertzman *et al.* 1988, Hertzman *et al.* 1997, Jones *et al.* 1986, Kalman and Horstman 1983, Kauppinen and Lindroos 1985, Pekari *et al.* 1991, Reigner *et al.* 1992a, Teschke *et al.* 1989, Teschke *et al.* 1996). Absorption from the respiratory tract was 76% to 88% in two human volunteers exposed in an enclosed area for 45 minutes (Casarett *et al.* 1969). About 90% of pentachlorophenol ingested by four human volunteers was detected in feces (~4%) and urine (~86%); the large percentage recovered in the urine indicates that absorption from the gastrointestinal tract is highly efficient (Braun *et al.* 1979). Evidence of toxicologically significant dermal absorption of pentachlorophenol comes from case reports of fatal poisonings due to extensive skin contact with pentachlorophenol (Gray *et al.* 1985, Jones *et al.* 1986, Smith *et al.* 1996, Wood *et al.* 1983). Horstman *et al.* (1989) reported that 62% of pentachlorophenol in diesel oil and 16% of sodium pentachlorophenate in an aqueous solution penetrated human skin *in vitro* over a 24-hour

period. Wester *et al.* (1993) reported that 0.6% to 1.5% of pentachlorophenol in acetone accumulated in the plasma receptor fluid while 2.6% to 3.7% accumulated in human skin *in vitro*, but the authors noted that receptor fluid accumulation greatly underestimated *in vivo* absorption for pentachlorophenol because of low solubility in the receptor fluid. Horstman *et al.* (1989) reported that *in vitro* penetration of pentachlorophenol and tetrachlorophenol through human cadaver skin were similar in diesel oil, but in a water-based commercial preparation, penetration of tetrachlorophenol was about twice that of pentachlorophenol.

Data for distribution of pentachlorophenol in human tissues are available from autopsies of individuals who died from pentachlorophenol intoxication or from other causes. These data show that pentachlorophenol was widely distributed, was bound extensively to plasma proteins and could cross the blood-brain and placental barriers, but it did not accumulate appreciably in any tissues. WHO (1987) reported that pentachlorophenol was detected in the liver, kidneys, lungs, and brain of individuals who died from pentachlorophenol poisoning. The data did not present clear evidence of accumulation in these tissues because the concentrations were similar to those observed in the blood. One study in Germany measured background levels of pentachlorophenol in urine and tissues collected during the autopsy of 21 people (Grimm *et al.* 1981, as cited in ATSDR 2001). The highest concentrations were detected in liver (0.067 µg/g), kidneys (0.043 µg/g), brain (0.047 µg/g), spleen (0.019 µg/g), and body fat (0.013 µg/g). The median level in the blood was 0.033 µg/mL. Geyer *et al.* (1987) used data from Grimm *et al.* (1981) and Uhl *et al.* (1986) and calculated bioconcentration factors for pentachlorophenol. The highest bioconcentration factors were for liver (5.7 to 7.0), kidneys (4.0), and brain (3.3 to 4.0) and indicate limited accumulation in body tissues. Other studies have shown that pentachlorophenol can cross the placental barrier with concentration ratios of 0.94 to 1.44 reported for maternal blood to cord blood (Gruenewald *et al.* 2003, Park *et al.* 2008). Uhl *et al.* (1986) reported high plasma protein binding (> 96%) in three volunteers that were administered single oral doses of 3.9 to 18.8 mg of pentachlorophenol. High plasma protein binding limits the amount available to the liver and kidneys for metabolism and excretion and, thus, may prolong retention in the body (ATSDR 2001).

Studies of various human populations exposed to pentachlorophenol show that urine is the primary route of excretion (Benvenue *et al.* 1967, Cline *et al.* 1989, Gomez-Catalan *et al.* 1987, Jones *et al.* 1986, Kalman and Horstman 1983, Pekari *et al.* 1991, Reigner *et al.* 1992a, Thompson and Treble 1994, 1996, Treble and Thompson 1996, Uhl *et al.* 1986, Wilson *et al.* 2007). Studies using human volunteers (oral or inhalation exposure) reported that 76% to 86% of the administered dose was excreted in the urine within 5 to 7 days while about 4% was excreted in the feces (Braun *et al.* 1979, Casarett *et al.* 1969). Uhl *et al.* (1986) showed that alkalinization of the urine resulted in a distinct increase in urinary excretion of pentachlorophenol. Half-lives reported for urinary excretion of pentachlorophenol in humans show considerable variation ranging from 33 hours (Braun *et al.* 1979) to 20 days (Uhl *et al.* 1986), which may be partially explained by differences in study inclusion criteria, urine pH, diet, chemical form of pentachlorophenol, and vehicle (see Section 2.3).

### 2.1.2 Laboratory animal studies

Pentachlorophenol is well absorbed in laboratory animals following oral, inhalation, or dermal exposure with no clear species differences (Table 2-1). The oral absorption efficiency showed some variability but was greater than 90% in most studies in rats, mice, and monkeys. Lower absorption was reported when the chemical was administered in feed or mixed with soil. One inhalation study in rats indicated that at least 70% to 75% of the administered dose was absorbed (Hoben *et al.* 1976). Lower absorption was observed for dermal exposure: about 29% of the dose applied to the skin of monkeys (Wester *et al.* 1993) and 29% to 50% applied to the skin of pigs (Qiao *et al.* 1997, Qiao and Riviere 2002) was absorbed when nonocclusive conditions were used. However, under occlusive conditions, dermal absorption from a soil-based mixture was 100% in pigs (Qiao *et al.* 1997).

**Table 2-1. Absorption of pentachlorophenol administered to laboratory animals**

Species (sex)	Exposure		% Dose absorbed	Reference
	Route	Dose/conc.		
Sprague-Dawley rats (M/F)	gavage	10–100 mg/kg	98–99	Braun <i>et al.</i> 1977
Wistar rats (M)	drinking water	1.4 mM [370 µg/mL]	90	Meerman <i>et al.</i> 1983
Sprague-Dawley rats (M)	gavage	2.5 mg/kg	91–97	Reigner <i>et al.</i> 1991
Sprague-Dawley rats (M)	drinking water	30 µg/mL	75–107	Reigner <i>et al.</i> 1992b
F344 rats (M)	gavage feed	9.5–38 mg/kg 302–1010 ppm	86–100 30–52	Yuan <i>et al.</i> 1994
Sprague-Dawley rats (M)	gavage (in soil)	0.1–0.2 mg/kg	36–77	Pu <i>et al.</i> 2003
B6C3F <sub>1</sub> mice (M)	gavage	15 mg/kg	106	Reigner <i>et al.</i> 1992c
Rhesus monkeys (M/F)	gavage	10 mg/kg	96–103	Braun and Sauerhoff 1976
Sprague-Dawley rats (M)	inhalation	5.7–1 mg/kg	70–75	Hoben <i>et al.</i> 1976
Rhesus monkeys (F)	dermal	0.7–0.8 µg/cm <sup>2</sup>	24–29 <sup>a</sup>	Wester <i>et al.</i> 1993
Pigs (F)	dermal	300 µg	29–101 <sup>b</sup>	Qiao <i>et al.</i> 1997
Pigs (F)	dermal	300 µg	50 <sup>c</sup>	Qiao and Riviere 2002

<sup>a</sup> Applied in soil (24%) or dissolved in acetone (29%) for 24 hours and monitored for 14 days.

<sup>b</sup> Applied in soil under nonocclusive (29%) and occlusive (101%) conditions and monitored for 17 days.

<sup>c</sup> Applied in ethanol vehicle and monitored for 17 days.

Tissue distribution data were available for rats (Braun *et al.* 1977, Hoben *et al.* 1976, Larsen *et al.* 1972), mice (Jakobson and Yllner 1971), chickens (Stedman *et al.* 1980), bats (Shore *et al.* 1991), sheep (Wilson *et al.* 1982), pigs (Qiao *et al.* 1997, Qiao and Riviere 2002), and monkeys (Braun and Sauerhoff 1976). In general, these data indicate that pentachlorophenol is widely distributed but does not accumulate in body tissues. Low tissue accumulation has been attributed to extensive binding of pentachlorophenol to plasma proteins (97% to 99% in rats) (Braun *et al.* 1977, Gomez-Catalan *et al.* 1991). The highest relative concentrations were usually found in organs associated with metabolism and excretion and included the liver, gall bladder, kidneys, and

gastrointestinal tract. Distribution data for laboratory animals are summarized in Table 2-2.

**Table 2-2. Distribution of pentachlorophenol in laboratory animals**

Species (route)	Dose/ conc.	Sample time	Tissues	Conc. ( $\mu\text{g/g}$ tissue)	Reference
Chicken (feed)	1000 ppm	8 wk	Kidneys Liver	33.7 17	Stedman <i>et al.</i> 1980
Sheep (intraruminal)	10 mg/kg	36 hr	Pericardial fat Lungs Adrenal glands Kidneys Subcutaneous fat Omental fat Intestinal lymph nodes Liver	96 <sup>a</sup> 59 48 44 41 29 21–25 23	Wilson <i>et al.</i> 1982
Mouse (intraperitoneal)	15–37 mg/kg	4–30 d	Gall bladder Liver Stomach Intestines Kidneys	60–90 3–26 10–21 8 0.3–8	Jakobson and Yllner 1971
Rat (gavage)	31–40 mg/kg	10 d	Liver Kidneys Stomach + intestines	$\sim 0.24$ <sup>b,c</sup> $\sim 0.18$ $\sim 0.1$	Larsen <i>et al.</i> 1972
Rat (inhalation)	5.7–1 mg/kg	72 hr	Liver Lungs	$\sim 20$ <sup>c,d</sup> $\sim 1.8$	Hoben <i>et al.</i> 1976
Rat (gavage)	10 mg/kg	9 d	Liver Kidneys	0.315 <sup>d</sup> 0.045	Braun <i>et al.</i> 1977
Bat (dermal)	65 mg/g <sup>e</sup>	24 hr	Subcutaneous fat Liver Kidneys Body	15.1–98.9 nd–64.7 nd–24.8 3.19–29.8	Shore <i>et al.</i> 1991
Pig (dermal)	40 $\mu\text{g}/\text{cm}^2$	17 d	Liver Lungs Large intestine Small intestine Kidneys	5.15 <sup>d</sup> 1.79 0.53 0.42 0.22	Qiao <i>et al.</i> 1997
Pig (dermal)	40 $\mu\text{g}/\text{cm}^2$	11 d	Liver Ovaries Kidneys Lungs Gall bladder Uterus Small intestines Large intestines	0.0128 <sup>b</sup> 0.0038 0.0034 0.0032 0.0026 0.0025 0.0024 0.0018	Qiao and Riviere 2002
Monkey (gavage)	10 mg/kg	15 d	Small intestines Large intestines Liver	5.0 <sup>d</sup> 2.6 1.1	Braun and Sauerhoff 1976

<sup>a</sup> 47% of the dose remained in the digestive tract including 37% in the rumen.

<sup>b</sup> Values represent the mean percent of administered activity per gram of tissue.

<sup>c</sup> Values were estimated from a figure.

<sup>d</sup> Values are the percentage of administered dose.

<sup>e</sup> Surface concentration measured in scrapings from treated wooden roost boxes (all bats died within 24 hr).

Studies in laboratory animals consistently show that pentachlorophenol is primarily excreted in the urine either unchanged or as metabolites (see Section 2.2). Moderate amounts of pentachlorophenol are excreted in the feces while trace amounts may be excreted in exhaled breath. Distribution data indicate that enterohepatic circulation and biliary excretion are involved. Most of the recovered dose was excreted within 24 hours in rodents. Studies in monkeys showed slower excretion compared with rodents. Treatment of monkeys with cholestyramine (an ion-exchange resin that binds phenols) resulted in a 2- to 7-fold decrease in urinary excretion, 9- to 18-fold increase in fecal excretion, and a 40% overall increase in pentachlorophenol excretion (Ballhorn *et al.* 1981, Rozman *et al.* 1982). Although the study authors attributed these effects to interruption of enterohepatic circulation and enhancement of intestinal elimination, it is more likely explained by decreased absorption of pentachlorophenol bound to cholestyramine and subsequent elimination in the feces. Data are summarized in Table 2-3.

**Table 2-3. Excretion of PCP in laboratory animals**

Species (sex)	Route	Duration (days) <sup>a</sup>	Excretion (% dose)			Reference
			Urine	Feces	Exhaled	
Mice (F)	i.p.	3–7	72–83	3.8–11.5	< 0.05	Jakobson and Yllner 1971
Mice (NR)	i.p.	4	79 <sup>b</sup>	NR	nd	Ahlborg <i>et al.</i> 1974
	oral	4	26 <sup>b</sup>	NR	nd	
Mice (M)	oral	2	54.6–57.4 <sup>c</sup>	6.4–8.8	NR	Reigner <i>et al.</i> 1992c
Rat (F)	oral	10	68.3	9.2–13.2	< 0.04	Larsen <i>et al.</i> 1972
Rat (NR)	i.p.	4	84 <sup>b</sup>	NR	nd	Ahlborg <i>et al.</i> 1974
	oral	4	46 <sup>b</sup>	NR	nd	
Rat (M/F)	oral	9	64–79.8	18.6–33.6	0.2	Braun <i>et al.</i> 1977
Rat (M)	i.v.	3	57.9	10.1	NR	Reigner <i>et al.</i> 1991
	oral	3	51.5	9.3	NR	
Rabbit (NR)	oral	7–12	47.7–66.1	0.8–4.0	NR	Deichmann <i>et al.</i> 1942
Monkey (M/F)	oral	7–15	68.6–78	11.9–23.8	NR	Braun and Sauerhoff 1976
Monkey (M)	oral	7	31.6–35.6	2–3.5	NR	Ballhorn <i>et al.</i> 1981
Monkey (M)	oral	6	35.4 <sup>d</sup>	2.8 <sup>d</sup>	NR	Rozman <i>et al.</i> 1982

i.p. = intraperitoneal injection, i.v. = intravenous injection, nd = not detected, NR = not reported.

<sup>a</sup> Following a single dose.

<sup>b</sup> Estimated from a graph.

<sup>c</sup> Sum of  $\beta$ -glucuronidase and sulfatase data for pentachlorophenol and tetrachlorohydroquinone.

<sup>d</sup> Animals were equipped with a bile duct bypass and ~ 70% of dose was detected in the bile.

## 2.2 Metabolism

Pentachlorophenol is excreted unchanged in the urine or is metabolized in the liver via oxidative and reductive dechlorination and/or conjugation. Enzymes involved in metabolism include cytochromes P450, peroxidases and hydroperoxides, UDP-glucuronosyl transferase and sulfotransferases (Ahlborg and Thunberg 1978, Mehmood *et al.* 1996, Reigner *et al.* 1991, Samokyszyn *et al.* 1995, Tsai *et al.* 2001). Metabolism was enhanced to different extents by pretreating with various inducers of P450 (Ahlborg

*et al.* 1978, Ahlborg and Thunberg 1978, Tsai *et al.* 2001, van Ommen *et al.* 1986a). Metabolites included tetrachlorohydroquinone, sulfate or glucuronide conjugates of pentachlorophenol and tetrachlorohydroquinone, and tetrachlorocatechol (ATSDR 2001, Reigner *et al.* 1992c, Renner and Hopfer 1990); however, there are qualitative and quantitative species differences that may partially explain differences in toxicity. Tetrachlorohydroquinone and tetrachlorocatechol may be further oxidized to form semiquinones and benzoquinones. The only metabolites confirmed in humans *in vivo* are the glucuronide or sulfate conjugates of pentachlorophenol; however, *in vitro* studies demonstrated that human microsomes can metabolize pentachlorophenol to tetrachlorohydroquinone. In addition, pentachlorophenol is a metabolite of lindane ( $\gamma$ -hexachlorocyclohexane),  $\gamma$ -2,3,4,5,6-pentachlorocyclohexene, hexachlorobenzene, pentachlorobenzene, and pentachloronitrobenzene (Betts *et al.* 1955, Engst *et al.* 1976, Stewart and Smith 1986, van Ommen *et al.* 1989). This section identifies the known and possible metabolic pathways of pentachlorophenol. Mechanistic implications are discussed in Section 5.

### 2.2.1 Humans

Pentachlorophenol metabolism in humans has not been extensively studied and is limited to two studies in human volunteers following a single dose of pure pentachlorophenol (Braun *et al.* 1979, Uhl *et al.* 1986) and a few chronic studies of non-occupational or occupational exposure to mixed chlorophenols (Gomez-Catalan *et al.* 1987, Noren and Sjoval 1987, Pekari *et al.* 1991). Only one study included more than four subjects, thus, the small sample sizes likely account for some of the variability.

Overall, the data indicate that conjugation with glucuronic acid is the major metabolic pathway in humans while excretion of unconjugated compound is a relatively minor pathway (Reigner *et al.* 1992a). Sulfate conjugates were only measured in one study but also were important, especially in workers exposed to lower pentachlorophenol concentrations in that study (Pekari *et al.* 1991). Tetrachlorohydroquinone was not detected in most of the studies and is a minor metabolite at best. The relative amounts of pentachlorophenol and its conjugated metabolites reported in human urine samples are shown in Table 2-4. Only one study indicated that most of the administered dose was excreted unchanged (Braun *et al.* 1979). Braun *et al.* used the same urine sample extraction and storage techniques that were used in a study in monkeys (Braun and Sauerhoff 1976) that reported no glucuronide metabolites in the urine (see Section 2.2.2). Reigner *et al.* (1992a) suggested that the different results reported by Braun *et al.* (1979) and Uhl *et al.* (1986) could be explained by the instability of the glucuronide conjugates and differences in urine sample treatment methods (see further discussion below).

**Table 2-4. Relative amounts of pentachlorophenol and conjugated metabolites recovered in human urine**

Reference	Route/subjects	Number of subjects	Urinary metabolites (%)	
			PCP	PCP conjugate <sup>a</sup>
Braun <i>et al.</i> 1979	oral/volunteers	4	86	14
Uhl <i>et al.</i> 1986	oral/volunteers	1	~35	~65
Gomez-Catalan <i>et al.</i> 1987	ns/general population	30	13.2	86.8
	ns/occupational	3	9.3	90.7
Noren and Sjobvall 1987	ns/non-occupational	3	1.5	98.5
Pekari <i>et al.</i> 1991	dermal/sawmill workers	7	23.8–30.9	69.1–76.2 <sup>b</sup>

ns = not specified, PCP = pentachlorophenol.

<sup>a</sup> Glucuronide conjugate unless otherwise noted.

<sup>b</sup> Includes both sulfate and glucuronide conjugates (sulfate was dominant but proportion of glucuronide conjugates increased at higher exposure levels).

Studies that examined metabolism of pentachlorophenol (> 99% purity) in human volunteers following a single exposure reported that only the unmetabolized compound and its glucuronide conjugate were detected in urine (Braun *et al.* 1979, Uhl *et al.* 1986). No traces of tetrachlorohydroquinone, tetrachlorophenols, or other metabolites were observed in these studies. Braun *et al.* (1979) reported that 74% of the administered dose (86% of the urinary excretion) was excreted unchanged after 7 days. Uhl *et al.* (1986) reported that the percentage of pentachlorophenol eliminated as the conjugate increased from about 25% to 40% over the first 10 days and reached a steady state of about 65% from day 12 to 37. Thus, the difference between the Braun *et al.* and the Uhl *et al.* study after 7 days is not as great as it appears in Table 2-4. Uhl *et al.* also reported that 61% to 70% of pentachlorophenol was excreted as the glucuronide in 13 non-occupationally exposed individuals but the source of these data was not clearly described.

Studies of chronic non-occupational or occupational exposure to chlorophenols also reported that the majority of pentachlorophenol was excreted as conjugates and that tetrachlorohydroquinone was not detected (Gomez-Catalan *et al.* 1987, Noren and Sjobvall 1987, Pekari *et al.* 1991). Two of the three studies showed an increase in the percentage excreted in conjugated form compared with the single dose study of Uhl *et al.* (1986) and may indicate toxicokinetic differences between acute and chronic exposures. Pekari *et al.* (1991) reported that sulfate conjugates were dominant in workers exposed to lower pentachlorophenol concentrations while the proportion of glucuronide conjugates increased with increasing chlorophenol concentrations. Because sulfation is a high affinity-low capacity process and glucuronidation is a low affinity-high capacity process, low concentrations would favor sulfation.

The variability among studies in the relative amounts excreted as the unconjugated versus the conjugated form may be partially explained by the different treatment methods used for urine samples, urine pH of the subjects, kinetic differences following single versus chronic exposures, and other study protocol differences (Gomez-Catalan *et al.* 1987, Reigner *et al.* 1992a). Subjects used in the Braun *et al.* study fasted prior to exposure and were known to have minimal exposure to pentachlorophenol prior to the study

(confirmed by urine analysis). Urine samples also were acidified and frozen prior to analysis. The glucuronide conjugates are unstable due to pH-dependent hydrolysis; therefore, analysis of urine samples generally leads to an underestimation of the conjugate originally excreted (Lilienblum 1985). Norén and Sjövall (1987) also reported that pentachlorophenol was released from the conjugate during storage at room temperatures and after repeated freezing and thawing of urine samples. Therefore, the free versus conjugated amounts in these studies should be regarded as estimates that likely overestimate the free pentachlorophenol.

Although most studies have not detected tetrachlorohydroquinone as a metabolite of pentachlorophenol in humans, Edgerton *et al.* (1979) reported that tetrachlorohydroquinone was detected at low concentrations in 4 of 11 urine samples collected from the general population. Ahlborg *et al.* (1974) also detected low levels of tetrachlorohydroquinone in urine samples from two workers (described as spraymen) exposed to pentachlorophenol on the job. However, interpretation of these studies is hampered by possible exposures to other chlorobenzenes or chlorophenols and the small sample size. Levels of pentachlorophenol were 2 to 150 times higher than the levels of tetrachlorohydroquinone detected in these samples. Edgerton *et al.* also detected tetrachlorophenols in 10 of the 11 samples.

*In vitro* studies indicate that human microsomes can metabolize pentachlorophenol to tetrachlorohydroquinone and provide some support for the findings reported by Ahlborg *et al.* (1974) and Edgerton *et al.* (1979). Juhl *et al.* (1985) demonstrated that human liver homogenates metabolized pentachlorophenol to tetrachlorohydroquinone and that the pharmacokinetics were comparable to results obtained with rat liver homogenates. Mehmood *et al.* (1996) also demonstrated that microsomal fractions and whole cells of *Saccharomyces cerevisiae* expressing human cytochrome P450 3A4 (CYP3A4) metabolized pentachlorophenol to tetrachlorohydroquinone. The rate of metabolism was low but no metabolism was detected in transformants lacking CYP3A4; however, the purity of the pentachlorophenol used in this study was not specified. Dubois *et al.* (1997, 1996) also demonstrated that pentachlorophenol was a strong inducer of CYP3A7 in human HepG2 cells but metabolites were not measured in that study.

### 2.2.2 Laboratory animals

Numerous metabolism studies of pentachlorophenol have been conducted in experimental animals. Pentachlorophenol is more extensively metabolized in rodents than in other species but the relative amounts of unmetabolized pentachlorophenol and its metabolites detected in the urine showed considerable differences among the various studies (Table 2-5). For example, Braun *et al.* (1977) reported that 48% of a single oral dose of 100 mg/kg administered to rats was excreted as unchanged pentachlorophenol, 6% as the glucuronide conjugate, and 10% as tetrachlorohydroquinone. In contrast, Reigner *et al.* (1991) reported that only about 5% of a single oral dose of 2.5 mg/kg was excreted as unchanged pentachlorophenol and about 90% of the conjugated metabolites were sulfates. The one inhalation study reviewed indicated that 70% to 75% of the administered dose was excreted as pentachlorophenol with only trace amounts of tetrachlorohydroquinone (Hoben *et al.* 1976). Lin *et al.* (1996, 1997, 1999) demonstrated that tetrachlorohydroquinone and tetrachlorocatechol could be further oxidized to their

corresponding benzo-semiquinones and benzoquinones in rats and mice. In rabbits, one study reported considerable amounts of pentachlorophenol glucuronide in urine (Tashiro *et al.* 1970) while two other studies reported little or no evidence of glucuronidation (Betts *et al.* 1955, Deichmann *et al.* 1942). Pentachlorophenol was excreted unchanged in the urine of monkeys (Braun and Sauerhoff 1976). Cravedi *et al.* (1999) reported that trout exposed to pentachlorophenol orally excreted the unchanged compound along with its glucuronide and sulfate conjugates. Urinary metabolites reported in experimental animals are summarized in Table 2-6 and metabolic pathways are shown in Figure 2-1.

Some of the variability may be explained by differences in sample treatment methods. Glucuronide and sulfate conjugates are unstable in acidic conditions (Reigner *et al.* 1991). Studies that extracted pentachlorophenol and tetrachlorohydroquinone after acidification with hydrochloric acid (Ahlborg *et al.* 1974, Braun *et al.* 1977) reported higher concentrations of unconjugated pentachlorophenol and tetrachlorohydroquinone than studies that performed urinary extraction after addition of a pH 7.4 buffer (Reigner *et al.* 1991). This also may explain why no conjugates of pentachlorophenol were found in the urine of monkeys since urine was extracted after acidification. Differences in the relative amounts of tetrachlorohydroquinone may be explained by the instability of this chemical in urine. Reigner *et al.* (1991) used ascorbic acid and EDTA to prevent tetrachlorohydroquinone degradation. Reigner *et al.* also was the only study to report sulfate conjugates in rodents; however, these authors noted that their results provided only indirect evidence for the occurrence of these metabolites even though the sulfatase enzyme used was considered specific (i.e., no  $\beta$ -glucuronidase activity).

Pentachlorophenol induced CYP1A1 in fetal rat hepatocytes and CYP2B in quail hepatocytes *in vitro* (Dubois *et al.* 1997, Dubois *et al.* 1996). Van Ommen *et al.* (1989, 1986a, 1988) conducted *in vitro* metabolism studies with microsomes derived from rats treated with different inducers and demonstrated that P450b (CYP2B2), P450d (CYP1A2), and P450p (CYP3A1) were effective at metabolizing pentachlorophenol. There is some evidence that tetrachloro-1,4-benzoquinone can be formed by direct oxidation of pentachlorophenol via peroxidases (Chung and Aust 1995, Samokyszyn *et al.* 1995); however, this observation was challenged by Kazunga *et al.* (1999) as an artifact of the extraction and analytical methods. Nevertheless, peroxidase-catalyzed oxidation of pentachlorophenol may be important, especially in extrahepatic tissues (Dai *et al.* 2005, Dai *et al.* 2003). Tsai *et al.* (2001) reported that under normal conditions the primary metabolic pathway involved oxidation to quinones and semiquinones via microsomal P450s; however, under conditions of oxidative stress, endogenous lipid hydroperoxides might increase the rate of pentachlorophenol metabolism and enhance its toxicity and carcinogenicity. Other metabolites identified from *in vitro* studies with mouse and rat liver microsomes are shown in Table 2-6.

**Table 2-5. Relative amounts of urinary metabolites of pentachlorophenol in rats and mice**

Reference	Dose			Metabolites (% total urinary metabolites or % dose)					
	Route	mg/kg/day	# Doses	PCP	PCP glucuronide	PCP sulfate	TCHQ	TCHQ glucuronide	TCHQ sulfate
<i>Rats</i>									
Hoben <i>et al.</i> 1976	inhalation	1–6	1–5 (20 min)	70–75 <sup>a</sup>			trace		
Braun <i>et al.</i> 1977	Gavage	100	1	48 <sup>a</sup>	6 <sup>a</sup>		10 <sup>a</sup>		
Renner 1989	Gavage	53	28	36–58 <sup>b</sup>	42–64 <sup>b</sup>		10–19 <sup>c</sup>	81–90 <sup>c</sup>	
Reigner <i>et al.</i> 1991	Gavage/i.v.	2.5	1	5 <sup>a</sup>	0.5–6.2 <sup>a</sup>	18–20 <sup>a</sup>	1 <sup>a</sup>	1 <sup>a</sup>	24–27 <sup>a</sup>
Ahlborg <i>et al.</i> 1974	i.p.	25	1	43 <sup>d</sup>	14 <sup>d,e</sup>		5 <sup>d</sup>	38 <sup>d,e</sup>	
Ahlborg <i>et al.</i> 1978	i.p.	10	1	60 <sup>d</sup>	9–16 <sup>d</sup>		7 <sup>d</sup>	16–22 <sup>d</sup>	
<i>Mice</i>									
Reigner <i>et al.</i> 1992c	Gavage	15	1	6.7–8.6 <sup>a</sup>	1 <sup>a</sup>	10–15 <sup>a</sup>	3.6–5.5 <sup>a</sup>	0.1–3 <sup>a</sup>	15–18 <sup>a</sup>
Ahlborg <i>et al.</i> 1974	i.p.	25	1	41 <sup>d</sup>	13 <sup>d,e</sup>		24 <sup>d</sup>	22 <sup>d,e</sup>	
Jakobson and Yllner 1971	i.p.	15–37	1	30 <sup>a</sup>	8 <sup>a</sup>		21 <sup>a,f</sup>		

i.p. = intraperitoneal, i.v. = intravenous, PCP = pentachlorophenol, TCHQ = tetrachlorohydroquinone.

<sup>a</sup> % of administered dose.

<sup>b</sup> % of PCP excreted unchanged or as glucuronide conjugate.

<sup>c</sup> % of TCHQ excreted unchanged or as glucuronide conjugate.

<sup>d</sup> % of recovered urinary metabolites or radioactivity.

<sup>e</sup> Based on increases in PCP and TCHQ concentrations after boiling the urine with hydrochloric acid.

<sup>f</sup> Reliable estimate of amount of TCHQ and glucuronide conjugate could not be determined separately due to insufficient sample.

**Table 2-6. Urinary metabolites of pentachlorophenol in experimental animals**

Compound	Rat <sup>a</sup>			Mouse <sup>b</sup>		Rabbit <sup>c</sup>	Monkey <sup>d</sup>	Trout <sup>e</sup>	<i>In vitro</i> <sup>f</sup>	
	oral	Inhal	i.p. or i.v.	oral	i.p.	oral	oral	oral	Mouse	Rat
Pentachlorophenol (PCP)	X	X	X	X	X	X	X	X		
PCP glucuronide	X		X	X	X	X		X		
PCP sulfate	X		X	X				X		
Tetrachlorohydroquinone (TCHQ)	X	trace	X	X	X					X
TCHQ glucuronide	X		X	X	X					
TCHQ sulfate	X		X	X						
Tetrachlorocatechol	X									X
Tetrachlororesorcinol	X									
Tetrachlorophenols and glucuronides <sup>g</sup>	X									
Tetrachloro- <i>p</i> -benzosemiquinone	X								X	X
Tetrachloro- <i>p</i> -benzoquinone (TCBQ)	X			X	X	X			X	X
Tetrachloro- <i>o</i> -benzosemiquinone	X			X					X	X
Tetrachloro- <i>o</i> -benzoquinone				X					X	X
2,3,4-Trichlorophenol and glucuronide	X									
Trichlorohydroquinone	X		X							
Trichlorobenzoquinone	trace									

<sup>a</sup> Sources: Ahlborg *et al.* 1978, Ahlborg *et al.* 1974, Ahlborg and Thunberg 1978, Braun *et al.* 1977, Edgerton *et al.* 1979, Engst *et al.* 1976, Hoben *et al.* 1976, Lin *et al.* 1996, Lin *et al.* 1999, Reigner *et al.* 1991, Renner 1989, Renner and Hopfer 1990.

<sup>b</sup> Sources: Ahlborg *et al.* 1974, Jakobson and Yllner 1971, Lin *et al.* 1997, Lin *et al.* 1999, Reigner *et al.* 1992c, Tashiro *et al.* 1970.

<sup>c</sup> Sources: Betts *et al.* 1955, Deichmann *et al.* 1942, Tashiro *et al.* 1970.

<sup>d</sup> Sources: Braun and Sauerhoff 1976.

<sup>e</sup> Sources: Cravedi *et al.* 1999.

<sup>f</sup> Sources: Ahlborg *et al.* 1978, Tsai *et al.* 2001, van Ommen *et al.* 1986a.

<sup>g</sup> Includes 2,3,4,5-, 2,3,4,6-, and 2,3,5,6-tetrachlorophenol.



were evident and included an initial rapid phase followed by a slower terminal phase. About 90% of the total was eliminated in the initial phase (Braun *et al.* 1977). The slower elimination phase in rodents likely was due to high plasma protein binding and retention in the liver. Reported clearance values in rats ranged from about 0.015 to 0.027 L/hr/kg while elimination half-lives showed some possible dose and sex differences (see Table 2-7). Braun *et al.* (1977) reported that the overall elimination in rats was biphasic in low- and high-dose males and in low-dose females but was monophasic in high-dose females. No explanation was provided for the difference in kinetics observed in high-dose females. Fecal excretion was much higher and urinary excretion was much lower in female rats in the high-dose group compared with the other groups and could indicate decreased absorption.

Elimination in monkeys was much slower than that observed in rodents and followed first-order kinetics (Braun and Sauerhoff 1976). Biliary excretion and enterohepatic circulation might explain the long half-life in monkeys; however, the authors presented no data to verify this assumption. The renal clearance rate of 14.5 mL/min corresponded to the glomerular filtration rate and indicated that pentachlorophenol was not actively transported into tubular filtrate or reabsorbed

In humans, renal clearance values increased in relation to urine flow, which indicated increased tubular reabsorption at lower urinary flow rates (Pekari *et al.* 1991). However, elimination half-lives and clearance values in humans following a single oral dose varied by more than an order of magnitude (Braun *et al.* 1979, Uhl *et al.* 1986). The reasons for these differences are not completely understood, but a review of pentachlorophenol in urine and plasma reported from 11 studies that included workers, the general population, and residents of log homes indicated that the elimination half-life and clearance values reported by Braun *et al.* appear to be outliers (Reigner *et al.* 1992a). Reigner *et al.* calculated 20 clearance values from these 11 studies that included more than 600 subjects. An overall weighted average clearance of 0.018 L/hr (range: 0.0064 to 0.0346 L/hr) was derived compared with 0.51 L/hr reported by Braun *et al.* and 0.0042 L/hr reported by Uhl *et al.* Reigner *et al.* also noted that the clearance value reported by Uhl *et al.* only represented renal clearance; therefore, they estimated that total clearance in that study was about 0.01 L/hr and compared favorably with other studies they reviewed.

Braun *et al.* (1979) selected volunteers with residual plasma levels of pentachlorophenol that were four to five times lower than average levels in the general population; therefore, their inclusion criterion might have selected subjects having a higher rate of clearance than the general population. Other factors that might have contributed to the different results reported by Braun *et al.* and Uhl *et al.* (1986) include differences in dosing solutions and study protocol. Subjects used in the Braun *et al.* study fasted for 8 hours before and 1 hour after receiving an oral dose of sodium pentachlorophenate (0.1 mg/kg) dissolved in water while subjects in the Uhl *et al.* study had no dietary restrictions before or after ingesting a solution of pentachlorophenol dissolved in ethanol (0.016 mg/kg).

**Table 2-7. Toxicokinetic parameters of pentachlorophenol reported in humans and experimental animals**

Reference	Species (sex)	Route	Dose (mg/kg)	Plasma t <sub>max</sub> (hours)	Clearance (L/hr/kg)	Plasma half-life		Elimination half-life	
						t <sub>½</sub> α (hr)	t <sub>½</sub> β (hr)	t <sub>½</sub> α (hr)	t <sub>½</sub> β (hr)
Reigner <i>et al.</i> 1992c	B6C3F <sub>1</sub> mice (M)	i.v. gavage	15	na	0.057 ± 0.007	5.2 ± 0.6	NA	—	NA
			15	1.5 ± 0.05	—	5.8 ± 0.6	—	—	—
Braun <i>et al.</i> 1977	SD rats (M)	gavage	10	4–6	—	6.9 <sup>a</sup>	24 <sup>a</sup>	17.4 ± 1.7	40.2 ± 6.3
	100		—			—	12.8 ± 1.1	121 ± 63.7	
	SD rats (F)	gavage	10	4–6	—	11 <sup>a</sup>	30 <sup>a</sup>	13.4 ± 2.3	32.5 ± 9.1
	100		—			—	27.2 ± 1.1		
Meerman <i>et al.</i> 1983	Wistar rats (M)	i.v.	10.6	na	—	2.17	7.24	—	—
Reigner <i>et al.</i> 1991	SD rats (M)	i.v.	2.5	na	0.026 ± 0.003	0.67 ± 0.46	7.1 ± 0.87	—	—
		i.v.	20	na	0.033	4.1–4.5	35.5–45		
		gavage	2.5	1.8 ± 0.3	0.027 ± 0.005	7.54 ± 0.44	NA		
			30 µg/mL	—	0.023 ± 0.008	7.99 ± 2.71	NA		
Reigner <i>et al.</i> 1992b	SD rats (M)	i.v. dw	2.5	na	0.023 ± 0.008	7.99 ± 2.71	NA	—	—
			30 µg/mL	—	0.025 ± 0.003	8.02 ± 2.08	—	—	—
Yuan <i>et al.</i> 1994	F344 rats (M)	i.v.	5	na	0.016 ± 0.0007	—	5.6 ± 0.37	—	—
		gavage	9.5	2	0.015 ± 0.0004	[8.6] <sup>b</sup>	NA		
	gavage	38	4	0.016 ± 0.0005	[6.3] <sup>b</sup>	NA			
	F344 rats (F)	i.v.	5	na	0.017 ± 0.002	—	9.5 ± 4.2	—	—
Braun and Sauerhoff 1976	Rhesus monkey (M)	gavage	10	12–24	[0.19] <sup>c</sup>	72.0	NA	40.8	NA
	Rhesus monkey (F)		10			83.5	NA	92.4	NA
Braun <i>et al.</i> 1979	Human (M)	oral	0.1	4	[0.0073] <sup>b</sup> [0.51] L/hr	30.2	NA	33.1 ± 5.4	NA
Uhl <i>et al.</i> 1986	Human (M)	oral	0.016	—	[0.000069] <sup>c</sup>	384 ± 60	NA	432 ± 57.6	NA
			0.31	—	[0.0042] L/hr <sup>c</sup>	—	NA	480 ± 81.6	NA
Pekari <i>et al.</i> 1991	Human (M/F)	inhalation and skin	—	—	[0.012–0.084] L/hr <sup>c</sup>	—	NA	384	NA
Reigner <i>et al.</i> 1992a	Human (M/F)	inhalation and skin	0.005–24 mg/day	—	0.018 L/hr	—	—	—	NA
Barbieri <i>et al.</i> 1995	Human (—)	inhalation and skin	—	—	—	—	—	240	NA

— = not reported, dw = drinking water, i.v. = intravenous, na = not applicable, t<sub>max</sub> = time to maximum concentration in plasma, [ ] = calculated value.

<sup>a</sup> Values estimated by Goodman 2001.

<sup>b</sup> Calculated from elimination rate constant (*k<sub>e</sub>*).

<sup>c</sup> Renal clearance.

## 2.4 Synthesis and summary

Studies in humans and experimental animals show that pentachlorophenol is efficiently absorbed following oral, inhalation, or dermal exposure. Although pentachlorophenol is widely distributed, accumulation in tissues appears to be limited by extensive binding to plasma proteins in rats and humans. Tissue distribution studies in experimental animals show that the highest concentrations are found in organs associated with metabolism and excretion and include the liver, gall bladder, kidneys, and gastrointestinal tract. Pentachlorophenol is mostly excreted in the urine, either unchanged or as metabolites.

Metabolism and toxicokinetics show considerable interspecies variation. The primary urinary metabolites in rodents include, tetrachlorohydroquinone, and their glucuronide or sulfate conjugates in addition to unmetabolized pentachlorophenol.

Tetrachlorohydroquinone may be further metabolized to form reactive benzoquinones and benzoquinones. Only one metabolism study has been conducted in monkeys and no metabolites were identified. Pentachlorophenol was excreted unchanged in the urine of monkeys. Metabolism in humans is controversial because two studies using pure compound reported that only the parent compound and its glucuronide conjugate were excreted in the urine. Although there was no evidence of tetrachlorohydroquinone or tetrachlorophenols in subjects administered single oral doses of pure pentachlorophenol; a few studies that included occupationally exposed individuals or subjects from the general population detected low levels of tetrachlorohydroquinone and tetrachlorophenols in urine. Exposures were not adequately characterized in the latter studies; therefore, the source of these metabolites could not be confirmed. However, an *in vitro* study demonstrated that human liver microsomes could metabolize pentachlorophenol to tetrachlorohydroquinone. Whether or not humans metabolize pentachlorophenol to tetrachlorohydroquinone is a particularly important consideration because this metabolite is thought to be important to the carcinogenic effects observed in rodents. Toxicokinetic studies indicate that clearance is much slower and the excretion half-life is much longer in humans compared with rats. Thus, the species differences in metabolism and toxicokinetics are important for mechanistic considerations discussed in Section 5.

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## 3 Human Cancer Studies

### Introduction

As mentioned in Section 1, the evaluation of pentachlorophenol includes by-products of its synthesis (hereinafter called pentachlorophenol). This section describes and evaluates the available epidemiologic data on exposure to pentachlorophenol and cancer, reaching a level of evidence conclusion according to the approach outlined in the “Protocol: Evaluation of Human Cancer Studies on Exposure to Pentachlorophenol for the Report on Carcinogens”

([http://ntp.niehs.nih.gov/NTP/roc/thirteenth/Protocols/PCPHumanStudies20130815\\_508.pdf](http://ntp.niehs.nih.gov/NTP/roc/thirteenth/Protocols/PCPHumanStudies20130815_508.pdf)). The steps in the cancer evaluation process, listed below, are captured in the following subsections or appendices.

1. Selection of the relevant literature included in the cancer evaluation (Section 3.1 and [Appendix A](#) for the literature search strategy).
2. Description of the study design, methodologies, and characteristics of the individual studies and identification of the tumor sites of interest (Section 3.2 and [Appendix C](#)).
3. Assessment of study quality (Section 3.3 and [Appendix C](#)).
4. Cancer assessment: (a) evaluation of the cancer findings from the individual studies (Section 3.4.1, Tables 3-4 to 3-6) and (b) synthesis of the evidence for human carcinogenicity across studies (Section 3.4.2).
5. Preliminary recommendation for the level of evidence of carcinogenicity (sufficient, limited, or inadequate) of pentachlorophenol from human studies (Section 3.5).

#### 3.1 Selection of the relevant literature

Details of the procedures used to identify and select the primary studies and supporting literature for the human cancer evaluation are detailed in [Appendix A](#). Primary epidemiologic studies of populations exposed to pentachlorophenol (including cohort, case-control, meta-analyses, pooled analyses, ecological or case-series studies) were considered for the cancer evaluation if (1) they provided exposure-specific analyses for pentachlorophenol or evidence, based on the authors’ report, that pentachlorophenol exposure was probable or predominant in the population or a job or occupation under study and (2) risk estimates for pentachlorophenol exposure were reported or could be calculated. Two publicly available reports, a cohort mortality study of New Zealand sawmill workers prepared for the New Zealand Department of Labour (McLean *et al.* 2007), and a cohort study of U.S. plywood manufacturers (Robinson *et al.* 1987) were identified but not included in the monograph because they were not peer reviewed. A population-based case-control study of non-Hodgkin lymphoma and occupations associated with exposure to chlorophenols and phenoxyherbicides, conducted in Washington State, (Woods *et al.* 1987) was identified but not included in this review. Exposure to pentachlorophenol was highly probably for one of the occupations (manufacturer of chlorophenols) included in the study because the only chlorophenol

producer plant located in Washington State produced pentachlorophenol. Workers at this manufacturing plant were most likely included in a cohort study (Ruder and Yiin 2011) included in this review (see Section 3.2).

### **3.2 Overview of the methodologies and study characteristics of the selected epidemiologic studies and identification of cancer endpoints**

This section provides an overview of the characteristics and methodologies of the individual studies included in the review and identifies the cancer endpoints of interest. For each of the reviewed studies, detailed data on study design, methods and findings were systematically extracted from relevant publications, as described in the study protocol, into [Tables C-1a,b,c and C-2](#) in Appendix C and Tables 3-4 to 3-6 in Section 3-4. In general, this assessment reports on the latest update of a cohort or case-control study unless there are additional relevant analyses or information in the previous publications.

The available epidemiologic studies that satisfy the criteria for consideration in the cancer evaluation consist of four cohort studies or nested case-control studies, one ecological study and six independent population-based case control studies with information specific for pentachlorophenol exposure and one-nested case-control and five population-based case-control studies with limited information on pentachlorophenol exposure (see Table 3-1).

#### *Studies specific for pentachlorophenol exposure*

The nested case-control studies and cohort studies include (1) one nested case-control study of non-Hodgkin lymphoma (NHL) and soft tissue sarcoma (Kogevinas *et al.* 1995), based on an IARC registry of workers exposed to phenoxy herbicides, chlorophenols, and dioxins (Kogevinas *et al.* 1992), (2) two historical cohort studies of U.S. pentachlorophenol producers (NIOSH and Michigan) and (3) one cohort study of sawmill workers in Canada (Demers *et al.* 2006). The NIOSH pentachlorophenol producers cohort consisted of workers from four U.S. plants (Ruder and Yiin 2011), one of which was the Michigan plant studied by Ramlow *et al.* (1996) and later Collins *et al.* (2009a), so that part of the NIOSH cohort overlaps with the latter study. Exposure was assessed in the two producers studies based on individual work history and occupational hygiene data. The Canadian sawmill study assessed cumulative dermal exposure to pentachlorophenol and the IARC registry nested case-control study assessed exposure using individual work history and company records. A cross-sectional ecological assessment study of residents in a district of China contaminated with sodium pentachlorophenate was also identified (Zheng *et al.* 2013). A series of Swedish population-based case-control studies among populations in Sweden were identified for whom potential exposure to pentachlorophenol was established by self-administered questionnaire on complete occupational histories and specific exposures. These consisted of a series of studies of NHL (Hardell *et al.* 1994, Hardell and Eriksson 1999), or hairy cell leukemia, which is a subtype of NHL (Nordstrom *et al.* 1998), and a pooled analysis of four case-control studies of soft tissue sarcoma (Hardell *et al.* 1995). Hardell *et al.* (2002) reported on a pooled analysis of the hairy-cell leukemia and the 1999 NHL case-control studies. There was also a case-control study of residential exposure to

pentachlorophenol, as assessed from carpet dust samples, and childhood acute lymphocytic leukemia (Ward *et al.* 2009).

#### *Studies with limited information on pentachlorophenol exposure*

A nested case-control study of combined childhood cancers based on the Canadian sawmill cohort is considered in this group of studies, because, although there was definite parental exposure to pentachlorophenol, analyses were only reported for total chlorophenols (consisting of pentachlorophenol and tetrachlorophenol) (Heacock *et al.* 2000). The remaining studies mainly consisted of a series of studies of NHL, soft tissue sarcoma and multiple myeloma among populations in New Zealand who were given self-administered job questionnaires designed to identify occupations with phenoxy herbicide and chlorophenol exposure (Pearce *et al.* 1986a (multiple myeloma), Pearce *et al.* 1986b NHL ICD 202), expanded by Pearce *et al.* 1987 (NHL ICD 200 and 202), and Smith *et al.* 1984 (soft tissue sarcoma). Findings from the updated and expanded NHL case-control study (Pearce *et al.* 1987) are reported in this evaluation. Finally, an Australian case-control study of soft tissue sarcoma and lymphomas was identified that assessed occupations and exposures likely to involve phenoxy herbicide or chlorophenol exposure, including pentachlorophenol, by interview with an occupational hygienist (Smith and Christophers 1992).

**Table 3-1. Human cancer studies of exposure to pentachlorophenol (PCP)**

Primary reference	Name of study	Exposure assessment	Cancer endpoints
<b>Cohort and nested case-control studies: PCP producers and users</b>			
Kogevinas <i>et al.</i> 1995, Kogevinas <i>et al.</i> 1992	IARC registry-based nested case-control study	Individual exposure assessment based on company records	Mortality (OR) NHL, soft tissue sarcoma
Collins <i>et al.</i> 2009a, Ramlow <i>et al.</i> 1996	Michigan pentachlorophenol producers cohort	Individual exposure assessment (cumulative exposure) based on work history, industrial hygiene data and expert assessment Exposure to dioxin by-products based on biomonitoring data (subset of workers), work history and industrial hygiene data	Mortality (SMR, RR) All cancers and > 20 specific cancers; detailed analyses for all cancers, NHL, and cancers of the lung and kidney in latest update (Collins <i>et al.</i> 2009a)
Ruder and Yiin 2011	NIOSH pentachlorophenol producers cohort	Individual exposure assessment (ever exposed) based on work history and industrial hygiene data	Mortality (SMR, SRR) All cancers and > 20 specific cancers; more detailed analyses for NHL and lung cancer
Demers <i>et al.</i> 2006	Canadian sawmill workers cohort	Individual exposure (dermal) assessment (cumulative) based on work history, expert assessment, and formulation data; calendar year and mill specific.	Incidence/mortality (SIR, RR) All cancers and > 20 specific cancers; more detailed analyses of NHL, multiple myeloma, soft tissue sarcoma,

Primary reference	Name of study	Exposure assessment	Cancer endpoints
			and cancer of the stomach, colon, rectum, liver, lung, and kidney
<b>Ecological assessment study of PCP exposure</b>			
Zheng <i>et al.</i> 2013	Chinese ecological study	Ecological assessment of residence in area sprayed with Na-PCP	Cross-sectional incidence rates and within region comparisons (SRR)  All cancers and 17 specific cancers
<b>Population-based studies of PCP users: specific exposure information</b>			
Hardell <i>et al.</i> 1994	Swedish 1994 NHL study	Self or proxy reported structured questionnaire on lifetime occupational history and exposure to chlorophenols and phenoxy herbicides	Incidence (OR) NHL
Hardell and Eriksson 1999	Swedish 1999 NHL study		Incidence (OR) NHL
Nordstrom <i>et al.</i> 1998	Swedish HCL study		Incidence (OR) HCL
Hardell <i>et al.</i> 2002 <sup>a</sup>	Swedish NHL/HCL pooled analysis		Incidence (OR) Combined NHL/HCL
Hardell <i>et al.</i> 1995 <sup>b</sup>	Swedish soft tissue sarcoma pooled analysis	Self-reported questionnaire on lifetime occupational history, specific job categories, and leisure time information on exposure to chemicals	Incidence (OR) Soft tissue sarcoma
Ruder <i>et al.</i> 2009	U.S. glioma study	Extensive self-reported questionnaire on farming practices, jobs on farm, crops, livestock, use of pesticides, fertilizers, solvents, wood preservatives (PCP one of multiple exposures analyzed)	Incidence (OR) Glioma
Ward <i>et al.</i> 2009	Northern California childhood leukemia study	Residential exposure to PCP assessed from PCP concentrations in carpet dust	Incidence Childhood acute lymphocytic leukemia
<b>Population-based or nested case-control studies of PCP users: limited exposure information</b>			
Heacock <i>et al.</i> 2000, Demers <i>et al.</i> 2006	Nested case-control study of Canadian sawmill workers	Cumulative parental (dermal) exposure to chlorophenols (not specific for PCP, primarily PCP or TeCP)	Incidence All childhood cancers
Pearce <i>et al.</i> 1987, 1986b (NHL),	New Zealand case-control studies	Interviews using structural questionnaire and follow-up questions on occupation/jobs	Incidence (OR) NHL, multiple myeloma, soft

Primary reference	Name of study	Exposure assessment	Cancer endpoints
Pearce <i>et al.</i> 1986a (MM) , Smith <i>et al.</i> 1984 (STS)		associated with exposure to phenoxy acid herbicides or chlorophenols	tissue sarcoma
Smith and Christophers 1992	Australian case-control study	Expert assessment from self-reported occupational information.	Incidence (OR) All lymphomas, soft tissue sarcoma

HCL = hairy-cell leukemia; LHC = lymphohematopoietic cancer; NHL = non-Hodgkin lymphoma; NIOSH = National Institute for Occupational Safety and Health; RR = relative risk; SIR = standardized incidence ratio; SMR = standardized mortality ratio; SRR = standardized rate ratio.

<sup>a</sup> Pooled analysis of Hardell and Eriksson (1999) (NHL) and Nordstrom *et al.* (1998) (HCL)

<sup>b</sup>The authors refer to this as a meta-analysis of four studies (Eriksson *et al.* 1990, Eriksson *et al.* 1981, Hardell and Eriksson 1988, Hardell and Sandstrom 1979); however, it appears to be more of a pooled analysis.

Not all the cohort studies reported all endpoints or reported comparable groups of cancer sites. Cancer endpoints were chosen for evaluation if there were detailed analyses (such as evaluation of exposure response relationships) on the endpoint from two or more studies: both case-control and cohort studies reported on NHL, soft tissue sarcoma and multiple myeloma and more than one cohort study provided detailed analyses for all cancers combined, and cancer of the kidney and lung. Liver cancer was also chosen for the evaluation because it is a site found in excess in animal studies.

Three case-control studies, the case-control study of glioma (Ruder *et al.* 2009), the nested-case control study of combined childhood cancers (Heacock *et al.* 2000), and the Northern California case-control study of childhood acute lymphocytic leukemia were not included in the quality and cancer assessment because the overall database was considered to be inadequate to evaluate the evidence for the cancer sites reported by these studies (See Tables C-1b and C-1c for details on the study characteristics and methodology). In the study of glioma (Ruder *et al.* 2009), a statistically significant increase in risk (OR = 4.55, 95% CI = 1.14 to 18.1, 6 cases) was observed among cases where proxy respondents were excluded, but not for all cases, but no analysis for potential confounding by other pesticides or farm exposures was conducted. No other studies reported risk estimates specific for glioma. Although two case-control studies reported on childhood cancer, only one study, the Northern California childhood acute lymphocytic leukemia study, was specific for pentachlorophenol exposure. In the nested case-control study of childhood cancers (Heacock *et al.* 2000), no association with parental chlorophenol exposure (which included pentachlorophenol and tetrachlorophenol) was noted for all cancers, or specifically for leukemia or brain cancers either in the overall analysis or by window of exposure or level of exposure. No statistically significant positive association was observed for exposure to residential pentachlorophenol exposure (as assessed by its concentrations in carpet dust) and childhood leukemia in the Northern California Study (Ward *et al.* 2009). Statistically non-significant risk estimates were elevated for some categories of exposure but no positive exposure-response relationship was observed.

### 3.3 Assessment of the quality of individual studies

This section discusses the assessment of study quality across individual studies and the utility of these studies to inform the evaluation of the potential effects of exposure to pentachlorophenol and cancer endpoints. Each study was assessed for the potential for biases and the adequacy of the ability to detect an effect and the adequacy of analytical methods, according to the guidelines for evaluating study quality described in the protocol for reviewing studies. Section 3.3.1 reports on the assessment of biases and other factors affecting study quality, Section 3.3.2 focuses on the assessment of potential confounding, and Section 3.3.3 integrates these assessments, reaching decisions on the utility of the individual studies to inform cancer identification.

#### 3.3.1 Assessment of potential bias, analytical methods, and other study quality characteristics

##### *Selection and attrition bias*

Overall, selection bias is not a major concern (i.e., potential for bias is not probable) in the cohort or nested case-control studies. The potential for selection bias is generally considered to be unlikely in occupational cohort studies, with the exception of the healthy worker (hire or survival) effect in studies using external comparison populations. Both a healthy worker hire effect and a healthy worker survival effect would tend to bias towards the null, so that positive associations are unlikely to be biased upward. The potential for a healthy worker hire effect can be indirectly assessed based on observed differences between all-cause and all-cancer mortality or incidence rates; no strong evidence of a healthy worker hire effect was identified in any of the cohort studies. No analyses were done in the studies to determine whether there was a healthy worker survival effect. However, the high proportion of short-term workers in the two pentachlorophenol producers cohorts (Collins *et al.* 2009a, Ruder and Yiin 2011) could suggest a possible healthy worker survival effect, if workers left or were re-assigned due to ill-health. In the IARC registry-based nested case-control study (Kogevinas *et al.* 1995) there is no *a priori* reason to assume selection bias in the original cohort, or in the cancer-registry-based identification of cases. Loss to follow-up is minimal in the U.S. pentachlorophenol producers cohorts (Collins *et al.* 2009a, Ruder and Yiin 2011) and the Canadian sawmill cohort (Demers *et al.* 2006). The potential for attrition bias was assessed via loss of follow-up in the cohort studies. None of the cohort studies report > 4% loss to follow-up across the cohort, and thus, the potential for attrition bias was considered to be unlikely or minimal.

In general, the cases and controls in the population-based case-control studies of pentachlorophenol were selected from the same population and matched on age, geographical location and other appropriate factors. There was no evidence that the cases and controls were selected on criteria related to exposure and thus the potential for selection bias was not a serious concern (i.e., was not considered to be probable) in these studies. The use of cancer controls in the New Zealand studies (Pearce *et al.* 1986a, 1987 Smith *et al.* 1984) may bias findings towards the null, if the cancers among the controls are related to exposure. In the earlier (not expanded) New Zealand case-control study of NHL, both cancer controls and population controls were used in the analysis (Pearce *et al.* 1986b) but only cancer controls in the expanded study (Pearce *et al.* 1987). Cancer

and population controls were also used in the Australian study (Smith and Christophers 1992). There is also a potential for differences in the social status of the population controls compared to the cases in this study because the cases were selected from a public (no fee) hospital whereas the controls were selected from the entire region and include individuals from all social classes.

Participation rates were high (< 10%) in the Swedish 1994 NHL (Hardell *et al.* 1994) and soft tissue sarcoma pooled case-control studies (Hardell *et al.* 1995), moderate ( $\leq 20\%$ ) in the other Swedish studies (Nordstrom *et al.* 1998, Hardell and Eriksson 1999) and the New Zealand studies (Pearce *et al.* 1986b, 1987, and Smith *et al.* 1984) and low (56 to 70%) in the Australian study (Smith and Christophers 1992). Although participation rates are lower among controls than cases in some studies (Smith and Christophers 1992, Nordstrom *et al.* 1998, Hardell and Eriksson 1999), there is no other information to suggest that any such differences would be specifically related to potential exposure to pentachlorophenol.

In the cross-sectional ecological assessment study in China (Zheng *et al.* 2013), selection bias would not be a risk if cancer registry data are mostly complete for each district in the study, but there is insufficient information in this study to evaluate the quality and completeness of the cancer registry data.

#### *Information bias: exposure assessment*

The adequacy of the characterization of intensity or duration of exposure to pentachlorophenol was assessed based on whether quantitative or semi-quantitative levels of pentachlorophenol exposure were estimated or reported, using either ambient air monitoring, knowledge of fungicide formulation, estimation of dermal exposure, or biomonitoring data. In general, the potential for misclassification in these studies was considered to be non-differential, as discussed below.

Studies considered to have good or adequate exposure assessments include the Canadian sawmill worker study (Demers *et al.* 2006), the Michigan pentachlorophenol producer study (Collins *et al.* 2009a) and to a lesser extent the NIOSH study of pentachlorophenol producers (Ruder and Yiin 2011) and the IARC registry-based nested case-control study (Kogevinas *et al.* 1995). The most detailed exposure characterization was conducted in the Canadian sawmill study by Demers *et al.* (2006), who used individual exposure assessments of cumulative full-time equivalent dermal exposure for exposure-constant calendar periods, using worker assessments of dermal exposure by job type validated by urine sampling and industrial hygienists, together with detailed information on the different formulations of pentachlorophenol and tetrachlorophenol-containing wood preservatives over time (Fenske *et al.* 1987, Hertzman *et al.* 1988, Teschke *et al.* 1989, Teschke *et al.* 1996). Pentachlorophenol was the main wood preservative used in the sawmills from 1941 to 1965, whereas tetrachlorophenol was mainly used from 1965 on.

Exposure in the Michigan pentachlorophenol producers study was assessed differently in the two updates. In the earlier update of this cohort, Ramlow *et al.* (1996) used individual work histories by job title and department, expert knowledge (veteran employees), and industrial data to calculate cumulative exposure to pentachlorophenol. In the latter

update, Collins *et al.* (2009a) assessed past exposure to higher chlorinated dioxins (OCDD, 1,4 HxCDD, 1,6, HxCDD, 1,9-HxCDD, HpCDD) that are by-products of pentachlorophenol synthesis (see Section 1) and to 2,3,7,8-TCDD. Briefly, the exposure assessment characterization of the earlier study was used to group pentachlorophenol-exposed jobs into different exposure categories. The authors then measured serum chlorinated dioxin levels from a subset of workers, selected to be representative of time spent in the different exposure categories (see Collins *et al.* 2007), and used pharmacokinetic modeling and work history information to estimate past dioxin levels for jobs in each exposure category including background exposure to dioxins (including 2,3,7,8-TCDD). The dose rates were integrated with work histories to estimate individual dioxin congener levels for each individual member of the entire pentachlorophenol cohort, including the 196 members with co-exposure to trichlorophenol. Some errors in the models used to estimate past exposure levels may arise because of the limited number of samples used to create the serum by-product profiles and in the pharmacokinetic models used to predict to past exposure. Half-life of dioxins is dependent upon body fat composition and peak exposure. The greater the percent body fat, the longer the half-life, particularly at low to moderate exposures. Dioxins also induce their own metabolism, such that at higher exposures they have a faster elimination (Emond *et al.* 2006). If the pharmacokinetic model used to back extrapolate blood levels does not account for changes in body fat composition or dose dependency over time, it is possible for misclassification of exposure at the low and medium exposure categories. Misclassification is not a concern for individuals in the highest chlorinated dioxin category; it is very likely that these workers were exposed to pentachlorophenol.

The NIOSH study (Ruder and Yiin 2011) conducted extensive independent ambient air monitoring in each of the four participating plants, indicating that workers included in the pentachlorophenol departments were exposed to measurable levels of pentachlorophenol; however, data were inadequate to evaluate exposure levels for individual workers, and thus the assessment was not considered to be as good as the Michigan study. With respect to the nested case-control study based on the IARC registry cohort, detailed exposure assessments based on questionnaires, work histories, and employment and industrial hygiene records were used to assign categories of cumulative exposure.

Exposure assessment for each of the population-based case-control studies is generally more limited than for the cohort studies. The Swedish studies rely either on self- or proxy report of lifetime use of pentachlorophenol-containing wood preservatives or related pesticide uses (the Swedish case-control studies of Hardell *et al.* [1994], Hardell and Eriksson [1999], Nordstrom *et al.* [1998], Hardell *et al.* [1995]); however, a validation study of the questionnaire used in two of the Swedish studies (Hardell *et al.* 1994, 1995) found a 97% agreement between information from self-reported exposure and employers (sawmill and pulp industry), suggesting that recall bias is unlikely. In addition, the potential for recall bias about exposures might also have been reduced given that subjects were asked about multiple specific exposures and appear to have been unaware of the specific hypotheses being tested in the studies.

Pentachlorophenol exposure is less certain in the New Zealand studies of NHL, soft tissue sarcoma, and multiple myeloma (Pearce *et al.* 1987, Pearce *et al.* 1986a, 1986b,

Smith *et al.* 1984) and the studies are of more limited utility. Although pentachlorophenol was sometimes used for fence posts mostly before 1955 and sodium pentachlorophenate may have been widely used in sawmills for sapstain treatment, it is not clear how many cases or controls engaged in sawmill or fencing or timber mill work were likely exposed to pentachlorophenol or sodium pentachlorophenate.

Finally, the Australian case-control study of Smith and Christophers (1992) relied on expert assessment (industrial hygienist) of self-reported job or task descriptions information obtained during the interview. The interviewer may not have been completely blind to population control status of the study subjects thereby increasing the likelihood of differential exposure misclassification in addition to non-differential misclassification. Cancer controls were also used and the interviewer was blinded to case/cancer control status. Although pentachlorophenol exposure was also specifically identified among individual cases and controls in this study, no risk estimates for pentachlorophenol were calculated.

In the Chinese ecological study (Zheng *et al.* 2013), exposure was assessed based on estimated cumulative application of pentachlorophenol to soil and water for snail eradication, but it is not clear how accurately this measure reflects actual community exposure, or how data on duration of individual residents' exposure (used in comparative analyses of cancer incidence by duration of exposure across districts with different amounts of pentachlorophenol application) were obtained or analyzed, and thus whether cumulative exposure by district was valid. The use of an ecological study design, involving large-scale aggregate data also means that limited inferences can be made about cancer risk at the individual level.

#### *Information bias: disease endpoints*

The potential for differential and non-differential misclassification of cancer endpoints depends on the accuracy and completeness of ascertainment of vital status or diagnosis, and varies depending on the cancer endpoint under consideration.

With respect to NHL, multiple myeloma, and soft tissue sarcoma, mortality data are less informative than incidence data, in part because these cancers, particularly soft tissue sarcoma, require histological confirmation for accurate and complete diagnosis, and in part because these cancer endpoints have been associated with a fairly wide range of survival times, including some long-term survivors, and thus incidence data more accurately reflects the risk of disease than mortality data. In addition, the classification systems for lymphohematopoietic cancers, including NHL and multiple myeloma, have changed since the 1980s and some non-differential misclassification of these cancers may be possible, depending on the year of the study. The Canadian sawmill cohort (Demers *et al.* 2006) is the most informative cohort study for evaluating NHL, multiple myeloma and soft tissue sarcoma because it reported cancer registry-based incidence the soft tissue sarcoma cases were histologically confirmed. The study also reported on mortality similar to the two U.S. pentachlorophenol producer studies (Ruder and Yiin 2010, and Collins *et al.* 2009a). In the IARC registry-based nested case-control study, cases of NHL and soft tissue sarcoma were identified from death certificates and cancer registries.

A strength of the case-control studies is the use of cancer incidence data, and histological confirmation of cases of NHL (Hardell *et al.* 1994, Hardell and Eriksson 1999, Pearce *et al.* 1987), soft tissue sarcoma (Hardell *et al.* 1995, Smith *et al.* 1994) and multiple myeloma (Pearce *et al.* 1986b) in most studies. Cancer misclassification is therefore considered to be minimal in these studies. It is not clear whether hairy-cell leukemia cases identified by Nordstrom *et al.* (1998) were histologically confirmed or re-reviewed, however, and in the Australian study, medical records of soft tissue sarcoma or NHL were confirmed but there was no review of pathology (Smith and Christophers 1992). The quality of the cancer incidence data in the Chinese ecological assessment study (Zheng *et al.* 2013) cannot be evaluated.

With respect to the solid tumors of *a priori* concern, i.e., cancers of the kidney and liver, diagnosis tends to be more accurate and average survival times may be shorter than for some lymphohematopoietic cancers, so the mortality cohort studies as well as incidence studies are informative. Only the NIOSH pentachlorophenol producers study reported multiple causes of death data, however, which could identify more cases of both solid and lymphohematopoietic cancers than underlying cause of death data alone (Ruder and Yiin 2011).

#### *Ability to detect an effect and adequacy of analytical methods*

Factors that affect the ability of a given study to detect an association if present include statistical power, the length of follow-up or follow-back, which should be sufficient to detect long latency cancers, and the levels, range and duration of exposure to pentachlorophenol. In addition, analytical methods should ideally include internal analyses (for cohort studies), exposure-response analyses, and appropriate assessment of, and if necessary, adjustment for, potential confounding. Among the cohort studies, the Canadian sawmill workers study (Demers *et al.* 2006) is considered to have good ability to detect an effect, based on the statistical power to detect relatively rare cancers such as soft tissue sarcoma, and adequate follow-up (approximately 45 years for mortality, 25 years for incidence). The NIOSH pentachlorophenol producers cohort (Ruder and Yiin 2011) has adequate ability to detect an effect for most of the cancer endpoints of interest with limited ability to detect an effect for soft tissue sarcoma, which is a rare outcome. The Michigan pentachlorophenol producers cohort (Collins *et al.* 2009a) has limited ability to detect an effect based on smaller numbers of exposed workers, although the length of follow-up is adequate in both cohorts.

With respect to the quality of analyses, the Canadian sawmill study (Demers *et al.* 2006) included the most informative analyses. Both external and internal incidence and mortality analyses (by estimated cumulative dermal exposure) were analyzed for workers exposed to pentachlorophenol and separately for the principal co-exposure (in this study, tetrachlorophenol). The NIOSH (Ruder and Yiin 2011) and Michigan (Collins *et al.* 2009a) pentachlorophenol producers studies each conducted external analyses separately for workers exposed only to pentachlorophenol as well as pentachlorophenol and the principal co-exposure, 2,4,5-trichlorophenol, but internal analyses by cumulative exposure or duration of exposure were conducted for only selected outcomes for the combined cohort. None of the available cohort studies conducted multivariate analyses in which co-exposures or other potential confounders were examined.

Case-control studies are usually more informative for studying rare cancer; however, some of the population-based case-control studies had relatively small numbers of exposed cases and controls because of a low exposure prevalence among controls (~ 10 to 15%) and relatively small numbers of total cases and controls. Studies with good statistical power include the 1999 Swedish study of NHL (Hardell and Eriksson 1999) and related combined analysis of NHL and HCL (Hardell *et al.* 2002), the Swedish pooled case-control study of soft tissue sarcoma (Hardell *et al.* 1995) and the New Zealand studies of NHL (Pearce *et al.* 1986b, 1987) and multiple myeloma (Pearce *et al.* 1986a) (for some occupations). The ability to detect an effect of exposure among cases and controls is limited because of lack of information on the level and range of exposures. The ability to detect an effect in the cross-sectional Chinese ecological study (Zheng *et al.* 2013) is unclear in the absence of reported population size in different exposure areas, and the 2-year window for cancer incidence.

### 3.3.2 Assessment of methods (or available information) to evaluate potential confounding by occupational co-exposures or other risk factors

As mentioned in Section 1, the candidate substance is defined as pentachlorophenol and by-products of its synthesis and thus the higher chlorinated dibenzodioxins (hereinafter called dioxins) formed during the synthesis of pentachlorophenol are not considered to be potential confounders. The evaluation of the potential for confounding from occupational exposures and other risk factors will be discussed in the cancer assessment for each endpoint of interest because whether a co-exposure is a potential confounder depends on whether it is a risk factor for a specific cancer in addition to being associated with exposure to pentachlorophenol. This section will provide a brief discussion on the methods or other data relevant to evaluating potential confounding from occupational co-exposures.

Table 3-2a lists the potential occupational co-exposures for each study and study methods or information relevant for evaluating the potential for confounding. The available studies include sawmill workers and pentachlorophenol production workers, and the types of co-exposures differ between the two groups. Most of the pentachlorophenol exposure in the more informative Swedish population-based case-control studies providing estimates specific for pentachlorophenol (Hardell *et al.* 1994, 1995, Nordstom *et al.* 1998, Hardell and Eriksson 1999) appears to be among workers in sawmills or the pulp industries. Almost none of the studies examined potentially confounding co-exposures or other risk factors, although some studies evaluated tobacco smoking as an independent risk factor. However, there are few known risk factors for several of the cancers of interest (soft tissue sarcoma, non-Hodgkin lymphoma, and multiple myeloma, see Section 3.4), and tobacco smoking is not a risk factor for these types of cancer. The Michigan (Collins *et al.* 2009a) and NIOSH (Ruder and Yiin 2011) pentachlorophenol production workers cohort studies also included workers exposed to 2,4,5-trichlorophenol, which is contaminated with 2,3,7,8-TCDD. In addition, workers were exposed to other chemicals that were produced at the same plants. The NIOSH pentachlorophenol producers study (Ruder and Yiin 2011) provided a detailed list of occupational co-exposures at the four plants, but not at the individual worker level, and there are no data on the extent or levels of potential exposure to these agents. It is also possible that cases identified in the nested case-control study (Kogevinas *et al.* 1995) in association with pentachlorophenol

production plant may have had other co-exposures. Whether or not these co-exposures have a potential for confounding also depends on the specific cancer site. Sawmill workers (Demers *et al.* 2006) are potentially exposed to other chlorophenols, primarily tetrachlorophenol and wood dust; creosote and copper chrome arsenate were not used regularly in the sawmills in Canada, however (Demers, personal communication).

Most of the population-based case-control studies were undertaken in rural and agricultural populations, and exposure to other wood impregnating agents (such as copper chrome arsenate or creosote) is possible. There is potential for exposure to formaldehyde (in the pulp industries) and to other pesticides, including phenoxyacetic acids and other chlorophenols; however, no information on co-exposures was provided. Potential confounding by other exposure or risk factors that differ across the districts under investigation may be a major concern in the ecological study of environmental exposure to pentachlorophenol reported by Zheng *et al.* (2013), but they were not identified or evaluated in this study.

Most of the studies did not consider or adjust for potential confounding from occupational co-exposures in formal statistical analyses. However, some studies provide other information or analyses that can help evaluate the potential for confounding. The two cohort studies of pentachlorophenol producers (Collins *et al.* 2009a, Ruder and Yiin 2011) conducted separate analyses on workers exposed to pentachlorophenol alone versus pentachlorophenol and trichlorophenol combined, and the Canadian sawmill cohort study (Demers *et al.* 2006) provided separate estimates (including exposure-response relationships) on pentachlorophenol, tetrachlorophenol and both chlorophenols combined. In addition, internal analyses and exposure-response analyses help mitigate concerns from confounding unless the confounder is highly correlated with exposure to pentachlorophenol. Multivariate analyses, which included total chlorinated phenols (of which pentachlorophenol was predominant), DDT, phenoxyacetic acids, and organic solvents were conducted in the Swedish 1994 study; however, residual confounding may be possible if the co-exposures are highly correlated. In addition, an early report (Hardell *et al.* 1981) of malignant lymphomas that included the NHL cases reported in the 1994 Swedish study (Hardell *et al.* 1994) and one of the individual case-control studies (Hardell and Sandstrom 1979) that contributed to the pooled case-control study on soft tissue sarcoma (Hardell *et al.* 1995) conducted analyses that excluded cases and controls exposed to phenoxyacetic acids.

Tables 3-2b list the major tumor site(s) associated with co-exposures across studies. (An evaluation of potential confounding from co-exposures in the individual studies is discussed in the cancer assessment, in relation to each cancer endpoint of interest). None of the co-exposures that are classified as known human carcinogens cause cancer (sufficient evidence) at the tumor sites of interest; however, there is limited evidence in humans at these sites for some of these exposures.

**Table 3-2a. Occupational co-exposure and methods relevant for evaluating confounding**

Study or studies	Co-exposures	Methods relevant to evaluating confounding
<b>Pentachlorophenol producers: nested case-control or cohort studies</b>		
Kogevinas <i>et al.</i> 1995	<p><i>Definite exposure<sup>a</sup></i> None No occupational exposure to other chlorophenols, phenoxy herbicides, and dioxins documented in British PCP producers cohort  No relevant information on other chemicals</p>	<p>Internal analysis (nested case-control analysis; controls also potentially exposed to the same chemicals)  No analysis of potential confounding</p>
Collins <i>et al.</i> 2009a, Ramlow <i>et al.</i> 1996	<p><i>Definite exposure<sup>a</sup></i> TCP: 25% of workers  2,3,7,8-TCDD: mainly as a result of TCP contaminant, slightly higher levels in PCP-only workers compared with reference  <i>Possible exposure:</i> List of other chemicals with potential exposure (from Ruder and Yiin<sup>b</sup>)</p>	<p>Separate analysis for pentachlorophenol versus PCP and TCP  Exposure-response analysis for some cancer sites (internal and external analyses)  Biomonitoring data available for 2,3,7,8-TCDD</p>
Ruder and Yiin 2011	<p><i>Definite exposure<sup>a</sup></i> 2,4,5-TCP: 33% of PCP production workers  2,3,7,8-TCDD: mainly as a result of TCP contaminant  <i>Possible exposure:</i> Other chemicals: 90% of all workers exposed; list of chemicals with potential exposure specific for each plant<sup>b</sup></p>	<p>Separate analysis for PCP versus PCP and TCP combined  Exposure duration analysis for some cancer sites (internal and external analysis)  Analysis by plant for some tumor sites</p>
<b>Pentachlorophenol users: Sawmill workers</b>		
Demers <i>et al.</i> 2006	<p><i>Definite exposure<sup>a</sup></i> Correlation coefficient for PCP and TeCP = 0.45; dermal exposure assessment for PCP and TeCP  Copper chrome arsenate and creosote not used  <i>Possible exposure: inferred</i> Wood dust</p>	<p>Separate analyses for pentachlorophenol, TeCP, and combined TeCP and PCP; cumulative exposure-response analysis (internal and external)</p>

Study or studies	Co-exposures	Methods relevant to evaluating confounding
<b>Pentachlorophenol users: Case-control studies</b>		
Swedish case-control studies Hardell and Eriksson 1999, Hardell <i>et al.</i> 1994, 1995, Nordstrom <i>et al.</i> 1998	<i>Definite exposure<sup>a</sup></i> <i>none</i>  <i>Possible exposure: inferred</i> Phenoxyacetic acids  Sawmills: wood dust, copper chrome arsenate or creosote  Pulp and paper: formaldehyde	Hardell <i>et al.</i> (1994) conducted multivariate analysis adjusting for exposure to other pesticides; Earlier report (Hardell <i>et al.</i> 1981) of lymphoma (which include NHL cases reported by Hardell 1994) and one of the four STS case-control studies (Hardell and Sandstrom 1979) included analyses that excluded cases and controls exposed to phenoxyacetic acids.  Some analyses for latency or level/duration of exposure
New Zealand studies: Pearce <i>et al.</i> 1987, Pearce <i>et al.</i> 1986a, 1986b, Smith <i>et al.</i> 1984 Australian study: Smith and Christophers 1992	<i>Definite exposure<sup>a</sup></i> None  <i>Possible exposure: inferred</i> Phenoxy herbicides, mixed chlorophenols	Risk estimates not specific for PCP

PCP = pentachlorophenol; 2,4,5-TCP = 2,4,5-trichlorophenol; 2,3,7,8-TCDD = 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TeCP = tetrachlorophenol.

<sup>a</sup> definite exposure is defined as the co-exposure is specifically identified by the authors of the publication

<sup>b</sup> specific co-exposures are discussed in the cancer evaluation of specific cancer sites, if they are risk factors for that cancer

**Table 3-2b. Carcinogenicity information (in humans) for occupational co-exposures<sup>a</sup>**

	Sufficient evidence	Limited evidence	Classification
Polychlorinated phenols (all) <sup>b</sup> 2,4,5-TCP TeCP		NHL, STS Not evaluated No studies	IARC: Group 2B RoC: RAHC; IARC: Group 3
2,3,7,8-TCDD	All cancers combined	NHL, STS, lung	RoC: Known human carcinogen IARC: Group 1
Formaldehyde	Myeloid leukemia, nasal cavity and paranasal sinus <sup>c</sup> and nasopharynx		RoC: Known human carcinogen IARC: Group 1
Wood dust	Nasal cavity and paranasal sinus <sup>b</sup> and nasopharynx		RoC: Known human carcinogen IARC: Group 1

	Sufficient evidence	Limited evidence	Classification
Creosotes (coal-based)		Skin	IARC: Group 2A
Phenoxy herbicides		Several sites (possibly NHL and STS)	IARC: Group 2B

NHL = non-Hodgkin lymphoma; STS = soft tissue sarcoma; IARC = International Agency on Research on Cancer; RoC = Report on Carcinogens; RAHC = reasonably anticipated to be a human carcinogen; 2,3,7,8-TCDD = 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; 2,4,5-TCP = 2,4,5-trichlorophenol; TeCP = tetrachlorophenol.

<sup>a</sup>Occupational co-exposures (other than TCP, TeCP and 2,3,7,8-TCDD) in the U.S. are discussed in the cancer evaluation of specific cancer sites, if they are risk factors for that cancer.

<sup>b</sup>Includes exposure to pentachlorophenol.

<sup>c</sup>IARC classifies nasal cavity and paranasal sinus as limited, whereas the RoC classifies the evidence as sufficient.

### 3.3.3 Summary of the utility of the studies to inform the cancer evaluation

Based on the methodological evaluation of the adequacy of study design, adequacy of exposure and disease assessment of cancer incidence or mortality, and the ability to detect an effect of pentachlorophenol on multiple cancer endpoints (NHL, soft tissue sarcoma, and liver or kidney cancer) the following studies were considered to have good or adequate utility to inform the cancer evaluation: the large Canadian sawmill cancer incidence and mortality (Demers *et al.* 2006), the NIOSH (Ruder and Yiin 2011) and Michigan (Collins *et al.* 2009a) mortality cohort studies of pentachlorophenol producers, the IARC registry-based nested case-control study (Kogevinas *et al.* 1995), and the series of Swedish case-control studies of NHL and soft tissue sarcoma (Hardell *et al.* 1994, 1995, 2002, Nordstrom *et al.* 1998, Hardell and Eriksson 1999).

Of these studies, the Canadian sawmill cohort (Demers *et al.* 2006) is the most informative based on the following: a large population of exposed workers, very low loss to follow-up; adequate duration of follow-up; analysis of both cancer incidence and mortality data, characterization of dermal exposure and evaluation of exposure-response relationships. The main strengths of the NIOSH and Michigan pentachlorophenol producer studies are the utilization of individual exposure characterization and complete and adequate duration of follow-up (Collins *et al.* 2009a, Ruder and Yiin 2011). The principal limitations are the use of mortality-only data, lower statistical power, and limited examination of potential confounding by co-exposure to trichlorophenol or other agents. The Michigan study was considered to be the more informative of the two producers studies because of its assessment of exposure-response relationships in both the earlier (Ramlow *et al.* 1996) and later follow-ups (Collins *et al.* 2009a). The IARC registry-based nested case-control study of NHL and soft tissue sarcoma (Kogevinas *et al.* 1995) can be considered to have moderate utility for the cancer evaluation, based on the collection of detailed exposure data; however, it had limited statistical power. The Swedish population-based case-control studies have the advantage of greater statistical power to detect less common cancer endpoints, and good disease ascertainment, but the exposure assessment is more limited and there are concerns in some of them about potential confounding from occupational co-exposures.

As a group, the series of Australian and New Zealand case-control studies of rural/agricultural populations (Pearce *et al.* 1986a,b, 1987, Smith *et al.* 1984, Smith and Christophers 1992) have limited utility to inform the evaluation because of concerns about the greater potential for misclassification of exposure, especially for exposure specific to pentachlorophenol. In addition, there are concerns about potential confounding, most notably by other chlorophenols or phenoxy herbicides.

The Chinese ecological study was considered to be inadequate for the full evaluation based on lack of documentation and its ecological design (Zheng *et al.* 2013).

### 3.4 Cancer assessment

This section summarizes and interprets the findings from the individual studies and then synthesizes the evidence for each cancer endpoint across the body of studies. Cancer sites of interest in the evaluation include non-Hodgkin lymphoma, multiple myeloma, soft tissue sarcoma, and cancers of the liver and kidney. The key question for evaluating the level of evidence across the body of studies is whether any observed associations between pentachlorophenol exposure and each cancer endpoint with sufficient data for evaluation could be explained by chance, bias, or confounding by co-exposures or other risk factors. Several of the guidelines developed by Austin Bradford Hill (Hill 1965) are relevant to the evaluation of the level of evidence for human carcinogenicity, including the magnitude (strength) and consistency of any observed associations across studies; evidence for exposure-response relationships and associations with appropriate latency; and the degree to which chance, bias, and confounding could plausibly explain observed associations. Observed associations from methodologically limited studies or negative findings from such studies are given less weight in the overall evaluation than findings from methodologically strong studies.

### 3.5 Individual studies

As noted, the focus of the majority of case-control studies is on non-Hodgkin lymphoma, multiple myeloma or all lymphomas, or soft tissue sarcoma. Available data on these endpoints are presented for both cohort and case-control studies in Tables 3-3 (non-Hodgkin lymphoma), 3-4 (NHL and multiple myeloma) and 3-5 (soft tissue sarcoma), respectively. Findings for kidney and liver cancer are presented in Table 3-6.

#### *NHL*

The available database for evaluating NHL consists of three cohort studies, two reporting only on mortality (Ruder and Yiin 2011, Collins *et al.* 2009a) and one reporting on incidence and mortality (Demers *et al.* 2006), one-nested case-control study (Kogevinas *et al.* 1995), three population-based case-control studies from Sweden that reported risk estimates specific for exposure to pentachlorophenol (Hardell *et al.* 1994, Hardell and Eriksson 1999, Nordstrom *et al.* 1998 (of hairy cell leukemia, a rare subtype of NHL), and the pooled analysis of the latter two case-control studies by Hardell *et al.* (2002) (Tables 3-3 and 3-4). In addition, there are two case-control studies from New Zealand (Pearce *et al.* 1987, 1986b) with more limited evidence of exposure to pentachlorophenol, which are discussed briefly. In general, the occupational cohort studies have better exposure characterization with lower risk of exposure misclassification and are subject to fewer types of biases (such as recall bias) than the available population-based case-

control studies. However, the case-control studies were able to evaluate NHL incidence and verify diagnoses using cancer registry or medical records, whereas two of the three cohort studies use death certificate-based mortality data only.

Occupational chemicals that have limited evidence for carcinogenicity of NHL in humans (according to IARC or the RoC; none were identified with known evidence) include benzene, ethylene oxide, 2,3,7,8-TCDD, mixed polychlorinated phenols (which include pentachlorophenol), phenoxy herbicides (possibly, but cancer tumors sites are unclear), styrene (associated with lymphohematopoietic cancers including NHL), tetrachloroethylene, trichloroethylene, and ionizing radiation (Cogliano *et al.* 2011, NTP 2011). Of these, 2,3,7,8-TCDD, other polychlorinated phenols, and styrene were potential co-exposures in the pentachlorophenol studies, and may be potential confounders. Non-occupational risk factors for non-Hodgkin lymphoma include viral infections (Epstein-Barr virus, HBV, HCV, HIV), immunosuppressive disorders, and exposure to immunosuppressive or chemotherapy drugs (Hardell and Axelson 1998). There is no *a priori* reason to suspect that these non-occupational factors would have a different distribution among pentachlorophenol-exposed and non-exposed people, and thus they are not considered to be potential confounders.

The most informative study, the Canadian sawmill worker study (Demers *et al.* 2006), provides convincing evidence of an association of NHL with exposure to pentachlorophenol, which is unlikely to be explained by confounding or biases. A clear exposure-response relationship (using exposure-year equivalents of dermal exposure) between pentachlorophenol exposure and NHL was observed for both mortality ( $P_{trend} = 0.06$ ) and incidence ( $P_{trend} = 0.03$ ). An approximately 1.7-fold increase in mortality and incidence risk was observed among workers in the highest exposure category (5+ exposure-years) compared with workers in the lowest exposure category (< 1 exposure year). Somewhat stronger exposure-response trends were observed in incidence analyses allowing for 10-year ( $P_{trend} = 0.02$ ) or 20-year ( $P_{trend} = 0.02$ ) latency periods (lagged mortality analyses were not reported).

Most of the cohort was also exposed to tetrachlorophenol in varying amounts; however, the correlation between pentachlorophenol and tetrachlorophenol exposure was not strong ( $r = 0.45$  based on cumulative exposure at the end of follow-up). To date, data from other (animal or human) studies have been inadequate to evaluate the carcinogenicity of tetrachlorophenol. Although no adjustment for tetrachlorophenol was made in the analysis by pentachlorophenol exposure, a separate analysis by tetrachlorophenol exposure reported lower relative risks of NHL than for pentachlorophenol compared with non-exposed workers and no overall trend in NHL risk with increasing exposure was observed. Additional support that exposure to pentachlorophenol and not tetrachlorophenol is linked to the increased risk of NHL in this cohort comes from follow-up exposure-response analyses (log-linear and log-log) that modeled cumulative exposure to chlorophenols as a continuous variable by assigning the mean cumulative exposure to all subjects in each category (Friesen *et al.* 2007). These analyses found a monotonic exposure-response relationship between exposure to pentachlorophenol or combined tetrachlorophenol and pentachlorophenol but not for tetrachlorophenol and NHL. The exposure-response relationship was stronger for

exposure to pentachlorophenol than for exposure to tetrachlorophenol or combined tetrachlorophenol and pentachlorophenol.

Although the Canadian sawmill workers were also exposed to wood dust, wood dust is not a risk factor for NHL. Little information was available on non-occupational exposures, except for smoking. Cigarette smoking is not a strong risk factor for NHL, and a survey of a subset of workers (~7%) found that age-adjusted cigarette smoking prevalence among workers was similar to that of the general population and was not associated with exposure to pentachlorophenol, so it is unlikely that smoking could explain the observed association between NHL and pentachlorophenol. Overall, the finding of strong positive exposure-response relationships for pentachlorophenol exposure using internal analyses and the lack of evidence of exposure to carcinogenic co-exposures argues against confounding by non-occupational or occupational co-exposures.

There is some evidence for an association between exposure to pentachlorophenol among producers and NHL, primarily based on the findings from the Michigan pentachlorophenol producers cohort study (Collins *et al.* 2009a, Ramlow *et al.* 1996). The evidence from the NIOSH pentachlorophenol producers study (Ruder and Yiin 2011), which includes workers in the Michigan study, is weaker; however, this study had a more limited exposure assessment (by production department only). The most predominant co-exposure in these studies is trichlorophenol. Trichlorophenol causes leukemia in experimental animals (listed in the RoC as *reasonably anticipated to be a human carcinogen*) and 2,3,7,8-TCDD, a trichlorophenol contaminant, is a risk factor for NHL (limited evidence).

Statistically significant increased risks for NHL in the pentachlorophenol-only subcohort (SMR = 2.8, 95% CI = 1.1 to 5.7, 7 deaths) and the combined pentachlorophenol/trichlorophenol cohort (SMR = 2.4, 95% CI = 1.0 to 4.7, 8 deaths) were found in the Michigan cohort (Collins *et al.* 2009a). Additional analyses using two different exposure assessments (reported in the two different updates) of specific, or surrogates for, cumulative pentachlorophenol exposure provide support for the hypothesis that the excess risk of NHL observed in the pentachlorophenol workers is caused by exposure to pentachlorophenol. In the earlier update (Ramlow *et al.* 1996), risks for NHL and multiple myeloma for workers with > 1 pentachlorophenol-year of cumulative (duration x intensity) exposure were reported for “other or unspecified” lymphohematopoietic cancers (4 deaths; ICD-8 200, 202, 203, or 209); however, it seems reasonable to assume that most if not all the deaths were NHL. In an internal analysis of these cancers, an increased relative risk (RR = 2.58, 95% CI = 0.98 to 6.80, 4 deaths) was observed among workers with at least one pentachlorophenol-year of cumulative exposure compared with non-exposed workers.

In the later update by Collins *et al.* (2009a), statistically significant increased SMRs (four to five fold) for NHL were found among workers in the highest cumulative exposure category for modeled exposure for all three chlorinated dioxins (HxCDD, HpCDD, and OCDD) pentachlorophenol by-products, considered to be exposure fingerprints for pentachlorophenol exposure (see Section 1) and for the total toxic equivalent (TEQ) (which include 2,3,7,8-TCDD, HxCDD, HpCDD and OCDD) (Table 3-3). SMRs did not

increase consistently in the lower and medium exposure categories (trend not reported) of the three chlorinated dioxins; however, as noted in Section 3.3.1, there is a potential for misclassification in these categories. No significant exposure-response trends were reported for modeled cumulative TEQ analysis using either discrete or cumulative continuous measures (see Table 3-4).

There is independent evidence that the excess risk of NHL observed in pentachlorophenol-exposed workers is unlikely to be explained by co-exposure to trichlorophenol. Only a small statistically non-significant increase in NHL mortality was reported in a separate analysis of the trichlorophenol production workers from this plant who did not have exposure to pentachlorophenol (SMR = 1.3, 95% CI = 0.6 to 2.6, 8 exposed deaths) (Collins *et al* 2009b). The risk of NHL also increased with increasing levels of 2,3,7,8-TCDD in this study, although not significantly. It is not known 2,3,7,8-TCDD exposure levels correlated with levels of the higher chlorinated dioxins that are pentachlorophenol by-products, and thus it is not known whether exposure to 2,3,7,8-TCDD contributes to the excess NHL risk observed in pentachlorophenol exposed workers.

**Table 3-3. NHL mortality and exposure to dioxin congeners: Michigan pentachlorophenol producers cohort study (Collins *et al.* 2009a)<sup>a</sup>**

Dioxin congener	Level of Congener <sup>a</sup> SMR (95% CI); # exposed deaths		
	Low	Medium	High
2,3,7,8-TCDD <sup>b</sup>	1.6 (0.2–5.7); 2	2.8 (0.6–8.1); 3	3.1 (0.6–9.1); 3
HxCDDs	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 (0.2–5.5); 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
TEQ	2.4 (0.5–7.2); 3	0.8 (0.0–4.7); 1	4.5 (1.2–11.6); 4

TEQ = toxic equivalent calculated using WHO recommended weights for 2,3,7,8-TCDD, HxCDDs, HpCDD and OCDD combined.

<sup>a</sup> Estimated cumulative levels of congeners (ppb-years) were divided into low, medium and high levels so that approximately equal numbers of deaths were assigned to each of the three categories.

<sup>b</sup> According to the paper, 196 of 773 workers were exposed to 2,3,7,8-TCDD, and only 1 NHL was observed in this group. The exposure assessment also included background levels of dioxin, and thus analysis of 8 NHL deaths most likely reflects background levels of 2,3,7,8-TCDD.

According to data reported in the NIOSH cohort, workers in the Michigan cohort were also exposed to several animal carcinogens and to styrene (which is a risk factor for lymphohematopoietic cancers including NHL), but there are no data on whether exposures to these chemicals were correlated with exposure to pentachlorophenol. Overall, the findings of excess risk of NHL with exposure-specific assessment mitigate concerns for confounding.

Although a statistically non-significant increased risk for NHL mortality was observed in the NIOSH cohort (SMR = 1.41, 95% CI = 0.64 to 2.67, 9 deaths) among pentachlorophenol only (no trichlorophenol) workers, it is not clear that this can be attributed to pentachlorophenol exposure in this study because of the lack of an exposure-response relationship with duration of work in pentachlorophenol departments (which may not be the best surrogate for exposure) and potential confounding from occupational co-exposures. The majority of workers appear to have had short-term exposure in the pentachlorophenol production departments (mean durations ranging from 1.3–3.2 years), however, so that an exposure duration-response relationship may be difficult to detect. In addition, the risk of NHL was higher in workers who were exposed to both pentachlorophenol and trichlorophenol (SMR = 2.50, 95% CI = 1.08 to 4.93, 8 deaths). The excess risk of NHL was observed in two of the four plants, Michigan and Illinois, which were the larger plants and the plants that also produced trichlorophenol. The authors also stated that approximately 90% of the workers in the entire cohort were also exposed to other chemicals. Potential exposures at the Michigan and Illinois plants included several chemicals that cause cancer in animals (for example, dichlorobenzene, nitrobenzene, ethylbenzene) or which are associated with limited evidence of carcinogenicity in humans (e.g., styrene).

Additional support for an association between exposure to pentachlorophenol among pentachlorophenol production users and NHL comes from the IARC registry-based nested case-control study (Kogevinas *et al.* 1995). Although the case-control study included workers from cohorts manufacturing phenoxy herbicides and chlorophenols, only one of the included cohorts produced pentachlorophenol. All of the NHL deaths occurred among production workers with the highest cumulative exposure to pentachlorophenol (OR = 4.19, 95% CI = 0.59 to 29.59, 3 deaths). The major limitation of the study is low statistical power; however, the findings are consistent with the findings for pentachlorophenol production workers in the United States.

Finally, the series of population-based case-control studies in Sweden also support an association between NHL and pentachlorophenol exposure. Increased ORs for exposure to pentachlorophenol and NHL were reported in the pooled analysis of hairy-cell leukemia and NHL (OR = 1.40, 95% CI = 0.99 to 1.98, 64 exposed cases and 101 exposed controls) (Hardell *et al.* 2002), and a smaller case-control study of NHL (OR = 8.8, 95% CI = 3.4 to 24.0, 15 exposed cases and 9 exposed controls) (Hardell *et al.* 1994). (Note that the evidence is weaker for NHL in the 1999 study of NHL alone than the pooled analysis.) In the 1994 study, the OR was not decreased in a multivariate analysis adjusting for phenoxy acid herbicide, DDT, asbestos and solvent exposure. A further analysis of the pooled data, by first or last date of exposure, suggested that the maximum increase in risk occurred at approximately 20 to 30 years after first exposure and 10 to 20 years after last exposure (Hardell *et al.* 2002). As noted, the major limitation in these population-based case-control studies is limited exposure assessment, especially where proxies were used for some subjects, which tends to result in non-differential exposure misclassification and a loss of precision. However, this concern is mitigated by the validation study of the questionnaire data conducted by the authors, which reported a high level of agreement (97%) between the questionnaire data and information obtained from employers regarding whether exposure to pentachlorophenol (or other agents) had occurred. Confounding by co-exposures, primarily phenoxy acid herbicides or other pesticides, in some of the studies cannot be ruled out, however.

In the New Zealand case-control study of NHL (Pearce *et al.* 1987), conflicting findings were reported for occupations thought to be associated with pentachlorophenol exposure; however, the probability and extent of exposure to pentachlorophenol is less clear, and thus these studies contribute little to the evaluation. No overall risk estimate specific for “exposure to pentachlorophenol” was reported in the Australian study (Smith and Christophers 1992), although specific types of pentachlorophenol exposure (e.g., pentachlorophenol in wood preservatives or carpet glues) were identified as exposures among specific cases of NHL and controls.

### *Multiple myeloma*

Multiple myeloma is also an uncommon cancer (rarer than NHL in the United States) with a relatively high survival rate, and, similar to NHL, cancer incidence studies with histological diagnoses are more informative than mortality studies using death certificates. Only two cohort studies, the NIOSH pentachlorophenol producers study (Ruder and Yiin 2011) and the Canadian sawmill workers study (Demers *et al.* 2006), reported findings for exposure specific to pentachlorophenol and only the latter study

reported incidence in addition to mortality data (Table 3-4). One population-based case-control study in New Zealand evaluated the risk of multiple myeloma among occupations thought to be associated with chlorophenol and phenoxy herbicide exposure, some of which might have involved pentachlorophenol exposure (Pearce *et al.* 1986a).

Occupational chemicals that have limited evidence (none identified with known) for multiple myeloma include benzene, ethylene oxide, and ionizing gamma radiation (Cogliano *et al.* 2011), none of which are potential co-exposures identified in the studies of pentachlorophenol. Potential non-occupational risk factors for multiple myeloma include obesity, certain autoimmune disorders, and race; however, none of these would be expected to be associated with pentachlorophenol exposure.

In the most informative study, the Canadian sawmill worker study (Demers *et al.* 2006), a statistically significant exposure-response relationship between dermal exposure to pentachlorophenol and multiple myeloma was observed for both incidence ( $P_{trend} = 0.02$ ) and mortality ( $P_{trend} = 0.03$ ) using the lowest exposure group (< 1 exposure-year) as a referent. Similar exposure-response relationships for incidence were found when exposure was lagged for 10 years ( $P_{trend} = 0.04$ ) or 20 years ( $P_{trend} = 0.03$ ). Risk estimates were approximately four-fold higher in the highest exposure category (5+ exposure-years) compared with the lowest category (<1 exposure-year) in lagged and unlagged incidence analyses. Although statistically non-significant elevated RRs for mortality and incidence were found in the highest exposure category of tetrachlorophenol, no exposure-response relationships were observed, suggesting that tetrachlorophenol was not a confounder.

In the NIOSH pentachlorophenol producers study, the SMR for multiple myeloma mortality among the pentachlorophenol only workers was 1.84 (95% CI = 0.68 to 4.00, 6 exposed deaths) (Ruder and Yiin 2011). A statistically non-significant elevated ORs for multiple myeloma was observed in one of the New Zealand case-control studies among workers engaged in fencing work (OR = 1.6, 95% CI = 0.9 to 2.7, 29 exposed cases), but not other occupations (treating fence posts or among sawmill/timber workers) associated with pentachlorophenol exposure, but the extent of exposure to pentachlorophenol is unclear (Pearce *et al.* 1986a). No other studies reported on this endpoint.

**Table 3-4. NHL and multiple myeloma among pentachlorophenol-exposed populations**

Reference	Study name Population Exposure assessment	Exposure group (N)	External analysis: SMR or SIR (95%CI); # exposed deaths or cases	Internal analysis: OR, SRR or RR; (95% CI); # exposed cases or cases/controls	Interpretation
<b>Cohort and nested case-control studies with specific exposure information for pentachlorophenol</b>					
Ruder and Yiin 2011	NIOSH PCP producer cohort 2122 male and female PCP production workers at 4 plants  Qualitative evidence of exposure assessment based on individual work/job/dept histories and investigators' industrial hygiene studies	PCP no TCP (1402) PCP + TCP (720) Total cohort (2122)  <i>Employment duration (days) in PCP department</i> Total cohort ≤ 57 58– < 182 182– < 650 ≥ 650  <i>Analyses by plant</i> Sauget, IL (788) Midland, MI (939) Other 2 plants (total 395)  PCP no TCP (1402) PCP + TCP (720) Total cohort (2122)	<u>NHL: SMR:</u> 1.41 (0.64–2.67); 9 2.50 (1.08–4.93); 8 1.77 (1.03–2.84); 17  2.45 (0.90–5.34); 6 1.56 (0.42–3.99); 4 1.63 (0.45–4.18); 4 1.42 (0.29–4.14); 3  1.81 (0.83–3.43); 9 2.18 (0.94–4.30); 8 0 deaths  <u>Multiple myeloma: SMR</u> 1.84 (0.68–4.00); 6 0.72 (0.02–3.99); 1 1.50 (0.60–3.10); 7	<u>NHL: SMR</u>    1.0 0.55 (0.15–1.97); 4 0.63 (0.18–2.28); 4 0.62 (0.15–2.55); 3	Adjusted for age, sex and calendar year  Some evidence of increase in risk of NHL among workers exposed to PCP and PCP+TCP; however, potential confounding from occupational co-exposures is possible.  Overall quality of evidence: limited

Reference	Study name Population Exposure assessment	Exposure group (N)	External analysis: SMR or SIR (95%CI); # exposed deaths or cases	Internal analysis: OR, SRR or RR; (95% CI); # exposed cases or cases/controls	Interpretation
Collins <i>et al.</i> 2009a, Ramlow <i>et al.</i> 1996	Michigan PCP producer cohort study  773 PCP male production workers, Midland, MI plant from NIOSH cohort  <i>Ramlow</i> : Exposure assessment based on work history, industrial hygiene data and expert assessment  <i>Collins</i> : Exposure assessment based on individual work/job histories and model exposure to chlorophenol dioxin by-products, and TCDD TEQ	<u>Ramlow <i>et al.</i> 1996</u> PCP 15-yr lag  <i>Cumulative exposure</i> ≥ 1 unit (PCP)  <i>15-yr lag cumulative exp</i> Low High  <u>Collins <i>et al.</i> 2009a</u> PCP no TCP (577) Total cohort (773)  <i>TEQ<sup>b</sup> (ppb-years)</i> <u>Cumulative (discrete)</u> 0.01–0.69 0.70–3.99 4.00–113.37 <i>P<sub>trend</sub></i>  <u>Continuous exposure</u> <i>P<sub>trend</sub></i>	<u>NHL &amp; MM<sup>a</sup>: SMR:</u> 2.0 (0.54–5.12); 4  <u>All LHC<sup>b</sup>: SMR</u> NR; 1 death 1.8 (0.48–4.61); 4  <u>NHL: SMR</u> 2.8 (1.1–5.7); 7 2.4 (1.0–4.7); 8  2.4 (0.5–7.1); 3 0.8 (0.0–4.7); 1 4.5 (1.2–11.5); 4 NR	<u>NHL&amp;MM<sup>a</sup> RR</u>  2.58 (0.98–6.80); 4  <u>All LHC<sup>b</sup>: RR</u> NR: no deaths 2.01 (0.90–4.45); 4  <u>NHL:RR</u>  RR coefficients unstable  0.61  1.006 (0.960–1.054) 0.80	All analyses adjusted for age and calendar year, in addition, internal analyses of cumulative exposure adjusted for employment stats and TEQ adjusted for hire year and birth year.  Evidence of an association between exposure to PCP and lymphoma or NHL based on analysis of cumulative exposure and hexa-, hepta-, and octachlorinated dibenzodioxins, which are by-products of PCP (not associated with TCP). Unclear whether exposure to TCDD contributes to NHL risk.  Overall quality of evidence: adequate - high
Demers <i>et al.</i> 2006, Friesen <i>et al.</i> 2007	Canadian sawmill workers cohort  Male sawmill workers (N = 27,464)  Cumulative exposure assessment based on individual work/job	<i>Total cohort</i> Mortality Incidence  <i>Cumulative exp (exp year)</i> <u>Mortality</u> < 1 1–2	<u>NHL</u> SMR 1.02 (0.75–1.34); 49 SIR 0.99 (0.81–1.21); 92	<u>NHL: RR</u> 1.0; 15 1.21 (0.46–3.15); 6	RR adjusted for age, calendar period and race  Positive exposure-response relationship observed in internal analysis of NHL and multiple myeloma incidence (lagged and



Reference	Study name Population Exposure assessment	Exposure group (N)	External analysis: SMR or SIR (95%CI); # exposed deaths or cases	Internal analysis: OR, SRR or RR; (95% CI); # exposed cases or cases/controls	Interpretation
Kogevinas <i>et al.</i> 1995	IARC registry-based nested case-control study of NHL  32 cases/158 controls  IARC registry cohort of 21,183 phenoxy herbicide-chlorophenol-, and dioxin- exposed workers in 11 countries  Exposure assessment based on individual work/job histories and plant records	Lagged 5 years Ever exposed <i>Cumulative exposure</i> No exposure Low exposure Medium exposure High exposure		<i>OR</i> 2.75 (0.45–17.00); 3/9  1.0; 29/149 0/2 0/2 4.19 (0.59–29.59) 3/5	PCP exposure limited to one cohort without exposure to other phenoxy herbicides or chlorophenols  Adjusted (via matching) by age, sex and country of residence  Small numbers of exposed cases and controls  Overall quality of evidence: adequate
<b>Population-based case-control studies with specific exposure information for pentachlorophenol</b>					
Hardell <i>et al.</i> 1994, Hardell <i>et al.</i> 1981	Swedish 1994 case-control study of NHL  Males 25–85 yrs old  Diagnosed 1974–1978  105 cases/335 controls  Structured questionnaire (self or proxy) for	High grade exposure (> 1 wk continuous or > 1 month total)		OR 8.8 (3.4–24.0); 15/9	97% agreement between self-reported questionnaire and employer records (sawmill and pulp industry), which mitigates concerns of recall bias.  Adjusted for age, and vital status; analysis of chlorophenols adjusted for exposure to solvents, phenoxyacetic acids, DDT,

Reference	Study name Population Exposure assessment	Exposure group (N)	External analysis: SMR or SIR (95%CI); # exposed deaths or cases	Internal analysis: OR, SRR or RR; (95% CI); # exposed cases or cases/controls	Interpretation
	information on lifetime working history and exposures				and asbestos  Overall quality of evidence: adequate
Hardell and Eriksson 1999	Swedish 1999 case- control study of NHL  Males $\geq$ 25 yrs old  Diagnosed 1987– 1990  404 cases/741 controls  Structured questionnaire (self or proxy) for lifetime work history and exposures	PCP exposure <i>Latency period (yrs)</i> 1–10 10–20 20–30 > 30		1.2 (0.7–1.8); 55/87  0 cases/4 controls 1.0 (0.3–2.9) 2.0 (0.7–5.3) 1.1 (0.7–1.8)	Potential recall bias from the use of proxies for exposure information  Adjusted for age, sex, year of death or county of residence. No excess risk of NHL from cigarette smoking or use of oral snuff.  Cannot rule out potential for confounding; no analysis or consideration of co-exposures or other risk factors  Overall quality of evidence: limited but adequate in pooled analysis
Nordstrom <i>et al.</i> 1998; HCL Hardell <i>et al.</i> 2002 (combined HCL and	Swedish HCL case- control study and pooled analysis of HCL+NHL  Males, diagnosed between 1987–1992  111 HCL cases, 400	Ever exposed to PCP (impregnating agent)  Ever exposed to PCP <i>Time (yrs) from 1<sup>st</sup> exp.</i> 1–10 > 10–20		<u>HCL</u> 2.6 (1.1–6.2); 9/14  <u>Combined NHL &amp; HCL</u> 1.40 (0.99–1.98); 64/101  0 exposed cases/controls 1.91 (0.82–4.44); NR	Pooled analysis (HCL and NHL) adjusted for age, study, study area, and vital status.  Cigarette smoking was not a risk factor for HCL in this study.

Reference	Study name Population Exposure assessment	Exposure group (N)	External analysis: SMR or SIR (95%CI); # exposed deaths or cases	Internal analysis: OR, SRR or RR; (95% CI); # exposed cases or cases/controls	Interpretation
NHL from Hardell and Eriksson 1999 and Nordstrom <i>et al.</i> 1998)	controls  Structured questionnaire (self-reported) lifetime work history and exposures. Minimum exposure 1 day, and induction period 1 year	> 20–30 > 30		2.13 (1.07–4.25); NR 1.13 (0.73–1.72); NR	Cannot rule out potential for confounding from other impregnating agent (creosote), which was also associated with an elevated risk in the pooled analysis but multivariate analysis controlled for exposure to other agents.  Overall quality of evidence: adequate
<b>Population-based case-control studies with limited exposure information for pentachlorophenol</b>					
Pearce <i>et al.</i> 1987, Pearce <i>et al.</i> 1986a, 1986b	New Zealand population-based case-control study of NHL & multiple myeloma (MM)  Males < 70 yrs old  Diagnosed 1977–1981  183 NHL cases, 338 controls  76 MM cases, 315 controls  Interview using structured questionnaire (self-	<i>Potential exposure to PCP</i>  Fencing work Fence post treater Sawmill/timber merchant  Fencing work Fence post treater Sawmill worker/timber merchant with potential for exposure to chlorophenols		<u>NHL: RR (90% CI)</u> 1.4 (1.0–2.0); 68/93 0.3 (0.1–1.3); 2/8 1.0 (0.5–2.0); 11/18  <u>MM: RR (90% CI)</u> 1.6 (0.9–2.7); 29/87 1.1 (0.2–5.6); 2/8 1.4 (0.5–3.9); 5/16	Exposure to PCP not specifically stated; misclassification of exposure is a concern  Adjusted for birth (decade) and self or proxy interview  Potential for confounding by phenoxy herbicides cannot be ruled out  Overall quality of evidence: limited

Reference	Study name Population Exposure assessment	Exposure group (N)	External analysis: SMR or SIR (95%CI); # exposed deaths or cases	Internal analysis: OR, SRR or RR; (95% CI); # exposed cases or cases/controls	Interpretation
	reported or proxy) on work history and use of herbicides				
Smith and Christophers 1992	Australian cancer registry-based case- control study  All male cases of lymphoma > 30 yrs old 1982–1988 plus cancer and population controls  Interview (self reported occupational or activities) and expert assessment of probability of exposure to chlorophenols	<i>Definite or probable exposure:</i>  PCP wood preservative Na-PCP as house painter PCP in carpet glues		NHL <i>case/pop control/cancer control</i> 1/1/1 2/0/1 1/0/0	No risk estimate specific for PCP exposure and no analysis for potential confounders  Overall quality of evidence: limited

Exp.= exposed; HpCDD = 1,2,3,4,6,7,8-hepta- chlorodibenzo-*p*-dioxin; HxCDD = 1,2,3,4,7,8- hexachlorodibenzo-*p*-dioxin (1, 4-HxCDD) or 1,2,3,6,7,8- hexachlorodibenzo-*p*-dioxin (1,6-HxCDD) or 1,2, 3,7,8,9-hexachlorodibenzo-*p*-dioxin (1,9-HxCDD); LH = lymphohematopoietic; MM = multiple myeloma; Na-PCP = sodium pentachlorophenate; NHL = non-Hodgkin lymphoma; OCDD = octachlorodibenzo-*p*-dioxin; PCP = pentachlorophenol; OR = odds ratio; RR = relative risk; SIR = standardized incidence ratio; SMR = standardized mortality ratio; SRR = standardized rate ratio; 2,3,7,8-TCDD = 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP = trichlorophenol; TeCP = tetrachlorophenol.

<sup>a</sup> Authors label as “other and unspecified” lymphohematopoietic cancer, as ICD 200, 202, 203, 209 (Ramlow *et al.* 1996)

<sup>b</sup> TEQ = toxic equivalent based on relative potency of 1,4-HxCDD, 1,6-HxCDD, 1,9-HxCDD, HpCDD, and OCDD relative to TCDD.

<sup>c</sup> HxCDD (combined) and HpCDD were statistically significantly increased among PCP-only workers vs. community referents; other dioxins were not significantly different from referents and are not reported here.

### *Soft tissue sarcoma*

Soft tissue sarcoma is a rare cancer with a higher survival rate, and most likely a long latency. A key challenge is disease diagnosis, which should be verified on the basis of both site and histology. The available studies reporting on soft tissue sarcoma mortality or incidence include the Canadian sawmill workers study (Demers *et al.* 2006), the Michigan pentachlorophenol producers study, a pooled analysis of four case-control studies in Sweden (Hardell *et al.* 1995), and case-control studies from New Zealand (Smith *et al.* 1984) and Australia (Smith and Christophers 1992). Only the Canadian sawmill cohort study (Demers *et al.* 2006) and the pooled case-control study (Hardell *et al.* 1995) were considered to be informative to evaluate this endpoint. The two U.S. producer studies and the IARC-based registry nested case-control study had insufficient statistical power (less than 20%) to evaluate this endpoint; no deaths were observed in the nested case-control study and only 1 death was observed among pentachlorophenol producer workers in each of the two producer cohort studies (Collins *et al.* 2009, Ruder and Yiin 2011). As mentioned previously, the New Zealand and Australian case-control studies had limited exposure information specific for pentachlorophenol. Potential occupational risk factors (with limited evidence of carcinogenicity in humans) include 2,3,7,8-TCDD and mixed chlorophenols (including pentachlorophenol).

In the Canadian sawmill workers cohort, cases of soft tissue sarcoma were identified via histological classification, and follow-up was relatively complete (Demers *et al.* 2006). Dermal exposure to pentachlorophenol was not associated with soft tissue sarcoma risk. Most of the cases of soft tissue sarcoma occurred among individuals in the lower exposure group (less than 1 exposure year) and the relative risk appears to decrease in both lagged and unlagged analyses.

In contrast, a statistically significant increased risk was found for soft tissue sarcoma and “high” (> 1 week continuous or > 1 month total) exposure to pentachlorophenol in the pooled analysis of four Swedish population-based case-control studies (OR = 2.8, 95% CI = 1.5 to 5.4, 27 exposed cases and 30 exposed controls) (Hardell *et al.* 1995). No difference between workers with longer (greater than 77 days) and shorter-term (1 up to 77 days) exposure to total chlorophenols was observed, of which pentachlorophenol was reported to be the predominant component (e.g., 27 of 33 exposed cases). A strength of the pooled analysis (Hardell *et al.* 1995) was the larger number of cases and histological re-review of the cases (in some of the individual case-control studies). Although exposure was assessed using self-reported or proxy data for exposure information, the authors stated that there was a 97% agreement between self-reported questionnaire data and employer records (in the sawmill and pulp industry), which mitigates concerns of recall bias. No increased risk was found for smoking or oral snuff use, which is consistent with the observation that tobacco smoking has not been identified as a risk factor for soft tissue sarcoma. An increase in risk was also observed for exposure to phenoxyacetic acids in these studies. However, in one of the four case-control studies included in the pooled analysis that excluded cases and controls exposed to phenoxyacetic acids (Hardell and Sandstrom 1979), an increased risk of soft tissue sarcoma and exposure to chlorophenols was observed. In the New Zealand case-control study (Smith *et al.* 1984), statistically non-significant risks of soft tissue sarcoma were found for some, but not all,

occupations that are thought to be associated with exposure to pentachlorophenol, and no cases of soft tissue sarcoma were associated with pentachlorophenol exposure in the Australian case-control study (Smith and Christophers 1992).

**Table 3-5. Soft tissue sarcoma among pentachlorophenol-exposed populations**

Reference	Study design/population Exposure Assessment	Exposure group (n)	External analysis: SMR or SIR (95%CI) # exposed deaths or cases	Internal analysis: OR, SRR or RR (95% CI) # exposed cases or cases/controls	Interpretation
<b>Cohort and nested case-control studies with specific exposure information for pentachlorophenol</b>					
Ruder and Yiin 2011	PCP producers See Table 3.6	PCP no TCP (1402) PCP + TCP (720) Total cohort (2122)	1.14 (0.03–6.36); 1 2.26 (0.06–12.6); 1 1.52 (0.18–5.48); 2		Limited statistical power for rare tumors  Connective tissue and soft tissue sarcoma (ICD code 171)  Overall quality of evidence: limited (only 2 cases)
Collins <i>et al.</i> 2009a	PCP producers See Table 3.6	PCP no TCP (577) PCP+/-TCP (773)	<u>SMR</u> 0.0 (0.0–10.7); 0 2.2 (0.0–12.1); 1		Limited statistical power for rare tumors  Overall quality of evidence: limited (only 1 case)
Demers <i>et al.</i> 2006	Canadian cohort of sawmill workers See Table 3.6	<i>Cumulative exposure</i> <u>Exp-yrs: incidence</u> < 1 1–2 2–5 5+ $P_{\text{trend}}$		<u>RR</u>  1 (ref.); 18 0.64 (0.18–2.20); 3 0.18 (0.04–0.85); 2 0 cases 0.11	STS (internal analysis) histologically confirmed  Limited statistical power for exposure-response analysis  No evidence of increase in risk  Smoking rates of workers similar to general population and not correlated with exposure  Overall quality of

Reference	Study design/population Exposure Assessment	Exposure group (n)	External analysis: SMR or SIR (95%CI) # exposed deaths or cases	Internal analysis: OR, SRR or RR (95% CI) # exposed cases or cases/controls	Interpretation
					evidence: high
Kogevinas <i>et al.</i> 1995	Nested case-control study of IARC cohort See Table 3.6	Ever exposed to PCP		No PCP exposure observed among cases or controls	Statistical power to detect an effect limited  Overall quality of evidence: limited
Hardell <i>et al.</i> 1995 <sup>b</sup>	Cancer registry-based case-control study (pooled analysis from four studies), rural Sweden  Structured questionnaire (self- or proxy-reported) on individual lifetime work history, exposures and lifestyle risk factors  434 cases, 948 controls  Cases histologically confirmed and reexamined in some studies	High grade PCP exposure (> 1 wk continuous or > 1 month total)  Chlorophenols exposure (most considered exposed to PCP) -days 1–77 days > 77 days		<u>OR</u> 2.8 (1.5–5.4); 27/30  3.0 (1.1–7.3); 12/15 3.4 (1.7–7.8); 22/19	97% agreement between self-reported questionnaire and employer records (sawmill and pulp industry), which helps mitigate concerns of recall bias.  Exposure primarily from sawmills or pulp (no clear potential confounders) and smoking not a risk factor in this study  Overall quality of evidence: adequate
<b>Population-based case-control studies with limited exposure information for pentachlorophenol</b>					
Smith <i>et al.</i> 1984	Cancer registry-based case-control study, New Zealand  82 cases, 92 cancer registry controls  Interviewed using structured questionnaire	<i>Potential exposure to PCP</i> Fencing as farmer Fencing contractor Sawmill or timber merchant  Potential chlorophenol exposure at sawmill or as		OR (90% CI) 0.8 (0.4–1.5); 20/26 1.9 (0.5–8.6); 5/3 1.3 (0.6–2.9); 12/11  OR (90% CI) 0.7 (0.1–2.7) 3/5	Exposure information not specific for PCP  Overall quality of evidence: limited

Reference	Study design/population Exposure Assessment	Exposure group (n)	External analysis: SMR or SIR (95%CI) # exposed deaths or cases	Internal analysis: OR, SRR or RR (95% CI) # exposed cases or cases/controls	Interpretation
	(self-or proxy-reported on lifetime work and herbicide exposure history)	timber merchant			
Smith and Christophers 1992	See Table 3-6	<i>Definite or probable exposure:</i> PCP wood preservative “Na-PCP as house painter” “PCP in carpet glues”  <i>Possible exposure:</i> Unknown wood preservative PCP laurate in woolen mill		<i>case/pop control/cancer control</i> 0/0/1 0/0/0 0/0/0  1/0/2  0/1/0	No specific risk estimate for PCP  Limited statistical power  Overall quality of evidence: limited

Na-PCP = sodium pentachlorophenate; OR = odds ratio; RR = relative risk; SIR = standardized incidence ratio; SMR = standardized mortality ratio; SRR = standardized rate ratio; STS = soft tissue sarcoma; 2,3,7,8-TCDD = 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP = trichlorophenol; TeCP = tetrachlorophenol; TEQ = toxic equivalent based on relative potency of 1,4-HxCDD, 1,6-HxCDD, 1,9-HxCDD, HpCDD, and OCDD relative to 2,3,7,8-TCDD.

<sup>a</sup>SMR and SIR calculated for total cohort and for connective tissue site diagnosis only: SMR = 1.10 (0.44–2.27) 7; SIR = 0.84 (0.49–1.44) 13; STS analyzed in internal analysis was diagnosed by both site (connective tissue) and histology.

<sup>b</sup>Combined analysis of 4 studies using similar populations and exposure assessment, Eriksson *et al.* 1990, Eriksson *et al.* 1981, Hardell and Eriksson 1988, Hardell and Sandstrom 1979.

*Other cancer site: Liver, kidney, lung and all cancers combined*

The available data to evaluate the solid tumors, kidney and liver, consists of the three cohort studies: the Canadian sawmill workers cohort (Demers *et al.* 2006) and the two pentachlorophenol production workers cohorts (Ruder and Yiin 2011, Collins *et al.* 2009a/Ramlow *et al.* 1996). Exposure-response analyses for kidney tumor were conducted in two studies (Demers *et al.* 2006, Ramlow *et al.* 1996), for liver in one study (Table 3-6) (Demers *et al.* 2006), lung in all three cohort studies, and all cancers combined in the two pentachlorophenol producers studies. Both liver and kidney cancers are relatively rare cancers with lower survival rates, and are not as subject to misclassification as lymphohematopoietic cancers and soft tissue sarcoma. Mortality data are therefore more closely comparable to incidence data for these endpoints. Potential risk factors for these cancers that may be relevant in the pentachlorophenol studies include smoking, arsenic (both endpoints), and alcoholic beverage consumption (liver only).

In the Canadian sawmill study (Demers *et al.* 2006), elevated risks for liver cancer mortality and incidence were observed for some exposure groups in the unlagged and 10-year lagged analyses; however, no exposure-response relationships were observed and increased risks were no longer present in the 20-year lagged analyses, which may be more relevant for solid tumors. In general, the magnitudes of the relative risks were weaker for exposure to tetrachlorophenol. A statistically nonsignificant increase in liver cancer mortality was observed in the pentachlorophenol only workers in the NIOSH cohort which was concentrated in the Illinois plant; only one liver cancer death was observed in the Michigan plant (Ruder and Yiin 2011). Potential confounding from other occupational co-exposures (several animal liver carcinogens and a possible human liver carcinogen, polychlorinated biphenyls, were produced or used at this plant) or smoking cannot be ruled out. Workers at this plant accumulated more pack-years than former unexposed workers at this plant; however, they were also older.

There is evidence for an association between kidney cancer and exposure to pentachlorophenol in the Canadian case-control study of sawmill workers (Demers *et al.* 2006) (Results not reported in Table 3-4). A statistically significant trend in risk for both mortality ( $P_{trend} = 0.02$ ) and to a lesser extent in incidence ( $P_{trend} = 0.07$ ) was observed when a separate analysis by exposure-years to pentachlorophenol was conducted; the response with incidence was strongest in models lagging exposure by 20 years ( $P_{trend} = 0.03$ ). A more modest but statistically significant trend was also observed in the mortality analysis by tetrachlorophenol exposure, but not for incidence, in lagged and unlagged models.

The evidence for an association between pentachlorophenol and kidney cancer is less clear among the pentachlorophenol producers cohorts, and there is limited power to examine exposure-response relationships due to the small number of deaths. A non-statistically significant excess of risk of kidney cancer mortality was found in the pentachlorophenol-exposed group in the Michigan cohort (Collins *et al.* 2009a) but not in the NIOSH study (Ruder and Yiin 2011). In the Michigan study, all three of the exposed deaths occurred in the highest cumulative exposure groups (RR = 4.27, 95% CI = 1.47 to 12.39, high exposure compared with low exposure) in the 1996 analysis by Ramlow *et al.*

(1996), however, in the subsequent analysis by Collins *et al.* (2009a) no exposure response was observed for total TEQ (which may not be a perfect surrogate for pentachlorophenol exposure since it includes 2,3,7,8-TCDD) in either internal or external analyses (no analyses for specific chlorinated dioxins were reported). In addition, workers in the Michigan plant were also exposed to a number of other chemicals, some of which cause renal tumors in experimental animals, and no information was available on tobacco smoking in this study.

In the three cohort studies, there was no evidence of an association of exposure to pentachlorophenol and lung cancer across studies. A statistically significant risk of lung cancer mortality (SMR = 1.56, 95% CI = 1.27 to 1.90; 99 exposed deaths) was observed among pentachlorophenol producers in the NIOSH study but no exposure-response relationship with employment in pentachlorophenol departments was observed in either internal or external analyses (total cohort, including workers also exposed to trichlorophenol) and there is a potential for confounding from other occupational co-exposures in this study. No increased risk of lung cancer was found among pentachlorophenol producers in the Michigan study (Collins *et al.* 2009a, Ramlow *et al.* 1996). Finally, no exposure-response relationships between dermal exposure to pentachlorophenol and lung cancer mortality ( $P_{\text{trend}} = 0.68$ ) or incidence ( $P_{\text{trend}} = 0.45$ ) were observed in the Canadian sawmill cohort study (Demers *et al.* 2006).

With respect to all cancers combined, there is little evidence for an increase in mortality or incidence in the three available cohort studies, although analyses are limited. In the earlier lagged analysis of the Michigan pentachlorophenol producers cohort by Ramlow *et al.* (1996), a marginal statistically non-significant increase in mortality in the higher exposure category with 15-year lag was observed in external and internal analyses, but no trend was observed. In the subsequent analysis (Collins *et al.* 2009a), relative risks were close to one for all levels of TEQ in internal analyses. In the NIOSH study (Ruder and Yiin 2011), a statistically significant increased SMR was observed among pentachlorophenol-only workers but no exposure-response was observed with employment in pentachlorophenol departments in the total cohort. In the Canadian sawmill cohort study (Demers *et al.* 2006), no increase in risk was observed in all cancer mortality and incidence for the total cohort; however, no exposure-response analyses were conducted.

**Table 3-6. Cohort studies of penachlorophenol exposure: liver and kidney cancer and all cancers combined**

Reference	Study design/population Exposure Assessment	Exposure group (N)	External analysis: SMR or SIR (95%CI); # observed deaths or cases	Internal analysis: OR, SRR, or RR (95% CI); # observed cases or exposed cases/controls	Interpretation
<b>Cohort studies with specific exposure information for pentachlorophenol</b>					
Ruder and Yiin 2011	NIOSH PCP producers cohort study  See Table 3-6	PCP no TCP (1402) PCP and TCP (720)  PCP no TCP (1402) PCP and TCP (720)  <i>Analysis by plant</i> Sauget, IL Midland, MI  PCP no TCP (1402) PCP and TCP (720)  <i>Employment duration (days) in PCP depart.</i> <u>Total cohort</u> ≤ 57 58– < 182 182– < 650 ≥ 650	<u>Kidney: SMR</u> 0.90 (0.25–2.31); 4 1.80 (0.49–4.61); 4  <u>Liver and biliary: SMR:</u> 1.76 (0.81–3.35); 9 No deaths observed  2.07 (0.89–4.08); 8 0.38 (0.01–2.09); 1  <u>All cancers: SMR</u> 1.25 (1.09–1.42); 238 1.01 (0.81–1.24); 88		Quantitative evidence of PCP exposure  Some evidence of increase in risk of liver cancer and all cancers combined among PCP-exposed workers not related to TCP co-exposure; however, exposure to other liver and human carcinogens possible  Overall quality of evidence is limited for kidney, liver, and all cancers combined
Collins <i>et al.</i> 2009a,	Michigan pentachlorophenol producers cohort	<u>Ramlow <i>et al.</i> 1996</u> PCP 15-yr lag	<u>Kidney: SMR:</u> 3.0 (0.62–0.88); 3	<u>Kidney: RR</u>	

Reference	Study design/population Exposure Assessment	Exposure group (N)	External analysis: SMR or SIR (95%CI); # observed deaths or cases	Internal analysis: OR, SRR, or RR (95% CI); # observed cases or exposed cases/controls	Interpretation
Ramlow <i>et al.</i> 1996	study See Table 3-6	<p><i>15-yr lag cumulative exp</i> Low High</p> <p><u>Collins <i>et al.</i> 2009a</u> PCP no TCP (577) Total cohort (773)</p> <p><i>TEQ<sup>b</sup> (ppb-years)</i> <u>Cumulative (discrete)</u> 0.01–0.69 0.70–3.99 4.00–113.37 <i>P<sub>trend</sub></i> (linear)</p> <p><u>Continuous exposure</u> <i>P<sub>tren</sub></i></p> <p><u>Collins <i>et al.</i> 2009a</u> PCP no TCP (577) PCP +/-TCP (773)</p> <p><u>Ramlow <i>et al.</i> 1996</u> <i>15-yr lag cumulative exp</i> Low High</p> <p><u>Collins <i>et al.</i> 2009a</u> PCP no TCP (577)</p>	<p>No deaths 5.02 (1.01–14.68); 3</p> <p>2.3 (0.6–5.8); 4 1.7 (0.5–4.4); 4</p> <p>0 3.6 (0.7–10.5); 3 1.6 (0.0–8.8); 1</p> <p><u>Liver and biliary: SMR</u> No deaths observed No deaths observed</p> <p><u>All cancers: SMR</u> 0.74 (0.40–1.24) 14 1.23 (0.83–1.74) 31</p> <p>1.0 (0.8–1.3) 71 1.0 (0.8–1.2) 94</p>	<p>No deaths 4.27 (1.47–12.39); 3</p> <p>RR unstable</p> <p>0.47</p> <p>1.008 (0.924–1.100); 4 0.86</p> <p><u>All cancers: RR</u> 0.78 (0.47–1.27) 14 1.11 (0.79–1.56) 31</p>	





### 3.5.1 Synthesis

Overall there is credible evidence for an association between exposure to pentachlorophenol and NHL, based on consistent findings across studies in different occupational populations with varying co-exposures, different geographical areas and study designs, and strong evidence of positive exposure-response relationships in the most informative study (Demers *et al.* 2006). An increased risk of NHL was found among workers exposed to pentachlorophenol in all of the studies specific for pentachlorophenol exposure. These studies include all three cohort studies (Collins *et al.* 2009a/Ramlow *et al.* 1996, Demers *et al.* 2006, Ruder and Yiin 2011), the nested case-control study of IARC herbicide workers (Kogevinas *et al.* 1995) and two Swedish population-based case-control studies (Hardell *et al.* 1994, 2002). Although the strength of the evidence varied among the studies, the finding of increased risk of NHL in both cohort and case-control studies, which have different types of strengths and limitations increases the confidence in the body of studies.

The strongest evidence comes from the large cohort of Canadian sawmill workers (Demers *et al.* 2006), which observed exposure-response relationships between cumulative dermal exposure to pentachlorophenol and both NHL mortality and incidence in lagged (10 and 20 years) and unlagged analyses. This finding is supported by findings from the Michigan pentachlorophenol cohort, in which a statistically significant increase in NHL was observed among workers who were only exposed to pentachlorophenol (Collins *et al.* 2009a). Analyses by exposure level found increases in NHL or NHL and multiple myeloma combined mortality among workers with at least one year of cumulative exposure (Ramlow *et al.* 1996) (in the earlier follow-up), and in the highest category of surrogates (chlorinated dioxins) for pentachlorophenol exposure in the subsequent follow-up (Collins *et al.* 2009a). The evidence for an association from the other individual studies with specific exposure information for pentachlorophenol (Hardell *et al.* 1994, 2002, Kogevinas *et al.* 1995, Ruder and Yiin 2011) is considered to be more limited, but as a group they provide evidence to support the associations found in the two most informative studies.

The next key question in the evaluation is whether the observed increases in risks in these studies can be explained by chance, bias, or confounding. There was little evidence for potential systematic biases in the studies. A potential bias in the Swedish case-control studies was the use of proxies for exposure information for some cases and controls; however, in most studies the dead cases were also matched with dead controls and proxies were used for both, and thus exposure misclassification would be expected to be non-differential and most likely bias findings toward the null.

The major co-exposures in the cohort studies are tetrachlorophenol for sawmill workers, and 2,4,5-trichlorophenol for some pentachlorophenol production workers. In addition there is potential exposure to 2,3,7,8-TCDD, a contaminant of trichlorophenol. (However, as noted in Section 1, 2,3,7,8-TCDD is not considered to be a contaminant of pentachlorophenol production.) There is limited evidence from studies in humans linking NHL to exposure to 2,3,7,8-TCDD (IARC 1997, 2012) or mixed polychlorophenols as a group (IARC, 1999); however, there are few independent studies that have adequately and specifically evaluated 2,4,5-trichlorophenol and tetrachlorophenol. Potential

confounding from tetrachlorophenol can reasonably be ruled out in the Canadian sawmill cohort (Demers *et al.* 2006) based on the lack of evidence of an exposure-response relationship with NHL in analyses of cumulative exposure to tetrachlorophenol as a continuous variable in this cohort, in contrast to a clear exposure-response relationship for pentachlorophenol (Friesen *et al.* 2007) and no exposure to 2,3,7,8-TCDD or other known or potential carcinogens would be expected in this cohort. Similarly, potential confounding by co-exposure to trichlorophenol can also reasonably be ruled out among the Michigan pentachlorophenol production workers. A separate analysis of the trichlorophenol-exposed cohort at the Michigan plant found only a small, statistically non-significant excess of NHL among trichlorophenol production workers without exposure to pentachlorophenol (Collins *et al.* 2009b).

The potential for confounding from co-exposures in the NIOSH cohort study cannot be reasonably ruled out. The population-based case-control studies also found an increased risk for NHL and exposure to phenoxy herbicides, suggesting the potential for confounding; however, ORs for NHL and exposure to chlorophenols (of which pentachlorophenol was the predominant agent) remained elevated in multivariate analyses controlling for exposure to other pesticides (Hardell *et al.* 1994).

Although most of the studies did not measure other occupational co-exposures or assess lifestyle information, the findings of an exposure-response relationship in internal analyses in the most informative study helps to mitigate these concerns. In addition, lifestyle factors such as smoking and alcohol use have not been shown to have a clear association with NHL. Finally, the pattern of co-exposures varies in the two occupational settings (production plant and sawmill) in the most informative studies and among the case-control studies, which adds strength to the hypothesis that pentachlorophenol is a common etiologic agent.

The associations between exposure to pentachlorophenol and other cancers were weaker. There was strong evidence for an association between multiple myeloma and moderate evidence for kidney cancer in the most informative (Canadian sawmill) cohort study (Demers *et al.* 2006), based on statistically significant exposure-response relationships; however, there was little evidence from other studies to support this finding. The pooled Swedish population-based case-control study of soft tissue sarcoma (Hardell *et al.* 1995) found an increased risk of this cancer with exposure to pentachlorophenol. However, no association was observed between pentachlorophenol exposure and soft tissue sarcoma incidence in the Canadian sawmill cohort study, which had an adequate number of cases to evaluate risks from this rare cancer; most of the cases of soft tissue sarcoma occurred in the lowest exposure group in this study (less than 1 to 2 dermal exposure-years). The Swedish pooled case-control study classified individuals as exposed based on very short duration periods (1 week of continuous exposure or 1 month of total exposure), and thus differences in exposure measures may help explain the inconsistency. The New Zealand (Smith *et al.* 1984) and Australian (Smith and Christophers 1992) case-control studies were inconclusive; however, the probability and extent of exposure to pentachlorophenol is less clear, and thus these studies contribute little to the evaluation. There was little evidence for an association with cancer of the liver, lung or all cancers combined.

### 3.6 Preliminary level of evidence recommendation

There is sufficient evidence for the carcinogenicity of pentachlorophenol from studies in humans. Epidemiological studies have found a consistent association between occupational exposure to pentachlorophenol and non-Hodgkin lymphoma that cannot be reasonably explained by chance, bias or confounding. The epidemiologic studies cannot distinguish the effects of pentachlorophenol itself from the effects of its by-products (e.g., chlorinated dioxins). Dioxin (specifically 2,3,7,8-tetrachlorodibenzo-*p*-dioxin) has been linked to NHL in humans and thus dioxin-like activity of its byproducts may contribute to the carcinogenicity observed in the human cancer studies of exposure to pentachlorophenol. There is some evidence to suggest an association between exposure to pentachlorophenol and multiple myeloma, soft tissue sarcoma, and kidney cancer; however, the evidence is either limited to one study or it is not consistent across studies.

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## 4 Studies of Cancer in Experimental Animals

This section reviews and assesses carcinogenicity studies in experimental animals exposed to pentachlorophenol and by-products of its synthesis. The steps in the cancer evaluation process are (1) identifying and describing the carcinogenicity studies in experimental animals (Section 4.1), (2) assessing the quality of these studies (Section 4.2), (3) synthesizing the findings from these studies (Section 4.3), and (4) reaching a preliminary listing recommendation (Section 4.4).

### 4.1 Identification and overview of the studies

Cancer studies in experimental animals were identified by searching databases, comprehensive reviews, and citations from studies retrieved from the literature searches as described in [Appendix A](#). Twelve studies (some studies are reported in multiple publications and some publications report on more than one study) met the inclusion/exclusion criteria requiring that included studies evaluate exposure specifically to pentachlorophenol and/or pentachlorophenol and by-products of its synthesis for long durations (> 12 months for rats and mice) or report neoplastic lesions, or non-neoplastic lesions relevant to carcinogenicity (see [Appendix D](#)).

The twelve studies were conducted in different species (mice and rats), using different routes of exposure (feed and dermal), different purities of pentachlorophenol (99% pure, technical grade and Dowicide EC-7 grade) and different study designs (standard two-year bioassays, transgenic mice, heterozygous *p53* gene knock-out mice, and mechanistic studies). All but one study (Spalding *et al.* 2000, dermal for Tg•AC mice) used a dietary route of exposure. Three studies were two-year NTP carcinogenicity studies that tested 90.4% pure technical grade pentachlorophenol or Dowicide EC-7 in B6C3F<sub>1</sub> mice (NTP 1989) or 99% pure pentachlorophenol in F344/N rats (Chhabra *et al.* 1999, NTP 1999). In order to look at the effects of dose intensity, the NTP (1999) also conducted a study in rats that included a stop-exposure group exposed to almost twice the concentration of pentachlorophenol for one year and evaluated at two years. The Schwetz (1978) publication tested Dowicide EC-7 in both a carcinogenicity study and a pre-mating to lactation reproductive study in Sprague-Dawley rats.

The study reported in the Mirvish (1991) publication was a co-carcinogen study, in which MRC-W rats were exposed to 2-hydroxyethylnitrosourea in drinking water for 40 weeks and to pentachlorophenol (86% pure technical grade pentachlorophenol with 25 µg/kg of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and 670 µg/kg 2,3,7,8-tetrachlorodibenzofuran (TCDF)) or other chemicals MRC-W rats in their feed for 94 weeks. The results reported in this monograph are from control groups from this study of either no treatment or treatment with pentachlorophenol and by-products of its synthesis only.

Three other mouse studies had exposure durations ranging from 10 to 18 months (Boberg *et al.* 1983, Delclos *et al.* 1986, Innes *et al.* 1969). The Innes *et al.* (1969) study was a screening study that tested Dowicide-7 and many other pesticides or industrial chemicals in two strains of mice ((C57BL/6x3H/Anf)F<sub>1</sub> and (C57BL/6xAKR)F<sub>1</sub>), initially by gavage starting at 7 days of age, then in the diet (from weaning at four weeks of age through 18 months of age). The Boberg *et al.* and Delclos *et al.* publications were mechanism studies that tested the ability of 99% pure pentachlorophenol to inhibit induction of liver tumors by 1'-hydroxysafrole or 4-aminoazobenzene, *N,N*-dimethyl-4-aminoazobenzene, or *N*-methyl-4-aminoazobenzene through inhibition of sulfotransferase activity in female CD-1 mice. However, both studies reported data from a pentachlorophenol-only dosed group.

Two short-term (25- to 26-week exposures) carcinogenicity studies tested 99% pure pentachlorophenol in transgenic mice with alterations in either a *Ha-ras* oncogene (FVB) or in a heterozygous *p53* gene knock-out mouse (C57BL/6) as an alternative to conventional 2-year carcinogenicity studies (Spalding *et al.* 2000).

**Table 4-1. Overview of studies of exposure to and by-products of its synthesis in experimental animals**

Strain (sex)	Substance	Experimental design	Exposure period/ study duration	Reference
<b>Rat: Diet</b>				
F344/N (M & F)	99% pure PCP	Carcinogenicity	2 yr/2 yr	Chhabra <i>et al.</i> 1999, NTP 1999
F344/N (M & F)	99% pure PCP	Carcinogenicity	1 yr/2 yr	Chhabra <i>et al.</i> 1999, NTP 1999
Sprague-Dawley (M & F)	Dowicide EC-7	Carcinogenicity and reproductive	M: 22 mo/22 mo F: 24 mo/24 mo	Schwetz <i>et al.</i> 1978
MRC-W (M & F)	Technical grade PCP	Co-carcinogen	94 wk/94 wk	Mirvish <i>et al.</i> 1991
<b>Mouse: Diet</b>				
B6C3F <sub>1</sub> (M & F)	Technical grade PCP	Carcinogenicity	2 yr/2 yr	McConnell <i>et al.</i> 1991, NTP 1989
B6C3F <sub>1</sub> (M & F)	Dowicide EC-7	Carcinogenicity	2 yr/2 yr	McConnell <i>et al.</i> 1991, NTP 1989
(C57BL/6xC3H/An f)F <sub>1</sub> , (M & F)	Dowicide-7	Carcinogenicity	18 mo/18 mo	Innes <i>et al.</i> 1969
(C57BL/6xAKR)F <sub>1</sub> (M & F)	Dowicide-7	Carcinogenicity	18 mo/18 mo	Innes <i>et al.</i> 1969
CD-1 (F)	99% pure PCP	Mechanism <sup>a</sup>	12 mo/16 mo	Boberg <i>et al.</i> 1983
CD-1 (F)	99% pure PCP	Mechanism <sup>a</sup>	10 mo/17 mo	Delclos <i>et al.</i> 1986
C57BL/6-Trp53(+/-)tm1Dol (M & F)	99% pure PCP	Short-term <i>p53</i> (+/-) knock-out carcinogenicity	26 wk/26 wk	Spalding <i>et al.</i> 2000
<b>Mouse: Dermal</b>				
Tg•AC hemizygous (M & F) <sup>b</sup>	99% pure PCP	Short-term transgenic carcinogenicity	20 wk/20 wk	Spalding <i>et al.</i> 2000

M = male, F = female.

<sup>a</sup> PCP inhibiting carcinogenic activation by sulfotransferase.

<sup>b</sup> Zetaglobin promoted v-Ha-ras on a FVB background.

#### 4.2 Assessing the quality of the studies

Each of these primary studies was systematically evaluated in a two-step process by first evaluating whether the level of detail reported for key elements of study design, experimental procedures, and cancer endpoints was adequate for evaluating its quality and interpreting results (Table 4-1). Key factors considered in the quality assessment include characterization of the

chemistry of the substance, dosing regimen, exposure and observation period, number of animals per exposure group, monitoring of animal health, and assessment for neoplasm endpoints. Details of each study assessment and quality criteria are reported in Appendix D, [Tables D-1, D-2a](#) and [D-2b](#). The reporting quality of key elements for all twelve studies was considered to be adequate. The two-year carcinogenicity studies by NTP were considered to be the most informative, and specific elements related to study quality and the interpretation of the findings are discussed in Section 4.3

### 4.3 Assessment of neoplastic findings

Findings from feed studies in rats are reported in Table 4-2, feed studies in mice are reported in Table 4-3 a, b, and the dermal application study in mice in Table 4-4. Findings across all studies for each species are discussed below.

#### 4.3.1 Feed studies: rats

Four feed studies using three different strains of rat and three grades of pentachlorophenol were found to be adequate for the cancer evaluation (Table 4-2). These studies found that pentachlorophenol and by-products of its synthesis causes malignant mesothelioma originating from the *tunica vaginalis* and squamous carcinomas of the nasal cavity in male rats.

The most informative studies were the stop-exposure and continuous-exposure feed studies with 99% pentachlorophenol in Fisher 344/N rats (NTP 1999, Chhabra 1999). These studies were informative due to appropriate dose selection, number of animals studied, duration of observation period, and comprehensive histopathologic evaluation of tissues. The stop-exposure study had a shorter exposure duration than the continuous-exposure study but they both used the same study period of two years, which approached the lifetime of the animal. The single dose level was higher (1,000 ppm) than the highest dose level of the continuous-exposure study (600 ppm) and decreased body weight with the greater dose in the stop-exposure study was evidence of some toxicity. There were no differences in survival between the concurrent control and high-dose groups in either the continuous-exposure study or the stop-exposure study. Treatment-related neoplasms occurred in the mesothelium and nasal cavity in rats exposed to pentachlorophenol in the stop-exposure study, but not the continuous-exposure study.

Malignant mesotheliomas originating from the *tunica vaginalis* and found throughout the abdominal cavity were significantly increased in male F344/N rats of the stop exposure study, but not in rats continuously exposed for two years (Chhabra *et al.* 1999, NTP 1999). The malignant mesothelioma incidence (21%) was also higher than the incidence range of historical controls (0% to 8%). The occurrence of malignant mesotheliomas in the stop-exposure group is considered an effect of 99% pentachlorophenol administration.

Squamous-cell carcinomas of the nasal cavity were also induced in male F344/N rats in the stop-exposure study. The incidences of squamous-cell carcinomas were not statistically significantly increased, but were greater than the historical control range for two-year feed studies (0% to 4%, based on 1,341 rats) and the concurrent controls (3%) were within the historical control range. The increased incidences were found in males exposed to 99% pure pentachlorophenol in the stop-exposure study (12%) and at the low dose level in the continuous-exposure study (8%). No squamous-cell carcinomas of the nasal cavity were observed in females. Respiratory epithelial hyperplasia and squamous metaplasia were also seen in the nasal cavity; however, these lesions were apparently associated with fungal infections and not with exposure to pentachlorophenol and by-products of its synthesis exposure as the incidences of hyperplasia and metaplasia

mirrored those of the infections, and decreased with increasing level of pentachlorophenol dose. Although not statistically significant, the occurrence of nasal squamous-cell carcinomas in the stop-exposure group is well above concurrent and historical control levels and is considered an effect of 99% pentachlorophenol administration.

A two-year feed study in Sprague-Dawley rats exposed to Dowicide EC-7 (96.4%) reported no significant increases in total neoplasms (Schwetz *et al.* 1978). The tumor incidences were high (around 50% in males and 100% in females) and similar between the untreated control and all exposed groups, but neoplasms were reported only as total neoplasms, a small number of animals were tested, and survival was not reported. Because no incidences of specific types of neoplasms were reported, the significance of specific tumor types could not be evaluated. Maximum exposure dose was 30-mg/kg bw/d as reported by the authors. Exposure concentrations used in this study are similar to that used in the NTP continuous-feed study in F344/N rats. The 600-ppm exposure in feed in that study is approximately a 30-mg/kg bw/d dose for male and female rats, similar to the high dose in the continuous-exposure study that reported no significant increase in neoplasms, and well below the stop-exposure dose of 1000 ppm (approximately 60-mg/kg bw/d dose in feed) that resulted in tumors.

The incidence of benign liver tumors (adenomas) was significantly increased in female MRC-W rats, but not in males after 94-weeks exposure to technical grade pentachlorophenol in feed (Mirvish *et al.* 1991). The Mirvish study was also the only study that identified TCDD and TCDF in the test substance. These compounds are considered contaminants of pentachlorophenol rather than production by-products as they are rarely present at detectable levels in technical grade or commercial grade pentachlorophenol (WHO 1987). The authors obtained technical grade pentachlorophenol from a U.S. chemical supplier, but the production source was not identified. The Mirvish study had a low number of rats per group, but survival could not be assessed because the original number of rats was not reported. These tumors are considered a treatment-related effect as a result of these contaminants and the significance of these contaminants on rat liver carcinogenesis is discussed in Section 5.

**Table 4-2. Studies of dietary exposure to pentachlorophenol and by-products of its synthesis in rats: tumor incidence**

Reference Strain, Sex Study Duration	PCP purity	Exposure duration ppm (# rats)	Liver (%) <sup>a</sup> Hepatocellular adenoma	Nose (%) <sup>a</sup> Squamous-cell carcinoma	Multiple organs including <i>tunica vaginalis</i> (%) <sup>a</sup> Malignant mesothelioma	Comments
NTP 1999 F344/N Male 2 yr	99% pure	<u>2 yr</u> 0 (50) 200 (50) <sup>b</sup> 400 (50) <sup>b</sup> 600 (50) <sup>b</sup> Trend		1/50 (2.7) <sup>c</sup> 3/50 (8.1) 1/50 (2.6) 0/50 (0.0) NS	1/50 (2.6) <sup>e</sup> 0/50 (0.0) 2/50 (5.1) 0/50 (0.0) NS	Survival was significantly increased compared to concurrent controls at 600 ppm. Body weights were lower than controls at 18 mo, but returned to control levels by the end of the study.
NTP 1999 F344/N Female 2 yr		0 (50) 200 (50) <sup>b</sup> 400 (50) <sup>b</sup> 600 (50) <sup>b</sup> Trend		0/50 [0] 0/50 [0] 0/50 [0] 0/50 [0] NS	NR (all dose groups)	Survival was the same as concurrent controls. Body weights were lower than controls at 18 mo, but returned to control levels by the end of the study.
NTP 1999 F344/N Male 2 yr		<u>Stop exposure: 1 yr</u> 0 (50) 1000 (50) <sup>b</sup>		1/50 (2.7) <sup>c</sup> 5/50 (11.6) <sup>d</sup>	1/50 (2.6) <sup>e</sup> 9/50 (20.6) <sup>*f</sup>	Survival was significantly increased compared to concurrent controls at 600 ppm. Body weights were lower than controls at the end of exposure, but returned to control levels by the end of the study.
NTP 1999 F344/N Female 2 yr		<u>Stop exposure: 1 yr</u> 0 (50) 1000 (50) <sup>b</sup>		0/50 [0] 1/50 [2]	NR	Survival was the same as concurrent controls. Body weights were lower than controls at 1 yr., but returned to control levels by the end of the study.
Mirvish <i>et al.</i> 1991 MRC-W Male 94 wk	86% pure with 25-ppb TCDD and 670-ppb TCDF	<u>94 wk</u> 0 (NR) 500 (NR)	0/9 [0] <sup>g</sup> 0/5 [0] <sup>g</sup>			Maximum mean body weights were similar between controls and exposed. The original number of rats were not reported <sup>g</sup> ; so survival effects cannot be evaluated. The number of exposed rats was low (5 males and 6 females).
Mirvish <i>et al.</i> 1991 MRC-W Female 94 wk		<u>94 wk</u> 0 (NR) 500 (NR)	0/18 [0] <sup>g</sup> 6/9 [67] <sup>**g</sup>			

Reference Strain, Sex Study Duration	PCP purity	Exposure duration ppm (# rats)	Liver (%) <sup>a</sup> Hepatocellular adenoma	Nose (%) <sup>a</sup> Squamous-cell carcinoma	Multiple organs including <i>tunica vaginalis</i> (%) <sup>a</sup> Malignant mesothelioma	Comments
Schwetz <i>et al.</i> 1978 Sprague-Dawley Male 22 mo	Dowicide EC-7 (90.4% pure PCP)	<u>22 mo</u> (mg/kg bw/day) 0 (27) 1 (27) 3 (27) 10 (27) 30 (27)	Authors reported that tumor incidences were not significantly different from controls, but incidences of specific tumor types were not reported.			Study terminated at 22 mo due to high mortality in control and experimental rats. Effects on body weight were not reported. Incidences of all tumors combined were not significantly increased; No incidences of the specific tumor types were reported, but included: pituitary, adrenal, thyroid glands, testes and pancreas.
Schwetz <i>et al.</i> 1978 Sprague-Dawley Female 24 mo		<u>24 mo</u> (mg/kg bw/day) 0 (27) 1 (27) 3 (27) 10 (27) 30 (27)				

\* $P \leq 0.05$ , \*\* $P \leq 0.01$ , \*\*\* $P \leq 0.001$  (compared with concurrent controls by poly-3 adjusted percent incidence after adjustment for intercurrent mortality); [] Statistical significance calculated by NTP using the Fisher Exact test for pair-wise comparisons.

NS = not significant, NR = not reported.

<sup>a</sup> (Adjusted tumor percent incidence—adjusted to account for survival) or [non-adjusted tumor percent incidence].

<sup>b</sup> Doses were based on toxicities from a 28 day feed study that caused lower body weights, increased liver weights, and liver lesions (hepatocyte degeneration and hepatocyte centriolobular hypertrophy) at 800 ppm, but not 400 ppm.

<sup>c</sup> Historical control levels ranged from 0% to 4% in the testing laboratory.

<sup>d</sup> Exceeded historical control range.

<sup>e</sup> Historical control levels ranged from 0% to 8% in the testing laboratory.

<sup>f</sup> Lesions originated from *tunica vaginalis*; lesions widely disseminated into the abdominal cavity in one control and 5 animals in the stop-exposure study.

<sup>g</sup> Denominators are the number of rats that survived to 11 weeks.

#### 4.3.2 Feed studies: mice

Seven feed studies using five different strains of mouse and three grades of pentachlorophenol were found to be adequate for the cancer evaluation (Tables 4-3a,b,c,d). The most informative studies were two chronic cancer studies in mice with each using different grades of pentachlorophenol (McConnell *et al.* 1991, NTP 1989) conducted by NTP. These studies had minimal quality concerns and provided detailed chemical analyses of the compounds tested. Neoplasms related to treatment with pentachlorophenol and by-products of its synthesis occurred in the liver, adrenal glands, and blood vessels in mouse feed studies using technical grade pentachlorophenol or Dowicide EC-7 and these outcomes are discussed below.

Malignant and benign neoplasms of the liver (hepatocellular carcinoma and adenoma combined) were induced in male and female B6C3F<sub>1</sub> mice exposed to Dowicide EC-7 and males exposed to technical grade pentachlorophenol. The benign neoplasm (hepatocellular adenoma) was the predominant neoplasm, being significantly increased in both males and females exposed to Dowicide EC-7 and in males exposed to technical grade of pentachlorophenol. However, only the males had significant increases in the malignant neoplasm (hepatocellular carcinoma). Females exposed to either grade of pentachlorophenol did develop carcinomas, but they were not significantly increased until combined with the adenomas. There were significant dose-response trends for the combined incidences of malignant and benign or benign liver neoplasms alone except for females exposed to technical grade pentachlorophenol.

Combined malignant and benign or benign alone adrenal-gland neoplasms (pheochromocytoma) and pre-neoplastic lesions (medullary hyperplasia) were induced in male and female B6C3F<sub>1</sub> mice exposed to Dowicide EC-7, while only benign neoplasms and pre-neoplastic lesions were induced in males exposed to technical grade. No malignant neoplasms of the adrenal gland were found in mice exposed to technical grade pentachlorophenol. The neoplasms induced by Dowicide EC-7 (benign and combined) also had significant dose-response trends. A few malignant pheochromocytomas were reported in male and female mice exposed to Dowicide EC-7 that were not statistically significant on their own, but were when the incidences were combined with benign pheochromocytomas.

Incidences of malignant tumors of the blood vessels (hemangiosarcoma) of the spleen and/or liver were significantly increased in female B6C3F<sub>1</sub> mice at the high dose levels after exposure to either technical grade pentachlorophenol or Dowicide EC-7. Significant trends were also reported in these groups. Hemangiosarcomas and hemangiomas were seen in males and a hemangioma was seen in one female exposed to Dowicide EC-7, but not at statistically significantly increased incidences.

Other feed studies in mice failed to show a statistically significantly increased incidence of neoplasms and were of different experimental designs than the NTP studies (Boberg *et al.* 1983, Delclos *et al.* 1986, Innes *et al.* 1969, Spalding *et al.* 2000).

The Innes (1969) study screened a large number of chemicals for tumors after neonatal gavage (postnatal days 7 to 28) and followed by feed exposures until necropsy at 18 months of age. Dowicide EC-7 was tested for slightly less than lifetime duration at a single, relatively low dose (130 ppm), comparable to the low doses used in the NTP (1989) and McConnell (1991) studies in both sexes of two strains of mouse (C57BL/6xC3H/Anf)F<sub>1</sub> and (C57BL/6xAKR)F<sub>1</sub>). Necropsy consisted of gross inspection of the pleural and peritoneal cavities for tumors and none

were reported for Dowicide EC-7. These results are similar to the NTP study that did not report tumors at the low dose (100 ppm) for Dowicide EC-7.

Pentachlorophenol was used in two studies of similar design, with the intent to examine the effect of pentachlorophenol inhibition of sulfotransferase activity on tumor induction (Boberg *et al.* 1983, Delclos *et al.* 1986). These studies were relatively short-term feed studies, exposing female CD-1 mice for a year or 10 months, at only one dose level of pentachlorophenol, with study durations of 16 and 17 months. Both studies used 99% pentachlorophenol in feed and the results for pentachlorophenol-only exposure (500 ppm) were compared with vehicle-only exposure for formation of hepatic nodules (“hepatomas”) by pentachlorophenol. These studies did not report liver tumors in female mice at 500 ppm. The results of the NTP study in female mice with Dowicide EC-7 did not conflict with these results, in that liver tumors were reported at a higher dose (600 ppm but not 200 ppm) and a longer exposure and observation period (2 years).

The Spalding study (2000) was a short-term study in a *p53*(+/-) gene knock-out mouse model and exposure was to 99% pentachlorophenol in feed for 26 weeks at up to 400 ppm. A complete necropsy was performed by NTP and results were reported as negative (no tumor incidence data was reported). The results of this study suggest that pentachlorophenol and by-products of its synthesis induced carcinogenesis through a pathway that does not involve *p53* (see Section 5 “Mechanisms”). However, no positive control groups were used in the study and none of the six experimental chemicals tested in this report induced neoplasms. Additionally, this is a model system for identification of mutagenic carcinogens and cannot be interpreted as a lack of carcinogenic activity (Eastin *et al.* 1998, French *et al.* 2001).

**Table 4-3a. Summary of dietary pentachlorophenol and by-products of its synthesis studies in mice: liver tumor incidence**

Reference Strain, Sex Study Duration	Purity	Exposure duration ppm (# mice)	Hepatocellular adenoma	Hepatocellular carcinoma	Combined neoplasms	Comments
NTP 1989 B6C3F <sub>1</sub> , Male 2 yr	Technical grade (90.4% pure)	<u>2 yr</u> 0 (35)	5/32 (27.6) <sup>b</sup>	2/32 (11.4) <sup>c</sup>	7/32 (35.8) <sup>d</sup>	Dose levels were based on liver lesions at 200 ppm from a 6-mo dietary study. Survival was not statistically different between concurrent controls (34%) and exposed groups (48% in low dose and 44% in high dose). Survival of untreated males (34%) was lower than that of untreated males in the Dowicide E-7 study (71%). Body weights of the male exposed groups were similar to the concurrent controls.
		100 (50)	20/47 (65.1)**	10/47 (33.2)	26/47 (75.7)**	
		200 (50)	33/48 (88.5)***	12/48 (39.5)*	37/48 (89.6)***	P < 0.001
		Trend	P < 0.001	P = 0.031		
NTP 1989 B6C3F <sub>1</sub> , Female 2 yr		<u>2 yr</u> 0 (35)	3/33 (10.7) <sup>e</sup>	0/33 [0] <sup>f</sup>	3/33 (10.7) <sup>g</sup>	Dose levels were based on liver lesions at 200 ppm from a 6-mo dietary study. Survival was similar between concurrent controls and exposed groups. Body weight of the high-dose female group was 5% to 13% lower than concurrent controls by 82 wks.
		100 (50)	8/49 (19.5)	1/49 [2]	9/49 (21.4)	
		200 (50)	8/50 (24.0)	1/50 [2]	9/50 (25.9)	P = 0.198
		Trend	P = 0.258	[NS]		
NTP 1989 B6C3F <sub>1</sub> , Male 2 yr	Dowicide EC-7 (91% pure)	<u>2 yr</u> 0 (35)	5/35 (20.0) <sup>b</sup>	1/35 (4.0) <sup>c</sup>	6/35 (24.0) <sup>d</sup>	Survival was similar in exposed groups and untreated controls. Survival of untreated males (71%) was higher than that of untreated males in the technical grade study (34%). Body weights were lower in exposed compared to untreated controls in the high-dose males.
		100 (50)	13/48 (41.6)	7/48 (20.2)	19/48 (53.8)*	
		200 (50)	17/48 (53.0)*	7/48 (24.1)	21/48 (65.5)**	P ≤ 0.001
		600 (50)	32/49 (84.1)***	9/49 (25.0)*	34/49 (87.1)***	
NTP 1989 B6C3F <sub>1</sub> , Female 2 yr		<u>2 yr</u> 0 (35)	1/34 (3.4) <sup>e</sup>	0/34 [0] <sup>f</sup>	1/34 (3.4) <sup>g</sup>	Survival rates were similar in untreated controls and mid- and high-dose females and were significantly lower for low-dose females compared with controls.
		100 (50)	3/50 (10.7)	1/50 [2]	4/50 (13.8)	

Reference Strain, Sex Study Duration	Purity	Exposure duration ppm (# mice)	Hepatocellular adenoma	Hepatocellular carcinoma	Combined neoplasms	Comments
		200 (50) 600 (50) Trend	6/49 (15.8) 30/48 (75.0)*** $P \leq 0.001$	0/49 [0] 2/48 [4] [NS]	6/49 (15.8) 31/48 (77.5)*** $P \leq 0.001$	Body weights were lower in exposed compared to untreated controls in mid- and high-dose females.
Innes <i>et al.</i> 1969 (C57BL/6xC3H/Anf)F <sub>1</sub> and (C57BL/6xAKR)F <sub>1</sub> , Male 18 mo	Dowicide-7	<u>18 mo</u> (ppm in food) 0 (79–90) 130 (18)	No significant increase at 0.01 significance level			Mice were originally administered PCP by gavage, then after weaning at 3 weeks were administered PCP in the diet. The dose level was based on the results of a 19 day study.  Screening study evaluated multiple chemicals, tumor incidence for individual chemicals not reported; no significant increase in any tumor at $P = 0.01$ significance level
Innes <i>et al.</i> 1969 (C57BL/6xC3H/Anf)F <sub>1</sub> and (C57BL/6xAKR)F <sub>1</sub> , Female 18 mo	Dowicide-7	<u>18 mo</u> (ppm in food) 0 (82–87) 130 (18)	No significant increase at 0.01 significance level			Mice were originally administered PCP by gavage, then after weaning at 4 weeks were administered PCP in the diet. The dose level was based on the results of a 19-day study.  A screening study to evaluate multiple chemicals, tumor incidence for individual chemicals not reported; no significant increase in any tumor at $P = 0.01$ significance level.
Boberg <i>et al.</i> 1983 CD-1 Female, 16	PCP > 99% pure	<u>12 mo</u> 0 (36) 500 (36)			Liver hepatoma <sup>h</sup> 0/32 [0] 0/31 [0]	This study examined PCP inhibition of tumor induction by 1'-hydroxysafrole and PCP inhibition of sulfotransferase activity.

Reference Strain, Sex Study Duration	Purity	Exposure duration ppm (# mice)	Hepatocellular adenoma	Hepatocellular carcinoma	Combined neoplasms	Comments
mo						
Delclos <i>et al.</i> 1986 CD-1 Female, 17 mo	PCP > 99% pure	<u>10 mo</u> 0 (35) 500 (35)			Liver hepatoma 0/20 [0] 0/27 [0]	This study examined PCP inhibition of liver tumor induction by other carcinogens.

$P \leq 0.05$ ,  $**P \leq 0.01$ ,  $***P \leq 0.001$  (compared with concurrent controls by Fisher's Exact test for pair-wise comparisons and Cochran-Armitage trend test for trends); [] Statistical significance calculated by NTP using the Fisher's Exact test for pair-wise comparisons or Cochran-Armitage trend test.

NS = not significant, NR = not reported.

<sup>a</sup> (Survival adjusted tumor percent incidence) or |non-adjusted tumor percent incidence|.

<sup>b</sup> Historical control levels ranged from 8% to 15% in the testing laboratory and 0% to 44% in NTP studies.

<sup>c</sup> Historical control levels ranged from 8% to 28% in the testing laboratory and 8% to 30% in NTP studies.

<sup>d</sup> Historical control levels ranged from 16% to 40% in the testing laboratory and 16% to 58% in NTP studies.

<sup>e</sup> Historical control levels ranged from 0% to 8% in the testing laboratory and 0% to 18% in NTP studies.

<sup>f</sup> Historical control levels ranged from 2% to 8% in the testing laboratory and 0% to 8% in NTP studies.

<sup>g</sup> Historical control levels ranged from 4% to 17% in the testing laboratory and 2% to 20% in NTP studies.

<sup>h</sup> Gross observation of liver for hepatic nodules.

**Table 4-3b. Summary of dietary pentachlorophenol and by-products of its synthesis studies in mice: blood vessels (%)<sup>a</sup> tumor incidence**

Reference Strain, Sex Study Duration	Purity	Exposure duration ppm (# mice)	Hemangioma	Hemangiosarcoma	Combined neoplasms <sup>b</sup>	Comments
NTP 1989 B6C3F <sub>1</sub> , Male 2 yr	Technical grade (90.4% pure)	2 yr 0 (35) 100 (50) 200 (50) Trend	1/36 [3] 0/49 [0] 2/49 [4] [NS]	0/35 [0] 2/49 [4] 1/49 [2] [NS]	1/35 (3.8) 2/49 (8.3) 3/49 (11.4) NS	See Table 4-3a
NTP 1989 B6C3F <sub>1</sub> , Female 2 yr	Technical grade (90.4% pure)	<u>2 yr</u> 0 (35) 100 (50) 200 (50) Trend	0/35 [0] 0/50 [0] 0/50 [0]	0/35 (0.0) <sup>c</sup> 3/50 (6.8) 6/50 (17.1)* <i>P</i> = 0.024		See Table 4-3a
NTP 1989 B6C3F <sub>1</sub> , Male 2 yr	Dowicide EC-7 (91% pure)	<u>2 yr</u> 0 (35) 100 (50) 200 (50) 600 (50) Trend	1/35 [3] 0/50 [0] 1/50 [2] 2/49 [4] [NS]	0/35 (0.0) 4/50 (13.2) 2/50 (6.7) 3/49 (8.6) <i>P</i> = 0.411	1/35 (4.0) 4/50 (13.2) 3/50 (10.0) 5/49 (14.3) <i>P</i> = 0.200	See Table 4-3a
NTP 1989 B6C3F <sub>1</sub> , Female 2 yr	Dowicide EC-7 (91% pure)	<u>2 yr</u> 0 (35) 100 (50) 200 (50) 600 (50) Trend	0/35 [0] <sup>o</sup> 0/50 [0] 0/50 [0] 1/49 [2] [NS]	0/35 (0.0) 1/50 (3.6) 3/50 (7.3) 8/49 (18.9)** <i>P</i> ≤ 0.001	0/35 (0.0) <sup>d</sup> 1/50 (3.6) 3/15 (7.3) 9/49 (21.3)** <i>P</i> ≤ 0.001	See Table 4-3a

\* $P \leq 0.05$ , \*\* $P \leq 0.01$ , \*\*\* $P \leq 0.001$  (compared with concurrent controls by Fisher's Exact test for pair-wise comparisons and Cochran-Armitage trend test for trends); [] Statistical significance calculated by NTP using the Fisher's Exact test for pair-wise comparisons or Cochran-Armitage trend test.

NS = not significant, NR = not reported, NOS = not otherwise specified.

<sup>a</sup> (Survival adjusted tumor percent incidence) or [non-adjusted tumor percent incidence].

<sup>b</sup> Blood vessel tumors occurred mostly in the spleen, but also in the liver.

<sup>c</sup> Historical control levels ranged from 0% to 4% in the testing laboratory and 0% to 8% in NTP studies.

<sup>d</sup> Historical control levels ranged from 0% to 6% in the testing laboratory and 0% to 12% in NTP studies.

**Table 4-3c. Summary of dietary pentachlorophenol and by-products of its synthesis studies in mice: adrenal gland (%)<sup>a</sup> tumor incidence**

Reference Strain, Sex Study Duration	Purity	Exposure duration ppm (# mice)	Medullary Hyperplasia	Benign	Malignant	Combined Pheo-chromocytoma	Comments
NTP 1989 B6C3F <sub>1</sub> , Male 2 yr	Technical grade (90.4% pure)	<u>2 yr</u> 0 (35) 100 (50) 200 (50) Trend	1/31 [3] 10/45 [22] <sup>[*]</sup> 10/45 [22] <sup>[*]</sup> [ <i>P</i> ≤ 0.05]	0/31 (0.0) <sup>b</sup> 10/45 (37.9) <sup>**</sup> 23/45 (84.9) <sup>***</sup> <i>P</i> < 0.001	NR		See Table 4-3a
NTP 1989 B6C3F <sub>1</sub> , Female 2 yr		<u>2 yr</u> 0 (35) 100 (50) 200 (50) Trend	0/33 [0] 4/48 [8] 2/49 [4] [NS]	0/33 [0] 2/48 [4] 1/49 [2] NS	2/33 [6] 0/48 [0] 0/49 [0] [NS]	2/33 [6] <sup>c</sup> 2/48 [4] 1/49 [2] [NS]	See Table 4-3a
NTP 1989 B6C3F <sub>1</sub> , Male 2 yr	Dowicide EC-7 (91% pure)	<u>2 yr</u> 0 (35) 100 (50) 200 (50) 600 (50) Trend	1/34 [3] 19/48 [40] <sup>[***]</sup> 13/48 [27] <sup>[**]</sup> 1/49 [2] [ <i>P</i> ≤ 0.01]	0/34 (0.0) 4/48 (13.8) 21/48 (67.5) <sup>***</sup> 44/49 (97.8) <sup>***</sup> <i>P</i> ≤ 0.001	1/34 (4.0) 0/48 (0.0) 0/48 (0.0) 3/49 (8.6) <i>P</i> = 0.084	1/34 (4.0) <sup>b</sup> 4/48 (13.8) 21/48 (67.5) <sup>***</sup> 45/49 (100.0) <sup>***</sup> <i>P</i> ≤ 0.001	See Table 4-3a
NTP 1989 B6C3F <sub>1</sub> , Female 2 yr	Dowicide EC-7 (91% pure)	<u>2 yr</u> 0 (35) 100 (50) 200 (50) 600 (50) Trend	2/35 [6] 1/49 [2] <sup>[***]</sup> 5/46 [11] <sup>[**]</sup> 17/49 [35] [ <i>P</i> ≤ 0.001]	0/35 (0.0) 1/49 (3.6) 2/46 (5.3) 38/49 (86.3) <sup>***</sup> <i>P</i> ≤ 0.001	0/35  0  1/49  2  0/46  0  1/49  2  [NS]	0/35 (0.0) <sup>c</sup> 2/49 (7.1) 2/46 (5.3) 38/49 (86.3) <sup>***</sup> <i>P</i> ≤ 0.001	See Table 4-3a

\**P* ≤ 0.05, \*\**P* ≤ 0.01, \*\*\**P* ≤ 0.001 (compared with concurrent controls by Fisher's Exact test for pair-wise comparisons and Cochran-Armitage trend test for trends);

[ ] Statistical significance calculated by NTP using the Fisher's Exact test for pair-wise comparisons or Cochran-Armitage trend test.

NS = not significant, NR = not reported, NOS = not otherwise specified.

<sup>a</sup> (Survival adjusted tumor percent incidence) or [non-adjusted tumor percent incidence].

- 
- <sup>b</sup> Historical control levels ranged from 0% to 2% in the testing laboratory and 0% to 8% in NTP studies (includes 2/1,969 malignant pheochromocytomas).
- <sup>c</sup> Historical control levels ranged from 0% to 4% in the testing laboratory and 0% to 6% in NTP studies (includes 2/1,969 malignant pheochromocytomas).

**Table 4-3d. Summary of dietary pentachlorophenol and by-products of its synthesis studies in mice: tumor incidence**

Reference Strain, Sex Study Duration	Exposure duration ppm (# mice)	Liver (%) Hepatocellular carcinoma or adenoma	Other reported tissues (%)	Comments
Innes <i>et al.</i> 1969 (C57BL/6xC3H /Anf)F <sub>1</sub> and (C57BL/6xAk R)F <sub>1</sub> , Male 18 mo	<u>18 mo</u> (ppm in food) 0 (79–90) 130 (18)		NS	Dowicide-7 Incidences for experimental groups that were negative were not reported. Mice were originally administered PCP by gavage, then after weaning at 3 weeks were administered PCP in the diet. The dose level was based on the results of a 19-day study.
Innes <i>et al.</i> 1969 (C57BL/6xC3H Anf)F <sub>1</sub> and (C57BL/6xAk R)F <sub>1</sub> , Female 18 mo	<u>18 mo</u> (ppm in food) 0 (82–87) 130 (18)		NS	
Boberg <i>et al.</i> 1983 CD-1 Female, 16 mo	<u>12 mo</u> 0 (36) 500 (36)	<u>Liver hepatoma</u> 0/32 [0] 0/31 [0]	Angioliposarcoma and hemangioma of the liver and lung adenoma (one mouse each (1/31), control (0/32).	PCP > 99% pure. This study examined PCP inhibition of tumor induction by 1'- hydroxysafrole and PCP inhibition of sulfotransferase activity. Results reported for control and PCP only groups.
Delclos <i>et al.</i> 1986 CD-1 Female, 17 mo	<u>10 mo</u> 0 (35) 500 (35)	<u>Liver hepatoma</u> 0/20 [0] 0/27 [0]	<u>Lymphoma</u> 1/20 [5] 3/27 [11] Mammary adenocarcinoma, malignant histiocytoma, hemangioendothelioma and angiosarcoma of the	PCP > 99% pure This study examined PCP inhibition of liver tumor induction by other carcinogens. Results reported for control and PCP-only groups.

Reference Strain, Sex Study Duration	Exposure duration ppm (# mice)	Liver (%) Hepatocellular carcinoma or adenoma	Other reported tissues (%)	Comments
			liver (one mouse each (1/27), control (0/20))	
Spalding <i>et al.</i> 2000 C57BL/6- Trp53(+/-) tm1Dol; N5 (heterozygous) Male, 26 wk	<u>26 wk</u> 0 (10) 100 (10) 200 (10) 400 (10)		NS	PCP 99% pure The number of animals per group was not reported. No tumor incidences were given and results reported as “-“ (negative)
Spalding <i>et al.</i> 2000 C57BL/6- Trp53(+/-) tm1Dol; N5 (heterozygous) Female, 26 wk	<u>26 wk</u> 0 (10) 100 (10) 200 (10) 400 (10)		NS	

NS = not significant, NR = not reported, NOS = not otherwise specified.

<sup>a</sup> (Adjusted tumor percent incidence – adjusted to account for survival) or [non-adjusted tumor percent incidence].

#### 4.3.3 Dermal studies: mice

Only one study tested dermal application of 99% pentachlorophenol in Tg•AC mice (Spalding *et al.* 2000). Papillomas of the skin were induced in transgenic female mice that are hemizygous with a zeta globin promoted *v-Ha-ras* oncogene after a six-month exposure period. The incidence of papillomas was significantly increased at the two highest dose levels and had a positive dose-response trend with 100% incidence at the highest dose level. In addition to increased incidences, there were increases in multiplicity, i.e., the number of papillomas per mouse. The multiplicity was not analyzed statistically, but was over 100 times higher in the high-dose group (11.6/mouse) than the vehicle-treated controls (0.07/mouse) and increased with dose. The study was well designed and included not only an untreated control, but also a positive control group of 12-*O*-tetradecanoyl-phorbol-13-acetate exposed mice. The finding of papillomas at high multiplicity provides support for carcinogenic activity of 99% pentachlorophenol in mice. This transgenic mouse model is more sensitive to tumor induction than conventional cancer bioassays, as it has an oncogenic mutation. However, this model has been questioned as neoplasms can be induced by non-carcinogenic treatments, such as skin irritation and wounding (Fuhrman 2005). This is the only cancer study in mice located using 99% pure pentachlorophenol.

**Table 4-4. Summary of dermal pentachlorophenol and by-products of its synthesis studies in mice**

Reference Strain Sex Study Duration	Exposure duration Dose in mg/mouse (# animals) 5 doses/week	Skin (%) <sup>a</sup> Papilloma	Comments
Spalding <i>et al.</i> 2000 Tg•AC hemizygous (zetaglobin promoted v-Ha- ras on a FVB background) Female 26 wk	20 wk 0 (15) <sup>b</sup> 0.75 (13) 1.5 (13) 3.0 (14) Trend  0 (15) 0.75 (13) 1.5 (13) 3.0 (14)	<u>Incidence</u> 1/15 [7] 1/13 [8] 8/13 [62] <sup>!*</sup> 14/14 [100] <sup>!****]</sup> [ <i>P</i> ≤ 0.0001]  <u>Multiplicity<sup>c</sup></u> 1/15 [0.07] 1/13 [0.08] 11/13 [0.85] 162/14 [11.6]	PCP 99% Survival was similar to untreated controls. A positive control of TPA <sup>d</sup> was used, which had an incidence of 15/15 [100%] and multiplicity of 405/15 (27.0 tumors/mouse).

\**P* ≤ 0.05, \*\**P* ≤ 0.01, \*\*\**P* ≤ 0.001, \*\*\*\**P* ≤ 0.0001 Statistical significance calculated by NTP using one-sided Fisher Exact test for pair-wise comparisons or Cochran-Armitage trend test for trends [].

<sup>a</sup> (Adjusted tumor percent incidence – adjusted to account for survival) or [non-adjusted tumor percent incidence].

<sup>b</sup> negative control of acetone.

<sup>c</sup> Multiplicity expressed as total tumors/# mice and [average # tumors/mouse].

<sup>d</sup> 12-*O*-Tetradecanoyl-phorbol-13-acetate, 1.25 µg, 3 doses/wk.

#### 4.4 **Preliminary recommendation of level of evidence**

There is sufficient evidence for the carcinogenicity of pentachlorophenol and by-products of its synthesis in experimental animals. The listing is based on exposure-related malignant and/or a combination of malignant and benign neoplasms of the liver, adrenal gland, blood vessels, nasal cavity, and *tunica vaginalis*. Incidences of liver (hepatocellular carcinoma and adenoma combined) and adrenal gland (combined malignant and benign pheochromocytoma) neoplasms were significantly increased in male and female mice, while malignant neoplasms of the blood vessels (hemangiosarcoma) were induced in female mice. In male rats, significant increases in malignant neoplasms of the *tunica vaginalis* (mesothelioma) and non-significant increases in rare nasal cavity (squamous-cell carcinoma) neoplasms occurred at incidences greater than historical controls.

## 5 Mechanistic Data and Other Relevant Effects

This section reviews data related to identifying and evaluating putative mechanisms for the potential carcinogenicity of pentachlorophenol and by-products of its synthesis including genetic and related effects and mechanistic considerations. The primary purpose is to identify potential mechanisms of action of carcinogenicity, review the strength of evidence for potential mechanisms, and discuss any key issues that address the relevance of carcinogenic effects observed in experimental animals to effects in humans.

### 5.1 Genetic and related effects

Pentachlorophenol has been tested in several short-term assays to evaluate mutagenicity and other potential genotoxic effects. The data presented here comes from primary peer-reviewed papers as well as from review articles (Seiler 1991, IARC 1999, and EPA 2010). Chemical purity is included if indicated by the authors; however, often only the source of purchase was indicated with no mention of purity, so there is an assumption that the material tested is at least of technical grade or better.

*In vitro* studies include assays for mutagenicity and DNA damage in bacteria (Section 5.1.1) and assessments of several types of cytogenetic effects in non-mammalian eukaryotes (Section 5.1.2) and cultured mammalian cells (Section 5.1.3). Pentachlorophenol-induced oxidative DNA damage and DNA and protein adduct formation is discussed in Section 5.1.4. *In vivo* studies include evaluations of cytogenetic effects in rodents (Section 5.1.5) and in workers occupationally exposed to pentachlorophenol (Section 5.1.6). Studies on the genotoxicity of some pentachlorophenol metabolites are described in Section 5.1.7. An overall assessment of the genotoxicity of pentachlorophenol is presented in the final section (Section 5.1.8). Summary tables of genotoxicity studies on pentachlorophenol and its metabolites are given in Tables 5-1 and 5-2, respectively. The data for all of the genotoxicity studies discussed in Section 5.1 are provided in Appendix E.

#### 5.1.1 *In vitro* studies in bacteria

Pentachlorophenol induced mutation in bacteria only under specific conditions. It was reported to be mutagenic by one laboratory, but only in *Salmonella typhimurium* strain TA98, using the preincubation protocol, with the addition of phenobarbital/benzoflavone-induced rat liver metabolic activation S9 (Nishimura *et al.* 1982, Nishimura and Oshima 1983). Although reported by Gopaldaswamy and Nair (1992) as weakly mutagenic in an assay using Aroclor-induced rat S9, that study's lack of control data and methodological issues limit its usefulness. All other available *Salmonella* mutation assays, with TA98 and all other tester strains, using plate incorporation and preincubation protocols, both with and without the addition of S9 metabolic activation (rat or hamster), were negative (for details of studies, see Appendix E, [Table E-1](#)). It is unclear whether the type of S9 affects the mutagenicity of pentachlorophenol in bacterial mutation assays because a study designed to compare the effects of five different induced rat liver S9 activation mixtures on the mutagenic potential of pentachlorophenol in bacterial strain TA98 reported all tests as negative; however, that study did not include phenobarbital/benzoflavone-

induced S9 (Markiewicz *et al.* 1996). A limitation of the Markiewicz *et al.* study, which used the plate incorporation protocol, was that no toxicity was reported for pentachlorophenol even at the highest dose tested (100 µg/plate), while the study that reported mutagenic activity in TA98 observed cytotoxicity at pentachlorophenol doses greater than 16 µg/plate. However, the only other study that reported cytotoxic effects due to pentachlorophenol treatment was Haworth *et al.* (1983)/NTP (1999) which, for all four strains tested using the preincubation protocol, reported total toxicity at 30 µg/plate without S9 but no toxicity at the highest dose (30 µg/plate) tested in the presence of rat or hamster S9.

There is some indication that pentachlorophenol causes DNA damage in bacteria. DNA damage following exposure to pentachlorophenol was reported in *Bacillus subtilis* but not in *Escherichia coli* (polA-) (Ozaki *et al.* 2004, Waters *et al.* 1982). However, in a different approach to DNA damage assessment, induction of prophage λ, due to DNA strand breaks, was observed in *E. coli* both with and without the addition of rat liver S9 metabolic activation (DeMarini *et al.* 1990).

Results of mutagenicity and DNA damage in all bacteria studies are summarized in Appendix E, [Table E-1](#).

#### 5.1.2 *In vitro* studies in non-mammalian eukaryotes

Studies in yeast have shown that exposure to pentachlorophenol induces both mutations and DNA damage. Mutations were induced in *Saccharomyces cerevisiae* MP-1 cultures (Fahrig *et al.* 1978), and DNA damage was reported in three different strains of *S. cerevisiae*: D4 (both *ade2* and *trp5*), MP-1, and D3 (Fahrig 1974, Fahrig *et al.* 1978, Waters *et al.* 1982). Although the studies assessing mutation and DNA damage were each limited to one treatment dose, and a repeat experiment in strain MP-1 (Fahrig *et al.* 1978) was negative, the consistency of results across studies supports the ability of pentachlorophenol to induce these effects in yeast.

Pentachlorophenol-induced genotoxicity has been reported in invertebrates. Effects include induction of point mutations in zebrafish, and DNA damage and micronuclei induction in mussels and snails (Yin *et al.* 2006, Pavlica *et al.* 2000, 2001). In addition, in the onion *Allium sp.*, increases in chromosomal aberrations and micronuclei were observed following exposure to pentachlorophenol (Pavlica *et al.* 1998, Ateeq *et al.* 2002, Repetto *et al.* 2001). In contrast to these positive results, no induction of sex-linked recessive lethal mutations or aneuploidy was observed in germ cells of the fruit fly *Drosophila melanogaster* following exposure of adult males to pentachlorophenol in feed (Vogel and Chandler 1974, Ramel and Magnusson 1979). The small number of chromosomes counted in three broods (around 600 each) by Vogel and Chandler limits the utility of that study, but similar results were reported by Ramel and Magnusson, who evaluated 73,000 flies treated with 400 ppm pentachlorophenol and found no non-disjunction or sex chromosome loss in the germ cells of treated *Drosophila* males (see Appendix E, [Table E-2](#)).

### 5.1.3 *In vitro* studies in mammalian cells

There is evidence that exposure to pentachlorophenol *in vitro* induces DNA damage in cultured rodent and human cells, but it did not induce mutations in mammalian cells (see Appendix E, [Table E-3](#)). In several studies using the comet assay, pentachlorophenol induced statistically significant increases in DNA damage in cells with endogenous metabolic capability, e.g., peripheral blood lymphocytes, Hep-G2, and epithelial (mucosal) nasal conchae (Stang and Witte 2010, Michałowicz 2010, Michałowicz and Majsterek 2010, Tisch *et al.* 2005) and in metabolically incompetent cultured cells in the presence of exogenous metabolic activation, e.g., human fibroblasts, HeLa cells, and V79 cells (Stang and Witte 2010). A weak positive result for DNA damage was observed in a precipitation assay in mouse C3H10T $\frac{1}{2}$  embryonic fibroblast cells in the presence of phenobarbital/ hydrocortisone-induced metabolic activation S9; no DNA damage was observed in this assay in the absence of S9 (Wang and Lin 1995). Pentachlorophenol induced DNA damage in the one study that tested Chinese hamster lung (V79) cells in the presence of S9, but was negative in all studies that tested the cells without S9; results were negative in Chinese hamster ovary (CHO) cells in the absence of S9, but were not tested in the presence of S9 (Dahlhaus *et al.* 1996, Stang and Witte 2010, Ehrlich 1990).

Mutagenicity assays in V79 cells reported negative results with pentachlorophenol, but treatments were only performed in the absence of S9 metabolic activation (Jansson and Jansson 1986). Another study reported negative results when using a hepatocyte-mediated assay (not S9), but the information available was limited to that provided in a review paper (Hattula and Knuutinen 1985, cited by IARC 1999).

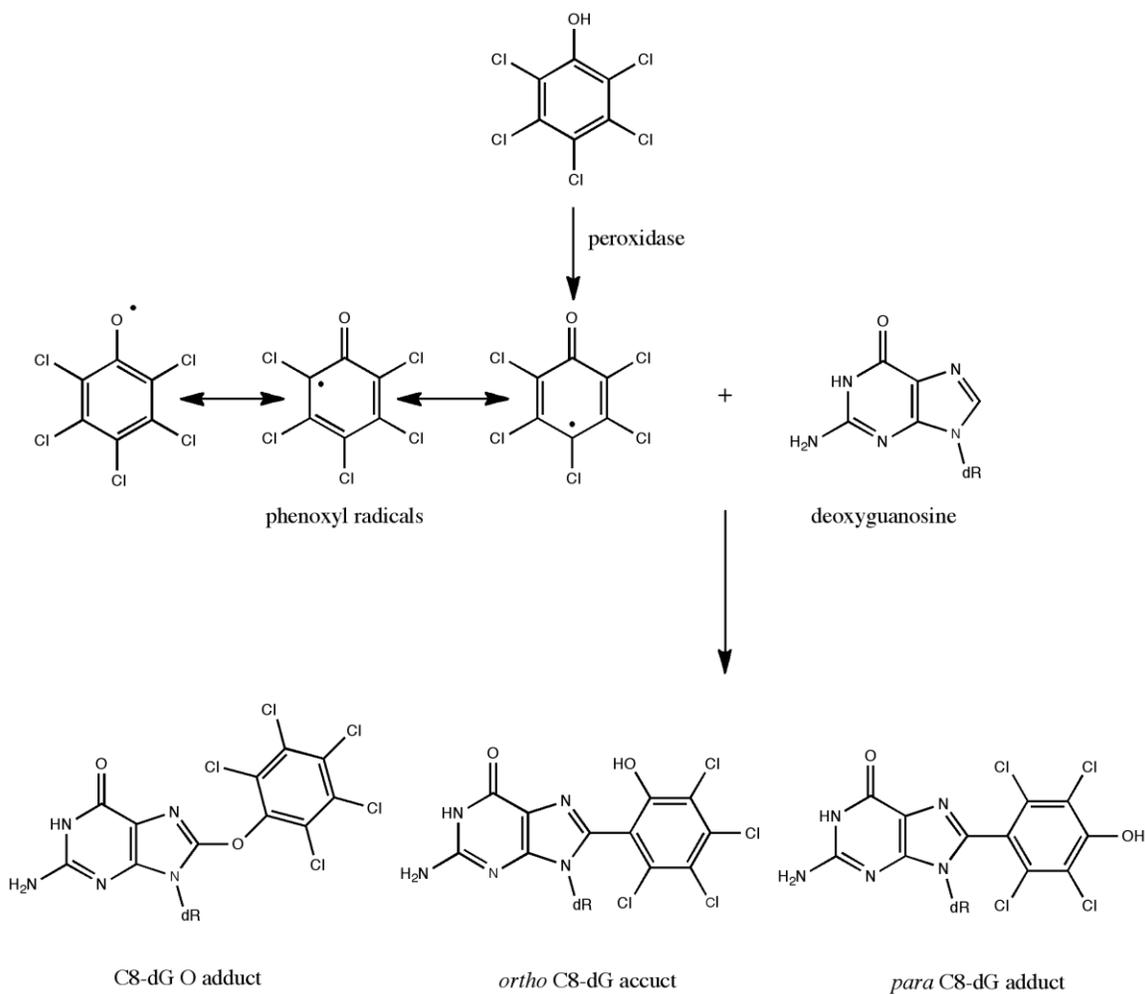
In considering the implications of the results from genotoxicity assays, it is important to consider the metabolic capability of the cells tested. In contrast to primary cell cultures, most secondary cell lines (e.g., V79) have greatly reduced or absent endogenous metabolic capability, so assays performed without adding S9 generally only identify direct-acting genotoxicants.

There is some evidence of induction of chromosomal damage and apoptosis in mammalian cells treated with pentachlorophenol *in vitro*. Induction of chromosomal aberrations was reported in V79 cells, both with and without the addition of mouse-derived S9, but only at the highest dose tested (Ishidate 1988). A small but statistically significant (pairwise for high dose as well as for trend test) induction of chromosomal aberrations was also observed in CHO cells in the presence of S9, but results were negative without S9 (Galloway *et al.* 1987, NTP 1999). No induction of chromosomal aberrations was observed in cultured human lymphocytes in the absence of S9; the assay was not conducted with S9. Weak induction of sister chromatid exchanges SCE was observed in CHO cells (significant at 3  $\mu\text{g/mL}$ ,  $P < 0.05$ ), but not in human lymphocytes, treated with pentachlorophenol in the absence of S9 activation; no induction of SCE was observed in CHO cells in the presence of S9 at concentrations up to 100  $\mu\text{g/mL}$  pentachlorophenol and the lymphocyte treatments were not conducted with S9 (Galloway *et al.* 1987, NTP 1999, Ziemsen *et al.* 1987). Apoptosis was observed in two studies in which human lymphocytes and human Jurkat T cells were exposed to pentachlorophenol in culture (Michałowicz and Sicińska 2009, Wispriyono *et al.* 2002).

#### 5.1.4 Oxidative DNA damage and DNA and protein adducts

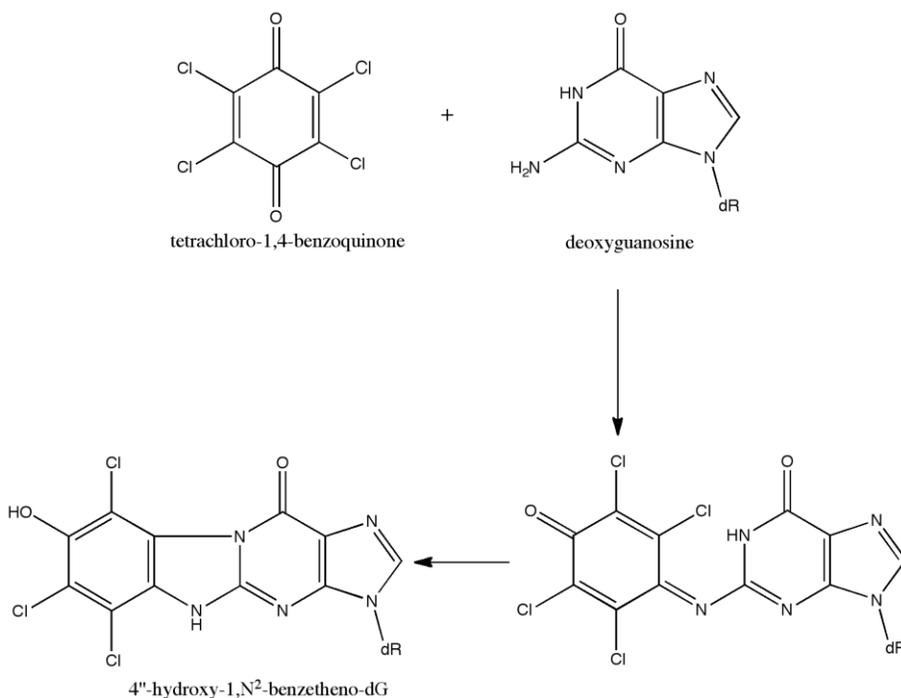
Oxidative DNA damage can result in the formation of DNA adducts after exposure to pentachlorophenol both *in vitro* and *in vivo* (see Appendix E, [Tables E-4](#) and [E-5](#)). Adducts were formed *in vitro* in studies using calf thymus DNA, fetal quail and rat hepatocytes, and human hepatoma (HepG2) cells (Dubois *et al.* 1997, Van Ommen *et al.* 1986b). DNA or nucleoside adducts were induced in calf thymus DNA following co-administration of pentachlorophenol and horseradish peroxidase or myeloperoxidase (from human lymphocytes) or when tested with an excess of deoxyguanosine (dG); formation of adducts was specific to dG as no adducts were detected with deoxyadenosine, deoxycytidine, or thymidine (Dai *et al.* 2003, 2005). Several *in vivo* studies reported that oxidative DNA (8-OH-dG) adducts were formed in the livers in mice and rats exposed to pentachlorophenol by gavage or in their food (Sai-Kato *et al.* 1995, Umemura *et al.* 1996, 1999, Lin *et al.* 2002, Tasaki *et al.* 2012). Protein adducts were reported *in vitro* (binding to microsomal protein from induced rats) as well as *in vivo* in liver nuclei and cytosol in rats and mice treated by gavage (Van Ommen *et al.* 1986b, Tsai *et al.* 2002).

Studies of DNA adduct formation have been used to identify specific chemical structures that result after pentachlorophenol exposure and to construct potential chemical pathways in the formation of reactive intermediates (Dai *et al.* 2003, 2005). For example, it has been shown that peroxidase-treated pentachlorophenol reacts with deoxyguanosine (dG) to yield the C8-dG oxygen (O) adduct, suggesting an intermediate radical for covalent bond formation. Although the C8-dG O-adduct was predominant, *ortho*- and *para*-C8-dG adducts are possible (Figure 5-1).



**Figure 5-1. Scheme of pentachlorophenol adduct formation: reactivity of phenoxyl radical toward dG (modified from Dai *et al.* 2005)**

Chlorophenoxy radical formation, such as postulated above for pentachlorophenol, can also result in 1,4-benzoquinone electrophiles that react with deoxyguanosine (dG) to form benzetheno-adducts. As shown in Figure 5-2, the pentachlorophenol metabolite, tetrachloro-1,4-benzoquinone reacts with dG to form the 4''-hydroxy-1,*N*<sup>2</sup>-benzetheno-dG adduct (Dai *et al.* 2005).



**Figure 5-2. Postulated mechanism for 4''-hydroxy-1,N<sup>2</sup>-benzetheno-dG formation. (Dai *et al.* 2005)**

#### 5.1.5 *In vivo* studies in rodents

There is limited evidence of genetic effects resulting from *in vivo* pentachlorophenol exposure in rodents. In the available studies, increases in response were reported for mRNA level changes, unscheduled DNA (UDS) repair, and sister chromatid exchange (SCE) (see Appendix E, [Table E-6](#)). In C57BL/6 mice (*p53*<sup>-/-</sup>) treated with pentachlorophenol in the diet, there was a significant decrease in CYP2B10 levels and an increase in NQ01 mRNA levels, suggesting the chemical affects gene expression. A significant increase in unscheduled DNA repair was observed in hepatocytes of rats treated one intraperitoneal (i.p.) injection of pentachlorophenol, although the results should be interpreted with caution since the study was limited to a single dose (10 mg/kg) administered in just two rats (sex not reported) (Monteith 1992). A significant induction of SCEs in male rat hepatocytes was reported following i.p. injection (10 mg/kg) of pentachlorophenol. In the same study, there was no increase in chromosomal aberrations in the hepatocytes of male rats treated with 10 mg/kg pentachlorophenol i.p. for five days, however the study was limited by the use of only one dose and treatment regimen (Daimon *et al.* 1997). From the described studies in rodents, the observations of DNA damage and repair (SCEs and UDS), decreased CYP2B10, and increased MNQ01 mRNA and UDS levels, support an assertion of *in vivo* effects due to pentachlorophenol treatment.

Pentachlorophenol induced DNA damage, measured as increased levels of 8-oxodeoxyguanosine (8-OH-dG), in the liver, but not the kidney or spleen, of exposed mice and rats, indicating formation of reactive oxygen intermediates in the liver (Sai-Kato *et al.* 1995, Umemura *et al.* 1996, 1999, Lin *et al.* 2002). In the Sai-Kato *et al.*

study, when pentachlorophenol treatment in mice was preceded by administration of antioxidants (vitamin E and diallyl sulfide), liver 8-OH-dG levels were greatly reduced compared with the levels seen in the mice that received pentachlorophenol alone, suggesting protection against oxidative damage induced by pentachlorophenol. In addition, pentachlorophenol-treated animals had a dose-dependent increase in hepatocellular proliferation, an event that has been associated with carcinogenesis.

A weak positive response was noted in the mouse spot test, an assay used to detect genetic alterations, especially point mutations, in somatic cells. Exposure to pentachlorophenol resulted in the appearance of colored spots, caused by gene mutation or recombination, as well as reduction in litter size and loss of offspring before or after birth. No increases in the frequencies of micronucleated polychromatic erythrocytes (reticulocytes) were observed in the bone marrow of male and female CD-1 mice administered pentachlorophenol by gavage up to 120 mg/kg (Xu 1996, as cited by IARC 1999) or male B6C3F1 mice treated i.p. up to 100 mg/kg (NTP 1999). Furthermore, no increases in micronucleated polychromatic erythrocytes were seen in male F344/N rats administered up to 50 mg/kg pentachlorophenol i.p. once daily for 3 days (NTP, 1999).

#### 5.1.6 Studies in lymphocytes from occupationally exposed workers

Three studies were identified that measured endpoints of genotoxicity in people occupationally exposed to pentachlorophenol, including one study of workers employed in a pentachlorophenol production factory (Bauchinger *et al.* 1982) and two studies of workers who used pentachlorophenol to treat wood (Wyllie *et al.* 1975, Ziemsen *et al.* 1987) (see Appendix E, [Tables E-7](#) and [E-8](#)). Based on measurements of pentachlorophenol in the workplace air and in the blood and urine of the study subjects, workers in the production factory had the highest exposure to the chemical. All three studies were limited to small numbers of subjects, particularly the Wyllie *et al.* study, which only evaluated six exposed workers. In all three studies, chromosomal aberrations (CA) were measured in the workers' peripheral blood lymphocytes; Bauchinger *et al.* and Ziemsen *et al.* also measured sister chromatid exchanges (SCE). Results of the Bauchinger *et al.* study provide evidence that pentachlorophenol induces chromosomal damage in humans, based on observations of statistically significant increases in dicentric chromosomes and acentric fragments in lymphocytes of the exposed workers in the pentachlorophenol-producing factory; the numbers of chromatid-type aberrations (breaks, and exchanges) were also increased over controls, but not with statistical significance. In the wood treatment workers, Wyllie *et al.* reported an increase (though not statistically significant) in the percentage of cells with chromosome breaks but, due to the small number of subjects, this study had limited power to detect a definitive effect. No effects were noted in the second wood-treatment plant study (Ziemsen *et al.*) but exposure levels were much lower in that study; data on types of chromosomal damage in workers were reported but the actual number of cells with aberrations (the definitive value for measuring CA) were not, so the percentage of cells with CAs cannot be accurately calculated. No effects on SCE frequencies were reported for pentachlorophenol-exposed workers (Ziemsen *et al.* 1987). Although the initial statistical analysis for SCEs in the Bauchinger *et al.* study showed that exposed production workers had significantly higher values compared to controls, a reanalysis of the data comparing the 22 exposed workers (all smokers) to control group smokers only (9 out of 22) showed no differences in SCE

frequencies between the two groups, suggesting that the effect on SCEs was attributable to smoking rather than exposure to pentachlorophenol. However, the exposure-related chromosomal damage in that study was not related to smoking status, as a comparison of the exposed workers (all smokers) with smoking controls showed statistically significant increases in dicentric chromosomes and acentric fragments in lymphocytes of the pentachlorophenol-exposed workers.

#### 5.1.7 Genotoxic effects of metabolites of pentachlorophenol

The genotoxicity of several pentachlorophenol metabolites, including tetrachlorohydroquinone, tetrachlorocatechol, tetrachloro-1,4-benzoquinone, and tetrachloro-1,2-benzoquinone has been evaluated in several *in vitro* studies. A summary table of the results from these studies is provided in Appendix E, [Table E-9](#).

A major pentachlorophenol metabolite, tetrachlorohydroquinone, induced mutations in Chinese hamster lung (V79) cells at the HPRT locus (6-thioguanine resistance) but not at the Na/K-ATPase locus (measured as ouabain resistance) (Jansson and Jansson 1991, Purschke *et al.* 2002). These results suggest that tetrachlorohydroquinone can cause genetic damage in the form of deletions, which may result in the loss of the HPRT enzyme function and produce a positive result in that assay. Since Na/K-ATPase is necessary for cell viability, ouabain resistance cannot arise from the loss of enzyme function and thus the results would be negative (if enzyme function is unaffected), as reported.

Tetrachlorohydroquinone was also shown to induce single-strand DNA breaks in mammalian (including human) cells *in vitro* as well as DNA adducts in calf thymus DNA; all of the tests were performed without the addition of exogenous metabolic activation. Ehrlich (1990) reported that, while the parent compound pentachlorophenol did not induce DNA single-strand breaks in CHO cells, the metabolite tetrachlorohydroquinone did so in a dose-dependent manner. Furthermore, tetrachlorohydroquinone induced DNA adducts in human HeLa S3 tumor cells; classes of adducts included both oxidative adducts (8-OH-dG) and adducts induced at apurinic/apyrimidinic sites. In an *in vivo* study, DNA adducts were induced in the liver of mice exposed to tetrachlorohydroquinone in the diet, but not when treated by i.p. injection (Dahlhaus *et al.* 1994).

Significant increases in micronucleated V79 cells were reported following treatment with tetrachlorohydroquinone in a study designed to investigate a possible mechanism of action (Jansson and Jansson 1992). When the V79 cells were also treated with DMSO, a hydroxyl radical scavenger, a significant inhibitory effect was observed on the frequency of micronucleated cells induced by tetrachlorohydroquinone. Treatment of cells with ethyl methanesulfonate, a potent alkylating agent, induced micronuclei (levels were similar to those induced by tetrachlorohydroquinone), but the addition of DMSO to the cell cultures resulted in no change, supporting the role of hydroxyl radicals in the tetrachlorohydroquinone-induced chromosomal damage (Jansson and Jansson 1992).

Two other metabolites of pentachlorophenol, tetrachloro-1,4-benzoquinone and tetrachloro-1,2-benzoquinone, induced DNA damage *in vitro* in human fibroblasts (comet

assay) and V79 cells (alkaline elution assay) (Purschke *et al.* 2002, Dahlhaus *et al.* 1996). The metabolite tetrachlorocatechol induced DNA damage, as measured by the comet assay, in cultured human peripheral blood lymphocytes (Michałowicz and Majsterek 2010). Tetrachlorocatechol was reported to be negative in tests for DNA damage and mutagenicity in V79 cells, although it was only tested in the absence of metabolic activation (Dahlhaus *et al.* 1996, Jansson and Jansson 1991).

#### 5.1.8 Synthesis of results

The available *in vitro* studies report that pentachlorophenol induces genotoxic effects in a variety of test systems. It was mutagenic (possibly via its metabolites) in studies in yeast, zebrafish and human lymphocytes, but in bacteria it induced mutations only in the presence of exogenous metabolic activation (S9), and in most bacterial studies it was nonmutagenic, with or without S9. Pentachlorophenol induced DNA damage in yeast, invertebrates, and plants as well as in human lymphocytes and nasal concha cells, without the addition of S9. In the only rodent assay in which DNA damage was investigated in the presence of S9, pentachlorophenol was weakly positive; it gave negative results in all *in vitro* rodent cell studies conducted without S9. Three studies evaluated chromosomal aberrations (CAs) in mammalian cells and each reported positive results in the presence of S9; one study also reported induction of CAs by pentachlorophenol without S9. Induction of sister chromatid exchanges (SCE) by pentachlorophenol was tested in two studies; it was judged to be weakly positive in one study without the addition of S9, but negative in the only study that tested in the presence of S9.

*In vivo*, pentachlorophenol induced SCEs in rat hepatocytes and gave a weak positive result in the mouse spot test, but negative results were obtained in all rodent tests for micronucleus or chromosomal aberration induction. In contrast with the rodent findings, a study in peripheral blood lymphocytes from workers exposed to pentachlorophenol showed some evidence of chromosomal damage, although results were based on a small number of workers. DNA adducts were induced in the liver of both rats and mice exposed to pentachlorophenol, apparently due to formation of reactive oxygen species; increased hepatocellular proliferation in these animals may also be related to carcinogenicity.

The body of evidence indicates that pentachlorophenol causes oxidative DNA damage, based on findings in cultured cells with endogenous or exogenous metabolic activation as well as in animals. Pentachlorophenol metabolites cause DNA damage (including oxidative damage) and mutation, in cultured cells or exposed animals. Overall, this suggests that the metabolism of pentachlorophenol, whether by endogenous or exogenous enzymes, results in the production of reactive metabolites that could play a role in the mechanism of carcinogenesis.

**Table 5-1. Summary of pentachlorophenol genotoxicity information**

Effect	<i>In vitro</i>		<i>In vivo</i>	
	-S9	+S9	Rodents	Humans
Mutation				
Bacteria	-	± <sup>a</sup>		
Yeast	+			
<i>Drosophila</i>	-			
Mammalian cells	-		+	
DNA damage				
Bacteria	±	+		
Yeast	+			
<i>Drosophila</i>	-			
Mammalian cells	+	(+)		
chlorophenol DNA adducts	+	-	+	
Chromosomal aberrations	±	+	-	±
Sister chromatid exchange	(+)	-	+	-
Micronuclei induction			-	

+ = Positive, (+) weakly positive, ± = both positive and negative, - = negative studies.

<sup>a</sup>Positive only in *S. typhimurium* TA98 with phenobarbital/bexoflavone-induced rat liver.

**Table 5-2. Summary of genotoxicity data for pentachlorophenol metabolites<sup>a</sup>**

Effect Metabolite	Result
Mutation	
Tetrachlorohydroquinone	+
Tetrachlorocatechol	-
DNA damage	
Tetrachlorohydroquinone	+ <sup>b</sup>
Tetrachlorocatechol	± <sup>c</sup>
Tetrachlorobenzoquinones	+ <sup>b</sup>
DNA adducts	
Tetrachlorohydroquinone	+ <sup>d</sup>
Tetrachlorobenzoquinones	+

+ = Positive, - = negative, ±, both positive and negative study results were reported.

<sup>a</sup>Unless noted otherwise, all studies were *in vitro* with no exogenous metabolic activation S9 added.

<sup>b</sup>Positive in both rodent and human cells.

<sup>c</sup>Positive in human peripheral lymphocytes; negative in hamster V79 cells.

<sup>d</sup>Positive in both *in vitro* and *in vivo* studies.

## 5.2 Mechanistic considerations

Carcinogenesis is a complex disease process with an extensive list of possible mechanisms; however, most can be grouped into a limited number of categories (Guyton

*et al.* 2009). Chemicals may be categorized according to their “mode of action” represented by the key events associated with the toxic effect. These events may include, but are not limited to, DNA reactivity (covalent binding), gene mutation, chromosomal breakage, aneuploidy, enzyme-mediated effects on DNA damage or repair, epigenetic effects, altered or disrupted cell signaling, immune response modulation, inflammation, cytotoxicity and compensatory cell proliferation, mitogenicity, chronic metabolic or physiologic overload, nutrient deficiency, and interference with intercellular communication. It is important to recognize that chemicals can act through multiple toxicity pathways and mechanisms to induce cancer or other health effects, and the relative importance of the various pathways may vary with life stage, genetic background, and dose. Thus, it is unlikely that for any chemical a single mechanism or mode of action will fully explain the multiple biological alterations and toxicity pathways that can cause normal cells to transform and ultimately form a tumor.

Pentachlorophenol was associated with liver and adrenal gland tumors in male and female B6C3F<sub>1</sub> mice, malignant vascular tumors (hemangiosarcoma) in female mice, benign skin tumors (papillomas) in mice, mesothelioma and nasal tumors in male F344 rats, and liver tumors in female Wistar rats (see Section 4). In humans, pentachlorophenol was associated with non-Hodgkin lymphoma, multiple myeloma, and soft tissue sarcoma (see Section 3). The mechanisms responsible for the carcinogenic effects of pentachlorophenol are complex and poorly understood. Although the available data indicate that multiple mechanisms are involved, none have been defined sufficiently to identify the key events or temporal relationships (EPA 2010). A further complication is the presence of various by-products of its synthesis in technical grade formulations (see Section 1). The by-products include several carcinogenic chemicals including other chlorophenols, dibenzo-*p*-dioxins, and dibenzofurans. Numerous studies suggest that metabolism to genotoxic metabolites, oxidative damage and inflammation, induction of stress genes, cytotoxicity, immunosuppression, and interference with gap junctional intercellular communication and apoptosis are likely involved (Dorsey *et al.* 2006, Dorsey *et al.* 2002, Dorsey *et al.* 2004, Goodman 2001, Mirvish *et al.* 1991, Sai *et al.* 2001, Sai *et al.* 2000, Zhu and Shan 2009). Section 5.2.1 compares carcinogenic effects in experimental animals exposed to analytical grade or technical grade pentachlorophenol to determine if the various carcinogenic effects can be attributed to pentachlorophenol, its by-products, or a combination of the two. Sections 5.2.2 to 5.2.6 discuss the possible modes of action for the reported carcinogenic effects including lymphoma/hematopoietic neoplasms in humans, liver and vascular tumors in mice, mesothelioma in rats, and skin tumors in mice. No mechanistic data were identified for adrenal gland tumors in mice, nasal tumors in rats, or soft tissue sarcomas and kidney cancer in humans; however, the identified genotoxic and nongenotoxic mechanisms likely contribute to the neoplastic effects in those tissues.

#### 5.2.1 Relative contribution of pentachlorophenol and its by-products to liver tumors

Conclusions reached from cancer studies in experimental animals are from different grades of pentachlorophenol containing different amounts of by-products. A comparison of available cancer studies from individual by-products will aid in elucidation of possible mechanisms of carcinogenicity. Some of these by-products are dioxins and furans that

have been assigned dioxin-like equivalency factors (TEFs), which rank biological potencies relative to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

For some of the by-products, cancer studies were available and most of the studies had liver tumors in mice as a common endpoint for comparison across studies. To inform an assessment of experimental animal cancer data, this discussion will focus primarily on pentachlorophenol cancer studies in mice (NTP 1989) using technical grade pentachlorophenol and Dowicide EC-7 with specific emphasis on mouse liver tumors. Studies chosen for comparison were of high quality (chemicals assessed for purity, adequate number of animals on study, adequate duration of observation period, comprehensive histopathologic evaluation of tissues).

Cancer studies of pentachlorophenol exposure in rats and mice were presented and discussed in Section 4 and included studies with different grades of pentachlorophenol: pure pentachlorophenol (99%), Dowicide EC-7 (90%), technical grade pentachlorophenol (86%). The NTP conducted three feeding studies in mice using different pentachlorophenol preparations (1) Dowicide EC-7, (2) technical grade pentachlorophenol, and (3) 99% pentachlorophenol in a dermal study in transgenic mice (Section 4, Tables 4.3a and 4.4). Based on the chemical analyses in the NTP reports, the by-products present in these test articles include polychlorophenols, hexachlorobenzene (HCB), dioxins and furans, and hydroxydiphenyl ethers ([Table F-1](#)). Unless specifically noted, individual chemical isomers were not identified and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) was not identified in these preparations of pentachlorophenol. However, other dioxin and furan by-products are present. Total dioxin-like equivalents (Van den Berg *et al.* 2006) were calculated and these values compared with induction of liver tumors by TCDD (NTP 1982). A number of assumptions are made in these comparisons: it is assumed that exposure in gavage studies is similar to exposure in diet, and it is assumed that toxicity of isomers in studies under comparison is similar. Available cancer studies in experimental animals of by-products present in the grades of pentachlorophenol tested were: trichlorophenol, hexachlorobenzene (HCB), hexachlorodibenzo-*p*-dioxin (HxCDD) and TCDD; no cancer studies were located on tetrachlorophenol. These studies are compared with the results for liver tumors in mice (NTP 1989). No liver tumors were identified in the dietary study in rats with pure pentachlorophenol (NTP 1999); however, hepatic nodules were noted in rats in a feed study using technical grade pentachlorophenol (Mirvish *et al.* 1991) with TCDD/TCDF contamination. The results in rats are discussed in the next section.

#### *Trichlorophenol (2,4,6-TCP)*

Trichlorophenol concentrations in the bulk pentachlorophenol chemical preparations were similar between the technical grade (0.01%) and the Dowicide EC-7 (0.007%) ([Table F-1](#)) and were much lower than the 5000-ppm concentration in feed that produced liver tumors in both sexes of mice in the bioassay of 2,4,5-trichlorophenol (NCI 1979) ([Table F-2a](#)). Therefore, trichlorophenol would not be expected to contribute to tumorigenicity of pentachlorophenol preparations.

### *Hexachlorobenzene (HCB)*

Liver tumors in mice were reported in the HCB cancer studies of Cabral *et al.* (1977) and are summarized in [Table F-2b](#). In comparing the data on liver tumors in Section 4, Table 4.3a to the data on HCB alone, HCB could not independently account for the liver tumors in mice because HCB was present in greater amounts with Dowicide EC-7 (65 ppm of HCB) which had fewer liver tumors than technical grade pentachlorophenol (50 ppm of HCB) at the same exposure concentration in feed. In addition, HCB would be present in the mixture at lower concentrations than those that induced liver tumors. In the Cabral *et al.* (1979) study using Swiss male mice, the lowest concentration of HCB that increased liver neoplasms was 100 ppm; whereas, the 50-ppm group did not. The 200-ppm group also had liver neoplasms, but had poor survival due to toxicity. In the technical grade pentachlorophenol, HCB is present at 50 ppm ([Table F-1](#)). In a 200-ppm technical grade formulation, HCB would be present at 0.01 ppm, or 1000-fold lower than the dose that induced liver tumors in the male Swiss mice. Therefore, it is unlikely the HCB contributed directly to liver tumor formation.

### *Dioxin-like by-products and cancer promotion*

Available data indicate that carcinogenic potency as well as toxicity of dioxin and dioxin-like chemicals are proportional to affinity for the cytoplasmic aryl hydrocarbon receptor (AhR), a cytoplasmic transcription factor that has been characterized in humans and in rodents. This receptor is conserved in vertebrate animals and has equivalent functions in humans and in experimental animals. Evidence suggests that carcinogenicity of dioxins and furans acts through similar mechanisms and requires initial binding to the AhR. Binding, nuclear translocation, coupling with aryl hydrocarbon nuclear translocator (ARNT) forming a AhR/ARNT heterodimer leads to activation of TCDD-responsive genes, some of which have a global effect on cell-cycle regulation, cell growth, apoptosis, immune surveillance, metabolism, and disruption of hormone and growth factor signal transduction pathways. All of these factors have a role in the promotion of cancer. AhR-mediated induction of *CYP1A1* and *CYP1A2* genes occurs with similar potencies in human and rodent cells, but the role of induction of these genes in carcinogenesis is unclear. No specific gene has been shown to have a definitive role in the mechanism of carcinogenesis by dioxin. Experimental data indicate that 2,3,7,8-TCDD and probably other polychlorinated dioxins and furans are not direct-acting genotoxic agents and most likely act as tumor promoters through activation of the AhR and disruption of cellular homeostasis (IARC 1997, Barouki *et al.* 2012).

Dioxin by-products of pentachlorophenol synthesis are primarily a mixture of isomers of hexa-, hepta-, and octadibenzo-*p*-dioxins. These dioxin congeners have been shown to be long-lived in the body and provide a chemical fingerprint of previous exposure to pentachlorophenol. Cancer studies of dioxin and dioxin-like chemicals have primarily focused on 2,3,7,8-TCDD and a limited amount of data are available on carcinogenicity of other congeners of dioxin.

According to the chemical analysis from the NTP studies, HxCDD is present at a low concentration of the bulk chemical in the technical grade preparation (10.1 ppm) and in the Dowicide EC-7 preparation (0.9 ppm) ([Table F-1](#)). NTP has tested two HxCDD

isomers in rats and mice in a two-year bioassay. HxCDD (mixture of 1,2,3,6,7,8- and 1,2,3,7,8,9-HxCDD isomers) was tested by gavage in mice for carcinogenicity (NTP 1980) ([Table F-2c](#)), and the results for liver tumors were compared with the NTP studies in feed of technical grade pentachlorophenol and Dowicide EC-7 (McConnell *et al.* 1991, NTP 1989) (see Appendix F, [Table F-3a](#)). Liver neoplasms were induced in the HxCDD gavage study as well as in the pentachlorophenol technical grade and Dowicide EC-7 feed studies in male mice. At equal doses of pentachlorophenol, a greater incidence of liver neoplasia occurred with technical grade pentachlorophenol than with Dowicide EC-7 and a liver tumor response occurred with HxCDD alone at greater concentrations than found in either of the pentachlorophenol preparations. Although there may be a cancer effect of the HxCDD, it does not account for the greater incidence of liver tumors observed with technical-grade pentachlorophenol or Dowicide EC-7 exposure.

While HxCDD is present in many of the pentachlorophenol formulations, it is not the only dioxin-like chemical present in pentachlorophenol formulations. Activation of aryl hydrocarbon receptor (AhR) can occur with a number of dioxin-like compounds and their relative potency with regard to toxicity and carcinogenicity in relation to TCDD has been determined (Van den Berg *et al.* 2006, [Table F-3b](#)). Technical grade pentachlorophenol induced liver aryl hydrocarbon hydroxylase activity, a marker for the AhR-dependent enzyme, CYP1A1, to a much greater extent (at least 10-fold greater in male mice) than did Dowicide EC-7 or pure pentachlorophenol in the 6-month subchronic feed study (NTP 1989). Liver tumor incidence was higher with technical grade pentachlorophenol than with Dowicide EC-7, a purer grade of pentachlorophenol. Given that AhR-dependent enzymes have been induced with technical grade pentachlorophenol, it is likely there are multiple mechanisms involved in liver carcinogenesis following exposure to technical grade pentachlorophenol and that by-products of synthesis play an important role in the carcinogenicity of pentachlorophenol.

In order to further assess the role of the dioxin-like by-products in the carcinogenicity of the different pentachlorophenol products tested, dioxin-like equivalents (TEQs) were calculated for the NTP feed studies in mice for technical grade and Dowicide EC-7 and compared with available liver cancer bioassay data (NTP 1982) for TCDD. Dioxin-like equivalencies rank biological potencies of dioxin and furan isomers relative to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. [Tables F-3c](#) and [F-3d](#) list dioxin equivalent calculations for the feed preparations for the high doses used in those studies. Calculations are based upon the 'worst case' scenario, *e.g.*, high dose of technical grade pentachlorophenol at 200 ppm and Dowicide EC-7 at 600 ppm; and if ppm are reported as < 10 or if 10 is the level of detection then 10 is used. [Tables F-4a](#) and [4b](#) list doses of TCDD by gavage for hepatocellular carcinoma in mice (NTP 1982).

For technical grade pentachlorophenol at 100 and 200 ppm, TEQ concentrations are above 0.5 micrograms/kg/week, which when given as TCDD alone caused liver tumors. However, the TEQ of 200-ppm Dowicide EC-7 was less than the concentration of TCDD that induced liver tumors. Since exposure to Dowicide EC-7 resulted in increased liver tumors compared with controls, it would appear that pentachlorophenol, possibly in concert with other by-products, contributed directly to the liver tumor response. No 2-year dietary cancer studies were available using 99% pure pentachlorophenol in mice;

however, a 6-month cancer study in Tg•AC mice (dermal application) was positive for papillomas and gave a positive effect of dose on tumor multiplicity, lending support to the hypothesis that pure pentachlorophenol has a role in the pathogenesis of cancer in the mouse. This model has been questioned as neoplasms can be induced by non-carcinogenic treatments, such as skin irritation and wounding (Fuhrman 2005). It would also appear that dioxin-like components contributed as well since the less pure technical grade pentachlorophenol had more liver tumors at the same exposure concentration (200ppm) than the Dovicide EC-7 that was of a higher purity.

In summary, it can be concluded from the data in these studies that pentachlorophenol causes liver tumors in mice and that dioxin-like by-products also have an apparent contribution to liver tumor formation. Most likely, multiple mechanisms are involved in this complex mixture and the contribution of other by-products to tumor formation cannot be ruled out. Importantly, technical grade pentachlorophenol used in these studies has levels of by-products similar to those found in commercial use, and the TEQ value for dioxin-like by-products in technical grade pentachlorophenol is within the range of TCDD liver carcinogenicity.

#### *TCDD/TCDF contamination and rat liver tumors*

It is unusual for technical grade preparations of pentachlorophenol to have 2,3,7,8-TCDD (TCDD) as a by-product of its synthesis. However, 2,3,7,8-TCDD and 2,3,7,8-TCDF were tested for and found in a technical grade pentachlorophenol preparation from a U.S. supplier that was used in a rat cancer study (Mirvish *et al.* 1991, see Section 4). No other chemicals related to pentachlorophenol synthesis that were analyzed for and detected by HPLC analysis contained 2,3,7,8-TCDD. MCR-Wistar rats, both sexes, were exposed to 500-ppm technical grade pentachlorophenol (86% pure technical grade pentachlorophenol with 25 µg/kg feed of 2,3,7,8-TCDD and 670 µg/kg feed of 2,3,7,8-tetrachlorodibenzofuran (TCDF) in the feed for 88 weeks and compared with pooled control groups (pelleted and powdered control feed groups, without pentachlorophenol). No liver tumors were reported in the control groups (males 0/9; females 0/18) and in the treated males (0/5), but a significant number of liver adenomas were noted in the female rats (6/9,  $P = 0.0003$ , one-sided Fisher's exact test, calculated by NTP). Several points support TCDD/TCDF induction of liver tumors in female rats. 1) In two other chronic feed studies in rats using purified pentachlorophenol (99%) with no measurable dioxin or furans, no liver tumors were detected. 2) TCDD has been shown to induce liver tumors in female rats by gavage (0.5 µg/kg bw/wk) at less than the estimated dose of TCDD in the pentachlorophenol feed preparation. 3) In a timed gavage study of TCDD over 13-week intervals (NTP 1982), liver tumor latency for the appearance of adenomas was comparable to this study (approximately 88 weeks). 4) The TEF factor for TCDF was not taken into account by the study authors in assessing the contribution of TCDD. 4) Other possible dioxin and furan by-products were not investigated; TCDD is usually present with other chlorinated dioxins and dibenzofurans increasing the total amount of dioxin-like equivalents in the feed. Based on other reports of TCDD in feed studies (Kociba *et al.* 1978) and by gavage (NTP 1982), it is concluded that the findings of liver tumors in female MCR-Wistar rats in the Mirvish *et al.* study can be attributed to dioxin-like activity and it is unlikely that pentachlorophenol induced these tumors.

### 5.2.2 Hematopoietic neoplasms in humans

Hematopoietic neoplasms have been associated with pentachlorophenol exposure in humans (see Section 3). Direct DNA adducts and immune suppression are possible mechanisms that have been linked to these malignancies; however, the dioxin by-products present in technical grade pentachlorophenol also suppress the immune system and have been associated with non-Hodgkin lymphoma. Thus, the dioxin by-products likely contribute to the carcinogenic effects of technical grade pentachlorophenol in humans.

Dai *et al.* (2005, 2003) demonstrated that incubation of pentachlorophenol with horseradish peroxidase or myeloperoxidase from human leukocytes in the presence of excess deoxyguanosine (dG) indicated that the oxygen-bonded C8-dG adduct was favored over the *ortho* and *para* C-adducts (see Figure 5-1). The *O*-C8-dG adduct did not form when pentachlorophenol was incubated with rat liver microsomes. Prostaglandin H synthase and other peroxidases are known to be important in the metabolic activation of some xenobiotics to toxic or tumorigenic metabolites, particularly in extrahepatic tissues that contain low levels of cytochrome P450 (Eling *et al.* 1990). Further, the leukemogenic activity of benzene has been linked to peroxidase-catalyzed activation of its phenolic metabolite in bone marrow (Dai *et al.* 2005, Dai *et al.* 2003). Peroxidase is known to oxidize pentachlorophenol to phenoxy radicals (Kazunga *et al.* 1999), and peroxidases and myeloperoxidases are present in bone marrow and leukocytes. Thus, this adduct could play a key role in pentachlorophenol-mediated hematopoietic malignancies (Dai *et al.* 2005, Dai *et al.* 2003).

Immune suppression and immune deficiency, as well as exposure to several immunosuppressive chemicals (e.g., PCBs, chlordane, dioxins, phenoxyacetic acids, organic solvents, chlorophenols, and immunosuppressive drugs) have been linked to an increased risk of non-Hodgkin lymphoma in humans (Filipovich *et al.* 1980, Hardell 2008, Hardell *et al.* 1998, Ziegler *et al.* 1984). The risk of non-Hodgkin lymphoma also increases with age (possibly due to an age-related decline in immune system response) (Hardell *et al.* 1998). Pentachlorophenol exposure has been associated with cellular and humoral immunodeficiencies in humans (Daniel *et al.* 1995, Daniel *et al.* 2001b, Daniel *et al.* 2001a, McConnachie and Zahalsky 1991). Several studies have demonstrated that pentachlorophenol decreased the tumor-cell killing function of human natural killer cells (Hurd *et al.* 2012, Nnodu and Whalen 2008, Taylor *et al.* 2005, Reed *et al.* 2004). Pentachlorophenol was one of the most effective compounds tested at decreasing natural killer cell function.

The decreased lytic function was partially attributed to reduced tumor-cell-binding capacity and cell-surface marker expression but did not appear to be related to oxidative metabolism or generation of reactive oxygen species. Lang and Mueller-Ruchholtz (1991) investigated human lymphocyte reactivity after *in vitro* exposure to technical and analytical grade pentachlorophenol. Lymphokine production and immunoglobulin secretion showed significant dose-dependent suppression after exposure to both grades of pentachlorophenol. The T-helper cell subset was especially sensitive to pentachlorophenol; however, both T-independent and T-dependent humoral responses were markedly suppressed.

The only significant differences observed between analytical and technical grade pentachlorophenol was that following mitogen stimulation, T-lymphocyte blastogenesis was significantly reduced when exposed to the highest concentration (200  $\mu$ M) of technical grade pentachlorophenol. Thus, pentachlorophenol itself was directly immunotoxic to human lymphocytes *in vitro*. However, some studies reported that technical grade but not analytical grade pentachlorophenol was immunosuppressive in mice (*in vivo* and *in vitro*) and that dioxin by-products (particularly some hexa- and hepta- congeners) in the technical grade formulation likely were responsible (Holsapple *et al.* 1987, Kerkvliet *et al.* 1982b, Kerkvliet *et al.* 1982a, Kerkvliet and Brauner 1987, Kerkvliet *et al.* 1985a, Kerkvliet *et al.* 1985b, White and Anderson 1985). However, Kerkvliet *et al.* (1982a) also reported that splenic tumors were increased when mice exposed to pure pentachlorophenol (low and high dose) were given a secondary challenge with Moloney sarcoma virus (MSV)-transfected sarcoma cells (MSB). These data suggest that some degree of immunosuppression was associated with pentachlorophenol itself and that splenic tumor development might have been a more sensitive marker for immunosuppression than the other immunoassays used in this study. Mirvish *et al.* (1991) also reported that technical grade pentachlorophenol acted synergistically with 2-hydroxyethylnitrosourea to induce acute myelocytic leukemia in rats. However, co-administration of methylprednisolone (an immunosuppressant), or Freund's adjuvant (an immune system stimulant) with 2-hydroxyethylnitrosourea did not affect tumor incidence.

### 5.2.3 Hepatocellular adenomas and carcinomas in mice

Experimental animal data show that pentachlorophenol induced liver tumors in B6C3F<sub>1</sub> mice but not in Sprague-Dawley or F344 rats. The different responses may be explained by species differences in disposition and toxicokinetics. These differences may result in increased formation of reactive metabolites, DNA and protein adducts, and oxidative damage to DNA in mice compared with rats (Lin *et al.* 2002, Lin *et al.* 1997, Lin *et al.* 1999, Tsai *et al.* 2001). In addition, several studies suggest that pentachlorophenol is a non-mutagenic liver tumor promoter in mice, inhibits enzymes involved in metabolism, inhibits gap junctional intercellular communication, and inhibits apoptosis (Sai *et al.* 2001, Sai *et al.* 2000, Sai *et al.* 1998, Umemura *et al.* 2003a, Umemura *et al.* 1999).

#### *Metabolic activation and adduct formation*

It is likely that differences in the metabolism of pentachlorophenol are at least partially responsible for the different tumor responses in mice and rats. Pentachlorophenol is not mutagenic or genotoxic itself but can form reactive metabolites that induce a variety of genotoxic effects including adduct formation, mutations, apurinic/apyrimidinic sites, single-strand breaks, and micronuclei (see Section 5.1). Although not completely understood, the most likely mechanism of pentachlorophenol's genotoxicity involves oxidative dechlorination by liver microsomal cytochrome P450s to form tetrachlorohydroquinone and tetrachlorocatechol (Lin *et al.* 1997). These quinols can be further oxidized to form their corresponding quinones (tetrachloro-1,4-benzoquinone and tetrachloro-1,2-benzoquinone) via their semiquinone intermediates (see Figure 2-1). These metabolites are strong electrophiles and readily bind to macromolecules.

A series of *in vitro* and *in vivo* studies investigated the formation of these chlorinated quinone and semiquinone metabolites and protein adducts in the livers of male Sprague-Dawley rats, male F344 rats, and male B6C3F<sub>1</sub> mice (Lin *et al.* 1996, Lin *et al.* 2002, Lin *et al.* 1997, Lin *et al.* 1999, Tsai *et al.* 2001, 2002). Waidyanatha *et al.* (1994, 1996) also reported dose-related production of quinone and semiquinone adducts in blood proteins (hemoglobin and albumin) in male Sprague-Dawley rats administered pentachlorophenol by gavage. The estimated tissue doses of benzoquinones to liver cytosolic and nuclear proteins in rats and mice are shown in Table 5-3. Estimated daily adduct production rates are shown in Table 5-4. The principle findings from these studies support the role of benzoquinone adducts in mouse liver neoplasms and are as follows:

- 1) pentachlorophenol is metabolized to reactive chlorinated semiquinone and quinone metabolites in rats and mice,
- 2) these reactive metabolites bind to sulfhydryl groups in liver cytosolic and nuclear proteins but the types and amounts of adducts differ,
- 3) semiquinone and quinone adducts are capable of further reactions resulting in multi-S-substituted cysteinyl conjugates (up to four per molecule) in blood and liver and may produce macromolecular crosslinks,
- 4) redox cycling associated with oxidation of tetrachlorohydroquinone and/or reduction of tetrachlorobenzoquinone generates oxygen radicals that can increase the level of oxidative damage to DNA,
- 5) the daily rate of protein adduct production per unit dose was greater in mice than in rats,
- 6) mice produced about five times more liver protein-binding species and had a 4-fold greater dose of quinone species to liver nuclei than rats (rats had a greater dose to liver cytosol),
- 7) adducts arising from tetrachloro-1,4-benzoquinone and tetrachloro-1,2-benzoquinone) occurred in mouse cytosolic and nuclear proteins but only low levels of one semiquinone adduct (tetrachloro-1,2-benzosemiquinone) were observed in mouse liver cytosolic proteins,
- 8) adduct production was linearly related to dose in mice except for the semiquinone adduct where less than proportional production occurred at doses > 20 mg/kg,
- 9) production of the tetrachloro-1,2-benzosemiquinone adduct was proportionally greater at low doses in rats and was 40-fold greater than in mice,
- 10) production of the tetrachloro-1,4-benzoquinone adduct was proportionally greater at high doses in rats but was 2- to 11-fold greater in mice than in rats,
- 11) types of adducts produced in Sprague-Dawley rats after a single dose (5 to 40 mg/kg) were comparable to those observed in F344 rats fed 60 mg/kg for six months, and
- 12) rates of adduct elimination were similar in rats and mice.

Thus, both the type and amount of adducts show interspecies differences. Specifically, the increased metabolism and greater dose to liver nuclei in mice suggest that mouse liver has a greater risk of hepatic DNA damage (Lin *et al.* 1997, Tsai *et al.* 2002). This is supported by data that show greater amounts of both oxidative and direct DNA damage in the liver and increased hepatotoxicity in mice compared with rats (Lin *et al.* 2002). About 40% of the estimated total dose to mouse liver nuclei was attributed to tetrachloro-1,2-benzoquinone (Table 5-3) (Lin *et al.* 1999). Since this metabolite did not form adducts with liver or blood proteins in rats, it might play a critical role in pentachlorophenol hepatocarcinogenesis.

**Table 5-3. Estimated tissue doses of tetrachlorobenzoquinone-derived electrophiles in rats and mice following a single oral dose of 20 mg/kg pentachlorophenol**

Electrophile	Dose (nM hr $\pm$ SE)			
	Liver cytosolic proteins		Liver nuclear proteins	
	Sprague-Dawley rat	B6C3F <sub>1</sub> mice	Sprague-Dawley rat	B6C3F <sub>1</sub> mice
Cl <sub>4</sub> -1,4-BQ <sup>a</sup>	416 $\pm$ 156*	117 $\pm$ 17	1.82 $\pm$ 0.55	4.94 $\pm$ 0.51*
Cl <sub>4</sub> -1,2-BQ	nd	24.2 $\pm$ 8.15*	nd	3.24 $\pm$ 0.46*
Total	416 $\pm$ 156*	141 $\pm$ 18.9	1.82 $\pm$ 0.55	8.18 $\pm$ 0.68*

Source: Lin *et al.* 1997.

Cl<sub>4</sub>-1,2-BQ = tetrachloro-1,2-benzoquinone, Cl<sub>4</sub>-1,4-BQ = tetrachloro-1,4-benzoquinone, nd = not detected.

\*  $P < 0.05$  (significant increase compared with the other species).

<sup>a</sup> Includes all monosubstituted and multisubstituted Cl<sub>4</sub>-1,4-BQ-derived quinones.

**Table 5-4. Estimated daily production of quinone adducts per unit dose of pentachlorophenol in rats and mice**

Adduct	Sprague-Dawley rats (pmol/g)/(mg/kg/day)		B6C3F <sub>1</sub> mice (pmol/g)/(mg/kg/day)
	R <sub>Lo</sub> <sup>a</sup>	R <sub>Hi</sub> <sup>b</sup>	R <sup>c</sup>
<i>Cytosolic proteins</i>			
Cl <sub>4</sub> -1,4-BQ <sup>d</sup>	124 $\pm$ 175	396 $\pm$ 28.8	547 $\pm$ 11*
Cl <sub>4</sub> -1,2-BQ	nd	nd	778 $\pm$ 25*
Cl <sub>4</sub> -1,4-SQ <sup>e</sup>	0.425 $\pm$ 0.37	NA	nd
Cl <sub>4</sub> -1,2-SQ <sup>e</sup>	32.5 $\pm$ 25.1	NA	0.822 $\pm$ 0.50
<i>Nuclear proteins</i>			
Cl <sub>4</sub> -1,4-BQ <sup>d</sup>	30.3 $\pm$ 17.4	57.2 $\pm$ 4.66	86.9 $\pm$ 3*
Cl <sub>4</sub> -1,2-BQ	nd	nd	9.6 $\pm$ 0.71*
Cl <sub>4</sub> -1,4-SQ <sup>e</sup>	0.307 $\pm$ 0.21	NA	nd
Cl <sub>4</sub> -1,2-SQ <sup>e</sup>	5.83 $\pm$ 3.01	NA	nd

Source: Lin *et al.* 1999.

\*  $P < 0.05$  (significant increase compared to the R<sub>Hi</sub> in rats).

Cl<sub>4</sub>-1,2-BQ = tetrachloro-1,2-benzoquinone, Cl<sub>4</sub>-1,4-BQ = tetrachloro-1,4-benzoquinone, Cl<sub>4</sub>-1,2-SQ = tetrachloro-1,2-benzosemiquinone, Cl<sub>4</sub>-1,4-SQ = tetrachloro-1,4-benzosemiquinone, R = estimated daily production of adducts, NA = not available, nd = not detected.

<sup>a</sup> Daily adduct production at low doses ( $\leq 4$  to 10 mg/kg).

<sup>b</sup> Daily adduct production at high doses ( $\geq 60$  to 230 mg/kg).

<sup>c</sup> Daily adduct production over the whole dose range (5 to 40 mg/kg).

<sup>d</sup> Includes all monosubstituted and multisubstituted Cl<sub>4</sub>-1,4-BQ-derived adducts.

<sup>e</sup> Statistical evaluations of semiquinone adducts were not conducted.

The induction of specific P450 isozymes in mice also may play a role in the formation of liver tumors as indicated by *in vitro* studies that examined the effects of various microsomes inducers on pentachlorophenol metabolism in rats and mice (Tsai *et al.* 2001, van Ommen *et al.* 1989, van Ommen *et al.* 1986a). Tsai *et al.* (2001) demonstrated that increased metabolism was primarily associated with products of tetrachloro-1,4-benzoquinone. The levels of adducts formed by this metabolite were similar in rat liver cytosolic proteins following induction by either phenobarbital or 3-methylcholanthrene (2.4 times control levels). Adduct levels in mouse liver cytosolic proteins were about 2.3 times the control values with phenobarbital-induced microsomes but were much higher following induction by 3-methylcholanthrene (8-fold increase vs. controls). Adduct levels of all other quinone and semiquinone metabolites were not affected by induction. Also, under conditions of oxidative stress, Tsai *et al.* speculated that lipid hydroperoxides could mediate the bioactivation of pentachlorophenol to quinones or semiquinones at a much greater rate than P450s, resulting in enhanced toxicity.

If the pentachlorophenol-derived quinones rather than semiquinones are responsible for the carcinogenic effects, the dosing regimens used in the chronic bioassays may have contributed to the negative results in rat liver (Lin *et al.* 1999). Dose levels in Sprague-Dawley rats (1 to 30 mg/kg) and F344 rats (10 to 60 mg/kg) would favor less than proportional production of reactive quinones and greater than proportional production of semiquinones. Further, liver DNA adduct levels in mice administered 15 mg/kg pentachlorophenol for 7 days were 50-fold greater than observed in F344 rats administered 60 mg/kg for 6 months.

#### *Oxidative DNA damage*

In addition to direct DNA adducts formed by reactive metabolites of pentachlorophenol, several studies indicate that oxidative damage likely contributes to the carcinogenic effects of this chemical. Redox cycling of quinones and semiquinones can produce oxidative stress through formation of reactive oxygen species such as superoxide, hydrogen peroxide, and the hydroxyl radical (Zhu *et al.* 2011a). The most common biomarker of oxidative damage is 8-hydroxy-2'-deoxyguanosine (8-OH-dG) and is formed by the interaction of DNA with the hydroxyl radical. Several studies indicate that hydroxyl radicals can be formed by tetrachlorohydroquinone and hydrogen peroxide via a metal-independent semiquinone-mediated organic Fenton reaction (Yin *et al.* 2013, Zhu *et al.* 2011b, Zhu *et al.* 2000, Zhu and Shan 2009, Zhu *et al.* 2011a).

8-OH-dG lesions were formed in deoxyguanosine and calf thymus DNA incubated with tetrachlorobenzoquinone or tetrachlorohydroquinone (Lin *et al.* 2001b, Naito *et al.* 1994, Yin *et al.* 2013), in human HeLa S3 tumor cells or Chinese hamster V79 cells incubated

with tetrachlorohydroquinone (Dahlhaus *et al.* 1995, Dahlhaus *et al.* 1996, Lin *et al.* 2001a) and in the liver of B6C3F<sub>1</sub> mice following acute (Sai-Kato *et al.* 1995) or subacute to subchronic oral exposure (2 to 8 weeks) to pentachlorophenol or tetrachlorohydroquinone (Dahlhaus *et al.* 1994, Umemura *et al.* 1999, Umemura *et al.* 1996). Umemura *et al.* (2006) reported clear differences in the sensitivity of *nrf2*-deficient and wild-type ICR mice to pentachlorophenol-induced oxidative stress, thus, indicating that Nrf2 (a transcriptional factor that regulates induction of phase-II and antioxidant enzymes) played a key role in *in vivo* prevention of pentachlorophenol-induced oxidative stress and cell proliferation. Lin *et al.* (2002) also reported 8-OH-dG lesions in the liver of male F344 rats exposed to pentachlorophenol for 27 weeks but not in rats exposed for 1 or 5 days. The increase in 8-OH-dG lesions in rat liver after 27 weeks (2-fold increase vs. controls) was slightly less than that observed in the mouse after 2 to 4 weeks (2.4- to 2.8-fold increase). Sai-Kato *et al.* (1995) also reported that 8-OH-dG lesions were not significantly increased in non-target tissues in mice (kidney and spleen). Further, Wang *et al.* (1997) reported that glutathione was depleted by more than 60% in the livers of mice treated with tetrachlorohydroquinone, thus, reducing protection against reactive oxygen species.

Although 8-OH-dG lesions can lead to point mutations (particularly G:C to T:A transversions) and oncogene activation, Umemura *et al.* (1999) found no evidence of an initiating effect of pentachlorophenol in mice. Tasaki *et al.* (2012) also reported that pentachlorophenol exposure significantly increased 8-OH-dG levels and mRNA levels of NAD(P):quinone oxidoreductase 1 (NQO1) in the liver of p53-proficient and -deficient mice without affecting the reporter gene mutation frequency. Thus, pentachlorophenol was shown to be a liver tumor promoter in mice, and the promoting action was related to oxidative stress and compensatory hepatocellular proliferation (Tasaki *et al.* 2012, Umemura *et al.* 2003a, Umemura *et al.* 1999, Umemura *et al.* 2003b, Umemura *et al.* 1996). An increase in sustained hepatocyte cell proliferation was observed in parallel with oxidative stress and without overt signs of hepatotoxicity, thus, suggesting that cell proliferation was induced by oxidative stress. Co-treatment of mice with antioxidants prevented oxidative stress and cell proliferation (Sai-Kato *et al.* 1995, Umemura *et al.* 2003a). These data, along with the studies reviewed above, suggest that pentachlorophenol induces less oxidative stress in rat liver than in mouse liver.

#### *Inhibition of gap junctional intercellular communication*

Pentachlorophenol inhibits gap junctional intercellular communication *in vitro* and *in vivo* and supports the hypothesis that it contributes to tumor promotion via non-mutagenic mechanisms (Sai *et al.* 2001, Sai *et al.* 2000, Sai *et al.* 1998, Vinken *et al.* 2009a). Inhibition of apoptosis also has been associated with tumor promotion, and gap junctions have been linked to the apoptotic process (Sai *et al.* 2001). Liver homeostasis (i.e., hepatocellular proliferation, differentiation, and cell death) is mediated via gap junctional intercellular communication by exchanging small molecules and second messengers (Vinken *et al.* 2009a). A general characteristic of chemicals that alter gap junctional intercellular communication is that the effects are often manifested in a species-specific or tissue-specific manner. These features, combined with a general lack of direct DNA damage, are characteristic of nongenotoxic carcinogens. Many compounds

(e.g., phorbol esters, phenobarbital, peroxisome proliferators, dieldrin, and DDT) that are known to suppress gap junctional intercellular communication are tumor promoters or epigenetic carcinogens (Sai *et al.* 2001, Sai *et al.* 1998). Therefore, inhibition of gap junctional intercellular communication may be a biological marker for nongenotoxic hepatocarcinogens (Vinken *et al.* 2009a).

Gap junctions are composed of connexin (Cx) proteins, and epigenetic regulation of connexin expression includes histone acetylation, DNA methylation, and microRNA-related control (Vinken *et al.* 2009b, Vinken *et al.* 2009a). Gap junctions occupy about 3% of the hepatocyte membrane surface and are organized in plaques that contain 10 to 10,000 channels. The importance of functional gap junctions in preventing liver cancer was demonstrated when Cx32 knockout mice were shown to be more susceptible to both spontaneous and chemically induced liver cancer than wild-type mice (Temme *et al.* 1997).

*In vitro* studies with v-myc-transfected rat liver epithelial cells showed that pentachlorophenol, but not tetrachlorohydroquinone, reversibly inhibited gap junctional intercellular communication prior to inhibition of apoptosis (Sai *et al.* 2001, Sai *et al.* 1998). These data were consistent with the hypothesis that gap junctional intercellular communication contributes to the tumor promotion process by increasing proliferation of transformed cells and decreasing programmed cell death. Further, decreased expression of p53 (a key molecule required for apoptosis induction) was observed but levels of Bcl-2 (an anti-apoptotic factor) were unchanged. These data suggest that the mechanism of pentachlorophenol-mediated inhibition of apoptosis likely involved decreased expression of p53 and provide evidence for a direct role of pentachlorophenol in tumor promotion.

Male B6C3F<sub>1</sub> mice exposed to carcinogenic doses of pentachlorophenol in their diet for 2 weeks also developed a dose-related inhibition of gap junctional intercellular communication in hepatocytes associated with a reduction in Cx32 plaques in the plasma membrane and an increase in cell proliferation (Sai *et al.* 2000). These effects were prevented when mice were given green tea as their only source of drinking water. Mechanisms contributing to the anti-promoting action of green tea include its antioxidative properties, inhibition of enzymes that degrade connexins, and induction of detoxifying enzymes such as glutathione-S-transferase and sulfotransferases.

#### *Mitogenic and cytotoxic effects*

Allen *et al.* (2004) reported that prechronic liver lesions in rodents could be used to predict liver carcinogens. In particular, chemicals inducing hepatocellular necrosis, hepatocellular hypertrophy, and hepatocellular cytomegaly in prechronic studies had a high likelihood (89.5% in mice and 64% in rats) of inducing liver neoplasms in a chronic study. Adding increased liver weight increased the percentage of liver carcinogens correctly identified but also increased the number of false positives.

Although there is some evidence that pentachlorophenol is more hepatotoxic in mice than in rats, the data also indicate that the by-products of its synthesis are contributing factors (Kimbrough and Linder 1978, Lin *et al.* 2002, NTP 1989, 1999). Suzuki *et al.* (1997) reported that pentachlorophenol caused intermediate cytotoxicity and slight peroxidative

damage to isolated rat hepatocytes *in vitro*. Rats fed technical grade pentachlorophenol at doses of 100 to 500 ppm for eight months had prominent to severe hepatic lesions while purified pentachlorophenol was only mildly hepatotoxic (Kimbrough and Linder 1978). Rats fed diets containing pure pentachlorophenol for 28 days or 2 years had increased liver weights, minimal to mild hepatocyte degeneration, and minimal centrilobular hepatocyte hypertrophy (observed at 28 days or 7 months but not after 2 years). Dorsey *et al.* (2004, 2006) reported that purified pentachlorophenol was acutely toxic *in vitro* to mouse AML 12 hepatocytes, caused a strong mitogenic response at sublethal concentrations, and induced stress-related gene expression. Stress-activated protein kinases were likely involved in facilitating the mitogenic response. Similar cytotoxic and mitogenic effects also were observed in human liver carcinoma (HepG2) cells (Dorsey *et al.* 2002). Mice fed purified pentachlorophenol at doses of 300 to 1,200 ppm for 2 to 4 weeks had severe hepatomegaly, hepatocyte swelling, and persistent hepatocyte proliferation, and significant elevation (2- to 3-fold) of serum AST levels; however, there were no extensive necrotic foci (Umemura *et al.* 1996). Hepatic lesions showed dose-related liver effects in mice (increased liver weights, centrilobular cytomegaly, karyomegaly, and necrosis) exposed to all grades of pentachlorophenol but were more severe in mice fed technical grade pentachlorophenol compared with mice fed EC-7 (a formulation containing less by-products of synthesis) or pure pentachlorophenol (NTP 1989).

#### 5.2.4 Vascular tumors in mice

No specific mechanistic studies for pentachlorophenol and vascular tumors were identified; however, Cohen *et al.* (2009) proposed a working mode of action for the induction of hemangiosarcoma in rodents. These authors noted that hemangiosarcomas were more common in mice than in rats (possibly due to lower antioxidant levels) and that most of the chemicals (pentachlorophenol was not included) associated with these neoplasms were non-DNA reactive. The general model included hypoxia, increase in reactive oxygen species, and macrophage activation leading to the release of angiogenic growth factors and cytokines with subsequent stimulation of endothelial cell proliferation. Sustained endothelial cell proliferation could lead to hemangiosarcoma formation.

#### 5.2.5 Mesothelioma in rats

Mesotheliomas of the *tunica vaginalis* are relatively rare but are seen most frequently in male F344 rats and are causally associated with the high background incidence of Leydig-cell tumors of the testes in this strain (Maronpot *et al.* 2009). Proliferating Leydig cells result in an altered hormonal milieu in these rats and may contribute to the development of mesotheliomas. In addition, oxidative damage from pentachlorophenol exposure may contribute to the increased incidence of mesothelioma observed in male F344 rats (Maronpot *et al.* 2009, Lin *et al.* 2002). Mesothelial cells have low levels of antioxidants and are susceptible to oxidative stress because cellular defenses are more easily depleted. Evidence supporting a possible role of oxidative damage for pentachlorophenol-induced mesothelioma in rats comes from studies with mineral fibers where free radical toxicity and 8-OH-dG lesions are known to be contributing factors (Adachi *et al.* 1994, Murata-Kamiya *et al.* 1997). Also, in the NTP (1999) chronic

bioassay, mesotheliomas were increased only in rats that were exposed to 1,000 ppm for 1 year and not in rats exposed to 600 ppm for 2 years (see Section 4). These data suggest a possible threshold for oxidative damage that was exceeded only in the stop-exposure study; however, the stop-exposure study did not test at lower doses.

#### 5.2.6 Mouse skin tumor models, tumor promotion/enhanced susceptibility

Two studies investigated the tumor-promoting potential of pentachlorophenol or tetrachlorohydroquinone in a mouse skin carcinogenesis model or in transgenic mice and provide some support for a nongenotoxic mechanism (Chang *et al.* 2003, Spalding *et al.* 2000). Chang *et al.* demonstrated that both pentachlorophenol and tetrachlorohydroquinone were weak promoters in the CD-1 mouse skin tumor model (dimethylbenz[*a*]anthracene used as the initiator). Both compounds induced epidermal hyperplasia, a biomarker of tumor promotion, and increased the cell proliferation index. Factors that likely contributed to the promotional effects of these compounds included oxidative stress, epidermal hyperplasia, and inhibition of gap junctional intracellular communication. Although, this study demonstrated that pentachlorophenol and tetrachlorohydroquinone were tumor promoters in mouse skin, the authors could not rule out the possibility that these compounds might have had a syncarcinogenic effect. Lin *et al.* (2004) also demonstrated *in vitro* that tetrachlorohydroquinone-induced skin tumor promotion reported by Chang *et al.* (2003) could occur through upregulation of Bcl-2 protein and subsequent inhibition of apoptosis. However, these data are not consistent with Sai *et al.* (2001) (see Section 5.2.3) who reported inhibition of apoptosis through reduced expression of p53 rather than increased Bcl-2 expression.

Spalding *et al.* (2000) reported that dietary administration of pentachlorophenol was not active when tested in the haplo-insufficient *p53* knockout mouse (*p53*<sup>+/-</sup>) but did cause papillomas (high-dose only) in transgenic mice that possessed an inducible *v-Ha-ras* gene (Tg•AC) exposed to pentachlorophenol dermally. The positive response only in the Tg•AC model is consistent with a nongenotoxic mechanism. However, this model has been questioned as neoplasms can be induced by non-carcinogenic treatments, such as skin irritation and wounding (Fuhrman 2005). Other studies provided evidence that pentachlorophenol could enhance or inhibit the carcinogenicity of other compounds by inhibiting various enzymes involved in oxidation, epoxidation, sulfation of phenols, and acetylation (Arrhenius *et al.* 1977, Goodman 2001, Meerman *et al.* 1983, Moorthy and Randerath 1996). Moorthy and Randerath (1996) demonstrated that pentachlorophenol inhibits epoxide detoxication *in vivo* and *in vitro* and glutathione-*S*-transferase *in vitro*. Thus, pentachlorophenol exposure could enhance DNA damage caused by chemicals that undergo epoxidation prior to DNA binding. Arrhenius *et al.* (1977) incubated liver microsomes with pentachlorophenol and reported that electron transport in the cytochrome P450 enzyme system was strongly inhibited. The effect was attributed to pentachlorophenol rather than a metabolite.

#### 5.2.7 Synthesis of mechanistic data

The carcinogenic actions of pentachlorophenol are not well understood but have been associated with multiple mechanisms including metabolism to genotoxic metabolites, oxidative damage, inflammation, cytotoxicity and sustained cell proliferation, induction of stress genes, immunosuppression, inhibition of enzymes involved in metabolism,

interference with gap junctional intercellular communication, and inhibition of apoptosis. All of these mechanisms are relevant to humans; however, there is some controversy over the importance of metabolic activation pathways involving oxidation to tetrachlorohydroquinone, semiquinones, and benzoquinones because the available studies do not conclusively demonstrate that these metabolites are formed *in vivo* in humans. Furthermore, technical grade pentachlorophenol contains various by-products (e.g., other chlorophenols, dibenzo-*p*-dioxins, and dibenzofurans) that are carcinogenic and likely contribute to, but are not solely responsible for, the carcinogenic effects observed in humans and experimental animals exposed to pentachlorophenol.

Plausible modes of action contributing to hematopoietic cancers in humans include metabolic activation by peroxidases in bone marrow and lymphocytes to phenoxy radicals that preferentially form *O*-bonded C8-dG adducts and immunosuppression. There is a strong association of non-Hodgkin lymphoma with immunosuppressive conditions, and pentachlorophenol is known to suppress both cellular and humoral immunity. Some studies in rodents indicate that the dioxin by-products (particularly the hexa- and hepta-substituted congeners) in the technical grade formulations are responsible for immunosuppression; however, there is sufficient evidence that pentachlorophenol itself is immunosuppressive in humans and other species. Therefore, both pentachlorophenol and its dioxin by-products contribute to immunosuppression.

There is some evidence that liver cancer in mice could be caused by direct adduct formation with electrophilic tetrachlorobenzoquinone metabolites and/or oxidative damage to DNA derived from the redox cycling of benzoquinone and semiquinone metabolites. The dioxin by-products also likely contributed to liver tumors in mice. A comparison of rats and mice indicate that key differences in the quantity and quality of benzoquinone liver nuclear protein adducts, hepatotoxicity, and liver DNA damage may partially explain why the mouse is more susceptible than the rat. However, there is strong evidence that pentachlorophenol acts as a liver tumor promoter in mice through a number of mechanisms including oxidative stress without gene mutations, sustained hepatocellular proliferation, inhibition of gap-junctional intercellular communication, and inhibition of apoptosis. Liver tumor promotion also could possibly explain why mice are more susceptible than rats because of the high spontaneous rate of liver tumors in B6C3F<sub>1</sub> mice.

Very few mechanistic data were available for other tumor sites; however, it is likely that all of the mechanisms discussed above are involved. There is evidence that oxidative DNA damage contributes to mesothelioma in rats. Transgenic mouse skin tumor models also provide evidence for nongenotoxic mechanisms. Several studies also suggest that pentachlorophenol may enhance or inhibit the carcinogenicity of other xenobiotics by inhibiting key metabolizing enzymes involved in oxidation, epoxidation, sulfation, and/or acetylation.

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## 6 Overall Cancer Evaluation – Synthesis of Human, Animal, and Mechanistic Data

This section synthesizes the information from cancer and toxicological studies in experimental animals and human epidemiologic studies and applies the RoC listing criteria to that body of knowledge to reach a preliminary listing recommendation.

‘Pentachlorophenol and by-products of its synthesis’ was defined as the substance under evaluation for the RoC because commercially available pentachlorophenol is a mixture of chemicals that are formed during the synthesis process and a part of human exposure to the primary chemical. The primary by-products are a mixture of isomers of higher chlorinated dibenzo-*p*-dioxins and dibenzofurans (hexa-, hepta-, octa-) and hexachlorobenzene. People exposed to pentachlorophenol have greater serum levels of total dioxin equivalents (TEQs) than unexposed people (Collins *et al.* 2007).

Pentachlorophenol is a multi-site carcinogen in humans and animals. Some of its synthesis by-products are carcinogens, and likely contribute to but do not explain all of its cancer risk. Epidemiologic studies found a credible association between exposure to pentachlorophenol and NHL risk; some studies found increased risks of cancers at other tissue sites among pentachlorophenol-exposed workers, but the body of evidence was weaker for these sites. Dietary exposure to pentachlorophenol caused tumors at multiple tissue sites in rats and humans. The mechanisms responsible for the carcinogenic effects of pentachlorophenol are complex and are not completely understood. Although the available data indicate that multiple mechanisms are involved, none have been defined sufficiently to identify the key events or temporal relationships for specific cancer sites in either humans or experimental animals (see Section 5).

### 6.1 Cancer studies in humans

There is sufficient evidence for the carcinogenicity of pentachlorophenol from studies in humans showing a causal relationship between exposure to pentachlorophenol and NHL. A credible association of exposure to pentachlorophenol and NHL was observed in studies of different occupational populations with differing co-exposures, in different geographical areas, and with different study designs (see Section 3.4). In addition, a strong exposure response relationship with cumulative dermal exposure was observed in the most informative study, a large cohort of Canadian sawmill workers. Overall, potential confounding from occupational or non-occupational co-exposures can reasonably be ruled out in the most informative studies and across the overall body of studies of NHL, although they cannot be ruled out in the less informative studies. With respect to other cancers, there was evidence for an association between exposure to pentachlorophenol and multiple myeloma and kidney cancer in the most informative study, but limited evidence to evaluate these endpoints from other studies. There was conflicting for soft tissue sarcoma and little evidence of an increased risks for cancers of the liver and lung, and all cancer combined.

## 6.2 Studies in experimental animals

There is sufficient evidence of the carcinogenicity of pentachlorophenol from studies in experimental animals. Dietary exposure caused statistically significant increases for malignant or a combination of malignant and benign liver and adrenal gland tumors in male and female B6C3F<sub>1</sub> mice, vascular tumors (hemangiosarcoma) in female mice, and mesothelioma and nasal tumors in male F344 rats (see Section 4). Pentachlorophenol caused liver tumors in mice and dioxin-like components contributed to carcinogenicity; less pure technical grade pentachlorophenol, which has a higher total TEQ amount than Dowicide EC-7, had more tumors at the same exposure concentration than Dowicide EC-7.

## 6.3 Mechanistic data

Although the mechanisms by which pentachlorophenol causes cancer in animals and potentially in humans are not known, the available data support biological plausibility for a multisite carcinogen. Little information is known about the pathogenesis of NHL, but proposed mechanisms include metabolism to genotoxic and mutagenic metabolites, immunosuppression, DNA damage and chromosome breakage, and inhibition of apoptosis. All of these proposed mechanisms are relevant to human carcinogenicity.

### *Metabolism*

Metabolism and toxicokinetic studies show considerable interspecies variation, which may account for differences in carcinogenicity and tissue endpoints reported in the mouse, rat, and human. Oxidative and reductive dechlorination of pentachlorophenol leading to potentially reactive metabolites, tetrachlorohydroquinones and semiquinones, followed by glucuronidation/sulfation is the primary metabolic pathway in rodents. These metabolites and/or glucuronidated forms have been detected in the serum and urine of rodents. Limited information is available on metabolism in humans; primarily free and glucuronide-conjugated pentachlorophenol have been detected in urine, although tetrachlorohydroquinone was identified in the urine of exposed workers (Ahlborg *et al.* 1974). Other studies have shown that human liver microsomes can metabolize pentachlorophenol to tetrachlorohydroquinone (Juhl *et al.* 1985) and pentachlorophenol glucuronide *in vitro* (Lilienblum 1985).

### *Metabolites and genotoxicity*

Pentachlorophenol genotoxicity is most likely mediated by its metabolites, primarily tetrachlorohydroquinone and tetrachlorobenzoquinone. The tetrachlorohydroquinone and tetrachlorobenzoquinone metabolites of pentachlorophenol were positive for DNA damage and DNA adducts, and tetrachlorohydroquinone was positive for mutations. These metabolites can form free radicals and through redox cycling generate reactive oxygen species. Metabolism can occur in the liver and also in extrahepatic sites. Activation of pentachlorophenol by peroxidase or myeloperoxidase activity in lymphocytes and in bone marrow presents a plausible mechanism for cancers of white blood cells such as NHL, lymphomas, and multiple myelomas. Peroxidases can metabolize pentachlorophenol to phenoxyl free radicals, preferentially forming *O*-bonded C8-dG DNA adducts at these sites resulting in DNA damage. This hypothesis is supported by the genotoxicity profile of pentachlorophenol. Pentachlorophenol caused

adducts, mutations, DNA damage, and chromosomal aberrations in experimental conditions with metabolic activation (e.g., presence of exogenous or endogenous metabolic enzymes). Pentachlorophenol was not mutagenic or genotoxic without metabolic activation in most of the standard *in vitro* assays. DNA adducts were found in primary cells exposed to pentachlorophenol and in the livers of rats and mice exposed to pentachlorophenol; the predominant adduct was the oxygen-bonded C8-dG adduct. These results are supported by evidence of DNA strand breaks with human primary and cancer cell lines exposed to pentachlorophenol. There was evidence that pentachlorophenol caused DNA damage (strand breaks) as measured by the comet assay in several human cancer cell lines and fibroblasts (Stang and Witte 2010), lymphocytes (Stang and Witte 2010 and Michałowicz 2010), and nasal mucosal cells (Tisch *et al.* 2005) with the addition of metabolic activation.

Karyotypic instability in the form of chromosomal breaks and translocations are found in NHL, multiple myeloma, and soft tissue sarcoma. There is limited evidence of an increase in acentric and dicentric chromosomal aberrations indicating chromosomal breakage were found in peripheral lymphocytes of workers exposed to pentachlorophenol (Bauchinger *et al.* 1982).

#### *Immunosuppression*

Organochlorine exposures can affect the immune system, and immunosuppression is an established risk factor for NHL (Hardell and Eriksson 2003). Pentachlorophenol exposure specifically has been associated with cellular and humoral immunodeficiencies in humans. Some studies in rodents indicate that the dioxin by-products (particularly the hexa- and hepta-substituted congeners) in the technical grade formulations are responsible for immunosuppression; however, there is sufficient evidence that pentachlorophenol itself is immunosuppressive in humans and other species.

#### *Inhibition of apoptosis*

Pentachlorophenol is an inhibitor of apoptosis, which may lead to accumulation of malignant cells. Inhibition of apoptosis also has been associated with tumor promotion, and interference with intercellular communication through gap junctions has been linked to the apoptotic process. In addition, several studies suggest that pentachlorophenol is also a non-mutagenic liver tumor promoter in mice, inhibits enzymes involved in metabolism, inhibits gap junctional intercellular communication, and inhibits apoptosis.

### **6.4 Preliminary listing recommendation**

Pentachlorophenol and by-products of its synthesis are *known to be a human carcinogen* based on sufficient evidence from studies in humans showing a causal relationship between exposure to pentachlorophenol and NHL. This conclusion is supported by sufficient evidence in experimental animals, and supporting mechanistic evidence.

From the available evidence, the observed carcinogenicity in experimental animals cannot be explained by the presence of by-products alone, and pentachlorophenol is carcinogenic when analyzed separately and combined with by-products. The epidemiologic studies cannot separate effects of pentachlorophenol from any effects of its

chlorinated dioxin by-products. Dioxin (specifically 2,3,7,8-tetrachlorodibenzo-*p*-dioxin) (Cogliano *et al.* 2011) has been linked to NHL in humans and it is reasonable that dioxin-like activity may contribute to the carcinogenicity of NHL observed in the cancer studies of exposure to pentachlorophenol. Most likely, tumor formation from this complex mixture is a contribution of pentachlorophenol and some of the by-products.

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## Abbreviations

<sup>1</sup> H NMR:	proton nuclear magnetic resonance
2,3,7,8-TCDD:	2,3,7,8-tetrachlorodibenzo- <i>p</i> -dioxin, TCDD
2,4,5-TCP:	2,4,5-trichlorophenol
8-OH-dG:	8-hydroxydeoxyguanosine
AAF:	2-acetylaminofluorene
ACGIH:	American Conference of Governmental Industrial Hygienists
AhR:	aryl hydrocarbon receptor
ARNT:	aryl hydrocarbon nuclear translocator
ATSDR:	Agency for Toxic Substances and Disease Registry
BDL:	below detection limit
CHO:	Chinese hamster ovary
Cl <sub>4</sub> -1,2-BQ:	tetrachloro-1,2-benzoquinone
Cl <sub>4</sub> -1,2-SQ:	tetrachloro-1,2-benzosemiquinone
Cl <sub>4</sub> -1,4-BQ:	tetrachloro-1,4-benzoquinone
Cl <sub>4</sub> -1,4-SQ:	tetrachloro-1,4-benzosemiquinone
Cx:	connexin
Cx32:	gap junction beta 1-protein; connexin32
dA:	deoxyadenosine
DEN:	diethylnitrosamine
dG:	deoxyguanosine
DNA:	deoxyribonucleic acid
dw:	drinking water
EG:	ethylguanine

Endo III:	endonuclease III
EPA:	Environmental Protection Agency
Exp.:	Exposed
F:	female
FDA:	Food and Drug Administration
G:	guanine
GI:	gastrointestinal
GIS:	Geographic Information System
HBV:	Hepatitis B virus
HCB:	hexachlorobenzene
HCL:	hairy-cell leukemia
HCV:	Hepatitis C virus
HDAC:	histone deacetylase
HEG:	(2-hydroxyethyl) guanine
HETA:	Health Hazard Evaluation and Technical Assistance
HGPRT:	hypoxanthine-guanine phosphoribosyl transferase
HHE:	Health Hazard Evaluation
HIC:	highest ineffective concentration
HID:	highest ineffective dose
HIV:	Human immunodeficiency virus
HpCDD:	1,2,3,4,6,7,8-heptachlorodibenzo- <i>p</i> -dioxin
HPLC:	high-performance liquid chromatography
hr:	hour
HxCDD:	1,2,3,4,7,8-hexachlorodibenzo- <i>p</i> -dioxin (1,4-HxCDD) or 1,2,3,6,7,8-hexachlorodibenzo- <i>p</i> -dioxin (1,6-HxCDD) or 1,2,3,7,8,9-hexachlorodibenzo- <i>p</i> -dioxin (1,9-HxCDD)

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I:	inconclusive
i.p.:	intraperitoneal
i.v.:	intravenous
IARC:	International Agency for Research on Cancer
IDLH:	immediately dangerous to life and health
kg:	kilogram
L:	liter
LEC:	lowest effective concentration
LED:	lowest effective dose
LH:	lymphohematopoietic
LHC:	lymphohematopoietic cancer
LOD:	limit of detection
LOH:	loss of heterozygosity
M:	male
m <sup>3</sup> :	cubic meter
MCL:	maximum contaminant level
MDEQ:	Mississippi Department of Environmental Quality
MG:	methylguanine
mg:	milligram
mL:	milliliter
MM:	multiple myeloma
MS:	mass spectrometry
N.D.:	not detected; not determined
NA	not available
Na-PCP:	sodium pentachlorophenate

NA:	not applicable
NCE:	normochromatic erythrocyte
NDMA:	<i>N</i> -nitrosodimethylamine
NHANES:	National Health and Nutrition and Examination Survey
NHL:	non-Hodgkin's lymphoma
NIOSH:	National Institute for Occupational Safety and Health
NLM:	National Library of Medicine
NOES:	National Occupational Exposure Survey
NOS:	not otherwise specified
NPL:	National Priorities List
NR:	not reported; none reported
Nrf2:	nuclear factor (erythroid derived-2)-like 2
ns:	not specified
NS:	not significant
NT:	not tested
OCDD:	octachlorodibenzo- <i>p</i> -dioxin
OR:	odds ratio
OSHA:	Occupational Safety and Health Administration
OTM:	olive tail moment
PCE:	polychromatic erythrocyte
PCNA:	proliferating cell nuclear antigen
PCP:	pentachlorophenol
PEL:	permissible exposure limit
ppm:	parts per million
R:	estimated daily production of adducts

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RAHC:	Reasonably anticipated to be a human carcinogen
REL:	recommended exposure limit
RoC:	Report on Carcinogens
ROS:	reactive oxygen species
RQ:	reportable quantity
RR:	relative risk
SAFE:	significance analysis of function and expression
SCE:	sister-chromatid exchange
SD:	standard deviation
SIR:	standardized incidence ratio
SMR:	standardized mortality ratio
SOCMI:	synthetic organic chemical manufacturing industry
SPA:	solid phosphoric acid
SRR:	standardized rate ratio
STS:	soft tissue sarcoma
TCBQ:	tetrachlorobenzoquinone
TCCAT:	tetrachlorocatechol
TCDF:	2,3,7,8-tetrachlorodibenzofuran
TCHQ:	tetrachlorohydroquinone
TCoBQ:	tetrachloro- <i>ortho</i> -benzoquinone
TCoSQ:	tetrachloro- <i>ortho</i> -benzosemiquinone
TCP:	trichlorophenol
TCPs:	tetrachlorophenols
TCR:	tetrachlororesorcinol
TCSQ:	tetrachlorobenzosemiquinone

TDS:	Total Diet Study
TeCP:	tetrachlorophenol
TEF:	toxic equivalency factor
TEQ:	toxic equivalents; toxic equivalent based on relative potency of 1,4-HxCDD, 1,6-HxCDD, 1,9-HxCDD, HpCDD, and OCDD relative to 2,3,7,8-tetrachlorodibenzo- <i>p</i> -dioxin
TL:	tail length
TLV-TWA:	threshold limit value time-weighted average
$t_{\max}$ :	time to maximum concentration in plasma
TRI:	Toxics Release Inventory
TriCBQ:	trichlorobenzoquinone
TriCHQ:	trichlorohydroquinone
TSCA:	Toxic Substances and Recovery Act
TWA:	time-weighted average
UDS:	unscheduled DNA synthesis
UK:	United Kingdom
WHO:	World Health Organization
wt%:	weight percent
$\mu\text{g}$ :	microgram

## Glossary

**Ames assay:** The Ames *Salmonella*/microsome mutagenicity assay is a short-term bacterial reverse mutation assay specifically designed to detect a wide range of chemical substances that can produce genetic damage that leads to gene mutations.

**Biexponential process:** A process of drug (or xenobiotic) clearance with two phases with different rates. The first phase often involves rapid distribution of a drug to peripheral tissues, while the second phase represents clearance mechanisms that eliminate the drug from the body. (See “Two-compartment pharmacokinetic model.”)

**Biodegradation:** Biotransformation; the conversion within an organism of molecules from one form to another. A change often associated with change in pharmacologic activity.

**Boiling point:** The boiling point of the anhydrous substance at atmospheric pressure (101.3 kPa) unless a different pressure is stated. If the substance decomposes below or at the boiling point, this is noted (dec). The temperature is rounded off to the nearest °C.

**Cochran-Armitage trend test:** A statistical test used in categorical data analysis when the aim is to assess for the presence of an association between a variable with two categories and a variable with  $k$  categories. It modifies the chi-square test to incorporate a suspected ordering in the effects of the  $k$  categories of the second variable.

**Comet assay: single cell gel electrophoresis for assessment of DNA damage in presumptive target tissues.**

**Connexin proteins:** A group of transmembrane proteins that form the intermembrane channels of gap junctions. They are used by inorganic ions and most small organic molecules to pass through cell interiors.

**Critical temperature:** The temperature at and above which a gas cannot be liquefied, no matter how much pressure is applied.

**Differential selection:** Selective pressure for self renewal. Gene mutations that confer a growth or survival advantage on the cells that express them will be selectively enriched in the genome of tumors.

**Dioxin congeners:** Members of the same family of chemicals (i.e., polychlorinated dibenzo-*p*-dioxins) with different configurations. Dioxin congeners differ in terms of the number, position, and combination of chlorine atoms on the molecule.

**Disposition:** The description of absorption, distribution, metabolism, and excretion of a chemical in the body.

**Dowicide EC-7:** A technical-grade formulation of pentachlorophenol.

**Ecological study:** A study in which the units of analysis are populations or groups of people rather than individuals.

**Epigenetic mechanisms:** Changes in gene function that do not involve a change in DNA sequence but are nevertheless mitotically and/or meiotically heritable. Examples include DNA methylation, alternative splicing of gene transcripts, and assembly of immunoglobulin genes in cells of the immune system.

**Fisher's exact test:** The test for association in a two-by-two table that is based on the exact hypergeometric distribution of the frequencies within the table.

**Follow-up:** Observation over a period of time of a person, group, or initially defined population whose appropriate characteristics have been assessed to observe changes in health status or health-related variables.

**Freund's adjuvant:** A water-in-oil emulsion injected with immunogen (Freund's incomplete adjuvant) or with immunogen and killed mycobacteria (Freund's complete adjuvant) to enhance the immune response to the immunogen.

**Genomic instability:** An increased propensity for genomic alterations that often occurs in cancer cells. During the process of cell division (mitosis) the inaccurate duplication of the genome in parent cells or the improper distribution of genomic material between daughter cells can result from genomic instability.

**Glioma:** A cancer of the brain that begins in glial cells (cells that surround and support nerve cells).

**Hairy-cell leukemia:** A rare type of leukemia in which abnormal B-lymphocytes (a type of white blood cell) are present in the bone marrow, spleen, and peripheral blood. When viewed under a microscope, these cells appear to be covered with tiny hair-like projections.

**Hemangiosarcoma:** A type of cancer that begins in the cells that line blood vessels.

**Henry's Law constant:** The ratio of the aqueous-phase concentration of a chemical to its equilibrium partial pressure in the gas phase. The larger the Henry's law constant the less soluble it is (i.e., greater tendency for vapor phase). The relationship is defined for a constant temperature, e.g., 25°C.

**Hepatoma:** A liver tumor.

**Loss of heterozygosity:** If there is one normal and one abnormal allele at a particular locus, as might be seen in an inherited autosomal dominant cancer susceptibility disorder, loss of the normal allele produces a locus with no normal function. When the loss of heterozygosity involves the normal allele, it creates a cell that is more likely to show malignant growth if the altered gene is a tumor suppressor gene.

**Melting point:** The melting point of the substance at atmospheric pressure (101.3 kPa). When there is a significant difference between the melting point and the freezing point, a range is given. In case of hydrated substances (i.e., those with crystal water), the apparent melting point is given. If the substance decomposes at or below its melting point, this is noted (dec). The temperature is rounded off to the nearest °C.

**Metabolic activation:** The chemical alteration of an exogenous substance by or in a biological system. The alteration may inactivate the compound or it may result in the production of an active metabolite of an inactive parent compound.

**Micronuclei:** Small nuclei separate from, and additional to, the main nucleus of a cell, produced during the telophase of mitosis or meiosis by lagging chromosomes or chromosome fragments derived from spontaneous or experimentally induced chromosomal structural changes.

**Miscible:** A physical characteristic of a liquid that forms one liquid phase with another liquid (e.g., water) when they are mixed in any proportion.

**Molecular weight:** The molecular weight of a substance is the weight in atomic mass units of all the atoms in a given formula. The value is rounded to the nearest tenth.

**Multiple myeloma:** A type of cancer that begins in plasma cells (white blood cells that produce antibodies). Also called Kahler disease, myelomatosis, and plasma cell myeloma.

**Mutations:** A change in the structure of a gene, resulting from the alteration of single base units in DNA, or the deletion, insertion, or rearrangement of larger sections of genes or chromosomes. The genetic variant can be transmitted to subsequent generations.

**Nasal conchae:** The three thin bony plates on the lateral wall of the nasal cavity.

**National Health and Nutrition Examination Survey:** A program of studies designed to assess the health and nutritional status of adults and children in the United States. The survey is unique in that it combines interviews and physical examinations.

**National Priorities List:** The list of national priorities among the known releases or threatened releases of hazardous substances, pollutants, or contaminants throughout the United States and its territories. The National Priorities List is intended primarily to guide the U.S. Environmental Protection Agency in determining which sites warrant further investigation.

**NIOSH Dioxin Registry:** A compilation of demographic and work history information for all U.S. production workers who have synthesized products known to be contaminated with polychlorinated dibenzo-*p*-dioxins, and in particular the isomers 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) or hexachlorodibenzo-*p*-dioxins (HxCDD).

**Non-Hodgkin's lymphoma:** A heterogeneous group of malignant lymphomas; the only common feature being an absence of the giant Reed-Sternberg cells characteristic of Hodgkin's disease.

**Normochromatic erythrocyte:** A mature erythrocyte that lacks ribosomes and can be distinguished from immature, polychromatic erythrocytes by stains selective for RNA.

**Nrf2:** A protein that controls how certain genes are expressed. These genes help protect the cell from damage caused by free radicals (unstable molecules made during normal cell metabolism). Also called NFE2L2 and nuclear factor (erythroid-derived 2)-like 2.

**One-compartment model:** A pharmacokinetic modeling approach that models the entire body as a single compartment into which a drug is added by a rapid single dose, or bolus. It is assumed that the drug concentration is uniform in the body compartment at all times and is eliminated by a first order process that is described by a first order rate constant.

**Osmotic mini pump:** A miniature implantable infusion pump that is used to continuously infuse laboratory animals with a drug or other material. Absorption of water from surrounding tissues by osmosis through an outer rigid shell provides the means by which the material is forced out of a collapsible internal chamber at a constant rate.

**Papilloma:** A small solid benign tumor with a clear-cut border that projects above the surrounding tissue.

**Pericardial fat:** A type of fat that surrounds the heart.

**Phenoxy herbicide:** A category of systemic weed killers that have a chemical structure composed of six carbon atoms joined together in a ring formation. Two examples are 2,4-D (2,4-dichlorophenoxyacetic acid) and mecoprop (MCP).

**Plate incorporation:** A commonly used procedure for performing a bacterial reverse mutation test. Suspensions of bacterial cells are exposed to the test substance in the presence and in the absence of an exogenous metabolic activation system. In the plate-incorporation method, these suspensions are mixed with an overlay agar and plated immediately onto minimal medium. After two or three days of incubation, revertant colonies are counted and compared with the number of spontaneous revertant colonies on solvent control plates.

**Poly-3 trend test:** A survival-adjusted statistical test that takes survival differences into account by modifying the denominator in the numerical (quantal) estimate of lesion incidence to reflect more closely the total number of animal years at risk.

**Polychromatic erythrocyte:** A newly formed erythrocyte (reticulocyte) containing RNA.

**Prills:** Hailstone-like pellets of pentachlorophenol.

**Prophage lambda ( $\lambda$ ):** A virus in *Escherichia coli* (*E. coli*) bacteria that has integrated itself into the host *E. coli* DNA.

**Pyrolysis:** The chemical and physical decomposition of organic material that occurs at high temperatures in the absence of oxygen.

**QUOSA:** A collection of scientific literature management software and services for researchers and information professionals in the life sciences and related scientific and medical areas designed to retrieve, organize, and analyze full-text articles and documents.

**Schistosomiasis:** Schistosomiasis is a chronic, parasitic disease caused by blood flukes (trematode worms) of the genus *Schistosoma*.

**Sister-chromatid exchange:** The exchange during mitosis of homologous genetic material between sister chromatids; increased as a result of inordinate chromosomal fragility due to genetic or environmental factors.

**Soft tissue sarcoma:** A cancer that begins in the muscle, fat, fibrous tissue, blood vessels, or other supporting tissue of the body.

**Solubility:** The ability of a substance to dissolve in another substance and form a solution. The Report on Carcinogens uses the following definitions (and concentration ranges) for degrees of solubility: (1) *miscible* (see definition), (2) *freely soluble*- capable of being dissolved in a specified solvent to a high degree (> 1,000 g/L), (3) *soluble*- capable of being dissolved in a specified solvent (10–1,000 g/L), (4) *slightly soluble*- capable of being dissolved in a specified solvent to a limited degree (1-10 g/L), and (5) *practically insoluble*- incapable of dissolving to any significant extent in a specified solvent (< 1 g/L).

**Specific gravity:** The ratio of the density of a material to the density of a standard material, such as water at a specific temperature; when two temperatures are specified, the first is the temperature of the material and the second is the temperature of water.

**Spot test:** Qualitative assay in which a small amount of test chemical is added directly to a selective agar medium plate seeded with the test organism, e.g., *Salmonella*. As the chemical diffuses into the agar, a concentration gradient is formed. A mutagenic chemical will give rise to a ring of revertant colonies surrounding the area where the chemical was applied; if the chemical is toxic, a zone of growth inhibition will also be observed.

**T-helper cell:** A type of immune cell that stimulates killer T cells, macrophages, and B cells to make immune responses. A helper T cell is a type of white blood cell and a type of lymphocyte. Also called CD4-positive T lymphocyte.

**Tg.AC:** A transgenic mouse model with the ability to mount a tumorigenic response within 6 months in skin paint assays when dosed topically with nongenotoxic carcinogens.

**Time-weighted average:** The average exposure concentration of a chemical measured over a period of time (not an instantaneous concentration).

**Toxic equivalents:** A method used to report the toxicity-weighted masses of mixtures of dioxins; the sum of the products of the concentration of each compound multiplied by its toxic equivalency factor (TEF) value, which represents an estimate of the total 2,3,7,8-TCDD-like activity of the mixture.

**Toxicokinetics:** The mathematical description (toxicokinetic models) of the time course of disposition of a chemical in the body.

**TOXMAP:** A Geographic Information System from the National Library of Medicine that uses maps of the United States to help users visually explore data from EPA's TRI and Superfund programs.

**Transitions:** DNA nucleotide substitution mutation in which a purine base is substituted for another purine base (adenine → guanine or guanine → adenine) or a pyrimidine base for another pyrimidine base (cytosine → thymine or thymine → cytosine).

**Transversions:** DNA nucleotide substitution mutation in which a purine base (adenine or guanine) is substituted for a pyrimidine base (cytosine or thymine) or vice versa.

**Tunica vaginalis:** The serous membranous covering of the testis.

**Two-compartment pharmacokinetic model:** A two-compartment pharmacokinetic model resolves the body into a central compartment and a peripheral compartment. The central compartment generally comprises tissues that are highly perfused such as heart, lungs, kidneys, liver and brain. The peripheral compartment comprises less well-perfused tissues such as muscle, fat and skin. A two-compartment model assumes that, following drug administration into the central compartment, the drug distributes between that compartment and the peripheral compartment. However, the drug does not achieve instantaneous distribution (i.e., equilibrium), between the two compartments. After a time interval (t), distribution equilibrium is achieved between the central and peripheral compartments, and elimination of the drug is assumed to occur from the central compartment.

**Vapor density, relative:** A value that indicates how many times a gas (or vapor) is heavier than air at the same temperature. If the substance is a liquid or solid, the value applies only to the vapor formed from the boiling liquid.

**Vapor pressure:** The pressure of the vapor over a liquid (and some solids) at equilibrium, usually expressed as mm Hg at a specific temperature (°C).

## Appendix A: Literature Search Strategy

This document identifies the data sources, search terms, and search strategies that were used to identify literature for the draft monograph on pentachlorophenol (CASRN 87-86-5). The literature search strategy used for pentachlorophenol involved several approaches designed to identify potentially useful information for the broad range of topics covered by a Report on Carcinogens (RoC) monograph, as listed below.

- Properties and Human Exposure (focusing on the U.S. population)
- Disposition (ADME) and Toxicokinetics
- Human Cancer Studies
- Studies of Cancer in Experimental Animals
- Mechanistic Data and Other Relevant Effects
  - Genetic and Related Effects
  - Mechanistic Considerations

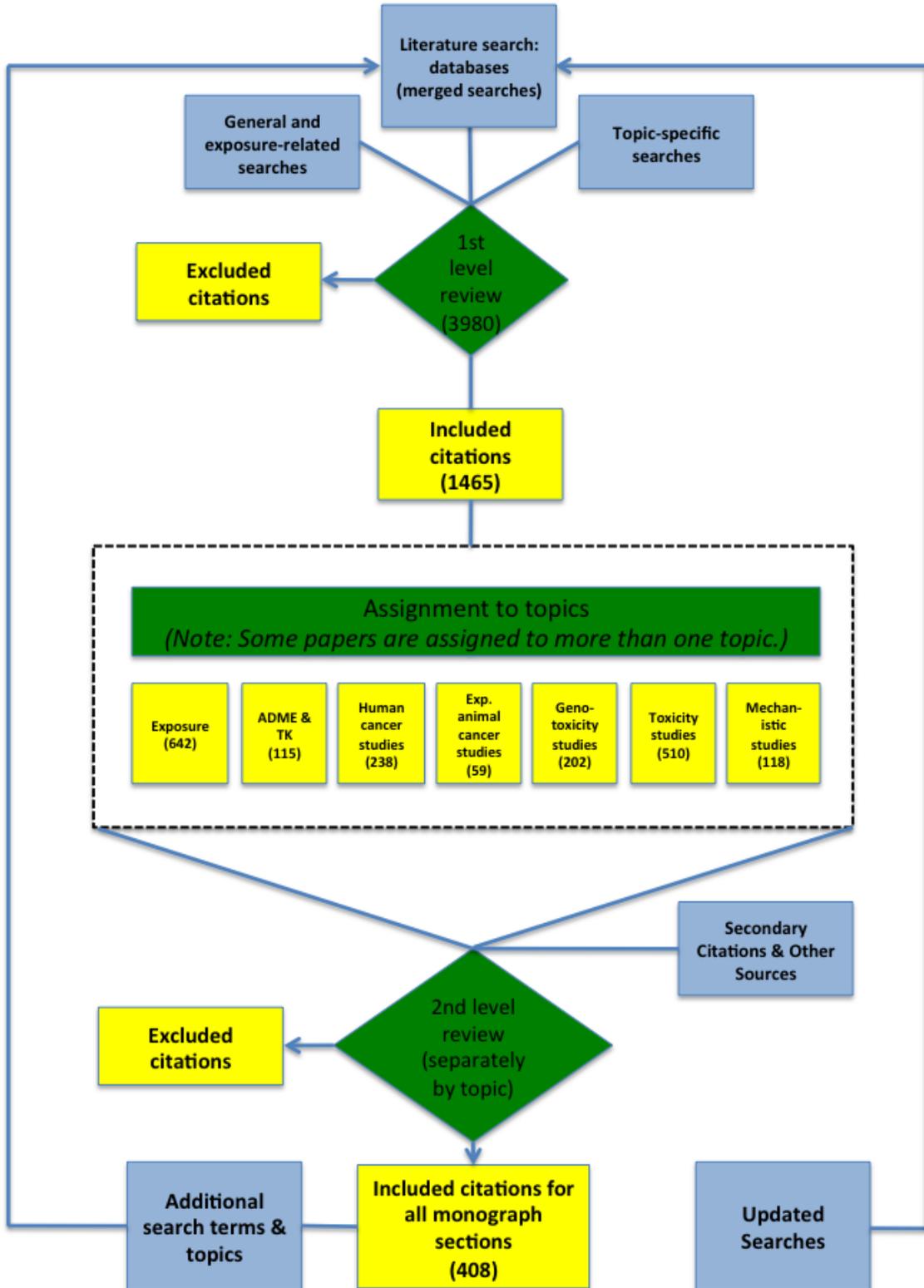
The methods for identifying the relevant literature for the draft pentachlorophenol monograph including (1) the search strategy, (2) updating the literature search, and (3) review of citations using web-based systematic review software are illustrated in Figure 1 and discussed below. The detailed literature search strategy, including all database sources, and exclusion/inclusion criteria, are available at <http://ntp.niehs.nih.gov/go/37898>.

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[To return to text citing Appendix A in Section 4, click here.](#)

Figure A-1. Literature search strategy and review



## Search strategies

Relevant literature is identified using search terms, data sources, and strategies as discussed below.

1. **General data search:** This search covers a broad range of general data sources (see Pentachlorophenol Literature Search Strategy, available at <http://ntp.niehs.nih.gov/go/37897> for information relevant to many or all of the wide range of monograph topics pertaining to pentachlorophenol.
2. **Exposure-related data search:** This search covers a broad range of potential sources (see Pentachlorophenol Literature Search Strategy, available at <http://ntp.niehs.nih.gov/go/37897> for exposure-related information and physical-chemical properties.
3. **Database searches in PubMed, Scopus, and Web of Science:** The majority of the primary literature used to draft the pentachlorophenol monograph was identified from searches of these three extensive databases available through the NIEHS Library. Synonyms, metabolites, and the chemical class for pentachlorophenol were identified from the sources listed in Table A-1 and the search terms are listed in Table A-2. The substance search terms were combined with the search terms for each of the monograph topics listed above to create the specific literature searches. See Table A-2 for details on this approach and Table A-3 for topic-specific search terms.

Searches for human cancer studies are somewhat unique because they involve the identification of search terms for exposure scenarios that might result in exposure of people to pentachlorophenol. For pentachlorophenol, these exposure-related search terms were based on the manufacture of pentachlorophenol and its use in wood preservation and the use of the handling of the treated wood by workers in sawmills and in fence building; the search terms for those uses were combined with search terms specific for human cancer (see Tables A2 and A3).

4. **QUOSA library of occupational case-control studies** search of the QUOSA-based library of approximately 6,000 occupational case-control studies, approximately 60% of which are currently available as searchable full-text pdfs, was conducted using the synonyms “pentachlorophenol,” “87-86-5 (CASRN),” “hydroxypentachlorobenzene,” “pentachlorobenzene,” “pentachlorophenate,” “Dowicide EC-7,” and “Dowicide 7.”
5. **Special topic-focused searches:** A topic-specific follow-up search was conducted for pentachlorophenol and immunosuppression using the terms (pentachlorophenol OR hydroxypentachlorobenzene OR pentachlorobenzene OR pentachlorophenate OR Dowicide) AND (immune AND (system OR suppress\* OR surveillance)) OR (immunosuppress\*).
6. **Secondary sources:** Citations identified from authoritative reviews or from primary references located by literature search, together with publications citing key papers identified using the Web of Science “Cited Reference Search,” were also added.

## Updating the literature search

The literature searches will be updated prior to submitting the draft monograph for peer review and prior to finalizing the monograph. Monthly search alerts for pentachlorophenol synonyms, metabolites, chemical class, exposure scenarios (human cancer), and topic-focused searches were created in PubMed, Scopus, and Web of Science, and the results of these searches from the closing date of the initial search will be downloaded for review.

## Review of citations using web-based systematic review software

Citations retrieved from literature searches were uploaded to web-based systematic review software and screened using inclusion and exclusion criteria. Multi-level reviews of the literature were conducted, with initial reviews (Level 1) based on titles and abstracts only to identify citations that could be excluded and to assign the included literature to one or more monograph topics; subsequent reviews (Level 2) for literature assigned to the various monograph topics (Exposure, ADME & TK, Human cancer studies, etc.) were based on full-text (i.e., PDFs) of the papers and were carried out by the writer and scientific reviewer for each monograph section. Two reviewers, at least one of whom is a member of the OROC at NIEHS, participated at each level of review. The inclusion/exclusion criteria are available in the pentachlorophenol Literature Search Strategy document, available at <http://ntp.niehs.nih.gov/go/37897>.

**Table A-1. Data sources for pentachlorophenol searches**

Information type	Data sources
Synonyms	National Library of Medicine databases (e.g., ChemIDplus, Hazardous Substances Data Base)
Metabolites	EPA (2010), NTP (1999), IARC (1991), Dalhaus <i>et al.</i> (1996)

**Table A-2. Literature search approach for pentachlorophenol**

Substance	Search terms	Topics (combined with) <sup>a</sup>
Pentachlorophenol 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
Pentachlorophenol metabolites and their synonyms	tetrachlorophydroquinone (TCHQ), tetrachloro-1,2-hydroquinone (TCoHQ), tetrachlorocatechol (TCpCAT), tetrachloro- <i>p</i> -benzoquinone (TCpBQ), tetrachloro-1,4-benzosemiquinone (TCpSQ), tetrachloro-1,2-benzosemiquinone (TCoSQ), tetrachlorophenol, and trichlorophenol	Human cancer studies Cancer studies in experimental animals (for the mechanistic section) Genotoxicity Toxicity Mechanism
Chemical class synonyms	chlorophenols/chlorinated phenols/polychlorinated phenols	Cancer studies in experimental animals (for the mechanistic section) Genotoxicity Toxicity Mechanism
Exposure scenarios (Dye industry, rubber chemical manufacturing, and herbicide manufacturing)	(wood and preserv*) OR lumber OR sawmill OR fenc*	Human cancer studies

<sup>a</sup> Search terms for each of these topics were developed in consultation with an informational specialist.

**Table A-3. Search terms for monograph topics for pentachlorophenol**

Monograph Topic	Search terms used in PubMed, Scopus, and Web of Science	MeSH terms used in Pubmed
Exposure	exposure OR occurrence OR oral OR dermal OR air OR water OR food OR soil OR environmental pollut* OR environmental exposure* OR occupational exposure*	("Environmental Pollutants" [MeSH] OR "Environmental Pollution" [MeSH])
ADME/ Toxicokinetics	<i>Toxicokinetic search terms-</i> administration OR absorption OR distribution OR tissue distribution OR bioavailab* OR biological availability OR metaboli* OR biotransform* OR activat* OR bioactivat* OR detoxif* OR excret* OR clearance OR eliminat* OR kinetic* OR pharmacokinetic* OR toxicokinetic* OR	<i>Toxicokinetic search terms-</i> "Pharmacokinetics"[Mesh] OR "Metabolism"[Mesh] OR "Cytochrome P450 Enzyme System"[Mesh]

Monograph Topic	Search terms used in PubMed, Scopus, and Web of Science	MeSH terms used in Pubmed
	cytochrome P450 <i>Combine with AND</i> <i>Animal study search terms-</i> in vivo OR animal* OR mouse OR mice OR rat OR hamster OR guinea pig OR rabbit OR monkey OR dog	
Human Cancer	<i>Cancer search terms-</i> cancer OR mortality OR follow-up OR incidence) <i>Combine with AND</i> <i>Epidemiology search terms</i> - epidemiologic* OR workers OR case-control OR cohort OR case-report OR case-series	None
Animal Tumors	<i>Cancer search terms-</i> cancer OR neoplasm* OR carcinogen* OR malignan* OR oncogene* OR tumor* OR tumour* <i>Combine with AND</i> <i>Animal study search terms-</i> animal* OR mouse OR mice OR rat OR hamster OR "guinea pig" OR rabbit OR monkey OR dog	<i>Cancer search terms-</i> "Neoplasms"[Mesh] OR "Carcinogens"[Mesh]
Genotoxicity	genetic toxicology" OR clastogen* OR "DNA strand break*" OR "unscheduled DNA synthesis" OR "UDS" OR aneuploid OR aneuploid* OR polyploid OR polyploid* OR "neoplastic cell transformation" OR "chromosom* aberration*" OR cytogenetic OR cytogenetic* OR "DNA adduct*" OR "DNA damage" OR "DNA repair" OR crosslink* OR "germ-line mutation" OR micronucle* OR mutagen OR mutagen* OR mutation OR mutation* OR oncogen* OR "sister chromatid exchange" OR "SCE" OR "SOS response*" OR "Ames test" OR "gene expression" OR "cell proliferation" OR cytotoxic OR cytotoxic* OR "comet assay"	"DNA Damage"[Mesh] OR "DNA Repair"[Mesh] OR "Mutagens"[Mesh] OR "Mutation"[Mesh] OR "Cytogenetic Analysis"[Mesh] OR "Oncogenes"[Mesh] OR "Mutagenicity Tests"[Mesh]
Toxicity	toxic* OR toxin*OR cytotoxic* OR (nephrotoxic* OR hepatotoxic* OR pneumotoxic* OR thyrotoxic*	"Toxic Actions"[Mesh] OR "Toxicity Tests"[Mesh] OR "adverse effects" [Subheading]
Mechanisms of Carcinogenicity	((mode OR mechanism*) AND action) OR (carcinogen OR genetic OR epigenetic OR inhibit* OR promot* OR interact* OR activate* OR detoxific* OR "oxidative damage" OR alkylat* OR adduct)) AND ((animal OR animals OR mouse OR mice OR rat OR hamster OR "guinea pig" OR rabbit OR monkey OR dog OR pig) OR (person* OR people OR individual* OR subject* OR participant*))	

## Appendix B: Human Exposure and Regulations and Guidelines

**Table B-1. U.S. pentachlorophenol manufacturing plants: air and wipe samples<sup>a</sup>**

Location (Reference)	Job type/area (Years)	Sample type (N)	Conc. range [TWA range] (mg/m <sup>3</sup> )
Wichita, KS Marlow and Fingerhut 1985a; Dioxin Registry Report <sup>b</sup>	Production, flaking (1980–1983)	Air, area (74) Air, personal breathing zone <sup>c</sup> (118) First class penta operator (45) Third class penta operator (73)	< 0.01–0.85 <sup>d</sup> [ $< 0.01$ –0.85]  0.005–0.84 [0.005–0.84]  < 0.006–4.65 [ $< 0.006$ –3.17]
Tacoma, WA Marlow and Fingerhut 1985b; site visit report	Production, prilling, blocking (1983)	Air, area (18) Air, personal breathing zone (28) (Highest value reported for maintenance man)	< 0.01–0.07 [0.01–0.058] < 0.01–71.21 [0.02–36.06]
U.S. PCP manuf. plant, location not specified Marlow 1986; IARC publication	Production, distillation, finishing (–)	Air, personal breathing zone (54) (Range of means; highest value reported for handyman)	0.059–2.66 [–]
Midland, MI Marlow <i>et al.</i> 1991; Dioxin Registry Report	Production, distillation, finishing, flaking (1965–1980)	Air, area (238) (Highest value reported for chlorination, torch burning) Air, personal (105) (Highest value reported for handyman)	0.003–68.69 [–]  < 0.001–33 [–]
Sauget, IL Marlow <i>et al.</i> 1997; Dioxin Registry Report	Production, flaking, prilling, blocking (1977)	Air, area (2) Air, personal (6)	< 0.001–0.026 [–] < 0.001–0.14 [–]
		Wipes - set 1 (7) <sup>e</sup> Wipes - set 2 (7)	12.5–216 µg/100 cm <sup>2</sup> 1.4–15.1 µg/100 cm <sup>2</sup>

<sup>a</sup>A subset of these data were also reported by Ruder and Yiin 2011.

<sup>b</sup>Data shown does not include samplings prior to 1980, which used a different sampling method and results were deemed unreliable; results from all methods used after 1980 are included here. Time-weighted averages (TWA) are shown if included in report.

<sup>c</sup>First class operators take samples from the primary and secondary chlorinators; third class operators clean the flaker, load flaked pentachlorophenol into the kiln, bag box and load glazed pentachlorophenol into trailers and hopper cars, and other general housekeeping duties.

<sup>d</sup>Only representative areas and job types are included from the report. Highest level in area air was in ‘Penta bagging house’ where glazed pentachlorophenol flakes are packaged, i.e., taken from bulk storage to a hopper and gravity fed into a specially designed bag on a pneumatic-operated machine.

<sup>e</sup>Wipes: first set of samples was in April and second set in August, after institution of more stringent industrial hygiene practices.

[To return to text citing Table B-1, click here.](#)

**Table B-2. Blood and urine pentachlorophenol levels for wood treatment workers**

Reference	Type of job		Number of workers	Concentration in blood (ppm), mean (range)		Concentration in urine (ppm), mean (range)
Cline <i>et al.</i> 1989	Wood preservation		6	Serum	0.490 (0.250–0.740)	–
	Chemical packaging		4	Serum <sup>a</sup>	57.6 (21.7–84.9)	–
				Whole blood	25.1 (8.6–45.2)	–
			6	Whole blood	15.9 (6–23)	–
McLean <i>et al.</i> 2009a	Sawmill workers	Mixers	8	–	–	2.8 <sup>b</sup> (0.14–13)
		Table hands	48	–	–	0.21 <sup>b</sup> (0.005–2.2)
		Diffusion plant, ordermen, graders, yardhands	49	–	–	0.05 <sup>b</sup> (0.004–0.73)
		Green and dry milling, drivers of mobile plant	59	–	–	0.01 <sup>b</sup> (< 0.002–0.44)
Gunter and Thoburn 1980	Manufacturing: wood fence posts and poles		9	–	–	–
Markel <i>et al.</i> 1977	Wood treatment: railroad ties, telephone poles		11	–	–	– (< 0.010–5.2) <sup>c</sup>
Markel and Lucas 1975	Wood treatment: lumber, fence posts		17	–	–	0.49 <sup>c</sup> (0.11–1.85) <sup>c</sup>
Wyllie <i>et al.</i> 1975	Wood treatment: timber		6	Serum	1.372 (0.348–3.963)	0.164 (0.041–0.760)

<sup>a</sup>These chemical workers are described in Cline *et al.* 1989 as formulating and packaging pentachlorophenol under very unsafe conditions. A worker in a different packaging plant with 23 ppm pentachlorophenol in whole blood died after breaking up blocks of pentachlorophenol using a jack hammer and other tools without adequate protective clothing.

<sup>b</sup>Geometric mean. All other means are arithmetic means unless stated otherwise.

<sup>c</sup>Corrected to specific gravity of 1.024.

[To return to text citing Table B-2, click here.](#)

**Table B-3 Levels of pentachlorophenol in blood and urine of various handlers and users of pentachlorophenol-treated wood**

Reference	Type of job	Number of Workers	Concentration in blood (ppm)		Concentration in urine
				Mean (Range)	Mean $\pm$ SD (Range); Median
Cline <i>et al.</i> 1989	Log home construction	2	Serum	0.083 (0.072–0.094)	–
	Telephone line maintenance	13	Serum	0.110 (0.026–0.260)	–
	Log museum	4	Serum	0.450 (0.350–0.630)	–
Bader <i>et al.</i> 2007	Painters	189	–	–	5.6 $\pm$ 8.1 (< 0.2–52); 2.4 ( $\mu\text{g/g}$ creatinine)
	Bricklayers	148	–	–	3.2 $\pm$ 3.9 (< 0.2–25); 1.8 ( $\mu\text{g/g}$ creatinine)
Thind <i>et al.</i> 1991	Electrical utility linemen <sup>a</sup>	Exposed 23 Control 5	–	–	Exposed 29.6 $\pm$ 1.74 Control 10.2 $\pm$ 1.74 (6-26) ( $\mu\text{g/g}$ creatinine)

SD = standard deviation.

<sup>a</sup>Two groups of linemen were based on required glove use (Group A) and ‘as needed’ glove use (Group B); groups were combined for comparison of all workers with controls (administrative staff not occupationally exposed).

<sup>b</sup>Geometric means and standard deviations were provided in study.

[To return to text citing Table B-3, click here.](#)

**Table B-4. Pentachlorophenol concentration in serum and urine samples in people living in the United States between 1967 and 2003 (Tables SI-7 and SI-8 from Zheng *et al.* 2011)**

Country/Location (Year of data collection)	Exposure	Sample type	N	PCP concentration, mean, µg/L (range)	Reference
USA (1980)	PCP-treated log homes	Serum	5 32	1126 (580–1750) 330 (116–1084)	MMWR 1980
USA (1980)	Control group	Serum	32	320 (2-7200)	Klemmer <i>et al.</i> 1980
USA (1980)	Control group Untreated log homes Conventional homes	Serum	42 2 11	– (4–68) 51 (34–75) 48 (15–55)	WHO 1987
USA (1980)	Conventional homes PCP-treated log homes	Serum	34 123	37 (15–75) 300 (69–1340)	Cline <i>et al.</i> 1989
USA (1967)	House-holds & pesticide users Honolulu heart program cohort	Urine	117 173	40 (ND–1840) 44 (3–570)	Benvenue <i>et al.</i> 1967
USA (1970)	Non-specific exposure		6	5 (2–11)	Cranmer and Freal 1970
USA (1978)	Human monitoring program		418	6.3 (ND–193)	WHO 1987
USA (1980)	PCP-treated log homes PCP-treated log homes Control group Untreated log homes Conventional homes		5 32 42 2 11	84 (47–216) 13 (2–87) – (0.7–11) 1.4 (1–2) 2.5 (1–7)	MMWR 1980
USA (1980)	Non-occupational exposure <sup>a</sup>		32	30 (< 10–1000)	Klemmer <i>et al.</i> 1980
USA (1981)	Non-occupational exposure		10	9 (3–16)	WHO 1987
USA (1981)	Non-occupational exposure (controls) Non-occupational exposure (controls)		38 31	24.2 (3–106) 19 (3–105)	Kalman 1984
USA (1981)	Non-specific exposure (control subjects)		10	8.2 (3–16)	Lores <i>et al.</i> 1981

Country/Location (Year of data collection)	Exposure	Sample type	N	PCP concentration, mean, µg/L (range)	Reference
USA (1982)	Non-occupational exposure		23	25.3 (10–108)	Kalman 1984
	Non-occupational exposure		22	32.2 (15–137)	
USA (1980–6)	Conventional homes		143	2.7 (–)	Cline <i>et al.</i> 1989
	PCP-treated homes		118	37 (1–340)	
USA (1989)	Community around herbicide plant (children)		197	14 <sup>b</sup> (> 1–240)	Hill <i>et al.</i> 1989
USA (1994)	Non-specific exposure		87	1.6 (0.5–9.1)	Thompson and Treble 1994
USA (1995)	NHANES III <sup>c</sup>		951	2.5 (ND–55)	Hill <i>et al.</i> 1995
USA (1997)	Non-specific exposure (children)		9	0.329 (0.175–0.666)	Wilson <i>et al.</i> 2003
USA (1998–2001)	Local fatty fish consumption		361	7 <sup>b</sup> (1–52) <sup>d</sup>	Berkowitz <i>et al.</i> 2003
USA (2001)	Non-specific exposure (children)		128	0.433 (< 0.262–3.45)	Wilson <i>et al.</i> 2007
	Non-specific exposure (children)		126	0.876 (< 0.536–23.8)	
USA (2003)	Environmental exposure (fetus-amniotic fluid)		20	0.23 (0.15–0.54)	Bradman <i>et al.</i> 2003

<sup>a</sup>Control group for Klemmer *et al.* 1980 described as workers without occupational exposure; no other exposure information was presented for control group.

<sup>b</sup>Median.

<sup>c</sup>National Health and Nutrition Examination Survey.

<sup>d</sup>Percentile range: 10%–90%.

[To return to text citing Table B-4, click here.](#)

**Table B-5. Pentachlorophenol ambient air levels**

Country	Location/sample	Mean concentration, ng/m <sup>3</sup>	Concentration range, ng/m <sup>3</sup>	Reference
<b>Industrial Settings</b>				
United States	Wood treatment facility fence line	–	29,000 (max)	ATSDR 2007
	Residence within 1 mile of wood treatment facility	–	8,100 (max)	
<b>Urban settings</b>				
United States	Raleigh-Durham-Chapel Hill, NC	–	ND–52.1	Wilson <i>et al.</i> 2007
Belgium	Urban area	–	5.7–7.8	Cautreels <i>et al.</i> 1977 <sup>a</sup>
Canada	White City	217.0	0.7–1,233	Waite <i>et al.</i> 1998
	Prince Albert	2.4	6.8 (max)	
	Yellowknife	1.7	4.2 (max)	
<b>Rural settings</b>				
Bolivia	Mountain rural area	–	0.25–0.93	Cautreels <i>et al.</i> 1977 <sup>a</sup>
Canada	Agriculture and Agri-Food Canada Research Station	0.4	0.6 (max)	Waite <i>et al.</i> 1998
	Waskesiu	0.7	1.5 (max)	
<b>Urban/rural/industrial setting not specified</b>				
Canada	–	0.64 <sup>b</sup>	0.30–0.87 <sup>c</sup>	Environment Canada 1990 <sup>d</sup>
Switzerland	–	–	0.9–5.1	Bundesamt für Umweltschutz 1983 <sup>a</sup>

ND = not detected.

All means are arithmetic means unless noted otherwise.

<sup>a</sup>As cited by WHO 1987.

<sup>b</sup>Grand mean of data sets for ambient air levels from a review of pentachlorophenol concentration data in published and unpublished reports for the period 1981–1990, weighted by sample size.

<sup>c</sup>Range of means from data sets for ambient air levels from a review of pentachlorophenol concentration data in published and unpublished reports for the period 1981–1990.

<sup>d</sup>As cited in Coad and Newhook 1992.

[To return to text citing Table B-5, click here.](#)

**Table B-6. Pentachlorophenol indoor air levels**

Country	Location/sample	Mean concentration, ng/m <sup>3</sup>	Concentration range, ng/m <sup>3</sup>	Reference
United States	Pentachlorophenol-treated log home in Kentucky, 1980	–	200–380	MMWR 1980
	Twenty-one pentachlorophenol-treated log homes in Kentucky, 1984	80 <sup>a</sup>	3–810	Hosenfeld 1986
	Fifteen pentachlorophenol-treated log homes in Montana	–	< 7,000 <sup>b</sup>	Lee and Gunter 1986
	Indoor air in two child day care centers (1997, Raleigh-Durham, NC) <sup>c</sup>	0.918	0.740–1.18	Wilson <i>et al.</i> 2003
	Indoor air in day care centers (2001–2002, coastal plain, Piedmont, and mountain regions, NC)	1.16 <sup>d</sup>	0.500–63.3	Wilson <i>et al.</i> 2007
	Indoor air in day care centers (2001–2002, northern, central, and southern regions, OH)	1.32 <sup>d</sup>	BDL–16.8	Wilson <i>et al.</i> 2007
	Indoor air at homes of nine children (1997, Raleigh-Durham, NC)	9.11 <sup>e</sup>	0.660–53.2	Wilson <i>et al.</i> 2003
	Indoor air in children's homes (2001–2002, coastal plain, Piedmont, and mountain regions, NC)	1.5 <sup>d</sup>	BDL–27.5	Wilson <i>et al.</i> 2007
	Indoor air in children's homes (2001–2002, northern, central, and southern regions, OH)	2.14 <sup>d</sup>	BDL–73.3	Wilson <i>et al.</i> 2007
	Basement of a building with highest ratio of treated wood surface area to room volume (no ventilation) among a group of treated wooden structures	–	38,000 (max) <sup>f</sup>	Saur <i>et al.</i> 1982 <sup>h</sup>
	Nine homes in Raleigh-Durham, NC	50 <sup>g</sup>	290 (max)	Lewis <i>et al.</i> 1994
	Germany	Indoor air samples in 104 homes	–	ND–25,000
Living room of house containing pentachlorophenol-treated wood		–	50,000–100,000	Gebefuegi <i>et al.</i> 1979 <sup>h</sup>
Building with an enclosed swimming pool with pentachlorophenol-treated walls and ceilings		–	1,000–160,000	Gebefuegi 1981, Gebefuegi <i>et al.</i> 1983 <sup>h</sup>

Country	Location/sample		Mean concentration, ng/m <sup>3</sup>	Concentration range, ng/m <sup>3</sup>	Reference
	Indoor air samples		–	< 0.3–576.4	Schnelle-Kreis <i>et al.</i> 2000
Netherlands	Family A, home with pentachlorophenol-treated timber and furniture, before house was heated and ventilated		–	140–1,200	Sangster <i>et al.</i> 1982
	Family A, home with pentachlorophenol-treated timber and furniture, after house was heated and ventilated		–	ND–240	
	Family B, home with pentachlorophenol-treated timber in basement		–	ND–400	
	Family C, restored home with pentachlorophenol-treated timber		–	440–950	
Switzerland	Home living rooms and bedrooms		–	1,000–10,000	Zimmerli <i>et al.</i> 1979 <sup>h</sup>
United Kingdom	House with pentachlorophenol-treated roof void, first week after treatment	In roof void	–	16,000–67,000	Dobbs and Williams 1983 <sup>b</sup>
		In landing	–	3,900–15,000	
		In bedroom	–	1,600–2,800	
	House with pentachlorophenol-treated roof void, 5–10 weeks after treatment	In roof void	–	1,700–6,700	
		In landing	–	600–5,000	
		In bedroom <sup>i</sup>	–	1,600–2,800	

ND = not detected, BDL = below detection limit.

<sup>a</sup>Geometric mean. Unless noted otherwise, all other mean values are arithmetic means.

<sup>b</sup>Reported as < 7 µg/m<sup>3</sup>.

<sup>c</sup>Two air samples averaged over 48 hours at each of the two day care centers.

<sup>d</sup>50<sup>th</sup> percentile.

<sup>e</sup>One air sample averaged over 48 hours at each of the nine homes.

<sup>f</sup>The pentachlorophenol level in the main floor of this house was 8.8 µg/m<sup>3</sup>, and the pentachlorophenol level in a warehouse was 3.52 µg/m<sup>3</sup>; these levels were higher than levels in 11 other rooms in different buildings evaluated in Saur *et al.* 1982 (as cited in WHO 1987).

<sup>g</sup>Two air samples were taken simultaneously at 12 and 75 cm above the floor. Result reported is the arithmetic mean of the two individual samples; individual sample values, though described as generally similar, were not reported.

<sup>h</sup>As cited in WHO 1987.

<sup>i</sup>Concentrations in or near the treated room rapidly decreased, but levels in the untreated bedroom remained stable, possibly due to adsorption and desorption processes.

[To return to text citing Table B-6, click here.](#)

**Table B-7. Pentachlorophenol in air and urine – other occupational exposures (exposed workers in a NIOSH HETA report)**

Location (source)	Type of job	Number of workers	TWA Range of concentrations in air (mg/m <sup>3</sup> )	Concentrations in urine <sup>a</sup> (ppm) # Samples - Mean (range)	# Wipe samples Mean (range) ng/cm <sup>2</sup>
Fort Stanwix National Monument – Rome, NY Rosensteel 1978	Park office staff (exposure to treated walls of office)	5	Area - two methods <sup>b</sup> : #1: 0.014–0.033 #2: 0.022–0.187	5 - Workers (1.4–4.2) 2 - Controls (< 0.8, 0.9)	NT
<i>Follow-up Study</i> Fort Stanwix National Monument – Rome, NY Lee and Lucas 1983	Park office staff (exposure to treated walls of office)	6	Area - all sampled locations were below LOD (< 0.008)	6 - Workers (< 0.004–0.0163) 4 - Controls (all < 0.004)  LOD = 0.004	6 - Personal (hand) < 10–70 3 - Work surface < 10–70  LOD = 10

HETA = Hazard Evaluation and Technical Assistance, LOD = limit of detection, NT = not tested.

<sup>a</sup>Corrected to specific gravity of 1.024.

<sup>b</sup>Used two different methods of air sampling.

[To return to text citing Table B-7, click here.](#)

**Table B-8. Measurements of pentachlorophenol in soil**

Country	Location/sample		Mean concentration, µg/kg	Concentration range, µg/kg	Reference
United States	LA, wood treatment facility (NPL <sup>a</sup> site)	Soil depth of 0–3 in	–	320–2,300	ATSDR 1995 <sup>b</sup>
		Subsurface soil	–	820–200,000	
	FL, inactive landfill (NPL site)		–	21,000 (max)	ATSDR 1993b <sup>b</sup>
	GA, wood preserving company	On-site samples	–	13,000 (max)	Anonymous 1999 <sup>b</sup>
		Off-site samples	–	1,300 (max)	
Canada	Former site of a pesticide plant		–	< 50	Garrett 1980 <sup>c</sup>
Finland	Sawmills, location unspecified	Soil depth of 0–5 cm, near trtmnt. basin	–	45,600 <sup>d</sup>	Valo <i>et al.</i> 1984 <sup>c</sup>
		Soil depth of 80–100 cm, near trtmnt. basin	–	1,000 <sup>d</sup>	
		In storage area for preserved wood	–	140 (max) <sup>d</sup>	
		Outside of storage area for preserved wood	–	12 <sup>d</sup>	
Germany	Agriculturally used soils in Bavaria		–	100	Gebefuegi 1981 <sup>c</sup>
Switzerland	Four sites near a penta-chlorophenol production facility	Soil depth of 0–10 cm	–	25–140	Bundesamt fur Umweltschutz 1983 <sup>c</sup>
		Soil depth of 20–30 cm	–	33–184	

<sup>a</sup>NPL = National Priorities List.

<sup>b</sup>As cited in ATSDR 2001.

<sup>c</sup>As cited in WHO 1987.

<sup>d</sup>Reported as a fresh weight sample.

[To return to text citing Table B-8, click here.](#)

**Table B-9. Measurements of pentachlorophenol in food**

Country	Type of sample/frequency of detection	Mean concentration, µg/kg	Concentration range, µg/kg	Reference
United States	10 out of 60 composite food samples (1973–4)	–	10–30	Manske and Johnson 1977 <sup>a</sup>
	5.4% of 240 samples	–	10–40	Johnson and Manske 1977 <sup>a</sup>
Canada	Fish	5.9 <sup>b</sup> [N = 36] <sup>c</sup>	0.2–24.0 <sup>d</sup>	Coad and Newhook 1992 <sup>e</sup>
	Shellfish	2.6 [N = 14] <sup>f</sup>	0.1–20.2	
	Milk	0.6 <sup>g</sup> [N = 1]	< 0.38–2.53 <sup>h</sup>	
	Beef	0.6 [N = 6]	0.47–3.2	
	Pork	0.8 [N = 3] <sup>f</sup>	0.54–2.70	
	Lamb	0.4 [N = 2]	0.3–1.1	
	Poultry	0.9 [N = 4] <sup>f</sup>	0.1–4.9	
	Offal	32.0 [N = 27] <sup>f</sup>	< 1.0–79.0	
	Eggs	2.7 [N = 4]	0.03–2.82	
	Grains and cereals	2.5 [N = 2]	0.22–4.80	
	Root vegetables	0.8 [N = 3]	0.36–1.4	
	Garden vegetables	0.5 [N = 2]	0.44–0.55	
	Fruit	0.4 [N = 7]	0.20–4.8	
	Sugars and adjuncts	2.3 [N = 8]	0.8–5.6	
	Oils and fats	4.2 [N = 7]	2.2–5.7	
	Soups, juices, and beverages	0.2 [N = 24]	0.1–0.8	
	Produce samples consisting mainly of potatoes and raw milk	–	< 10	Jones 1981
	Isolated produce samples stored in containers made of treated wood	–	2,700	
	Chicken meat	10	–	Ryan <i>et al.</i> 1985 <sup>i</sup>
	Pork liver	50	–	Ryan <i>et al.</i> 1985 <sup>i</sup>
Marine fish	5	3–8.3	Crosby <i>et al.</i> 1981	
Potatoes	–	ND–0.043	Crosby <i>et al.</i> 1981 Ministry of Agriculture, Fisheries, and Food MAFF 1989 <sup>i</sup>	
Grain cereal	0.001	–		
Poultry	9	ND–40		

Country	Type of sample/frequency of detection	Mean concentration, µg/kg	Concentration range, µg/kg	Reference
United Kingdom	Eggs	60	ND–300	Ministry of Agriculture, Fisheries, and Food MAFF 1989 <sup>i</sup> Gebefuegi 1981 <sup>a</sup>
	Milk	4	ND–20	
	Daily diet samples	16.3 <sup>j</sup>	2.6–27.5	
Germany	Two-thirds of food basket samples of persons applying wood preservatives in private homes	6 <sup>k</sup>	2–13 <sup>l</sup>	Krause 1982 <sup>a</sup>
	11 out of 17 fresh mushroom samples	–	> 10	Meemken <i>et al.</i> 1982 <sup>a</sup>

<sup>a</sup>As cited in WHO 1987.

<sup>b</sup>Grand mean weighted by sample size unless noted otherwise for Coad and Newhook 1992.

<sup>c</sup>N = number of data sets.

<sup>d</sup>Range of calculated means unless noted otherwise for Coad and Newhook 1992.

<sup>e</sup>Coad and Newhook 1992 cites original study authors for data for pentachlorophenol levels in food. All food commodities are expressed on a wet weight basis.

<sup>f</sup>Some data sets include means where non-detected values equal to zero are included because detection limits were not specified or number of samples with non-detected values was not specified.

<sup>g</sup>Reported as sample mean.

<sup>h</sup>Reported as sample range.

<sup>i</sup>As cited in Wild and Jones 1992.

<sup>j</sup>Arithmetic average.

<sup>k</sup>Median.

<sup>l</sup>Control samples were between less than 0.1 and 5 µg/kg.

[To return to text citing Table B-9, click here.](#)

**Table B-10. Measurements of pentachlorophenol in drinking water, ground and surface water**

Country	Location/sample	Mean concentration, µg/L	Concentration range, µg/L	Reference
<b>Drinking water</b>				
United States	Domestic well water, Oroville, CA	–	< 1–50	Wong and Crosby 1981 <sup>a</sup>
	Willamette River	–	0.06 <sup>b</sup>	Buhler <i>et al.</i> 1973 <sup>a</sup>
	Florida drinking water	–	0.003–0.34	Morgade <i>et al.</i> 1980 <sup>a</sup>
Germany	Ruhr area	–	0.01–0.02	Dietz and Traud 1978 <sup>a</sup>
Unspecified	Unspecified	–	0.1 <sup>b</sup>	Dougherty and Piotrowska 1976 <sup>a</sup>
<b>Groundwater</b>				
United States	SC wood preserving site	–	19,000 (max)	ATSDR 1993a <sup>c</sup>
	Inactive FL landfill	–	0.6 <sup>b</sup>	ATSDR 1993b <sup>c</sup>
	GA wood preserving company	–	4,300 (max)	ATSDR 2001
	Wood preservation plant near Lake Superior	–	2,050–3,350	Thompson <i>et al.</i> 1978 <sup>a</sup>
<b>Surface water</b>				
United States	Willamette River	–	0.1–0.7	Buhler <i>et al.</i> 1973 <sup>c</sup>
	Great Lakes	–	0.1–1	EPA 1980 <sup>c</sup>
	Sewage discharge site in Sacramento, CA	–	< 1	Wong and Crosby 1978 <sup>c</sup>
	Stream running through industrial district in PA	–	38–10,500	Fontaine <i>et al.</i> 1975 <sup>c</sup>
	Streams in HI	–	0.01–0.48	Young <i>et al.</i> 1976 <sup>c</sup>
	Estuary in Galveston Bay, TX	–	ND–0.01	Murray <i>et al.</i> 1981 <sup>a</sup>
	Pond in MS contaminated by waste from pole treatment plant	–	< 1–82	Pierce <i>et al.</i> 1977 <sup>a</sup>
Canada	British Columbia freshwater sites	–	Trace–0.3	Environment Canada 1979 <sup>a</sup>
	British Columbia marine sites	–	ND–7.3	
Germany	Weser River and estuary	–	0.05–0.5	Ernst and Weber 1978 <sup>a</sup>

Country	Location/sample	Mean concentration, µg/L	Concentration range, µg/L	Reference
	German Bight	–	< 0.002–0.026	
	Ruhr river	0.1 <sup>d</sup>	< 0.1–0.2	Dietz and Traud 1978 <sup>a</sup>
	Rhine River, Cologne	–	0.1 <sup>b</sup>	Fischer and Slemrova 1978 <sup>a</sup>
Japan	Tama River, Tokyo	–	0.01–0.9	Matsumoto <i>et al.</i> 1977 <sup>a</sup>
	Sumida River, Tokyo	–	1–9	
	River water, Tokyo area	–	0.18 ± 0.14	Matsumoto 1982 <sup>a</sup>
Netherlands	Rhine River, 1976	0.7 <sup>d</sup>	2.4 (max)	Wegman and Hofstee 1979 <sup>a</sup>
	Rhine River, 1977	1.1 <sup>d</sup>	11 (max)	
	River Meuse, 1976	0.3 <sup>d</sup>	1.4 (max)	
	River Meuse, 1977	0.8 <sup>d</sup>	10 (max)	
South Africa	124 sampling points, location unspecified	–	ND–0.85	van Rensburg 1981 <sup>a</sup>
Sweden	River water downstream from pulp mill	–	9 <sup>b</sup>	Rudling 1970 <sup>a</sup>
	Lake receiving discharges	–	3 <sup>b</sup>	

<sup>a</sup>As cited in WHO 1987.

<sup>b</sup>Only 1 value was reported.

<sup>c</sup>As cited in ATSDR 2001.

<sup>d</sup>Arithmetic mean unless reported otherwise.

[To return to text citing Table B-10, click here.](#)

## Regulations and guidelines

### Regulations

#### *U.S. Environmental Protection Agency (EPA)*

##### *Clean Air Act*

National Emission Standards for Hazardous Air Pollutants:

Requires major and area sources to sharply reduce routine emissions of toxic air pollutants in accordance with specific performance-based standards for all air emission sources that emit one or more of the listed pollutants. Pentachlorophenol is listed as a hazardous air pollutant.

##### *Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)*

All pesticides must be registered and EPA must approve uses. In the 2008 FIFRA reregistration review, EPA determined that certain wood preservative uses of pentachlorophenol will not pose unreasonable risks to humans or the environment provided that certain risk mitigation measures are implemented.

##### *Safe Drinking Water Act*

Maximum contaminant level (MCL) = 1 µg/L

##### *Comprehensive Environmental Response, Compensation, and Liability Act*

Reportable quantity (RQ) = 10 lb

##### *Resource Conservation and Recovery Act*

When pentachlorophenol becomes a waste, it must be managed according to Federal and/or State hazardous waste regulations. Listed hazardous waste codes = D037, F021, F027, F028, F032, K001.

#### *Occupational Safety and Health Administration (OSHA)*

Permissible exposure limit (PEL) = 0.5 mg/m<sup>3</sup> [0.05 ppm] (skin)

### Guidelines

#### *American Conference of Governmental Industrial Hygienists (ACGIH)*

Threshold limit value – time-weighted average (TLV-TWA) = 0.5 mg/m<sup>3</sup> [0.05 ppm] (skin)

#### *National Institute for Occupational Safety and Health (NIOSH)*

Recommended Exposure Limit (REL) =  $0.5 \text{ mg/m}^3$  [0.05 ppm] (skin)

Immediately dangerous to life and health (IDLH) limit =  $2.5 \text{ mg/m}^3$  [0.23] ppm

*U.S. Environmental Protection Agency (EPA)*

Integrated Risk Information System (IRIS) oral reference dose (RfD) = 0.005 mg/kg-day

IRIS oral cancer slope factor =  $4 \times 10^{-1}$  per mg/kg/day

IRIS drinking water unit risk =  $1 \times 10^{-5}$  per  $\mu\text{g/L}$

*Regional Screening Levels (formerly called Preliminary Remediation Goals)*

Screening levels for pentachlorophenol are as follows: Residential soil = 0.89 mg/kg; Industrial soil = 2.7 mg/kg; Residential air =  $0.48 \mu\text{g/m}^3$ ; Industrial air =  $2.4 \mu\text{g/m}^3$ ; Tap water =  $0.035 \mu\text{g/L}$ ; MCL =  $1 \mu\text{g/L}$ .

## Appendix C: Human Cancer Studies

This appendix contains background information related to the cancer assessment on pentachlorophenol in humans including detailed (1) data information on study design, methods, and findings for human cancer studies (Tables C-1a,b,c, and C-2) and (2) detailed information on the quality assessment of the individual studies (Table C-3). Tables C-1a,b,c) summarize studies specific for pentachlorophenol, including nested case-control studies of pentachlorophenol users and producers (Table C-1a), a pentachlorophenol ecological study (Table C-1b) and population based case-control studies (Table C-1c). Table C-2 summaries data for population based case-control studies with limited information on exposure to pentachlorophenol.

### ***Methodologies and study characteristics of the selected epidemiologic studies and identification of cancer endpoints***

The data from the three cohort studies, one nested case-control study and one ecological study, and nine case-control studies (as delineated) were systematically extracted from relevant publications, as described in Table 3-1, the study protocol; they are summarized in the tables below

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**Table C-1a. Cohort and nested case-control studies of PCP producers and users**

<b>Kogevinas et al. 1995</b>	
<i>Related References</i>	<i>Geographic Location</i>
<u>Cohort</u> : Kogevinas et al. 1992, Saracci et al. 1991, Vena et al. 1998	8 Western European countries, Australia, New Zealand, and Canada (IARC registry)
<b>Population Characteristics</b>	
<i>Cases: Selection and ascertainment</i>	<i>Controls: Selection and ascertainment</i>
<u>Cases</u> : 32 NHL (20 deaths, 12 incident cases) 11 STS (4 deaths, 7 incident cases)	<u>Referents</u> : 158 (NHL), 55 (STS)
<u>Case eligibility criteria</u> : Male or female with with NHL or STS as underlying or contributory cause of death identified in IARC Dioxin international registry  <u>Participating cohorts</u> : All (21,183) workers in 24 cohorts from 11 countries ever exposed to phenoxy herbicides, chlorophenols or dioxins (some cohorts had minimum employment of 1 month to 1 yr).  <u>Participation rate</u> : 2 controls excluded in NHL analysis due to missing work histories	<u>Referent eligibility criteria</u> : Members of participating cohort in IARC registry with complete job histories  <u>Matching criteria</u> : 5 controls per case by incidence density sampling and matched for age, sex and country of residence
<u>Length of follow-back</u> : Cohorts followed up for an average of 17 years	
<u>Loss to follow-back</u> : Average for all cohorts: 5% (max. for individual cohort 10%)	
<b>Study Design and Analytical Methods</b>	
Nested occupational case-control study  Conditional logistic regression analysis lagged by 5 years. Risks calculated for four levels (including unexposed) of cumulative exposure	
<b>Exposure Data and Information Assessment</b>	
<i>Exposure: Levels and Co-exposures</i>	<i>Exposure assessment</i>
Levels of PCP and other exposures NR  Potential co-exposures:  Although the cohort consisted of members exposed to 21 chemicals, exposure to PCP only occurred in one British cohort and no other-co-exposures were reported.	Exposure assigned to individual workers based on company exposure questionnaires and records, department and jobs, likelihood of contact, and personal protection. Workers were considered exposed if they had a cumulative exposure score corresponding to 1 day or more. Ever-worked workers were classified into three categories of cumulative exposure: low= less than 1 year, medium = 1 to up to 10 years, high = 10 years or more.
<i>Assessment of potential confounders</i>	<i>Disease Assessment</i>
No information on smoking or other lifestyle factors Risk estimates not adjusted for these co-exposures	NHL (coded ICD-8 or 9 as 200, 201, 202); STS (coded ICD-8 and 9 as 171)  Death certificates or cancer registrations, depending on country, used to identify cases

<b>Collins et al. 2009a/Ramlow et al. 1996</b>	
<b>Related References</b>	<b>Geographic Location</b>
Ott et al. 1987; Bond et al. 1989 (earlier cohort updates)	Michigan, US
<b>Population Characteristics</b>	
<b>Exposed Cohort and Ascertainment</b>	<b>Reference Population</b>
<p><u>Eligibility criteria:</u> Subcohort of white male workers from total cohort ever employed in departments where PCP exposure could have occurred 1940-1989</p> <p><u>Exposed cohort:</u> 773 workers ever exposed to PCP between 1940 and 1989 (770 workers, Ramlow)</p> <p><u>Total cohort:</u> Workers in production or finishing of pesticides who were potentially exposed to polychlorinated dibenzodioxins (N = 2,192) from 1937-1980</p> <p><u>Follow-up:</u> Ramlow 1940-1989 (average 26 years); Collins 1940-2004 (average 35 years)</p> <p><u>Loss to follow-up:</u> 0%</p>	<p><u>External analysis:</u> U.S. white male population or State of Michigan</p> <p><u>Internal analysis:</u> Michigan Division workers employed 1940 to 1989, employed in plants without potential exposure to PCP or PCDD</p>
	<b>All-cause and all-cancer mortality</b>
	All-cause mortality: SMR 0.94 (0.8-1.1) 229
	All-cancer mortality: SMR 0.95 (0.7-1.25) 50
<b>Study Design, Analytical Methods/ Control for Confounding</b>	
<p>Historical cohort mortality study</p> <p>Ramlow: (a) SMR analyses: Life table analysis by age and calendar period for white males; unlagged and lagged by 15 years. (b) Cumulative exposure to PCP, TCDD, and H/OCDD using two reference groups: external (U.S. expected rates) or internal analysis of Michigan division workers (nonexposed and categories of cumulative exposure) and lagged for 15 years</p> <p>Collins: (a) PCP only and PCP and TCP exposed workers: external (SMR) analysis, and (b) Dioxin congeners (related to PCP exposure): external for exposure categories (ppt-years) and internal (proportional hazard regression model) using exposure categories (ppt-years) and linear models (1 part per billion increases in cumulative exposure) and adjusted for age, hire year and birth year.</p>	
<b>Exposure Data and Information Assessment</b>	
<b>Exposure: Levels and Co-Exposures</b>	<b>Exposure Assessment</b>
No individual quantitative exposure assessment but industrial hygiene data from company data and NIOSH investigators	<p>Ramlow: Individual work histories by job title and department, expert knowledge (veteran employees) and industrial hygiene data used to calculate cumulative exposure to PCP and higher chlorinated dioxins</p> <p>Collins: TCDD TEQ for 5 dioxin by-products in PCP or TCP and the levels of individual congeners estimated using a model that incorporated serum dioxin analyses from a subsample of past workers, work history, and industrial hygiene monitoring data</p>
<b>Assessment: Other Exposures</b>	<b>Disease Assessment</b>
Not reported	Death certificates (underlying COD); coding converted to ICD-8

<b>Ruder and Yiin 2011</b>	
<b>Related References</b>	<b>Geographic Location</b>
Fingerhut <i>et al.</i> 1991b, Marlow 1986 (exposure data)	U.S.A., 4 manufacturing plants
<b>Population Characteristics</b>	
<b>Exposed Cohort and Ascertainment</b>	<b>Reference Population</b>
<p><u>Eligibility criteria:</u> All members of the NIOSH Dioxin Registry* with complete demographic data ever employed in PCP production departments at one of four plants in the Registry that produced PCP from 1936 to 2006.</p> <p>0.8% excluded due to missing data</p> <p><u>Exposed cohort:</u> 1402 workers ever exposed to PCP but not TCP; 720 workers exposed to PCP + TCP</p> <p><u>Total cohort:</u> 2122 workers exposed to PCP, TCP and/or other chemicals</p> <p><u>Follow-up:</u> 1940 or first date of PCP production (whichever was later) to 2005</p> <p><u>Loss to follow-up:</u> 0.4% (workers exposed to PCP or other chemicals but not TCP); 0.1% (workers exposed to PCP and TCP)</p>	<p><u>External analysis:</u> U.S. national mortality rates</p> <p><u>Internal analysis:</u> less than 58 days of exposure to PCP</p>
	<b>All-cause and all-cancer mortality</b>
	<p>All-cause mortality: SMR 1.04 (0.97–1.11); 818</p> <p>All-cancer mortality: SMR1.25 (1.09–1.42); 238</p>
<b>Study Design and Analytical Methods/ Control for Confounding</b>	
<p>Historical cohort mortality study</p> <p>NIOSH life table analysis system used to calculate person-years at risk</p> <p>External analysis: race-, sex- and calendar period-adjusted SMR (Poisson distribution); underlying and multiple cause of death analyses conducted</p> <p>Internal analysis: Standardized rate ratios used to calculate cumulative and duration of exposure trends</p>	
<b>Exposure Data and Information Assessment</b>	
<b>Exposure: Levels and Co-Exposures</b>	<b>Exposure Assessment</b>
<p>PCP: Exposure data limited to most recent dates of PCP production at each plant. Exposure across plants ranged from 0.006 to 45 mg/m<sup>3</sup> (see Appendix B, Table B-1)</p> <p>Duration of exposure 1 day – 30.7 yr (2.5 ± 4.71 yr)</p> <p>90% workers exposed to multiple chemicals reported in 1 or more plant, including IARC Group 1, 2A, 2B carcinogens; however, few are risk factors for cancer site of interest; 172 workers exposed only to PCP and no TCP or other chemicals</p> <p>TCP (contaminated with 2,3,7,8-TCDD made in 2 of the 4 plants (MI and IL)</p>	<p>Exposure coded via company personnel records and work histories from start of PCP production through 1983, updated to 1992 for workers employed after 1983 and new workers employed after 1983; insufficient data to create a job exposure matrix</p> <p>Missing data: No coding of work history and exposures for workers in Plant 4 after 1992, although PCP production continued to 2006</p>
<b>Assessment: Other Exposures</b>	<b>Disease Assessment</b>
Smoking data available for a subset of one of the plants	<p>Death certificates: ICD-9 used for analysis</p> <p>Missing Data: Vital status unknown for 0.3% workers</p>

<b>Demers et al. 2006</b>	
<b>Related References</b>	<b>Geographic Location</b>
Hertzman et al. 1997 (earlier follow-up); Heacock et al. 2000 (nested case-control study of childhood ALL); Friesen et al. 2007 (additional analysis) Exposure: Hertzman et al. 1988; Teschke et al. 1989, 1996, 1998, Campbell et al. 1996	British Columbia, Canada
<b>Population Characteristics</b>	
<b>Exposed Cohort and Ascertainment</b>	<b>Reference Population</b>
<u>Eligibility criteria:</u> Male workers employed $\geq 1$ year (or 260 days total) from 1950–1995 at 1 of 14 sawmills in British Columbia, Canada	Provincial and national standardized referent mortality and incidence rates
<u>Exposed cohort:</u> 26,464 male workers in mortality study; 25,685 in incidence study	<b>All-cause and all-cancer mortality/incidence</b> All-cause mortality: SMR: 0.95 (0.93–0.98); 5,872
<u>Follow-up:</u> 1950–1995 (mortality); 1969–1995 (incidence)	All-cancer mortality/incidence: SMR: 1.00 (0.95–1.05); 1,495
<u>Loss to follow-up:</u> 4% (mortality); < 0.1% (incidence)	SIR: 0.99 (0.95–1.04); 2,571
<b>Study Design and Analytical Methods/ Control for Confounding</b>	
Retrospective cancer registry-based mortality and incidence study External analysis: SMR and SIR using provincial referent rates (age and year-adjusted Poisson distribution) Internal analysis: Relative risks (RR) estimated using maximum likelihood methods; age-, race- and calendar period-adjusted using Poisson regression, unlagged and lagged by 10 or 20 year intervals 3 separate analyses for all chlorophenols, mostly PCP-exposed workers and mostly TeCP-exposed workers; no adjustment for co-exposures or other potential confounders	
<b>Exposure Data and Information Assessment</b>	
<b>Exposure: Levels and Co-Exposures</b>	<b>Exposure Assessment</b>
Most formulations contained both PCP and TeCP (mainly PCP from 1941–1965; mainly TeCP 1965–on). Urinary levels on chlorophenols measured on subset of current workers for two seasons. Dermal exposure: PCP: 0.062–0.41 mg/cm <sup>2</sup> /day; TCP 0.15–0.82 mg/cm <sup>2</sup> /day Models using fat levels of PCP congeners; 2,3,7,8-TCDD similar to background population No information on other co-exposures; possible co-exposures are wood dust and formaldehyde	History of chlorophenol formulation use and individual worker histories/job titles (from employment records) plus validated senior worker exposure assessment used to create exposure-constant calendar time periods for each worker Exposure estimated to be almost all dermal; 1 year full-time exposure (FTE) estimated as equivalent to 2000 hr dermal contact; expert assessment correlated (0.72 and 0.76) with urinary levels measured in subset of current workers Cumulative exposure estimated and weighted by proportion of PCP and TeCP exposure levels categorized as < 1, 1–2, 2–5, and 5+ FTE exposure-years.
<b>Assessment: Other Exposures</b>	<b>Disease Assessment</b>
Smoking history available (personal interview) on 2000 workers, age-adjusted smoking rates similar to general population and not correlated with exposure	Cancer registry and death certificates (underlying cause) using ICD-9; Soft tissue sarcoma diagnosed using site and histology data

**Table C-1b. Pentachlorophenol (PCP) ecological study**

<b>Zheng <i>et al.</i> 2013</b>	
<b>Related References</b>	<b>Geographic Location</b>
Zheng <i>et al.</i> 2012	Tongling district, China
<b>Population Characteristics</b>	
<b>Population</b>	<b>Reference Population</b>
Eligibility criteria: All cancer cases reported to local cancer registry from hospitals, community health centers, and death registries 2009–2011 for all residents in district	World population, age-standardized incidence rates Low – high exposure residency areas
<b>Study Design and Analytical Methods/ Control for Confounding</b>	
Cross-sectional ecological study Age-standardized incidence rate per 100,000 population reported for males and females separately SRR analysis using low exposure category as reference and by duration of exposure (residence) No analyses for potential confounding	
<b>Exposure Data and Information Assessment</b>	
<b>Exposure: Levels and Co-Exposures</b>	<b>Exposure Assessment</b>
Low exposure area: 0–< 2.117 mg/m <sup>2</sup> /yr Medium exposure area: 2.117–34.002 mg/m <sup>2</sup> /yr High exposure area: > 34.002–80.142 mg/m <sup>2</sup> /yr Cumulative exposure 1–40 years	Ecological assessment of residence in area sprayed with Na-PCP from 1960–2002 Pollution Index: PCP average application mg/m <sup>2</sup> /year calculated using schistosomiasis control records. Average exposure: pollution index/year for each of 10 districts Exposure grade across districts: low, medium and high corresponding to pollution index (PCP usage/square meter)
<b>Assessment: Other Exposure</b>	<b>Disease Assessment</b>
Not reported	Cancer registry

**Table C-1c. Population-based case-control studies of pentachlorophenol users: specific exposure information**

<b>Hardell et al. 1994</b>	
<b>Related References</b>	<b>Geographic Location</b>
Hardell et al. 1981; Hardell and Sandström 1979 (questionnaire validation study)	Umea, Sweden
<b>Population Characteristics</b>	
<i>Cases: Selection and ascertainment</i>	<i>Controls: Selection and ascertainment</i>
<u>Cases</u> : 105 cases of NHL included in the analysis	<u>Referents</u> : 338
<u>Case eligibility criteria</u> : All cases of histologically verified NHL among males 25–85 years old admitted to Dept. Oncology, Umea, Sweden 1974–1978 with a completed lifetime work history/exposure questionnaire (self or proxy)	<u>Referent eligibility criteria</u> : Suicides and cancer deaths excluded; controls from same or adjacent municipality only; deceased controls who had not worked 5 years before death excluded with a completed lifetime work history/exposure questionnaire (self or proxy)
<u>Participation rate</u> : 100% cases, 99.2% controls	<u>Matching criteria</u> : Age, sex, municipality, and vital status; 8 living controls per living case identified via National Population Registry; 10 deceased controls per deceased case identified via National Registry for Causes of Death
<b>Study Design and Analytical Methods</b>	
Hospital-based case-control study Maentel-Haenzl OR, stratification by age and vital status; multivariate analysis that included chlorophenols, phenoxyacetics acids, organic solvents and DDT	
<b>Exposure Data and Information Assessment</b>	
<i>Exposure: Levels and Co-exposures</i>	<i>Exposure assessment</i>
Low exposure: < 1 week (continuous) or < 1 month (total) High grade exposure: ≥ 1 week (continuous) or ≥ 1 month (total) Co-exposures: NR	Structured questionnaire (self or proxy) for information on lifetime working history and exposure to chlorophenols including PCP, phenoxyacetic acid herbicides, and other exposures Low grade: less than one week of continuous use or less than 1 month total use High grade: one week or more of continuous use or 1 month or more total use Validation study of a similar questionnaire in the same area found a 97% agreement between information from self-reported exposure and employers (saw mill and pulp industry).
<i>Assessment of potential confounders</i>	<i>Disease Assessment</i>
Questionnaire (self or proxy) report of exposure to chlorophenols including PCP, phenoxyacetic acid herbicides, and smoking and other exposures	Histological data from NHL cases re-examined and classified by authors according to subtype stage, and anatomical site

<b>Hardell and Eriksson 1999</b>	
<b>Related References</b>	<b>Geographic Location</b>
Hardell <i>et al.</i> 2002 (pooled analysis)	Mid and northern Sweden
<b>Population Characteristics</b>	
<i>Cases: Selection and ascertainment</i>	<i>Controls: Selection and ascertainment</i>
<u>Cases:</u> 402 male cases of NHL included in the analysis	<u>Referents:</u> 741 controls
<u>Case eligibility criteria:</u> All male NHL cases, 25 years or older, reported to regional cancer registry between 1987 and 1990, confirmed by pathological report (N = 442, including 192 deceased cases)	<u>Referent eligibility criteria:</u> Living controls identified from National Population registry and deceased controls identified from National Registry for Causes of Death. Suicides excluded
<u>Participation rate:</u> 91% of cases and 84% controls (living cases or proxies) completed self-reported (mail + interview) lifetime exposure questionnaire (occupational and non-occupational use of pesticides) and non-occupational risk factors; participation rate for proxies similar to living respondents	<u>Matching criteria:</u> Age, sex, county of residence (living cases); age, sex, year of death (deceased cases) and vital status; 2 male controls per case.
<b>Study Design and Analytical Methods</b>	
Cancer registry-based population case-control study Logistic conditional regression analysis NHL only (Hardell <i>et al.</i> 1999): No adjustment for co-exposures or assessment of potential confounding. NHL and HCL (Hardell <i>et al.</i> 2002): multivariate analyses that includes impregnating agents (PCP 60% of cases), herbicides, insecticides and fungicides	
<b>Exposure Data and Information Assessment</b>	
<i>Exposure: Levels and Co-exposures</i>	<i>Exposure assessment</i>
PCP levels and cumulative duration of exposure NR Duration of exposure reported for all herbicides and phenoxyacetic acids only No co-exposures reported for PCP-exposed subjects	Self-reported, structured questionnaire, including complete employment history, questions on specific pesticides, brands, methods of use, years of exposure. Follow-up interviews conducted when exposure information unclear  Exposures within 1 year of diagnosis excluded from analysis  Time since first and last exposure
<i>Assessment of potential confounders</i>	<i>Disease Assessment</i>
Information on smoking, medical history and diet requested on questionnaire but data not reported or included in analyses.	All cases identified in regional cancer registry subject to pathological report confirmation; 29 of initial 442 cases excluded due to wrong diagnosis or wrong date of diagnosis

<b>Nordstrom et al. 1998</b>	
<b>Related References</b>	<b>Geographic Location</b>
Hardell and Eriksson 1999 (NHL); Hardell <i>et al.</i> 2002 (pooled analysis of NHL and HCL)	Sweden
<b>Population Characteristics</b>	
<i>Cases: Selection and ascertainment</i>	<i>Controls: Selection and ascertainment</i>
<u>Cases:</u> 111 male cases of HCL included in the analysis	<u>Referents:</u> 400 males included in the analysis
<u>Case eligibility criteria:</u> All living males with hairy-cell leukemia (subtype of NHL) reported to Swedish Cancer Registry 1987–1992 (including 1 case from 1993) (N = 121)	<u>Referent eligibility criteria:</u> 4 living males per case identified from National Population Registry (n = 482)
<u>Participation rate:</u> 91% cases and 83% controls completed a questionnaire on lifetime work history + occupational and recreational exposures	<u>Matching criteria:</u> Age and county of residence;
<b>Study Design and Analytical Methods</b>	
Cancer registry-based case-control study  Logistic regression controlling for age (matching was dissolved to increase statistical power); multivariate analysis (including pesticides, solvents, animals and exhausts) conducted only for combined “impregnating” agents (including creosote and other unspecified agents) by 2 categories of exposure duration	
<b>Exposure Data and Information Assessment</b>	
<i>Exposure: Levels and Co-exposures</i>	<i>Exposure assessment</i>
Levels of PCP NR  No co-exposures reported for PCP-exposed subjects	Self-reported by respondent on (mail + interview) questionnaire on lifetime working history, information on specific exposure and lifetime activities  Minimum exposure of 1 working day and induction period of 1 year
<i>Assessment of potential confounders</i>	<i>Disease Assessment</i>
No assessment of co-exposures for PCP-exposed cases  Smoking data for total cohort indicated OR 0.6 (0.4–1.1) for active smokers; not examined for PCP-exposed cases and controls	Compulsory reporting of cancers to national cancer registry but possibility of misdiagnosis, according to authors

<b>Hardell et al. 1995</b>	
<b>Related References</b>	<b>Geographic Location</b>
Individual studies in pooled analysis: Hardell and Sandstrom 1979; Eriksson <i>et al.</i> 1981; Hardell and Eriksson 1988; Eriksson <i>et al.</i> 1990	Sweden
<b>Population Characteristics</b>	
<i>Cases: Selection and ascertainment</i>	<i>Controls: Selection and ascertainment</i>
<u>Cases</u> : 434 cases of STS included in the analysis	<u>Referents</u> : 948 population controls
<u>Case eligibility criteria</u> : Male or female cases of STS >25 or 26 years old; admitted to Umea hospital 1970–79, or reported to Swedish cancer registry 1974–1978 from southern counties, Umea regional cancer registry 1978–1983; regional cancer registry in Uppsala 1978–1986; alive or deceased.	<u>Referent eligibility criteria</u> : Controls selected from national population registries; cancer controls excluded from pooled analysis; controls who had not worked 5 years before retirement or death of cases excluded.
<u>Participation rate</u> : Not reported for all studies, appears to range from < 1 to 6% for cases, less < 1 to 10% for controls	<u>Matching criteria</u> : 1–2 controls per case matched on age, gender, and county of residence.
<b>Study Design and Analytical Methods</b>	
Cancer registry-based case control studies; pooled analysis of 4 studies with similar methods and population base  Mandel-Haenszel odds ratios stratified for age, viral status, and study; no adjustment for life style factors or occupational co-exposures. Cases and controls with exposure to phenoxyacetic acids were excluded from two of the individual case control studies (Hardell and Sandstrom 1979; Eriksson <i>et al.</i> 1990)	
<b>Exposure Data and Information Assessment</b>	
<i>Exposure: Levels and Co-exposures</i>	<i>Exposure assessment</i>
Levels of PCP exposure Not Reported (length of potential exposure reported)  No co-exposures reported for PCP-exposed subjects	Self-reported (mailed) questionnaire completed by subject or proxy (deceased cases or controls) on complete work history and information on specific job categories, smoking habits and leisure time information on exposure to chemicals  Validation study of a similar questionnaire in the same area found a 97% agreement between information from self-reported exposure and employers (saw mill and pulp industry)  High grade exposure—one week or more continuous exposure or one month or more total exposure
<i>Assessment of potential confounders</i>	<i>Disease Assessment</i>
Smoking information obtained via questionnaire, No effect of smoking or use of oral stuff	Cases of STS identified in cancer registry or hospital and histologically verified by site and type by independent pathologists (blinded to status of cases and controls)

<b>Ruder et al. 2009</b>	
<b>Related References</b>	<b>Geographic Location</b>
Ruder et al. 2004, 2006; Carreon et al. 2005	U.S. (Iowa, Michigan, Minnesota, Wisconsin)
<b>Population Characteristics</b>	
<i>Cases: Selection and ascertainment</i>	<i>Controls: Selection and ascertainment</i>
Cases: 798 cases of brain glioma included in the analysis	<u>Referents</u> : 1,175 population controls
Case eligibility criteria: Histologically-confirmed brain gliomas (ICD-O 2 <sup>nd</sup> Edition 938–948) ≥ 18 years old diagnosed in 4 states 1995–1997 identified via participating medical facilities and neurosurgeons offices in 4 states and border city practices  Cases with previous cancer other than glioma not excluded	<u>Referent eligibility criteria</u> : Residents as of Jan 1995 in a nonmetropolitan county in one of 4 states; eligible controls with previous cancer other than glioma not excluded; controls identified from DMV (18–64 year olds) or HCFA records (65–80 year olds)
<u>Participation rate</u> : 91.5% eligible cases (or proxies) and 70.4% eligible controls (or proxies) completed questionnaires	<u>Matching criteria</u> : 2 potential controls randomly matched per case on sex and within 10 years of age at diagnosis of case
<b>Study Design and Analytical Methods</b>	
Population-based case-control study Maximum likelihood unconditional logistic regression analysis No analysis for potential confounding	
<b>Exposure Data and Information Assessment</b>	
<i>Exposure: Levels and Co-exposures</i>	<i>Exposure assessment</i>
Levels of PCP NR No co-exposures reported for PCP-exposed subjects	Extensive self-reported questionnaire on farming practices, jobs on farm, crops, livestock, use of pesticides, fertilizers, solvents, wood preservatives
<i>Assessment of potential confounders</i>	<i>Disease Assessment</i>
No assessment of co-exposures or other potential confounders among PCP-exposed subjects (exposures and other risk factors compared for all cases and controls)	Cases of brain glioma (ICD-O 2 <sup>nd</sup> edition 938–948) identified via physicians, medical practices and neurosurgeons and histologically confirmed  Missing data: comparison with state cancer registry data indicated 78% case ascertainment

<b>Ward et al. 2009</b>	
<b>Related References</b>	<b>Geographic Location</b>
Ma et al. 2004	U.S. (35 counties in northern and central California) (Northern California Childhood Leukemia Study)
<b>Population Characteristics</b>	
<i>Cases: Selection and ascertainment</i>	<i>Controls: Selection and ascertainment</i>
<u>Cases:</u> 184 Acute lymphocytic leukemia (ALL) (2 <sup>nd</sup> tier) included in the analysis	<u>Referents:</u> 212 (2 <sup>nd</sup> tier)
<u>Case eligibility criteria:</u> ≤ 7 years of age, diagnosed in December 1999. Cases were identified from 9 major pediatric clinical centers and who completed two tiered interviews and assessment.	<u>Referent eligibility criteria:</u> selected from CA birth certificate files. Survey found no evidence that the participating controls were different from the sampled population in terms of parental age, parental education, and mother's reproductive history (Ma et al. 2004)
<u>Participation rate:</u> 86% < 8 years old for cases, and 88.5% for controls after 1 <sup>st</sup> tier, and 92 % cases and 80% controls after second tier.	<u>Matching criteria:</u> individually matched on age, sex, race, Hispanic ethnicity, and material residence
<b>Study Design and Analytical Methods</b>	
<p>Case-control study of childhood leukemia (acute lymphoblastic leukemia, ALL).</p> <p>Evaluated quartiles of exposure (based on distribution in controls) of chemical concentration and chemical loading.</p> <p>Analysis adjusted for age, and race/ethnicity (non-Hispanic with, Hispanic, non-Hispanic other race), and confounding factors that changed ORs of ≥ 10% (income, year and season of the dust sample).</p> <p>Evaluated potential effect modification by breast-feeding status and maternal age.</p>	
<b>Exposure Data and Information Assessment</b>	
<i>Exposure: Levels and Co-exposures</i>	<i>Exposure assessment</i>
Carpet concentrations (ng/g) ranged from < 32 to 22,676	<p>Residential exposure to PCP assessed via concentration in carpet dust.</p> <p>1<sup>st</sup> tier – Interviews with primary provider on residential and parental occupational history; 2<sup>nd</sup> tier interviews, information on home and garden pesticide use, inventory pesticides in home storage, and obtained carpet dust samples</p> <p>PCP carpet dust concentrations converted to natural log; Chemical loading– amount of chemical/m<sup>2</sup> of carpet – concentration x dust loading</p>
<i>Assessment of potential confounders</i>	<i>Disease Assessment</i>
<p>Interview</p> <p>Other chemicals (PCB and organochloride pesticides highly correlated)</p>	<p>Newly diagnosed – prospectively ascertained;</p> <p>Although cases were identified from hospitals, a comparison with population-based cases obtained via registry found that 88% of the cases were identified from the hospital in a 3 yr period.</p>

**Table C-2. Nested or population-based case-control studies: Limited exposure information**

<b>Heacock et al. 2000</b>	
<b>Related References</b>	<b>Geographic Location</b>
Hertzman <i>et al.</i> 1997, Teschke <i>et al.</i> 1994, 1996	British Columbia, Canada
<b>Population Characteristics</b>	
<b>Cases: Selection and ascertainment</b>	<b>Controls: Selection and ascertainment</b>
Cases: 40 cases of childhood cancer (females: 22 cases: 5 leukemia (3 ALL); 6 brain cancer (4 astrocytoma); 2 lymphoma; 2 ovarian; 1 cervical; 2 bone; 2 eye; 1 liver; 1 skin  Males: 18 cases: 6 leukemia (3 ALL); 3 brain; 3 bone and connective tissue; 2 lymphoma; 1 liver; 1 thyroid; 1 kidney; 1 skin	Referents:
<u>Case eligibility criteria:</u> All children (10,104 male and 9,570 female births) born in British Columbia between 1952 and 1988 to a cohort of male sawmill workers (Demers <i>et al.</i> 2006) and diagnosed with cancer < 20 years of age between 1969 and 1993.	<u>Referent eligibility criteria:</u> Controls identified from non-cancer births among cohort members using the eligibility criteria for cases
<u>Participation rate:</u> NR	<u>Matching criteria:</u> 5 controls per case frequency matched on sex and year of birth
<u>Length of follow-back:</u> Paternal exposure from start of employment	
<b>Study Design and Analytical Methods</b>	
Nested case-control study (cases of childhood cancer among offspring of sawmill cohort workers) SIR Stepwise logistic regression using maternal and paternal age, birthweight, gestational age, total births	
<b>Exposure Data and Information Assessment</b>	
<b>Exposure: Levels and Co-exposures</b>	<b>Exposure assessment</b>
TeCP	Cumulative dermal exposure measure (see Demers <i>et al.</i> 2006) exposure to combined PCP + TeCP among fathers linked to 4 windows of exposure (start of father's employment through diagnosis of childhood cancer)
<b>Assessment of potential confounders</b>	<b>Disease Assessment</b>
Cumulative dermal exposure to TeCP among fathers No other exposures reported	Record linkage and cancer registry data used to identify cancers among offspring of cohort

<b>Smith et al. 1984</b>	
<b>Related References</b>	<b>Geographic Location</b>
None	New Zealand
<b>Population Characteristics</b>	
<i>Cases: Selection and ascertainment</i>	<i>Controls: Selection and ascertainment</i>
<u>Cases:</u> 82 male cases of STS	<u>Referents:</u> 92 male cancer controls
<u>Case eligibility criteria:</u> All male cases of STS (ICD-9 171) reported to national cancer registry (from public hospitals) 1976–1980 and histologically confirmed	<u>Referent eligibility criteria:</u> registrants in national cancer registry from public hospitals
<u>Participation rate:</u> Approx. 2% cases and 3% controls refused (subject or next of kin); loss of approx. 16% possible cases and 17% eligible controls due to loss of information, unable to contact or refusal	<u>Matching criteria:</u> 1 cancer control per case matched on gender, age within 2 years of birth of case
<b>Study Design and Analytical Methods</b>	
Cancer registry-based case-control study	
Crude odds ratios reported (matching not retained in analysis); however, analysis checked by stratification on matching variable (year of birth and year of registration, and proxy or subject interviews; 90% CI, one-sided <i>P</i> value)	
No analysis for potential confounding	
Risk estimates reported for specific occupation and activities and chlorophenol exposure categories (ever, and two different latency periods)	
<b>Exposure Data and Information Assessment</b>	
<i>Exposure: Levels and Co-exposures</i>	<i>Exposure assessment</i>
Levels of PCP exposure NR	Not specific for PCP
Jobs considered to be associated with chlorophenol exposure included fencing as a farmer or contractor, saw mill or timber merchant, meat work or tannery worker	Interviews (phone) with subject or proxy (if subject unable to participate) using structured questionnaire on occupation/jobs associated with exposure to phenoxy acid herbicides or chlorophenols, followed by specific questions on specific tasks, exposures and chemicals. Questions also asked on farming and medical conditions
No co-exposures reported for PCP-exposed subjects; meat and tannery workers considered to be exposed to TCP (ORs reported separately)	
<i>Assessment of potential confounders</i>	<i>Disease Assessment</i>
No assessment of co-exposures or other confounders among PCP-exposed subjects	Cases identified by cancer registry and histologically confirmed by pathologist
Missing data: NR	Missing data: (7 cases had incompatible histology and were excluded)

<b>Pearce <i>et al.</i> 1987, 1986a</b>	
<b>Related References</b>	<b>Geographic Location</b>
Pearce <i>et al.</i> 1985, 1986b (earlier NHL study)	New Zealand
<b>Population Characteristics</b>	
<b><i>Cases: Selection and ascertainment</i></b>	<b><i>Controls: Selection and ascertainment</i></b>
<u>Cases:</u> 183 NHL cases (100 cases of ICD 200 (lymphosarcoma and reticulosarcoma) and 83 cases of ICD 202) (Pearce <i>et al.</i> 1987).  102 multiple myeloma cases (ICD 203) (Pearce <i>et al.</i> 1986a)	<u>Referents:</u> 315 used for both NHL and multiple myeloma; 23 extra controls to ensure blinding in NHL study
<u>Case eligibility criteria:</u> New Zealand cancer registry: males < 70 years old diagnosed between 1977–1981 in New Zealand cancer registry, presume alive at time of study	<u>Referent eligibility criteria:</u> New Zealand cancer registry; controls with other cancers, except for NHL, Hodgkin lymphoma, multiple myeloma, or STS; occupational data available in registry; alive at time of study
<u>Participation rate:</u> approx. 16% eligible cases and 19% eligible controls excluded due to missing information, unable to contact, and refusal (latter by 2 cases and 14 controls)	<u>Matching criteria:</u> 4 controls selected per case with cancer registration same year as case; birth year within 2 years of case; 2 per case randomly selected for interview plus 30 additional in NHL study
<b>Study Design and Analytical Methods</b>	
Cancer registry-based case-control study  Logistic regression analysis adjusting for decade of birth and proxy or self interview; no adjustment for lifestyle factors or occupational co-exposures; risk estimates reported for specific occupation (meat work and fencing, and fencing only) and activities and chlorophenol exposure categories (ever, and two different latency periods).	
<b>Exposure Data and Information Assessment</b>	
<b><i>Exposure: Levels and Co-exposures</i></b>	<b><i>Exposure assessment</i></b>
Occupations or activities associated with exposure to chlorophenols included fencing, sawmill or timber merchant, meat works, and tannery  Potential co-exposures: Copper chrome arsenate (CCA) was commonly used mostly from 1955; meat (pelt) workers considered to be exposed to 2,4,6-TCP or zoonotic oncogenic viruses	Not specific for PCP; PCP occasionally used as a wood preservative and Na-PCP was commonly used for sapstain treatment  Interviews (phone) with subject or proxy (if subject unable to participate) using structured questionnaire on occupation/jobs associated with exposure to phenoxy herbicides or chlorophenols, followed by specific questions on specific tasks, exposures and chemicals, farming and medical conditions
<b><i>Assessment of potential confounders</i></b>	<b><i>Disease Assessment</i></b>
Not Reported	Cancer registrations ICD 200 and 202; most cases histologically classified; ~15% unclassified, and 5 cases not NHL, but all included in analysis

<b>Smith and Christophers 1992</b>	
<b>Related References</b>	<b>Geographic Location</b>
None	Victoria, Australia
<b>Population Characteristics</b>	
<i>Cases: Selection and ascertainment</i>	<i>Controls: Selection and ascertainment</i>
<u>Cases:</u> 30 cases STS (ICD 171, 1977) 52 cases malignant lymphoma (ICD 200–202, 1977)	<u>Referents:</u> 30 cancer controls for STS, 52 cancer controls for lymphomas; 82 population controls from electoral register
<u>Case eligibility criteria:</u> Male cases > 30 years old identified in Victoria, Australia cancer registry after 1982–1988 and who were patients at one of 6 Melbourne hospitals (public, no fee) and alive at time of study selection (note: some cases were first diagnosed as early as 1976)	<u>Referent eligibility criteria:</u> cancer controls identified in cancer registry (leukemia, multiple myeloma and sarcoma not eligible); population controls > 18 years old identified in electoral register; population controls had to have no record of cancer except for non-melanoma skin cancer
<u>Participation rate:</u> 30% of eligible cases, 44% cancer controls and 30% population controls did not participate (refused or presumed refused interview)	<u>Matching criteria:</u> 1 cancer control and 1 population control per case from cancer registry matched for sex and age within 3 years of birth of case and current residence in same statistical division of state
<u>Length of follow-back:</u> Lifetime	
<u>Loss to follow-back:</u> Not Reported	
<b>Study Design and Analytical Methods</b>	
Cancer registry-based case-control study Conditional regression analysis (matched triad: cases and both types of controls) for probability of exposure to chlorophenols; exposures in the last 5 years ignored in analyses. Additional analyses carried out in which exposure to phenoxy herbicides or clofibrate was considered as no exposure.	
<b>Exposure Data and Information Assessment</b>	
<i>Exposure: Levels and Co-exposures</i>	<i>Exposure assessment</i>
Levels of PCP not reported; estimated length of exposure (> 30 days) reported separately Exposure defined as at least 1 day No co-exposures reported for PCP-exposed subjects	No specific data on PCP but authors report that PCP is the main chlorophenol used in Victoria, Australia Expert assessment from self-reported occupational information. In-person interview with industrial hygienist on occupation history and activities related to chlorophenols or chlorophenoxy acid herbicides, medical history, smoking and lifestyle. Potential exposure to chlorophenols or chlorophenoxy acid herbicides coded as none, possible or definite/probable
<i>Assessment of potential confounders</i>	<i>Disease Assessment</i>
Cigarette smoking and drinking habits assessed Past and current cigarette smoking (but not drinking) associated with a statistically non-significant risk of STS and lymphoma	Cancer registration (ICD codes 171, 200–203), histologically confirmed by review of hospital records in sequence until 30 STS and 52 lymphoma cases interviewed.

### ***Assessment of potential bias, analytical methods, and other study quality characteristics***

Biases in observational studies are often classified into three major categories: (1) selection bias, (2) information bias, and (3) confounding (discussed in section 3.3.2). Studies with lower potential for bias are generally considered to be the most informative for cancer evaluation. However, the presence of a potential bias in a study does not necessarily mean that the findings of the study should be disregarded. Therefore, an important step in the process of evaluating biases is to determine the probable impact of the described biases on study results—that is, the magnitude of distortion and the direction in which each bias is likely to affect the outcome of interest (if known). The impact of the potential bias or confounding on the study findings is discussed in the cancer assessment (See Section 3.4).

For this review, overall conclusions on the concern for the potential (unlikely/minimal, possible or probable) of selection and information bias and the adequacy of other quality factors (good, adequate, or limited) for each study were made using the questions and guidelines outlined in the protocol (see [http://ntp.niehs.nih.gov/NTP/roc/thirteenth/Protocols/PCPHumanStudies20130815\\_508.pdf](http://ntp.niehs.nih.gov/NTP/roc/thirteenth/Protocols/PCPHumanStudies20130815_508.pdf)). In some cases there is insufficient information to evaluate the level of concern. The guidelines describe the ideal methods and design for each study element. The terms used for defining the potential for bias are as follows:

- Unlikely/minimal: Information from study designs and methodologies indicate that the potential for bias is unlikely or minimal and are close to the ideal study characteristics.
- Possible: Study designs or methodologies are close to but less than ideal, recognizing that in observational studies, there is almost always some methodological or informational limitation and thus some potential for certain types of bias.
- Probable: Study designs or methodologies suggest that the potential for a specific type of bias is likely.
- Unknown: Insufficient information is provided to enable an evaluation to be made.

If adequate information is available, each type of bias is also characterized as to whether it is differential or non-differential. Differential (systematic) biases in the selection of study participants or information assessment are related to both exposure and disease status, and have the potential to bias findings in one direction or another, whereas non-differential (random) biases, which are not related to both exposure and disease, tend to reduce the precision of the risk estimates and often bias the findings toward the null. For example, occupational cohort studies may have limited exposure data across exposure groups, increasing the potential for non-differential exposure misclassification, and may also have the potential for a healthy worker (hire or survival) effect, a type of selection bias that tends to bias findings away from finding an effect (if present) in studies where the comparison group comes from the general population.

An overview of the approach and conclusions is discussed in Section 3.3 and details of the quality assessment are provided below in Table C-3.

Table C-3. Summary of study quality

Study	Selection/participation bias Attrition bias (Loss to Follow-up)	PCP exposure assessment: Adequacy	Cancer assessment: Adequacy	Ability to detect an effect and analytical methods: Adequacy
<b>Cohort and nested case-control studies of PCP producers and users</b>				
<p>Kogevinas <i>et al.</i> 1995</p> <p>NHL, STS</p> <p>IARC registry-based multi-country nested case-control study of workers occupationally exposed to phenoxy herbicides, chlorophenols and dioxins (see IARC registry cohort study of Saracci <i>et al.</i> 1991, Kogevinas <i>et al.</i> 1992)</p>	<p><i>Selection/participation bias</i></p> <p><u>Unlikely/minimal</u>: cohort members selected based on registry of workers and all cases of NHL and STS (and matched controls) identified from within cohort</p>	<p><i>Exposure characterization</i></p> <p><u>Adequate</u>: exposure based on questionnaires, factory or spraying records and job histories, though may vary across different subcohorts; PCP exposure confined to member of one UK production cohort (n = 149)</p> <p><i>Exposure misclassification</i></p> <p><u>Possible (non-differential)</u>: exposure categories ever exposed (&gt;1 day)</p>	<p><i>Misclassification of deaths</i></p> <p><u>Possible (non-differential)</u>: underlying and contributing causes of deaths based on death certificate for 20 of the 32 NHL cases and 4 of the STS cases; sarcomas were sarcomas of the connective tissue and other soft tissue (ICD-171)</p> <p><i>Misclassification of cases</i></p> <p><u>Possible (non-differential)</u>: Additional cases (12 NHL and 7 STS) identified by cancer registry data. Histologic diagnosis available for most of the cancer cases. In addition, cancer incidence is considered to be more informative for endpoints e.g. NHL, STS, MM, which are longer survival cancers</p>	<p><i>Ability to detect an effect</i></p> <p><u>Limited statistical power</u> ~ 26% (NHL) and &lt; 10% (STS) to detect 2-fold; few workers exposed to chlorophenols or PCP in total cohort</p> <p><i>Analysis</i></p> <p><u>Adequate</u>: lagged external and internal analysis by categories of exposure; no analysis for potential confounding but no other herbicides were produced at the factory making PCP</p>
<p>Collins <i>et al.</i> 2009a, Ramlow <i>et al.</i> 1996</p> <p>Michigan pentachlorophenol producers cohort mortality study</p>	<p><i>Selection bias</i></p> <p><u>Possible</u>: All-cause and all-cancer mortality rates close to expected rates for population, but high % short-term workers may increase risk of HWE or HWSE</p>	<p><i>Exposure characterization</i></p> <p><u>Good</u>: quantitative exposure assessment based on area samples, individual work histories. Exposure to chlorinated dioxins based on serum profiles of dioxins,</p>	<p><i>Misclassification of deaths</i></p> <p><u>Possible (non-differential)</u>: death certificates used to determine underlying COD</p> <p><i>Misclassification of cases</i></p> <p><u>Possible (non-differential)</u>:</p>	<p><i>Ability to detect an effect:</i></p> <p><u>Limited statistical power</u> approx. 37% NHL), 14%, (STS) and 29% (kidney) statistical power to detect 2-fold increase; <u>adequate</u> length of follow-up and</p>

Study	Selection/participation bias Attrition bias (Loss to Follow-up)	PCP exposure assessment: Adequacy	Cancer assessment: Adequacy	Ability to detect an effect and analytical methods: Adequacy
	<p><i>Loss to follow-up bias</i></p> <p><u>Unlikely/minimal</u>: no loss to follow-up reported</p>	<p>furans and PCBs in sample of past workers and work histories</p> <p><i>Exposure misclassification</i></p> <p><u>Minimal for highest category of cumulative exposure to chlorinated dioxins and possible for lower cumulative categories (non-differential)</u>: individual workers assigned to cumulative exposure categories (ppt-yrs) for chlorinated dioxins based on biomonitoring data (for subset of workers), occupational history, and pharmacokinetic modeling.</p>	<p>mortality data limited for some cancer endpoints (see above)</p>	<p>level and range of estimated exposure to PCP, but <u>limited duration</u>: earlier follow-up (Ramlow <i>et al.</i> 1996) reported that approx. 50% workers had &lt; 1 year cumulative exposure to PCP</p> <p><i>Analysis</i></p> <p><u>Adequate</u>; external analysis only for most tumor sites; internal analyses by cumulative exposure for all cancers combined and 4 specific cancer sites only and for workers potentially exposed to combined PCP + TCP group only; no analysis of other potential confounders</p>
<p>Ruder and Yiin 2011</p> <p>NIOSH pentachlorophenol producers cohort mortality study</p>	<p><i>Selection bias</i></p> <p><u>Possible</u>: all-cause and all-cancer mortality rates close to expected rates for population, but high % short-term workers may increase risk of HWE</p> <p><i>Loss to follow-up bias</i></p> <p><u>Unlikely/minimal</u>: 0.3% overall loss to follow-up</p>	<p><i>Exposure characterization:</i></p> <p><u>Adequate</u>: some area, personal and wipe sampling conducted by investigators in each plant but insufficient data to compare PCP levels across departments/plants or assign levels of exposure to individual workers</p> <p><i>Exposure misclassification:</i></p> <p><u>Possible (non-differential)</u>: individual work/job histories used to assign exposure but</p>	<p><i>Misclassification of deaths</i></p> <p><u>Possible (non-differential)</u>: multiple sources used to ascertain vital status; multiple causes of death mortality rates using NDI</p> <p><i>Misclassification of cases</i></p> <p><u>Possible (non-differential)</u>: mortality data limited for some cancer endpoints (see above)</p>	<p><i>Ability to detect an effect</i></p> <p><u>Limited to adequate statistical power</u> depending on outcome; approx. 67% (NHL), 19% (STS) and 54% (kidney) statistical power to detect 2-fold increase in risk; <u>adequate</u> length of follow-up; <u>limited</u> duration of exposure in PCP</p> <p><i>Analysis</i></p> <p><u>Adequate for NHL, lung and all cancers combined</u>;</p>

Study	Selection/participation bias Attrition bias (Loss to Follow-up)	PCP exposure assessment: Adequacy	Cancer assessment: Adequacy	Ability to detect an effect and analytical methods: Adequacy
		no JEM or levels of exposure used		<u>limited</u> for other cancer sites; separate external mortality analyses for all tumor sites for PCP only and PCP + TCP groups; internal analyses by duration of exposure for combined cohort only and for lung cancer and NHL only; no analyses of other potential confounders
Demers <i>et al.</i> 2006 Canadian sawmill workers cohort incidence and mortality study	<i>Selection bias:</i> <u>unlikely/minimal</u> ; all-cause and all-cancer incidence rates same as expected rates for population <i>Loss to follow-up bias</i> <u>unlikely/minimal</u> ; loss to follow-up 4% deaths and < 0.1 for incidence	<i>Exposure characterization</i> <u>Good</u> : dermal exposure predominant, and formulations of fungicide used at different time periods used to estimate historical exposure and individual work histories used to construct individual dermal exposure equivalent (1 FTE year = 2000 hr exposure)  <i>Exposure misclassification</i> <u>Unlikely/minimal (non-differential)</u> : workers' and industrial hygienists' estimate of (dermal) exposure by job title validated by urine PCP levels in sample of workers	<i>Misclassification of cases</i> <u>Unlikely/minimal (non-differential)</u> : British Columbia cancer registry or Canadian cancer registry used to identify cases; incidence data more reliable and informative for some cancers e.g. NHL, STS, MM; STS cases histologically confirmed  <i>Misclassification of deaths:</i> <u>Possible (non-differential)</u> ; multiple sources used to ascertain vital status and provincial and national mortality databases used to ascertain COD	<i>Ability to detect an effect</i> <u>Good</u> statistical power: approx. power 99% (NHL), 67% (STS) and 99% (kidney) to detect 2-fold increase in risk cancer incidence; <u>adequate</u> length of follow-up and range of estimated exposure to PCP  <i>Analysis</i> <u>Good</u> external and internal analyses including exposure-response analyses lagged for 10 and 20 years. Separate analysis of major co-exposure (TeCP). Some information on smoking
<b>Ecological study of pentachlorophenol exposure</b>				

Study	Selection/participation bias Attrition bias (Loss to Follow-up)	PCP exposure assessment: Adequacy	Cancer assessment: Adequacy	Ability to detect an effect and analytical methods: Adequacy
Zheng <i>et al.</i> 2013 Chinese ecological exposure assessment incidence study	<i>Selection bias</i> Unknown between different areas of study district	<i>Exposure characterization</i> <u>Inadequate</u> : aggregate residential exposure assessed indirectly using data on cumulative amount of PCP spraying across study area  <i>Exposure misclassification</i> <u>Probable (not clear if differential or non-differential)</u> ; no data on length of residence, occupations, or likelihood of exposure	<i>Misclassification of cases</i> <u>Possible (non-differential)</u> : completeness and accuracy of cancer registry data unknown	<i>Ability to detect an effect</i> Cannot be determined based on limited data reported  <i>Analysis</i> <u>Inadequate</u> : reporting of 2-year cancer rates for district qualitatively compared with world population rates (not vs. Chinese population); in internal comparison of medium and high exposure vs. low exposure areas and length of exposure, no data on the relative size and demographics of population at risk in each exposure category (level or duration of exposure) was provided
<b>Population-based case-control studies of pentachlorophenol users – specific exposure information</b>				
Hardell <i>et al.</i> 1994 NHL  Swedish 1994 NHL study	<i>Selection bias</i> <u>Unlikely/minimal</u> : 0.5% (all controls) did not complete exposure questionnaire	<i>Exposure characterization</i> <u>Limited</u> : self-reported exposure/work history including the use of wood preservatives and other pesticides (supplemented by phone interview and expert review); interviewers blind to case status  <i>Exposure misclassification</i> <u>Unlikely/minimal (non-</u>	<i>Misclassification of cases</i> <u>Unlikely/minimal (non-differential)</u> : use of local hospital registry for cases and national registry for death certificates; cases histologically confirmed	<i>Ability to detect an effect:</i> <u>Limited statistical power</u> : approx. 26% power to detect 2-fold increase in risk for NHL incidence in association with PCP; <u>limited exposure information</u> : no data on exposure levels, duration or range of exposure  <i>Analysis</i> <u>Adequate</u> : OR for PCP by

Study	Selection/participation bias Attrition bias (Loss to Follow-up)	PCP exposure assessment: Adequacy	Cancer assessment: Adequacy	Ability to detect an effect and analytical methods: Adequacy
		<u>differential</u> ): reliance on self-report; use of proxies for deceased cases and controls; minimum exposure duration of 1 week (continuous) or 1 month total used for “low” exposure, more than that for high exposure; exposure verified by employers		high and low exposure categories lagged by 1 year; multivariate analysis of chlorophenols (mostly PCP) controlling for exposure to phenoxyacetic acids and solvents.
Hardell and Eriksson 1999 NHL; Hardell 2002 (Combined HCL and NHL)  Swedish 1994 NHL case-control study	<i>Selection/participation bias</i> <u>Unlikely/minimal</u> : all cases reported to regional cancer registries eligible; 9% of cases and 16% controls (or proxies) did not complete exposure questionnaire; interviewers blind to case status	<i>Exposure characterization</i> <u>Limited</u> : self-reported exposure/work history by detailed questionnaire including use of wood preservatives (supplemented by phone interview);  <i>Exposure misclassification:</i> <u>Possible (non-differential)</u> : reliance on self-report; proxies used for some cases and controls	<i>Misclassification of cases</i> <u>Unlikely/minimal (non-differential)</u> : use of regional cancer registry for cases and national registry for deaths; cases histologically confirmed and re-reviewed by authors	<i>Ability to detect an effect</i> <u>Good statistical power (pooled analysis)</u> : approx. 99% power to detect 2-fold increase in risk for NHL incidence in association with PCP; <u>limited exposure information</u> : no data on exposure levels, duration or range of exposure  <i>Analysis</i> <u>Limited</u> : OR for any level/duration of exposure to PCP (presumably 1 day minimum based on previous study methods); analysis by time since first and last exposure but no exposure-response analysis or adjustment for potential confounding. 2002 analysis, multivariate analysis adjust for impregnating agents (60% of which are PCP)

Study	Selection/participation bias Attrition bias (Loss to Follow-up)	PCP exposure assessment: Adequacy	Cancer assessment: Adequacy	Ability to detect an effect and analytical methods: Adequacy
<p>Nordstrom <i>et al.</i> 1998 HCL</p> <p>Swedish HCL case-control study</p>	<p><i>Selection/participation bias:</i> <u>Possible</u>: appears all cases reported to cancer registry eligible; 91% cases and 83% population controls completed questionnaires</p>	<p><i>Exposure characterization</i></p> <p><u>Limited</u>: self-reported exposure by detailed questionnaire (supplemented by phone interview) to occupations or exposures including use of specific “impregnating agents”; minimum exposure of 1 day</p> <p><i>Exposure misclassification</i> <u>Possible (non-differential)</u>: reliance on self-report; a few proxies were used for some cases and controls</p>	<p><i>Misclassification of cases</i> <u>Possible (non-differential)</u>: histological or pathological verification of diagnosis not specified</p>	<p><i>Ability to detect an effect</i> <u>Limited statistical power</u>: approx. 39% power to detect 2-fold increase in risk for HCL incidence in association with PCP; limited exposure information: no data on exposure levels, duration or range of exposure</p> <p><i>Analysis</i> <u>Limited</u>: OR for PCP subset of “impregnating agents”-exposed group only; multivariate analysis and analysis by 2 categories of exposure duration conducted for “impregnating agents” group only; no analysis of potential confounders</p>
<p>Hardell <i>et al.</i> 1995<sup>a</sup> STS</p> <p>Swedish pooled analysis of STS case-control studies</p>	<p><i>Selection/participation bias</i> <u>Unlikely/minimal</u>: cases selected from cancer registries and controls from population registries</p> <p>Refusal to participate (complete questionnaire) varied between &lt; 1.0 to 10% in the individual studies</p>	<p><i>Exposure characterization:</i> <u>limited</u>: self-reported exposure by detailed questionnaire to occupations or exposures including use of wood preservatives (supplemented by phone interview)</p> <p><i>Exposure misclassification:</i> <u>Possible (non-differential)</u>: reliance on self-report,</p>	<p><i>Misclassification of cases</i> <u>Unlikely/minimal (non-differential)</u>: cases identified via regional cancer registries and national mortality data, histologically confirmed by pathologist and medical records</p>	<p><i>Ability to detect an effect:</i> <u>Good statistical power</u>: approx. 96% power to detect &lt; 2-fold increase in risk for STS; <u>limited exposure information</u>: no data on exposure levels, duration or range of exposure</p> <p><i>Analysis</i> <u>Limited</u>: OR for PCP</p>

Study	Selection/participation bias Attrition bias (Loss to Follow-up)	PCP exposure assessment: Adequacy	Cancer assessment: Adequacy	Ability to detect an effect and analytical methods: Adequacy
		although some caes had exposure verified by employer although minimum exposure of 1 day in “low grade” exposure group		exposure for any duration of exposure only and no analysis for potential confounding
<b>Population-based case-control studies of pentachlorophenol users – limited exposure information</b>				
Pearce <i>et al.</i> 1986b, 1987, Smith <i>et al.</i> 1984 NHL, MM, STS  New Zealand case-control studies	<i>Selection/participation bias</i> <u>Possible</u> : use of cancer and population controls but unclear if cancers among cancer controls related to occupations or exposures under study; not clear if interviewers blind to all case status; approx. 80% cases and similar percentage of controls completed questionnaires	<i>Exposure characterization</i> <u>Limited</u> : no specific data on PCP exposure, only occupations associated with types of chlorophenol use  <i>Exposure misclassification</i> <u>Probable for PCP</u> : self or proxy report; no data on duration or extent of exposure or specific PCP use	<i>Misclassification of cases</i> <u>Unlikely/minimal (non-differential)</u> : use of national cancer registry data; cases histologically confirmed	<i>Ability to detect an effect</i> <u>Good statistical power</u> : power approx. 99% to detect 2-fold increase in risk for NHL incidence, 99% for MM incidence, in association with fencing and sawmill work in association with possible exposure to chlorophenols including PCP; <u>limited length of follow-back</u> (3 years); <u>limited exposure information</u> : no data on exposure levels, duration or range of exposure  <i>Analysis</i> <u>Limited</u> : total numbers potentially exposed to PCP unknown; OR analysis of occupations with presumed exposure to chlorophenols including PCP; no analysis for potential confounding

Study	Selection/participation bias Attrition bias (Loss to Follow-up)	PCP exposure assessment: Adequacy	Cancer assessment: Adequacy	Ability to detect an effect and analytical methods: Adequacy
<p>Smith and Christophers 1992 NHL, STS Australian case-control study</p>	<p><i>Selection/participation bias</i> <u>Possible for both cases and population controls</u>: unclear if cancers among cancer controls related to exposures under study; restricted to living cases &gt;30 years old in cancer registry and treated at one of 6 hospitals (public, non-fee paying) whereas population controls from entire state (all social classes); response bias possible (70% cases, 56% cancer controls and 70% population controls completed interview)</p>	<p><i>Exposure characterization</i> <u>Limited</u>: qualitative data only on possible PCP exposure  <i>Exposure misclassification</i> <u>Probable</u>: self-reported data only (by personal interview); interviewer not blind to case status</p>	<p><i>Misclassification of cases</i> <u>Unlikely/minimal for lymphomas, possible for STS (non-differential)</u>: use of cancer registry cases histological types and codes confirmed by hospital records but no review of pathology specimens</p>	<p><i>Ability to detect an effect</i> <u>Limited statistical power</u>: approx. 13% power (NHL) and 8% power (STS) to detect 2-fold increase in risk in association with jobs that involve definite or probable exposure to PCP; exposure; <u>limited</u> length of follow-back; low percent of controls exposed to PCP; limited exposure information: no data on exposure levels, duration or range of exposure  <i>Analysis</i> <u>Limited</u>: no OR specific for PCP calculated; analysis for chlorophenols lagged by 5 years; analyses considered potential confounding from smoking and alcohol use</p>

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## Appendix D: Assessment of the Quality of the Individual Animal Cancer Studies on Exposure to Pentachlorophenol and by-products of its synthesis

Twelve studies were identified in which experimental animals were exposed to pentachlorophenol and by-products of its synthesis for long-term durations ( $\geq 12$  months for mice and rats), or they reported neoplastic lesions, or non-neoplastic lesions that are relevant to carcinogenicity (see Section 4, Cancer Studies in Experimental Animals). Some of these studies are reported in multiple publications and some publications report more than one study (Table D-1).

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[To return to text citing Appendix D in Section 4, click here.](#)

**Table D-1. Overview of studies of exposure to pentachlorophenol and by-products of its synthesis in experimental animals**

Strain (sex)	Substance	Experimental design	Exposure period/ study duration	Reference
<b>Rat: Diet</b>				
F344/N (M & F)	99% pure PCP	Carcinogenicity	2 yr/2 yr	Chhabra <i>et al.</i> 1999, NTP 1999
F344/N (M & F)	99% pure PCP	Carcinogenicity	1 yr/2 yr	Chhabra <i>et al.</i> 1999, NTP 1999
Sprague-Dawley (M & F)	Dowicide EC-7	Carcinogenicity and reproductive	M: 22 mo/22 mo F: 24 mo/24 mo	Schwetz <i>et al.</i> 1978
MRC-W (M & F)	Technical grade PCP	Co-carcinogen	94 wk/94 wk	Mirvish <i>et al.</i> 1991
<b>Mouse: Diet</b>				
B6C3F <sub>1</sub> (M & F)	Technical grade PCP	Carcinogenicity	2 yr/2 yr	McConnell <i>et al.</i> 1991, NTP 1989
B6C3F <sub>1</sub> (M & F)	Dowicide EC-7	Carcinogenicity	2 yr/2 yr	McConnell <i>et al.</i> 1991, NTP 1989
(C57BL/6xC3H/Anf) F <sub>1</sub> , (M & F)	Dowicide-7	Carcinogenicity	18 mo/18 mo	Innes <i>et al.</i> 1969
(C57BL/6xAKR)F <sub>1</sub> (M & F)	Dowicide-7	Carcinogenicity	18 mo/18 mo	Innes <i>et al.</i> 1969
CD-1 (F)	99% pure PCP	Mechanism <sup>a</sup>	12 mo/16 mo	Boberg <i>et al.</i> 1983
CD-1 (F)	99% pure PCP	Mechanism <sup>a</sup>	10 mo/17 mo	Delclos <i>et al.</i> 1986
C57BL/6-Trp53(+/-) tm1Dol	99% pure PCP	Short-term <i>p53</i> (+/-) knock-out	26 wk/26 wk	Spalding <i>et al.</i> 2000

Strain (sex)	Substance	Experimental design	Exposure period/ study duration	Reference
(M &F)		carcinogenicity		
<b>Mouse: Dermal</b>				
Tg•AC hemizygous (M & F) <sup>b</sup>	99% pure PCP	Short-term transgenic carcinogenicity	20 wk/20 wk	Spalding <i>et al.</i> 2000

M = male, F = female.

<sup>a</sup>PCP inhibiting carcinogenic activation by sulfotransferase.

<sup>b</sup>Zetaglobin promoted v-Ha-*ras* on a FVB background.

[To return to text citing Table D-1, click here.](#)

Each of these primary studies were systematically evaluated in a two-step process by first evaluating whether the level of detail reported for key elements of study design, experimental procedures, and cancer endpoints were adequate for evaluating its quality and interpreting its results. All twelve studies were adequately reported and further assessed for concerns of study quality that might negatively impact the ability to evaluate carcinogenicity (Table D-2a, b). Quality assessment of studies with similar experimental design and exposure route reported in a single publication are shown in a single column; the two Spalding (2000) studies from one publication are reported in two columns as the animal strain, exposure route, and tumor endpoints differ. Tables D-2a,b. Section 4, Cancer Studies in Experimental Animals, discusses the results and study quality findings from all of the studies in Table D-1.

### Study quality assessment

Study quality was assessed using questions related to the following study performance elements: substance characterization, animal husbandry, study design, endpoint assessment, and data interpretation. In most cases, each question inquires whether there are concerns (minimal, some, major, and no information reported) that the quality of a specific study element is adequate for attributing any neoplastic endpoints to exposure of pentachlorophenol and by-products of its synthesis. In general, the ranking of the concerns for the study elements is based on how far each study element deviates from the ideal (see below).

The assessment of the overall quality of a study is based on consideration of the individual elements and how they impact the usefulness of that study in assessing carcinogenicity. Studies that were given the most weight in the evaluation (e.g., those with no or minimal concerns in key elements) are those with the following key characteristics:

1. Use a chemical that is representative of the candidate substance (in terms of purity and stability) so that any observed effects can be attributed to the candidate substance.
2. No evidence of poor animal husbandry conditions (such as high mortality due to infection). Often information on animal husbandry conditions is not known and while this information is desirable, it is not a requirement.

3. Exposure of animals to high enough doses (result in tolerable toxicities) for a sufficiently long duration (approaching the lifetime of the animal), but not to a dose that limits survival over the exposure period. The use of more than one dose level is ideal, but is not a requirement.
4. Have an appropriate comparison group (e.g., ideally unexposed, sham treated concurrent controls). The absence of an appropriate control group, by itself, is sufficient for judging a study to be inadequate for cancer evaluation.
5. Have adequate statistical power to detect an effect, which is based on the number of animals used in a study, the incidence of tumors in control vs. treated group, and the rarity of the tumor.
6. Perform full necropsies and histopathological examinations on all tissues. Ideally, animals are exposed to multiple doses that allow for statistical comparisons to the control group and dose-response analysis.

An ideal study would have the following characteristics, which are related to interpreting the study. In general, with the exception of route of exposure, these do not contribute as much weight to the overall evaluation of the study as the characteristics related to the validity of the study discussed above.

7. The use of an exposure route comparable to human exposure.
8. The use of animal model that is sensitive for detecting tumors and does not have high background rates for the observed tumors. Studies in both sexes are more informative than those testing only one sex. Often this information is not available.
9. Availability of historical control data, which can be helpful in assessing the significance of a finding, especially in the case of rare tumors, lower powered studies, or assessment of background tumor incidences. Rare tumors will be considered in the assessment even if their incidences do not reach significance.
10. Appropriate reporting of incidence data and statistical methods. If statistical tests are not reported, the study should at a minimum present incidence data for specific tumors so that statistical tests can be run.

Study having elements that are judged to have some or major concerns may still be considered in the evaluation or can be considered to provide support to the more informative studies. It should also be noted that some concerns about a study element (such as inadequate observation and exposure period and statistical power) would decrease the sensitivity of a study to detect an effect; however, if despite these limitations positive findings were described, these studies would inform a cancer assessment.

**Table D-2a. Assessment of the quality of cancer studies in rats**

	<b>NTP 1999 (Diet)</b>	<b>Schwetz <i>et al.</i> 1978 (Diet)</b>	<b>Mirvish <i>et al.</i> 1991 (Diet)</b>
<b>Substance characterization</b>			
Are there concerns that the purity solubility and stability of the chemical are not adequate for attributing any neoplastic effects to the substance?	<b>Concerns: minimal</b>	<b>Concerns: some</b> No stability testing	<b>Concerns: some</b> The substance contained 25 ppb of TCDD, no other studies reported detectable TCDD.
<b>Animal husbandry</b>			
Are there concerns that the quality of the animal husbandry (e.g., care, diet, maintenance and disease surveillance) is not adequate for attributing any neoplastic effects to the substance?	<b>Concerns: minimal</b>	No information reported	<b>Concerns: minimal</b>
<b>Study design</b>			
Are there concerns that the study design did not include randomization of animals to dose groups and blinding of dose groups?	<b>Concerns: minimal</b> Rats were randomized, but blinding was not reported.	No information reported	<b>Concerns: minimal</b> Rats were randomized, but blinding was not reported.
Are there concerns that the dosing regimen (dose selection and dose groups, or other factors) is either not adequate for detecting a neoplastic effect (if present) or for attributing any tumor effects to the substance?	<b>Concerns: some</b> Only one dose level for the stop exposure study and tumor incidences suggest the doses were too low in the continuous exposure study. The dose levels were based on a 28 day dietary study. Significant loss of weight did occur, but survival was similar to controls.	<b>Concerns: minimal</b> Four doses used, No effect on mean food consumption or survival, except survival in males decreased the last two months. Body weights of females was significantly decreased.	<b>Concerns: some</b> Only one dose level tested and neither hematology, body weight, nor mean survival indicated significant toxicity, however survival could not be determined from report

	<b>NTP 1999 (Diet)</b>	<b>Schwetz <i>et al.</i> 1978 (Diet)</b>	<b>Mirvish <i>et al.</i> 1991 (Diet)</b>
Are there concerns that the study duration (exposure and observation) is not adequate to detect a neoplastic effect, if present?	<b>Concerns: minimal</b>	<b>Concerns: minimal</b> Duration near lifespan, but cut short in control and exposed males by 2 mo (to 22 mo) due to high mortality.	<b>Concerns: minimal</b>
Are there concerns that the concurrent control group was not adequate for evaluating the study?	<b>Concerns: minimal</b>	<b>Concerns: minimal</b>	<b>Concerns: minimal</b>
Are there concerns that the study does not have adequate statistical power (number of animal per exposure and control group) to detect a neoplastic effect, if present?	<b>Concern: minimal</b>	<b>Concerns: minimal</b> Each sex and dose had 27 rats.	<b>Concerns: some</b> Low numbers of exposed rats (5 males and 9 females) and control rats (9 males and 18 females). Inadequate information on survival.
<b>Endpoint assessment</b>			
Are there concerns that the assessment of study outcome (gross and microscopic tissue analysis) was not done blind?	<b>Concerns: minimal</b> Histological examination was not blinded.	No information reported	No information reported
Are there concerns that the methods to access tumor outcome and the pathology procedures (necropsy, histology, or diagnosis) are not adequate for attributing the effects?	<b>Concerns: minimal</b>	<b>Concerns: minimal</b>	<b>Concerns: minimal</b>
<b>Data interpretation</b>			
Are there concerns that survival-related effects could affect attributing the study findings to exposure?	<b>Concerns: minimal</b>	<b>Concerns: minimal</b> Survival of both control and exposed males was shortened, but not until after 22 mo.	<b>Concerns: some</b> Survival can't be adequately assessed.

	<b>NTP 1999 (Diet)</b>	<b>Schwetz <i>et al.</i> 1978 (Diet)</b>	<b>Mirvish <i>et al.</i> 1991 (Diet)</b>
Are there concerns that the route of exposure is not adequate for evaluating the potential for human carcinogenicity	<b>Concerns: minimal</b>	<b>Concerns: minimal</b>	<b>Concerns: minimal</b>
Are there concerns about the animal model (source, species, strain, or sex) that could affect study interpretation?	<b>Concerns: minimal</b>	<b>Concerns: minimal</b>	<b>Concerns: minimal</b>
Are historical control data reported? If not, this would be a concern for rare tumors, or tumors with high background.	<b>Yes</b>	<b>No</b>	<b>No</b>
Are there concerns that reporting of the data and statistical analysis are inadequate for evaluating the results?	<b>Concerns: minimal</b>	<b>Concerns: some</b> Tumor incidences were high, but only total tumors were reported, tumor types not specified.	<b>Concerns: some</b> Statistical analysis not reported and tumor incidences based on the number of rats surviving 11 weeks; the original number of animals in each group were not reported.
<b>Overall assessment of study quality and utility for cancer assessment</b>			
Does this study have utility for cancer assessment? What is the overall level of concern for the quality of the study, and how would any concerns affect its interpretation?	<b>Yes</b> , some concerns about the dose levels being low as only the highest dose level out of four exposed groups had significant tumors.	<b>Yes</b> , some concerns of not reporting specific tumor incidences.	<b>Yes</b> , some concerns about the low numbers of rats; the inability to assess survival; only one dose level was tested and most toxicity measures were negative; and that the substance was the only one that reported containing TCDD.

[To return to text citing Table D-2a, click here.](#)

Table D-2b. Assessment of the quality of cancer studies in mice

	NTP 1989 (Diet)	Innes <i>et al.</i> 1969 (Diet)	Boberg <i>et al.</i> 1983 (Diet)	Delclos <i>et al.</i> 1986 (Diet)	Spalding <i>et al.</i> 2000 (Diet) [p53 (+/-) knock-out]	Spalding <i>et al.</i> 2000 (Dermal) [Transgenic]
<b>Substance characterization</b>						
Are there concerns that the purity solubility and stability of the chemical are not adequate for attributing any neoplastic effects to the substance?	<b>Concerns: minimal</b>	<b>Concerns: some</b> No stability testing	<b>Concerns: some</b> No stability testing, but bulk chemical re-purified every 6 months.	<b>Concerns: some</b> No stability testing, but bulk chemical re-purified every 6 months.	<b>Concerns: minimal</b>	<b>Concerns: minimal</b>
<b>Animal husbandry</b>						
Are there concerns that the quality of the animal husbandry (e.g., care, diet, maintenance and disease surveillance) is not adequate for attributing any neoplastic effects to the substance?	<b>Concerns: minimal</b>	<b>Concerns: minimal</b>	No information reported	No information reported	<b>Concerns: minimal</b>	<b>Concerns: minimal</b>
<b>Study design</b>						
Are there concerns that the study design did not include randomization of animals to dose groups and blinding of dose groups?	<b>Concerns: minimal</b> Mice randomized, but blinding not reported.	No information reported	No information reported	No information reported	<b>Concerns: minimal</b> Mice were randomized, but blinding was not reported	<b>Concerns: minimal</b> Mice were randomized, but blinding was not reported
Are there concerns that the dosing regimen (dose selection and dose groups, or other factors) is either not adequate for detecting a	<b>Technical Grade: Concerns:</b>	<b>Concerns: some</b> Only one	<b>Concerns: some</b> Only one dose level used which	<b>Concerns: some</b> Only one dose level used which	<b>Concerns: minimal</b> Three dose level	<b>Concerns: minimal</b> Three dose levels

	<b>NTP 1989 (Diet)</b>	<b>Innes <i>et al.</i> 1969 (Diet)</b>	<b>Boberg <i>et al.</i> 1983 (Diet)</b>	<b>Delclos <i>et al.</i> 1986 (Diet)</b>	<b>Spalding <i>et al.</i> 2000 (Diet) [p53 (+/-) knock-out]</b>	<b>Spalding <i>et al.</i> 2000 (Dermal) [Transgenic]</b>
neoplastic effect (if present) or for attributing any tumor effects to the substance?	<p><b>minimal</b></p> <p>Only two dose levels with acceptable weight loss in females. Dose levels were based on liver lesions (karyomegaly, cytomegaly, hepatocellular degeneration, and necrosis) in 6 month dietary studies.</p> <p><b>Dowicide EC-7: Concerns: minimal</b></p> <p>Three dose levels with acceptable toxicity except low survival in low-dose females. Dose levels were based on liver lesions (karyomegaly, cytomegaly,</p>	exposure level that is a relatively low dose (130 ppm in food)	did not significantly decrease body weight gain or survival, but the concentration in the feed (500 ppm) was comparable to that of the NTP (1989) studies.	did not significantly decrease body weight gain or survival, but the concentration in the feed (500 ppm) was comparable to that of the NTP (1989) studies.	used that were comparable to the NTP (1989) study, but no overt toxicities were reported.	used and initially caused toxicity, so were reduced.

	<b>NTP 1989 (Diet)</b>	<b>Innes <i>et al.</i> 1969 (Diet)</b>	<b>Boberg <i>et al.</i> 1983 (Diet)</b>	<b>Delclos <i>et al.</i> 1986 (Diet)</b>	<b>Spalding <i>et al.</i> 2000 (Diet) [p53 (+/-) knock-out]</b>	<b>Spalding <i>et al.</i> 2000 (Dermal) [Transgenic]</b>
	hepatocellular degeneration, and necrosis) in 6 month dietary studies.					
Are there concerns that the study duration (exposure and observation) is not adequate to detect a neoplastic effect, if present?	<b>Concerns: minimal</b>	<b>Concerns: minimal</b> Exposed and observed for less than lifespan (18 months)	<b>Concerns: some</b> Mice exposed for less than lifespan, 12 months and observed for a total of 16 months.	<b>Concerns: some</b> Mice exposed for less than lifespan, 10 months and observed for a total of 18 months.	<b>Concerns: some</b> Exposure was only for 26 wk, None of the 6 chemicals tested induced tumors and no positive control was used.	<b>Concerns: minimal</b> Exposure was only 20 weeks, but the mice are transgenic and tumors were induced by PCP and a positive control.
Are there concerns that the current control group was not adequate for evaluating the study?	<b>Concerns: minimal</b>	<b>Concerns: minimal</b>	<b>Concerns: minimal</b>	<b>Concerns: minimal</b>	<b>Concerns: minimal</b>	<b>Concerns: minimal</b>
Are there concerns that the study does not have adequate statistical power (number of animal per exposure and control group) to detect a neoplastic effect, if present?	<b>Concerns: minimal</b>	<b>Concerns: minimal</b>	<b>Concerns: minimal</b> Each dose level had 36 females.	<b>Concerns: minimal</b> Each dose level had 35 females.	<b>Concerns: some</b> The number of mice in each group was low (10 males and 10 females).	<b>Concerns: some</b> The number of mice in each group was relatively low (13 to 15/dose level) and only females were tested.
<b>Endpoint assessment</b>						
Are there concerns that the assessment of study outcome	<b>Concerns:</b>	No information	No information	No information	No information	No information

	<b>NTP 1989 (Diet)</b>	<b>Innes <i>et al.</i> 1969 (Diet)</b>	<b>Boberg <i>et al.</i> 1983 (Diet)</b>	<b>Delclos <i>et al.</i> 1986 (Diet)</b>	<b>Spalding <i>et al.</i> 2000 (Diet) [p53 (+/-) knock-out]</b>	<b>Spalding <i>et al.</i> 2000 (Dermal) [Transgenic]</b>
(gross and microscopic tissue analysis) was not done blind?	<b>minimal</b> Histological examination not blinded.	reported	reported	reported	reported	reported
Are there concerns that the methods to access tumor outcome and the pathology procedures (necropsy, histology, or diagnosis) are not adequate for attributing the effects?	<b>Concerns: minimal</b>	<b>Concerns: minimal</b> Full necropsy, except for brain and thyroid gland.	<b>Concerns: minimal</b> Necropsies focused on the liver, but also included the pleural and peritoneal cavities and subcutaneous tissue.	<b>Concerns: minimal</b> Necropsies focused on the liver, but also included the pleural and peritoneal cavities and subcutaneous tissue.	<b>Concerns: minimal</b>	<b>Concerns: minimal</b>
<b>Data interpretation</b>						
Are there concerns that survival-related effects could affect attributing the study findings to exposure?	<b>Concerns: minimal</b>	No information reported	<b>Concerns: minimal</b>	<b>Concerns: minimal</b>	<b>Concerns: minimal</b>	<b>Concerns: minimal</b>
Are there concerns that the route of exposure is not adequate for evaluating the potential for human carcinogenicity?	<b>Concerns: minimal</b>	<b>Concerns: minimal</b>	<b>Concerns: minimal</b>	<b>Concerns: minimal</b>	<b>Concerns: minimal</b>	<b>Concerns: minimal</b>
Are there concerns about the animal model (source, species, strain, or sex) that could affect study interpretation?	<b>Concerns: minimal</b>	<b>Concerns: minimal</b>	<b>Concerns: some</b> Only females used.	<b>Concerns: some</b> Only females used.	<b>Concerns: some</b> Knock-out mice (p53 (+/-)) were used without a positive control	<b>Concerns: some</b> Only females were tested. The mice were transgenic, but

	<b>NTP 1989 (Diet)</b>	<b>Innes <i>et al.</i> 1969 (Diet)</b>	<b>Boberg <i>et al.</i> 1983 (Diet)</b>	<b>Delclos <i>et al.</i> 1986 (Diet)</b>	<b>Spalding <i>et al.</i> 2000 (Diet) [p53 (+/-) knock-out]</b>	<b>Spalding <i>et al.</i> 2000 (Dermal) [Transgenic]</b>
					and none of the 6 chemicals tested induced tumors.	positive and negative controls were used with expected outcomes. The mechanism of carcinogenesis in the model may not be relevant to mechanisms in humans.
Are historical control data reported? If not this would be a concern for rare tumors, or tumors with high background.	<b>Yes</b>	<b>No</b>	<b>No</b>	<b>No</b>	<b>No</b>	<b>No</b>
Are there concerns that reporting of the data and statistical analysis are inadequate for evaluating the results?	<b>Concerns: minimal</b>	<b>Concerns: some</b> Incidences were not reported	<b>Concerns: minimal</b>	<b>Concerns: minimal</b>	<b>Concerns: some</b> Incidences were not reported, only a statement of negative findings.	<b>Concerns: minimal</b>
<b>Overall assessment of study quality and utility for cancer assessment</b>						
Does this study have utility for cancer assessment? What is the overall level of concern for the quality of the study, and how would any concerns affect its interpretation?	<b>Yes</b> , minimal concerns in most key elements.	<b>Yes</b> , some concerns of a single, relatively low, exposure level.	<b>Yes</b> , some concerns of no stability testing; only tested in females; only tested one dose level without significant	<b>Yes</b> , some concerns of no stability testing; only tested in females; only tested one dose level without significant	<b>Yes</b> , some concerns with a low number of mice used in each group, a short-term p53 (+/-) knock-out model without	<b>Yes</b> , Some concerns with a low number of mice used in each group. The mechanism of carcinogenesis in the model can be

	<b>NTP 1989 (Diet)</b>	<b>Innes <i>et al.</i> 1969 (Diet)</b>	<b>Boberg <i>et al.</i> 1983 (Diet)</b>	<b>Delclos <i>et al.</i> 1986 (Diet)</b>	<b>Spalding <i>et al.</i> 2000 (Diet) [p53 (+/-) knock-out]</b>	<b>Spalding <i>et al.</i> 2000 (Dermal) [Transgenic]</b>
			decreases in body weight or survival; and less than life-time exposure.	decreases in body weight or survival; and less than life-time exposure.	the use of a positive control with none of the 6 chemicals inducing tumors and no toxicities reported. This model is positive primarily with mutagenic chemicals.	activated by dermal irritation and wounding.

[To return to text citing Table D-2b, click here.](#)

## Appendix E: Genotoxicity Studies

The tables on the following pages contain data discussed in the “Mechanisms and Other Relevant Effects” section (Section 5) for genetic and related effects (Section 5.1).

Data are reported for *in vitro* studies of pentachlorophenol, including mutagenicity and DNA damage in bacteria (Table E-1) and genotoxicity studies of pentachlorophenol in non-mammalian eukaryotes (Table E-2) and mammalian cells (Table E-3). Studies on the formation of adducts in cells or DNA treated with pentachlorophenol *in vitro* and animals treated *in vivo* are included in Tables E-4 and E-5. *In vivo* studies of pentachlorophenol are shown for cytogenetic effects in rodents (Table E-6), as well as chromosomal aberrations (Table E-7) and sister chromatid exchange (Table E-8) in lymphocytes of occupationally exposed workers. A summary of genotoxicity studies of pentachlorophenol metabolites is provided in Table E-9.

Table E-1. *In vitro* studies of pentachlorophenol mutagenicity and DNA damage in bacteria

Reference	Effect	Test system / strain (Method)	LED/HID (µg/plate)		Results		Cytotoxicity		Purity	Evaluation: limitations and conclusions
			- S9	+ S9	- S9	+ S9	- S9	+ S9		
EPA 2010, Waters <i>et al.</i> 1982	Mutation	<i>Salmonella typhimurium</i> TA98, TA100, TA1535, TA1537, TA1538	10 µg/plate (all strains)	10 µg/plate (all strains)	-	-				Negative all strains ±S9. Aroclor 1254-induced rat S9. Data tables not available; multiple doses tested but not specified; EPA cites LED as 10µg/plate ±S9.
Nishimura <i>et al.</i> 1982	Mutation	<i>S. typhimurium</i> TA98 TA100 (preincubation)	26.6 µg/plate <sup>a</sup> NR	5.3 µg/plate <sup>a</sup> NR	- -	+ -	TA98 > 16 µg/plate <sup>a</sup>	TA98 > 16 µg/plate <sup>a</sup>	“Standard sample” (not commercial grade)	Positive in TA98 +S9; otherwise negative. Phenobarbital/benzoflavone-induced rat liver S9; significant induction of mutants above 5.3 g/plate with maximum induction at 10.7µg/plate <sup>a</sup> . Statistical analysis not specified.
Nishimura and Oshima 1983, as cited in IARC 1999 (same group as above)	Mutation	<i>S. typhimurium</i> TA98 TA100	NR	NR	- -	+ -				Positive in TA98 +S9 (phenobarbital/benzoflavone induced); otherwise negative. Results based on control vs. 10.7µg/plate <sup>a</sup> treatment (only dose for which data was reported); Nishimura group repeated their earlier experiment, confirming results reported in 1982 paper. Statistical analysis not specified.
Haworth <i>et al.</i> 1983, NTP 1999	Mutation	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537 (preincubation)	10 µg/plate	30 µg/plate	-	-	All strains, slightly toxic at 10 µg/plate, total toxicity at 30 µg/plate	Not toxic at 30 µg/plate	91.6 <sup>b</sup>	Negative all strains ±S9. Tested 0.3, 1, 3, 10, 30 µg/plate; Aroclor 1254-induced rat or hamster S9; NTP 1989 reported same data and confirmed results in a second trial
Gopaldaswamy and Nair 1992	Mutation	<i>S. typhimurium</i> TA98 (plate)	100 µg/plate	50 µg/plate	-	(+)			NR	Weakly positive TA98 +S9; negative -S9. Aroclor 1254-induced rat S9;

Reference	Effect	Test system / strain (Method)	LED/HID (µg/plate)		Results		Cytotoxicity		Purity	Evaluation: limitations and conclusions
			- S9	+ S9	- S9	+ S9	- S9	+ S9		
		incorporation)								only tested 50 and 100 µg/plate. Induced mutant frequency cannot be calculated due to incomplete reporting but authors report weak positive both doses +S9.
Markiewicz <i>et al.</i> 1996	Mutation	<i>S. typhimurium</i> TA98 (Plate incorporation)	100 µg/plate	100 µg/plate	-	-	None noted	None noted	NR	Negative for all induction compounds: 30% S9 induced in male Sprague-Dawley rats: phenobarbital, commercial and prepared Aroclor and TCDD.
Donnelly <i>et al.</i> 1998	Mutation	<i>S. typhimurium</i> TA97a, TA98, TA100 (Plate incorporation)	200 µg/plate	200 µg/plate	-	-	None reported (all strains)	None reported (all strains)	> 98%	Negative all strains ±S9. Tested 2, 20, 50, 100, 200 µg/plate; Aroclor-induced rat S9 (30%); no toxicity observed up to and including highest dose tested.
DeMarini <i>et al.</i> 1990	Prophage λ induction	<i>Escherichia coli</i>	NR	3.4 µg/ml <sup>c</sup>	(+)	+	12.5 µg/mL	25 µg/mL	92%	Positive +S9; weakly positive - S9. Aroclor 1254-induced rat S9.
Waters <i>et al.</i> 1982	DNA damage	<i>E. coli</i> (polA-)			-	ND				
		<i>Bacillus subtilis</i>			+	ND				
Ozaki <i>et al.</i> 2004	DNA damage (Rec-assay)	<i>Bacillus subtilis</i> M45 Rec- and H17 Rec+	µg/disc 3.0 6.0		+	+			> 99%	Positive in both strains.
Witte <i>et al.</i> 1985	DNA damage (strand breaks)	Bacteriophage PM2 DNA	100 mM		-				NR	Negative. Data not shown.

LED/HID = lowest effective dose/highest ineffective dose, NR = not reported, NT = not tested. + = positive, (+) = weak positive, - = negative.

<sup>a</sup> Data for LED/HID estimated from figure; to facilitate comparison with other studies, data reported by these authors as µmol/plate were converted to µg/plate by NTP.

<sup>b</sup> Although Haworth *et al.* noted 96% purity, NTP reported 91.6%.

<sup>c</sup> To facilitate comparison with other studies, doses reported by these authors as µM were converted to µg by NTP. [To return to text citing Table E-1, click here.](#)

Table E-2. Studies of pentachlorophenol in non-mammalian eukaryotes

Reference	Effect	Test system / strain	Concentration (LEC or HIC) µg/mL	Cytotoxicity	Results		Evaluation: limitations and conclusions
					-S9	+S9	
YEAST							
Fahrig <i>et al.</i> 1978	Forward mutation	<i>Saccharomyces cerevisiae</i> MP-1	400	59% survival	+ <u>Convertants/10<sup>7</sup> survivors</u> Control    Treated 0.61    2.00*		NT Positive. Purity 99% Only tested one dose.
Fahrig 1974	DNA damage (gene conversion)	<i>S. cerevisiae</i> D4	50.6 <sup>a</sup>	30% survival	+ <u>Convertants/10<sup>5</sup> survivors</u> Control    Treated <i>ade2</i> 0.45    6.62*** <i>trp5</i> 0.36    4.31***		NT Positive. Solvent 1% DMSO, 6-hr treatment, 8 expts; positive mitotic gene conversion at two loci.
Fahrig <i>et al.</i> 1978	DNA damage (gene conversion)	<i>S. cerevisiae</i> MP-1	400	59% survival	+ <u>Recombinants/10<sup>5</sup> survivors</u> Control    Treated Expt 1 2.93    5.64*** Expt 2 0.49    0.47		NT Positive. Purity 99% Only tested one dose; repeat experiment did not show increase.
Waters <i>et al.</i> 1982	DNA damage	<i>S. cerevisiae</i> D3			+		Positive.
INVERTEBRATES							
Vogel and Chandler 1974	Sex-linked recessive lethal mutations	<i>Drosophila melanogaster</i>	1864 <sup>a</sup> in feed		-		Negative. Tested pentachlorophenol, sodium salt; purity not reported.
Ramel and Magnusson 1979	Aneuploidy	<i>D. melanogaster</i>	400 in feed		-		Negative in XXY and XO offspring Purity not reported.
Yin <i>et al.</i> 2006	Point mutation ( <i>p53</i> gene)	<i>Tuebingen</i> (zebrafish)	5 µg/L in aquarium water		+ Conc    Base Mutation (µg/L)    Rate x10 <sup>-4</sup> 0    2.12 0.5    3.15 5    7.33**		Positive. Purity > 98%

Reference	Effect	Test system / strain	Concentration (LEC or HIC) µg/mL	Cytotoxicity	Results		Evaluation: limitations and conclusions
					-S9	+S9	
					50	10.73**	
Pavlica <i>et al.</i> 2001	DNA damage - haemocytes (comet assay)	<i>Dreissena polymorpha</i> Pallas (zebra mussel)	80 µg/L in aquarium water	Above 87% in all treatment groups		+	Positive. Purity not reported. Tested at 10, 80, 100 and 150 µg/L; all doses except lowest were significant to $P < 0.01$ .
Pavlica <i>et al.</i> 2000	Micronuclei induction	<i>D. polymorpha</i> (mussel) <i>Planorbarius corneus</i> L. (great ramshorn snail)	(14 d treatment) Mussel: 10 Snail: 100			+	Positive for both test animals. Purity not reported. Tested for 4, 7, 14 days Mussel: 10, 80, 100, 150 µg/L Snail: 10, 100, 450, 600 µg/L
PLANTS							
Pavlica <i>et al.</i> 1998	Chromosome aberrations and Micronuclei induction (MN)	<i>Allium ascalonicum</i>	0.001			+	Positive. Purity not reported. pH 6.0; MN at pH 8.0 MN results per 1000 cells
					Conc (µg/mL)	% Aberrant cells	MN
					Control	0.9	3.0
					0.001	3.0*	13.2*
					0.01	5.6*	14.0*
					0.1	7.7*	24.3*
Ateeq <i>et al.</i> 2002	Chromosome aberrations	<i>Allium cepa</i>	0.5			+	Positive. Purity 99%
					Conc (µg/mL)	% Aberrant cells	
					0	1.33	
					0.5	7.15*	
					1	4.50*	
					2	6.73*	
					3	8.57*	

Reference	Effect	Test system / strain	Concentration (LEC or HIC) $\mu\text{g/mL}$	Cytotoxicity	Results		Evaluation: limitations and conclusions
					-S9	+S9	
Repetto <i>et al.</i> 2001	Micronucleus induction (MN)	<i>Allium cepa</i>	0.5		+		Positive. Purity not reported. Data are expressed relative to mean value in unexposed controls.
					Conc ( $\mu\text{g/mL}$ )	MN (%)	
					0	0.1	
					0.27	0.1	
					1.33	0.1**	
					2.66	1.7**	

NT = not tested.

\* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ .

<sup>a</sup>To facilitate comparison with other studies, concentration reported by authors as 0.19 mM (Fahrig), 7.0 mM (Vogel and Chandler) and 1 to 10  $\mu\text{M}$  (Repetto) were converted to  $\mu\text{g/mL}$  by NTP.

[To return to text citing Table E-2, click here.](#)

**Table E-3. *In vitro* studies of cytogenetic effects of pentachlorophenol in mammalian cells**

Reference	Effect	Test system / strain	Concentration $\mu\text{g/mL}$ (LEC or HIC)	Cytotoxicity	Results		Purity (%)	Evaluation: limitations and conclusions
					-S9	+S9		
Hattula and Knuutinen 1985, as cited in IARC 1999	Mutation, hepatocyte-mediated	V79 Chinese hamster lung fibroblasts	15	Cloning efficiency 55.3%	–	NT	> 99.95	Negative Information limited to that provided in review study
Jansson and Jansson 1986	Mutation (forward)	V79 Chinese hamster lung fibroblasts	50	Survival at top dose 27% (see comments)	–	NT	> 99.5	Negative 0, 6.5, 12.5, 25 50 $\mu\text{g/mL}$ ; dose-dependent decrease in cell survival with increasing dose, i.e., 100, 90, 73, 53 and 27%

Reference	Effect	Test system / strain	Concentration µg/mL (LEC or HIC)	Cytotoxicity	Results			Purity (%)	Evaluation: limitations and conclusions	
					-S9		+S9			
Helleday <i>et al.</i> 1999	Mutation (Intragenic recombination; reversion assay)	SPD8 and Sp5 (derived from V79 Chinese hamster lung cells)	SPD8: 35 Sp5: 40	Viability (%) 8 15	Conc (µg/mL)	Reversion freq (x10 <sup>-5</sup> ) SPD8 Sp5		NT	NR	Negative. Authors report that no results from any doses in treated cultures were significantly different from control ( <i>P</i> < 0.05) using Student's t-test.
					0	2.0	3.4			
					10	1.7	4.1			
					20	2.1	2.3			
					30	4.1	3.2			
					35	4.9	ND			
					40	ND	3.2			
Dahlhaus <i>et al.</i> 1996	DNA damage (single strand breaks)	Alkaline elution assay/V79 Chinese hamster lung fibroblasts	6.6 <sup>a</sup>		-			NT	NR	Negative.
Ehrlich 1990	DNA damage (single strand breaks)	Alkaline elution assay/Chinese hamster ovary cells	10	Slightly toxic 10 µg/mL; toxic 20 µg/mL	-			NT	NR	Negative. Tested 5, 10, 20 µg/mL.
Wang and Lin 1995	DNA damage (single strand breaks)	Precipitation Assay/Mouse embryonic fibroblasts C3H10T½	-S9: 59 <sup>b</sup> +S9: 37 <sup>b</sup>	> 67%	-			(+)	NR	Weakly positive +S9; negative -S9. Phenobarbital/hydro cortisone-induced S9.

Reference	Effect	Test system / strain	Concentration µg/mL (LEC or HIC)	Cytotoxicity	Results			Purity (%)	Evaluation: limitations and conclusions	
					-S9		+S9			
Michałowicz 2010	DNA damage (single and double strand breaks) (comet assay)	Human lymphocytes	0.2 <sup>a</sup>	Viability 67% <sup>b</sup> at 125	Conc (µg/mL)	+	Damaged DNA (%)	NT	99.5	Positive. Results based on 3-4 individual experiments; subjects (4) healthy male non-smokers
					0		0.2			
					0.2		0.7*			
					1		3.8***			
					5		5.6***			
Michałowicz and Majsterek 2010	DNA damage (comet assay)	Human lymphocytes	0.2		Conc (µg/mL)	+	Damaged DNA (%) <sup>c</sup>	NT	99.5	Positive.
					0		0.3			
					0.2		2.8*			
					1		6.0*			
					5		8.6*			
Stang and Witte 2010	DNA damage (comet assay, high-throughput)	V79	1.0 <sup>c</sup>			NT		+	NT	Positive without S9; negative for cells tested with S9. Purity not reported.
		Human fibroblasts	1.25 <sup>c</sup>			NT		+		
		HeLa cells	1.15 <sup>c</sup>			NT		+		
		HepG2 cells	1.0 <sup>c</sup>			+		NT		
		Human lymphocytes	0.5 <sup>c</sup>			NT		+		
Tisch <i>et al.</i> 2005	DNA damage (single and double strand breaks) – DNA migration	Human epithelial (mucosal) nasal cells - microgel electrophoresis	For both inferior and middle nasal mucosa 1.2 mmol/mL (see comments)	From low to high dose, undamaged cell # decreased for both middle nasal concha	Conc (mmol/mL)	+	Cell migration (µm) middle concha    inferior concha	NT	> 99.5	Positive. Authors reported test concentrations as 0.3, 0.75, 1.2 mmol/mL; results are given as µm cell migration. For inferior and middle nasal concha, significant DNA migration
					0		29.1    25.9			
					0.3		40.3    30.7			
					0.75		63.1    45.3			
					1.2		81.6 ***    60.1***			

Reference	Effect	Test system / strain	Concentration $\mu\text{g/mL}$ (LEC or HIC)	Cytotoxicity	Results		Purity (%)	Evaluation: limitations and conclusions
					-S9	+S9		
					Undamaged cells decreased for middle (79.5 to 8%)*** and inferior nasal concha (85.6 to 36.6%)***, compared with controls.			increase (92% of cells exposed to 1.2 mmol/mL) and the number of undamaged cells decreased significantly with increasing dose.
Galloway <i>et al.</i> 1987, NTP 1999	Chromosomal aberrations	Chinese hamster ovary cells	-S9 100 +S9 100	NR	-	(+) high dose* and trend***	91.6	Weakly positive +S9; negative -S9. Tested $\pm$ S9 to 100 $\mu\text{g/mL}$ ; weakly positive with +S9 at the highest dose and for <i>p</i> -trend. Repeat expt. results were '?'. Repeat expt. results were '?'.
Ishidate 1988, as cited in IARC 1999	Chromosomal aberrations	V79 Chinese hamster lung fibroblasts	-S9 300 +S9 240	-S9 NR +S9 300	+	+	99.9	Positive, but only at high dose for both $\pm$ S9. Mouse S9 (chemical used to induce S9 NR). Limited reporting of protocol and data.
Ziemsens <i>et al.</i> 1987	Chromosomal aberrations	Human lymphocytes from healthy male donors	90	Slowed cell proliferation at 60 $\mu\text{g/mL}$ treatment	-	NT	85	Negative -S9.
Galloway, 1987, NTP, 1999	Sister chromatid exchange	Chinese hamster ovary cells	-S9 3 +S9 100		(+)	-	91.6	Weakly positive -S9; negative +S9. Tested (-S9): 1, 3, 10, 30 $\mu\text{g/mL}$ ; significantly increased at only

Reference	Effect	Test system / strain	Concentration $\mu\text{g/mL}$ (LEC or HIC)	Cytotoxicity	Results		Purity (%)	Evaluation: limitations and conclusions
					-S9	+S9		
								one dose 3 $\mu\text{g/mL}$ . Weakly positive, $P$ -trend < 0.008. Tested (+S9): 3, 10, 30, 100 $\mu\text{g/mL}$ , all negative.
Ziemsens <i>et al.</i> 1987	Sister chromatid exchange	Human lymphocytes from healthy male donors	90	Slowed cell proliferation at 60 $\mu\text{g/mL}$ treatment	–	NT	85	Negative –S9. Tested 30, 6, 90 $\mu\text{g/mL}$ .
Monteith 1992	Unscheduled DNA repair (UDS)	Hepatocytes from male Wistar rats treated with corn oil or 3-MC (80 mg/kg)	0.003		– Net grains/ nucleus ( $\pm\text{SD}$ ) Corn oil Control -1.0 $\pm$ 2.3 Treated -0.1 $\pm$ 2.0 3-MC Control 0.2 $\pm$ 2.0 Treated 0.2 $\pm$ 2.1		99	Negative. Hepatocytes were isolated from rats treated with 3-methyl-cholanthrene (3-MC) or corn oil; only one dose (0.003 $\mu\text{g/mL}$ ) of pentachlorophenol was used to treat hepatocytes.
Hogberg <i>et al.</i> 2009	Gene expression	Rat primary neuronal cultured cells	13.3 <sup>a</sup>		+ For 50 $\mu\text{M}$ treatment, mRNA expression decreased by (%) NF-68 78*** NF-200 91*** NMDA 79*** GABA 46 S100 $\beta$ 41** Nestin 54***			Positive. At 50 $\mu\text{M}$ treatment, mRNA expression of all studied genes was decreased.
Wang <i>et al.</i> 2000	Apoptosis and related gene expression	Human cell lines: Chang liver cells		Chang cells 400 $\mu\text{M}$ T-24 cells 100 $\mu\text{M}$	– Hsp70 gene expression unchanged			Negative. Induced cell death, but was more like necrosis than

Reference	Effect	Test system / strain	Concentration µg/mL (LEC or HIC)	Cytotoxicity	Results		Purity (%)	Evaluation: limitations and conclusions
					-S9	+S9		
		and T-24 bladder carcinoma cells						apoptosis
Michałowicz and Sicińska 2009	Apoptosis	Human lymphocytes	25 <sup>a</sup>		Conc (µg/mL)	+ Apoptotic cells (%) <sup>ac</sup>	99.5	Positive.
					0	1		
					5	2		
					25	5**		
					50	10**		
					100	27**		
Wispriyono <i>et al.</i> 2002	Apoptosis	Jurkat human T cells	5.3 <sup>a</sup>		Conc (µg/mL) <sup>a</sup>	+ Apoptotic cells (%) <sup>c</sup>		Positive
					0	2		
					1.3	3		
					2.7	8		
					5.3	20*		

Exp = Exposure, LEC/HIC = lowest effective concentration/highest ineffective concentration, ND = not done, NR = not reported, RTG = relative total growth, SD = standard deviation.

\* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ . NR = not reported, + = positive, (+) = weak positive, - = negative.

<sup>a</sup>To facilitate comparison with other studies, data reported by authors as µM or ppm were converted to µg/mL by NTP.

<sup>b</sup>Values read from figures; to facilitate comparison with other studies, data reported by authors as 220 and 140 µM were converted to µg/mL by NTP.

<sup>c</sup>Values read from figure.

[To return to text citing Table E-3, click here.](#)

**Table E-4. *In vitro* studies of adducts in mammalian cells (or DNA) treated with pentachlorophenol**

Reference	Effect	Test system	Concentration µg/mL (LEC or HIC)	Cytotoxicity	Results		Evaluation: limitations and conclusions
					-S9	+S9	
Witte <i>et al.</i> 1985	DNA adducts	Calf thymus DNA	10 mM		-		Negative. Data not shown.
Dubois <i>et al.</i> 1997	DNA adducts (covalent binding to DNA)	Fetal quail and fetal rat hepatocytes  Human hepatoma (HepG2) cells	13.3 <sup>a</sup>		+ (10 adducts identified in three cell types)	NT	Positive. Purity 99% Tested with single dose. One adduct was dominant in rat hepatocytes and Hep G2 cells (50 and 47% of total, respectively); quail cells had a different major adduct (46%); some adducts were specific to cell type, others were found in all types.
Dai <i>et al.</i> 2003	DNA adducts (covalent binding to dG, deoxyguanosine)	Excess dG (2 mM)	26.6 <sup>a</sup>	NR	+ O-bonded C8-dG adduct	-	Positive. Treatment with horseradish peroxidase or myeloperoxidase (from human lymphocytes) in presence of excess dG.
Dai <i>et al.</i> 2005	DNA adducts (covalent binding to DNA)	Calf thymus DNA (1 mg/mL)	26.6 <sup>a</sup>	NR	+ O-bonded C8-dG adduct	NT	Positive. Treatment with horseradish peroxidase
Van Ommen <i>et al.</i> 1986b	DNA adducts	Calf thymus DNA	26.6 <sup>a</sup>		+ Microsomal DNA adduct: 12pmol/mg DA/min		Covalent binding to DNA was less than for protein.
	Protein adducts	Microsomal protein from induced male and female Wistar rat liver	26.6 <sup>a</sup>		+ Microsomal protein adduct: 63 pmol/mg/protein/min		Formed 1,4- and 1,2- tetrachloro- <i>p</i> -hydroquinone

<sup>a</sup>To facilitate comparison with other studies, data reported by authors as µM or ppm were converted to µg/mL by NTP. [Return to text citing Table E-4.](#)

**Table E-5. *In vivo* studies of adducts in rodents exposed to pentachlorophenol**

Reference	Endpoint (cell type)	Species/sex/ # in dose group	Exposure	Results	Evaluation: limitations and conclusions
Sai-Kato <i>et al.</i> 1995	DNA adducts (liver, kidney and spleen)	Mouse (B6C3F <sub>1</sub> ) male/5	Treatment by gavage; 30, 60 or 80 mg/kg (daily) for one or five days	+ 8-OH-dG levels for single and repeat doses significantly increased over controls in liver	Positive. Purity 98.6% Increase only in liver, not in kidney or spleen. Effects are blocked by pre-treatment with antioxidants vitamin E and diallyl sulfide.
Umemura <i>et al.</i> 1996	DNA adducts (liver)	Mouse (B6C3F <sub>1</sub> ) male/5	Treatment in food; 0.03, 0.06, 0.12% for 2 or 4 weeks	+ 8-OH-dG levels significantly increased over controls (both time- and dose-dependent)	Positive. Purity 98.6%. BrdU labeling index and hepatic DNA content (hyper-proliferation) were also elevated; may be involved in carcinogenesis.
Umemura <i>et al.</i> 1999	DNA adducts (liver)	Mouse (B6C3F <sub>1</sub> ) male/5	Treatment in food; 600 or 1200 ppm for 8 weeks	+ 8-OH-dG levels significantly increased over controls (dose dependent).	Positive. Purity 98.6%. Cell proliferation increased in a treatment dose-dependent manner.
Lin <i>et al.</i> 2002	DNA adducts (liver)	Rat (F344) male/3-4	Treatment by gavage; 30, 60 or 120 mg/kg (x1 day) or 30 or 60 mg/kg (x5 days); dietary 60 mg/kg-day 27-wk treatment	+ 27-wk treatment increased 8-OH-dG 2x over controls; negative other treatments	Positive. Adduct may be derived from TCpBQ (metabolite of pentachlorophenol).
Tasaki <i>et al.</i> 2012	DNA adducts (liver)	Mouse C57BL/6 p53 (+/+ and -/-) male/5	Treatment in food; 600 or 1200 ppm, 13 weeks.	+ Significant elevations of 8-OHdG levels for both genotypes.	Positive.
Tsai <i>et al.</i> 2002	Protein adducts	Sprague-Dawley rats/male/3 and B6C3F <sub>1</sub> mice/male/3	Treatment by gavage; 20 mg/kg bw	+ Radiolabel binding (% of total) Protein    Rat    Mouse Np        97.9    100 Cp        67.0    100* Alb        1.3     2.63*	Positive Purity >98%. Three protein solutions: liver nuclei (Np), liver cytosol (Cp) and albumin (Alb); covalent binding with cysteinyl adducts; mice metabolized 5x more than rats.

[To return to text citing Table E-5, click here.](#)

**Table E-6. *In vivo* studies of cytogenetic effects of pentachlorophenol in rodents**

Reference	Endpoint (cell type)	Species/sex/#	Exposure	Results	Evaluation: limitations and conclusions
Fahrig <i>et al.</i> 1978	Mouse spot test - mutation/recombination	Mouse C57BL/6JHan x T-stock	Treatment i.p. 50 mg/mL	(+)	Weakly positive. Purity 99% Tested 50 and 100 mg/kg. Although limited to small numbers of offspring in study, considered a weak positive.
Xu 1996, as cited by EPA 2010	Micronuclei (bone marrow)	Mouse (CD-1)/ male and female/NR	Treatment by gavage: males 24, 60, 120 mg/kg; females 10, 50, 100 mg/kg	–	Negative. Unpublished report reviewed by EPA 2010; information is limited to that provided in review; purity 88.9%; number animals not given. No increase in micronuclei frequency was reported.
NTP 1999	Micronuclei (bone marrow)	Mouse (B6C3F <sub>1</sub> ) male/5 per dose group	Treatment i.p. 50, 100, 150 mg/kg (3x at 24-hr intervals)	– MN-PCEs/1000 Dose #Mice Mean ±SE 0 5 2.2±0.3 50 3 1.0±0.0 100 3 2.0±0.8	Negative. Purity 99% Corn oil control; high dose 150 mg/kg lethal. 2000 polychromatic erythrocytes (PCEs) scored No increased micronucleated PCEs in treated animals.
		Rat (F344/N)/ male/5 per dose group	Treatment i.p. 25, 50, 75 mg/kg (3x at 24-hr intervals)	– MN-PCEs/1000 Dose #Rats Mean ±SE 0 5 0.8±0.3 25 4 0.8±0.3 50 5 1.5±0.4	Negative. Purity 99% Corn oil control; high dose 75 mg/kg lethal. No increase in micronucleated polychromatic erythrocytes (PCEs) in treated animals.
Daimon <i>et al.</i> 1997	Chromosomal aberrations (hepatocytes)	Rat (F344/Du Crj)/ male/5 per dose group	Treatment i.p. 10 mg/kg bw (repeated x5 days)	– Cells with aberrations (%) Control 2 <sup>a</sup> Treated 1.2	Negative. Only one treatment dose, repeated 5 days. Evaluated 100 metaphase cells/animal. No increase in chromosome aberrations over controls.
	Sister chromatid exchange (hepatocytes)	Rat (F344/Du Crj)/ male/5 per dose group	Treatment i.p. 10 mg/kg bw	+ SCE/chromosome Control 0.59 Treated 0.71*	Positive. Only one treatment dose. Scored 25 second-division metaphase cells/animal. Treated had significant ( <i>P</i> < 0.01) SCE induction.

Reference	Endpoint (cell type)	Species/sex/#	Exposure	Results	Evaluation: limitations and conclusions
Tasaki <i>et al.</i> 2012	mRNA levels	Mouse C57BL/6 p53 <sup>(+/+)</sup> and <sup>(-/-)</sup> and male/5 per dose group	Treatment in diet 600 or 1200 ppm, 13 weeks.	+ Significant decrease in CYP 2B10 in p53 <sup>-/-</sup> and increase in NQO1 mRNA levels for both genotypes	Positive. No effect on CYP1A1 or 1A2
Monteith 1992	Unscheduled DNA repair (UDS)	Rats 3 control 2 treated (sex not reported)	Treatment i.p.; 10 mg/kg pentachlorophenol dissolved in propane-1,2-diol	+ Net grains/ nucleus ( $\pm$ SD) Control 0.07 $\pm$ 1.96 Treated 3.30 $\pm$ 4.13***	Positive. Purity 99% Significant increase for treated over control. Only tested one dose.

<sup>a</sup>Value estimated from figure.

\*\*\* $P < 0.001$  ( $t$ -test)

[To return to text citing Table E-6, click here.](#)

**Table E-7. *In vivo* studies of chromosomal aberrations (CA) in lymphocytes from workers occupationally exposed to pentachlorophenol**

Reference (location)	Study population (yrs employed)	Number of subjects	PCP exposure Mean (range)			Results Mean (range) Exposure response	Evaluation: limitations and conclusions
			Air ( $\mu\text{g}/\text{m}^3$ )	Blood serum ( $\mu\text{g}/\text{L}$ )	Urine ( $\mu\text{g}/\text{L}$ )		
Wyllie <i>et al.</i> 1975 <sup>a</sup>  (Idaho, USA)	Wood treatment plant workers, overlapping job duties. (2–11 years)	Exposed 6  Controls 4	0.263–1.89	1,372.1 (348.4–3,963.0)  47.7 (38.0–68.0)	163.8 (41.3–760)  3.4 (2.6–4.3)	– (% Cells with chromosome breaks)  1.1 (0.6–6.0)  0 (0–0.1)	Negative  Unmatched controls but similar age range; gender not identified.  Workers potentially exposed to other substances, smoking and other lifestyle variables not considered.  Cell harvest 48 h; methods indicate 25 cells scored, but data provided as % for 150 cells; very small sample size.  Serum exposure based on monthly assessment for workers during 5-month study Jan-May, but May-Oct has highest production; air exposure values are levels measured monthly at 11 sites.  Non-statistically significant increase in chromosome aberrations; information was provided on gaps but not considered in analysis.  Deficiencies in reporting (missing data and calculation errors); stated there four control workers, but serum and urine measurement data only provided for one.  Statistics: not specified.
Bauchinger <i>et al.</i> 1982 <sup>b</sup>  (West Germany)  [same study]	PCP-producing factory, male workers (1–30 yr)  Controls	Exposed 22 (handled PCP (14) or Na-PCP (8))  Controls	< 100–> 500	PCP workers: 4,730  Na-PCP workers: 2,230	2,380  840	+  <i>Exposed</i> S-cells (%) 1.02***  <u>Types of CA</u> Chromatid  0.0020	Positive.  Matched controls, all subjects male.  Workers not exposed to other industrial chemicals; 14 workers were sacking PCP and 8 were sacking Na-PCP; all 22 exposed workers and 9/22 of control subjects were smokers. Results are for

Reference (location)	Study population (yrs employed)	Number of subjects	PCP exposure Mean (range)			Results Mean (range) Exposure response	Evaluation: limitations and conclusions
			Air ( $\mu\text{g}/\text{m}^3$ )	Blood serum ( $\mu\text{g}/\text{L}$ )	Urine ( $\mu\text{g}/\text{L}$ )		
as reported by Schmid <i>et al.</i> 1982]	included 9 smokers and 13 non-smokers.	22 (workers with no known exposure)				0.0028 breaks Chromatid 0.0005 0.0008 exchange Acentric 0.0022 0.0057* fragments Dicentrics 0.0005 0.0016*	all 44 workers. Cell harvest 44 hr, 300 cells scored for exposed and 500 for controls. Structural chromosome changes (S-cells): dicentrics and acentric fragments were increased in the exposed group, compared with all controls or compared with only smokers in controls. No increase in chromatid-type aberrations (breaks and exchanges) or gap frequency due to exposure. Statistics: Mann-Whitney rank <i>U</i> test.
Ziensen <i>et al.</i> 1987  (West Germany)	Wood preservative production plant, two groups of workers <sup>d</sup> <i>Group 1:</i> Low exposure (6 to 34 yr) <i>Group 2:</i> High exposure (3 to 23 yr)	Group 1: 9  Group 2: 11	All workers: 1.2 to 180	Group 1: 23 to 116  Group 2: 59 to 775	ND	–	Negative. Workers in two groups, low and high exposure, based on main type of exposure; gender not identified. Occupational history examined for other chemical exposure. Cell harvest time not indicated; scored 100 metaphases per subject. No effect of PCP exposure on CA frequency for all workers, for groups, or for smokers (14) vs. non-smokers (6). Individual data reported; types of CAs and total number of cells analyzed were reported for each worker but number of cells with aberrations was not, thus the % of cells with CAs cannot be calculated. Statistics: $\chi^2$ test.

\* $P < 0.05$  \*\*, \*\*\* $P < 0.005$ .

ND = not determined, NR = not reported.

<sup>a</sup>To facilitate comparison with other studies, data reported by these authors as  $\text{ng}/\text{m}^3$  and ppb were converted to  $\mu\text{g}/\text{m}^3$  and  $\mu\text{g}/\text{L}$  respectively.

<sup>b</sup>To facilitate comparison with other studies, air exposure data reported by these authors as  $\text{mg}/\text{m}^3$  were converted to  $\mu\text{g}/\text{m}^3$ .

<sup>c</sup>Chromosomal aberrations as measured by number of chromosome breaks.

<sup>d</sup>Group 1 transported and weighed raw material – inhalation of dry dust, 96% pure, and technical water soluble Na-PCP, 85% pure; Group 2 handled finished PCP solutions.

[To return to text citing Table E-7, click here.](#)

**Table E-8. *In vivo* studies of sister chromatid exchange (SCE) in lymphocytes from workers occupationally exposed to pentachlorophenol**

Reference (location)	Study population (yrs employed)	Number of subjects	PCP exposure Mean (range)			Results SCE/cell: Mean ± SE (range)	Comments		
			Air (µg/m <sup>3</sup> )	Blood serum (µg/L)	Urine (µg/L)				
Bauchinger <i>et al.</i> 1982 <sup>a</sup> (West Germany)  [same study as reported by Schmid <i>et al.</i> 1982]	PCP-producing factory, male workers (1-30 yr)  Controls included 9 smokers and 13 non-smokers.	Exposed (22)	~100– 500	PCP workers: 4,730	2,380	Exposed (22) 9.41±0.35 (6.68-12.8)	Negative. Matched controls, all subjects male. Workers not exposed to other industrial chemicals; all exposed workers and 9/22 of control subjects were smokers. Cultured 54 h; 50 M <sub>2</sub> cells scored/individual. Workers were not exposed to other industrial chemicals, but all exposed workers and 9/22 of control subjects were smokers. Exposed workers had significantly higher SCE values when compared with all controls, but there was no effect when exposed workers were compared with control group smokers only; the control group smokers also had a significant higher incidence of SCEs. Thus these SCE effects are attributable to smoking, not PCP exposure. Statistics: Mann-Whitney U-test.		
		Controls (All 22)		Na-PCP workers: 2230				840	8.13±0.26
		Controls (9 smokers)							8.89±1.24
		Controls (13 non- smokers)				7.60±0.95			

Reference (location)	Study population (yrs employed)	Number of subjects	PCP exposure Mean (range)			Results SCE/cell: Mean ± SE (range)	Comments
			Air (µg/m <sup>3</sup> )	Blood serum (µg/L)	Urine (µg/L)		
Ziemsens <i>et al.</i> 1987  (West Germany)	Wood preservative production plant, two groups of workers <sup>d</sup> <i>Group 1</i> : Low exposure (6 to 34 yr) <i>Group 2</i> : High exposure (3 to 23 yr)	Group 1: 9  Group 2: 11	All workers: 1.2 to 180	23 to 116  59 to 775	ND	– 7.49±0.8 <sup>e</sup> (6.40-8.97)  7.65±1.37 <sup>e</sup> (5.63-10.00)	Workers in two groups, low and high exposure, based on predominant type of exposure; gender not identified. Occupational history examined for other chemical exposure. Cultured 72 hrs; scored 60 metaphases per subject. No correlation between SCE frequency and any exposure index. No effect of smoking on SCE (6 non-smokers vs. 14 smokers). Means of two groups were not statistically different. Statistics: Student's <i>t</i> -test.

NR = not reported; ND = not determined.

<sup>a</sup>To facilitate comparison with other studies, air exposure data reported by these authors as mg/m<sup>3</sup> were converted to µg/m<sup>3</sup>.

<sup>b</sup>Group 1 transported and weighed raw material – inhalation of dry dust, 96% pure, and technical water soluble Na-PCP, 85% pure; Group 2 handled finished PCP solutions.

<sup>c</sup>Means and SDs in results for Ziemsens *et al.* were calculated by NTP from data provided in publication.

[To return to text citing Table E-8, click here.](#)

**Table E-9. Summary of *in vitro* and *in vivo* studies of pentachlorophenol metabolites**

Test System	Effect	Tetrachloro- <i>p</i> -hydroquinone	Tetrachloro-catechol	Tetrachloro- <i>p</i> - or - <i>o</i> -benzoquinone
<b><i>In vitro</i></b>				
Mammalian cells (non-human)	Mutation	+ <sup>a</sup>	- <sup>b</sup>	
	DNA damage	+	- <sup>b</sup>	+
	DNA adducts	+ <sup>c</sup>		+ <sup>c</sup>
Human cells	DNA damage	+	+ <sup>d</sup>	+ <sup>d</sup>
	DNA adducts			
<b><i>In vivo</i></b>				
Mammals	DNA adducts	+ <sup>d</sup>		

Sources: EPA 2010, IARC 1999.

+ = Positive in all or most of available studies; +/- positive and negative studies; - = negative in all or most of available studies.

<sup>a</sup>Positive at HPRT, but not Na/K-ATPase, locus.

<sup>b</sup>Tested in V79 cells without metabolic activation.

<sup>c</sup>Calf thymus DNA.

<sup>d</sup>Result based on one study.

[To return to text citing Table E-9, click here.](#)

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## Appendix F: Mechanistic Data for By-products of Pentachlorophenol Production

**Table F-1. Results of analyses for by-products in pentachlorophenol**

Impurity	Mice (TR 349 NTP 1989)		Rats (TR 483 NTP 1999)
	Technical Grade	Dowicide EC-7	Pure
Dichlorophenol*	--	--	NR
Trichlorophenol (TCP) *	0.01%	0.007%	NR
Tetrachlorophenol *	3.8%	9.4%	NR
Hexachlorobenzene (HCB)	50 ppm	65 ppm	113.3 ppm
Tetrachlorodibenzodioxin (TCDD)	--	< 0.04 ppm	--
Hexachlorodibenzodioxin (HxCDD)	10.1 ppm	0.19 ppm	--
Heptachlorodibenzodioxin (HpCDD)	296 ppm	0.53 ppm	0.03 ppm
Octachlorodibenzodioxin (OCDD)	1,386 ppm	0.69 ppm	≥ 0.32 ppm
Pentachlorodibenzofuran (PeCDF)	1.4 ppm	--	--
Hexachlorodibenzofuran (HxCDF)	9.9 ppm	0.13 ppm	--
Heptachlorodibenzofuran (HoCDF)	88 ppm	0.15 ppm	--
Octachlorodibenzofuran (OCDF)	43 ppm	--	≥ 0.10 ppm
Heptachlorohydroxydiphenyl ether	0.11%	--	NR
Octachlorohydroxydiphenyl ether	1.91%	--	NR
Nonachlorohydroxydiphenyl ether	3.56%	--	NR
Hexachlorohydroxydibenzofuran	0.16%	--	NR
Heptachlorohydroxydibenzofuran	0.47%	--	NR
Pentachlorodibenzodioxin (PeCDD)	NR	NR	--
Tetrachlorodibenzofuran (TCDF)	NR	NR	--
Pentachlorobenzene (PCB)	NR	NR	17.0 ppm
Not quantitated	--	--	--

Sources: 1) Pentachlorophenol, NTP-TR 349 (NTP 1989), 2) Pentachlorophenol, NTP-TR 483 (NTP 1999)

Notes: 1) McConnell *et al.* 1991 reported impurities similar to those shown above for technical grade and Dowicide EC-7 in NTP-TR 349 (NTP 1989).

2) NR = not reported; \* also metabolite of PCP; -- below detection limit.

3) This analysis is on the obtained chemicals and not on the food preparations.

[To return to text citing Table F-1, click here.](#)

**Table F-2a. Comparison of liver neoplasm percent incidences in 2,4,6-trichlorophenol (2,4,6-TCP) (NCI 1979) studies in male B6C3F<sub>1</sub> mice**

2,4,6-TCP (in feed for 105 weeks)			
Dose, ppm	Incidence of Liver Tumors (%)		
	Adenoma	Carcinoma	Combined
vehicle control	3/20 (15)	1/20 (5)	4/20 (20)
5,000	22/49 (45) <sup>a*</sup>	10/49 (20)	32/49 (65) <sup>***</sup>
10,000	32/47 (68) <sup>****</sup>	7/47 (15)	39/47 (83) <sup>***</sup>
Trend	N.R.	N.S.	$P < 0.001$

N.R. = not reported; N.S. = not significant.

\* $P \leq 0.05$ , \*\*\* $P \leq 0.001$ .

<sup>a</sup> $P$  value calculated by Fisher's exact test by RoC Group.

**Table F-2b. Comparison of liver neoplasm percent incidences in hexachlorobenzene (HCB) (Cabral *et al.* 1977) studies in male Swiss mice**

HCB (in feed for 101–120 weeks)	
ppm in feed	Incidence of Liver-Cell Tumors <sup>a</sup> (%)
vehicle control	0/47 (0)
50	0/30 (0)
100	3/29 (10)
200	7/44 (16) <sup>**</sup>
300 <sup>b</sup>	1/16 (6)
Trend	$P = 0.0053$

<sup>a</sup>Effective number of mice based on number of survivors at moment of appearance of first tumor (of any type) in each group.

<sup>b</sup>Mice exposed to 300 ppm for 15 weeks only.

<sup>c</sup> $P$  values calculated by Fisher's exact test by RoC Group and trend by the Cochran-Armitage trend test by NTP.

\*\* $P \leq 0.01$ .

**Table F-2c. Comparison of liver neoplasm percent incidences in hexachloro-*p*-dibenzodioxin<sup>a</sup> (HCDD) (NTP 1980) studies in male B6C3F<sub>1</sub> mice**

HCDD (gavage 2x per week for 104 weeks)			
Dose, $\mu\text{g}/\text{kg}/\text{wk}$	Incidence of Liver Tumors (%)		
	Adenoma	Carcinoma	Combined
vehicle control	7/73 (10)	8/73 (11)	15/73 (21)
1.25	5/50 (10)	9/50 (18)	14/50 (28)
2.5	9/49 (18)	5/49 (10)	14/49 (29)
5.0	15/48 (31) <sup>**</sup>	9/48 (19)	24/48 (50) <sup>***</sup>
Trend	$P = 0.001$	N.S.	$P = 0.001$

\*\* $P \leq 0.01$ , \*\*\* $P \leq 0.001$ .

<sup>a</sup>Mixture of 1,2,3,7,8,9- and 1,2,3,6,7,8-HxCDD.

[To return to text citing Tables F2a-F2c, click here.](#)

**Table F-3a. Comparison of liver neoplasm incidences in male B6C3F<sub>1</sub> mice in the hexachlorodibenzo-*p*-dioxin studies (NTP 1980) and in the pentachlorophenol studies (NTP 1989)**

HxCDD (gavage)		Technical Grade PCP (feed)			Dowicide EC-7 (feed)		
Dose of HxCDD (ug/kg/wk)	Percent incidence of liver tumors	Technical-grade PCP ppm	Dose of HxCDD (ug/kg/wk)	Percent incidence of liver tumors	EC-7 ppm	Dose of HxCDD (ug/kg/wk)	Percent incidence of liver tumors
0.0	21	0	0	22	0	0.000	17
1.25	28	100	0.77	55	100	0.014	40
2.50	28	200	1.54	77	200	0.028	44
5.00	50	---	---	---	600	0.070	69

**Male mice food consumption at PCP high dose**

*Technical grade:* 35 mg PCP/kg bw/d in feed (200 ppm)

*Dowicide EC-7:* 118 mg PCP/kg bw/d (600 ppm)

**Hepatocellular Carcinoma TCDD, male mice gavage (TR 209). See Table F-4a.**

**Table F-3b. TEF Values of Compounds**

Compound	Formula	TEF
Tetrachlorodibenzodioxin	2,3,7,8-TCDD	1
Hexachlorodibenzodioxin	1,2,3,4,7,8-HxCDD	0.1
	1,2,3,6,7,8-HxCDD	0.1
	1,2,3,7,8,9-HxCDD	0.1
Heptachlorodibenzodioxin	1,2,3,4,6,7,8-HpCDD	0.01
Octachlorodibenzodioxin	OCDD	0.0003
Pentachlorodibenzodioxin	1,2,3,7,8-PeCDD	1
Tetrachlorodibenzofuran	2,3,7,8-TCDF	0.1
Pentachlorodibenzofuran	1,2,3,7,8-PeCDF	0.03
	2,3,4,7,8-PeCDF	0.3
Hexachlorodibenzofuran	1,2,3,4,7,8-HxCDF	0.1
	1,2,3,6,7,8-HxCDF	0.1
	1,2,3,7,8,9-HxCDF	0.1
	2,3,4,6,7,8-HxCDF	0.1
Heptachlorodibenzofuran	1,2,3,4,6,7,8-HpCDF	0.01
	1,2,3,4,7,8,9-HpCDF	0.01
Octachlorodibenzofuran	OCDF	0.0003

Source: Van den Berg *et al.* 2006

[To return to text citing Tables F-3a and F-3b, click here.](#)

**Table F-3c. Exposure of male mice to by-products with TEFs in 2-yr PCP feed studies\* (worst case, high dose)**

Impurity	TEF**	Technical Grade		Dowicide EC-7	
		Dose µg/kgbw/d @ 200 mg/kgfd	TEQ/ kgbw/d	Dose µg/kg/d @ 600 mg/kg	TEQ/kgb wt/d
Tetrachlorodibenzodioxin	---	--	--	--	--
Hexachlorodibenzodioxin	0.1	0.23	0.023	0.01	0.001
Heptachlorodibenzodioxin	0.01	6.7	0.067	0.04	0.0004
Octachlorodibenzodioxin	0.0003	31	0.0093	0.05	0.000015
Pentachlorodibenzofuran	0.3	0.03	0.009	--	--
Hexachlorodibenzofuran	0.1	0.24	0.024	0.009	0.0009
Heptachlorodibenzofuran	0.01	2.0	0.020	0.01	0.0001
Octachlorodibenzofuran	0.0003	1.0	0.0003	--	--
Pentachlorodibenzodioxin	1	NR	--	NR	--
Tetrachlorodibenzofuran	0.1	NR	--	NR	--
Sum of TEQs		--	0.1526 µg TEQ/kg bwt/d		0.002415 µg TEQ/kg bwt/d

[To return to text citing Table F-3c, click here.](#)

See TR 349 Table 23 pages 66-67.

\*\* Van den Berg *et al.* 2006; \* the dose in feed of each chemical per kg body weight per day for males and females was reported in TR 349; below level of detection.

**Table F-3d. Exposure of female mice to by-products with TEFs in 2-yr PCP feed studies\* (worst case, high dose)**

Impurity	TEF**	Technical Grade		Dowicide EC-7	
		Dose (µg/kg/d) @ 200 mg/kg	TEQ/kg bwt/d	Dose (µg/kg/d) @ 600 mg/kg	TEQ/kgbwt/d
Tetrachlorodibenzodioxin	---	--	--	--	--
Hexachlorodibenzodioxin	0.1	0.22	0.022	0.01	0.001
Heptachlorodibenzodioxin	0.01	6.5	0.065	0.03	0.0003
Octachlorodibenzodioxin	0.0003	31	0.0093	0.05	0.000015
Pentachlorodibenzofuran	0.3	0.03	0.009	--	--
Hexachlorodibenzofuran	0.1	0.22	0.022	0.008	0.0008
Heptachlorodibenzofuran	0.01	1.9	0.019	0.01	0.0001
Octachlorodibenzofuran	0.0003	1.0	0.0003	--	--
Pentachlorodibenzodioxin	1	NR	--	NR	--

Impurity	TEF**	Technical Grade		Dowicide EC-7	
		Dose ( $\mu\text{g}/\text{kg}/\text{d}$ ) @ 200 mg/kg	TEQ/kg bwt/d	Dose ( $\mu\text{g}/\text{kg}/\text{d}$ ) @ 600 mg/kg	TEQ/kgbwt/d
Tetrachlorodibenzofuran	0.1	NR	--	NR	--
Sum of TEQs		--	0.1466 $\mu\text{g}/\text{kg}/\text{d}$	--	0.00221 $\mu\text{g}/\text{kg}/\text{d}$

[To return to text citing Table F-3d, click here.](#)

See TR 349 Table 23 pages 66–67.

\*\* Van den Berg *et al.* 2006; \* The dose in feed of each chemical per kg body weight per day was reported in TR 349; --- below level of detection.

#### Female mice food consumption at PCP high dose

*Technical grade:* 35 mg PCP/kgbwt/d in feed (200 ppm)

*Dowicide EC-7:* 114 mg PCP/kgbwt/d (600 ppm)

#### Hepatocellular Carcinoma TCDD, female mice gavage (TR 209) See Table F-4b.

**Table F-4a. Comparison of liver neoplasm percent incidences in PCP (NTP 1989) and in TCDD (NTP 1982) studies in male B6C3F<sub>1</sub> mice**

TCDD (gavage twice a week)			
Dose $\mu\text{g}/\text{kg}/\text{wk}$	Incidence of Liver Tumors (%)		
	Adenoma	Carcinoma	Combined
vehicle control	7/73(10)	8/73(11)	15/73(21)
0.01	3/49(6)	9/49(18)	12/49(24)
0.05	5/49(10)	8/4 (16)	13/49(27)
0.5	10/50(20)	17/50(34) <sup>^^</sup>	27/50(54) <sup>^^^</sup>
Trend	$P \leq 0.05$	$P \leq 0.01$	$P \leq 0.001$

Technical-Grade PCP (feed)				
ppm* In Feed	TEQ*** $\mu\text{g}/\text{kg}/\text{wk}$	Incidence of Liver Tumors (%)		
		Adenoma	Carcinoma	Combined
0	---	5/32 (16)	2/32 (6%)	7/32 (22)
100	0.534	20/47 (43) <sup>^^</sup>	10/47 (21)	26/47 (55) <sup>^^</sup>
200	1.068	33/48 (69) <sup>^^^</sup>	12/48(25) <sup>^</sup>	37/48 (77) <sup>^^^</sup>
Trend		$P \leq 0.001$	$P \leq 0.05$	$P \leq 0.001$

Dowicide EC-7 (feed)				
ppm** in Feed	TEQ*** µg/kg/wk	Incidence of Liver Tumors (%)		
		Adenoma	Carcinoma	Combined
0	---	5/35 (14%)	1/35 (3)	6/35 (17)
100	0.0028	13/48 (27)	7/48 (15)	19/48 (40)^
200	0.0056	17/48 (35)^	7/48 (15)	21/48 (44)^^
600	0.0169	32/49 (65)^^^	9/49 (18)^	34/49 (69)^^^
Trend		$P \leq 0.001$		$P \leq 0.001$

\*Technical grade PCP: 100 ppm = 17; 200 ppm = 35 mg/kg bw/d.

\*\*Dowicide EC-7: 100 ppm = 19.8; 200 ppm = 37; 600 ppm = 118 mg/kg bw/d.

\*\*\*To obtain these TEQ values: Table 3b (males) and 3c (females) calculated these values for the high dose (200 ppm for technical grade, 600 ppm for EC-7). This value was multiplied by 7 to obtain µg/kg/wk for the high doses, then reduced based on relative amount in feed for the other exposures.

See TR-349 Table F3 page 231; ^^^ $P < 0.001$ , ^^  $P < 0.01$ , ^  $P < 0.05$ .

[To return to text citing Table F-4a, click here.](#)

**Table F-4b. Comparison of liver neoplasm percent incidences in PCP (NTP 1989) and in TCDD (NTP 1982) studies in female B6C3F<sub>1</sub> mice**

TCDD (gavage twice a week)			
Dose µg/kg/wk	Incidence of Liver Tumors (%)		
	Adenoma	Carcinoma	Combined
vehicle control	2/73 (3)	1/73 (1)	3/73 (4)
0.01	4/50 (8)	2/50 (4)	6/50 (12)
0.2	4/48 (8)	2/48 (4)	6/48 (13)
2.0	5/47 (11)	6/47 (13)^	11/47 (23)^^
Trend		$P \leq 0.01$	$P \leq 0.01$

Technical-Grade PCP (feed)				
ppm* In Feed	TEQ*** µg/kg/wk	Incidence of Liver Tumors (%)		
		Adenoma	Carcinoma	Combined
0	---	3/33	0/30	3/33
100	0.513	8/49	1/49	9/49
200	1.026	8/50	1/50	9/50

Dowicide EC-7 (feed)				
ppm** in Feed	TEQ*** µg/kg/wk	Incidence of Liver Tumors (%)		
		Adenoma	Carcinoma	Combined
0	---	1/34 (2)	0/34(0)	1/34
100	0.0026	3/50 (6)	1/50 (2)	4/50

<b>Dowicide EC-7 (feed)</b>				
<b>ppm** in Feed</b>	<b>TEQ*** μg/kg/wk</b>	<b>Incidence of Liver Tumors (%)</b>		
		<b>Adenoma</b>	<b>Carcinoma</b>	<b>Combined</b>
200	0.0052	6/49 (12)	0/49 (0)	6/49
600	0.0155	30/48 (63)	2/48 (4)	31/48 <sup>^^</sup>
Trend		$P \leq 0.001$		$P \leq 0.001$

\* Technical grade PCP: 100 ppm = 17; 200 ppm = 35 mg/kg bw/d.

\*\* Dowicide EC-7: 100 ppm = 17; 200 ppm = 34; 600 ppm = 114 mg/kg bw/d.

\*\*\*To obtain these TEQ values: Table 3b (males) and 3c (females) calculated these values for the high dose (200 ppm for technical grade, 600 ppm for EC-7). This value was multiplied by 7 to obtain μg/kg/wk for the high doses, then reduced based on relative amount in feed for the other exposures.

See TR 349 Table F4 page 231; <sup>^^^</sup> $P < 0.001$ , <sup>^^</sup> $P < 0.01$ , <sup>^</sup> $P < 0.05$ .

[To return to text citing Table F-4b, click here.](#)

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## Part 2

# Draft RoC Substance Profile

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## Pentachlorophenol and By-products of Its Synthesis

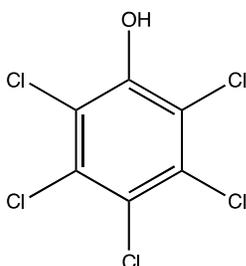
**CAS No. 87-86-5 (Pentachlorophenol)**

**CAS No. 131-52-2 (Pentachlorophenol, sodium salt)**

Known to be a human carcinogen

First listed in the *Thirteenth Report on Carcinogens* (2014)

Also known as Dowicide EC-7 (a registered trademark of Dow Chemical Company)



### Carcinogenicity

Pentachlorophenol and by-products of its synthesis are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans. This conclusion is supported by sufficient evidence of carcinogenicity from studies in experimental animals and mechanistic studies whose findings are consistent with the biological plausibility of its carcinogenicity in humans. Pentachlorophenol and by-products of its synthesis (hereinafter referred to collectively as “pentachlorophenol”) include higher chlorinated dioxins specified below, under Properties. Dioxin (specifically 2,3,7,8 tetrachlorodibenzo-*p*-dioxin) (Cogliano *et al.* 2011) has been linked to NHL in humans and thus dioxin-like activity may contribute to the carcinogenicity observed in the cancer studies of exposure to pentachlorophenol.

### Cancer Studies in Humans

Epidemiologic studies have demonstrated a causal relationship between exposure to pentachlorophenol and non-Hodgkin lymphoma (NHL) in humans. This conclusion is based on evaluation of two cohort studies and one nested case-control study of pentachlorophenol producers (Collins *et al.* 2009b, Ruder and Yiin 2011, and Kogevinas *et al.* 1995, respectively), one cohort study of sawmill workers exposed to pentachlorophenol as a wood preservative (Demers *et al.* 2006), and two population-based case-control studies (Hardell *et al.* 1994, 2002) with risk estimates specific for pentachlorophenol. The cohorts in the two studies of pentachlorophenol producers overlapped. The National Institute for Occupational Safety and Health (NIOSH) cohort study (Ruder and Yiin 2011) included workers at four U.S. production plants, and the second cohort study included workers at one of these four plants (the Michigan plant); independent analyses of the latter cohort were reported for two different follow-up periods by Ramlow *et al.* (1996) and Collins *et al.* (2009b). The largest and most informative study, the Canadian sawmill workers cohort study (Demers *et al.* 2006), included a detailed assessment of dermal exposure, reported on both mortality and

incidence, and had a sample size adequate to detect significant increases in NHL and other cancer end points.

Overall, there is credible evidence of an association between NHL and exposure to pentachlorophenol, based on consistent findings across studies in different occupational populations with differing co-exposures, in different geographical areas, and with different study designs, and on evidence of an exposure-response relationship. Increased risks of NHL were observed among workers exposed to pentachlorophenol in all of the studies specific for pentachlorophenol exposure. Although the strength of the evidence varied among the studies, the finding of increased risk of NHL in both cohort and case-control studies, which have different types of strengths and limitations, increases confidence in the body of studies. The strongest evidence comes from the Canadian sawmill cohort study, which found an exposure-duration response relationship, with risk of NHL incidence and mortality approximately doubled (Demers *et al.* 2006). This finding is supported by the observation of increased risk of NHL among pentachlorophenol workers in the Michigan production-plant cohort (Collins *et al.* 2009b). In the two follow-ups of that cohort, the highest risks of NHL or NHL and multiple myeloma combined mortality were observed among individuals with higher cumulative exposure or surrogates for exposure (e.g., measures of exposure to chlorinated dioxin by-products of pentachlorophenol synthesis). The evidence for an association from the other individual studies (Hardell *et al.* 1994, 2002, Kogevinas *et al.* 1995, Ruder and Yiin 2011) is considered to be more limited; however, these studies collectively support the associations found in the Canadian sawmill study and the Michigan production-plant study.

Overall, potential confounding from occupational or non-occupational co-exposures can reasonably be ruled out in the most informative studies and across the overall body of studies of NHL, although they cannot be ruled out in every individual study. The major occupational co-exposures in the cohort studies were to 2,4,5-trichlorophenol in the pentachlorophenol-producer studies (Collins *et al.* 2009b, Ruder and Yiin 2011) and tetrachlorophenol in the Canadian sawmill study (Demers *et al.* 2006). The risk of NHL was only slightly elevated among 2,4,5-trichlorophenol production workers at the Michigan plant (Collins *et al.* 2009a), and no clear exposure-response relationship was found between tetrachlorophenol exposure and NHL among the Canadian sawmill workers (Friesen *et al.* 2007). Therefore, potential confounding by co-exposure to these compounds can reasonably be ruled out. The U.S. pentachlorophenol-producer studies were potentially subject to confounding from exposure to other chemicals that are potential risk factors for NHL. There is some independent evidence of an association of phenoxy herbicide exposure with NHL. However, adjustment for co-exposures to phenoxy herbicides and other pesticides in one of the case-control studies (Hardell *et al.* 1994) did not substantially decrease the risk of NHL among mostly pentachlorophenol-exposed workers. Finally, although few studies investigated lifestyle risk factors, such as smoking or alcohol use, these have generally not been associated with NHL. There is also little *a priori* reason to assume that they are associated with pentachlorophenol exposure, and the use of internal analyses mitigates concern about uncontrolled confounding by these factors.

More limited evidence was found for positive associations between pentachlorophenol exposure and cancer at other tissue sites — specifically, multiple

myeloma, soft-tissue sarcoma, kidney cancer, and liver cancer. The most informative study, of the Canadian sawmill cohort (Demers *et al.* 2006), reported a strong positive association with multiple myeloma and a moderate association with kidney cancer. However, the statistical power to evaluate these cancers was limited in the other studies. In the Canadian sawmill cohort, no exposure-response relationships were observed for liver cancer or soft-tissue sarcoma. In contrast, a pooled analysis of population-based case-control studies found an increased risk of soft-tissue sarcoma (Hardell *et al.* 1995). Limitations in statistical power or exposure assessment may explain some study inconsistencies. The other case-control studies of soft-tissue sarcoma were not adequate to evaluate this end point.

### ***Cancer Studies in Experimental Animals***

There is sufficient evidence for the carcinogenicity of pentachlorophenol from studies in experimental animals, based on increased incidences of malignant tumors or combined incidences of benign and malignant tumors in rats and mice at several different tissue sites. Twelve studies were conducted in rats and mice, using different routes of exposure (dietary and dermal), different purities of pentachlorophenol (with different levels of chemical by-products of synthesis), and different study designs (two-year carcinogenesis bioassays, studies in transgenic mice, and mechanistic studies). These included four feeding studies in four different rat strains (Schwetz *et al.* 1978, Mirvish *et al.* 1991, Chhabra *et al.* 1999, NTP 1999), seven feeding studies in five different mouse strains (Innes *et al.* 1969, Boberg *et al.* 1983, Delclos *et al.* 1986, NTP 1989, McConnell *et al.* 1991), and a dermal-exposure study in mice (Spalding *et al.* 2000). The National Toxicology Program (NTP) two-year carcinogenicity studies in rats and mice (Chhabra *et al.* 1999, NTP 1989, 1999) were the most informative and were of high quality (the chemicals were assessed for purity, the numbers of animals on study and the durations of observation periods were adequate, and comprehensive histopathologic evaluations of tissues were conducted).

Increased incidences of malignant mesothelioma and nasal tumors (squamous-cell carcinoma) were observed in male F344 rats after dietary exposure to 99% pure pentachlorophenol for one year, followed by one year of observation (Chhabra *et al.* 1999, NTP 1999). The increase in squamous-cell carcinoma of the nose was not statistically significant, but was considered to be biologically significant, because these tumors are rare, and the tumor incidence exceeded the range for historical controls. Benign liver tumors (adenoma) were significantly increased in female MRC-W rats following dietary exposure to technical-grade pentachlorophenol (86% pure) containing 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD) and 2,3,7,8-tetrachlorodibenzofuran (2,3,7,8-TCDF) (Mirvish *et al.* 1991). These tumors were most likely caused by these contaminants, based on comparison of the results with those of studies of TCDD in experimental animals. In a two-year feeding study, Sprague-Dawley rats exposed to Dowicide EC-7 (~90% pure) showed no significant increases in tumor incidence (Schwetz *et al.* 1978); however, only total tumors were reported, there was no information on survival, and only a small number of animals were tested at doses lower than those that caused nasal and mesothelial tumors in rats.

Malignant and benign liver tumors (hepatocellular carcinoma and adenoma combined) were observed in male and female B6C3F<sub>1</sub> mice following dietary exposure to

either technical-grade pentachlorophenol (90.4% pure) or Dowicide EC-7 (~91% pure). The incidence of hepatocellular adenoma was significantly increased in both males and females exposed to both grades of chemical, and the incidence of hepatocellular carcinoma was significantly increased in males. Exposure to technical-grade pentachlorophenol, which had a higher total dioxin-like activity than Dowicide EC-7, resulted in a higher tumor incidence at the same exposure concentration, indicating that the dioxin-like by-products contributed to the carcinogenicity. The incidences of benign or combined benign and malignant adrenal-gland tumors (pheochromocytoma) and preneoplastic lesions (medullary hyperplasia) were significantly increased in male and female B6C3F<sub>1</sub> mice exposed to Dowicide EC-7. Incidences of malignant tumors of the blood vessels (hemangiosarcoma) of the spleen and/or liver were significantly increased in female B6C3F<sub>1</sub> mice exposed to technical-grade pentachlorophenol or Dowicide EC-7 (NTP 1989, McConnell *et al.* 1991).

Dermal exposure of transgenic female mice carrying an oncogenic mutation in the *v-Ha-ras* oncogene to 99% pure pentachlorophenol caused dose-related increases in the incidences and increased multiplicity of skin tumors (papilloma) (Spalding *et al.* 2000).

No exposure-related effects were observed in the other feeding studies in mice; however, these studies, which used different experimental designs than used in the NTP carcinogenesis studies, had some methodological limitations (Innes *et al.* 1969, Boberg *et al.* 1983, Delclos *et al.* 1986, Spalding *et al.* 2000).

### Studies on Mechanisms of Carcinogenesis

Although the mechanisms by which pentachlorophenol causes cancer are not fully understood, the available evidence suggests biologically plausible mechanisms in both experimental animals and humans. Proposed mechanisms include metabolism to genotoxic and mutagenic metabolites resulting in DNA damage and chromosome breakage, immunosuppression, and inhibition of apoptosis. Although little is known about the pathogenesis of NHL in humans, proposed mechanisms include immunosuppression and DNA damage (strand breaks).

Metabolism and toxicokinetic studies of pentachlorophenol show considerable variation among species, which may account for differences in the tissue sites at which cancer was reported in mice, rats, and humans. A primary metabolic pathway in rodents is oxidative and reductive dechlorination of pentachlorophenol leading to generation of potentially reactive metabolites (tetrachlorohydroquinones and semiquinones), followed by glucuronidation or sulfation. These metabolites and/or glucuronidated forms have been detected in the serum and urine of rodents. Limited information is available on metabolism of pentachlorophenol in humans. Primarily free and glucuronide-conjugated pentachlorophenol have been detected in urine; however, tetrachlorohydroquinone was identified in the urine of exposed workers (Ahlborg *et al.* 1974). Human liver microsomes have been shown to metabolize pentachlorophenol to tetrachlorohydroquinone (Juhl *et al.* 1985) and pentachlorophenol glucuronide *in vitro* (Lilienblum 1985).

Genotoxic effects of pentachlorophenol are most likely mediated by its metabolites, primarily tetrachlorohydroquinone, which is mutagenic, and tetrachlorobenzoquinone, which causes DNA damage and DNA adduct formation. These metabolites can generate reactive oxygen species through redox cycling. Metabolism can occur at other sites in

addition to the liver. A plausible mechanism for cancers of the white blood cells, such as NHL, lymphoma, and multiple myeloma, involves activation of pentachlorophenol by peroxidase or myeloperoxidase activity in lymphocytes and bone marrow. Peroxidases can metabolize pentachlorophenol to phenoxy free radicals, preferentially forming *O*-bonded C8-deoxyguanosine (C8-dG) DNA adducts at these sites, resulting in DNA damage. Pentachlorophenol caused adducts, mutations, DNA damage, and chromosomal aberrations *in vitro* under experimental conditions that included endogenous or exogenous mammalian metabolic activation. DNA adducts were found in primary cells exposed to pentachlorophenol and in the livers of rats and mice exposed to pentachlorophenol; the predominant adduct was the *O*-bonded C8-dG adduct. These results are supported by evidence of DNA strand breaks in human primary and cancer cell lines exposed to pentachlorophenol. Pentachlorophenol was not mutagenic or genotoxic without metabolic activation in most of the standard *in vitro* assays.

Immunosuppression is an established risk factor for NHL (Hardell and Eriksson 2003), as well as other cancers. Pentachlorophenol exposure specifically has been associated with cellular and humoral immunodeficiencies in humans. Studies in rodents indicate that the dioxin by-products (particularly the hexa- and hepta-substituted congeners) in the technical-grade formulations of pentachlorophenol are responsible for immunosuppression; however, there is sufficient evidence that pentachlorophenol itself is immunosuppressive in humans and other species.

Pentachlorophenol is an inhibitor of apoptosis, which may lead to accumulation of malignant cells. Inhibition of apoptosis also has been associated with tumor promotion, and interference with intercellular communication through gap junctions has been linked to the apoptotic process.

## Properties

### ***Pentachlorophenol and By-products of Its Production***

The listing is defined as pentachlorophenol and by-products of its synthesis because people who are exposed to pentachlorophenol are also exposed to products formed during its synthesis, and many of the cancer studies in experimental animals also involved co-exposures to these by-products. During production of pentachlorophenol, the elevated temperatures and pressures used in the production processes result in the formation of several additional chlorinated molecules. The concentrations of these by-products can be altered somewhat by changes in the conditions of the manufacturing process, but all commercial forms of pentachlorophenol contain by-products of its synthesis in detectable amounts. Pentachlorophenol has been produced in the United States only by direct chlorination of phenol (Williams 1982, ATSDR 2001, Ruder and Yiin 2011), but alkaline hydrolysis of hexachlorobenzene (HCB) might have been used in some instances in other countries (e.g., Europe or China) (Collins 2013, Dunn 2013).

Commonly found by-products of both synthesis processes are polychlorinated phenols (tetra- and tri-); HCB; hexa-, hepta-, and octachlorodibenzo-*p*-dioxins (HxCDD, HpCDD, and OCDD); and hexa-, hepta-, and octachlorodibenzofurans (Collins 2013, Dunn 2013). The alkaline hydrolysis of HCB to pentachlorophenol also results in formation of 2,3,7,8-TCDD; however, 2,3,7,8-TCDD has rarely been detected in commercial preparations of pentachlorophenol (IPCS 1987). Thus, the presence of TCDD

in a pentachlorophenol preparation is considered to be a contaminant rather than a by-product of synthesis.

Biomonitoring studies provide evidence that people who are exposed to pentachlorophenol or pentachlorophenol-containing products are always exposed to the combination of pentachlorophenol and its by-products of its synthesis. The pentachlorophenol by-products most commonly found in serum samples from exposed individuals are the dioxin congeners 1,2,3,6,7,8-HxCDD, 1,2,3,4,6,7,8-HpCDD, and OCDD (Collins *et al.* 2006, McLean *et al.* 2009a), which reflect the spectrum of by-products of synthesis found in pentachlorophenol. Levels of 2,3,7,8-TCDD in the same individuals differed little, if at all, from those observed in a non-exposed reference population (Collins *et al.* 2008). These specific by-products have been found consistently in serum samples from people exposed to pentachlorophenol in different geographical areas (e.g., the United States, New Zealand, and China), in different types of occupational settings (Päpke *et al.* 1992, Schecter *et al.* 1994, Smith and Lopipero 2001, Collins *et al.* 2006, 2007, 2008, McLean *et al.* 2009), and from the environment (Schecter *et al.* 1994, Dahlgren *et al.* 2007, Karouna-Renier *et al.* 2007). These same by-products have also been found in tissues and milk from cows and pigs exposed to pentachlorophenol-treated wood (Fries *et al.* 1999, 2002, Huwe *et al.* 2004).

### **Pentachlorophenol**

Pentachlorophenol is a chlorinated aromatic compound. Pure pentachlorophenol exists as light-tan to white needle-like crystals at room temperature. It is relatively volatile and practically insoluble in water at the pH generated by its dissociation ( $pK_a = 4.7$ ), but soluble in most organic solvents (IPCS 1987, NTP 1989). Salts of pentachlorophenol, such as sodium pentachlorophenate, are readily soluble in water. Technical-grade pentachlorophenol consists of brown flakes; technical-grade sodium pentachlorophenate consists of cream-colored beads. Physical and chemical properties of pentachlorophenol are listed in the following table.

<b>Property</b>	<b>Information</b>
Molecular weight	266.3 <sup>a</sup>
Density	1.978 g/cm <sup>3</sup> at 22°C <sup>a</sup>
Melting point	188°C <sup>a</sup>
Boiling point	310°C <sup>a</sup>
Log $K_{ow}$	5.12 <sup>a</sup>
Water solubility	14 mg/L at 25°C <sup>b</sup>
Vapor pressure (mm Hg)	0.0003 at 25°C <sup>a</sup>
Vapor density relative to air	1.98 <sup>a</sup>

Sources: <sup>a</sup>Akron 2013, <sup>b</sup>ChemIDplus 2013.

### **Use**

Pentachlorophenol was first used in the United States in 1936 as a wood preservative to prevent decay from fungal organisms and damage from insects. It also was used as a biocide and was found in ropes, paints, adhesives, leather, canvas, insulation, and brick

walls. Since 1984, pentachlorophenol has been regulated in the United States as a restricted-use pesticide (restricted to certified applicators) for the treatment of utility poles, cross arms, railroad ties, wooden pilings (e.g., wharf pilings), fence posts, and lumber or timbers for construction. Utility poles and cross arms account for about 92% of all uses of pentachlorophenol-treated lumber (ATSDR 2001, EPA 2010).

Pentachlorophenol has also been used in the laboratory as a competitive inhibitor of sulfotransferase (Mulder and Scholtens 1977), but this use would involve very small quantities of the substance.

## Production

Pentachlorophenol was listed by the U.S. Environmental Protection Agency (EPA) as a high-production-volume chemical in 2011, indicating that annual production exceeded 1 million pounds. In 2012, pentachlorophenol was reported to be manufactured by at least six companies worldwide, including at least one company in the United States (SRI 2012). No companies reported production activities in the United States in 2013, but one company in North America reported producing pentachlorophenol at a plant in Mexico and operating a formulation facility in the United States (Dunn 2013). Reported recent and historical volumes of U.S. production, imports, and exports of pentachlorophenol are listed in the following table.

Category	Year	Quantity (lb)
Production + imports <sup>a</sup>	2011	> 1 million to 10 million
U.S. imports: <sup>b</sup> recent	2012	14.6 million
historical	2007	0
U.S. exports: <sup>b</sup> recent	2012	99,000
historical	2007	697,000

Sources: <sup>a</sup>EPA 2013; EPA Chemical Data Reporting Rule, formerly the Inventory Update Rule. <sup>b</sup>USITC 2013.

## Exposure

A significant number of people living in the United States are or have been exposed to pentachlorophenol because of its widespread presence in the workplace and environment. Exposure has been documented by measurements of pentachlorophenol levels in blood and urine reflecting current exposure (e.g., Dahlgren *et al.* 2007, CDC 2013) and levels in tissues such as liver, brain, kidneys, spleen, and body fat that likely reflect long-term exposure (ATSDR 2001).

Occupational exposure to pentachlorophenol still occurs in the United States among workers who formulate pentachlorophenol for use, who treat lumber (such as fence posts, telephone poles and railroad ties), or who come in contact with treated lumber in their work activities. Exposure from treating lumber is primarily (~95%) through dermal contact (Fenske *et al.* 1987, Demers 2013). Wearing of protective equipment (e.g., gloves and aprons) in areas where pentachlorophenol is sprayed or where basic joinery occurs (e.g., construction of roof trusses or pallets) can help mitigate these exposures (Jones *et al.* 1986). Inhalation exposure to pentachlorophenol can also occur in occupational

settings where it is used; during pressure-treating of wood, for example, inhalation exposure can occur when the door to the pressure chamber is opened.

In the past, the most important route of exposure for pentachlorophenol-production workers was inhalation. Pentachlorophenol was found in air samples taken at four U.S. manufacturing plants between 1971 and 1983 as part of NIOSH Dioxin Registry. In addition, elevated levels of dioxin congeners (2 to 10 times the levels in unexposed workers), which are considered to be indicators of pentachlorophenol exposure, were found in the blood of former U.S. pentachlorophenol-production workers at least 20 years after last exposure (Collins *et al.* 2007, 2008). Elimination half-lives of up to 10 years have been reported for dioxin by-products of pentachlorophenol synthesis (McLean *et al.* 2009, Collins 2013).

Although the use of pentachlorophenol has been restricted since 1984, there is evidence that people in the United States continue to be exposed to pentachlorophenol and by-products of its synthesis in the environment. This evidence includes (1) elevated levels of chlorinated dioxins in the blood of people living near wood-treatment facilities and in the soil at their homes (Dahlgren *et al.* 2007), (2) detection of pentachlorophenol in the urine of preschool children and in samples of indoor and outdoor air and dust from their homes and daycare centers (Wilson *et al.* 2003, 2007), and (3) detection of pentachlorophenol in the urine of U.S. residents in the National Health and Nutrition Examination Survey (NHANES). In the most recent NHANES that reported results for pentachlorophenol (2003 to 2004), the 95th-percentile urinary levels were 4.58  $\mu\text{g/L}$  for men and 3.20  $\mu\text{g/L}$  for women (CDC 2013). Another potential source of human exposure to pentachlorophenol is metabolic transformation of other chlorinated compounds within the body (IPCS 1987). Chlorinated compounds whose metabolism can give rise to pentachlorophenol include hexachlorobenzene, pentachlorobenzene, pentachloronitrobenzene, pentachlorocyclohexene, and lindane and other hexachlorocyclohexanes.

Although environmental and urinary levels in recent studies are consistent with continuing exposure to pentachlorophenol for many individuals in the United States, these levels are generally lower than those three or four decades ago. Pentachlorophenol levels in the range of 10s to 100s of micrograms per liter in blood and generally around 10  $\mu\text{g/L}$  in urine were reported for people living in the United States in studies published from the late 1960s through the 1980s (Zheng *et al.* 2011). Levels were also higher in the 1976 to 1980 NHANES II, which detected pentachlorophenol in the urine of 71.6% of the general population, at geometric mean concentrations of 6.7 ng/mL ( $\mu\text{g/L}$ ) in males and 5.9 ng/mL in females (Kutz *et al.* 1992).

Exposure of the general population to pentachlorophenol was and is most likely to result from inhalation of air or from dietary or nondietary ingestion (e.g., in dust or soil). Dermal exposure also could occur. Exposure is primarily attributable to its release during production and, particularly, during its processing and use in treating wood products. Pentachlorophenol can also be released into the environment from treated wood.

According to the EPA's Toxics Release Inventory, on- and off-site environmental releases of pentachlorophenol from about 30 facilities in 2011 totalled slightly over 96,000 lb (TRI 2013), of which 92.9% was released to landfills, 6.3% to off-site disposal, 0.5% to water, and 0.3% to air. Pentachlorophenol can be transported over substantial distances (1,500 to 3,000 km [930 to 1,860 mi]), with a half-life in the environment of

approximately 1.5 months (Borysiewicz 2008). Pentachlorophenol has been detected in air samples at concentrations ranging from less than 1 ng/m<sup>3</sup> in rural settings to about five orders of magnitude higher in industrial settings where pentachlorophenol is manufactured or used, in homes near sites where it is used (e.g., wood-treatment facilities), or in log homes treated with pentachlorophenol (IPCS 1987, Zheng *et al.* 2011). Several reports indicated that log homes were a source of high exposure to pentachlorophenol in the past, with the blood levels of some inhabitants exceeding 1000 µg/L (MMWR 1980, Cline *et al.* 1989). Similar exposures were reported for workers in the log home museum at Fort Stanwix National Monument in Rome, NY; however, washing the surfaces of the logs with ethyl alcohol to remove crystals of pentachlorophenol greatly reduced their exposure (Lee and Lucas 1983).

Pentachlorophenol has been detected in drinking-water supplies (at < 1 to 50 µg/L), groundwater (at 0.6 to 19,000 µg/L), and surface water (from nondetectable to 10,500 µg/L); most measurements were made before use of pentachlorophenol was restricted (IPCS 1987, ATSDR 2001, Zheng *et al.* 2011). Higher levels were reported for groundwater near industrial areas such as wood-preserving facilities (ATSDR 2001).

Contact of pentachlorophenol-treated wood products (e.g., utility poles) with soil provides another potential route of exposure, especially for small children (ATSDR 2001), who may eat soil or to put their hands or foreign objects in their mouths. Nondietary ingestion of pentachlorophenol, such as that associated with dust, has been considered a minor contributor to exposure (Wilson *et al.* 2007, 2010), but it might be more important for small children.

Pentachlorophenol in food was found to be a major source of exposure (75% or more of total exposure) in some environmental-exposure models from the 1980s (e.g., Hattamer-Frey and Travis 1989). Its presence was reported in a wide variety of foods, such as meats, fish, dairy products, grains, and vegetables, in studies from Canada, the United Kingdom, and Germany during that period (Crosby *et al.* 1981, Jones 1981, IPCS 1987, Wild and Jones 1992). Low levels of pentachlorophenol continued to be found in food after restrictions were instituted (e.g., in 1991–93 and 2003) (FDA 2006).

## Regulations

### **U.S. Environmental Protection Agency (EPA)**

#### *Clean Air Act*

*National Emission Standards for Hazardous Air Pollutants:* Pentachlorophenol is listed as a hazardous air pollutant.

#### *Safe Drinking Water Act*

Maximum contaminant level (MCL) = 1 µg/L

#### *Comprehensive Environmental Response, Compensation, and Liability Act*

Reportable quantity (RQ) = 10 lb.

#### *Regional Screening Levels (formerly called Preliminary Remediation Goals)*

Screening levels for pentachlorophenol are as follows: Residential soil = 0.89 mg/kg; Industrial soil = 2.7 mg/kg; Residential air = 0.48  $\mu\text{g}/\text{m}^3$ ; Industrial air = 2.4  $\mu\text{g}/\text{m}^3$ ; Tap water = 0.035  $\mu\text{g}/\text{L}$ ; MCL = 1  $\mu\text{g}/\text{L}$ .

#### *Resource Conservation and Recovery Act*

Hazardous Waste Codes for which the listing is based wholly or partly on the presence of pentachlorophenol = D037, F021, F027, F028, F032, K001.

Listed as a hazardous constituent of waste.

#### **Occupational Safety and Health Administration (OSHA)**

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Permissible exposure limit (PEL) = 0.5  $\text{mg}/\text{m}^3$  [0.05 ppm] (skin).

#### **Guidelines**

##### **American Conference of Governmental Industrial Hygienists (ACGIH)**

Threshold limit value – time-weighted average (TLV-TWA) = 0.5  $\text{mg}/\text{m}^3$  [0.05 ppm] (skin).

##### **National Institute for Occupational Safety and Health (NIOSH)**

Recommended Exposure Limit (REL) = 0.5  $\text{mg}/\text{m}^3$  [0.05 ppm] (skin).

Immediately dangerous to life and health (IDLH) limit = 2.5  $\text{mg}/\text{m}^3$  [0.23 ppm].

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